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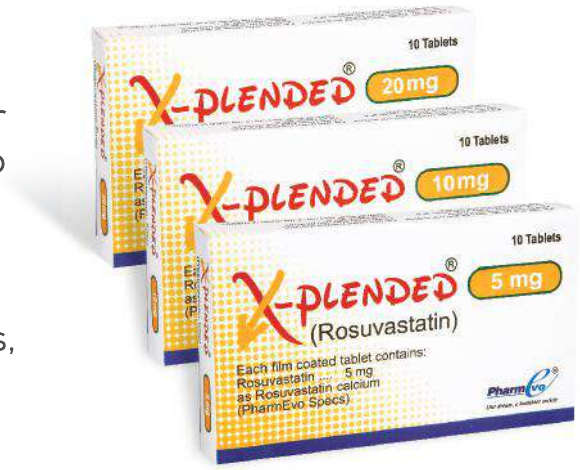

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Brugada Syndrome: An update - 2019

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Introduction

Almost 30 years ago, a manuscript titled "*Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome*" was published in the Journal of the American College of Cardiology [(1)]. This publication described eight individuals with a common clinical and electrocardiographic syndrome: all had a structurally normal heart and had been resuscitated from sudden cardiac death (SCD) caused by documented ventricular fibrillation (VF). All of them had a characteristic ST segment elevation in the right precordial leads (Figure 1). It looked like a scientific curiosity, however, after all these years, this syndrome, now known as Brugada Syndrome (BrS) is recognized as a major disease that integrated previous syndromes like idiopathic ventricular fibrillation, sudden unexplained death syndrome, and some forms of sudden infant death syndrome. BrS and other syndromes like long or short QT syndromes and catecholamine polymorphic ventricular tachycardia (CPVT) have a common denominator: Alteration of ionic currents leading to depolarization and/or repolarization abnormalities that result in ventricular arrhythmias causing sudden cardiac death. At least 19 different genetic variants of BrS are known nowadays, with more than 300 mutations reported, most of them affecting the *SCN5A* gene that encodes for the cardiac sodium channel. The extremely wide genetic heterogeneity of BrS and other inherited cardiac disorders makes this new arena of Genetic Arrhythmology a fascinating one.

We will here review the present knowledge, progress made, and future research directions on BrS.

Electrocardiographic features and diagnosis

The diagnosis of BrS is a clinical-electrocardiographic one. The clinical presentation can be very variable: from completely asymptomatic to episodes of syncope and sudden death, but also other manifestations like atrial fibrillation and AV block.

Characteristically, patients with BrS have no apparent structural heart disease. The hallmark of BrS is the transient or persistent appearance of typical ECG changes in the right precordial leads[(2)].

Three different ECG patterns (Figure 1: A, B and C), all featuring ST segment elevation in the right precordial leads, have been recognized:

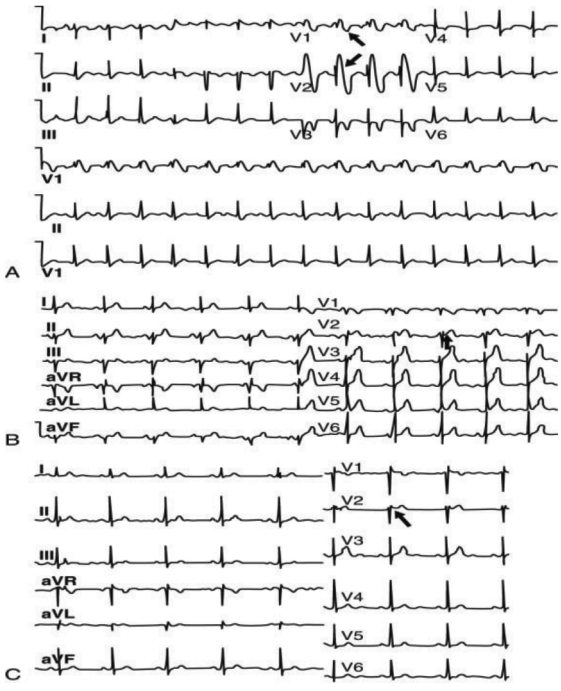

Figure 1- Brugada electrocardiogram (ECG) patterns.

A- A diagnostic coved-type (type I) Brugada ECG pattern documented in a 9-year-old girl who presented with syncope and positive family history of BrS. Note the pattern resembling a right bundle branch block (arrows) in leads V1 and V2, with typical ST elevation.

B- Baseline ECG of a 58-year-old asymptomatic man with positive family history of BrS. Example of a type II saddleback Brugada ECG pattern. Genetic analysis revealed a mutation in the SCN5A gene. Note the saddleback-shaped patterns, with a high initial augmentation followed by an ST elevation greater than 2 mm in lead V2.

C- Example of a baseline type III saddleback Brugada ECG pattern (arrow) documented in a 61-year-old asymptomatic man who was diagnosed on the basis of a positive result on class IC antiarrhythmic drug testing.

Type I is the only pattern that is diagnostic for BrS. It consists of a coved-type ST segment elevation equal or greater than 2 mm, followed by a descending negative T wave in at least one right precordial lead (V_1 to V_3). Type II and type III are saddleback patterns, with a broad R' followed by a convex saddle-type ST configuration with elevation greater than 2 mm for type II and less than 2 mm for type III. Both patterns are suggestive of but they are not diagnostic for BrS. The ECG in BrS is very variable. When sufficient number of ECGs are recorded during the follow-up of these patients, practically all of them will have a completely normal ECG at a certain point of time. This has important implications for the diagnosis of BrS because the diagnosis can be completely missed if it is not suspected and a pharmacologic challenge is not performed to unmask the typical type I ECG.

A pharmacologic test can be performed using ajmaline, procainamide or flecainide (Figure 2). In Japan pilsicainide is used for that purpose. On the basis of the results of comparative studies, ajmaline, in a dose of 1 mg/kg bodyweight given over a 5 min period, seems to be the best drug. The full stomach test was proposed as an alternative tool in diagnosing BrS [3].

Here, the ST segment changes appear to be provoked by an enhanced vagal tone. Adrenergic stimulation decreases the ST segment elevation, whereas vagal stimulation increases it.

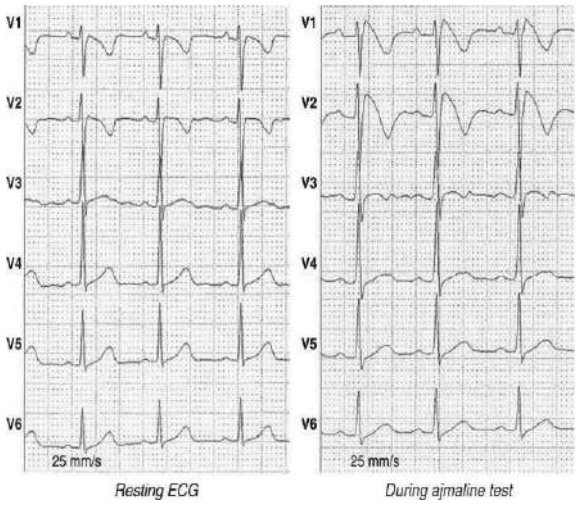

Figure 2- Induction of a diagnostic coved-type (type I) electrocardiogram (ECG) by administration of a sodium channel–blocking agent.

It is important to exclude other causes of ST segment elevation before making the diagnosis of BrS, the so-called "phenocopies", i.e. ECGs that look like BrS but have another cause (Table 1).

A diagnosis of BrS requires a high degree of suspicion from the part of the physician. Symptoms that should suggest a possible BrS and promote its intensive search are: syncope of unknown origin, atrial fibrillation with a normal heart, peripheral or cerebral embolism (as a complication of atrial fibrillation) and cardiac arrest of unknown cause. These symptoms and signs can be the first and only manifestation of Brugada syndrome. We recommend an ajmaline test in these circumstances to prove exclude the diagnosis. The suspicion becomes even stronger when there is a family history of sudden death.

Genetics

BrS is a familial disease. The most common type of inheritance is an autosomal dominant pattern. To date, more than 300 pathogenic variants in 19 different genes have been reported (Table 2). The first gene that was associated with BrS was the *SCN5A* gene which encodes for the alpha subunit of the cardiac sodium channel [4]. The sodium current is responsible for the phase 0 of the cardiac action potential. Mutations in the *SCN5A* gene result in loss of function of the sodium channel. About 20-25% of patients with BrS have a mutation in the *SCN5A* gene, classified as BrS type 1 [5]. Recently, an individual diagnosed with BrS and concomitant conduction system disease had a large-scale deletion of the *SCN5A* gene [6]. This copy number variation (CNV) is the only rearrangement identified as a cause of the disease to date. Despite these ongoing developments in understanding the genetic causes of BrS, only 30-35% of clinically diagnosed cases are genetically diagnosed, and most of these (25-30%) result from pathogenic alterations in *SCN5A* [5]. In a recent study, a comprehensive genetic evaluation of main BrS-susceptibility genes and CNV in a Spanish BrS cohort has been published. Selga et al reported that the mean pathogenic variation discovery yield is higher than that described for other European BrS cohorts (32.7% vs 20-25%, respectively), and is even higher for patients in the 30-50 years age range [7].

Review

Table 1. - Acquired Brugada Syndrome (phenocopies): Differential Diagnosis of ST Segment Elevation in Electrocardiogram Leads V_1 and V_2.

Drugs	Antiarrhythmic drugs	• Class 1C sodium channel blockers (e.g., flecainide, pilsicainide, propafenone) • Class 1A sodium channel blockers (e.g., procainamide, disopyramide, cibenzoline) • Verapamil (L-type calcium channel blocker) • Beta-blockers (inhibit $I_{Ca,L}$)
	Antianginal drugs	• Nitrates • Calcium channel blockers (e.g., nifedipine, diltiazem)
	Psychotropic agents	• Tricyclic antidepressants (e.g., amitriptiline, desipramine, clomipramine, nortriptyline). • Tetracyclic antidepressants (e.g., maprotiline). • Phenothiazines (e.g., perphenazine, cyamemazine). • Selective serotonine uptake inhibitors (e.g., fluoxetine). • Cocaine intoxication
Anti-allergic agents		• Histamine H1 antihistaminics. First-generation (dimenhydrinate)
Acute ischemia in RVOT		
Electrolyte disturbances		• Hyperkalemia • Hypercalcemia
Hyperthermia and hypothermia		
Elevated insulin level		
Mechanical compression of RVOT right ventricular outflow tract		

Table 2: Brugada Syndrome (BrS) types

INHERITANCE	LOCUS	GENE	PROTEIN
	3p21-p24	*SCN5A*	Nav1.5
(Sodium)	3p22.3	*GPD1-L*	Glycerol-3-P-DH-1
Autosomic	19q13.1	*SCN1B*	Navß1
dominant	11q24.1	*SCN3B*	Navß3
	11q23.3	*SCN2B*	Navß2
	3p22.2	*SCN10A*	Nav1.8
	17p13.1	*RANGRF*	RAN-G-release factor (MOG1)
	3p14.3	*SLMAP*	Sarcolemma associated protein
	12p11.21	*PKP2*	Plakofilin-2
	12p12.1	*ABCC9*	Adenosine triphosphate (ATP)- sensitive
(Potassium)	11q13-	*KCNE3*	MiRP2
Autosomic	q14	*KCNJ8*	Kv6.1 Kir6.1
dominant	12p12.1	*HCN4*	hyperpolarization cyclic nucleotide-gated 4
	15q24.1	*KCND3*	Kv4.3 Kir4.3
Chromosome X	1p13.2	*KCNE5*	potassium voltage-gated channel subfamily E member 1
	Xq22.3		
(Calcium)	2p13.3	*CACNA1C*	Cav1.2
Autosomic	10p12.33	*CACNB2B*	voltage-dependent ß-2
dominant	7q21-q22	*CACNA2D1*	voltage-dependent α2/ δ 1
	19q13.33	*TRPM4*	transient receptor potential M4

Other mutations associated with BrS affect the *SCN1B* gene (codifying for the sodium channel beta-1 subunit) [8], the *SCN2B* gene (sodium channel beta-2 subunit), and the *SCN3B* gene (sodium channel beta-3 subunit) [9]. All these mutations modify the function of the channel (increasing or decreasing I_{Na}) [8-10]. Recently, the *SCN10A* gene (neuronal sodium channel $Na_v1.8$), has been shown to modulate *SCN5A* expression and the electrical function of the heart [11]. Another gene reported as responsible for BrS is the *GPD1-L*. Mutations in *GPD1-L* reduce both the surface membrane expression and the inward sodium current [12]. Kattygnarath et al have published a study supporting that *RANGRF* can impair the trafficking of Na_v 1.5 to the membrane, leading to I_{Na} reduction and clinical manifestation of BrS[13]. In 2012, Ishikawa et al. reported pathogenic variations in the sarcolemmal membrane-associated protein (*SLMAP*) gene, a gene of unknown function that is found at T-tubules and the sarcoplasmic reticulum. SLMAP causes BrS by modulating the intracellular trafficking of the Na_v 1.5 channel [14]. Pathogenic variations in the plakophilin-2 (*PKP2)* gene have been also reported to be associated with BrS[15,16]. *PKP2* is the primary gene responsible for arrhythmogenic right ventricular cardiomyopathy (ARVC), a desmosomal disease characterized by fibro-fatty replacement of myocardium leading to SCD in young men, mainly during exercise. Correlation between the loss of expression of plakophilin-2 and reduced I_{Na} has been identified in BrS patients. Apart from sodium channels, several potassium channels have been also related to BrS. The first one described was *KCNE3* which codifies the MiRP2 protein (β-subunit that regulates the potassium channel I_{to}), and that modulate some potassium currents in the heart [17]. Another gene associated to BrS is the *KCNJ8 GENE* also previously related to early repolarization syndrome (ERS)[18]. The *KCNJ8* was described as a novel J-wave syndrome susceptibility gene and a marker of gain of function in the cardiac $K_{(ATP)}$ Kir 6.1 channel [19]. In 2011, Giudicessi et al. provided the first molecular and functional evidence implicating novel *KCND3* gain-of-function mutations (Kir4.3 protein) in the pathogenesis and phenotypic expression of BrS, with enhanced I_{to} current gradient within the right ventricle where *KCND3* gene expression is the highest[20].

Also in 2011, novel variants in *KCNE5* were shown to cause gain-of-function effects on I_{to}. The *KCNE5* gene is located in the X chromosome and encodes an auxiliary β-subunit for K channels[21]. Similar is the role of the sulfonylurea receptor subunit 2A (SUR2A), encoded by the ATP-binding cassette, subfamily C member 9 (*ABCC9*) gene [22]. Gain-of-function pathogenic variants in *ABCC9* induce changes in ATP-sensitive potassium (K-ATP) channels, and, when coupled with loss-of-function pathogenic variants in *SCN5A*, these pathogenic variants may underlie the severe arrhythmic phenotype of BrS. The BrS was also associated to the gene *HCN4*, which codifies for HCN4 channel or If channel (hyperpolarization-activated cyclic nucleotide-gated potassium channel 4). Its mutations also predispose to inherited sick sinus syndrome (SSS), and LQTS associated with bradycardia[23]. Calcium channels have also been associated to BrS. Mutations in the *CACNA1C* gene are responsible for a defective a unit of the type-L calcium channel. Mutation of the *CACNB2B* gene leads to a defect in the L-type calcium channel. Both induce a loss of channel function [24]. In 2010 it was reported that the *CACNA2D1* gene was also responsible for BrS. The alpha-2/delta subunit of the voltage-dependent calcium channel regulates current density, and activation/inactivation kinetics of the calcium channel [25]. Finally, pathogenic variations have also been reported in the transient receptor potential melastatin protein number 4 (*TRPM4*) gene, a calcium-activated nonselective cation channel that is a member of a large family of transient receptor potential genes[26]. This gene is involved in conduction blocks, and the consequences of pathogenic variations are diverse. Thus, reduction or increase in TRPM4 channel function may reduce the availability of the sodium channel and lead to BrS.

It is clear therefore, that BrS is a heterogeneous genetic disease. It is not a surprise that many overlapping syndromes can exist due to this very variable and large spectrum of possible genetic causes.

It has also to be clear that a direct cause-to-effect relation between these mutations and BrS has not been completely established in the majority of the genetic variations.

Genetic and environmental modulators

In recent years, several genetic and environmental modulators of the phenotype have been described. It is well known that environment may play a role in the predisposition to arrhythmias in patients with BrS. The identification of several triggering factors of the Brugada ECG pattern and of SCD, as fever, cocaine, electrolyte disturbances, class I anti-arrhythmic medications, and a number of other non-cardiac medications [27], some of them with a genetic predisposition, has important implications for the prevention of arrhythmias in patients with BrS [28]. In addition, the incomplete penetrance of the disease, as well as the variable expressivity, has brought into question the role of additional genetic factors in the final phenotype. Single nucleotide polymorphisms (SNPs) became one of the first players to be studied in defining this variability.

The *SCN5A* polymorphism p.H558R is present in 20% of the population. This polymorphism has been shown to partially restore the sodium current impaired by other simultaneous BrS causing mutations in *SCN5A* [29]. Thus, this common variant is a genetic modulator of BrS among carriers of an *SCN5A* mutation, in whom the presence of the less common allele makes BrS less severe[30].

Genetic variants in the *SCN5A* promoter region may also play a pathophysiologic role in BrS. A haplotype of six polymorphisms in the *SCN5A* promoter has been identified and functionally linked to a reduced expression of the sodium current in the Japanese population [31]. Other studies have shown the role of double or even triple mutants in causing a more severe phenotype [32,33].

The role of the genetic mutation in risk stratification has yet to be clearly defined. Recent data proposed the type of genetic mutation as a tool for risk stratification in BrS. In this study, patients and relatives with a truncated protein had a more severe phenotype and more severe conduction disorders. Despite this proof of concept that some of the mutations appear to confer a worse prognosis, data are not yet sufficiently strong as to help in risk stratification [34].

Overlapping syndromes

Individuals in families with BrS may show different phenotypes within the same family even when they share the same mutation. But also some individuals may present with two different phenotypes at the same time, like BrS with a long or a short QT interval. These so called "overlapping syndromes" represent a tremendous challenge to physicians for diagnosis and risk stratification.

Early repolarization syndrome

The Early Repolarization Syndrome (ERS) is a common electrocardiographic variant characterized by J-point elevation, ST-segment elevation with upper concavity and prominent T waves in at least 2 contiguous leads [35]. The ERS and BrS share cellular, ionic, and ECG similarities (appearance of J waves), representing parts of a phenotypic spectrum called "J-wave syndromes", although the degree to which ERS and BrS may overlap remains undetermined [36]. Patients with BrS and ERS have been recently reported37. ERS has been linked to mutations in the *CACNA1C, CACNB2, CACNA2D1*, and *KCNJ8* genes [38].

Lev-Lenègre syndrome

Lev-Lenègre syndrome (also called progressive cardiac conduction disease -PCCD) is a rare entity characterized by conduction disturbances at the atrio-ventricular level leading to complete AV block. The syndrome is a cause of syncope and even SCD. The presence of PCCD in the BrS families is not uncommon, as they both result from a reduction in the sodium current, and it has been described as a different expression of the same genetic phenotype. The first mutation associated with PCCD was described in the *SCN5A* gene [39,40] and on its B1 subunit [8]. Patients with clear BrS can die suddenly because of AV block and asystole, not only because of ventricular fibrillation.

Sick Sinus Syndrome

Sick Sinus Syndrome (SSS) is characterized by persistent inappropriate sinus bradycardia, sinus arrest, atrial standstill, and tachycardia–bradycardia syndrome, associated with dysfunction of the sinoatrial node (SAN). Patients may exhibit varied symptoms including syncope, and even SCD. The course of SSS can be intermittent and unpredictable, related to the severity of the underlying heart disease [41]. So far, both autosomal recessive and dominant forms have been described. In 2003 the association between *SCN5A* mutations and congenital SSS [42] was reported. In 2005, a novel *SCN5A* mutation was identified in patients presenting both SSS and BrS [43], showing that in the same family both diseases may be related to the expression of a loss-of-function mutation in I_{Na}. The presence of SSS has important prognostic implications in BrS (see risk stratification): it increases the risk of sudden death, particularly in children.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common atrial arrhythmia found in BrS [44]. Atrial fibrillation can be the first manifestation of BrS, and sometimes the first manifestation of BrS can be peripheral or cerebral embolization as a complication of AF. The administration of class I antiarrhythmic drugs in these patients can lead to ventricular fibrillation and sudden death. BrS should be excluded by drug challenge in all individuals with atrial flutter or fibrillation and a normal heart and a normal ECG. Approximately 15-20% of patients with BrS develop supraventricular arrhythmias [45]. Some studies have reported prolongation of atria - His and His - ventricular (HV) interval; these changes occur principally in patients with *SCN5A* mutations [46], and are consistent with a decreased excitability in the conduction system secondary to the loss of function of sodium channel activity [47].

Long QT Syndrome type 3

Long QT syndrome (LQTS) is an inherited arrhythmogenic disease characterized by prolongation of the QT interval and susceptibility to ventricular tachyarrhythmias. Among all described subtypes of LQTS, the type 3 (LQT3) has a relative prevalence of 7–10% [48]. LQT3 is caused by mutations in the *SCN5A* gene. A most intriguing report showed that some individuals may display the electrocardiographic pattern of LQT3, while others the pattern of BrS in the same family and with the same mutation [49]. The overlap between the LQT3 and BrS phenotypes was also reported in other *SCN5A* mutations [50]. However, it is still unclear whether development of the BrS phenotype in a patient with LQT3 is solely determined by the biophysical properties of the mutant channel, or by co-inherited genetic variations, gender, ethnicity, or other environmental factors [51].

Epilepsy and schizophrenia

Cardiac arrhythmias are associated with abnormal channel function due to mutations in ion channel genes. Epilepsy is a disorder of neuronal function also involving abnormal channel function. It is increasingly demonstrated that the aetiologies of BrS and epilepsy may partly overlap. It has been reported that *SCN5A* mutations may confer susceptibility for recurrent seizure activity, supporting the emerging concept of a genetically determined cardio cerebral channelopathy [52,53]. A high percentage of patients with schizophrenia (around 12%) shows and ECG pattern of BrS which is unrelated to the use of sodium channel blocker drugs. The reasons for these findings are unclear.

Myotonic phenotypes

To date, except for nonspecific cardiac arrhythmias described in two *SCN4A*-associated case reports [54], no overlapping phenotypes between muscular and cardiac sodium channelopathies have been reported. In a recent study, Bissay et al reported a high number of patients with coexisting BrS and sodium channel myotonia, suggesting a possible impact of *SCN4A* variants on the pathophysiological mechanism underlying the development of a type 1 ECG pattern and of malignant arrhythmias in some patients diagnosed with myopathies[55].

Risk stratification

After a diagnosis of BrS the first questions that arise are mainly related to the future outcomes and the prognosis. To date, some markers of high risk in BrS patients have been clearly identified and accepted by all groups, but the issue of risk stratification of asymptomatic BrS patients remained controversial until the recent report by our group [56]. The reported annual rate of events has decreased from the patients initially reported to the most recent published series, the change probably reflecting the inherent bias during the first years following the description of a novel disease, in which particularly severe forms of the disease were most likely to be diagnosed[57]. A recent study by Sieira et al shows that arrhythmic events in asymptomatic BrS patients are not insignificant (0.5% annual incidence rate). In this cohort, inducibility of ventricular arrhythmias, spontaneous type I ECG and presence of sinus node dysfunction might be considered as risk factors and used to plan long term management[58]. A meta-analysis recently published also showed that asymptomatic subjects with either spontaneous diagnostic ECG pattern or inducible ventricular arrhythmias on programmed ventricular stimulation are at an increased risk [59]. Several clinical variables have been demonstrated to predict a worse outcome in patients with BrS. In almost all the analysis, the presence of symptoms before diagnosis, a spontaneous type-1 ECG at baseline and male gender have consistently shown to be related to the occurrence of cardiac events in follow-up [60,61]. Little controversy exists on the value of a previous cardiac arrest as a risk marker for future events (between 17% and 62% of patients will have a new arrhythmic event within 48 and 84 months of follow-up). Similarly, the presence of syncope identifies patients with a high risk for events (6% to 19% at 24 to 39 months follow-up), thus, there is general agreement that these patients should be protected with an ICD irrespective of the presence or absence of other risk factors.

Spontaneous ECG type 1 has been identified as an independent predictor of ventricular arrhythmias in multivariate analysis of the largest cohort of BS patients published to date[62] (HR=1.8; 95% CI 1.03 to 3.33; p=0.04) and in the majority of series by others.

Male sex has consistently shown a trend to present with more arrhythmic events in all the studies, and even has been defined as an independent predictor for a worse outcome in a meta-analysis [63].

Spontaneous AF, which can appear in 10 to 53% of cases, has been shown to have prognostic significance and spontaneous AF was associated with higher incidence of syncopal episodes (60.0% vs. 22.2%, p<0.03) and documented VF (40.0% vs. 14.3%, p<0.05) [64].

The risk of lethal or near-lethal arrhythmic episodes among previously asymptomatic patients with BrS varies according to the series: 8% recurrence rate at 33±39 months of follow-up reported by Brugada et al. [65], 6% recurrence rate at 34±44 months by Priori et al [66]; 1% recurrence rate after 40±50 months and 30 ± 21 months of follow-up, respectively by Eckardt et al. [67] and Giustetto et al. [68], and finally, Probst et al. reported a 1.5% recurrence rate at 31 months of follow-up [62].

Although large registries agree that EPS inducibility is greatest among BrS patients with previous SD or syncope [65], there is no consensus on the value of the EPS in predicting outcome. The analysis of Our previous data[65] indicated that inducibility during EP study was an independent predictor for cardiac events, and Giustetto et al. [68] stressed the good negative predictive value (none of the patients with a negative EPS developed arrhythmic events vs. 15% of patients with a positive EPS result during 30 ± 21 months of follow-up); while other registries failed to demonstrate this[62].

The largest series of BrS patients published so far, found that inducibility of sustained ventricular arrhythmias was significantly associated with a shorter time to first arrhythmic event in the univariate analysis but when performing the multivariable analysis, inducibility did not predict arrhythmic events[62].

In 2015, a single center study has been recently published, showing results in a cohort of 96 BrS patients with various clinical presentations and who have inducible VF using an aggressive PVS protocol. The authors reported an excellent protective effect of class 1 AAD (mainly quinidine) during EP testing and an excellent clinical outcome in drug-treated patients [69]. In addition, Sieira et al published a series of 403 BrS cases. Authors conclude that programmed ventricular stimulation of the heart is a good predictor of outcome in individuals with BrS.

It might be of special value to guide further management when performed in asymptomatic individuals. The overall accuracy of the test makes it a suitable screening tool to reassure non inducible asymptomatic individuals [70].

A family history of SD or the presence of an *SCN5A* mutation have not been proven to be risk markers in any of the large studies conducted thus far [63]. However, recent data suggests that other genetic findings, like the presence of mutations leading to a truncated protein, or the presence of common polymorphisms located in *SCN5A* might have some prognostic implications[34]. A recent publication by Meregelli of 147 BrS patients with *SCN5A* identified mutations showed a significantly higher rate of syncope among patients carrying *SCN5A* truncation mutations (caused by a premature stop codon) and those with *SCN5A* missense mutations resulting in a decrease of more than 90% of the I_{Na} (non-functional Na^+ channels), compared to patients with *SCN5A* missense mutations that produce a decrease of Na current (≤90%). They could not demonstrate a higher rate of more serious arrhythmic events (SCD or VF) in those patients with mutations encoding non-functional Na^+ channels. The first two groups of patients also presented longer PR interval in the basal ECG, and showed a greater increase of PR and QRS intervals after the class I AAD test. This is the first study that proposed the use of genetics in risk stratification for BrS. The recent finding that common polymorphisms located in *SCN5A* may modulate the effect of mutations resulting in a counterbalance of its deleterious consequences with improvement of the BrS phenotype, opens the possibility of identification of polymorphisms as risk stratification tools.

These data also suggest that polymorphisms may be possible targets for therapeutical interventions. In summary, few things are clear from the risk stratification data: symptomatic patients are at higher risk than asymptomatic ones; sudden death survivors are at higher risk than patients with syncope, males are at higher risk than females; patients with type I ECG at baseline have a higher risk than those who require class I antiarrhythmics; and asymptomatic patients may also die suddenly.

This latter statement is based on the fact that all symptomatic patients with BrS have remained asymptomatic for decades. Thus, at present the biggest challenge is the detection of these few asymptomatic who will develop symptoms.

Non-invasive markers of arrhythmic risk in Brugada syndrome

In an effort to solve the complex issue of risk stratification in BrS, several non-invasive methods have been postulated as markers of arrhythmic events among these patients: A decreased nocturnal standard deviation of the 5 minutes averaged NN intervals (SDANN) measured in Holter recordings; an S wave width in V1 ≥ 80 msec and ST-segment elevation ≥ 0.18 mV in V2; spontaneous changes in ST-segment, a corrected QT interval (QTc) higher than 460 ms in V2, prolonged T peak-T end (Tp-e) interval and T p-e dispersion; the "aVR sign" (R wave ≥ 0.3 mV or R/q ≥ 0.75 in lead aVR); prolonged QRS duration in precordial leads (r-J interval in V2 ≥ 90 ms and QRS ≥ 90 ms in V6; QRS ≥ 120 ms in V2); even an indicator of inter-ventricular mechanical dyssynchrony has been recently found to be associated with high risk of fatal or near-fatal arrhythmias in BrS. The usefulness of late potentials (LP) assessed by signal-averaged ECG (SAECG) as a marker of high risk has been extensively studied by various groups, and a recent prospective study showed that positive LP was an independent marker of high risk in BS patients, with a hazard ratio of 10.9 (95% confidence interval 1.1-104.3, p=0.038), sensitivity of 95.7%, specificity of 65%, positive predictive value of 75.9%, negative predictive value of 92.9% and predictive accuracy 81.4%. Before including LP as a marker for risk, there is the need of more prospective studies, including more patients and with a longer follow-up, evaluating the value of different non-invasive markers of risk in BrS.

Scoring system

Risk stratification was the aim of the study we recently reported [56]. Analysis of the long-term follow-up of 400 patients with BrS showed that six variables were related to a poor outcome and contributed with a certain value to a scoring system developed by careful statistical analysis (table 3 and figure 3). Multivariate analysis showed that the presence of a spontaneous type I ECG, a family history of sudden death (<35 years or several cases), a history of syncope, inducibility during programmed ventricular stimulation, sick sinus syndrome and a previous cardiac arrest were the six variables that could be assigned a certain value in points (table 3).

RISK FACTOR	POINTS
Spontaneous type I ECG	**1**
Family history of sudden death	**1**
Inducibility during PES	**2**
History of syncope	**2**
Sick sinus syndrome	**3**
Resuscitated SCD	**4**

Table 3; Risk factors for sudden death in BrS [56]

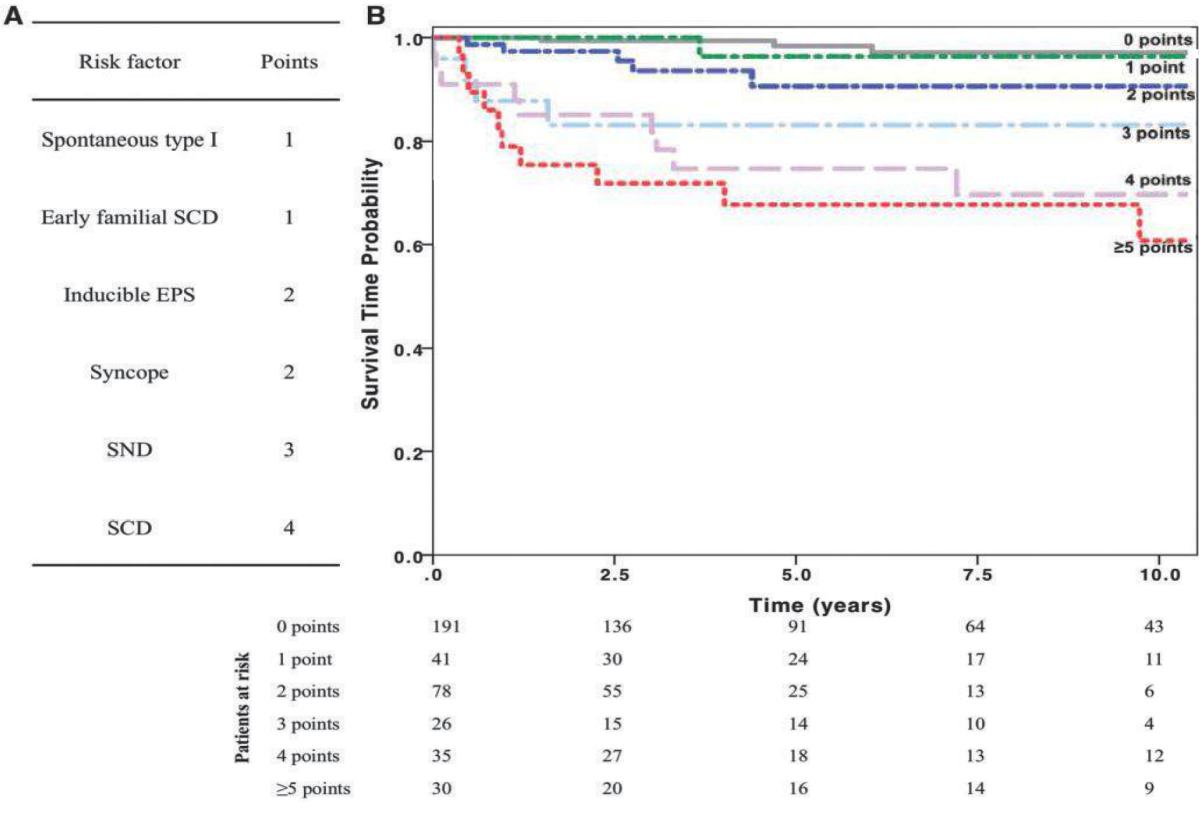

Figure 3. Survival curves in BrS depending on score [56]

The survival curves without sudden death or appropriate defibrillator discharge are shown for the different score categories in figure 3. While the incidence of events increases clearly depending on the number of points, it has to be stressed that the first two categories (0 and 1 point) have still a high incidence of sudden death as compared to the general population without BrS. Thus, a possible risk of sudden death of 0.3% per year in the first category (0 points) represents at least a 30 times increase of the risk as compared with an individual of the same age without BrS (who has a general risk of sudden death of 1:10.000 per year at age 40).

Therapeutic options and recommendations for Brugada syndrome patients

- Implantable cardioverter defibrillator (ICD)

To date, the only proven effective therapeutic strategy for the prevention of SCD in BrS patients is the ICD. This fact is supported by a recent study of Conte et al, treating potentially lethal arrhythmias in 17% of patients during a follow-up period of nearly 85 months. Appropriate shocks were significantly associated with the presence of aborted sudden cardiac death [71]. It is important to remark that ICDs are not free from several disadvantages, especially in this group of patients, sharing a particular profile: active young individuals, facing a long-lasting coexistence with the device and multiple device replacements, long life expectation (especially since the device implantation). Some series have reported low rates of appropriate shocks (8-15%, median follow-up 45 months) and high rate of complications, mainly inappropriate shocks (20-36% at 21-47 months follow-up)[72-74]. In a recent study, Rodriguez-Mañero et al published that T-wave over-sensing is a potential reason of inappropriate shocks in patients with BrS receiving ICDs. In the vast majority it can be solved by reprogramming. However, in some patients it still requires invasive intervention. Importantly, incidence is significantly lower using an integrated bipolar lead system when compared with a dedicated bipolar lead system and hence the latter should be routinely used in BrS cases [75].

- Pharmacological treatment in Brugada syndrome

With the objective of rebalancing the ionic currents affected in BrS during the cardiac AP, drugs that inhibit the Ito current or increase the Na^+ and Ca^{+2} currents have been tested in BrS:

-Isoproterenol (which increases the Ica L current), has proved to be useful for treatment of electrical storm in BrS [76].

-Quinidine, a class Ia AAD with Ito and I-Kr blocker effects, has shown to prevent induction of VF and suppress spontaneous ventricular arrhythmias in a clinical setting, being currently used in patients with ICD and multiple shocks, cases in which ICD implantation is contraindicated, or for the treatment of supraventricular arrhythmias. It has been suggested that it could be also useful in children with BrS, as a bridge to ICD or as an alternative to it, however, recent data from the international SABRUS registry have shown that quinidine is of no value to prevent sudden death in BrS [77].

- Ablation in Brugada syndrome

After the demonstration that VF events were triggered by similar ventricular ectopy, radiofrequency ablation (RFCA) of ventricular ectopy has been postulated as a therapeutical approach in BS patients. Few anecdotic cases in high-risk BrS implanted with an ICD, have shown no short-term recurrence of VF, syncope or SCD[78,79].

Nademannee presented the first series showing that electrical disconnection of the right ventricular outflow tract can prevent VF inducibility in a high risk population[80]. In 2014, a BrS case of an ablation of the epicardial substrate in the right ventricular outflow tract was published[81]. In 2015, Forkmann et al reported a BrS case in which epicardial ventricular tachycardia ablation was performed and noninducibility of any VT during programmed ventricular stimulation was identified. During 9 months of follow-up, device interrogation showed no recurrence of any VT episodes[82]. Recently, a study focused on epicardial ablation has been published showing an apparent elimination of the BrS phenotype [83]. We perform epicardial ablation during subcostal implantation of the ICD where the ICD leads are implanted around the heart epicardially (figure 4).

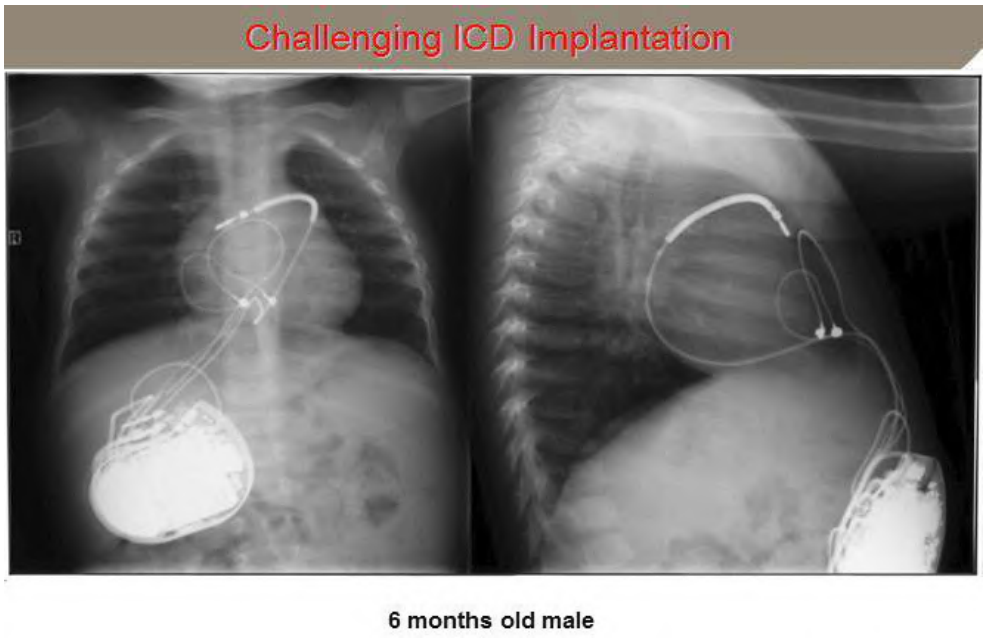

Figure 4: X-ray after ICD implantation in a 6 months old child: Epicardial electrode on epicardial right ventricle free wall, defibrillation electrode around the heart in the sinus tranversus. Generator in abdominal position.

While ablation of the BrS substrate is promising, we need long-term follow-up data before ablation can ever be considered an alternative to the ICD. It is unlikely that we will ever have scientifically sound randomized studies on ablation of BrS.

- Pre-implant genetic diagnosis (PGD) of embryos.

A therapeutic option that can be considered to stop further transmission of the disease is PGD. The use of this technique is only possible when the genetic cause of the disease is known. Embryos are prepared via an in vitro fertilization. When the embryos are large enough (about 16 cells) - the embryos are biopsied and tested genetically. Only embryos not affected by the mutation are implanted in the mother. In this way one can be sure that the offspring will not suffer from the mutation.

Use of this technique has been criticized from the ethical and philosophic point of view, however, this is only a moral and not scientific issue. There have been also retractors to this technique that state that BrS may be a polygenic and not a monogenic disease, so that eliminating a single mutation may be not sufficient to eliminate the disease. On the other side, the theory of multiple genetic hits favours this PGD approach:

According to the multiple genetic hits theory a single mutation is not sufficient to cause a disease, but multiple abnormalities (hits) from mutations to polymorphisms, may be necessary to really suffer from the disease.

According to this theory, eliminating one genetic hit (one mutation) may thus also be sufficient to prevent all manifestations of the disease. The patients that we have managed this way at our centre have not suffered from any unwanted consequences so far, however, the offspring is still too young to make any conclusions about manifestations of the BrS. A first follow-up after puberty will be essential to make the first conclusions.

Brugada syndrome, the environment and external factors.

The ECG in BrS typically changes over time and can change between the three patterns or even become completely normal [84]. It is thus, imperative to record serial ECGs when the syndrome is suspected. Modulating factors play a major role in the dynamic nature of the ECG and also may be responsible for the ST-segment elevation in genetically predisposed patients.

Sympathovagal balance, hormones, metabolic factors, and pharmacologic agents, by means of specific effects on transmembrane ionic currents, are thought to modulate not only the ECG morphology, but also to explain the development of ventricular arrhythmias under certain conditions. Indeed, bradycardia and vagal tone may increase ST-segment elevation and arrhythmia initiation by decreasing calcium currents [85]. This explains the greater ST-segment elevation recorded in vagal settings [86], and the notorious incidence of cardiac arrhythmias and SD at night in patients with BrS [87].

The role of sex hormones is currently being established. Published data suggest that they might also play a role in the phenotypic manifestations of BrS[88]. For example, regression of the typical ECG features has been reported in castrated men[89], and levels of testosterone seem to be higher in Brugada male patients as compared with controls [90]. Two main hypotheses have been proposed for the sex differences, perhaps interacting with each other: the sex-related intrinsic differences in ionic currents and the hormonal influence. Consequently with the hormonal hypothesis, the few available data existing thus far of BrS in children have not shown a difference in phenotypic presentation between boys and girls [91]. Temperature may be an important modulator in some patients with BrS. Premature inactivation of the sodium channel has been shown to be accentuated at higher temperatures in some *SCN5A* mutations, suggesting that febrile states may unmask certain BrS patients or temporarily increase the risk of arrhythmias [92]. It seems that fever would be a particularly important trigger factor among the paediatric population [91]. Thus, temperature control is crucial in BrS patients.

Brugada syndrome and pregnancy

The gender-related differences in the phenotypic expression of BrS have been widely reported, but the basis for gender distinction is not yet fully understood [93]. During pregnancy, autonomic and hemodynamic alterations occur, and estrogen and progesterone blood levels are reduced at peripartum. The largest study of pregnant women with BrS has been reported from our institution [94].

This study showed a relatively benign course of pregnancy and peripartum period among women with BrS. In addition, only a few cases exhibiting syncope were found, and the presence of syncope during pregnancy did not seem to be related to a worse outcome of the disease, neither in postpartum nor peripartum periods.

Nevertheless, the management of pregnant women affected by BrS should be very strict and multidisciplinary in cooperation with a cardiologist and an anaesthesiologist [95]. Further clinical assessment and follow-up during the pregnant, postpartum, and peripartum periods should be performed, taking into account the favourable maternal and fetal outcome of disease.

Brugada syndrome in children

Sudden cardiac death accounts for approximately 20% of sudden deaths on paediatric age group. Inherited arrhythmias are increasingly known as responsible for these deaths. The prevalence of BrS in children is variable among different studies, accounting up to 0.0098% in Japanese series [96]. Despite massive progress in characterizing BrS, little is known about this disease in the paediatric population. In the initial description of the disease, three out of eight patients were children[1]. Since then, several authors have reported isolated cases[97]. In 2007 Probst et al published a study with 30 affected individuals less than 16 years of age from 13 European institutions[91], the largest series in paediatric BrS patients by that time, but nowadays most of our understanding of the BrS in children has come from the SABRU registry [77]. This study has confirmed our previous reports of the very poor prognosis of children with BrS and particularly the inability of quinidine to prevent sudden death.

The largest series of children with BrS and with the largest follow-up has been reported from our Institution [98].

Data on a total of 95 children with an age <19 years and BrS were used to create a risk stratification system. Results were similar as in adults showing that a spontaneous type I ECG, syncope, sick sinus syndrome, conduction disturbances and inducibility during programmed ventricular electrical stimulation of the heart could be used to create the scoring system.

Diagnostic and clinical presentation

Brugada ECG pattern in children remains the same as in adults, taking into account its transiency. Moreover, there are no standardized data for optimal positioning of the right precordial leads in children and the shape of the chest in a growing body can lead to confusion. With all these characteristics, symptoms of syncope associated with typical ECG pattern should alert to the possibility of BrS.

From asymptomatic patients (mainly discovered in routine ECG screening or familial screening) to sudden death, in children as in adults the whole spectrum of clinical presentations is possible. In contrast to adults, no male predominance in symptomatic patients is found. This could be related to lower levels of testosterone in prepubertal children [91].

Several case reports have demonstrated the importance of fever as a precipitating factor for ventricular arrhythmias in children, probably not because of special predisposition of children. Interestingly, as febrile state can unmask BrS pattern, a 12-lead ECG should be recorded during fever. Also, as febrile convulsions are a relatively common occurrence in childhood, we wonder if an ECG should be part of the diagnostic routine when a febrile seizure occurs [91] to exclude BrS and ventricular arrhythmias as the cause of the convulsions.

Drug challenge test

Sodium channel blockers test (ajmaline 1 mg/kg over 5 minutes or flecainide 2 mg/kg over 10 minutes) [99] should be restricted to children with normal baseline ECG and typical symptoms with positive family history. As in adults, spontaneous type I ECG pattern is enough to establish the diagnosis. The existence of an age-dependent response to ajmaline challenge is an intriguing recent finding and might have relevant clinical implications [100].

Thus, in a recent study, Conte et al showed that repeat ajmaline challenge after puberty unmasked BrS in 23% of patients with a previously negative drug test performed before puberty. The ECG phenotype does not appear during childhood in most cases, but may develop later in response to hormonal, autonomic, or genetic factors [101].

EPS in children

If controversy exists whether performing EPS testing or not in adult population, even more conflict appears if children should undergo programmed extrastimulation techniques to test malignant arrhythmias inducibility[65]. When indicated, the stimulation protocol remains the same as in the adult population.

Therapeutic implications and ICD implantation

As seen in other parts of this chapter, BrS can overlap with other entities as long QT syndrome type 3 or Lev-Lenègre syndrome.

Bradyarrhythmias can be a cause of death in these patients, thus pacemaker implantation is mandatory in certain cases [91]. Hydroquinidine has not shown to be a good alternative to ICD implantation [77].

Patients presenting with aborted SD and syncope with spontaneous type I ECG are clearly at high risk of malignant arrhythmias, thus ICD should be considered, irrespective of age. Special approaches for ICD implantation have been described for small children when needed (Figure 4).

Familial screening

First-degree relatives of affected individuals should be screened by clinical examination, interrogation and performance of a 12-lead ECG (basal and upper intercostal space recording). Genetic test should be performed in index cases and when a positive result is obtained, mutation analysis can be done in children, whatever age they are, in order to follow recommendation on fever control and avoidance of listed drugs. Mutation carriers should be annually screened for ECG when asymptomatic, taking into account that whenever symptoms of dizziness occurs a 12-lead ECG should be carried out.

In the era of personalized medicine using high-throughput tools (Next Generation Sequencing -NGS-), is the best cost-effective approach to identify the cause of the disease. The main problems in using NGS technologies are the large amount of data provided and the insufficient experience to translate this information into clinical practice [102, 103].

One of the crucial elements for the correct interpretation of pathogenicity is the genotype–phenotype correlation in families. This leads to the need for each family to be studied separately, analyzing the variations in each relative, and correlating clinical-genetic information. Final decisions should be made by a group consensus based on the experience of each of the members of the working group in each institution dedicated to this purpose.

Brugada syndrome in older individuals

The fourth decade of life is the mean age of clinical manifestations of BrS, mainly in men. Thus, the clinical course and prognosis of BrS in older individuals is unknown. Recently, Conte at al. published a systematic analysis of BrS in the aging population, reporting a benign prognosis and lower risk category of BrS patients in comparison to younger patients. Consequently, older patients presented with less ventricular arrhythmias and less family history of SCD. However, two main challenges remain controversial: use of drug-induced tests and device-guided management. Thus, despite Conte et al. reporting in the above mentioned study that "*BrS was diagnosed after ajmaline challenge in 86% of elderly patients*", the value of unmasking a type I ECG as well as its safety has not been methodically assessed [104]. Regarding the use of an ICD, a consensus conference reported that older BrS patients with syncope should undergo ICD implantation if life expectancy is at least 6 months [105]. Recently, Kamakura et al reported that long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in those aged >70 years. Considering the increasing risk of inappropriate shocks because of the relatively late onset of supraventricular tachycardia and lead failures, avoidance of ICD implantation, or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age[106]. However, clinical decisions regarding both controversies should be analyzed on a case-by-case basis.

Is Brugada syndrome a rare disease?

After all these years of scientific research much has been learned about BrS in terms of pathophysiologic mechanisms, prognosis and the value of the ICD to prevent sudden death. However, all the considerations have been made accepting that BrS was a rare disease. Clear data to really assess the true prevalence and incidence of the disease have not been available. It is only recently that a study by Papadakis et al [107] has brought a completely different picture about BrS and its prevalence. In their study they analyzed data from 303 individuals who died suddenly and where no diagnosis could be done even after autopsy. In the 911 relatives studied by ECG, echocardiogram, exercise test, adrenaline and ajmaline test, a diagnosis of inherited cardiac disorder could be made in 42% of the families. Of them, 85 suffered from BrS (28% of the total) followed by 22 individuals (7%) in whom a diagnosis of long QT syndrome was made. Thus, the general idea that long QT syndrome is the most common cause of sudden death in individuals with a structurally normal heart has to be abandoned. The most common cause is BrS, but the diagnosis can only be done with the systematic use of ajmaline test. Thus, BrS is not a rare disease, on the contrary it is the first diagnosis that has to be considered after a sudden death of an individual with a structurally normal heart.

The future

In recent years, cardiovascular studies have been focused on personalized risk assessment and to determine the most optimal therapy for an individual. The BrS syndrome has also benefited from these advances although there remains several key points to be elucidated. Future genetics, epigenetics, transcriptomics, proteomics, metabolomics and animal model approaches can help us to understand the complexity of BrS-like diseases through the establishment and use of more reliable models at *in silico*, *in vitro* and *in vivo* levels.

The genetic revolution in cardiac diseases was initiated with the knowledge of the human genome and has advanced exponentially linked to the development of new genomic technologies (Next Generation Sequencing -NGS-) [108].

These new genetic technologies will allow the performance of comprehensive genetic analysis in BrS patients, improving the identification of pathogenic variations.

Research in stem cells is one of the latest fields that has been incorporated into the cardiac arrhythmia scenario. It has improved the identification, derivation and characterization of human stem or progenitor cells, comprising embryonic stem cells -ESC-, and the recently described induced pluripotent stem cells - iPS-. The human iPS cells from patients diagnosed with long QT syndrome can differentiate into cardiomyocytes, allowing electrophysiological and molecular understanding of arrhythmic mechanisms [109, 110]. However, BrS has not yet fully benefited from all these advances.

Another interesting point is the use of animal models. They constitute useful tools for addressing the role of genetic and environmental modifiers on cardiac electrical activity. The only genetic model of the BrS to date is the *SCN5A* knockout mouse. The heterozygous *SCN5A* null allele results in impaired AV conduction, delayed intra myocardial conduction, increased ventricular refractoriness, and ventricular tachycardia [111].

Computational power allows molecular modelling and molecular dynamics simulations of complex proteins. A full *in silico* model of potassium channel has been developed based on the available structures of channels which includes all transmembrane segments [112].

Altogether, there is still a long way to be made towards the future of cardiac diseases associated to SCD, supporting the need to use the new emerging tools in the field of biomedicine.

In spite of these limitations, it has to be recognized that the progress in the understanding of BrS has been steady and that the future of patients with BrS looks very promising. It should not take too long before we will be able to genetically manipulate and cure the disease.

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Editorial comment

Brugada Syndrome was first described in 1992 by Pedro and Joseph Brugada. Currently it is a rich field of extensive research into the genetics and cellular mechanisms of arrhythmogenesis. In this issue of the journal, Professor Pedro Brugada presents an authoritative "state of the art" resume of the Brugada syndrome with extensive references. It would surely be a rewarding read for all grades of arrhythmologists who would profit from its practical implications and insights.

Review

TAVR: The good, the bad and the ugly of interventional cardiology

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Abstract

Since its introduction into clinical practice, transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of degenerative aortic valve stenosis and has entered the clinical arena in a big way for inoperable or even high-risk patients because of better hemodynamic performance and even survival. While the therapy has advanced to newer generation devices some concerns like prosthetic valve regurgitation, need for permanent pacemaker and some unusual complications still persist. Despite this there is a trend of TAVR therapy moving to younger patients, lower risk patients, patients with bicuspid and rheumatic aortic valve disease and even aortic regurgitation. This a cause for concern because very limited favorable data is available in these sub-sets of the population. Furthermore in low-resource countries the cost of procedure may be a significant limiting factor.

Keywords: TAVR, SAVR, Younger patients, Low risk patients, Rheumatic aortic stenosis

Introduction

Transcatheter aortic valve replacement (TAVR) was developed as an alternative to medical therapy in inoperable and high risk patients with severe aortic stenosis (AS). With improvements in design and imaging analysis as well as increasing ease of implantation and operator expertise it has recently been used as an alternative to valve replacement surgery for intermediate risk patients with possible application even in lower risk patients. As far as clinical benefits are considered the hardest end-point for any therapy is reduction in mortality[1]. Indeed several randomized controlled trials (RCTs) have clearly demonstrated a survival benefit with TAVR versus surgical replacement of aortic valve (SAVR) in inoperable patients and an equipoise for high risk population[2,4]. Furthermore, valve performance in post percutaneous procedure seems to be better than in the post-surgical one. However, many issues need still to be sorted out before this therapy can be applied widely in real-world patients at least in low resource countries.

Some of these concerns are not only the continuing higher complication rates: para valvular aortic regurgitation (PVR), valve performance, valve durability, leaflet thrombosis, stroke and pacemaker requirement but also the suitability in younger patients and in non-degenerative etiologies (the bulk of patients in developing world) and the cost of the percutaneous option. Thus strengths and weaknesses of TAVR need to be balanced.

THE GOOD

- **Impact on mortality**

Very few interventions in cardiology improve life-expectancy in relatively healthy patients but the sicker the patient gets the number of procedures resulting in mortality benefit as well as quantum of benefit increases. In the context of severe symptomatic AS, classically, valve replacement was the only known procedure that not only led to survival benefit but also led to improved quality of life. 5 Western series have estimated that at least 1/3rd of these patients, however, are deprived of the surgery due to the invasive nature of this therapy in sicker patients [6,7]. TAVR is a less invasive intervention and provides comparative survival advantage and marked symptom benefit in suitable patients versus only medical management [2]. Compared with SAVR, in patients with high-surgical risk and intermediate risk there seems to be an equipoise in early results but on long term follow-up, PVR seems to be more common with TAVR (which was also associated with increased mortality)[3, 8]. However data in lower risk, younger patients and patients with non-degenerative etiologies though not available is likely to be worse for percutaneous option for mechanistic reasons.

In low resource countries like India the bulk of patients with severe AS are younger and of non-degenerative origin (rheumatic heart disease being still prevalent here) and therefore there is a tendency to apply TAVR in this group as well. However, whether Western guidelines can be applied to this setting is a big question mark [9].

- **Hemodynamic performance**

TAVR has consistently demonstrated better hemodynamic outcomes versus SAVR: better valve area and lower aortic valve gradients, whether it is self-expanding or balloon expandable prosthesis [10]. Furthermore, this improved hemodynamic performance seems to persist at least up to 2 years [8]. The reason for this could be defective intra-operative valve sizing vis a vis sizing on multi-detector computerized tomography (CT), It was recently estimated that TAVR could achieve valve areas 25-40% larger than with the surgical replacement[11] .

- **Bleeding Risk**

Bleeding after SAVR is not an uncommon (around half the patients requiring at least one blood transfusion) but generally a minor complication. However, major bleeding may be a strong predictor of mortality at one year [10]. PARTNER trial has shown that major bleeding may be lower with TAVR than SAVR (by nearly 50%) [3].

- **Acute kidney injury**

Acute kidney injury (AKI) is possible but rare after both SAVR and TAVR. Several trials have shown that this complication is at least three times lower with TAVR than SAVR. However, this problem does have an effect on survival with a fivefold increase in 30 day mortality and a threefold increase in yearly mortality. Several refinements of the TAVR technique has been proposed to further decrease this dreaded complication: improved imaging (of patients with chronic renal dysfunction), reduced utilization of contrast, utilizing 3-D TEE guidance, as well as utilization of lower French access sheath (and resultant lower bleeding risk; one of the strongest predictors of AKI) and improved operator experience [10].

THE BAD

- **Paravalvular aortic regurgitation**

Prosthetic valve aortic regurgitation is a much frequent complication after TAVR than after SAVR, at least with early devices (both self-expanding and balloon expanding), moderate to severe PVR occurring in up to 1/4th of all patients[12].

The clinical importance lies in increased mortality with this complication. The simplest solution is inter-procedural post-dilatation, often by an upsizing balloon. Several design innovations in later devices have focused on attempts to reduce this complication and small studies have revealed marked reduction in these rates [10].

- **Pacemaker Implantation**

TAVR can lead to mechanical compression of the conduction system by its prosthetic frame, which can be further predisposed to by pre-existing conduction defects such as right bundle-branch block and left anterior fascicular block. Consequently, atrioventricular conduction abnormality which may require permanent pacemaker implantation (PPI) is one of the commonest complications occurring with TAVR. While nearly 1/3rd of the patients developed significant conduction abnormalities (10-50%) requiring PPI, with newer generation devices these rates may be < 10% [13]. Although it is generally considered as a minor complication, with no effect on mortality it does affect the quality of life (increased duration of hospitalization, rates of re hospitalizations and complications associated with PPI). Finally, implantation of PPI after TAVR does have some financial implications [10].

- **Stroke**

Cerebrovascular accidents are one of the major devastating complications following both SAVR and TAVR. Reported incidence of stroke varies depending on stroke definition and duration of follow-up. With SAVR the rate is generally <2%, although with the early generation TAVR this rate was more than double [14] .Attempts to reduce this stroke risk have led to new strategies: protecting the aortic arch vessels with filters or deflectors, excluding the left atrial appendage, improved post-procedure antithrombotic strategy. With refinement of the techniques of TAVR, similar stroke rates (compared with SAVR) may have been achieved but they certainly add to the cost of the procedure [10].

- **Serious procedural complications**

Catastrophic complications like aortic dissection / perforation, aortic valve injury / rupture and left ventricular perforation are now quite rare (in the range of 1% or less) [10].

One particular complication, coronary obstruction is rare but occurs occasionally (0.4%) and is comparable to SAVR. Complications involving the aorta (aortic dissection or perforation), aortic valvar complex (injury or rupture), or left ventricle (perforation) have become very rare (0.2% to 1.1%), but potentially catastrophic. Coronary obstruction after TAVR has become comparable to SAVR in randomized trials (0.4%) [15,16].

- **Structural valve degradation**

THE UGLY: Off-label use of TAVR

Anatomical valve degradation is a time bound complication occurring with any valve replacement. Mechanically, it involves general wear and tear, disruption of mechanical integrity, stress fracture, calcification and pannus formation. It is defined as alteration in valve function related to development of mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9–1.1 cm^2 and/or dimensionless valve index <0.35 m/s, and/or moderate or severe prosthetic valve regurgitation[17]. While most surgical aortic bio-prosthesis have a 10-year freedom from reoperation that is above 97% ,data for long term durability after TAVR is not known (some trials have shown excellent 5-year results)[10,18].

However early degradation of percutaneous valve with valve thrombosis or stenosis does remain a concern although it could be managed by percutaneous closure, post-dilatation or valve-in-valve TAVR, depending on the cause (being regurgitation or stenosis) [10]. Of particular concern are the younger patients with longer life-expectancy who are likely to do better with mechanical SAVR than TAVR.

- **Low risk individuals**

Inoperable patients have a clear cut mortality benefit with TAVR, but with high risk and intermediate surgical risk group of patients this mortality benefit seems to wane off. However for lower risk patients, convincing data is still lacking.

NOTION trial recently presented in a Featured Clinical Research session on Saturday the 10th of March at American College of cardiology (ACC)[18] in Orlando, Florida, revealed that after five years, there were no differences in all-cause -mortality, stroke or myocardial infarction (MI) in lower-risk patients ages 70 and older between patients who had TAVR (n=139) versus those who had SVAR (N=135), 39.2% vs. 35.8%, although 61.1% with TAVR vs. 22.6% with SAVR had some aortic regurgitation [19]. However, a recently published meta-analysis does raise a "red flag" regarding the use of TAVR in low risk subsets. The meta-analysis, analyzing 6 studies published between 2012 and 2017 and enrolling a total of 3,484 patients found that the 2-year mortality rate for TAVR was higher (17.2% vs. 12.7%, P = 0.006) [20]. Another recently reported trial in minimal risk, elderly patients reported a near identical result: higher 2-year mortality (OR: 0.31; 95%CI: 0.16-0.61), higher PVR (OR: 4.9; 95%CI: 3.34–7.20), renal injury (OR: 2.86; 95% CI: 1.79–4.55) and new pacemaker implantation (OR: 3.33; 95%CI: 1.76–6.26) at 30 days [21].

Three trials are underway in this subset: PARTNER 3, Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients, and NOTION 2 and they are likely to put this controversy to rest.

- **Younger individuals**

Recent data has raised a concern about increased mortality in younger patients receiving bio-prosthesis. Analysis from a huge cardiac surgery data-set of SAVR (nearly 40,000 patients) revealed that in the youngest patient sub-group (65-69 years) there was a 23% higher risk of mortality (adjusted HR, 1.23; 95%, CI, 1.16–1.31) and 10.5% higher 12-year risk of reoperation with bio-prosthetic valves vs. mechanical valves [22]. Another small study (n=206) in patients ≤60 years age reported reduced mid-term survival with bio-prosthetic valves [23]. Yet another study in even younger patients (50-70 years) demonstrated that mechanical valves were correlative of long term survival [24]. Not only survival, structural valve degeneration also seems to be more rapid at younger age: At > 70 year, 15 year freedom from valve degeneration was documented in 90% but only 63% at ≤60 year age [25].

When this is the situation with SAVR what could be the outcome in TAVR where need for crimping, balloon dilatation, stent deformation, and over / under expansion can contribute to un-predictable shear stress distribution and ultimately early valve deterioration can only be speculated [26].

- **Rheumatic aortic valve and bicuspid aortic valve**

While degenerative aortic valve disease is common in West, rheumatic aortic stenosis is much more common in low resource countries. Interventionists are now adept in implanting TAVR in degenerative valves but rheumatic or bicuspid aortic valves can be a different "ball game." In particular, rheumatic aortic valve pathology compared with degenerative pathology is usually different and therefore the site for appropriate placement of the valve may be different than in a degenerative valve. Furthermore, rheumatic valve being essentially non-calcific, utilizing "calcium landmarks" may not be possible, thus making the implantation of a percutaneous valve using fluoroscopy and echocardiography unique and more challenging. Finally, crushed hydroxyapatite deposits (typical in older patients with degenerated valves) provide a sufficient scaffold or "anchor" to the deployed valve but being deficient in rheumatic patients there is a need for additional anchoring techniques for the devices, implying that current design of the TAVR may be inadequate for this application. Thus, not only will this require additional "learning curve" for the operators but also innovations in device designs. Likewise, due to unique morphological features associated with bicuspid aortic valves, the technique of implantation and even the valve design is likely to be different [27].

- **Aortic regurgitation**

The use of TAVR for pure aortic regurgitation is fraught with several challenges. These patients have less valve calcification (less ability to anchor) and a higher stroke volume through the valve orifice both making the implanted valve more unstable.

Small trials suggest that TAVR in pure aortic regurgitation may be feasible, with fairly good outcomes, but variable mortality (0-30%). The results may be better with newer generation valves but even so they can be recommended in only highly selected patients who are surgically inoperable [28].

- **Economics of TAVR**

Utilization of TAVR technology shows a wide variation even in West (6-89%). The most important co-relate of use of TAVR is the re-imbursement policy of the country or insurance scheme rather than actual indication for the procedure; expanded use of TAVR where re-imbursement exists versus restricted use where no re-imbursement exists [29]. Even in the West, cost-effectiveness analysis reveal clear cost saving only in inoperable patients with probably no cost effectiveness in other patients and possibly unacceptable cost in younger patients (due to need for multiple re-interventions) [26]. In India and other resource challenged countries the situation may be even more challenging:

1. Majority of individuals pay from the pocket,

2. Cost of SAVR is a fraction compared with cost of TAVR [30].

Conclusions

TAVR therapy has practically become the gold-standard in inoperable and high surgical risk patients with degenerative aortic stenosis because of superior hemodynamic function and even mortality benefit at least in inoperable patients. However, some serious complications like PVR and need for pacemaker implantation persist while high cost of this procedure limits its application in resource disadvantaged countries and individuals. Off-label use of this technology in younger, low risk patients with non-degenerative pathology and with pure aortic regurgitation are a matter of some concern.

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Review

Cardiohepatic interactions: Part 1 of a 3 part series: Heart diseases that affect the liver.

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Introduction

The increasingly complex nature of patients that present to our clinics and hospitals has challenged our traditional concepts of medicine. With ever sicker patients with multiple comorbidities and multiple organ failure, it is becoming more and more evident that cardiologists and cardiac intensivists need to know not only about the heart but also its complex interactions with other organ systems. Interactions between the heart and lung and between the heart and kidney (cardiorenal syndromes) have been well described in literature. Much less however is known about interactions between the heart and liver (cardiohepatic interactions) but is an area of increasing research interest.

Heart failure is increasingly prevalent, contributing to more frequent hospitalizations, impaired quality of life, and shorter life expectancy[1,2]. It is a complex clinical syndrome in which patients experience signs and symptoms of reduced cardiac output, pulmonary and systemic congestion. The heart failure syndrome can span a variety of presentations including acute decompensated heart failure, chronic heart failure, reduced ejection fraction (HFrEF), and preserved ejection fraction (HFpEF)[2]. As cardiac dysfunction worsens, there is an inability to meet the metabolic requirements of end-organs. Though not as well described as other organs such as the lungs and kidney, hepatic dysfunction is commonly seen in patients with heart failure and patients may present with ascites, nausea, early satiety, anorexia, abdominal pain, coagulopathies or abnormal liver function tests. These symptomologies are secondary to complex hemodynamics in heart failure associated with decreased cardiac output, congestive physiology, and possibly even drug induced toxicities [3,4].

Conversely, patients who have chronic liver disease are increasingly prevalent due to viral, alcohol, autoimmune and metabolic causes[5].

Hepatic dysfunction has a direct impact on the systolic, diastolic and electrical functioning of the heart. Furthermore, sequelae of liver disease directly impact systemic and pulmonary hemodynamics and subsequent cardiac function and cardiologists need to be aware of these consequences when we are performing diagnostic and therapeutic tests for this group of individuals as well as in assisting hepatologists who are involved in treating these patients with potentially complex interventions such as liver transplant.

There are also a few systemic diseases such as amyloidosis that are associated with both hepatic and cardiac dysfunction concurrently. The care of these patients is exceedingly difficult and often requires a multi-disciplinary approach [6].

In this 3-part series on cardiohepatic interactions, we will review cardiohepatic interactions for the cardiologist and cardiac intensivist as well as for other groups such as general physicians and hepatologists who may be involved in the care of these patients. Under the umbrella of cardiohepatic interactions, in part 1, we will discuss how the liver is affected by cardiac failure; in part 2 we will discuss how the heart is affected by liver failure; and in part 3 we will discuss how both the liver and heart are affected by systemic diseases.

Basics of the Liver for the Non Hepatologist

Liver anatomy

The liver weighs 1.2 to 1.4 kg in women and 1.4 to 1.5 kg in men and lies in the right upper quadrant of the abdomen just below the diaphragm[7]. It can be anatomically divided into the left and the right lobes which are divided by the falciform ligament, with each receiving its own blood supply. The liver is further subdivided into eight segments based on venous drainage and bile duct distribution.

Despite being only 2-3% of total body weight, the liver may receive up to 25% of the cardiac output [8].

The liver has a dual circulatory system with two-thirds of oxygenated blood flow being provided by the portal system and one-third being provided by the hepatic artery system. By definition, the portal system (because it is blood flow that goes from one organ, the gut, to another organ, the liver) has a lower pressure gradient with portal vein pressures being usually less than 7 mmHg (compared to a central venous pressure of 0-3 mmHg) and a lower saturation usually around 85%. This compares to the hepatic artery which comes in at a pressure equivalent to mean arterial pressure (usually 65 mmHg) compared to the central venous pressure (CVP) of 0-3 mmHg and a saturation of close to 100%. This difference in perfusion pressure (7 mmHg – 3 mmHg = 4 mmHg versus 65 mmHg – 3 mmHg = 62 mmHg) is critical to how the liver is affected in cardiac dysfunction[9,10]. Venous drainage of the liver is through the right, left, and middle hepatic veins and flows into the inferior vena cava, subsequently returning to the heart[4]. Blood enters an acinus (smallest functional unit of the liver) through branches of the hepatic artery and portal vein in the portal and peri-portal regions. Blood then flows through sinusoids subsequently draining into the terminal hepatic venules.

Liver histology

Liver cells can be divided into two types: parenchymal and non-parenchymal. Hepatocytes are the key parenchymal cells and make up 80% of the liver volume and are clustered into individual acini and grouped around the terminal branches of hepatic arterioles and venules[8]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are concentrated in hepatocyte tissue, with ALT localized in the cellular cytoplasm and AST in both the cytoplasm and mitochondria. AST is not as specific as ALT as it is found in a variety of tissues including the heart. Both AST and ALT go up during hepatocyte inflammation and injury and an elevation of <5 times the upper limit of normal (ULN) is mild, 5-10 times the ULN is moderate, and >10 times the ULN is severe [11]. Individual acini can be divided into three zones including the periportal region known as zone 1, perivenular region known as zone 3, and the transitional region known as zone 2. Zone 3 is most prone to circulatory insults given it receives the least amount of oxygen and nutrients and is subject to the highest venous pressures being closest to the central veins thereby reducing perfusion pressure [8,12]. Ductal cells line the bile ducts and are the predominant cells that release alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and 5'-nucleotidase (5-NT).

Liver injury presentations with a predominantly cholestatic pattern are less frequently encountered in cardiac clinical practice than the pattern of hepatocellular damage and will typically develop in the setting of extrahepatic or intrahepatic biliary obstruction. Other potential causes include related to total parental nutrition or as a drug toxicity[11,13].

Liver function

For the cardiologist and cardiac intensivist who may be taking care of patients that have liver dysfunction either primarily or secondary to cardiac dysfunction, it is important to know the critical functions of the liver to anticipate what potential issues may arise in the cardiac intensive care unit. The liver's functions can be subdivided into synthetic, metabolic, storage, and immunologic functions. Synthetic functions include synthesis of proteins including albumin, coagulation factors, and angiotensinogen, carbohydrates through gluconeogenesis, glycogenolysis, and glycogenesis, and lipids including cholesterol and bile acids. In patients that have liver failure, typical synthetic abnormalities that occur include hypoalbuminemia, coagulopathy with elevations in prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT), and hypoglycemia that can be life threatening. [14,15] Metabolic functions of the liver revolve around its enzymatic functions such as the glucuronic acid conjugation of bilirubin as well as the metabolism of multiple drugs and toxins [16]. Again, in liver failure, we typically find elevations in bilirubin due to the lack of the metabolic function of the liver and we must be cognizant of the effect on drug concentrations such as statins, antibiotics, and other commonly used medications in the cardiac intensive care unit. Ancillary functions of the liver include the storage of glucose, vitamins, iron, and copper as well as immunologic effects through the reticuloendothelial system.

Heart Diseases Affecting the Liver

In part 1 of this 3-part series, we will be describing how heart diseases directly affect the liver. There are two major clinical syndromes that have been described in heart failure that affect the liver: acute cardiogenic liver injury and chronic passive liver congestion (Figure 1). We will describe each in detail below.

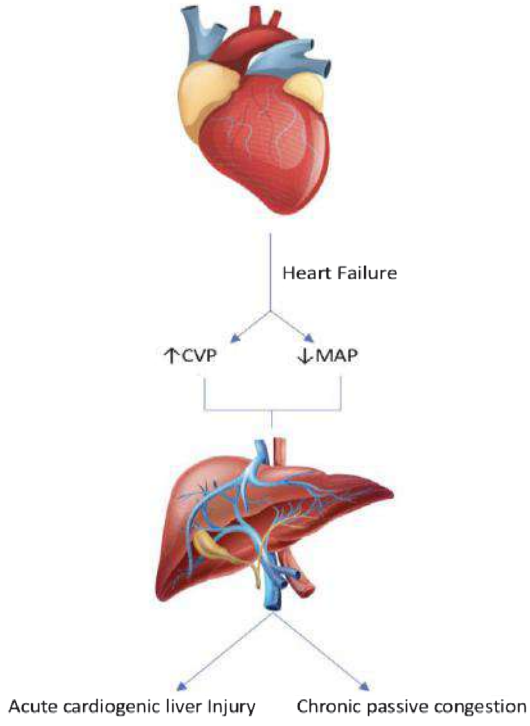

Figure 1: How cardiac disease affects the liver

Acute cardiogenic liver injury

Patients in critical cardiogenic shock with decreased cardiac output may experience acute cardiogenic liver injury (ACLI). ACLI, originally termed 'shock liver' or 'ischemic hepatitis', presents with fulminant liver failure and a very large transaminitis (with AST and ALT often in the thousands) due to ischemia causing release of hepatic proteins. Histologically, there is necrosis surrounding the central vein, in zone 3, where oxygenation is limited. If the ischemic period is prolonged, then adjacent zones may also experience necrosis [17]. This entity was initially thought to only be due to low mean arterial pressure. However, studies have suggested that systemic hypotension alone does not induce acute liver injury. In a cohort by Seeto et al. comparing 31 patients with shock due to cardiac failure to 31 patients with shock due to trauma, it was found that no patients with shock secondary to trauma experienced liver injury. Though the mean arterial pressures in the two groups were similar, only the patients with cardiac failure had elevated right sided pressures [18,19]. This suggests that ACLI requires two hits: both a decrease in mean arterial pressure as well as an increase in hepatic venous pressures. In another study by Henrion et al., patients with low cardiac output were divided by those with ACLI and those without.

The ACLI group had a mean CVP of 22.5 cmH_2O versus the no ACLI group who had a CVP of 14 cmH_2O[20]. This once again suggests that venous pressures likely play an integral role in liver injury in acute cardiogenic failure. Pathophysiologically, this is likely due to stasis of flow in the portal venous system in patients that have elevated CVP as the portal vein to central venous pressure gradient is much lower than the hepatic artery to central venous pressure gradient. In ACLI, the two thirds of perfusion that the liver normally gets through the portal vein is likely heavily diminished due to the elevated CVP.

Therapeutic targets for ACLI include maintaining both mean arterial pressures as well as reducing CVP. The latter goal of reducing CVP has been less well understood until recent data has shown that elevated CVP may be detrimental to both the kidney and liver which is possibly one reason why over-resuscitation can be associated with poorer outcomes. In the cardiac intensive care unit these goals can be achieved by aggressive diuresis and initiation of intravenous vasoactive medications including dobutamine, norepinephrine, and vasopressin. In patients who are refractory to diuresis, ultrafiltration can be considered, though there have not been any trials that have looked at this in the ACLI population. Moreover, it is important in these patients to examine for sequelae of liver failure on rounds and be aware of potential changes required to cardiac anti-coagulation and anti-platelet regimens.

When patients present to the intensive care unit with presumed ACLI, it is important to always remember that acute liver failure (ALF) has a broad differential diagnosis including viral, toxin-related, auto-immune mediated, and acute fatty liver of pregnancy among others (Table 1). This makes early recognition and intervention critical for patient outcomes. With any patient presenting with presumed ACLI, it is imperative to rule out these other pathologies rapidly as misdiagnosis could potentially lead to significant morbidity and mortality. An interesting article by Cassidy et al. looks at biomarker changes that can help differentiate the different causes of ALF. Lactate dehydrogenase (LDH) has five subunits with LD5 being highly activated in anaerobic conditions. Unlike in toxin or viral mediated acute hepatitis where AST and ALT go up dramatically compared to LDH, in ACLI the LDH typically is extremely elevated to levels higher than AST or ALT. An ALT:LDH ratio of <1.5 suggests ACLI as opposed to other causes of ALF[21].

Table 1: Acute liver failure (ALF) etiologies

ALF aetiologies
Viruses
Hepatitis A, B, D or E viruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Varicella zoster virus
Parvovirus
Drug-induced liver injury
Acetaminophen
Non-acetaminophen (eg, isoniazid, phenytoin, valproate, propylthiouracil, nitrofurantoin)
Recreational drugs (eg. Cocaine, 3,4-methylenedioxymethamphetamine - MDMA)
Autoimmune hepatitis
Ischemic/congestive hepatitis
Budd-Chiari syndrome
Wilson's disease
Amanita phalloides
Pregnancy (eg, acute fatty liver of pregnancy, HELLP syndrome)
Heat stroke
Malignant infiltration
Seronegative (indeterminate)

***Data from Cardoso *et al*. [28]**

Chronic passive liver congestion

Colloquially known as 'congestive hepatopathy', this is a clinical syndrome in which chronic transmission of elevated right sided pressures is associated with passive congestion of the hepatic veins causing post-sinusoidal portal hypertension. Clinical situations that may lead to congestive hepatopathy include severe biventricular failure, severe tricuspid regurgitation, constrictive or restrictive cardiomyopathy, and Fontan circulations. Symptomatically, patients may be indistinguishable from end-stage liver disease or cirrhosis of other aetiologies (with the exception of varices, explained below) and may experience RUQ pain, early satiety and anorexia [22,23]. Chronic increased right atrial pressures and heart failure lead to increased hepatic venous pressures, decreased hepatic blood flow, and decreased oxygen saturation in arterial blood.

Hepatic veins are valveless and so elevated CVP is easily transmitted to the sinusoids. Histopathologically, this results in impaired oxygenation of hepatocytes causing centrilobular necrosis and extravasation of protein with subsequent cirrhosis. The typical laboratory abnormality is an elevation in cholestatic type biomarkers including ALP and total bilirubin levels [18,24]. In the CHARM heart failure study, elevated total bilirubin was found to be an independent predictor of worsening heart failure symptoms, cardiovascular death, and all-cause mortality (hazard ratio: 1.14; 95% confidence interval: 1.08-1.21) [25]. Moreover, recognition of subclinical chronic passive liver congestion is essential prior to considering advanced therapies such as mechanical circulatory support and transplant in cardiac patients at highest risk such as Fontan circulations.

Though these patients are very similar to other cirrhosis patients, they have one major clinical difference in that they do not get portosystemic shunts in their early course as they have postsinusoidal portal hypertension. Esophageal, gastric and anal varices as well as caput medusae only occur when the hepatic venous pressure gradient (HVPG) is >10mmHg (normal HVPG is <5mmHg). The HVPG equals the portal vein pressure minus central venous pressure. In chronic passive congestion, both portal vein pressure and central venous pressure go up together; therefore, HVPG is unchanged and they do not manifest portosystemic shunts [26]. However, if congestion continues, the liver can become fibrotic/cirrhotic eventually increasing the HVPG. In considering patients for mechanical circulatory support or transplant who are undergoing right heart catheterization, it is prudent to check the HVPG at the same time by checking pressures in the hepatic vein (free hepatic vein pressure) and then getting the portal pressure through wedging (similar to a pulmonary capillary wedge pressure) – wedged hepatic vein pressure [27]. This can be used to assess both the degree of congestion as well as whether an irreversible intrahepatic pressure gradient has been established due to long standing cirrhosis.

The mainstay of therapy is aggressive diuresis to maintain a euvolemic state. Ultrafiltration has not been independently shown to decrease rate of congestion. In refractory heart failure cases, advanced therapies such as mechanical circulatory support or transplant can be considered. However, it is important to ensure that irreversible liver damage has not occurred especially in high risk populations such as Fontan circulations prior to embarking on these therapies. At our centre, we check the HVPG at time of right heart catheterization and will consider ultrasound, fibroscan, or computed tomography of the liver to assess for cirrhosis. If there is any risk of undiagnosed cirrhosis, we have a low threshold to proceed to liver biopsy if any of the above tests are inconclusive.

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Review

Cardiohepatic interactions: Part 2 of a 3 part series: Liver diseases that affect the heart

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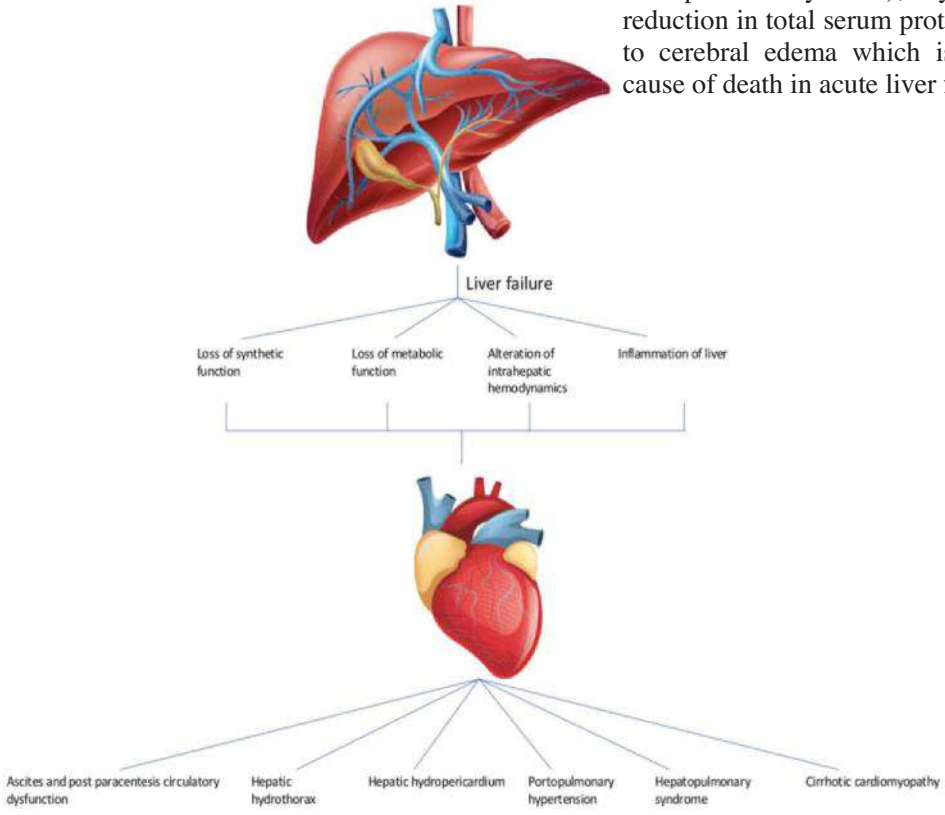
Liver Diseases Affecting the Heart

In part 2 of this 3-part series, we will look at liver diseases which affect the heart (Figure 1). As non-hepatologists, it is important for cardiologists and cardiac intensivists to understand the intricacies of liver failure patients as we are directly involved in the diagnostics of many liver failure complications as well as the treatment of these patients in cardiac intensive care units. These complications also have direct consequences on the heart's systolic, diastolic, and electrical function that we must be aware of.

Figure 1: Liver failure and how it affects the heart



Complications of liver failure

The complications of liver failure can be broadly divided into four categories:

1) Loss of the synthetic function of the liver
2) Loss of the metabolic function of the liver
3) Inflammation of the liver
4) Alteration of intrahepatic hemodynamics

The first consequence of liver failure is loss of the synthetic and metabolic functions of the liver. Synthetic function loss causes coagulopathy (with elevated prothrombin time/international normalized ratio - PT/INR and partial thromboplastin time - PTT), hypoalbuminemia, lack of sex hormone binding globulin (causing spider angiomas, testicular atrophy, gynecomastia, and palmar erythema), hypoglycemia, and a reduction in total serum protein load that can lead to cerebral edema which is the most common cause of death in acute liver failure.

For patients in our intensive care units that may have liver failure, it is important to be cognizant that they have risks of hypoglycemia and cerebral edema (acute liver failure only) that require brain protective measures (including cerebral perfusion pressure maintenance, sedation, pCO2 and pO2 control, temperature control, and possibly continuous renal replacement therapy)[1]. This management is beyond the scope of this article, but we suggest referring to clinical practice guidelines for patients with liver failure for more information[2]. With regards to coagulopathy, it is important to remember that patients lose not only procoagulant factors but also anticoagulant factors and there is a growing body of literature that INR is not a reliable estimate of bleeding risk for liver failure patients undergoing procedures[2,3].

With regards to the loss of the metabolic activity of the liver, this is associated with multiple effects:

1. Increased bilirubin due to lack of metabolism of heme degradation products (causing jaundice and scleral icterus)
2. Clubbing
3. Altered drug metabolism
4. Hepatic encephalopathy and asterixis due to lack of metabolism of unknown factors derived from gut digestion of food.
5. Hepatorenal syndrome and the hyperdynamic state due to unmetabolized splanchnic vasodilators causing a reduction in systemic vascular resistance.
6. Hepatopulmonary syndrome due to an unmetabolized vasodilating factor causing pulmonary intravascular dilations.
7. Portopulmonary hypertension due to an unmetabolized factor causing pulmonary vasoconstriction.
8. Cirrhotic cardiomyopathy due to partially unmetabolized factors that affect the heart

Cardiologists are directly responsible in helping diagnose and treat several of these complications of liver failure which we will discuss in detail below.

Many liver failure patients will also complain of pain in the right upper quadrant due to inflammation of the liver and the capsule surrounding the liver. This inflammation is also associated with a risk of hepatocellular carcinoma which has an incidence of 1-8% per year in compensated cirrhosis [4].

Finally, liver failure patients have an alteration in intrahepatic hemodynamics. Cirrhosis increases the resistance to flow through the liver leading to portal hypertension. This directly leads to splenomegaly which can then cause pancytopenia from sequestration. Increased resistance also leads to stasis which can cause portal and splenic vein thrombosis. The increased pressures in the liver leads to fluid buildup that can lead to ascites, hepatic hydrothorax and hepatic hydropericardium each with a risk of spontaneous bacterial infection. And the increase in the hepatic venous portal gradient (HVPG) causes portosystemic shunts to develop which can be complicated by variceal bleeding with the shunts further worsening the degree of unmetabolized products bypassing the liver worsening all of the metabolic complications of cirrhosis. Many of these complications have a direct effect on the heart which will be discussed in turn:

Ascites

Occurs in patients that have portal hypertension with direct leak of fluid from the liver surface. Ascites can cause direct elevation of the diaphragm and can reduce preload to the right side of the heart. The typical treatment is large volume paracentesis. For every 3-4 liters of fluid removed, 25 g (100 mL of 25% concentration) of albumin is returned to reduce the risk of cardiac decompensation due to post-paracentesis circulatory dysfunction (described below). It is important in these patients to be aware of the risk of spontaneous bacterial peritonitis and consider diagnostic paracentesis early along with antibiotics. Serum ascites albumin gradient (SAAG) score will be >11g/L in portal hypertension or chronic passive liver congestion. Ascitic fluid total protein is generally >25g/L in chronic passive liver congestion[5].

Hepatic hydrothorax

Defined as the accumulation of 500 mL of pleural fluid without a primary cardiac, pulmonary or pleural cause. Caused by direct communication between the pleural and peritoneal space due to anatomic defects in the tendinous portion of the hemidiaphragms. Flow is unidirectional due to negative intrathoracic pressure and as a result, ascites is not always present. It occurs in 5-10% of cirrhotic patients and like heart failure, 85% are right-sided. Spontaneous bacterial empyema is possible with an associated 20% mortality. Chest tubes are contraindicated as they are associated with high mortality. As cardiologists, we may be called to assess patients to determine whether these pleural effusions are cardiac in nature, which can be very difficult.

The diagnosis hinges on an intraperitoneal injection of 99mTc-sulphur colloid or 99mTc-human serum albumin to look for direct passage into the chest. Treatment options include consideration of liver transplant or transjugular intrahepatic portosystemic shunts and in refractory cases pleurodesis or thoracoscopic repair [6,7].

Hepatic hydropericardium

As with hepatic hydrothorax, hepatic hydropericardium is due to a direct connection and passage of fluid between the peritoneum and pericardium. It also can occur in the absence of ascites and is associated with hepatitis C and cryoglobulinemia. These patients should be treated similar to hepatic hydrothorax as the primary etiology is noncardiac[8].

Portopulmonary hypertension

A type 1 pulmonary arterial hypertension requires a mean pulmonary artery pressure (mPAP) greater than 25 mmHg and a pulmonary capillary wedge pressure less than 15 mmHg. These patients must have portal hypertension and should have no alternative cause for pulmonary arterial hypertension. Occurs in 5-10% of liver transplant candidates[9]. The exact cause is unknown, but it is thought that there is a factor not metabolized properly by the liver that causes it. It is known to not be due to the hyperdynamic state or due to thromboembolism. As cardiologists, it is important for us to assist in this diagnosis whether by echocardiography or right heart catheterization.

Notably, the hyperdynamic state of liver failure can make echocardiography unreliable. It is important during cardiac catheterization to properly characterize the severity and the reversibility.

Mild portopulmonary hypertension with a mPAP between 25-34 mmHg is not a contra-indication to liver transplant assuming the right ventricle is normal. Moderate portopulmonary hypertension with a mPAP between 35-50 mmHg is associated with a 50% mortality post-liver transplant and requires appropriate reversibility testing (nitric oxide or epoprostenol) during cardiac catheterization. Severe portopulmonary hypertension with a mPAP > 50 mmHg is a contraindication to liver transplant with mortality approaching 100%. All of these patients require a multi-disciplinary approach including consideration for anticoagulation, pulmonary hypertension treatments, as well as liver transplant[10]

Hepatopulmonary syndrome

The presence of intrapulmonary vascular dilations caused by either an uncleared factor normally cleared by the liver and/or the lack of the “hepatic factor” which stops the formation of intrapulmonary vascular dilations in the lung. In the 1960’s to 1970’s in certain post-operative congenital heart patients where the superior vena cava was anastomosed to one lung and the inferior vena cava to the other lung, this same phenomenon occurred where intravascular dilations formed in the lung that did not receive any hepatic blood flow. This was thought to be due to that lung not receiving the “hepatic factor.” Patients with the hepatopulmonary syndrome will typically have hypoxemia and orthodeoxyplatypnea (defined as a drop in the partial pressure of oxygen by more than 5% or 4 mmHg) when going from the supine to standing position[9]. These patients can also have arteriovenous malformation in the lungs and as such should have arterial precautions for venous lines as well as the use of filtered intravenous lines much like our congenital heart patients that have right to left shunts. Typically, these patients do not get right ventricular failure as the shunt fraction is < 1.5:1.

The hepatopulmonary syndrome is not correlated to the severity of liver disease and is associated with a worse prognosis than patients that do not have it.

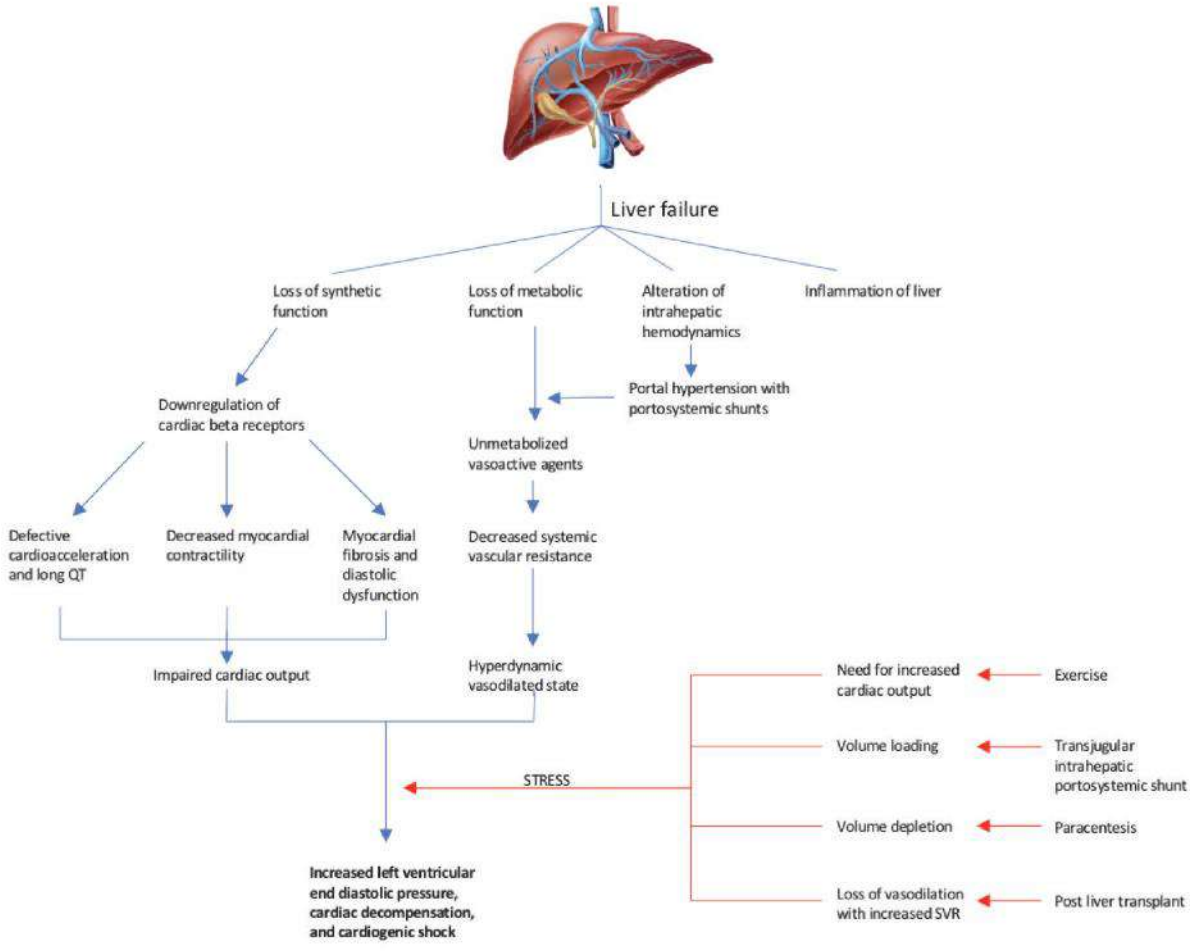
However, post-liver transplant, the syndrome completely resolves and patients have a mortality that is no different post-transplant to those patients that did not have the syndrome and as such it is an American Association for the Study of Liver Diseases (AASLD) indication for expedited transplant. As cardiologists, we are involved in the diagnosis. Diagnosis requires portal hypertension, impaired oxygenation with blood gases both supine and erect, as well as an agitated saline echocardiogram looking for the late crossing of bubbles (3-6 cardiac cycles). A pulmonary angiogram can also be considered.

Cirrhotic cardiomyopathy

Cirrhotic patients develop a hyperdynamic state due to a reduction in systemic vascular resistance due to factors that are unmetabolized by the liver causing splanchnic vasodilation. This can chronically lead to a high output type heart failure[11,12].

The traditional model suggested that the insult was all due to a drop in systemic vascular resistance and that the heart itself was relatively normal. However, more recent evidence suggests actual abnormalities in cardiac myocytes with a desensitization and downregulation of beta-adrenergic receptors which results in impaired intracellular signaling and reduced calcium release from the sarcoplasmic reticulum and decreased myocardial contractility (Figure 2). It is believed that there is a reduced G-protein expression on one of the 7 cardiac beta-receptor subunits in cirrhotic animal models, leading to impaired cellular signaling, likely due to the liver producing a protein that is integral to this subunit[13]. The vasodilated state in liver failure may actually protect the heart by reducing afterload keeping cardiac pressures relative normal[14,15].

Figure 2: Pathophysiology of cirrhotic cardiomyopathy



The vasodilatory effect of liver failure is to a certain degree analogous to using an angiotensin converting enzyme inhibitor chronically. However, in certain stressed states, the inability of the heart to meet the demands of cardiac output can be brought out. As an example, physical exercise will often increase left ventricular end diastolic pressures[11]. As cardiologists, diagnosing cirrhotic cardiomyopathy can be difficult as the systolic function of the heart will look normal on echocardiography due to the immensely low systemic vascular resistance. However, these patients have increased myocardial hypertrophy, fibrosis, and edema all leading to diastolic dysfunction. Diastolic dysfunction is present in as many as 56% of patients with cirrhosis and is in itself a predictor of survival. This increased stiffness in the myocardium is represented as an echocardiographic change in transmitral inflows with an E/A ratio of <1. Furthermore, an E/A ratio <1 is shown to have a higher one-year mortality after transjugular intrahepatic portosystemic shunt placement or liver transplantation[16,17]. As cardiologists, it is important to pay careful attention to the diastolic function of patients with liver failure as it is a clue as to whether the patient has cirrhotic cardiomyopathy.

Cirrhosis also affects the electrical conduction of the heart. Electromechanical decoupling has been established by cardiac catheterization lab data, although the clinical relevance is uncertain[18]. Due to the lack of cardiac beta-receptors, these patients also have defective cardioacceleration in response to stress, to the vasodilated state of liver failure, and to pharmacologic stimuli such as dobutamine or epinephrine. Prolongation of the QT interval is also seen in cirrhotic patients though the pathophysiology is unclear. It seems there are two factors involved in the prolongation of the QT interval. First, in portal hypertension, liver metabolites and cardiotoxins may interfere with the functionality of intracellular potassium channels [18]. Second, the increased sympathetic tone driven by the high output state results in further lengthening of the QT interval. As such, prescription of QT prolonging medications and monitoring of secondary causes of QT prolongation should be routinely assessed.

The systolic, diastolic, and electrical dysfunction of the heart caused by cirrhotic cardiomyopathy leads to several clinical consequences. The heart though relatively protected by the vasodilatory state of liver failure does not respond well to exercise or stress. One such example of stress is the volume unloading that occurs with paracentesis.

Traditionally, it was thought that the post-paracentesis renal failure that occurs is all related to loss of volume thus requiring the return of albumin. This entity is now called post-paracentesis circulatory dysfunction (PPCD) and likely represents an inability for a heart with cirrhotic cardiomyopathy to increase cardiac output in a relatively volume contracted state causing renal failure[19] The same is true for the decompensation that occurs post-transjugular intrahepatic portosystemic shunt placement where the heart now has to deal with extra volume [19,20].

In fact, much of the entity known as hepatorenal syndrome has more to do with the heart and circulation than with the kidney itself. Hepatorenal syndrome is an end organ manifestation of the splanchnic vasodilation and heart failure associated with cirrhotic cardiomyopathy and by definition the kidney is normal with a urine sodium less than 10 meq/L [21]. Another time of decompensation occurs post-liver transplant, when patients can go into acute heart failure as the new liver no longer allows splanchnic vasodilators into the circulation causing a sudden increase in systemic vascular resistance causing reloading of the heart. This can be manifest as a rapid loss of systolic function on echocardiography and may in some patients also manifest as left ventricular outflow tract obstruction due to regional differences in contractility [11,22] . It is believed that this is the second highest cause of death early post-liver transplant after infection.

After establishing the diagnosis, cardiologists treating cirrhotic cardiomyopathy should be cognizant of certain diagnostic and therapeutic points. First, we must be wary of the limitations of some of our diagnostic tests in this patient population such as dobutamine stress echocardiography (due to defective cardioacceleration) and the use of dipyridamole for stress testing (due to the already vasodilated state).

In terms of therapy for systolic dysfunction, standard guideline directed heart failure therapies should be initiated. However, in a small study by Banares et al., carvedilol was found to have greater effects on hemodynamics. Carvedilol is superior in reducing portal pressures, splanchnic pressures, and the hepatic venous pressure gradient[23]. In patients with severely reduced systolic function requiring intravenous inotropic agents, the inotropic response is blunted due to beta adrenergic receptor downregulation.

Therefore, once in a decompensated state the patient may require higher doses of intravenous inotropes to get the same response. Cirrhotic cardiomyopathy does resolve after orthotopic liver transplant so it is important to follow patients closely post-operatively and try and get them through the first 72-96 hours when they are most unstable. Since the hyperdynamic circulation state in cirrhosis masks cirrhotic cardiomyopathy, there are significant implications with regards to liver transplantation. Generally, an EF < 50% is a contraindication since the ejection fraction will likely be significantly lower post liver transplant because of increases in afterload[24].

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Review

Cardiohepatic interactions: Part 3 of a 3 Part Series: Diseases that concurrently affect the heart and liver

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Diseases that concurrently affect the heart and liver

In part 3 of this 3-part series we will be describing diseases that concurrently affect the heart and the liver and how certain disorders lead to concurrent hepatic and cardiac dysfunction (Figure 1). These disorders often require a multi-disciplinary team-based approach to appropriately treat these complex patients. A detailed description of the diagnosis and management of these diseases is beyond the scope of this article, but we outline situations where both cardiologists and hepatologists need to consider disease processes occurring simultaneously.

Alcohol

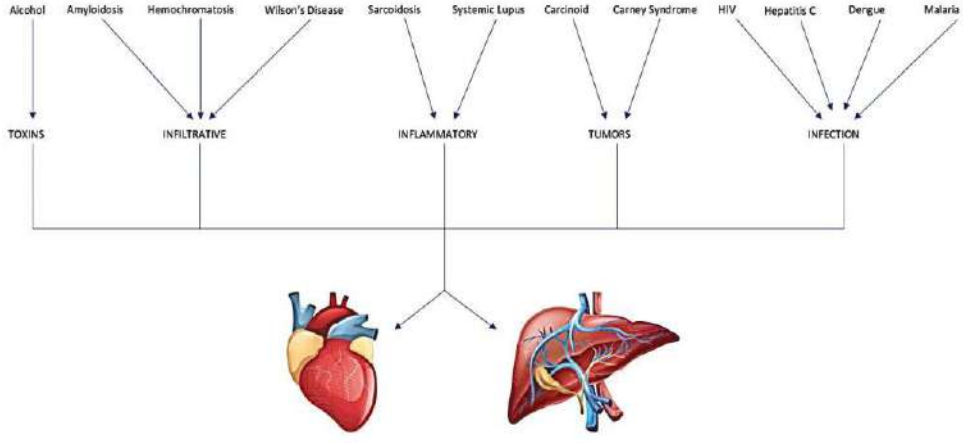
Alcohol abuse has independent deleterious effects on both the heart and liver. The amount and chronicity of alcohol consumption to cause changes in cardiac function varies but is generally thought to be >90g/day for 5 years. In contrast, moderate alcohol consumption for longer periods of time, 25g/day for men and 12g/day for women, over 10 years may lead to cirrhosis. Not all patients who have alcohol related cirrhosis develop cardiomyopathy[(1)].

Therefore, patients with varying degrees of alcohol consumption may have cardiac dysfunction, hepatic dysfunction, or both. All patients with alcoholic cirrhosis should have a screening echocardiogram to look for alcohol associated cardiac dysfunction. Notably, there is a thought that alcoholic cardiomyopathy also has a genetic predisposition with many of the genes associated with dilated cardiomyopathy being also found in patients that are predisposed to alcoholic cardiomyopathy[(1)].

Infiltrative disorders

Patients with certain systemic conditions can have both cardiac and hepatic manifestations. Amyloidosis can lead to restrictive cardiomyopathy which is best diagnosed with cardiac MRI (CMR). In primary AL amyloidosis (associated with multiple myeloma), amyloid light chain deposition can also occur in the liver. A total of 60-90% of patients with primary amyloidosis may have hepatic involvement. The treatment for these patients involves the use of chemotherapy to treat the underlying plasma cell dyscrasia[(2)].

Figure 1: Diseases that affect the heart and lung concurrently



Transthyretin amyloidosis (TTR), a hereditary amyloidosis, is caused by a mutation in the TTR gene (also known as pre albumin). TTR is produced by the liver and its deposition mainly affects the heart leading to diastolic dysfunction. The recent ATTR-ACT trial improved mortality for patients with TTR amyloidosis using tafamadis which stabilizes the TTR tetramer reducing its formation [3] Liver transplant can also be considered in these patients as it is the source of the protein.

Other infiltrative processes including hemochromatosis may lead to cardiomyopathy and cirrhosis. This inherited disorder in which mutations in the HFE gene causes lifelong increased intestinal iron absorption resulting in iron overload and tissue damage. Progressive iron deposition may lead to hepatomegaly, liver enzyme elevation, and cirrhosis [4]. Hemochromatosis can also lead to dilated cardiomyopathy, heart failure, and conduction disturbances due to excess iron within the myocardium. Diagnosis of cardiac involvement can be on the basis of history, physical exam, and lab testing; however, cardiac magnetic resonance by T2* imaging is becoming the gold standard[5]. Treatment includes phlebotomy and iron chelation therapy along with dietary restriction of iron. Similar to hemochromatosis, Wilson's disease with copper accumulation can affect both the liver and heart.

Inflammatory conditions

Sarcoidosis is a multi-organ inflammatory systemic disease characterized by non-caseating granulomatous infiltration. Cardiac sarcoidosis is relatively rare with only 5% of patients having clinical evidence; however, 25% of patients have histologic evidence during autopsies[6]. Patients can present with conduction system diseases, especially AV block. Hepatic sarcoidosis is more prevalent being observed in 50-80% of autopsy studies; however, 10-30% have abnormal liver enzymes[7,8]. FDG-PET/CT scan is useful in systemic assessment for active sarcoidosis including looking at the liver [9]. Myocardial FDG uptake is useful in assessing inflammation attributable to the sarcoidosis. Cardiac MRI also is useful to look at late-gadolinium enhancement to assess cardiac scar burden[10]. A recent meta-analysis demonstrated that evidence of late gadolinium enhancement had a positive odds-ratio of 7.4 for all-cause mortality and ventricular arrhythmia[11]. Early electrophysiology consult should be considered for patients with cardiac sarcoid.

Systemic lupus erythematosus (SLE) is associated with a range of cardiovascular symptoms and conditions including coronary artery disease and acute coronary syndromes, myocarditis, vasculitis, pericarditis, conduction disease, and valvular disease. These conditions should promptly be assessed by cardiology and rheumatology and treated accordingly. Lupus hepatitis involves a transaminitis and is often a subclinical condition with a lower rate of progression to end-stage liver disease[12].

Tumors

Certain tumours can affect the heart and liver simultaneously. Carcinoid tumours arising from the gut must metastasize first to the liver prior to releasing their hormones into the systemic circulation eventually causing carcinoid heart disease. It is a paraneoplastic effect through vasoactive substances including histamine, 5-hydoxytryptamine (serotonin), prostaglandins, and tachykinins rather than a direct metastatic effect on the heart. Any patient that has either carcinoid liver metastases or carcinoid heart disease should have imaging of the other organ. The Carney complex is associated with both cardiac myxomas and liver cancer.

Infections

Lastly, cardiologists must be aware of systemic infections that may lead to cardiac and hepatic dysfunction. Human immunodeficiency virus if untreated may result in hepatitis and HIV-associated cardiomyopathy. Hepatitis C can also affect both liver and heart through cardiomyopathy or cryoglobulinemia[13]. Dengue fever is amongst the most prevalent mosquito borne illnesses in the world. Dengue can present with systemic illness, hemorrhagic fever, and shock syndrome. Dengue can result in hepatic necrosis as a result of profound hypoperfusion and hypoxia rather than a direct viral effect. Cardiovascular manifestations of dengue include fulminant myocarditis and arrhythmia. Supportive therapy is generally required for patients to allow for myocardial recovery. Plasmodium falciparum malaria can cause massive hepatic necrosis through direct infection and inflammation. It can also cause a myocarditis picture with cardiac involvement. Plasmodium vivax can rarely also have similar liver and cardiac involvement. Malaria with either liver or cardiac involvement is associated with much higher mortality than uncomplicated malaria.

Conclusion

The liver is an important and complex organ with synthetic and metabolic functions which are associated with many molecular and haemodynamic changes in patients. Cardiologists, cardiac intensivists, and hepatologists should recognize that cardiohepatic interactions are complex and need to be taken into consideration in the diagnostics and therapeutics of these patients.

An ideal framework when dealing with these increasingly complex patients is to divide the interactions into how the heart affects the liver, how the liver affects the heart, and which conditions affect both organs concurrently. This framework is then helpful in proceeding with diagnosis and therapy at the bedside for our patients and is also useful in subdividing the pathophysiological processes for further research study.

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Review

Ischaemia-guided Revascularization; Personalizing coronary artery disease management

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Percutaneous coronary intervention (PCI) has become the most utilized form of revascularization therapy for the treatment of coronary artery disease (CAD). Following its seminal use forty years ago there have been profound advances in both pharmacotherapy and device technology, now routinely at the disposal of interventional cardiologists. This has led to more complex coronary anatomy, such as multi-vessel disease and left main stem disease being treated percutaneously, which were historically reserved for coronary artery bypass surgery (CABG). The impetus behind these advances has been the ability to treat patients more completely, with reduced major complications. This has therefore improved the patient journey, by reducing recovery times allowing patients to continue with their lives with limited impact. Nonetheless, despite these significant changes to revascularization methods and complexity, the importance of critically appraising each individual patient's clinical presentation, anatomy and circumstances remains of paramount importance in the current era. These technical advances have been in conjunction with improvements in patient assessment, in terms of risk stratification, delineation of disease complexity and ischaemic burden, which, in conjunction with an understanding of the patient's preferences, all contribute to the subsequent allocation of revascularization modality with PCI or CABG.

PCI guided by functional assessment of coronary stenoses, either non-invasively or invasively, by selective treatment of ischaemia-inducing stenoses confers improved cardiovascular outcomes [1,2]. The use of sensor-equipped guidewires for the invasive assessment of functional coronary lesion severity has emerged as a standard diagnostic modality, enabling objective evidence of myocardial ischemia during cardiac catheterization [3,4] . The current era has been dominated by pressure-derived indices of stenosis assessment, such as Fractional Flow Reserve (FFR).

Revascularization guided by ischaemia – an important entity

A Hachamovitch et al [5] provided observational evidence that revascularization, in the correct setting, is likely to represent the optimal strategy in patients with stable CAD. The study also laid the foundation for subsequent prospective trials, such as COURAGE, [6] to further assess this topic. COURAGE, a randomized control trial, which assigned patients with stable CAD, to a medical or a PCI strategy, subsequently reaffirmed the findings of the 'low ischaemia group' in this earlier observational study. The COURAGE nuclear sub-study[2] pointed to a signal that ischaemia-guided PCI improved patient symptoms, reduced overall ischaemic burden and therefore may provide an improved prognosis.

Fractional Flow Reserve - reference standard in invasive ischaemia assessment?

Since the seminal work by Pijls et al [7] FFR has become the most widely used invasive measure to quantitatively assess the functional severity, and therefore physiological importance, of a coronary artery stenosis. It has been used to provide an objective guide for the potential clinical importance and sequelae of a coronary artery stenosis, and the degree to which that stenosis can invoke ischaemia.

FFR is defined as the ratio of maximal flow through a stenotic artery compared with hypothetical flow in that same artery in the absence of a stenosis, measured during maximal hyperaemia (when myocardial resistance is minimal and constant) (Figure 1). Therefore, an FFR ratio of 1.0 is accepted as 'normal', and a stenosis with an FFR of ≤0.80 is widely accepted as an ischaemia provoking stenosis requiring intervention. There is debate regarding the significance of those with a ratio of 0.75-0.80, but the overall the use of an upper limit of 0.80 has been widely accepted.

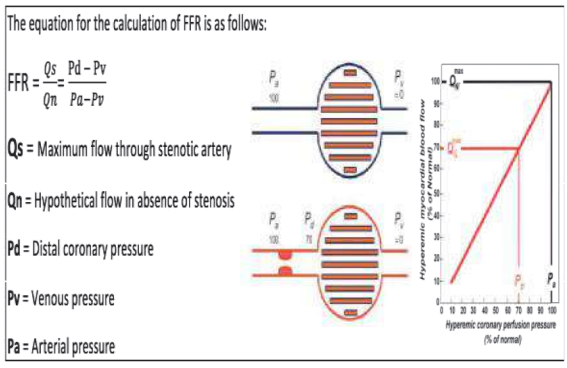

Figure 1: Fractional Flow Reserve (FFR) Equation

FFR is measured by guiding a pressure wire across the stenosis during angiography to calculate the ratio between the pressure distal to the stenosis and the aortic pressure, this is performed under conditions of myocardial hyperaemia usually achieved by intravenous or intracoronary adenosine. With appropriate training and experience of the technique the readings should be relatively straightforward to acquire and should not cause any inappropriate delays during angiography.

There is robust randomized clinical data to support the use of ischaemia guided intervention for PCI, with trials such as FAME [8], FAME 2 [9] and DEFER trial [10]. The FAME [8] (Fractional Flow Reserve vs. Angiography for Multivessel Evaluation) study was a landmark study, demonstrating the clinical application for using FFR to guide revascularization decisions. This was a multi-centre, prospective Randomized Control Trial (RCT), which recruited a total of 1005 patients with multi vessel coronary artery disease (CAD). The patients were randomly assigned to either angiography guided PCI (standard technique) or FFR guided PCI, FFR was measured in all significant lesions and those with an FFR ≤0.80 received treatment with a drug eluting stent. The trial showed a significant reduction in the primary end points (death, MI, CVA and revascularization at one year) in the FFR group compared with the angiographically-guided PCI group (13.2% vs. 18.3%, p=0.02) (Figure 2) and also showed superiority in numerous secondary end points. The trial demonstrated no significant increase in procedural duration using the FFR technique and importantly showed significantly reduced stent use per person. Importantly the FAME trial reiterated the suspicion that there is a general tendency to overestimate stenosis severity from visual assessment alone, showing a marked discordance between angiography and FFR assessment of a stenosis.

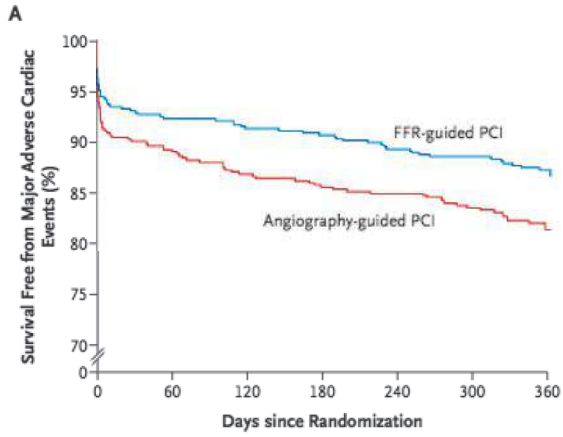

Figure 2: FAME study Kaplan-Meier event curve

The DEFER study [10] was the prelude to the FAME series of trials; it was also a multi-centre, prospective randomized study, recruiting 325 patients who were planned for PCI to an intermediate stenosis. This study measured the FFR value in these lesions and for those with an FFR >0.75 patients were randomized to either PCI or medical management alone; for those with FFR <0.75 they proceeded to PCI as planned. The trial concluded that in those with non-significant coronary artery stenoses (those with an FFR ≥ of 0.75) PCI precludes no prognostic or symptomatic benefit and should therefore be discouraged. Further to this they concluded that the risk of a haemodynamically non-significant stenosis resulting in death or acute MI was <1% per year and was not reduced by stenting.

The FAME-2 (FFR-guided PCI versus Medical therapy in stable coronary disease)[9] trial has added further weight to data suggesting ischaemia-guided PCI is the optimal strategy to guide PCI decision making. In this cohort, comparison was made between FFR-guided PCI and medical therapy, in patients with coronary arterial disease. The trial was halted early due to the disproportionate number of end-points in the medically treated arm. This was due to the markedly increased rate of urgent revascularizations in medically treated group (1.6 vs 11.1, p<0.001). However, no difference was observed in the more meaningful end-points of rate of MI (3.4 vs 3.2, p=0.89) or cardiac (0.2 vs 0.2, p=.98) or all-cause mortality (0.2 vs 0.7, p=0.31), potentially due to the early cessation of the trial and subsequent loss of clinical events and therefore statistical power.

Nonetheless this trial reiterated the benefit of targeted ischaemia-driven PCI, which is likely to be due to the ability of accurately determining the most important (ischaemia-inducing) lesions whilst appropriately deferring those that are not of functional significance. This consequently results in more judicious use of stents, minimizing stent length, which subsequently reduces rates of restenosis and stent thrombosis.

This increasing body of evidence has led to FFR becoming the reference standard for invasive ischaemia assessment in clinical practice and its subsequent inclusion in international clinical guidelines as a tool for guiding revascularization strategies.

Physiological assessment in Acute Coronary Syndromes – ready for prime time?

It is important to highlight that current guidance is in relation to stable coronary artery disease. In the presence of ACS, either non-ST elevation (NSTEMI) or ST-elevation myocardial infarction (STEMI) there remains some uncertainty about its validity and accuracy in assessing non-culprit bystander disease in the context of recent myocardial infarction. There has been observational data that support the use of FFR for guided revascularization in the setting of ACS[11,12]. More recently the DANAMI 3-PRIMULTI randomized control trial assessed the use of FFR following STEMI. In n=627, FFR-guided deferral or treatment of bystander disease benefitted those that had angiographic 3-vessel disease, with a reduction in a composite primary outcome of all-cause mortality, reinfarction, and ischemia-driven revascularization (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.17-0.64; P=0.001) or in those that had high grade >90% diameter stenosis in the bystander vessels (HR, 0.32; 95% CI, 0.18-0.62; P=0.001). However, in those with 2-vessel bystander disease there was no significant effect (HR, 0.77; 95% CI, 0.47-1.26; P=0.29; P for interaction =0.046). The basis of the potential for inaccuracy is based on the premise that the diagnostic validity for an FFR value in a non-culprit vessel may be affected by the ischaemic insult and myocardial stunning in adjacent myocardial territories, due to acute microvascular dysfunction. This subsequently reduces the ability to achieve maximal flow during hyperaemic stimulus thus potentially reducing the pressure difference, which may lead to a falsely negative FFR value. The time interval required before an accurate FFR can be obtained is not clear and would theoretically depend on a variety of factors such as infarct size, the degree of pre-existing microvascular dysfunction in adjacent myocardial territories, and the impact of acute impairment of LV function. The current consensus is that FFR may be a safe and reliable tool in the setting of ACS however validation from trials remains critical in allowing the technology to be used reliably in the clinical practice.

Conclusion

Invasive functional assessment of coronary disease is an important and increasingly validated modality of assessing haemodynamic sequelae of coronary stenoses. It has heralded a paradigm shift in the way PCI procedures are being performed, with physiology guided procedures now regarded as the reference standard in guiding revascularization strategies. Importantly the physiological basis of coronary disease and the treatment of it, is being scrutinized both in the clinical trial setting but increasingly in daily practice. This new found enthusiasm, however, has to be tempered with the knowledge that despite having a number of indices at the clinician's disposal, there are limitations to each of them and that continued development of techniques and understanding is paramount in progressing physiology guided revascularization moving forward.

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Research

Quantitative coronary angiography as a method of assessing the coronary artery size in a cohort of adult Sri Lankans

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Abstract

Introduction: Among the several procedures to estimate the coronary artery size, Quantitative Coronary Angiography (QCA) is a well-recognized and a simple technique that can be performed on a conventional coronary angiogram.

Objective : To assess the sizes of disease free coronary arteries in a cohort of adult Sri Lankans by Quantitative Coronary Angiography (QCA) technology and to compare the size with other south Asian and diabetic subgroups.

Methodology: Descriptive cross-sectional study was conducted at cardiology unit, Teaching Hospital Kandy, Sri Lanka in 2016 and 2017. All the patients who had normal coronary angiograms were selected for size evaluation. The dimensions of the coronary arteries were measured by QCA software of Seimons Axiom Sensis XP - Digital Cardio Imaging system. The actual and corrected sizes for body surface area of the coronaries were compared between subgroups.

Results: A total of 250 subjects with 52.80% (n=132) of males and 47.20 %(n=118) females were included. The mean age of the sample was 51.80±9.79 years. Out of these subjects, 69.20% (n=173) had right dominant system. Mean diameter of Left Main Coronary Artery (LMCA) and proximal Left Anterior Descending (LAD) were 4.04±0.56mm and 3.02±0.60 mm respectively. Proximal Left Circumflex (LCX) and proximal Right Coronary Artery (RCA) were 2.90 ±0.56mm and 3.17±0.55 mm respectively. There was a significant correlation (r=0.89, p<0.05,) noted between body surface area and proximal LAD diameter. In the group comparison, Caucasians had larger coronary arteries compared to Indians, Pakistanis, Bangladeshis and our study group. However, their Coronary Artery Index (CAI) were nearly equal among all. Out of the study group, 41.20% (n=103) were diabetics. In the diabetic arm, the size of LMCA, LAD and RCA were narrower than controls without a statistical significance. However, proximal LCX diameter was significantly narrower among diabetics (2.82±0.48mm vs. 2.95±0.52mm, p<0.05).

Conclusion: The study reflects that the Sri Lankans, as well as the other south Asians have generally smaller coronary arteries compared to Caucasians though their coronary artery indexes are nearly equal. Addition to that the study reveals diabetics also have relatively smaller coronaries compared to non-diabetics.

Keywords: Coronary artery diameter, Quantitative coronary angiography, Diabetes mellitus, Coronary flow dynamics, Coronary artery index.

Introduction

Various studies across the different populations have constantly discovered an increased prevalence of coronary artery disease (CAD) among south Asians at an earlier age than in western populations [1,2,3,4,5].

The etiology of this higher prevalence among Asians is still an unanswered question. Prevalence of traditional risk factors such as cigarette smoking, high serum cholesterol, diabetes mellitus and hypertension alone have failed to explain the high occurrence of CAD in Asians [6,7,8,9].

Whether the size of the coronary artery is an influencing factor for this higher incidence of CAD or not is a subject, which is still open for discussion.

There are some emerging evidence that shows that subjects having a smaller internal diameter of a coronary arteries are found to have a greater association with Myocardial Infarctions (MI) and cardiac failure than patients who are having large coronary arteries [10,11].

Interestingly, it has been suggested by some studies that the presence of small coronary arteries may have contributed towards the occurrence of severe CAD and high mortality in some of the people of south Asian origin [12].

There are several ways to estimate the coronary artery luminal diameter and among these, Quantitative Coronary Angiography (QCA) is a well-recognized and a simple method that can be performed on a conventional coronary angiography film.

The place of QCA in cardiology practice is mainly complementary to standard conventional coronary angiography and other imaging techniques, such as intravascular ultrasound, computed tomography and optical coherence tomography. However, QCA has advanced in the current era of cardiology to provide more sensitive measurements and anatomical descriptions of coronary arteries and shows continuous evolution into 3D coronary angiographic techniques acquiring more descriptive power of anatomical evaluation of complex coronary lesions.

Published data on the dimensions of normal coronary arteries in Sri Lankans is not widely available in current medical literature. Therefore, this prospective study was designed to establish a database for normal dimensions of coronary artery segments by using the QCA technique. In addition, the aim was to compare the coronary artery dimensions of Sri Lankans with that of other south Asian and western populations.

Material and methods

Study design and setting

A descriptive observational study was conducted at cardiology unit, teaching (General) hospital Kandy, Sri Lanka obtaining a consecutive sample of 250 cases over 20 months from 2016 October onwards.

Inclusion criteria

All the patients who were above the age of 18 years were subjected for routine evaluation of CAD, but happened to have no plaque disease were selected for the study. Mostly, the group consisted of patients with inconclusive or falsely positive imaging or stress testes.

Exclusion criteria

Coronary angiograms of the patients who were given vasodilators before or during the procedure and angiograms showing any degree of ectatic segments were excluded from the study. Apart from that any patient with inotrope support, haemodynamically significant valve disease, shunts or patients with cardiomyopathy also were excluded from the study.

Data collection

Demographic, anthropometric and other clinical data was collected by an interviewer administered questionnaire. Patient's cardiovascular risk factors (hypertension, diabetes mellitus, smoking and hypercholesterolemia) were obtained by detailed history taking and studying the health records.

Angiographic technique and vascular access

Percutaneous trans-femoral or trans-radial access was established by Seldinger technique for all the coronary angiogram procedures. 6 French (6F) arterial sheath was placed in the femoral or radial artery under local anaesthesia and selective coronary catheterization was performed with 5F or 6F Judkins or Amplatz right and left diagnostic coronary angiography catheters. Selective engagement of the coronary ostia were performed under fluoroscopy guidance.

Angiographic views and the analysis

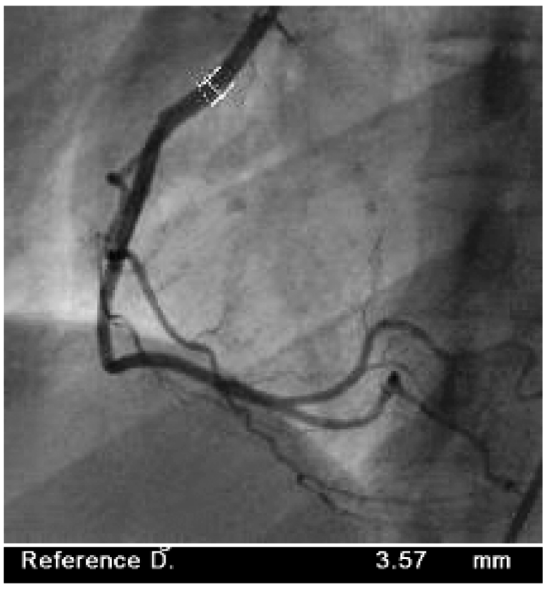
All the angiograms were acquired using Seimons Axiom Sensis XP - Digital Cardio Imaging system. Operation of the QCA [13,14] programme was carried out by a method in which the diagnostic coronary catheter itself was used as the calibrating object by automated edge detection technique. The dimension of the coronary artery was then measured as a fraction of the catheter diameter. The absolute diameter in millimeter was calculated by computerized software analysis (Figure 01). The actual and corrected sizes for Body Surface Area (BSA) of the coronary arteries were compared between groups. Coronary Artery Index (CAI) was calculated by dividing the maximum coronary artery diameter by BSA.

Angiographic views were selected to minimize the foreshortening of the relevant coronary segments and to separate them from adjacent intervening structures. All angiograms were reviewed by a cardiologist and a cardiac radiographer both for definition of normal vessels and subsequent quantitative analysis. All films were reviewed by an experienced second observer who was blinded for the patients' identity and the clinical history.

Selection criteria for target vessels

Standard angiographic views [14] were obtained and QCA was carried out on longest possible disease-free segments of the coronary arteries which were uniformly distended & contrast filled, without kinking, overlap segments or having free of tortuosity. The vessels were assessed in an end diastolic frame. Standard anatomical definition of coronary arteries [15] were used to identify each segments of coronary arterial system.

Figure 01, Size of the proximal right coronary artery measurement by QCA technique



Statistical analysis

Continuous variables were presented as mean with Standard Deviation (SD) and categorical variables as percentages. Independent sample t test was used to compare the quantitative data. Pearson's correlation coefficient was performed to evaluate the correlations. Differences were considered statistically significant when the p value was < 0.05. The Statistical Package for Social Sciences (SPSS) version 17 was used for all calculations and statistical analyses.

Ethical Clearance

Ethical clearance was obtained from the ethical review committee of Teaching Hospital Kandy, Sri Lanka. Informed written consent was obtained from all patients.

Results

Demographic characteristics

A total of 250 subjects with 52.80% (n=132) of males were included. The mean age of the sample was 51.80±9.79 years. There were 69.20% (n=173) who had right dominant system and 10.00% (n=25) had co-dominant system. Out of the sample, 41.20% (n=103) had diabetes mellitus, 42.40% (n=106) had hypertension and 32.80% (n=82) had dyslipidemia as co-morbidities (*Table 01*).

Table 01, Baseline characteristic of the study sample

Variable	Results n (%)
Age in years (mean ± SD)	51.80±9.79
Gender	
Male	132(52.80%)
Female	118(47.20%)
Mean BSA (m^2)	1.29±0.66
Co-morbidities	
Diabetes Mellitus	103(41.20%)
Hypertension	106(42.40%)
Dyslipidemia	82(32.80%)
Coronary Dominance	
Right	173(69.20%)
Left	52(20.80%)
Co-dominance	25(10.00%)

SD = Standard deviation
BSA= Body Surface Area

Research

Coronary artery diameters

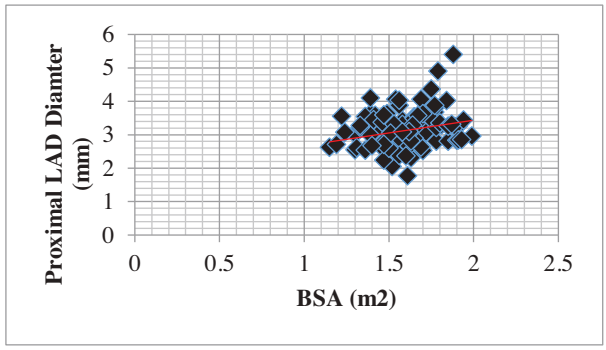
Mean diameter of Left Main Coronary Artery (LMCA) was 4.04±0.56mm of the study sample. Mean diameter of proximal, mid and distal Left Anterior Descending (LAD) was 3.02±0.60 mm, 2.58±0.47 mm and 2.13±0.44 mm respectively. Proximal and distal Left Circumflex (LCX) was 2.90 ±0.56 mm and 2.45 ±0.57 mm respectively. The mean diameter of proximal, mid and distal Right Coronary Artery (RCA) was 3.17±0.55 mm, 2.86±0.48 mm and 2.38±0.50 mm respectively (*Table 02*). There was a significant correlation (r=0.89, p<0.05,) noted between body surface area and proximal LAD diameter (Figure 02). However, there was no significant difference noted in the size of coronary artery in male and females (p=0.26).

Table 02, Coronary artery diameters and coronary artery indexes of the study group

Variable	Results (mm)
Coronary Artery Diameter (Mean ± SD)	
LMCA	4.04±0.56
Proximal LAD	3.02±0.60
Mid LAD	2.58±0.47
Distal LAD	2.13±0.44
Proximal LCX	2.90±0.56
Distal LCX	2.45±0.57
Proximal RCA	3.17±0.55
Mid RCA	2.86±0.48
Distal RCA	2.38±0.50
Coronary Artery Index	
LMCA	2.55±0.47
Proximal LAD	1.97±0.39
Mid LAD	1.64±0.41
Distal LAD	1.33±0.42
Proximal LCX	1.77±0.47
Distal LCX	1.45±0.52
Proximal RCA	2.01±0.50
Mid RCA	1.55±0.66
Distal RCA	1.34±0.60

SD= Standard Deviation ,LMCA= Left Main Coronary Artery, LCX= Left Circumflex, LAD= Left Anterior Descending, RCA= Right Coronary Artery

Figure 02, Correlation between body surface area and proximal LAD diameter



The Coronary Artery Index (CAI)

CAI of the LMCA was 2.55±0.47mm. CAI of proximal, mid and distal LAD was 1.97±0.39 mm, 1.64±0.41 mm and 1.33±0.42 mm respectively. Proximal and distal LCX had CAI of 1.77 ±0.47 mm and 1.45±0.52 mm respectively. The CAI of proximal, mid and distal RCA was .01±0.50 mm, 1.55±0.66 mm and 1.34±0.60 mm respectively *(Table 02)*.

Comparison of coronary artery diameter in diabetics versus non-diabetics

Out of the study group, 41.20% (n=103) were diabetics. In the diabetic arm, the size of LMCA, LAD and RCA were narrower than the control group. However, only the proximal LCX had statistically significant smaller diameter among all other coronary artery segments (Table 03).

Table 03, Comparison of coronary artery diameters in diabetic versus non diabetic group

Coronary Artery Diameter	Diabetic (n=103) (mm)	Non Diabetic (n=147) (mm)	P Value (<0.05)
(Mean±SD)			
LMCA	4.02±0.47	4.08±0.48	0.26
LAD	2.21±0.42	2.22±0.43	0.78
LCX	2.82±0.48	2.95±0.52	0.01
RCA	3.15±0.54	3.18±0.62	0.65

LMCA= Left Main Coronary Artery
LAD= Left Anterior Descending
LCX=Left Circumflex
RCA= Right Coronary Artery

Comparison of coronary artery dimensions with other south Asians and Caucasians

According to the absolute value comparison, Caucasians' had larger diameters of the coronary arteries compared to Indians, Pakistanis, Bangladeshis and our study sample. However, the CAI was found to be nearly equal among all (*Table 04*)

Discussion

The variation of coronary artery dimensions are dependent on various factors, such as genetics, gender, age and the body composition according to many studies [17, 18, 19, 20, 21, 22, 23]. Apart from that several correlations between weight of the heart and the lumen size of the coronary artery also have been revealed by some investigators [16].

Table 04, Comparison of coronary artery diameters and coronary artery index between different nations.

	LMCA	P LAD	M LAD	D LAD	P LCX	D LCX	P RCA	D RCA
Maximum coronary artery diameter (Mean±SD) (mm)								
Study group	4.04±0.56	3.02±0.60	2.58±0.47	2.13±0.44	2.90±0.56	2.45±0.57	3.17±0.55	2.38±0.50
Caucasians	4.44±0.91	5.53±0.69	3.13±0.68	2.44±0.62	3.17±0.63	2.47±0.58	3.35±0.69	2.01±0.50
Indians*	3.72±0.65	2.85±0.59	2.24±0.49	1.63±0.38	2.82±0.63	2.10±0.68	2.75±0.60	2.14±0.61
Pakistan	4.28±0.82	3.22±0.74	-	-	3.02±0.75	-	3.08±0.78	-
Indu Asians	3.98±0.67	3.22±0.56	2.77±0.56	2.26±0.60	3.01±0.66	2.37±0.67	2.98±0.63	1.69±0.48
Bangladesh	-	3.14±0.50	3.10±0.42	2.42±0.45	3.01±0.25	2.44±0.43	3.28±0.25	2.87±0.32
Coronary Artery Index (Mean±SD) (mm)								
Study group	2.55±0.47	1.97±0.39	1.64±0.41	1.33±0.42	1.77±0.47	1.45±0.52	2.01±0.50	1.34±0.60
Caucasians	2.38±0.47	1.89±0.37	1.68±0.37	1.31±0.32	1.71±0.32	1.32±0.29	1.79±0.39	1.06±0.26
Indians*	2.16±0.42	1.69±0.37	1.34±0.33	0.96±0.23	1.67±0.39	1.19±0.41	1.89±0.39	1.46±0.40
Pakistan	-	-	-	-	-	-	-	-
Indu Asians	2.26±0.41	1.83±0.34	1.57±0.29	1.28±0313	1.71±0.39	1.34±0.37	1.70±0.39	1.97±0.27
Bangladesh	-	-	-	-	-	-	-	-

*SD= Standard Deviation, LMCA= Left Main Coronary Artery, P LCX=Proximal Left Circumflex, D LCX= Distal Left Circumflex, P LAD= Proximal Left Anterior Descending, M LAD= Mid Left Anterior Descending, D LAD= Distal Left Anterior Descending, P RCA= Proximal Right Coronary Artery, D RCA= Distal Right Coronary Artery, *Only Indian males were considered , Indo Asians= Indian living in the United Kingdom*

This finding may reflect their smaller body habitus with proportionate coronary artery sizes rather than an absolute size difference. Interestingly, our study showed that Sri Lankans had nearly equal CAI to the Caucasians for LMCA and proximal segments of the main three coronary arteries. However, the real anatomical significance of such an observation should be evaluated with further studies.

Therefore, the interest is generated to explore whether the dimension of coronary artery has important diagnostic, prognostic and therapeutic implications in a patient with CAD.

In addition, as for any coronary interventional procedure the absolute size of the coronary arteries matters in making treatment decisions re-enforcing this concept. It has been evident by a study conducted by Dodge JT at el that acute or sub-acute stent occlusion or thrombosis is more common in vessels less than 2.5 mm in diameter [19].

Similarly, a moderate stenosis in a 2.5 mm (relatively small) vessel would have more effects on the flow dynamics than the same degree of stenosis in a 3.5 mm (relatively large) vessel as the cross-sectional area significantly differs in these two situations [16].

During our study, we were able to formulate the absolute diameters and CAI for individual coronary arteries in Sri Lankan patients. During the analysis, we found that only the LAD has a significant correlation to BSA. Interestingly, this type of similar finding was observed in some other studies conducted on Caucasians and Asians as well [23,24].

More interestingly, against the common belief, there was no significant difference of the size of the coronary arteries noted among males and females in our study, and this is in contrast to a previous study conducted on Indians where the males had larger coronary arteries compared to females [16]. The diabetics had small coronary arteries compared to non-diabetics but only the LCX diameter was statistically significant in our study. To strengthen this finding, several studies had shown that small coronaries and diffuse vessel narrowing were observed as morphological changes in diabetes as well as in patients with impaired glucose tolerance [25]. However, that study was conducted on patients with plaque disease in contrast to our study group, which was conducted in diabetic patients who belonged to possible pre-plaque stage. Therefore, the clinical significance of this findings should be followed up on long term basis to achieve a solid conclusion of whether the smaller coronaries in diabetics has clinically significant influence on their prognosis.

Though Sri Lankans are found to have more frequent coronary artery disease even in an early age, the data on the dimensions of their coronary artery sizes are limited in the medical literature.

Similarly, coronary artery sizes of Sri Lankans are believed to be significantly smaller compared to the westerners due to lack of comparable data. Nevertheless, some Indian studies had proven that their coronary artery sizes are smaller to Caucasians [23,26,27]. Interestingly, our data suggests that Sri Lankans have relatively smaller coronary arteries compared to Caucasians but have relatively equal CAI compared to Caucasians. However, the statistical and clinical significance of their relative differences are still open for further investigators.

Conclusion

In this study, we have attempted to establish coronary artery dimensions for Sri Lankans who are having no visible coronary plaques in angiography and to make an opportunity to compare the data with other south Asian populations and Caucasians. The study reflects that the Sri Lankans, as well as the other south Asians have generally smaller coronary arteries compared to Caucasians though their coronary artery indexes are nearly equal. Addition to that the study reveals that diabetics also have relatively smaller coronaries compared to non-diabetics. Therefore, this comparative size differences may encounter more severe haemodynamic compromise with subsequent plaque disease compared to bigger arteries, and may create more technical difficulties during coronary interventions.

Limitations

There were a few limitation in our study that we would like to highlight. Firstly, the study was restricted by its cross-sectional nature of patients attending a single center and its outcomes may not be generalizable to the whole population as a whole. However, our institute has a wide range of population drainage from various parts of the country as the center is one of a main interventional cardiology center in Sri Lanka. Secondly, we have studied disease free coronary angiograms in patients who had vascular risk factors and some other reasons to undergo the stress tests. Therefore, such a selected sample may not solely represent an absolutely 'normal' population. However, performing diagnostic coronary angiography on apparently healthy controls would be unethical and unfeasible as this investigation uses ionizing radiation. Finally, our QCA technique measures the luminogram rather than the actual artery size, which would be slightly larger, and this may have contributed to undersize the vessel diameter compared to actual anatomical arterial size.

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Conflicts of interests: None

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Research

A descriptive interventional study analyzing the effectiveness of cardiac rehabilitation program for patients with heart failure at the Institute of Cardiology, National Hospital of Sri Lanka.

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Abstract

Introduction: Cardiac rehabilitation is a vital component of comprehensive cardiac care. Cardiac rehabilitation is a proven treatment modality for the patients with heart failure. The objective of this study was to assess the effectiveness of the cardiac rehabilitation (CR) programme conducted at the Institute of Cardiology, National Hospital of Sri Lanka.

Method: This study was designed as a descriptive interventional study. Patients with ejection fraction (EF) lower than 40% were enrolled into the cardiac rehabilitation programme using the convenient sampling method. Clinical status, knowledge, exercise tolerance of the patients were assessed before and after the CR programme.

Results: Hundred and six (106) patients were followed up in this study. Majority (n=67, 63.20%) of the patients with low EF had background ischaemic heart disease. Mean ejection fraction before and after the CR was 31.94% and 41.47% respectively ($p< 0.01$). Six minute walking distance before and after the CR was 339m and 440.8m respectively ($p< 0.01$). Mean hospital admission rate of 1.89 times for a period of 6 months prior to CR was reduced to 0.61($p< 0.01$). Before cardiac rehabilitation the overall awareness regarding disease and therapy had a mean score of 0.54 (SD 1.20). The study population was reassessed after 6 months of CR, and awareness rose to a mean of 5.63 (SD1.21) ($p< 0.01$)

Discussion and Conclusion: Patients who underwent the Cardiac rehabilitation programme demonstrated improvement in clinical status, knowledge and exercise tolerance. The effectiveness of the cardiac rehabilitation can be appreciated by the reduction in morbidity by reducing hospital admissions. Hence, the cardiac rehabilitation programme conducted at the Institute of Cardiology is proven to be effective and it helps improve patient outcome.

Keywords: Heart failure, Cardiac rehabilitation, Exercise tolerance, Ejection fraction.

Introduction

Cardiovascular disease remains the leading cause of death worldwide as a non-communicable disease as per statistics of the World Health Organization [(1)]. Sri Lanka, belonging to South Asian region, also has a high prevalence of ischaemic heart disease [(2)]. Two decades ago, though cardiac care was available, cardiac rehabilitation remained as an outlandish concept. The recognition of cardiac rehabilitation (CR) as an integral component of comprehensive cardiac care was evident through numerous publications. Researchers have demonstrated that CR resulted in overall improvement in morbidity and mortality. These evidences paved the way for the establishment of the CR program 17 years ago at the Institute of Cardiology, National Hospital of Sri Lanka (NHSL). Since then more than 5000 patients have benefitted from the comprehensive cardiac care along with cardiac rehabilitation [(3)]. However, the assessment of the future direction and effectiveness of this CR program was a felt need, for long term sustainability. The purpose of this study was to assess the effectiveness of the CR program at the Institute of Cardiology NHSL.

Methods

This study was designed as a descriptive longitudinal study with pre and post evaluation components. CR program was considered as the intervention in this study. Patients with acute coronary syndrome with a low ejection fraction (EF- less than 40%) during echo assessment either at clinic or during follow up were considered eligible candidates and underwent comprehensive echo assessment and were referred to the CR program. Patients were enrolled in to the study according to the convenience of patients. Informed consent was obtained prior to the enrollment. The patients were registered and were evaluated by a trained and experienced multi-disciplinary team including consultant cardiologist, medical officers, nurses, physiotherapists, pharmacists, psychologists. The patient along with a family member is then enrolled into a 6 week programme of moderate intensity cardiac rehabilitation targeted at improving heart failure as per the world health organization standards.

This involves education, structured aerobic exercise, counselling along with question and answer sessions. This patient population is the study populace for this research. Patient's basic demographic details and personal medical details were recorded. These patients were regularly followed up along the course of a 6 week cardiac rehabilitation program and reassessed at 6 months following the completion of the CR program. Data including EF (assessed via biplane Simpson's method using a Phillips IE 33 echo machine) before and after the CR program, knowledge regarding disease and management, 6 minute walking distance, BORG rating of perceived exertion and symptoms according to the New York Heart Association (NYHA) functional classification on shortness of breath along with compliance to medication (in three separate categories defined as good, intermediate and poor) were assessed before and after the program.

Results

Total number of subjects enrolled into the study was 106. Majority of the study participants were males (n=74, 69.8%). The average age of the study populace was 55.75 years (SD= 10.67). The average body mass index (BMI) was 22.44 kg/m2 (SD = 3.26). Majority had an education level up to GCE ordinary levels, (n=67, 63.2%) and only (n=25, 23.6%) educated up to GCE advanced level. Most of the study population (n=61, 57.5%) were currently unemployed and (n=73, 68.9%) accepted they had difficulties (attending or completing due tasks) in their occupation due to their illness. Majority of the patients(n=99,93.4 %) accepted they required the aid of a caregiver. Most, (n=102, 97.2%) of the study subjects did not have clinical feature of depression. More than half of the study population (n=58,54.7%) were ex-smokers and (n=56,52.8%) had consumed alcohol. Less than half of the study population (n=47,44.43%) had multiple non communicable disease as comorbidities where 33.96%, 30.18%, 63.2% were diagnosed with diabetics, hypertension and ischaemic heart disease respectively (Table 1).

Table 1: Description of the study population

Parameter	Descriptive statistics (n, %, mean, SD)*
Gender:	
Male	74 (69.8%)
Female	32 (30.2%)
Age:	55.7 years (SD=10.67)
Ethnicity:	
Sinhala	84 (79.2%)
Muslim	13 (12.5%)
Other	09 (8.4%)
Marital Status	
Married	100 (94.5%)
Never married	06 (5.7%)
Education	
Grade 5 or below	09 (8.5%)
Up to O/L	68 (64.1%)
A/L or higher	29 (27.4%)
Occupation	
Yes	62 (58.5%)
No	44 (41.5%)
Smoking:	
Current or Ex- Smoker	58 (54.7%)
Never	48 (45.3%)
Alcohol:	
Current or Ex- User	56 (52.8%)
Never	50 (47.2)
P/H of NCD	
No	16 (15.1%)
Yes	90 (84.9%)

The mean EFs before and after the CR program were 31.94% (SD 6.73) and 41.47% (SD 11.08) respectively. When analyzed with paired sample T test these differences were statistically significant at 5% level. BORG scale was used to assess patient's rating of perceived exertion. Prior to CR the mean BORG scale score was 13.28 and following CR the mean value was 12.1. When analyzed with paired sample T test these differences were statically significant at 5% level. Similarly 6 minute walking distance was assessed and before CR the mean distance was 339m which following CR rose to 440.8m, a 30% increase from the base line distance. When analyzed with paired sample T test these differences were statically significant at 5% level.

Patients were regularly followed up. At 6 months review n=70(66%) maintained follow-up. N=28(26.4%) dropped out and n=3 (2.8%) died. Knowledge & awareness regarding disease and treatment was also analyzed.

A seven point scale was used with each question being given 1 point. Before cardiac rehabilitation the overall awareness mean score was 0.54 (SD 1.20). The study population was reassessed again 6 months later in regard to knowledge, the overall awareness mean score rose to 5.63 (SD 1.21). Prior to cardiac rehabilitation the mean number of admissions were 1.89 (SD 3.1) and 6 months after cardiac rehabilitation the mean number of hospital admission were 0.61 (SD 1.46). When comparing the significance with one sample T test the P value was 0.00 (P<0.05). (Table 2) Prior to cardiac rehabilitation most of the subjects n=47 (44.3%) belonged to NYHA III and n=11 (10.4%) belonged to NYHA IV. 6 months post cardiac rehabilitation (CR) only n=12 belonged to NYHA III while none belonged to NYHA IV. Prior to CR, 17% had poor compliance and this was reduced to 4% following the CR (Table 3).

Table 2: Comparison of parameters – before and after the CR program (paired t test)

Parameter	Mean difference	Number of pairs	Statistics
Ejection Fraction	9.1 %	86	t= -8.181, df=85 p<0.001
Awareness and Knowledge	5.115	87	t= -33.083, df=86 p<0.001
Hospital admissions	1.280	75	t=3.651, df=84 p<0.001
BORG scale	1.080	88	t=9.425, df=87 p<0.001
6 MWD	96.932	88	t=-11.649, df=87 p<0.001

Table 3: Drug compliance before and after cardiac rehabilitation

	Before cardiac rehabilitation		After cardiac rehabilitation	
	Number	**%**	**Number**	**%**
Compliance				
Good	69	65.71%	50	66.66%
Intermediate	18	17.14%	22	29.33%
Poor	18	17.14%	3	4%
Total	105		75	

Discussion

In addition to established drug therapy, CR is a recognized modality of therapy for a broad range of cardiovascular diseases including heart failure [3]. CR of heart failure patients has shown to improve morbidity and mortality. Our study mainly focused on the assessment of short term outcomes of those who are following CR programme at Institute of Cardiology, NHSL.

Our study analysis revealed that CR in HF resulted in improvement in patient perceived symptoms as both NYHA and BORG scale showed overall improvement with reduction in BORG scale& improvement in NYHA class in most of the study. These findings are consistent with large scale studies which demonstrate class improvements in NYHA[4]. There are evidences to support the objective improvement of 6 minute walking distance test [5].

Patient education is considered a core component of CR (6). The program also improved knowledge level among our patients and this remained sustained even 6 months later, suggesting that CR education programmes are effective. We attempted to assess whether patients education level could have affect the improvement in their knowledge but statistical analysis failed to delineate any significant relationship. However, considering the overall improvement from base line knowledge one could surmise we should educate the patients irrespective of their educational level as studies have shown that knowledge may ultimately facilitate behavioral change that facilitate improvement in lives of patients with HF[6]. This is clearly seen as an improvement of patient's compliance with oral medication. The number of hospital admissions following CR also declined, stressing the importance of improving patient knowledge as this creates an overall cost effective health care system for patients with heart failure.

Our study population showed significant improvement in systolic ejection fraction. We cannot categorically attribute CR as the sole cause for this improvement as all patients underwent optimization and up titration of their drug therapies. But it's reassuring to note the CR may have had a contributory role in improving cardiac function as studies have proven in settings elsewhere [7].

Conclusion

The cardiac rehabilitation program conducted at the Institute of Cardiology , National Hospital of Sri Lanka seems be effective and has a positive impact on patients with heart failure with overall improvement in patients symptoms and clinical state along with sustained improvement in patient knowledge base regarding their disease and treatment. Cardiac rehabilitation will help create and sustain a cost effective health care system for patient with heart failure as well.

Conflicts of interests: None

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Research

Survival patterns and development of late cardiac events following Coronary Artery Bypass Grafting (CABG) surgery

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Abstract

Introduction: Coronary Artery Bypass Grafting (CABG) is increasingly becoming popular as a main stay treatment modality for coronary artery disease. Aim of this study is to assess event free survival from late cardiac events and factors influencing such survival patterns.

Methods: Retrospective data was prospectively analysed in a descriptive study design. Post CABG patients attending the Cardiology Clinic at the National Hospital of Sri Lanka (NHSL) were recruited consecutively and health records were traced up to the point of CABG. Records were traced prospectively to explore predefined cardiac events viz. unstable angina, myocardial infarction, arrhythmia and heart failure. Time duration in months was calculated to the most proximal event from the date of CABG. Socio economic data and health profile factors were taken into Cox Regression analysis.

Results: Total of 421 CABG patients were studied and the 5 years and 10 years event free survival was found to be 79.1% and 58.1% respectively. Sex difference of the survival rates was statistically not significant. Cox regression analysis yielded non employment (HR 1.77, 95% CI: 1.02 – 3.07; p=0.043), positive family history for hypertension (HR 2.54, 95% CI: 1.19 – 5.04, P= 0.016), Urgent CABG (HR 1.77, 95% CI: 1.12 – 2.81; p=0.015) and ADL with help (HR 0.09, 95% CI: 0.019 – 0.428; p=0.002) as statistically significant factors associated with survival.

Conclusion: Follow up plan of CABG patients should be based on anticipation of late cardiac events.

Keywords: Survival, CABG, Cardiac events

Introduction

Cardiovascular disease (CVD) is recognized as the leading cause of death worldwide. CVD accounts for 17.9 million deaths (31% of all global deaths) annually [(1)]. Coronary artery bypass graft (CABG) surgery has been proven to be the best option available for treatment of multi-vessel coronary artery disease. CABG has also been a time-tested surgical intervention to relieve angina and to preserve myocardial function after acute myocardial infarction [(2, 3)].

CABG has demonstrated a clear reduction in post –operative mortality and increased long-term survival[(4)]. In the recent years, operative procedures of the CABG have sustained many improvements to deliver better results. Today the CABG is carried out even in older patients as a safe procedure. Though CABG is reported to have high reoperation rate especially in elderly patients, there are surgical advancements recently added including more arterial graft utilization and off-pump surgery [(4)].

CABG was introduced to Sri Lanka in early 1980's. Today both the private sector and state sector tertiary care institutions carry out CABG operations. However, the data evaluation on post CABG survival and development of cardiac events are limited in Sri Lanka. The objective of this study is to describe survival patterns of the CABG patients in relation to development of late cardiac events and factors associated thereof.

Methods

This was designed as a retrospective, descriptive study with an analytical component to examine factors associated with late cardiac events and time. Data were collected from the post CABG patients attending the Cardiology clinics at the Institute of Cardiology, National Hospital Sri Lanka (NHSL). Patients who underwent CABG within a period of 12 months or less, critically ill and psychologically unsound were excluded from the study. Survival was calculated up to late cardiac events, not to mortality. Late cardiac events were defined as development of unstable angina (UA), Myocardial infarction (STEMI and NSTEMI), Heart Failure (HF) and Arrhythmia as recorded in medical records 1 year following the CABG. Time duration was calculated in months from the date of surgery to the most proximal point of the occurrence of any of the cardiac events as defined. Kaplan- Meier survival estimations were carried out censoring the data points where clinical end point did not occur before the study end date. Cox regression analysis was carried out to examine socio demographic factors associated with time – cardiac event data.

Results

Total of 421 CABG patients were enrolled in the study. Socio – demographic characteristics of the study group are given in table 1.

Table 1: Socio demographic characteristics of CABG patients (n=421)

Characteristic	Statistics (Frequency, Percentage, Mean, SD)
Sex:	
Male	314 (74.6)
Female	107 (25.4)
Age	63.2 years (SD:7.86)
Ethnicity:	
Sinhala	370 (87.9)
Tamil	20 (4.8)
Muslim	31 (7.4)
Marital status:	
Married	369 (87.6)
Widowed	37 (8.8)
Other	15 (3.5)
***Education**	
No formal education	16 (3.8)
Up to grade 5	101 (24.0)
Up to grade 10	232 (55.1)
O/L and higher	65 (15.4)
***Employment:**	
Yes	155 (36.8)
No	261 (62.0)
***Income:**	
Adequate	316 (75.1)
Inadequate	98 (23.3)
***Family History:**	
MI (Myocardial Infarction)	63 (15.0)
DM (Diabetes mellitus)	26 (6.2)
HPT (Hypertension)	30 (7.1)
Dyslipidemia	22 (5.2)
Combination of 2 or more NCD [1] s	135 (32.1)
None	130 (30.9)
***PMH:**	
DM	26 (6.2)
HPT	54 (12.8)
Combination of 2 or more	260(61.8)
None	43 (10.2)
***Smoking (Before CABG):**	
Yes	177 (42.0)
No	239 (56.8)
***Alcohol (Before CABG):**	
Yes	281 (66.7)
No	134 (31.8)
***Activities of Daily Living (ADL):**	
Independent	266 (63.2)
Need help	141 (33.5)
Dependent	03 (0.7)

***Not totaled to 421 due to missing data** **[1]NCDs – Non Communicable Diseases.**

The majority who had undergone CABG were males. Majority of the study population were elderly. Nearly 70% and 90% of the respondents had reported of presence of Non- Communicable Diseases (NCDs) in their families and were recorded to have had an NCD in the past medical history respectively. Majority of the respondents were independent on ADL and less than 1% of them were dependent.

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Table 2: Cardiac profile of the respondents prior to CABG

*Cardiac profile	Frequency (Percentage)
Diagnosis prior to CABG:	
Stable Angina	66 (15.7)
STEMI (ST elevated MI)	90 (21.4)
NSTEMI (Non ST elevated MI)	130 (30.9)
Unstable Angina	92 (21.9)
Mixed Diagnosis	40 (9.5)
Ex ECG	
Positive	288 (68.4)
Not done	120 (28.5)
Negative	04 (1.0)
Inconclusive	02 (0.5)
PCI before CABG	12 (2.9)
Valvular lesions	
None	306 (72.7)
MR (Mitral Regurgitation)	84 (20.0)
AR (Aortic Regurgitation)	4 (1.0)
AS (Aortic Stenosis)	4 (1.0)
Combinations	23 (5.4)
Number of diseased Vessels	
One	13 (3.1)
Two	55 (13.1)
Three	350 (83.1)
Types of vessel involved	
LMCA (Left main coronary artery)	120 (28.5)
LAD (Left Anterior Descending)	404 (96.0)
LCX (Left Circumflex)	365 (86.7)
RI (Ramus Intermidius)	37 (8.8)
RCA (Right coronary Artery)	361 (85.7)
Pump status	
On pump	247 (60.0)
Off pump	40 (9.5)
Not stated	125 (29.7)
Late Cardiac events	
Total	102 (25.4)
UA (Unstable Angina)	56 (13.3)
STEMI	2 (0.5)
NSTEMI	13 (3.1)
HF	36 (8.6)
Arrhythmia	15 (3.6)

***Not totaled to 421 due to missing data or multiple answers**

Majority of the study population had no valvular lesions but had multi vessel disease. Commonly involved vessels were LAD, LCX and RCA. It was noted that less than 3% of the respondents had undergone PCI before the CABG and the 'on pump' surgeries reported were 60%. More than a quarter of the participants had experienced one or more 'late cardiac events'.

Table 3: Five year and Ten year Survival free of cardiac events

Survival period and survival time in months	Percentage survived/Statistic	95% CI	Significance within sex
Overall Survival			
5 yr	79.1	75.1 – 84.1	
10 yr	58.1	49.9 – 66.3	
Mean survival time	145.3	121.2 – 160.3	Mental –Cox, p= 0.508
Median survival time	144	118.3 – 169.7	Breslow p=0.447
Male			Tarone-Ware p=0.448
5yr	81.0	75.9 – 86.1	
10yr	57.0	47.4 – 61.6	
Mean survival time	146.6	121. 7 – 163.5	
Median survival time	145	105.9 – 184.1	
Female			
5yr	75.1	64.6 – 85.4	
10yr	62.4	47.9 – 76.9	
Mean survival time	124.7	105.9 – 143.6	
Median survival time	144	138.6 – 149.3	

5 year survival rate up to the development of defined clinical end point in both males and females were slightly higher than 75%. Though the ten years survival rate was better in females, differences in survival rates of both sexes are not statistically significant. Figure 1, depicts survival function for both sexes in the study population.

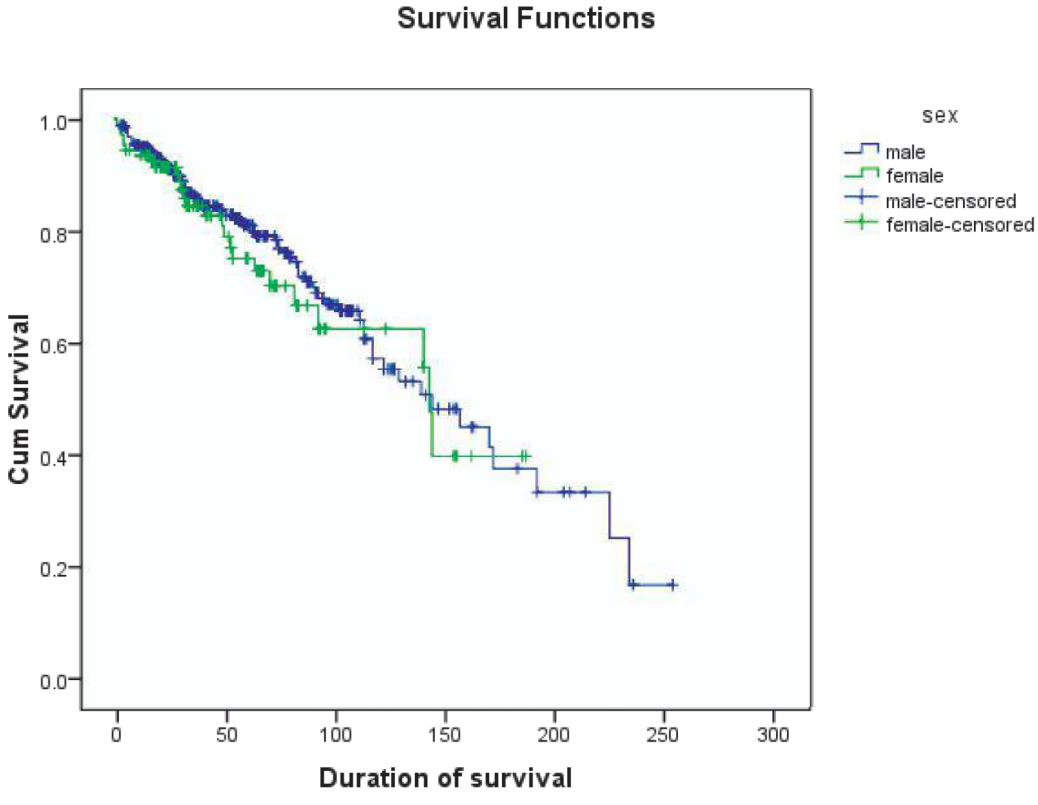

Figure 1: Survival function according to the sex of the participants

Table 4: factors associated with the survival up to the development of cardiac events

Factor (reference Category)	Hazard Ratio (HR)	95% Confidence Interval (CI) for HR	Significance
Male Sex (Female)	1.047	0.553 – 1.981	0.889
Age less than 60 (60 years or more)	1.575	0.935 – 2.652	0.087
Education			
Grade 5 or below	0.680	0.162 – 2.841	0.597
Grade 10 or below	0.508	0.132 – 1.949	0.324
(*AL or higher)			
Non Employment (Currently employed)	1.77	1.02 – 3.07	**0.043**
Positive Family history (FH) for Hypertension (Negative FH for NCDs)	2.54	1.19 – 5.04	**0.016**
Non Smoking (Current smokers)	1.199	0.654 – 2.199	0.556
Non- Alcohol (Current Alcohol users)	0.906	0.497 – 1.650	0.747
Light work (Unable to perform)			
Independent	0.582	0.141 – 2.407	0.455
With help	0.701	0.258 – 1.903	0.485
Heavy work (Unable to perform)			
Independent	0.907	0.262 – 3.141	0.878
With help	0.632	0.282 – 1.416	0.265
Urgent CABG (Elective)	1.77	1.117 – 2.809	**0.015**
ADL (Dependent)			
Independent	0.214	0.035 – 1.296	0.093
With help	0.09	0.019 – 0.428	**0.002**

***AL – Advanced level ADL – Activities of Daily Living**

According to the table 4, non- employment, family history of hypertension and urgent CABGs bear a significantly greater hazard compared to the reference category. Though it is not statistically significant, young age group had more cardiac events than the elderly. Partial ADL independency was shown to be a protective factor against the development of late cardiac complications.

Discussion

Socio demographic profile of the patients under study had shown male sex preponderance and representation of elderly age group. Senol-Durak et al reported similar demographic characteristics of study participants who underwent psychological assessment following myocardial infarction [5]. Nearly 70% of the present study group had positive history for one or more NCDs in their families. Harpaz and colleagues pointed out that the patients with a positive family history developed their first myocardial infarction early. This is more than 1 decade earlier in comparison to those without such a history. The severity and the extent of their CAD are similar to the older patients without a positive family history [6].

In this study, CABG rates are relatively low in poorly educated and employed group. In a study done in Iran, it was reported that the proportion of patients with higher educational qualifications is greater in CABG group compared to the PCI group[7]. Nearly one third of our study population did not have a family history of NCDs while 10% reported negative past history for NCDs. Alcohol consumption and smoking rates were greater in this group compared to the Sri Lankan figures reported previously [8]. In addition, the smoking rate in the Iranian study was nearly 35% and was well below to the figure of our study.

Pre CABG diagnosis spreads out more or less in proportions among all types of myocardial infarction related diagnosis. Only very few (<3%) had under gone PCI before CABG. Majority of this study had no structural valvular lesions. Majority had multi vessel disease. Commonly involved vessels were LAD, LCX and RCA.

Estimation of survival time free of late cardiac events

Five and ten year survival free of predefined cardiac events was calculated for total and both sexes in this study. Occurrence of any of the predefined cardiac events after one year of CABG is taken as a late event. This was done by following the records prospectively from the date of surgery. This study showed that more than 75% of the CABG patients live their first 5 years without significant cardiac events. However, this rate dropped nearly to 60% within next 5 years. Increasing trend on reporting more cardiac events should be anticipated in patients after the 5th post CABG year.

According to the cox regression analysis of the current study, non -employment bears greater hazard to develop cardiac events compared to the employed counterparts. Family history of hypertension compared to negative family history and CABGs in urgent nature compared to electives also bear greater hazards of developing late cardiac events. In this study, performing ADL with help was a significant protective factor compared to the inability. Restoration of functional status in post CABG patients should be considered by means of cardiac rehabilitation or similar process in order to minimize the occurrence of late cardiac events. Patients with positive family history should be followed up closely for late cardiac events.

Our findings are supported by Myers et al where they assessed the long -term survival of 8221 primary CABG patients in Coronary Artery Surgery Study (CASS) data base from 15 centers of North America and revealed that 90%,74%,56% survival at 5 years, 10 years and 15 years respectively. They further reported that late hazard is associated with young age (less than 35 years), obesity, past-history of myocardial infarction, smoking, LMCA and LAD disease, the use of diuretics and only use of venous grafts during surgery [9].

In a recent study done by Geissler and Aggestrup, it was reported that 33% of CABG patients were re-hospitalized due to acute myocardial infarction, arrhythmia or angina [10]. Some of the risk factors for re-hospitalization were female gender, age and diabetes. Thus, a significant number of patients are re-hospitalized following CABG. Similarly, our study too suggests nearly 20% of post CABG patients seek medical advice in the second 5 years of CABG which is reflected as drop in survival rates due to the development of cardiac events.

Cervera et al stated that the limited functional ability was not taken as an independent risk factor for early postoperative CABG complications or death. There were no significant differences in long term survival depending on functional status of the CABG patients [11]. However, ADL independency reduces risk for development of cardiac events as reflected in our study.

Current study warrants the adoption of anticipatory follow up strategies for CABG patients giving priority to establish functional status or to restore livelihoods. Cardiac rehabilitation of CABG patients should be considered seriously and effectiveness of such interventions should be evaluated against survival profile of the patients. Limited sample size, recording inaccuracies, physician bias and loss to follow up were the major limitations of this study.

Conflicts of interests: None

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Milestones

The Changing Scenario of Heart Disease in Children in Sri Lanka

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Introduction

I would like to describe the changes I have personally experienced in the field of heart disease in children, during the last fifty years of my academic life. During my student days in the 1960s, acute rheumatic heart disease (RHD) was rampant together with all varieties of congenital heart disease (CHD). There were a few cases of cardiomyopathies and arrhythmias. However Kawasaki disease was not heard of. There were few patients with CHD and RHD who developed infective endocarditis.

Congenital Heart Disease (CHD)

It is estimated that between 2427-3236 children are born with CHD each year and two-thirds would require intervention or surgery [(1)]; if properly treated 85-95% of such patients would reach adulthood [(2)].

In one of the first studies on CHD, among 555 consecutive cases (from infancy to 60 years), atrial septal defects (ASDs) were the commonest (174 patients), of whom 92 patients were over 16 years of age accounting for 48.7% of adults with CHD. The second commonest abnormality was ventricular septal defect (VSD), followed by patent ductus arteriosus (PDA). Under 16 years of age the commonest type was VSD. Persistent truncus arteriosus had been unusually common, while coarctation of aorta and aortic stenosis had been rare compared to other defects [(3)].

The incidence of CHD has somewhat declined after the administration of the rubella vaccine prior to conception and its introduction to the national immunization schedule in the mid-1990s.

In 1950, Dr ATS Paul was appointed as the cardio-thoracic surgeon to the General Hospital, Colombo. He had to deal with many patients with RHD and tuberculosis.

ASDs were closed under hypothermia after being diagnosed clinically (soft systolic murmur in pulmonary area with a fixed split second sound) and confirmed later with an ECG, CXR and cardiac catheterization. PDAs were ligated as well. Most cases of cyanotic CHD were not touched except for a few patients with Tetralogy of Fallot (ToF), who underwent palliative surgery. As students we saw young adults with shaven heads, cyanosed and with gross finger clubbing, walking with a hemiplegic gait, in the neurosurgical unit, and awaiting drainage of a cerebral abscess after paradoxical embolism. Those were patients with un-operated ToF. Such was their unfortunate fate until about the mid-1990s, when total corrections were successfully performed at the Teaching Hospital Sri Jayawardenepura. When patients with ventricular septal defects (VSDs) were referred to adult cardio-thoracic surgeons, we were advised to refer them when they attained a weight of 15kg. Most of them developed Eisenmenger Syndrome or perished after developing recurrent lower respiratory tract infections, while awaiting surgery.

Patients with ASDs were placed on a waiting list and asked to wait until 4 to 5 years of age. Sometimes on the scheduled date, their surgery was postponed further because an adult with coronary heart disease had to be accommodated for emergency by-pass surgery. They too used to develop Eisenmenger Syndrome and eventually become inoperable.

In the Professorial Paediatric Unit (PPU) at Lady Ridgeway Hospital (LRH), CHD was found to be the second commonest cause of death, accounting for 16%-30.8% of deaths, the commonest being lower respiratory tract infections[(4,5,)]. Two-dimensional echocardiography was introduced to the country in 1983 and thereby accuracy of diagnosis of CHD improved but surgical intervention was minimal due to lack of facilities. Since the 1990s facilities for diagnosis and treatment of CHD has dramatically improved at LRH and few other centers such as at the Teaching Hospitals in Karapitiya and Sri Jayawardenepura.

During a period of 12 months (August 1998 to August 1999), in a prospective study carried out in the Professorial Paediatric Unit (PPU) at the LRH, a total of 102 patients with CHD were admitted and investigated further. Sixty nine (67.6%) patients had acyanotic CHD and 33 (32.4%) patients had cyanotic CHD. Of these patients, 22 had a VSD and 10 had ToF. Only 12 patients underwent surgery due to lack of facilities (10 in Sri Lanka and 2 in India). Case fatality rate was 18.6% [6].Very often patients with cyanotic and other forms of complex CHD were sent to centers in South India, at great cost and inconvenience to patients.

Since the 1990s the facilities for diagnosis and treatment of CHD has dramatically improved at LRH and in few other centers such as the Teaching Hospitals at Karapitiya and Sri Jayewardenepura. The Cardiology Unit at the LRH was established in 1999, with the appointment of a permanent paediatric cardiologist, Dr. S Narenthiran. The infrastructure facilities and human resources gradually improved thereafter [1].

Device closure of ASD was the commonest catheter intervention performed in that unit. From January 2006 to April 2013, a total of 1716 patients had been taken up for device closure of ASD; it had been successful in 1612(94%) and unsuccessful in 95(5.5%). During first three years the initial success rate was 75% but improved to 97% during the next three years [7]. These results are remarkable for a fledgling unit.

Rheumatic Heart Disease (RHD)

Until the early 1950s, acute rheumatic fever (ARF) was prevalent in western countries as well as in developing countries. During the next seven decades there has been an exponential decline of ARF in developed countries such as the United States[8]. However in the mid -1980s there were few isolated outbreaks in the US. In one such outbreak in an inter-mountainous area in the US, between January 1985 and June 1986, 74 children had developed ARF and 91% had evidence of carditis on echocardiography [9]. In Sri Lanka until about the 1980s, RHD was the predominant type of acquired heart disease in children and young adults. According to records maintained in the Registrar General's Department, there has been a significant decline in the mortality rate due to RHD (3.6/100,000 in 1971, 1.6/100,000 in 1977 and 0.4/100,000 in 1989)[10] over the years.

Since then, Kawasaki Disease has gradually surpassed RHD in our country except perhaps in Jaffna. During a period of three years in the Jaffna Teaching Hospital cardiology unit, out of echocardiograms done in 11,956 patients, 38% (4449) children who were newly referred had abnormal findings on echocardiography. Of these children with abnormalities on echocardiography, 89 children were diagnosed with RHD. A total of 123 children had RHD (34 new cases and 89 established patients) [11].

At LRH, the PPU conducts a bi-weekly clinic for patients with rheumatic fever to administer benzathine penicillin therapy for prophylaxis. Over one hundred patients used to attend this clinic since the 1960s for several decades. During a five year period between1994 to 1999, ninety one (91) patients with acute rheumatic fever had been managed in the PPU at LRH and 28% of patients had evidence of RHD on echocardiography. During the five year period between 2004 to 2009, only 29 patients had been admitted to the same unit and 28% of patients had evidence of RHD on echocardiography [12].

The number of patients with ARF attending the rheumatic fever clinic at LRH between 2013 and 2018, are shown in Table 1. The increase in the number of new cases of ARF in 2018, is a factor for some concern.

Table 1- Numbers of patients with ARF, attending the rheumatic fever clinic at the Lady Ridgeway Hospital (LRH)

Year	< 5 years	5-10 years	>10years	Total
2013	0	5	0	5
2014	4	7	0	11
2015	2	10	1	13
2016	2	10	3	15
2017	0	9	3	12
2018	1	20	17	38
Total				94

The probable reasons for the decline in the incidence of ARF, are better housing conditions and the more frequent use of antibiotics for the management of upper respiratory tract infections (primary prophylaxis).

Kawasaki Disease
(Mucocutaneous Lymphadenopathy Syndrome)

Kawasaki Disease was described for the first time by a Japanese doctor working for the Red Cross, in an obscure Japanese medical journal [14].

It took over one or two more decades for it to be a well- known entity in other countries. During the pre-measles vaccine era, when outbreaks of measles were rampant, I very well remember many patients who had a measles like illness with very high pyrexia, generalized maculopapular rash, lymphadenopathy, conjunctivitis and cheilosis, who were managed as complicated cases of measles but were probably patients with Kawasaki Disease. In addition to the classical clinical features, these patients have a thrombocytosis, with the platelet counts sometimes exceeding a million. On ultrasonography of the abdomen, they often have hydrops of the gall bladder. On echocardiography coronary arteritis is detected sometimes leading to myocardial infarction. Early use of intra venous immunoglobulin prevents cardiac complications.

Kawasaki Disease was first described in Sri Lanka in the 1980s from Galle [15]. Since then 19 patients were reported in a study done in the PPU at the LRH over a period of eleven months [16]. Thereafter three patients with Kawasaki Shock Syndrome were reported from the Teaching Hospital Jaffna [17] as well as many other case reports from rest of the country.

Other types of heart disease

Cardiomyopathies which are sometimes associated with septic syndromes but are rarely seen. Associated arrhythmias are also rarely seen. Sometimes viral fevers are complicated with myocarditis leading to ventricular dysfunction resulting in heart failure. Few such cases are encountered during epidemics of dengue fever.

Infective Endocarditis (IE)

During the earlier decades infective endocarditis used to complicate patients with CHD and RHD. At present it is rarely seen. It may be due to better oral hygiene and to regular school medical inspections, frequent use of antibiotics and antibiotic prophylaxis prior to dental and surgical procedures.

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Perspectives In Medicine

Responding to the Growing Challenges of Non-communicable Diseases in Sri Lanka: Reorganizing Primary Care under Limited Resources and Fiscal Space

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Abstract

Despite its history of strong performance at low cost, Sri Lanka's healthcare system is facing multiple challenges in the face of a rapidly ageing population and the growing burden of non-communicable diseases (NCDs). Responding to these issues requires a commitment for higher spending and a more efficient service delivery system. Given the limited opportunity for budgetary increase, fiscal space may be sought by reduced disease burden and efficiency gains in the health system. Curative services for NCDs at the primary level are limited to episodic management not featuring the people-centered continuum of care. This diverts the patients to seek direct care from higher level institutions; a major source of inefficiency of the health system. In response to these limitations, Sri Lanka is undertaking an ambitious agenda to strengthen and expand the primary health care (PHC) services from the ground up. The report 'Reorganizing Primary Health Care in Sri Lanka' by the Ministry of Health, Nutrition and Indigenous Medicine (MoH) makes a case for why, and how, Sri Lanka must reimagine its PHC systems to address the growing challenges associated with NCDs. The five-year 'Primary Health Care System Strengthening Project' is implemented by the MoH with assistance from the World Bank, aiming to increase the utilization of PHC services emphasizing on the early detection and management of NCDs. The project is expected to improve the efficiency of the health systems by shifting a significant portion of NCD care to be provided at the primary level, which in turn will expand the fiscal space for the government to use the freed-up resources in a more effective way.

Keywords: Non Communicable Diseases (NCD), Primary Health Care (PHC), Disability adjusted Life Years (DALYs).Gross Domestic Product (GDP),Ministry of Health (MoH)

Introduction

Sri Lanka is well regarded as having favourable health indicators for its income level. Maternal and child health outcomes are markedly better compared to other countries in the region with similar economic status. Infant and under-five mortality rates were 9.1 and 10.6 per 1,000 live births in 2018, respectively, and a maternal mortality ratio of 39.3 per 100,000 live births in 2017 [(1)]. One of the underlying contributing factors is its effective health system that has demonstrated strong performance at low cost [(2)]. As a result, Sri Lanka is now hosting one of the fastest aging populations in the region as well as among other middle-income countries.

Between 1981 and 2012 the proportion of the population above 60 years of age almost doubled from 6.6 percent to 12.4 percent [(3)]. Life expectancy at birth was 77 years in 2017; significantly higher than the South Asian and Southeast Asian average of 69 and 73 years, respectively [(4)]. Nonetheless, the healthy life expectancy at birth in 2017 was 68 years, 8 years lower than the crude life expectancy [(4)]. This is primarily a result of the increasing burden of non-communicable diseases (NCDs) that now accounts for 85% of total morbidity [(4)]. Figure 1 provides the share of NCDs in aggregate disability-adjusted life years (DALYs) over time, which has risen from 53% in 1990 to 77% in 2017, and the total DALYs from NCDs have increased by 36%.

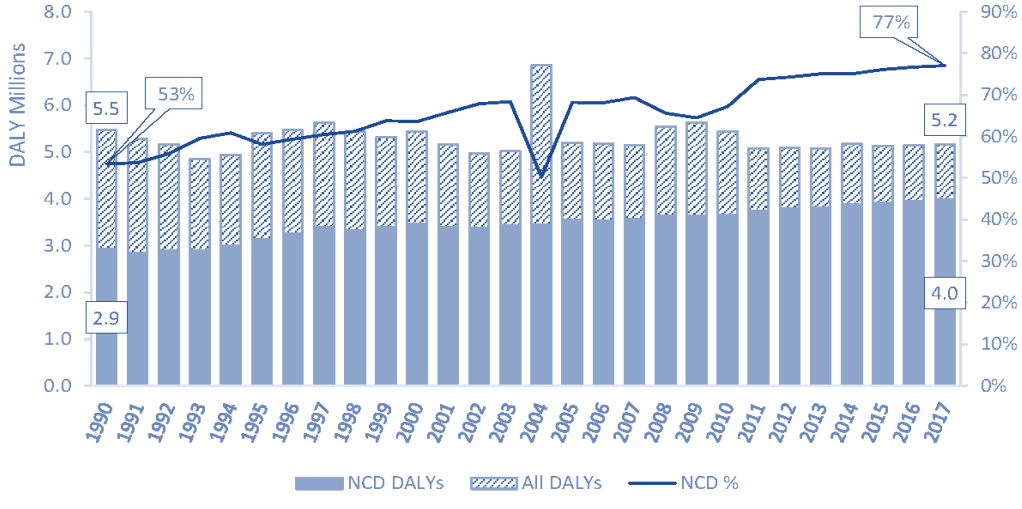

Figure 1: Increasing burden of NCDs over time in Sri Lanka (Source: GBD 2017 (4))

Rising NCDs puts pressure on the existing health system that has not been well equipped to cater to NCDs that require more long-term care and follow up of patients. Responding to the changing disease patterns and adapting to an ageing population requires a greater financial commitment and a more efficient service delivery system in health to maximize the use of available resources.

Macro Fiscal Profile and Health Financing

Since the end of the 26-year civil war in 2009, Sri Lanka's economy has enjoyed a rapid growth at an average rate of approximately six percent between 2010 and 2016 [5]. This reflects a peace dividend and a determined policy thrust toward reconstruction and growth, although there were some signs of slowdown in recent years [6]. The industry is transitioning from a previously predominant rural-based economy to a more urbanized one oriented towards manufacturing and services. The current Government that came into power in 2015 envisions promoting a globally competitive export-led economy with an emphasis on governance and inclusion.

However, Sri Lanka's fiscal position is undermined by the low revenues, limiting critical development spending and making it vulnerable to adverse shocks. It has one of the lowest tax-GDP ratios in the world (12.5 percent in 2017) particularly for its income level [5]. The major reasons for the low level of revenues are a small tax base (less than seven percent of the labour force and formal establishments pay income tax [7], reductions in statutory rates without commensurate efforts to expand the tax base, inefficiencies in administration, and numerous exemptions. Low revenues combined with largely nondiscretionary expenditures in salary bill, transfers, and interest payments have constrained critical development spending including expenditure on health, education, and social protection.

The health system of Sri Lanka is managed at a relatively low cost by the MoH and its nine provincial counterparts. Government health spending has been as small as 1.6% of the gross domestic product (GDP) over the last decade [8]. Health accounted for only 3-4% of the Government expenditure, with a per capita health spending of LKR 22 thousand in 2016 [8]. After the end of the civil war in 2009, Government health spending had been growing steadily over years until 2015, after which the spending turned to a downward trend in real terms [6].

The public health system is funded through general tax revenue. Despite the provision of free public health care, public spending on health constitutes less than half of the country's total health expenditure [8]. In 2016, out-of-pocket (OOP) health payments constituted 50 percent of total health spending, which is, for example, substantially higher than the corresponding figure for Thailand (12 percent) [8]. A significant share of total OOP spending is associated with payments for laboratory tests and drugs from private providers despite receiving public sector consultations. This pattern will likely be exacerbated by the rising NCDs and the subsequent burden on the health system that would result in patients incurring more of the incremental cost of care by seeking health care at higher levels and the private sector.

Addressing the NCD challenges with limited resources and fiscal space

Given the limited opportunities for rapid budgetary increase, fiscal space may be sought by reduced disease burden and efficiency gains in the health system. On the primary prevention side, Sri Lanka has already some strong regulations and fiscal measures to control risk factors and prevent the onset of NCDs. For instance, the country has a robust tobacco taxation policy. Tobacco excise is widely recognized as the single most cost-effective measure to curb NCDs [9]. Part of the ongoing discussion is to increase the tax rate on tobacco from the existing 63 percent to the WHO-recommended level of 75 percent of retail price. To discourage consumption of sweetened beverages that are associated with increased risks of obesity and diabetes, Sri Lanka has introduced a 'traffic light labelling' system on beverage bottles in August 2016 that signals the level of sugar content by colours, and 'sugar tax' on sugar-sweetened beverages since November 2017. There is a growing body of evidence that suggests sugar tax and labelling strategies to be highly cost-effective[10, 11]. The MoH is also discussing regulatory measures such as the mandatory front-of-package labelling of foods to reduce consumption of unhealthy diets.

On the other hand, the curative side of the public health system is not well aligned in dealing with the increasing burden of NCDs that require more coordinated and people-centered care. Currently, primary-level facilities do not routinely initiate NCD care.

While opportunistic NCD screening of women is provided during reproductive health care visits, adult men are left oblivious to their health circumstances. As such, the absence of a routine initiation of NCD care appears to particularly harm working adult men. Although 'healthy lifestyle centers' (HLCs) were introduced in 2011 to help address NCDs [12], the population has yet to fully embrace this model. As of 2017, only 27% of adult population visited an HLC due to various reasons such as limited outreach activities and follow-up [13].

Reorganising Primary Curative Healthcare Facilities

In response to these challenges, Sri Lanka is undertaking an ambitious agenda that will strengthen and expand primary health care (PHC) services from the ground up as documented in the report 'Reorganising Primary Healthcare in Sri Lanka', which is backed by strong evidence [14]. The report captures the findings of wide-ranging conversations among hundreds of stakeholders from every level of the country's healthcare system. Components of this PHC system strengthening paper are also reflected in the National Health Policy 2016–2025, which outlines the broad strategic directions focusing on a people-centered health system. These strategic directions include commitments to develop referral and back referral system for patients in each defined catchment area and ensure patient rights and patient/client satisfaction at all health institutions. It also includes strategic directions to reduce OOP spending and reduce financial risk through providing all diagnostic services, including medical laboratory investigations, with public financing arrangement. A commitment is also included in the National Health Policy to rationalise the development and deployment of human resource for health, to expand the training capacity of nurses and other paramedics, and to establish a new structure for management of primary-level curative services.

In operationalising the framework, the MoH is implementing the 'Primary Healthcare System Strengthening Project' (PSSP) since 2018 with support from the World Bank for a five-year period. The development objective of the project is 'to increase the utilization and quality of primary healthcare services, with an emphasis on the detection and management of NCDs in selected areas of the country' [15].

This objective is based on the current healthcare challenges that are centered around the rise of NCDs such as diabetes, cancer, cardiovascular disease and diseases of old age.

One of the critical objectives includes to ensure that primary care institutions are the most utilised by citizens across the country, which can free up resources at the secondary and tertiary care institutions for those in real need of advanced care. As the major source of inefficiency in the Sri Lanka's health system rests with patients bypassing the primary level and seeking care directly from higher level institutions, achieving this objective is expected to bring about substantial efficiency gains and hence enhanced fiscal space. The project will address both the demand- and supply-side constraints. On the demand side, it includes proactive outreach activities and strong citizen feedback mechanism to change health seeking behaviour. On the supply side, it incentivises the use of PHC through improving their capabilities and responsiveness to population demands. The project will further focus on screening and early detection of high-risk adults based on standard risk stratification, with an effective follow-up mechanism to ensure successful control of NCD risks at the PHC level. This is meant to prevent the onset of NCDs and subsequent complications that can result in significant cost. A review conducted under the Disease Control Priorities 3rd Edition (DCP3) suggests that prevention of cardiovascular diseases, diabetes and its complications, and breast cancer are all cost-effective [16]. NCD screening was scaled up by the PSSP's predecessor 'Second Health Sector Development Project' (SHSDP), which has brought up the adult screening rate for NCDs from a baseline of 3% to 27% in 2017 [13]. The estimated health and economic gains from the NCD screening and management (limited to hypertension) under the SHSDP was substantial; over 50 thousand DALYs were averted in 2017 with an economic benefit of over USD 200 million (Table 1). The potential cost savings that result from the intervention could be substantial, particularly through the reduced morbidity. Nonetheless, the follow-up and treatment outcomes of those screened as hypertensive remained relatively low (less than half of the screened patients were successfully controlled), indicating that the program has yet to exploit the gains to its full potential. The PSSP aims to improve the follow-up and health outcomes of high-risk adults, which could further expand the fiscal space for health.

Table 1: Health and economic gains from scaling up hypertension screening and management targeting population aged ≥ 40 in 2017

Items	Achievements/benefits
Incremental % screened from a baseline of 3%[a]	24.0%
Incremental % controlled for hypertension [b]	6.4%
Actual DALYs attributable to hypertension [c]	549,623
Counterfactual DALYs attributable to hypertension (in absence of health benefit from incremental % of population screened and managed)[d]	608,444
Averted DALYs (and %) attributable to hypertension	58,821 (9.7%)
Economic gains from the averted hypertensive population (USD millions)[e]	241.2

[a] The values are incremental to the baseline of 3 percent (e.g., 3 percent + 24 percent = 27 percent were screened)

[b] This was calculated using the findings from a study conducted in the Western province by the World Bank [17], which revealed 57 percent of screened population were diagnosed as hypertensive, of which 47 percent were successfully controlled (e.g., an extra 24.0 percent x 56.6 percent x 47.0 percent = 6.4 percent were controlled for hypertension)

[c] From GBD 2017 study [4]

[d] Details of the estimation methods are provided in the SHSDP Implementation Completion and Results Report [13]

[e] Assumed per capita GDP (USD 4,101) as proxy for economic gains from each DALY averted [18, 19]

Conclusion

In responding to the growing burden of NCDs within the available resources and fiscal space, it is imperative to strengthen the PHC system to become capable of providing essential NCD services that are cost-effective. Therefore the country is embarking on a PHC system strengthening programme. The successful implementation of this initiative will allow Sri Lanka to effectively manage and control the rise of NCDs. Additionally, the reorganisation of health care delivery systems into primary, secondary and tertiary care institutions will increase the utilization of primary care facilities as the first point-of-contact. Thus, with this initiative, Sri Lanka's healthcare system is expected to become more efficient, sustainable and better equipped to address current health challenges as well as become better prepared for the wellbeing of the nation.

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Perspectives In Medicine

Empathy in the practice of medicine

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"What is at stake is a fundamental recasting of the traditional image of physicians. One with profound implications for their social situation as well as their image of themselves. The need for this recasting is implicit in the disquetitude expressed by many patients who call for a more 'humanistic profession"

Prof. Edmund Pellagrino, in "Humanism and the Physician".

The semantics of the words 'Heart' and 'Empathy' are closely linked. If you are a sensitive and responsive person, people will pull at "your heart-strings". It can be said that only if patients are able to "pull at a doctor's heart-strings" that she/he will become an "empathic" doctor. Many emotions are idiomatically ascribed to the heart – 'heavy-hearted', 'light-hearted', 'cold-hearted', and 'hard-hearted'. So, it is not surprising that we call an empathic story "heart-warming"; "warming the cockles of your heart". Therefore, the 'heart' is a metaphor for a multiplicity of emotions.

What really is empathy?

Let us take some similar words – sympathy, compassion, kindness, humanity, pity; and the Buddhist concepts of Meththa (loving kindness); Karuna (compassion), Muditha (vicarious joy - the pleasure that comes from delighting in other people's well-being.)

What is sympathy? – It is a feeling of sorrow for someone else's misfortune; Compassion? – The concern for the sufferings or misfortunes of others; Kindness? - A pleasant disposition, and a concern for others; Humanity? - A set of strengths focused on "tending others"; Pity? – A feeling of sorrow and compassion caused by the suffering and misfortunes of others; they all have to do with "the other".

Empathy is distinctly different. It is the capacity to understand or feel what another person is experiencing from within the other person's frame of reference, i.e., the capacity to place oneself in another's position. It is elicited by a sense of altruism. Altruism is implicit in its true meaning. Phrases such as 'being in another's shoes', 'seeing things through their eyes', 'imagining their frame of reference', all suggest empathy.

Jean Decety et al [(1)], even consider it a "drive". The word "drive" suggests that empathy is automatic, spontaneous, beyond one's control, and thus worthy of neither praise nor blame. That it is a state of mind – it is there, or it is not.

Considering the above definitions and interpretations, I would like to think that a combination of "empathy" and "Muditha" would be the ideal state of mind of an ideal doctor.

That is,

(i) having the capacity to understand or feel what another person is experiencing from within the other person's frame of reference, i.e., the capacity to place oneself in another's position;

and

(ii) having the pleasure that comes from delighting in another's well-being. In other words - those amongst us, who have the capacity to feel a patient's feelings and gain pleasure in the joy of a cured happy patient.

But it is also said that this second aspect must be distinguished from the pleasure or self-satisfaction a doctor will get from his/her achievement of curing a patient of illness. That would be an emotion of egoistical self-aggrandizement. That is an acceptable human reaction. But that is not the quality of Muditha.

Therefore, it is not surprising why many doctors fall below achieving this difficult ideal. But it is for the 'good' doctor not to despair but continue to strive for his/her ideal.

Empathy in the Practice of Medicine

It is increasingly being accepted within the medical profession that 'empathy' is a necessary attribute in a doctor. Therefore, some believe that this attribute should be evaluated in the doctor at different times of their careers. Either at the point of entry (selection) as medical students; or during the period of their undergraduate and postgraduate training. In order to do this, a reliable and valid test of empathy is required.

Hemmerdinger et al [2] did a systematic review of tests of empathy and found that there are 59 instruments used for the assessment of empathy.

But they found

(i) that there aren't any systematic reviews on the use of empathy tests on doctors or potential doctors;

and

(ii) that evidence is insufficient to support the use of empathy tests in the selection of students for medical courses.

Nevertheless, it is surmised that empathy can be learnt [3]. Which means that it can be taught. Different researchers have recommended different approaches. Teaching methods include making students and doctors sensitive to, and developing the ability to, read facial expressions for emotions in their patients; recognizing body language and other non-verbal cues of patients; and maintaining constant eye contact with the patient. But a fundamentally important characteristic would be developing a doctor's ability to be a good and patient listener.

Another characteristic that is said to go hand in hand with empathy is the "expression of enthusiasm". Though it is generally accepted that 'empathy' must be genuine, it is argued that 'enthusiasm' can also be faked. A doctor can pretend to be 'enthusiastic'. Sheehan [4] argued that it is neither necessary nor possible to 'create a humanistic doctor'. The quality of 'humanism' is an inherent core value in humans and that a medical student or doctor who is not humanistic at the outset, cannot be converted/transformed during medical training into a humanistic doctor. Even if one can, the time and energy utilized for such a project is not necessary and therefore, wasteful. In other words, Sheehan's argument was to not try to achieve a "change of heart" – but to just try to achieve a "change of behaviour" – which is the basic definition of learning. Sheehan continued to stress that what medical schools should be trying to do is to develop 'humanistic skills' in students. Just like all the other skills that medical students acquire during their training. When you get the student or doctor to practice the skill, he will automatically or better, autonomically get into a "humanistic mode" of behaviour. This is what is usually attempted in medical school. Make an 'external' change in behaviour and not make-believe that what is being achieved is an internal change of personality and core values of medical students. – The objective is to develop a 'humanistic mask'.

Dilemmas and Challenges

The inherent understanding in the phrase 'modern scientific western medicine' is that modern physicians belong to a profession that has increasingly placed itself within the logico - scientific tradition. Medicine's hard-wound worldview, which prioritizes technological progress, hierarchy and a complacent sense of certainty, encourages thinking of patients as objects. This can lead to the doctor feeling alienated from, rather than empathic towards, the patient. Not too rarely, patients are often considered by doctors as tasks to finish or by medical students as objects from which to extract learning.

A widely-accepted view of medical professionalism is that its practitioners should respond to the suffering of patients with objectivity and detachment. Hence the operative phrases are 'clinical detachment'; 'detached concern'; clinical neutrality' or 'affective distance'.

Doctors are expected to maintain emotional detachment and distance from patients – i.e., not get 'emotionally involved' in the patient's illness or condition. The doctor's objectivity and efficiency in the urgent tasks ahead will depend on that 'clinical detachment'. An 'emotionally attached' doctor may not be objective and efficient. But that detachment is expected to be not just plain detachment, but 'detachment with concern'. A clear distinction should be made between 'empathy' for the patient and 'emotional attachment' to the patient.

This expected conflict in the mind-set of the doctor – that of 'detachment' and 'empathy' is said to lead the doctor/medical student to 'emotional burnout' or 'compassion fatigue' [5]. It is this dual and contrary 'emotional' requirement of developing empathy while at the same time acquiring 'concerned detachment' that puts a doctor in an emotional dilemma; in mental discomfort - in a state of 'cognitive dissonance'. How does a doctor develop empathy in this situation? At best, it is difficult. Unless the doctor has that urge to go that 'extra mile' to be concerned and caring.

What are the major challenges that we face in Sri Lanka towards developing an empathic doctor? One factor is what is disinterestedly called the "patient load". Doctors are expected to see too many patients – both in the state as well as the private sector. This creates a mind-set where doctors "clear the crowd" at the OPD or post-casualty in State Hospitals and limit the time of patient encounters to a bare minimum in the private sector – the notorious "2-minute consultation" followed by a plethora of tests - that many patients who have experienced it, describe. A serious, negative fallout of this is that the medical students and young doctors are faced with a lack of role models to emulate.

Unless there is a complete overhaul of the State health system, this situation will not change. There must be a change in the mind-set of the profession from within as well as a more dependable systematic national health/medical administrative structure.

But we must be thankful for small mercies or, in fact miracles. The fact is that despite all these limitations and stresses at the workplace, there are many doctors who continue to be 'empathetic'. That is remarkable indeed.

A subject for discussion and debate among medical professionals

On the one hand, there is increasing research evidence [6, 7] that 'empathy' improves positive patient outcomes. More patients recover when treated by an empathic doctor. The corollary that 'healthier doctors have healthier patients' is also a subject of current interest within the profession [7].

The argument here is that doctors will find it easier and gain greater satisfaction in their work if they are empathetic; if they are fully committed to the patient – they can expect better health outcomes for themselves.

What is worrying is that the general weight of opinion is that there is a discernible erosion of empathy during the process of becoming a doctor; a perception that medical education and the 'clinical culture' erode empathy - even pre-existing empathy that students come with at the outset.

Several reasons are being attributed to this phenomenon:

- Students face humiliation and neglect at the hands of their teachers – a matter of serious concern in Sri Lanka and the world over;
- Focus of medical education is on learning facts about diseases rather than learning how to understand people with diseases;
- Medical education pays little attention to the social and political determinants of health;
- The undergraduate curriculum and the working conditions of medical staff are intensely pressured;
- A lack of role models.

There is another more general socio-politico-economic factor that is said to contribute to the observed erosion of empathy in the doctor.

The traditional model of medicine is that it is a vocation; that health care is a public good; and that the sick patient is a vulnerable citizen who has a right to care (and for whom the physician has a duty of care).

This is steadily being replaced by a new era of values determined by the 'market' where medicine is big business; providing health care is a financial transaction; and the sick patient is a customer, client or consumer.

Hojat, et al [8] found that empathy decreases during clinical training and the greatest decrease in empathy occurred after the third year of medical school - the first full year of clinical exposure. These results imply an important but uncomfortable question. Is working closely with patients making medical students less empathetic?

Medical students undergo a lot of stress during their years at clinical training. So do young doctors. The stories are many the world over – and very similar to each other. Therefore, these periods of medical student training are not the best to instill "empathy and understanding" among them; therefore, is it any wonder that 3rd year medical students show a dramatic drop in their 'empathy scores'?

This cynical transformation was likened to the "battered child syndrome" and attributed to inappropriate treatment of medical students by clinical teachers. The metamorphosis has been described as "traumatic de-idealization" [9]. To reiterate, this is commonly seen, if not rampant, in undergraduate medical training in Sri Lankan medical schools.

Spiro [10] says: "Medical students lose some of their empathy as they learn science and detachment, and hospital residents lose the remainder in the weariness of overwork and in the isolation of the intensive care units that modern hospitals have become." The work and the workplace itself seems a disincentive towards developing empathy in the doctor.

Empathy studies have not been done in Sri Lanka. Therefore, we cannot make any categorical statement on the state of empathy, or lack of it, in our doctors. But there is substantial circumstantial evidence to show that there is a crisis at hand; that it is increasingly, a matter for concern.

It is also not easy to directly explore this question. Other than the fact that - "empathy has been described as a notion that is difficult to define and hard to measure" [11] - it is perhaps a subject that is "disconcerting in nature" for medical professionals. Doctors do not like the subject to be taken up for detailed discussion, nor to let others highlight deficiencies in empathy in them.

But then again, would our culture steeped in Eastern philosophy and the concepts of "meththa", "karuna", "dana" and "ahimsa" make any differences to the statistics on 'empathy skills' in our students and doctors as against those from the West? The circumstantial evidence in Sri Lanka is not encouraging.

Developing empathy among doctors is a very difficult task. If it was not, more doctors in the world would be empathetic than they are now.

A final quote:

"Medicine stands at the head of natural sciences and does not know which way to go. It has a record maximum of knowledge and a minimum of understanding. It has art and wonders if it has science, it is suffering from an intellectual imbalance of virtues."

Scott Buchanan
"The Doctrine of Signatures: A Defense of Theory in Medicine"

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Perspectives In Medicine

Artificial Intelligence in Patient Care - A Perspective

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Abstract

One of the most disruptive modalities of healthcare since the advent of antibiotic treatment is the future use of Artificial Intelligence (AI) and Machine Learning (ML) in healthcare. During the last two decades, the instant availability of patient data in such formats like Electronic Health Records (EHR) and Electronic Medical Records (EMR) has laid the foundation for the next leap in technology, where this data can be used in the diagnosis and treatment of diseases. The application of AI in patient care will make healthcare more efficient, cost-effective and help prevent catastrophic medical conditions through early diagnosis and prevention. Along with wearable devices, AI will change how the health of humans is monitored, diagnosed and maintained.

Keywords: Artificial intelligence (AI), Patient care, Machine learning (ML), Electronic medical records (EMR), Intelligent patient care (IPC)

Artificial Intelligence has improved significantly during the past decade to make it useful in patient care to provide an enormous resource for healthcare providers.

Human life in the world has arrived at a juncture where "data" about ourselves is an integral part of our life itself. Data on populations and on persons are readily available for both good and evil use. In fact, the use of data by others in one's daily life is unavoidable. The use of data for one's own benefit, such as in one's healthcare can be a definite plus. Since electronic health records have been adopted by healthcare providers both in the US and in the European Union, many other countries have started adopting these digital records at varying levels and sophistication. The current practice of the use of electronic medical records is not without faults. Especially in the United States, as compared to specific countries in the European Union, the presence of multiple EHR systems has made the communication between these EHRs virtually impossible. Data of a patient admitted to one hospital may not be readily transportable to another hospital situated even in the same city even when both hospitals use the same EHR system. This is less of a problem in European countries, as most European countries have a national healthcare system where hospitals and doctors, in general, are part of this system. For other countries embarking on digital health records, it would be essential that all such systems are developed on an open source platform to provide connect-ability between systems enabling the transportability of digital health data.

As the foundation of the use of AI in patient care is the patient data and the transportability of his or her data, the lack thereof introduces an insurmountable challenge for the general and uniform introduction of AI and ML in patient care.

The use of AI and ML will become a powerful tool in healthcare because computers can analyze large data sets quickly and without bias that the human mind is not capable of and because the human eye is not sharp enough to see such details. Computers inherently do not have the ability to think on their own, however computers are well known for the ability to use and analyze what they learned in compartments and analyze data objectively in order to come up with conclusions and predictions. Humans can teach the computers how to make decisions based on patient data. However, AI aims to mimic human cognitive functions [(1)]. The other significant advantage the AI and ML systems have over human healthcare workers, i.e. physicians, nurses, surgeons, is that they can analyze a large database of patient data on similar patients, match with evidence-based medicine (EBM), environmental factors, food habits of the patient population, etc. within a few seconds. The physician taking care of the patient doesn't have the luxury of analyzing all these data within the set time available, to see his patient, to make a diagnosis and formulate a treatment plan. Therefore, the use of AI and ML systems will enable the attending physician to call on these tools to make his diagnosis and treatment plan more precise and personal as well as help track the patient's progress effectively and respond to patient's recovery process adequately.

The day when a computer can perform the function of a physician is many decades away and may not even ever happen. There are regulations, licenses, and practices adopted by nations that limit the practice of medicine to those with proper schooling, training, and experiences. Therefore, AI and ML should be thought of just the same way as MRI machines or CT scan machines. These are tools that the physician can use in his or her decision making as to how a particular patient should be treated. AI and ML make the job of the physician more efficient, precise and fast while helping to keep track of any adverse developments of the patient via wearables and communication methods now widely used in the world like cell phones or Wi-Fi and blue tooth connected devices.

Today, a considerable effort in the development of AI and ML-based healthcare is taking place all over the world. Especially in the United States, there are multiple projects at various prestigious universities and also at private companies developing the use of AI and ML in the diagnosis and treatment of patients. Most of the development projects are specific in areas such as image analysis, decision-making software, analyzing electrocardiograms, mental and physical health screening, clinical research, and drug discovery. While these developments, for the time being, are somewhat compartmentalized, in the near future these individual developments can all be integrated for the common purpose of using data for the benefit of decision making.

Patient care based on symptoms has been slowly taken over by more of a holistic approach, such as in functional medicine. A patient's background plays an important role in his life and the diseases he acquires naturally as well as based on his environment. AI is able to connect all this information about the patient into a big bag and filter it to make sense that is almost impossible for a treating physician perform during the physician-patient interaction, which is often very limited in most countries. One factor that helps to sort and silo the data is "money", - how it is earned and how and where it is spent. Does the patient work outside a building? In a harsh environment? What type of food does he consume? Where has the patient been in the past - such as areas prevalent with certain infectious diseases, like dengue, so on and so forth? As we digitize how money is earned and spent, this data can be compiled, categorized, and made available for good use.

While there are privacy issues that need be resolved, the wealth of information from how money is earned and used will play an important role in predictive analysis of patient's health issues.

In development projects like the Intelligent Patient Care (IPC) now under development by the author, the privacy issues are resolved by not having any patient name, national ID and patient's address among other personal details in the patient EHR. The patient is identified using biometrics and by two factor or three-factor verification methods, like those used in banks and in passports of certain countries. Thereby it does not require layers of security settings in the EHR database which would make it less attractive to hackers.

AI and ML have even excellent usefulness in the field of cardiology. Systematic and comparative analysis of patient's condition obtained from echocardiograms, EKG, cardiac images along with history, physical and lab reports can all be evaluated based on what is commonly known in the field of AI as "supervised machine learning". Supervised machine learning uses data from known situations, such as from patients who have similar test results or have undergone additional testing based on initial tests, all of which are siloed in a relational database. As cardiac events can be catastrophic, the use of wearables along with connectivity and AI can help in preserving life in these types of situations. As such the entry of AI use in varying degrees into normal cardiac care would be more likely will be accepted relatively early on.

In addition to AI and ML, Personalized Medicine (PM) has reached the center stage in the United States and other developed countries and is been rapidly adopted around the world. Pharmacogenomics is widely used in determining the effectiveness of drugs on individual patients and once the cost of genetic tests become affordable, disease proneness based on one's genetic makeup will also become equally popular in the United States as well as other countries. Once these technologies become standard in medical care, this data can also be integrated into AI and ML platforms, which will provide another dimension in the diagnosis of disease and the effectiveness of medicines for the given patient.

One area that will make a huge difference is in the advancements in the Artificial Neural Networks (ANN). As humans we learn to think by comparing; comparing activities, images, spoken language, etc.

Computer scientists have developed and continue to develop ANN similar to human and animal-like thinking i.e. neural networks, to analyze a vast amount of data and compare them to make intelligent decisions. This technology is currently used in many non-medical applications, such as people's habits, tendencies, expense patterns and even in political affiliations. The use of ANN in sieving large amounts of data can quickly identify the relevant data and discard the noise when making clinical decisions. One area that will effectively speed up the process will be Natural Language Processing (NLP). Today vast amount of nurse's and physician's time is used in typing information into the computer. While the younger physicians type faster than the ones from the older generations, it is still an unnecessary task in light of NLP. Although we see users of smartphones still type texts into their screens, nowadays this is totally unnecessary as most smartphones have NLP capabilities, yet the habit continues even among young people. Hence it is a clue that NLP adoptability in years to come would be of slow making. However, NLP will be a cornerstone in the true use of AI and ML in healthcare.

Though an oversimplification, the basis of analysis in AI is the identification of similarities and differences between the subject data and the known knowledge, i.e. known. For example, a chest X-ray from a given patient can be compared to thousands of chest X-rays of known pathologies to determine any similarities between them [(2)]. Exact pathologies need be defined and classified. This is known knowledge. The algorithms have to be developed that compare the subject with the known knowledge. The trick is the development of these algorithms, not only in its function but also in its speed. If the algorithms are not efficient, then the clarity and details can be lost or can take a considerable time for its iterations. Research has shown that algorithms have come close to human diagnosis, sometimes greater than 90% accuracy. Even more exciting is when the human diagnosis is complimented by the AI algorithms, the precision of the diagnosis of more than 96% has been achieved in some cases published in the literature. The same is true of doppler images or graphs and charts in electro-cardiology practice or images of tissue slides in pathological studies.

With language processing, i.e. NLP, the nurse can initially ask relevant questions from a patient before the patient sees the doctor. The computer understands the complaint and can prompt relevant questions from the patients.

The computer can repeat this process based on the patients answers to the prior questions until a tentative diagnosis based on past history, physical examination, present complaint and any other factors that may be available in the patient's database. Obviously, the more data there is in one's database, the computer can ask better questions from the patient. Once the patient has been interviewed by the nurse/computer combination, the predictive analysis can be forwarded to the attending physician with all relevant information, such as the current complaint, medications that are taken, lab results, patient's medical, family and social history and any conclusions from diagnostic images. The computer can also provide any cautions if relevant "highlighted" in the physician's dashboard. This is the basis of Intelligent Patient Care or IPC. For a specific diagnosis, the care plan using AI is relatively straight forward. Drugs and labs can be ordered based on the diagnosis validated by the attending physician also based on a vast database for a specific category of the patient, such as sex, age, race, etc.

AI-based diagnosis is not without challenges. As more and more research groups come up with AI-based tools for diagnosis and treatment, there will be many unresolved issues that will affect their utility in real-life patient care. Most drugs and medical devices are controlled by authorities in the country they are used. In the United States, drugs and devices require the Food and Drug Administration (FDA) approval before they are introduced into commerce. There are stringent rules and verifications required for such approval. The approval of drugs and devices in the US can take 5-10 years of submissions of relevant safety and efficacy data to justify their commercial use. These include diagnostic as well as therapeutic means of patient care. Then what about diagnostic tools using AI? It would be a matter of time before the regulatory bodies will regulate the use of AI and ML in the diagnosis and treatment of patients. Often the clinical testing of drugs and devices is limited to a practical number of patients even though the information is simply complementing the physician's diagnosis. Additionally, the drug company is required to regularly report adverse effects as they happen and regularly during post-marketing of the drug to the FDA. There arises a complication in the use of AI, as AI requires tens of thousands of verified past data. Would this data be available in public? Are they verified? Are the algorithms themselves validated? What would be the margin of error? What systems are in place to identify when the AI has made an error?

These and other issues will make the use of AI and ML in the diagnosis and treatment of patients a difficult task to achieve as a norm. However, its use as a tool to complement the attending physician's decision in the treatment of his or her patient will be a welcome new addition to the tools, like the MRI and CT Scan, ECHO cardiogram that has evolved during the last century. This process is Intelligent Patient Care (IPC).

In IPC, the patient data which would be available anonymously allow the computer to ask the right questions before the patient sees the physician. This can eliminate a busy physician forgetting to ask an important yet appropriate question from the patient that would be very relevant to his or her presenting illness. More the computer knows about the patient based on his or her medical, family, social, earning, spending, environmental history, the computer using AI can ask more relevant questions. Along with lab results and diagnostic images, AI can make good predictions of the patient's illness.

In order to implement AI to complement the work of physicians and other health care providers in Sri Lanka and other developing countries, respective authorities can learn from the experiences from countries that have established digital health record systems, I.e. EHR systems.

In order for an effective AI based health care service, a seamless EHR system must be in place. It is essential that such a system be uniform in the entire country and is cloud based with open source software. It should be controlled and monitored by the national healthcare authority. As most AI-based systems will be developed in the English language, there is additional work that is required to handle translations of Sinhala and Tamil to the working language. NLP in each language should be developed to mesh with the AI engine and AI infrastructure.

Implementation of AI based healthcare should take place in stages. For example, initially, it can be limited to reading of images, graphs, charts, and lab reports. With time, a system as in IPC can be introduced, where the patient interacts with the computer answering questions generated based on patient's presenting illness. Within a few years, a validated system can be put in place to ease the burden for the national health care system, while providing precise, connected, resource managed care to the people of Sri Lanka. It would be advisable to implement a system that is developed organically as an internally developed system would meet the cultural and economic barriers facing its implementation.

The overall block diagram of IPC is shown in Figure.1.

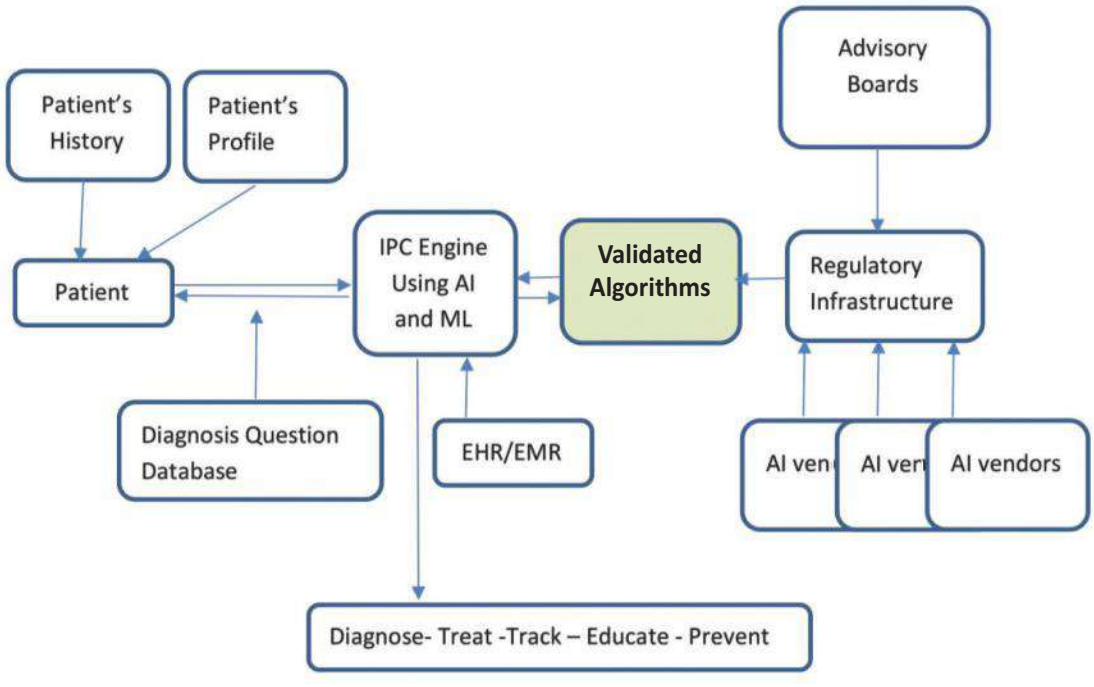

Figure: 01

The above flow chart describes the principle of IPC in which patient interacts with the computer which uses the validated AI system. The basic record keeping is performed by a standard EHR system. Only approved AI algorithms are working within the AI engine. These algorithms are supervised by a board of physicians within the respective specialty who along with regulatory bodies approve the use of AI modules provided by AI vendors. The IPC engine also has the ability to continuously learn on how the care provider is responding to the subject patient and save such logic in its decision-making database.

In conclusion, AI and ML along with NPL are tools the physician can use to provide effective medical care at a reasonable cost in any national healthcare system. An AI-based system will not only provide benefits to the individual patient and to the physician, but it can also help manage resource planning at a national level. It can also provide reports on the hotspots of specific infectious diseases, vector-borne diseases, diseases prevalent in certain areas of the country such as CKDu or diseases among certain genetically predisposed populations.

Open source platforms are essential to make the AI-based systems to properly work properly at a national level and therefore regulatory and governmental control would be essential and should be in place long before such systems enter the actual practice. Data security would be a major concern once a full-fledged AI system is in place for any national healthcare system. While Intelligent Patient Care doesn't contain any personal information, the data can be hacked and destroyed to disrupt its effective use which may cause a national healthcare emergency.

Regulatory bodies and advisory bodies are essential pillars that hold up a national AI based healthcare system that continuously updates the algorithms used, based on known knowledge and how that knowledge is used in identical instances by a board of qualified physicians and the system shall continuously learn to update itself based on these actual practices.

Finally, it should be recognized that AI-based diagnosis and treatment is the future of healthcare and systems need to be in place to adopt the new developments as they evolve, including taking a hard look at the current medical education that produces future doctors.

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Updates

Rapid Journal Scan

From the Editorial desk

ESC Position Paper on Depression and CHD

Vaccarino et al
American College of Cardiology Feb 07, 2019

The prevalence of depression is 15–30% in patients with CHD and is approximately twice as high in women as men, and particularly affects young women who have a high mortality post-myocardial infarction. Higher degrees of depression are associated with higher risk.

Studies suggest that specific subtypes of depression may be more strongly associated with CHD risk than others. Patients with new-onset depression after acute coronary syndrome (ACS), with treatment-resistant depression, or with somatic depressive symptoms (as opposed to cognitive symptoms), are all at increased risk of developing adverse CHD outcomes and poorer quality of life (QoL).

Depression and sudden negative emotions have been associated with atrial fibrillation (AF) and recurrence after electrical cardioversion. AF may worsen symptoms of depression.

Whether treating depression would affect arrhythmias is not known.

Acute and chronic stress exposure can lead to disruptions in the synthesis or activity of norepinephrine, dopamine, serotonin, cortisol, aldosterone, and angiotensin II, each of which may influence mood and risk factors including hypertension, platelet reactivity, endothelial dysfunction, and diabetes and the metabolic syndrome, which can also cause depression. Several of these changes may affect the immune system leading to excessive secretion of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-a. Inflammation is common in mood disorders and CVD and thus might play a role in plaque development and ACS, as well as AF. Twin studies have shown common genetic pathways involving neuroendocrine, immune, and inflammatory systems that may simultaneously increase the risk for both depression and CHD.

Clinicians should be aware of the "high" prevalence of depression in CHD.

Non-pharmacologic interventions such as exercise and psychotherapy should be considered as additional treatment options.

Asleep blood pressure: significant prognostic marker of vascular risk and therapeutic target for prevention

Ramón C Hermida
European Heart Journal (2018) 39, 4159–4171

Sleep-time blood pressure (BP) is a stronger risk factor for cardiovascular disease (CVD) events than awake and 24 h BP means.

The authors evaluated 18078 individuals with baseline ambulatory BP ranging from normotension to hypertension during the 5.1-year median follow-up.

Primary outcome was a composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke.

The progressive attenuation of asleep SBP was the most significant marker of event-free survival.

Treatment-induced decrease of asleep, but not awake SBP, is a novel hypertension therapeutic target requiring periodic patient evaluation by ambulatory monitoring, and is associated with significantly lower risk for CVD morbidity and mortality.

Updates

Residual Cardiovascular risk in statin-treated patients with elevated triglycerides:

REDUCE-IT doi:10.1093/eurheartj/ehz179

The reduction of cardiovascular events with icosapent ethyl-Intervention trial (REDUCE-IT) has established a new standard of care in addressing residual risk in patients with elevated triglycerides already treated with statins. The study found that icosapent ethyl, a highly purified ethyl ester of icosapentaenoic acid (EPA), reduced the risk of major adverse cardiovascular events (MACE) by 25%. This included a statistically significant 20% reduction in death from cardiovascular causes, as well as statistically significant reductions in a variety of other pre specified endpoints, including a 31% reduction in myocardial infarction (MI), a 28% reduction in stroke, a 32% reduction in hospitalization for unstable angina, and a 35% reduction in urgent or emergent coronary revascularization.

The large relative and absolute risk reduction noted in REDUCE-IT would be expected to make icosapent ethyl highly cost effective. In fact, in prespecified analyses, when examining not only first events, but also recurrent and total ischaemic events, a 30% reduction was seen using the negative binomial method (P=0.00000000036), and a 32% reduction was seen using the Andersen-Gill method (P =-. 0.00000000000000000003), which likely has significant implications with respect to formal evaluations of cost effectiveness.

Atrial Fibrillation and Cognitive Function

Diener et al.
American college of cardiology Feb 07, 2019

There is strong evidence from many prospective registries and studies that AF is associated with cognitive impairment, cognitive decline, and dementia.

There is only indirect evidence that effective anticoagulation in AF reduces the risk of cognitive impairment and dementia.

The most likely mechanism linking AF and cognitive impairment is covert embolism to the brain causing silent cerebral macro- and micro infarcts. Chronic cerebral hypoperfusion is also a possibility.

Efficacy and Safety of Statin Therapy in Older People: Meta-Analysis

Rubenfive et al.
American college of cardiology Feb 04, 2019

Cholesterol Treatment Trialists' Collaboration.

- Statin therapy produces significant reductions in major vascular events irrespective of age, but there is less direct evidence of benefit among patients >75 years without established ASCVD.
- Statin therapy is safe in the elderly and has no effect at any age on nonvascular mortality, cancer death, or cancer incidence.
- In persons >75 years, the absolute reduction in vascular events was about 0.5% per year per mmol/L decrease in LDL-C.
- The value of statins in the elderly who are at higher risk for events and mortality may be limited by impact of poorly controlled hypertension, hypotension, chronic renal disease, atrial fibrillation, and nonadherence.

From Cardiology Update 18 London

Report in European Heart Journal (2019) 40, 640–650

Patrick W. Serruys convinced the audience with an impressive lecture of the enormous potential of modern coronary computed tomography (CT) for the assessment of patients prior to cardiac procedures. Indeed, coronary CT provides with less and less radiation, not only precise structural information of coronary arteries including the SYNTAX Score but also the haemodynamic significance of plaques using CT-based fractional flow reserve (FFR). This allows proper and non-invasive planning of coronary and valvular procedures. Indeed, the vision of Patrick W. Serruys is that eventually surgeons and interventional cardiologists will reach therapeutic decisions and precisely plan their procedures non-invasively using CT, with hopefully better results to the benefit of the patients.

Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data

Frederik M. Zimmermann
European Heart Journal (2019) 40, 180–186

Aims of this study were to assess the effect of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) with contemporary drug-eluting stents on the composite of cardiac death or myocardial infarction (MI) vs. medical therapy in patients with stable coronary lesions.

A total of 2400 subjects were recruited from 54 sites world-wide with 1056 randomly assigned to FFR-guided PCI and 1344 to medical therapy. The pre-specified primary outcome was a composite of cardiac death or MI.

Conclusion: In this meta-analysis of the three available randomized controlled trials to date, FFR-guided PCI resulted in a reduction of the composite of cardiac death or MI compared with medical therapy, which was driven by a decreased risk of MI.

Transportation noise linked to cardiovascular disease independent from air pollution

Mette Sørensen et al.
European Heart Journal (2019) 40, 604–606

Air pollution and traffic noise are the two major environmental pollutants affecting health according to the World Health Organization (WHO). For air pollution, the American Heart Association has concluded already in 2010 that 'the overall evidence is consistent with a causal relationship between particulate matter ($PM_{2.5}$) exposure and cardiovascular morbidity and mortality.

In a systematic review produced as a basis for the new WHO guidelines on environmental noise, it was concluded that there is high-quality evidence linking exposure to road traffic noise with an increased risk of ischaemic heart disease. Epidemiological evidence also exists for hypertension and stroke, but this is less conclusive.

A strong feature of the study by Héritier et al. is that they have estimated exposure to three sources of noise separately: road traffic noise, aircraft noise, and railway noise. They found significant associations with Ml mortality of similar size for all three modes of transport, with hazard ratios of 1.03 for road traffic, 1.03 for aircraft, and 1.02 for railway noise per 10 dB increase (both before and after adjustment for air pollution). These findings are very important, because residential exposure to noise from aircraft and trains is less correlated with residential air pollution than noise from road traffic.

Three sources of transportation noise are associated with MI mortality independent of air pollution. This adds to the evidence that transportation noise is an important risk factor for cardiovascular disease.

Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis

Nelson Wang et al.
European Heart Journal (2019) 40, 476–484

A systematic search was done for studies reporting clinical outcomes of patients with TR. The primary endpoint was all-cause mortality and secondary endpoints were cardiac mortality and hospitalization for heart failure (HF). Overall risk ratios (RR) and 95% confidence intervals (CIs) were derived for each endpoint according to the severity of TR by meta-analyzing the effect estimates of eligible studies. Seventy studies totaling 32 601 patients were included in the analysis, with a mean (±SD) follow-up of 3.2 ± 2.1 years.

Moderate/severe TR was associated with a two-fold increased mortality risk compared to no/mild TR.
Moderate/severe TR remained associated with higher all-cause mortality among 13 studies which adjusted for systolic pulmonary arterial pressures, and 15 studies, which adjusted for right ventricular (RV) dysfunction. Moderate/severe TR was also associated with increased cardiac mortality and HF hospitalization. Compared to patients with no TR, patients with mild, moderate, and severe TR had a progressively increased risk of all-cause mortality ($P < 0.001$ for trend).

Updates

Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial.

Jorrit S. Lemkes
European Heart Journal (2019) 40, 283–291

Patients with acute coronary syndrome who present initially with ST-elevation on the electrocardiogram but subsequently show complete normalization of the ST-segment and relief of symptoms before reperfusion therapy are referred to as "transient ST-segment elevation myocardial infarction (STEMI)" and pose a therapeutic challenge. It is unclear what the optimal timing of revascularization is for these patients and whether they should be treated with a STEMI-like or a non-ST-segment elevation myocardial infarction (NSTEMI)-like invasive approach. The aim of the study is to determine the effect of an immediate vs. a delayed invasive strategy on infarct size measured by cardiac magnetic resonance imaging (CMR).

In a randomized clinical trial, 142 patients with transient STEMI with symptoms of any duration were randomized to an immediate (STEMI-like) [0.3 h; interquartile range (IQR) 0.2–0.7 h] or a delayed (NSTEMI-like) invasive strategy (22.7 h; IQR 18.2–27.3 h). Infarct size as percentage of the left ventricular myocardial mass measured by CMR at day four was generally small and not different between the immediate and the delayed invasive group (1.3%; IQR 0.0–3.5% vs. 1.5% IQR 0.0–4.1%, P = 0.48). By intention to treat, there was no difference in major adverse cardiac events (MACE), defined as death, reinfarction, or target vessel revascularization at 30 days (2.9% vs. 2.8%, P = 1.00).

However, four additional patients (5.6%) in the delayed invasive strategy required urgent intervention due to signs and symptoms of reinfarction while awaiting angiography.

Conclusion: Overall, infarct size in transient STEMI is small and is not influenced by an immediate or delayed invasive strategy. In addition, short-term MACE was low and not different between the treatment groups.

Impaired endogenous fibrinolysis in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention is a predictor of recurrent cardiovascular events: the RISK PPCI study

Mohamed Farag
European Heart Journal (2019) 40, 295–305

The endogenous fibrinolytic system serves to prevent lasting thrombotic occlusion and infarction following initiation of coronary thrombosis. The study aimed to determine whether impaired endogenous fibrinolysis can identify patients with ST-segment elevation myocardial infarction (STEMI) who remain at high cardiovascular risk despite dual antiplatelet therapy (DAPT).

A prospective, observational study was conducted in 496 patients presenting with STEMI for primary percutaneous coronary intervention (PPCI). Blood was tested on arrival pre-PPCI, at discharge and at 30 days to assess thrombotic status using the automated point-of-care global thrombosis test and patients followed for 1 year for major adverse cardiovascular events (MACEs).

Endogenous fibrinolysis was significantly impaired [baseline lysis time (LT) >_2500 s] in 14% of patients and was highly predictive of recurrent MACE, driven by cardiovascular death (P < 0.001) and myocardial infarction (P < 0.001), particularly within 30 days. Fibrinolysis remained strongly predictive of MACE after adjustment for conventional risk factors (HR 8.03, 95% CI 4.28–15.03; P < 0.001). Net reclassification showed that adding impaired fibrinolysis improved the prediction of recurrent MACE by >50% (P < 0.001). Patients with spontaneous ST-segment resolution pre-PPCI had more rapid, effective fibrinolysis [P < 0.001] than those without. Lysis time was not altered by standard of care STEMI treatment including DAPT and was unchanged at 30 days.

Conclusion: Endogenous fibrinolysis assessment can identify patients with STEMI who remain at very high cardiovascular risk despite PPCI and DAPT. Further studies are needed to assess whether these patients may benefit from additional, personalized antithrombotic/ anticoagulant medication to reduce future cardiovascular risk.

Early vascular damage from smoking and alcohol in teenage years: the ALSPAC study

Marietta Charakida et al.
European Heart Journal (2019) 40, 345–353

Aims to determine the impact of smoking and alcohol exposure during adolescence on arterial stiffness at 17 years.

Smoking and alcohol use were assessed by questionnaires at 13, 15, and 17 years in 1266 participants (425 males and 841 females) from the ALSPAC study. Smoking status (smokers and non-smoker) and intensity ('high' ≥100, 'moderate' 20–99, and 'low or never' <20 cigarettes in lifetime) were ascertained. Participants were classified by frequency (low or high) and intensity of drinking [light (LI <2), medium (MI 3–9), and heavy (HI >10 drinks on a typical drinking day).

Carotid to femoral pulse wave velocity (PWV) was assessed at 17 years (mean ± standard deviation and/or mean difference).

Current smokers had higher PWV compared with non-smokers (P =0.003). Higher smoking exposure was associated with higher PWV compared with non-smokers [5.81 ± 0.725 vs. 5.71 ± 0.677 m/s, mean adjusted difference 0.211 m/s, P = 0.001]. Participants who stopped smoking had similar PWV to never smokers (P = 0.160). High-intensity drinkers had increased PWV [HI 5.85 ± 0.8 vs. LI 5.67 ± 0.604 m/s, mean adjusted difference 0.266 m/s, P = 0.013]. There was an additive effect of smoking intensity and alcohol intensity, so that 'high' smokers who were also HI drinkers had higher PWV compared with never-smokers and LI drinkers (mean adjusted increase 0.603 m/s, P = 0.002).

Smoking exposure even at low levels and intensity of alcohol use were associated individually and together with increased arterial stiffness. Public health strategies need to prevent adoption of these habits in adolescence to preserve or restore arterial health.

Mechanisms linking preterm birth to onset of cardiovascular disease later in adulthood

Mahesh Bavineni et al.
European Heart Journal (2019) 40, 1107–1112

Cardiovascular disease (CVD) rates in adulthood are high in premature infants; unfortunately, the underlying mechanisms are not well defined. Studies show intense oxidant stress and inflammation at tissue levels in these neonates. Alterations in lipid profile, foetal epigenomics, and gut microbiota in these infants may also underlie the development of CVD. Recently, probiotic bacteria, such as the mucin-degrading bacterium Akkermansia muciniphila have been shown to reduce inflammation and prevent heart disease in animal models. All this information might enable scientists and clinicians to target pathways to act early to curtail the adverse effects of prematurity on the cardiovascular system. This could lead to primary and secondary prevention of CVD and improve survival among preterm neonates later in adult life.

Workplace bullying and workplace violence as risk factors for cardiovascular disease: a multi-cohort study.

Tianwei Xu et al.
European Heart Journal (2019) 40, 1124-1134

Participants were 79 201 working men and women, aged 18–65 years and free of CVD and were sourced from three cohort studies from Sweden and Denmark. Exposure to workplace bullying and violence was measured at baseline using self-reports.
Nine percent reported being bullied at work and 13% recorded exposure to workplace violence during the past year. The authors recorded 3229 incident CVD cases with a mean follow-up of 12.4 years (765 in the first 4 years). After adjustment for age, sex, country of birth, marital status, and educational level, being bullied at work vs. not was associated with a hazard ratio (HR) of 1.59 for CVD. Experiencing workplace violence vs. not was associated with a HR of 1.25 for CVD. The population attributable risk was 5.0% for workplace bullying and 3.1% for workplace violence. The excess risk remained similar in analyses with different follow-up lengths, cardiovascular risk stratifications, and after additional adjustments.

Dose–response relations were observed for both workplace bullying and violence ($P_{trend} < 0.001$). There was only negligible heterogeneity in study-specific estimates.

Conclusion: Bullying and violence are common at workplaces and those exposed to these stressors are at higher risk of CVD

Updates

Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea.

Shin-Young Park et al.
European Heart Journal (2019) 40, 1138-1145

Oral health problems such as periodontal disease, dental caries, and tooth loss have been suggested to have associations with cardiovascular disease.

The data of 247696 healthy adults aged 40 years or older who underwent an oral health screening program and had no history of major cardiovascular events were extracted from the National Health Insurance System-National Health Screening Cohort.

The risk of cardiovascular events was higher when a subject had periodontal disease, a higher number of dental caries, or more tooth loss. Performing one more tooth brushing a day was associated with a 9% significantly lower risk of cardiovascular events after multivariable adjustment. Regular dental visits (once a year or more) for professional cleaning were also shown to reduce cardiovascular risk by 14%. Improved oral hygiene behaviors were shown to attenuate the cardiovascular risk originating from periodontal disease, dental caries, and tooth loss.

Updates

Extracts from expert reports 1

From the Editorial desk

Cardiovascular disease medication during pregnancy

Halpern et al
American college of cardiology Jan 29, 2019

Arrhythmias

Unstable arrhythmias should be treated with electrical cardioversion. Antiarrhythmic medications should be avoided in the first trimester, and the lowest effective dose should be used. Amiodarone should be avoided due to the risk of fetal thyroid and neuro developmental complications.

Supraventricular tachycardia (SVT) can be treated initially with vagal maneuvers, then adenosine, beta-blockers, and verapamil as third-line therapy. Beta-blockers (with or without digoxin) or oral verapamil can be used for suppressive therapy for SVT in the absence of pre-excitation.

Atrial fibrillation and atrial flutter can be treated with beta-blockers, verapamil, and digoxin.

Beta-blockers are used frequently for the treatment of several cardiovascular conditions during pregnancy. Large, retrospective studies show no association between the use of beta-blockers and major congenital abnormalities.

Atenolol is not recommended due to increased risk of fetal growth restriction.

Digoxin can be used during pregnancy.

Ventricular tachycardia (VT): Electric cardioversion should be performed for unstable VT. If a pregnant woman is hemodynamically stable, electric cardioversion or lidocaine or beta-blockers can be considered.

Hypertension

The placenta does not auto regulate blood flow; therefore, acute maternal hypotension due to antihypertensive treatment may cause fetal distress.

First-line agents for chronic or gestational hypertension include labetalol, nifedipine, and methyldopa. Dose reduction may be needed in the second trimester when a 5-10 mm Hg decrease in mean blood pressure is often observed due to the physiologic changes of pregnancy. Diuretics can cause placental hypoperfusion.

Heart failure

Beta-blockers can be used, and digoxin can be considered. Diuretics (furosemide, bumetanide, hydrochlorothiazide) can be used for pulmonary edema, but excessive dosing carries the risk of placental hypoperfusion and fetal electrolyte abnormalities.

ACE inhibitors, angiotensin-receptor blockers, direct renin-inhibitors, angiotensin receptor neprysilin inhibitors, spironolactone, and eplerenone are contraindicated.

Enalapril, captopril, and benazepril can be safely considered during lactation.

Statins

Statins continue to be considered contraindicated during pregnancy.

Anticoagulation for mechanical valves

Embryopathy, miscarriage, and stillbirth are more common with daily doses of warfarin >5 mg. If the warfarin dose is >5 mg/day, women should switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) by the end of the sixth week of gestation to decrease the risk of warfarin embryopathy. LMWH does not cross the placenta.

Antiplatelet medications

Low-dose aspirin is considered safe during pregnancy and lactation, and is commonly used for the prevention of pre-eclampsia. High-dose aspirin should be avoided due to the risk of premature closure of the ductus arteriosus.

Pulmonary arterial hypertension

Parenteral and inhaled prostaglandins can be used in the appropriate setting and phosphodiesterase-5 inhibitors may be considered. Endothelin receptor blockers (bosentan, ambrisentan, macitentan) are teratogenic and should not be used.

Emergency situations

Standard medications should be used for the treatment of cardiopulmonary resuscitation or cardiogenic shock.

Updates

Extracts from expert reports 2

From the Editorial desk

Recommendations for participation in leisure time or competitive sports in athletes-patients with coronary artery disease: a position statement from the Sports Cardiology Section of the European Association of Preventive Cardiology (EAPC)

Mats Borjesson et al
European Heart Journal (2019) 40, 13–18

Coronary artery disease

- In general, if the maximal exercise-test is normal, and cardiovascular risk factor profile is low, the presence of relevant CAD is assumed to be unlikely. In this instance, no additional tests are mandatory and no restriction for competitive sports is advised. Risk factor management should be adequate and annual follow-up is recommended.

- In case of a borderline or equivocal exercise test result (e.g. ST depression of 0, 15 mV, not typically ascending ST segment, etc.) as well as in the case of an uninterpretable electrocardiogram (ECG) (pre-existing left-bundle branch block (LBBB) or ventricular pacing), we recommend performing an additional stress test such as stress-echo/-CMR/PET/SPECT. This panel advices maximal exercise SPECT as first diagnostic step in athletes. However, we also acknowledge the option of exercise echocardiography or nuclear perfusion techniques (exercise or pharmacological). The choice of these tests is guided by their diagnostic accuracy, being dependent on local expertise and by their availability.

- If the exercise test is positive, preferentially CT or coronary angiogram should be performed to confirm presence and extent of CAD. In case CT shows the presence of significant lesions, according to routine clinical criteria, the patient-athlete should undergo coronary angiography.

It should be noted that master endurance athletes show a higher degree, and a more diffuse distribution of coronary calcium in the coronary tree compared with non-athletes at similar low risk-factor level. At present, the long term clinical implications of these findings are debated.

Clinically proven coronary artery disease

- Athletes-patients with clinically proven CAD and considered to be at low-risk for cardiac events may be selectively advised to participate in competitive sport. However, as a measure of caution due to the high haemodynamic load and possible electrolyte imbalance, restrictions may apply on an individual basis for certain sports with the highest CV demand (such as extreme power and endurance disciplines). Moreover, older athletic patients with CAD and even low risk profiles deserve special attention, and a more cautious advice, as recent studies have shown that the risk of SCD during endurance events may be considerably higher in men >60-year old. (Level of recommendation: Class IIa, level of evidence C).

- Patient-athletes with clinically proven CAD, defined as high risk, should be temporarily restricted from competitive sport and receive appropriate management. As in all patients, also in patient-athletes with CAD and significant ischaemia during exercise, anti-ischaemic therapy needs to be optimized. In case of continued ischaemia, revascularization ought to be performed.
(Level of recommendation: Class IIa, level of evidence C).

Non-coronary artery disease related myocardial ischaemia

Congenital coronary artery anomalies (CAA)

- Specifically, in CAA originating from the wrong sinus, with acute angled take-off from the aorta and anomalous coursing between the aorta and the pulmonary artery, the risk for SCA/SCD is believed to be the highest. Strong consideration should be given to surgical correction of such an anomaly in symptomatic patients. Prior to successful correction, participation in high-intensity sport is discouraged. (Level of recommendation: Class II, level of evidence C).

- Traditionally, CAAs without inter-arterial course have been considered having a low risk of SCA/SCD. In the absence of ischaemia and arrhythmias on stress testing or symptoms (dizziness, fainting or syncope), there is no indication for surgical repair or treatment. At present, because of a lack of adequate data, an individualized approach for competitive sports participation is recommended, based on comprehensive evaluation (N.B.: expert consensus. Level of recommendation: Class III, level of evidence C).

- In case of previous surgical correction and lack of persistent, inducible ischaemia, all competitive sports are allowed. (Level of recommendation: Class III, level of evidence C).

- In other types of CAA, such as anomalous origin of the circumflex artery from the right sinus, it is relevant to confirm the absence of inducible ischaemia and, in this case, no restrictions exist regarding competitive sport participation.
  (Level of recommendation: Class IIa, level of evidence C).

Myocardial bridging (MB)

Myocardial bridging may be occasionally discovered at imaging testing required to solve the ambiguity of an abnormal exercise ECG. Similar to CAA, MB should be suspected in athletes who present with exertional angina or syncope.

Evaluation of the individuals with MB aims primarily at assessing the presence of inducible ischaemia. Recently, it has been shown that the percentage of arterial compression in MB may be directly related to the atherosclerotic burden, proximal to the MB. Observational studies have shown that in patients without obstructive CAD on coronary CT, the presence of an intramural course of a coronary artery was not associated with a clinical worsening in 5-year follow-up.

Thus, MB without other underlying diseases (e.g. hypertrophic cardiomyopathy) and with no evidence of inducible myocardial ischaemia/ CAD, seems to have a good prognosis.

- In the absence of inducible effort-related ischaemia or complex ventricular tachyarrhythmias (i.e. NSVT, polymorphic or very frequent VEBs, induced by exercise), there is little evidence for exercise-induced harm. Therefore, asymptomatic athletes-patients with myocardial bridging can participate in all competitive and leisure-time sports. (Level of recommendation: Class IIa, level of evidence C).

- Conversely, in those with evidence of ischaemia or symptoms, beta-blockers are the first line therapy. If this therapy fails, then surgical repair may be considered, whereas stenting is discouraged. These individuals should be restricted from participation in competitive sports, and should be properly advised regarding leisure-time activities. (Level of recommendation: Class IIa, level of evidence C).

Update

HDL-cholesterol over 100mg/dL: Good or Bad?

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Abstract

High-density lipoproteins play a protective role in coronary artery disease and an elevated HDL cholesterol level is considered a negative risk factor. However studies have shown a tendency towards increased morbidity and mortality in those with very high HDL-cholesterol values.
Accurate measurement of HDL-cholesterol facilitates identifying those with extreme values as well as accurate calculation of LDL-cholesterol, the target of treatment for hyperlipidaemia.
Our laboratory reported HDL-cholesterol >100 mg/dL on 445 individuals within a period of 4 years. The median was 105 mg/dL and 42% were females over the age of 60 years.
Accurate reporting of very high HDL-cholesterol is required together with further evaluation of such individuals.
Keywords: HDL-C, Very high HDL-C

Introduction

High-density lipoprotein cholesterol (HDL-C) has for decades enjoyed being the 'Good Samaritan' of an individual's lipid profile. With multi-centric research endorsing the cardiovascular benefits of higher HDL-C values, there is little wonder that people try to improve on it, for good cardiac health.

However, what impact would an extremely high HDL-cholesterol level have on an individual?

(a) Is the benefit limited or unlimited?
(b) Could it be detrimental?

Main function of HDL

High-density lipoprotein (HDL) particles serve the important role of reverse cholesterol transport. This process allows excess tissue cholesterol, to be removed via macrophages which transfer cholesterol from cell membranes to HDL particles to be excreted from the body in bile [(5)].

History of HDL estimation

By definition, HDL-particles have a density ranging from 1.063 – 1.210. Historically HDL was demonstrated by ultra-centrifugation of the sample and harvesting the fraction with the given range of density for gravimetric estimation [(2)]. This method is limited to research because of the cost of equipment and the cumbersome nature of the procedures involved.

For routine laboratory purposes, the HDL particles therefore need to be isolated from the rest, using simpler technology. The isolated HDL fraction is not measured in its entirety. Instead, either the protein moiety or the lipid moiety is measured as an indirect means of quantifying HDL [(2)]. HDL is composed of approximately 50% proteins (predominantly Apo A-1). The phospholipid content is the largest lipid by mass (30%) with cholesterol and its esters contributing about 20 %[(3)].

What do we mean by HDL-cholesterol measurement?

HDL-C measurement is a cheap substitute for the number of HDL particles carried by a unit volume of plasma. In the absence of facilities for reference methods for measuring the HDL ***particles***, the routine clinical chemistry laboratory has resorted to giving an ***estimate*** by measuring only the 20% cholesterol constituent carried by all the HDL particles put together. This is reported as the HDL-C level in serum. It doesn't provide a breakdown of the HDL particle type, size or their distribution in plasma.

The goal of HDL-cholesterol measurement

The goal is to find out how many milligrams (or millimoles) of cholesterol are carried by the HDL particles found in 100 mL (or 1 Litre) of plasma. This becomes a tall order when one considers the fact that plasma would normally contain a mixture of multiple lipoprotein particles: *viz* high-density (HDL), low-density (LDL), intermediate-density (IDL), very-low-density (VLDL) and lipoprotein 'a' (Lpa) with chylomicrons being present in non-fasted samples.

Second generation HDL-cholesterol assays

Due to poor isolation techniques used in the past, the HDL-C measurement has taken a bumpy ride over the decades. The second generation HDL-C assays use combinations of polyanions and divalent cations to selectively precipitate Apo-B-containing lipoprotein particles (e.g. Heparin-$MnCl_2$, dextran sulphate-$MgCl_2$ and Na phosphotungstate[2]). Following centrifugation, the cholesterol content of the supernatant will be the HDL-C level, and hence represent the HDL particles. Various precipitants perform differently, with incomplete precipitation leading to an over-estimation of HDL-C. Assays have subsequently been optimized by using the reagent, instrument and calibrator from the same supplier [3].

Third generation HDL-cholesterol assays

A major breakthrough in HDL determination was reported in 1994 with publications of the homogeneous methods that are capable of full automation [3]. With the elimination of manual pre-treatment steps, precision improved greatly. In these methods, the cholesterol in non-HDL particles is ***'masked'*** with (anti-apo B) antibodies, polymers or detergents, allowing the cholesterol in the HDL component to be determined enzymatically [5].

Homogeneous assays were initially introduced to Sri Lanka at the turn of the new millennium. The majority of medical testing laboratories in the world have adopted them even though questions have been raised regarding their specificity, especially in specimens with unusual lipoprotein compositions [2]. Deviations from reference methods have been observed in the presence of high triglycerides, at low HDL values and in the presence of atypical lipoproteins [5].

Influence of HDL-C on calculated LDL-C report

The determination of HDL-C by itself is hardly affected by prior consumption of food [5]. However, a 12-14 hour fast allows chylomicrons to be metabolized, which otherwise interfere with the triglyceride assay in a lipid profile. LDL-cholesterol is calculated using the **Friedewald formula** [1] which is validated for samples having a serum triglyceride level <400 mg/dL, when all results are in mg/dL;

LDL cholesterol = Total cholesterol – HDL cholesterol – (Triglycerides/5)

Accordingly, errors in HDL-C measurement will adversely affect the calculated LDL-C level, which is the target of therapy for hyperlipidaemia. Falsely high HDL-C can falsely reduce the calculated LDL-C and vice versa. For samples with triglycerides between 400 – 2000 mg/dL, direct estimation of LDL-C (Direct LDL-C test) is recommended.

Alternatives for HDL and LDL particles

HDL-C and LDL-C analysis could be replaced by the determination of Apo A1 and Apo B respectively. These assays can be readily standardized and are not significantly distorted by high triglycerides. In addition, Apo B reflects all atherogenic lipoproteins taken together [5].

Sub-classes of HDL particles

Discrete HDL particle sub-classes have been identified on the basis of differences in size or charge, including two major ultracentrifugation sub-classes HDL_2 and HDL_3. HDL_2 is larger and thought to be more cardio-protective [4]. Double precipitation methods with polyanions [2] or nuclear magnetic resonance (NMR) spectroscopy could quantify HDL sub-fractions [5].

Personal experience in reporting very high HDL-cholesterol

Our hospital laboratory caters to in-patients, out-patients and screening for non-communicable diseases in the community. We use a homogeneous method using reagents, calibrators and instruments from the same source (Roche Diagnostics) and practice meticulous internal quality control and external quality assurance (EQA) procedures. Periodically we encountered very high HDL-cholesterol levels. The test was repeated in 1:1 dilution for values above the Analytical Measurement Range (AMR) for HDL-C, in order to issue the final result. Although we received an occasional negative feed-back comment from some clinicians, we were encouraged by the success of the EQA results on samples having HDL-C as high as 120 mg/dL.

From routine fasting lipid profiles performed from 2014-2018 and available in the laboratory information system (LIS), we identified 445 individuals having HDL-C levels >100 mg/dL (with the total cholesterol <300 mg/dL)[6]. The male: female ratio was 1:4. 42% of the total were females >60 years old.

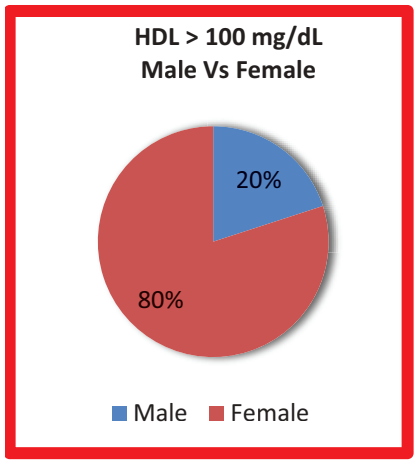

Figure 01:Distribution of high HDL-C according to gender

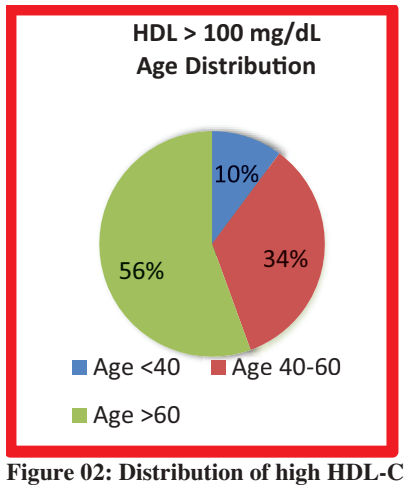

Figure 02: Distribution of high HDL-C according to age

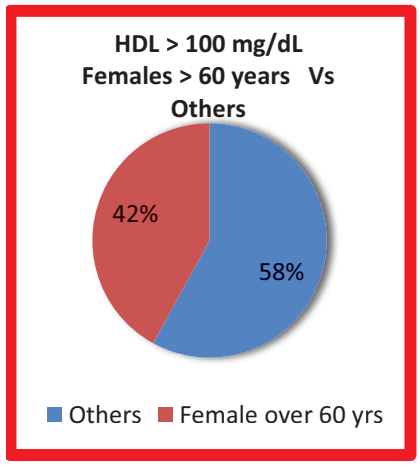

Figure 03: Distribution of high HDL-C females > 60 years vs. others

The highest HDL-C was 167 mg/dL (median 105). (The gender ratio and the median HDL-C value are comparable to some of the published literature [9, 10, 11].

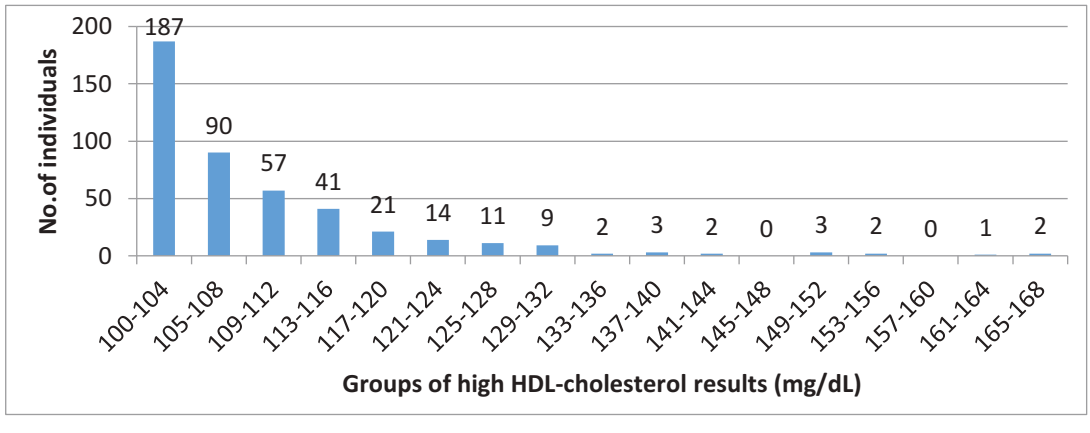

Figure 04: Distribution of invidividual values of HDL- C >100 mg/dL

The variability of HDL-C on those who had multiple lipid profiles on record was low (median 6%), indicating that it was a relatively stable parameter in serum over time. However, the LIS cannot identify those repeating the test using the name differently, which could potentially over-estimate the total number.

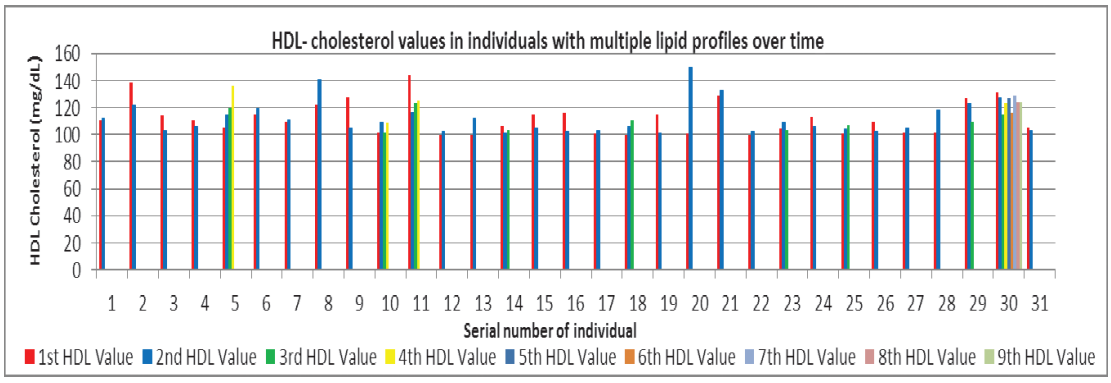

Figure 05: HDL-cholesterol values in individuals with multiple lipid profiles over time.

Are we seeing more individuals with very high HDL-C now?

Probably we identify individuals with very high HDL-C better and with more confidence now. In the past, a very high HDL-C was often considered a laboratory error both by clinicians and laboratory technicians carrying out the manual precipitation method. The laboratories were often not supported by adequate EQA for HDL-C. The focus was on reporting accurately in the 30 – 60 mg/dL range. Laboratory standards have definitely improved since then.

Is very high HDL-C clinically important?

There is emerging evidence that very high HDL-C in an individual is a clinically important finding. Recent research has shed light on a paradoxical increase in morbidity and mortality in individuals with very high HDL-C values [7, 8, 9, 10, 11]. Therefore we need to understand the high-HDL-C burden in our community too and carefully evaluate them.

A publication based on the IDEAL and EPIC-Norfolk studies [8] concludes that very high plasma HDL-C (>70 mg/dL) and very large HDL particles are associated with an increased risk of coronary artery disease (CAD). In this study, those with HDL-C >80 mg/dL in IDEAL and >97 mg/dL in EPIC were evaluated as one group, with no further subdivisions.

The prevailing view that large particle size confers a lower CAD risk, was disputed by this study which measured particle size using NMR spectrometry. However, Apo-A1 remained protective across the major part of its distribution and more uniformly represents a lower risk.

Wijesundera et al [10] endorsed in a CANHEART sub-study in 2017 that they observed an inverse relationship of HDL-C with both cardiovascular and non-cardiovascular outcomes and regarded low HDL-C as a marker of poor overall health. They too evaluated all those >90 mg /dL of HDL-C as one group.

Similarly Wilkins[11] et al reported a plateau effect for CHD risk at very high levels of HDL-C and believe that they are at least partially identifiable through assessment of traditional risk factors.

Interestingly, in a study on a large cohort of (116,508) individuals from the general population in Denmark, Madsen et al[9] observed that the association between HDL-C and all-cause-mortality was ***U-shaped***, with both extreme high and low HDL-C being associated with high mortality. The HDL-C level associated with the lowest risk for all-cause-mortality was 73 mg/dL for men and 93 mg/dL for women. This study had better categorization of individuals with 97-115 mg/dL (n=5795), 116-134 mg/dL (n=1109) and > 135 mg/dL (n=218) as separate groups. Those in the >97 mg/dL group comprised 6.1% of the total subjects. One likely explanation for the U-shape was that genetic variants associated with both high risk of CAD and high HDL-C may play a role (e.g. mutations in *CETP, ABCA 1, LIPC* and *SCARB 1*).

Future of individuals with very high HDL-cholesterol

Those with very high HDL-C need to be identified by using an assay with proven quality as well as performance of dilution tests whenever the result is above the cut-off for AMR as verified by the laboratory periodically. There is evidence to indicate that once identified, they too should to be evaluated for both cardiac and non-cardiac health. Pertinent tests include Direct LDL-C measurement, Apolipoprotein A-1, Apo A-1/B ratio, HDL sub-classes and genetic mutation studies amongst others.

In the past, such individuals were reassured as belonging to a group with low risk for CAD. However, with the current evidence available to us, we can no longer dismiss them placidly!

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Editorial Comment

This paper highlights the current concept of dysfunctional HDL wherein, some HDL forms are thought to be pro thrombotic, pro inflammatory and pro atherogenic. At present laboratory identification of these dysfunctional HDL particles is not feasible. A similar problem exists with the dense and fluffy LDL particles which need expensive laboratory procedures for identification. The presence of different types of HDL and LDL particles make the routine "lipid profile" a "battered gold standard" in risk profiling patients.

Case Report

Three Cases of Cerebral abscesses by Streptococcus anginosus group in patients with congenital heart diseases

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Abstract

We present three cases of cerebral abscesses caused by *Streptococcus anginosus* (*milleri*) group in patients with congenital heart diseases found within a period of three months. Three patients diagnosed to have complex congenital heart diseases and who were on proper follow up presented with clinical features of space occupying lesions in the brain. They were diagnosed to have cerebral abscesses and underwent aspiration of pus. The pus samples revealed three different Streptococcal species, *S. anginosus, S. intermedius and S. constellatus* which belong to the *Streptococcus anginosus* (*milleri*) group. The three patients did not have features of infective endocarditis or positive blood cultures at the time of presentation and had no history of dental or other surgical procedures. All three patients underwent surgical interventions to drain the cerebral abscesses and two patients had to undergo re-aspiration. The bacterial isolates from the pus samples, were sensitive to penicillin and ceftriaxone and the patients responded well to six weeks of IV ceftriaxone. *Streptococcus anginosus* group can give rise to cerebral abscess following bacterial dislocation to the blood leading to hematogenous spread. This evidences *Streptococcus anginosus* group being a common pathogen of cerebral abscess in patients with congenital heart disease. Since these organisms are sensitive to ceftriaxone it could be suggested as the empirical treatment. Surgical intervention and prolonged antibiotic therapy are the mainstays of treatment.

Introduction

Streptococcus anginosus (*milleri*) group is a subgroup of viridans group of Streptococci and consists of three different Streptococcal species, *S. anginosus, S. intermedius and S. constellatus*. They are harmless inhabitants of oral cavity, gastrointestinal tract and female genital tract but can cause systemic infections [(1)]. The distinct feature from the other *Streptococcus* species is their ability to form deep abscesses and they are considered as true pathogens when they are isolated from humans [(2)].

Historically, *S. anginosus* has been found to be the species most frequently isolated from clinically significant specimens and *S. intermedius* the least common [(3)].

Like other Streptococcal species they are Gram positive cocci in chains. They have typically small colonies and demonstrate variable hemolysis patterns in sheep blood agar. The identification of this group is difficult in many laboratories due to the diversity of hemolytic and Lancefield groupings [(1)].

The virulence factors of the organisms are the polysaccharide capsule, pyrogenic endotoxins, presence of super antigens that can excessively stimulate the immune system and hydrolytic enzymes [(4)].

Hydrolytic enzymes like hyaluronidase can facilitate the spread the pathogens through tissues and the liquefaction of pus [(1)]. These organisms poorly stimulate chemotaxis and are able to survive phagocytosis. Abscess formation is usually polymicrobial with oral and gastrointestinal microorganisms and anaerobic flora which enhance the growth of *S. anginosus* group organisms [(5)].

We present three cases of cerebral abscesses in patients with congenital heart diseases found within a period of three months duration. The identification and minimum inhibitory concentration values were taken from the BD Phoenix Automated Identification system.

Case reports

Case Number 01

A twenty-three-year-old lady diagnosed to have complex congenital heart disease i.e. large VSD, hypoplastic right ventricle, moderate mitral regurgitation with Eisenmenger's syndrome and pulmonary hypertension presented with fever of seven days and seizure episodes. With the onset of symptoms, she was hospitalized and found to have a right parietal infarction, which was managed medically with anticoagulants. With persistence of symptoms, the repeat CT scan done showed a right sided parietal abscess and burr hole aspiration of pus revealed Streptococcus intermedius.

Case Number 02

A forty-four-year-old lady diagnosed to have a large VSD, double outlet right ventricle and a balanced shunt on medical management presented with a history of fever, headache, vomiting of five days and altered behavior and right sided body weakness of one day. She also had neck stiffness and positive Kernig's sign. MRI showed a left occipital abscess leading to a midline shift. The burr hole aspiration of pus revealed *Streptococus constellatus*. After two weeks of intravenous antibiotic therapy she again developed headaches and behavioral changes. The contrast enhanced CT evidenced refilling of the abscess and re-aspiration was performed and this time the pus did not reveal a bacterial growth.

Case Number 03

An eight-year-old girl diagnosed to have severe right ventricular outflow tract obstruction, hypoplastic tricuspid valve, patent foramen ovale and hypertrophic right ventricle presented with a history of recurrent headaches of one month and vomiting and visual disturbance of 4 days. The MRI scan revealed the presence of multiple cerebral abscesses in the right frontal region. The pus drained revealed *Streptococcus anginosus*.

The three patients did not have any signs of infective endocarditis. They had no history of dental or other surgical procedures in the recent past. They were regularly followed up in cardiology clinics with medical management.

At the time of presentation they were investigated for infective endocarditis and the blood cultures done at that point were found to be negative, 2-D echocardiograms and trans-oesophageal echocardiograms did not reveal any vegetations.

All three culture isolates from the aspirated pus grew typical colonies of *Streptococcus anginosus* group after 24 hours of aerobic incubation but two of them grew only on chocolate agar and not on quality-controlled sheep blood agar. All three were sensitive to penicillin and ceftriaxone according to the Minimal Inhibitory Concentration given by the BD Phoenix Automated Identification system.

The patients were treated with a combination of intra-venous ceftriaxone high dose that cover central nervous system and metronidazole for a total period of six weeks.

All three had undergone burr hole aspiration of the cerebral abscess pus and the latter two cases had to undergo re-aspiration. All three patients showed good clinical, radiological and biochemical response with six weeks of intra-venous antibiotic therapy.

Discussion

Cerebral abscess is a serious focal infection of the brain parenchyma that begins as a localized cerebritis [6,7]. Bacteria are the causative agents in more than 95% of brain abscesses in immunocompetent patients [6]. The pathogenesis is described as contiguous spread (ear and sinus infection, neurosurgery or trauma) in 40% to 50% of cases, or via haematogenous dissemination in 30% to 40% of cases or due to distant suppurative foci (e.g. dental or lung abscess). In patients with congenital heart disease or infective endocarditis pathogens access the brain tissue via haematogenous route [6].

In patients with congenital cyanotic heart disease the development of cerebral abscess is a consequence of associated hypoxia and the resultant polycythemia and hyperviscosity. Due to the hyperviscosity, blood flow of the cerebral microcirculation becomes sluggish and microthrombi are formed leading to focal encephalomalacia. The permeability of the blood brain barrier is altered. Right to left cardiac shunts lets the Infectious organisms in the blood escape the bacterial phagocytosis in the lungs. They infect the sites having focal encephalomalacia leading to cerebritis [7].

Streptococcus anginosus group is a well-recognized cause of cerebral abscesses. The primary source of infection could be oral, dental, gastro intestinal or another distal abscess. It could be due to septic emboli of infective endocarditis in patients with risk factors but may also occur in the absence of obvious other infective foci [8].

These three patents with cyanotic congenital heart diseases were at the risk of endocarditis and cerebral abscess and they presented with symptoms of infection of the central nervous system.

In a study of 30 children with cerebral abscesses and congenital heart disease 37% had cyanotic heart disease and the most common microbe in children with cyanotic congenital heart disease was of the *Streptococcus milleri* group i.e.52% [7].

Even though this group is not a common organism causing infective endocarditis, it can be the pathogen in bacteraemic patients especially when they have damaged or prosthetic heart valves. Studies show that this group represent between 3% to 15% of the streptococcal blood culture isolates from patients with endocarditis [9,10].

The unique feature of this Streptococcus group is suppurative infections leading to intra-cardiac lesions like peri annular or myocardial abscesses or metastatic abscesses. In a review of infective endocarditis by *Streptococcus anginosus* group, out of 29 cases 25% had distant suppurative complications [11].

These three similar cases are evidence for the *Streptococcus anginosus* group being a common pathogen in cerebral abscess with patients with congenital heart disease.

We observed that the organism did not grow in the quality-controlled sheep blood agar and therefore could be misinterpreted as a laboratory contaminant. So, enrichment of the sample and 48 hours incubation have to be emphasized. It is always important to direct the aspirated pus samples for microbiological investigations.

For the cerebral abscesses until the results of aspiration samples and blood cultures are available empirical antibiotic should be given to cover streptococci, staphylococci, anaerobes and enterobacteriaceae. The pharmacokinetic and pharmacodynamic properties should include the ability to cross the blood brain barrier and good activity in acid environment i.e. bacterial abscess. The experts recommend six weeks of antibiotic treatment for immunocompetent patients in the absence of clinical complications. Most clinicians suggest a combination of third generation cephalosporin (cefotaxime or ceftriaxone, CNS dose) plus intravenous metronidazole for community acquired brain abscesses. Repeat radiological brain imaging is suggested at the sixth week of antibiotic therapy [6].

Conclusion

Patients with congenital cyanotic heart disease can develop cerebral abscesses, caused by *Streptococcus anginosus* (*milleri*) group and the risk factors like dental caries should be regularly screened. Surgical intervention and prolonged antibiotic therapy are the mainstay of treatment.

Conflicts of interests: None

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Case Report

Challenges of a Transcatheter aortic valve implantation (TAVI) in a calcified Bicuspid aortic valve.

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Abstract

The first case in Sri Lanka of successful implantation of a transcatheter aortic valve (TAVI) in severe bicuspid aortic stenosis, represented an opportunity to analyze the unique challenges encountered by clinicians when right bundle branch block is present and eccentric severe calcification extending to left ventricular outflow tract is encountered with calcific aortic stenosis. The need to prevent occurrence of both heart block and paravalvular leaks, in the era when low risk patients also now have an upgraded US FDA approval for TAVI, critically requires the accurate selection of device and dimensions and intra procedural considerations, based on precise CT and Echo

Introduction

Morphologically abnormal aortic valves present a unique challenge to treatment. Surgical aortic valve replacement has been the cornerstone of treatment of severe aortic stenosis or regurgitation, but with the advent of transcatheter aortic valve therapy, new opportunities for aortic valve replacement is available, along with it, there are unique challenges that must be overcome for a successful result. The prime concern of the process involves the prevention of substantial paravalvular leak (PVL) of the new valve, particularly in relation to eccentric closure lines with heavy calcification.

Case summary

A 59-year-old male, with a previous history of acute anterolateral STEMI in 2014, treated with Primary PTCA of LAD in United Kingdom, presented with worsening exertional shortness of breath. Despite optimal medical therapy, echocardiography demonstrated progressive global decline of LVEF over a period of two years, down to 42%, with progressive calcification and severe restriction of opening of a bicuspid aortic valve with a calculated valve area of <0.99 cm^2 (Severe AS).

ECG showed baseline RBBB, coronary angiogram demonstrated patent LAD stent with mild plaque disease. He was given advice to proceed to surgical aortic valve replacement as he was perceived to have a low-to-medium surgical risk, both in Sri Lanka and in UK, but following extensive discussion, he declined this decision. Refusal of surgery resulted in consideration for TAVI.

CT analysis

Accurate ECG gated CT analysis (figure 1) was crucial for determining device type/size and chances of success or complications. There was fused (single) RCC (Right Coronary Cusp) and LCC (Left Coronary Cusp) and a large NCC (Non Coronary Cusp) with eccentric closure line and heavy calcification that extended into the LVOT (Left Ventricular Outflow Tract- figure 2), which could impinge on the Left bundle of His, making the whole process challenging, in the presence of RBBB (Right Bundle Branch Block). Iliac arteries were tortuous, but of good caliber.

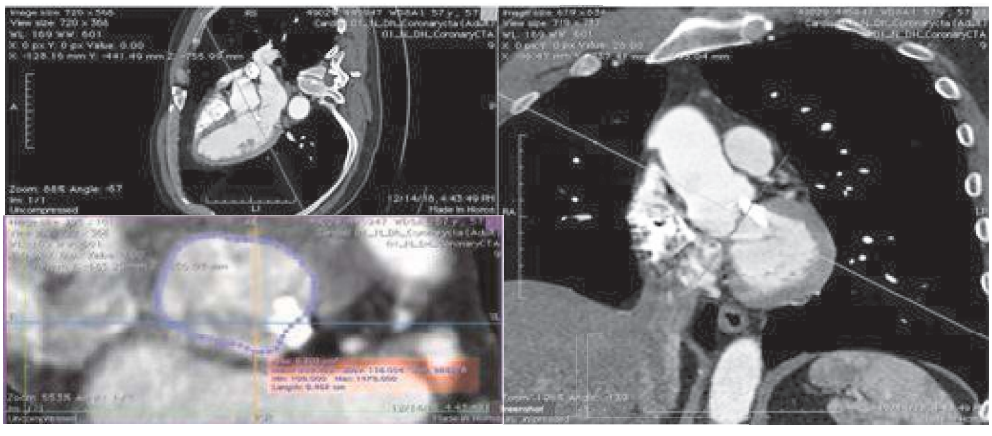

Figure 1-Multiplanar

CT reconstruction at the level of virtual calcific annulus of the bicuspid aortic valve. Dense calcification In to LVOT seen.

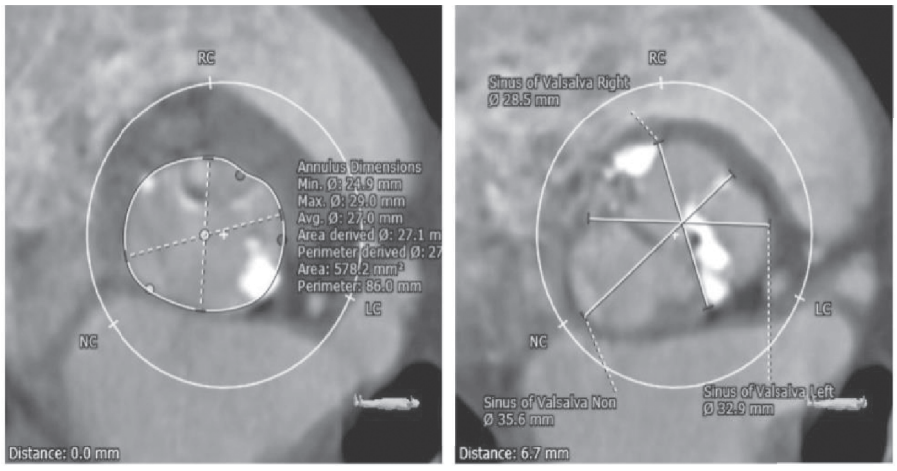

Figure 2:

Calcification artefact at 4 o'clock position interferes with correct measurements of the valve annulus.

Dilemma of device selection

Whilst the choice of a balloon expandable vs self-expanding prosthetic valves has recently narrowed down substantially in bicuspid aortic stenosis, the wider experience with self-expanding valves and the results of the non-inferiority Evolut Low Risk Trial [(1)] released in March 2019 and the revised FDA approval on its use for this indication in 2019 prompted us to select a Medtronic Evolut R device.

The biggest concern was the accuracy of required sizing of the device: At the level of the annulus, the perimeter was 872mm (3 Mensio Systems) but 5 mm above annulus it tapered to 780 mm and, 8mm above annulus 796mm. Hence at annular level, best fit appeared to be a 34 mm Medtronic Evolut R valve, but it is imperative to recognize, that with this supra-annular valve, in this case, sealing maximally occurs at 5 to 8mm level above the virtual annulus. This indicated that a smaller 29 mm valve would suffice. As the device still has no skirt (compared to the newer generation Evolut Pro devices), there was a risk that, under sizing could result in substantial PVL, which is directly linked to poor outcomes and mortality post TAVI implantation [(2)].

Procedural summary

Procedure was performed under total conscious sedation and local anaesthesia with full percutaneous suture closure of access site. Procedure time was 60 minutes. Temporary pacing was established via right subclavian vein. Pre-dilatation was performed of the bicuspid valve using a 20 mm pre- dilatation balloon, whilst assessing the movement of the bulky leaflets, which did not occlude the coronary ostia.

The 29 mm Evolut R valve was navigated easily, positioned and released on the Confida guidewire, with excellent deployment height (figure 3) and no heart block was noted. The pre-operative peak to peak gradient of >40 mmHg reduced to <9 mmHg post procedure (figure 4). More importantly, there was no PVL (echo /aortography / haemodynamics (figure 4)). Patient was mobilized at 12 hours and discharged by 72 hours with no complications.

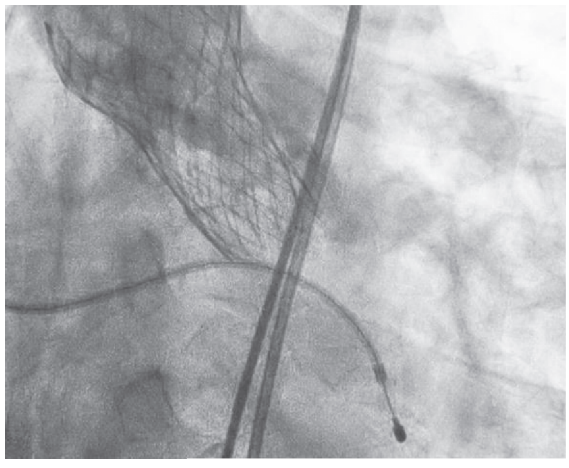

Figure 3: Post Implantation aortography demonstrates excellent position/ seal and no evidence of AR/PVL

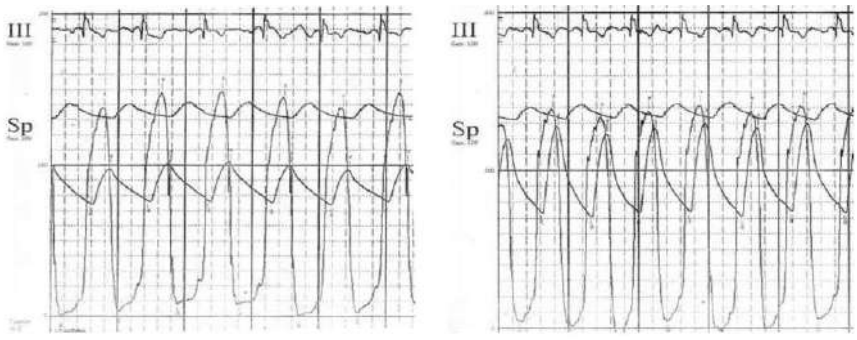

Figure 4:
Haemodynamic data pre (left) and post (right) TAVI implantation: substantial reduction of Peak to peak gradient, with an excellent Aortic regurgitation index2 suggests good outcome

Discussion

Accurate interpretation of CT aorta is essential in bicuspid aortic stenosis patients undergoing TAVI procedures. The plane of seal must be understood and a strategy of 3 level analysis at 0, 5, 8 mm levels is mandatory. Presence of excessive calcification extending to LVOT carries a risk of complete heart block, in the presence of baseline RBBB; however, careful pre-procedural sizing and intra-operative care can avert complications and achieve perfect results in this difficult anatomy.

Conflicts of interests: None

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Case Report

Granulicatellae elegans endocarditis presenting as leukocytoclastic vasculitis: A rare presentation of endocarditis with a rare organism.

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Abstract

Background - Sub-acute bacterial endocarditis (SABE) is a serious medical condition with different clinical presentations. In rare instances it can present as a cutaneous small vessel vasculitis and leads to a delay in diagnosis which may result in a fatal outcome. Therefore it is important to have a high degree of clinical suspicion with early diagnosis and initiation of an empirical antibiotics regime to achieve a favorable outcome.

Case presentation - Here we are reporting a case of a sixty one year old man who presented with constitutional symptoms and biopsy proven leucocytoclastic vasculitis secondary to sub-acute bacterial endocarditis involving the mitral valve caused by an unusual organism, *Granulicatella elegans*. The vasculitic rash completely resolved with the empirical antibiotic therapy along with improvement of inflammatory and echocardiographical parameters. Therefore the management strategy used here for cutaneous vasculitis is different from primary vasculitis management where immunosuppressives are the mainstay of the management.

Conclusion - This case highlights the importance of considering sub-acute bacterial endocarditis as a differential diagnosis, in the context of cutaneous small vessel vasculitis.

Key Words - Sub-acute bacterial endocarditis (SABE), *Granulicatella elegans,* leukocytoclastic vasculitis

Introduction

Infective endocarditis is a life threatening medical condition affecting the endocardial surface of the heart .The presence of predisposing cardiac conditions such as degenerative valvular lesions and congenital defects are considered to be strong risk factors. Infective endocarditis is mainly caused by oral Streptococcus species in the general population, whereas *Staphylococcus* aureus and coagulase negative staphylococci are commonly involved in endocarditis in intravenous drugs abusers, individuals with prosthetic valves and in health care related endocarditis [(1)].

Granulicatella species is a nutritionally variant streptococci (NSV) which is a coagulase and oxidase negative commensal organism in the oral cavity [(3)]. Endocarditis is a relatively rare manifestation of *Granulicatella elegans,* where it can be erroneously labeled as culture negative endocarditis due to the difficult nature of the organism to grow in conventional culture media[(7)]. Consequently Granulicatella endocarditis leads to a more extended clinical course with large vegetations (more than 10mm) and more complications which might necessitate valve replacement [(4, 9, 10)].

Cutaneous leukocytoclastic vasculitis (LCV) is an immune complex mediated disorder due to infectious & noninfectious etiologies [(11)]. Management strategies would be different in the two clinical contexts.

The empirical antibiotic therapy would be the management of choice in infective etiologies whereas non infective cases are being managed with immunosuppressive therapy. Therefore the wrong management strategy would result in a devastating outcome.

Case presentation

A sixty one year old male presented with constitutional symptoms of one month and painful erythematous rashes on both lower limbs of two weeks duration to a dermatology unit. On examination he was pale, cachectic and a vasculitic rash was noticed over both lower limbs. (Figure.01)

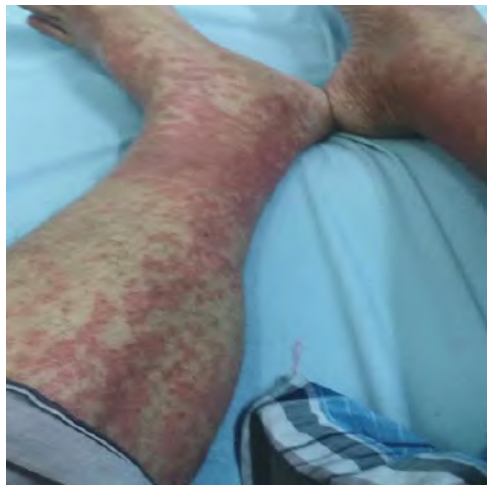

Figure 01: Erythematous papular rash on both lower limbs

He did not have clubbing, splinter hemorrhages or Janeway lesions. Cardiovascular examination revealed a thrusting cardiac apex with a grade III pansystolic murmur which was radiating to the axilla suggestive of mitral regurgitation. Rest of the examination findings were unremarkable. His initial hematological and biochemical profiles revealed, White Blood Cell count of 18 x103/mm3 with Neutrophil of 73%, Lymphocytes of 20%, Hemoglobin of 7.8 g/dl, C Reactive Protein of 148 mg/dl, Erythrocyte Sedimentation Rate of 48mm/hr, blood picture revealed normochromic normocytic picture compatible with anaemia of chronic disease, and the three sets of Blood cultures were positive for gram positive cocci arranged in short chains on light microscopy (Figure. 02).

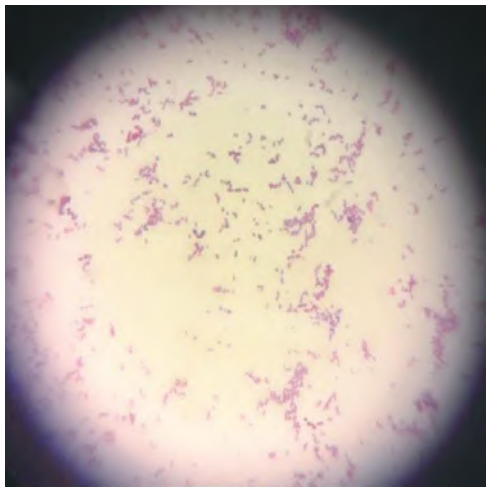

Figure 02: Light microscopy: Gram positive cocci arranged in short chains

This organism was identified as Granulicatella elegans by VITEK 2 automated method and antibiotic sensitivity testing revealed the organism to be sensitive for vancomycin, levofloxacin, trimethoprim/sulfamethoxazole. His antinuclear antibody, ANCA study, hepatitis B and C serology, rheumatoid factor, cryoglobulins and tuberculosis testing were all negative. Trans thoracic echocardiography showed severe mitral regurgitation without obvious vegetations, However two and three dimensional Trans-Esophageal Echo (TEE) study revealed multiple small vegetations attached to both leaflets of mitral valve and to the left atrial surface over the aortic bulge (Figure.03a, 03b, 03c). Skin biopsy report further elaborated neutrophil infiltration of the wall of the dermal blood vessels with red cell extravasation suggestive of leukocytoclastic vasculitis (figure 04).

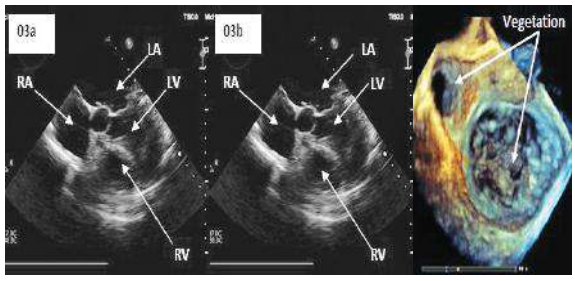

Figure 03a, 03b : Multiple vegetations over mitral valves and atrial surface on 2D echocardiogram
Figure 03c: Multiple vegetations over mitral valves and atrial surface on 3D echocardiogram

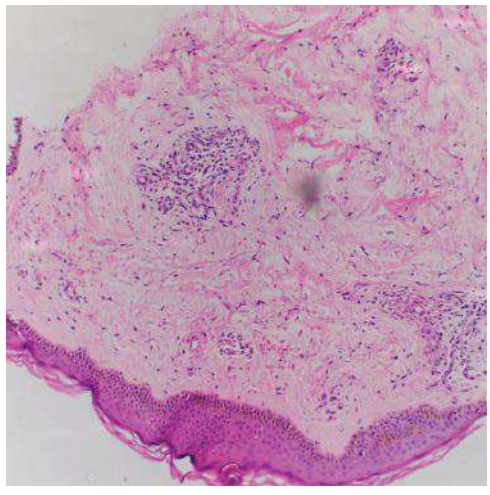

Figure 04: Skin biopsy: Neutrophil infiltration of the wall of dermal blood vessel

He was initially managed with three pints of A+ blood and treated with a 42 day course of intravenous vancomycin and 14 days of intra venous gentamycin as he was allergic to penicillin. His vasculitic rash completely disappeared on the seventh day of the treatment and by that time his blood cultures were also negative. After 42 days of antibiotic therapy he achieved dramatic improvement of clinical, laboratory and echocardiographic parameters. His repeat white blood cell count was 8x103/mm3, with neutrophils 60%, lymphocytes 28%, hemoglobin 12.5g/dl. His C Reactive Protein was 5mg/dl, erythrocyte sediment rate 18 mm/hr and repeat TEE revealed disappearance of all vegetations leaving the residual grade III mitral regurgitation. As the patient had well responded to the antibiotic therapy, he was offered an interval mitral valve repair by the cardiothoracic team.

Discussion

Leukocytoclastic vasculitis (LCV) is a cutaneous small vessel vasculitis, which is characterized by nutrophilic infiltration of post papillary venules with fibrinoid necrosis, endothelial damage and extravasation of red blood cells [11]. Manifestations of LCV are associated with diverse clinical conditions, ranging from noninfectious to infectious etiologies. Though SABE is a well-known associated clinical entity for vasculitis, LCV as the initial presentation of SABE is extremely uncommon [12]. As in our case, patients can be erroneously referred to irrelevant specialties, due to this atypical nature of the presentation, especially in the absence of other peripheral signs of SABE. This referral bias may lead to a delay in the diagnosis with an unfavorable clinical outcome. Initiation of immunosuppressive medication as in the case of primary vasculitis may also result in catastrophic complications especially in the presence of a systemic infection. According to the available literature, endocarditis patients with dermatological manifestations have shown more extra cardiac complications, mainly in the form of cerebral embolization than the others who did not have dermatological manifestations [13].

In this clinical vignette, we also try to highlight the rarity of the causative organism: *Granulicatella elegans* in SABE [4]. *Granulicatella* species consist of *Granulicatella adiacens, Granulicatella elegans* and *Granulicatella balaenopterae*. However *Granulicatella elegans* as a causative organism for endocarditis is comparatively rare than *Granulicatella adiacens*, mainly due to the lack of fibrinonectin bindings[5,6] .They were initially considered as the NVS of commensal oral flora and often labelled as culture negative endocarditis because of poor growth of the organism in conventional culture media[2,4]. Therefore it is very important to address the possibility of these organisms especially in a context of culture negative endocarditis [7]. In addition to endocarditis, *Granulicatella* elegance rarely can cause bacteremia due to abdominal infections and chronic maxillary sinusitis [8]. *Granulicatella* endocarditis commonly involves the aortic and mitral valves with rare extension to left atrial surface as in our case [4]. The clinical evidence for endocarditis purely due to Granulicatella elegans is extremely rare. According to available literature, reported complications of endocarditis caused by Granulicatella species include heart failure (30%), embolic phenomena (30%), perivalvular abscess (11%) and a mortality rate of 17% [10].

Based on the 2015 European Society of Cardiology endocarditis guide line, infective endocarditis caused by Granulicatella species should be treated with penicillin G, Ceftriaxone or vancomycin for 6 weeks, including aminoglycosides for at least the first 2 weeks [9, 10] .Due to high treatment failure and relapse rates, this is considered as a challenging clinical condition to be treated and in some situations early surgical vegetectomy is warranted [4]. Since our patient had an excellent clinical response, he was offered an interval cardiothoracic intervention along with medical management of mitral regurgitation.

Conclusion

SABE is a serious clinical entity where the early diagnosis and empirical antibiotic therapy is essential for an excellent clinical outcome .However atypical presentation of SABE such as LCV as in our case may lead to erroneous referral bias which may result in further delayed the diagnosis. In addition to the atypical presentation, this case also highlights the rarity of the organism: *Granulicatella* elegance as the causative organism for SABE and its characteristic clinical and echocardiographic features according to the available evidences. This case also emphasizes the importance of considering SABE as a differential diagnosis, among patients with cutaneous small vessel vasculitis and constitutional symptoms.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of interests: None

Acknowledgements

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Case Report

Proximal migration of stent after deployment in coarctation of aorta: an uncommon complication and successful bailout.

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Abstract

Introduction: Coarctation of aorta (CoA) though a relatively common congenital cardiac defect is an uncommon cause for systemic hypertension in young adults. Trans-catheter approach with balloon dilation and stenting has been used for nearly four decades and remain a viable treatment option. Complications though rare have been reported, and include stent migration. Proximal stent migration however is uncommon.

History and procedure: A 27 year old patient who was diagnosed to have hypertension was found to have a coarctation of aorta. His 2Decho showed left ventricular hypertrophy with a 70 mmHg pressure gradient across the coarctation. Percutaneous stenting was planned.

Aortography revealed a left subclavian level aortic diameter of 17.04mm, with the narrowest diameter measuring 2.83mm with a length of 27.06mm. Using a .034 Terumo guide wire, a 6Fr Judkins right catheter was used to cross the CoA. A hand crimped CP stent was loaded on a 12mm X 4cm balloon in balloon and inflated across CoA via an 11Fr Cook sheath. Following the deployment, a proximal displacement of stent was noted.

The same balloon was advanced and by sequential inflation the stent was dragged towards the CoA as far as possible. Afterwards a new 3.4cm CP stent was hand loaded over the same balloon and with overlap deployed across the CoA. Afterwards using a Numed 23mmX3cm balloon the proximal stent was re dilated at 6 ATM and overlap was re dilated at 4 ATM. Final results showed preserved blood flow across the aorta with successful drop in pressure gradient.

Conclusion: Failure to fully withdraw the Cook sheath was the cause for the complication. Balloon angioplasty and Stenting of CoA though is a safe procedure, can be complicated with challenging complications like stent migration. However with careful manipulation and use of additional stents successful results can be achieved despite initial shortcomings.

Keywords: Coarctation of aorta, complication, proximal stent migration.

Introduction

Coarctation of aorta (CoA) is a common congenital cardiac defect with an incidence of 3 per 10,000 live births. It commonly causes a discrete narrowing along the lumen of aorta, but anatomical variations can be seen [(1)]. Commonly located in the juxtaductal position , after the origin of the left subclavian artery in the descending aorta it restricts flow of blood distal to that of the constriction[(2)] and doing so paves the way for causing complications through a process of maladaptation. It has a heterogeneous presentation, and has a propensity to increase the overall risk of mortality by the virtue of its impact on the cardiovascular system. When left un-attended, nearly 75% of patients with CoA died before the age of 50 years [(3)], stressing the need for timely intervention. Correction of CoA was initially approached surgically, but the last four decades have seen advances in percutaneous interventions to the point where successful results have been achieved through endo-vascular intervention. Initially this was done through balloon dilation only. Then subsequently the utilization of stents to place across the narrowest region was used to gain and maintain a good blood flow.

However, each step in the evolution of management is fraught with a spectrum of complications [(4)]. Complications due to the procedural steps may range from vascular trauma, stent and balloon based complications, infection, systemic complications, need for urgent surgery (rare) and death [(4)]. Stent migration is one such known complication, however proximal displacement of the stent, post deployment is rare and is a challenging complication to overcome. In this case vignette we describe a situation in which we faced a scenario of proximal stent migration, and how we successfully overcame the complication to achieve procedural success.

Case presentation

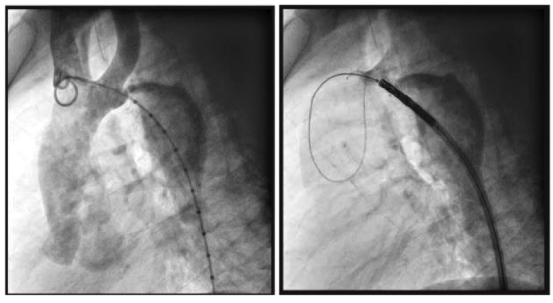
A 27 year old South-Asian male was investigated for young hypertension, and was discovered to have Coarctation of aorta. He was clinically otherwise asymptomatic. His pulse was 90 beats per minute, with an elevated blood pressure of 160 mmHg systole, 90 mmHg diastole. Cardiac apex was not shifted in position, but was heaving in nature. Rest of the systemic examination was normal.

A 12 lead electrocardiograph revealed sinus rhythm, with a LV strain pattern. A transthoracic 2D echo revealed, preserved ejection fraction with mild left ventricular hypertrophy, with no other valvular abnormalities. The pressure gradient across the stenosis (short axis view) was elevated at 70mmHg. Whole blood analysis and other basic blood workup was normal.

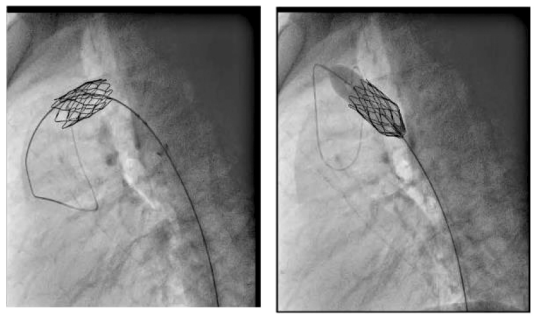
The patient underwent an aortogram for pre-procedural assessment, which revealed the CoA to be 27.06mm in length, with the narrowest diameter measuring 2.83mm in diameter. The ascending aorta measured 17.04mm at the level of the subclavian artery and 16.6 mm at the level of the diaphragm.

A clinical decision was taken to attempt balloon dilation and stenting of the CoA. The procedure was done under general anaesthesia. Right side femoral arterial access was taken with an 11 Fr sheath. The narrowest point of the CoA was crossed with a Terumo guide wire 0.035 inches, with a Judkins right 6 Fr catheter for guidance. Afterwards using a 11Fr Cook sheath a hand crimped, bare 3.4cm Cheatham Platinum (CP) stent was introduced on a balloon in balloon (BIB) measuring 12mm X 4mm and deployed across the narrowest point. Following the deployment of the stent, it was visualized proximal to that of CoA, freely floating in the transverse aortic arch suggesting that stent migration had taken place. Angiography revealed compromising of the blood flow to surrounding vessels including the left subclavian artery.

To overcome the complication, initially the same balloon was used and inflated across the stent and the stent was slowly dragged distally as possible close to the CoA, with multiple sequential inflations and deflations. Afterwards a 2nd similar stent was used and deployed across the CoA, while maintaining the overlap of the now repositioned migrated stent. To achieve good approximation and to open up the stent a 23mm X 3cm Numed balloon was used and the stent including overlap was post-dilated to 6 atm. Repeat angiography revealed good placement across the CoA, with preserved uncompromised blood flow across the vessels, including left subclavian artery (Image 1A-8A).



1A 2A



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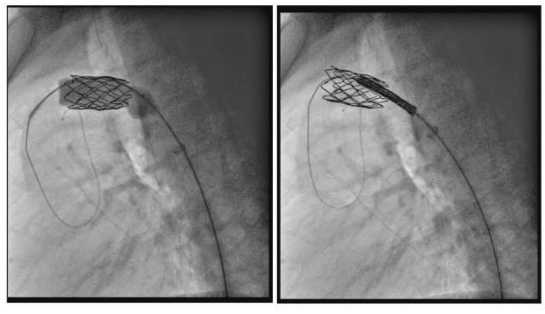

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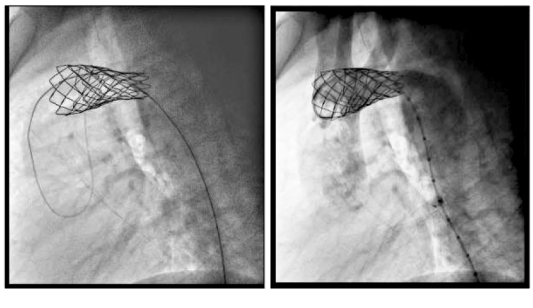

7A 8A

Case Report

Discussion

Post deployment migration of stent, in CoA is not uncommon, and occurs about 3-5% of the time. However, most are seen to migrate distally, along with the flow [5]. Retrograde migration is very uncommon and is rarely reported in literature [6]. Displacement of the stent post deployment, requiring an additional intervention to achieve success is known as a malposition[7].Usually migration is an early complication , occurring soon after deployment, rarely however it can occur even late, weeks or even months after deployment, though its suspected to be a late detection , rather than a late migration[5]. The reasons behind migration is attributable to multiple causes which include preparatory or procedural errors and errors in decision making. Inaccurate assessment of CoA, is considered the most important reason, resulting in inaccurate sizing and utilization of hardware. Using an oversized balloon (>2mm than that of the proximal aorta) and an undersized balloon catheter can result in stent migration. Furthermore the balloon catheter during deployment can also contribute towards malposition, when the balloon catheter migrates during inflation. Alternatively the balloon used to inflate the stent may also play a role, including rapid uncontrolled inflation or rarely when the balloon ruptures. Using techniques such as a delayed sheath retraction, which allows the distal stent to expand first while keeping the proximal part both balloon and stent within the sheath potentially can also possibly result in stent slipping and in stent malposition. Additional considerations, include the choice of anaesthesia. Conscious sedation triples the risk in comparison to general anaesthesia in regard to possible stent migration, due to patient movement [7, 8].

Stent migration poses a challenge for the interventionist, in view of overcoming the complication. A slight migration distally, allows the possibility for manipulation using the balloon catheter to accurately reposition and dilate. Failing which, if possible, a stent retraction is an alternate bailout. Alternatively a secondary stent may need to be deployed covering both the CoA and the prior stent to achieve procedural success[8]. Unsuccessful bailout may require open surgery in view of stent retrieval and repair of CoA. Proximal stent displacement into the ascending aorta poses a unique problem, where manipulation is both difficult and can be fraught with potential complications. Surgery is the preferred option when proximal/retrograde migration had taken place due procedural complexities and possible complications[5, 6, 9].

Rarely a few interventionists chose to proceed with repeat intervention to achieve success, Kannan et al used a novel approach by using a snare to reposition and stent CoA[10].

In our case vignette the reason for stent migration was attributed to the use of delayed sheath retraction technique, in which failure to withdraw the sheath fully during the final phase of deployment resulted in the stent slipping proximally into the ascending aorta.

Avoidance of complications such as stent migration mainly depend on good preparation beforehand. Accurate assessment of CoA using advanced imaging e.g. CT or MRI imaging modalities and sizing using balloons. Use of new generation hardware e.g. balloons such as BIB which allow graduated rise in pressure and avoidance of older generation of stents. Following the technical steps to the letter without haste is also essential.

Conclusion

In CoA, stenting is a safe and viable solution. Complications though rare can occur and are attributable mainly due to technical and operator decisions. Good preparation and accurate sized hardware with patient delivery will help achieve success. Stent migration, including proximal displacement though uncommon is a complication which can be overcome with careful manipulation and use of additional stents rather than opting for surgery.

Conflicts of interests: None

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Case Report

A case report of femoral angioplasty in a patient with severe coronary artery disease.

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Abstract

We describe a case of a 70 years-old male patient, who underwent percutaneous transluminal angioplasty (PTA) for a 10-cm total occlusion of his left superficial femoral artery, which had resulted in pre-procedural significant pain at rest and dry gangrene of the big toe. His pain improved markedly after angioplasty and a good blood flow was noted clinically and radiographically after the procedure.

This case highlights the fact that, among well selected patients who present with critical limb ischemia (CLI) and are at a higher risk for bypass surgery, PTA of femoral-popliteal district can still be a safe and an effective alternative method [1-5].

Keywords: Femoral angioplasty, dry gangrene, critical limb ischaemia

Case report

A 70-year-old male with CLI on his left leg was admitted to our Institution, with dry gangrene of his right big toe. He gave a clinical history of type 2 diabetes mellitus for over twenty years and he was a heavy smoker. Ultrasonographic and doppler studies of his left leg showed the presence of a lengthy occlusion at the mid third of superficial femoral artery (SFA) with a very poor distal flow. He was scheduled for a femoro-popliteal bypass surgery and was referred for cardiac assessment prior to the surgery. His 2D echocardiogram revealed an ejection fraction of 40% with multiple hypokinetic segments. Subsequently, he underwent a coronary angiogram which showed severe triple vessel disease (TVD). He was a high-risk patient for a femoral arterial bypass surgery. The patient was also subjected to bilateral femoral angiograms at the same time, which revealed a left sided long segment of chronic total occlusion (CTO) of the superficial femoral artery with bridging collaterals and multiple skip lesions of the anterior tibial artery (fig1).

Right femoral angiogram showed a totally occluded anterior tibial artery. Because of the high risk of surgery, he was peri procedurally planned for PTA.

Ipsilateral common femoral artery puncture was done under fluoroscopy guidance. Antegrade percutaneous approach was performed with a 7Fr sheath. JR 7F catheter was selected to reach the lesion. The CTO lesion was crossed with a Gaia third guide wire. The lesion was initially dilated with 2*20 mm' MOZEC NPB' at 15 atm (fig 2) then with a 6*40mm' MOZEC PTA 'at 4 to 6 atm (fig3).

The anterior tibial artery lesions were dilated with 'QUANTAM APEX' 4*12 mm HPB at 16 atm. The post procedure femoral angiogram showed very good results with a TIMI iii flow in the femoral artery and all its distal branches (fig4).

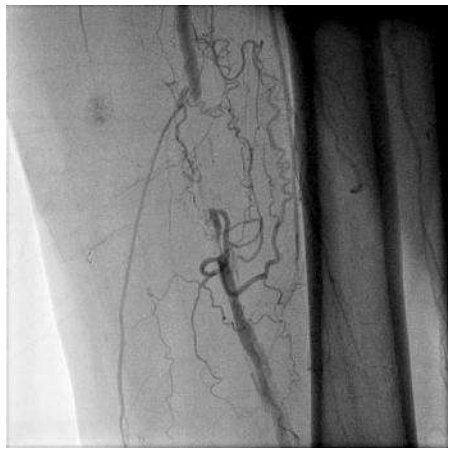

Fig 1- The long CTO segment of superficial femoral artery with bridging collaterals.

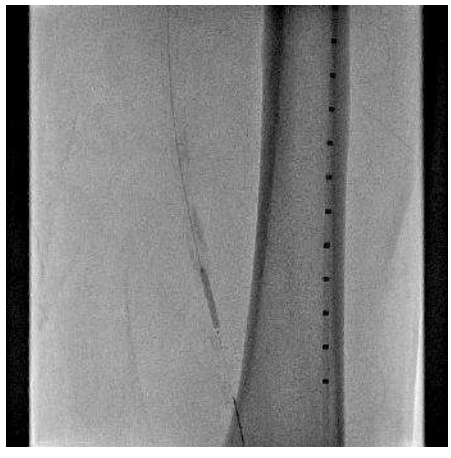

Fig 2- The initial dilatation with a compliance balloon.

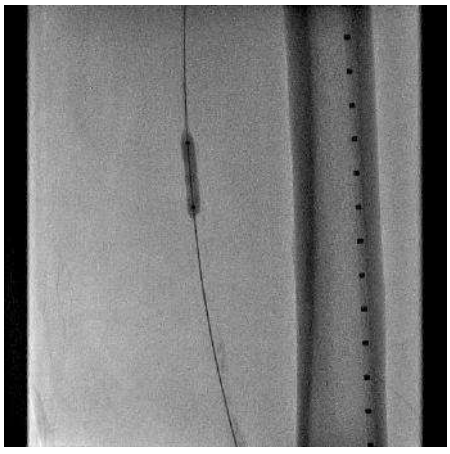

Fig 3- The second dilation with a peripheral balloon.

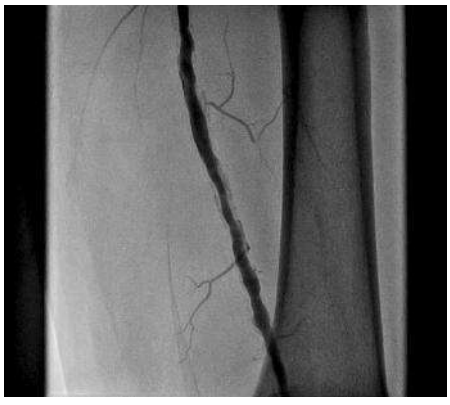

Fig 4 final angiogram showed good result.

His pain improved markedly after angioplasty and good blood flow was noted clinically after the procedure. He was transferred to a vascular surgical ward for specialized wound care.

Discussion

These patients with peripheral artery disease usually have multiple lesions in the aorto-iliac-femoral-popliteal-tibial axis. There are multiple alternative methods of treatment such as medical therapy, balloon angioplasty, primary stenting and surgical revascularization. In high risk patients on whom the surgical procedures are deemed inappropriate, angioplasty is the best option [6-8]. Our patient was a high risk candidate for surgical femoral and tibial revascularization as he was known to have triple vessel coronary artery disease and was awaiting coronary artery bypass graft surgery. Hence we decided to go ahead with superficial femoral artery angioplasty which resulted in a remarkable post procedure outcome with a TIMI iii flow in the right SFA and all its branches as shown in angiography.

The analgesics the patient was on for the severe limb pain could be tailed off soon after the procedure due to the alleviation of the ischemia.

Conclusion

PTA of the superficial femoral artery is a safe and effective modality of treating PVD with good short-term and long-term outcomes. A major benefit of this treatment modality can be achieved in symptomatic patients who have intermittent claudication with a single stenosis. Patients suffering from CLI also will benefit significantly from this procedure. In well selected patients who present with critical limb ischemia and are at a higher risk for anesthesia, on whom open surgery cannot be performed, PTA of femoral-popliteal district can be a safe and effective alternative method.

Conflicts of interests: None

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Case Report

Case Report

Three case scenarios of prosthetic valve thrombosis.

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Abstract

Prosthetic valve thrombosis is becoming a common clinical encounter due to increasing implantation of prosthetic valves. If not detected early and managed properly, it leads to considerable morbidity and mortality. All cases described here were either due to patient factors or improper management. These three cases highlight prosthetic valve thrombosis occurring in a child bearing age female, a pregnant mother and a post-menopausal female. Severe breathlessness was the commonest symptom. All three cases were successfully treated with intravenous alteplase or streptokinase.

Case number 01

A 52 year old lady had undergone mechanical mitral valve replacement in May 2018 for severe mitral regurgitation resulting from a chordal rupture. She presented with shortness of breath, faintishness and orthopnea of one day duration in July 2108. On examination she was hypotensive (90/60mmHg) and had a tachycardia of 102 beats per minute. Her lungs were clear and saturation was 99% on air.

On admission her Serum creatinine was marginally high at 124 mmol/L (subsequently it came down to 105mmol/L). Serum electrolytes were normal (serum sodium 137 mEq/L and Serum Potassium 3.9 mEq/L).

ALT (Alanine Aminotransferase) was 88 U/L, AST (Aspartate Aminotransferase) was 73 U/L.

The INR (International Normalized Ratio) was 1.54.

Investigation Findings: (Table 01)

	07/07/2018	25/07/2018	26/07/2018
WBC	14.05×10^3	9.8×10^3	17.49×10^3
Neutrophil %	81.5%	81.4%	82%
Lymphocyte %	13.3%	13.3 %	10.4 %
Hb	10.2 g/dl	12.6 g/dl	11.0 g/dl
PLT	129×10^3	163×10^3	127×10^3
Troponin I		0.056	

Echocardiography parameters were as follows: (Table 02)

	Prior to thrombolysis.	After the thrombolysis.	Follow up at six months
TRPG(Tricuspid valve Pressure Gradient)	50 mmHg	12mmHg	12mmHg
MV mean PG (Mitral valve mean Pressure Gradient)	18 mmHg	2mmHg	2 mmHg
MV peak PG	10 mmHg	6mmHg	6mmHg
Doppler mitral valve area	$1cm^2$	2.1 cm^2	2.1 cm^2
Aortic valve	Trivial AR, No AS	Trivial AR	Trivial AR

The Ultra sound scan revealed bilateral small pleural effusions. 2D Echo study revealed high trans- mitral pressure gradients with restricted mitral valve leaflet motion. A provisional diagnosis of prosthetic mitral valve thrombosis was made and the decision was taken to commence thrombolytic therapy.

IV streptokinase 250000 iu was given over 1 hour, and then was continued 100000 iu hourly for 25 hours. The patient improved clinically. The subsequent echocardiogram showed a well-functioning mitral valve prosthesis with good valve motion.

The patient was given subcutaneous enoxaparin as bridging therapy until the INR came up to the therapeutic range.

Case number 02

A 32 year old pregnant lady who had undergone mechanical mitral valve replacement in 1999 for rheumatic valvular heart disease was referred for pre pregnancy counselling, and was advised on the importance of proper cardiac and obstetric follow up at a tertiary care center. Her Echo study done at the pre pregnancy clinic showed a well-functioning mitral valve with no evidence of pulmonary hypertension. She was also referred to the hematology clinic for close follow-up of her anticoagulation where she was given enoxaparin 50mg SC daily by the hematologist (body weight 50kg).

Warfarin was withheld due to potential adverse effects on the fetus during the first trimester.

At POA of 10 weeks she presented with a cough and severe breathlessness. On admission she was dyspneic at rest. She gave a history of having had chicken pox one week prior. Her C-reactive protein on admission was 27 (Investigation results in table 3).

Chicken pox pneumonitis, pulmonary embolism, prosthetic valve thrombosis and LV dysfunction due to chickenpox myocarditis were considered as differential diagnoses. An Echo study was done, and revealed a high trans-mitral gradient with poor motion of the mitral valve, indicative of prosthetic valve thrombosis. In addition, she had severe pulmonary hypertension. The decision to initiate thrombolysis was made to save the mother. Her INR at that time was 1.16.

She was referred to a Consultant Obstetrician. An ultrasound scan of the abdomen and pelvis showed a single live fetus. The patient's consent was obtained and she was given alteplase for thrombolysis (25mg infused over 25 hours followed by unfractionated heparin (UFH) 70u/kg bolus & 16 unit/kg/hr). She underwent repeat Echo & TOE studies (findings given in table 4). She was also started on the therapeutic dose of warfarin and was discharged once her INR reached 3.37. Subsequently she delivered a normal baby in March 2019. Both mother and baby are doing well on follow up.

Investigation findings: (Table 03)

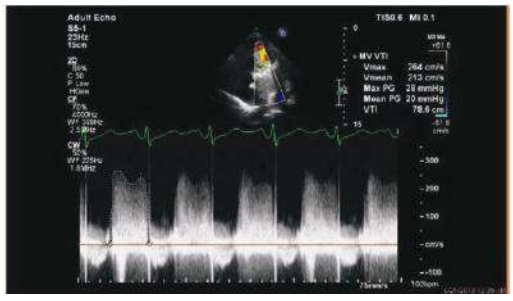
	26/07/2018	31/07/2018	29/08/2018	03/09/2018
WBC	7.23×10^3	12.37×10^3	19.70×10^3	8.06×10^3
RBC	4.05×10^6	3.99×10^6	3.97×10^6	3.93×10^6
Hb	11.4 g/dl	11.1g/dl	11.4g/dl	11.3g/dl
PLT	301×10^3	243×10^3	303×10^3	247×10^3

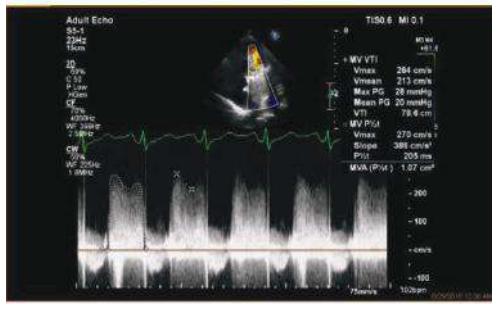
Echocardiography parameters were as follows: (Table 04)

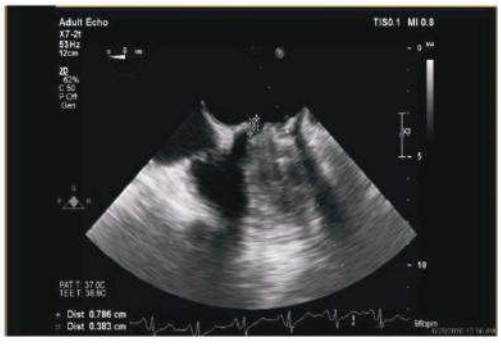
	Prior to thrombolysis.	After the thrombolysis.	follow up in 6 months
TR PG	60mmHg	17 mmHg	16mmHg
MV mean PG	20mmHg	3 mmHg	3mmHg
MV peak PG	28mmHg	6 mmHg	6mmHg
Doppler mitral valve area	$1cm^2$	$2\ cm^2$	$2.34cm^2$
Aortic valve	Mild AR	Trivial AR	Normal
Findings	One leaflet of mitral valve was opening but the other leaflet was not opening properly. Tight mitral prosthesis re-narrowing with valve thrombosis. Severe pulmonary hypertension	Well-functioning mitral valve prosthesis. Both leaflets opening well. No thrombosis. Trivial perivalvular MR	Hyperechoic mass attached to the mitral valve 6×7mm in size Well-functioning mitral valve prosthesis.

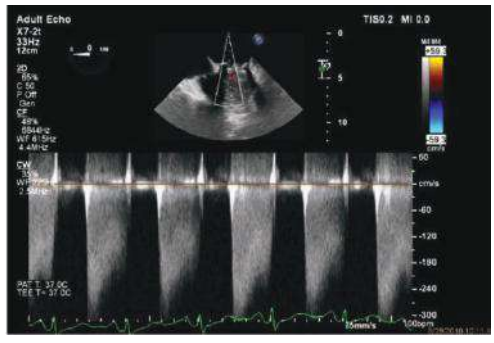
Case Report

Echo images prior to thrombolysis. **(Case number 02)**

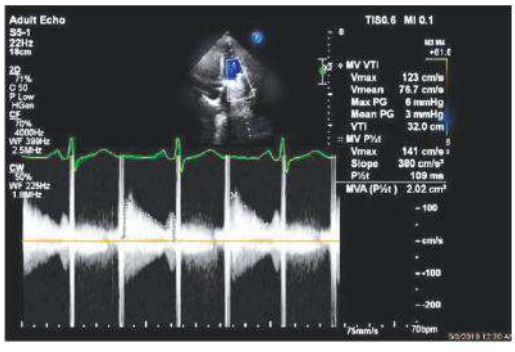


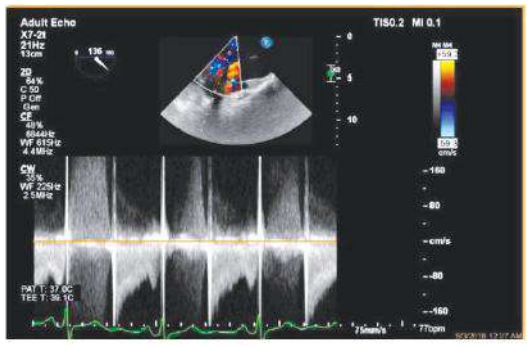




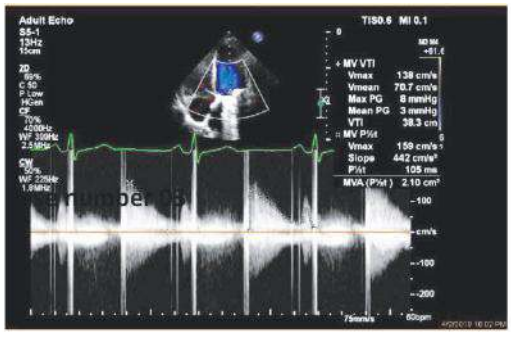


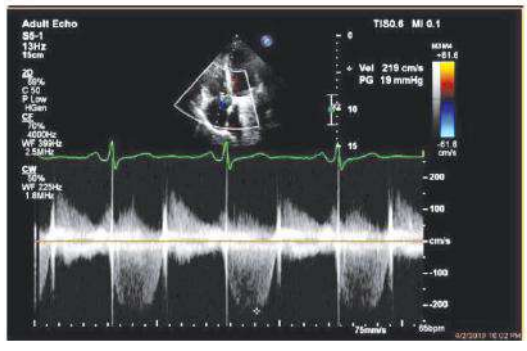
Echo images after the thrombolysis.





Follow Up in 6 months.





Case number 03

An 18 year old girl (41kg) presented with tightening chest pain, cough and shortness of breath of two days duration. She was severely dyspneic at rest, with an oxygen saturation of 95%. She had undergone mitral valve replacement in December 2017 for infective endocarditis. She underwent Echo study which revealed normal LV function, poorly opening mechanical mitral valve prosthesis with a thrombus on mitral valve. Right Atrium (RA), Right Ventricle (RV), and the Main Pulmonary Artery (MPA) were dilated. Mean PG across the mitral valve was 36mmHg; max PG 53mmHg and TRPG 65mmHg.On admission the INR was 1.8.

She was started on alteplase (25mg/over 25 hours) infusion. Heparin infusion was started immediately after thrombolysis. Warfarin was commenced concurrently. Daily INR was estimated and the anticoagulant was stopped when the INR became 2.4.

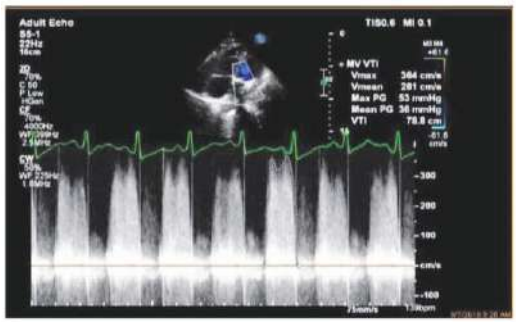
Investigation results: (Table 05)

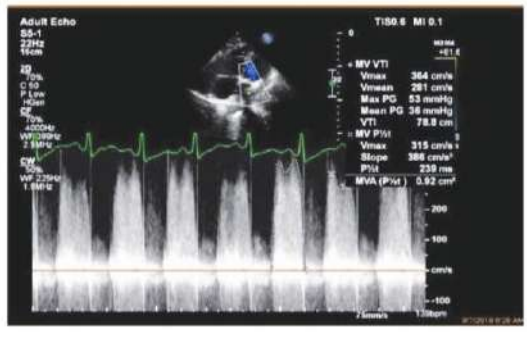
	09/07/2018	11/07/2018
WBC	13.01×10^3	10.88×10^3
RBC	3.87×10^6	4.29×10^6
Hb	10.1 g/dl	11.6g/dl
PLT	272×10^3	333×10^3

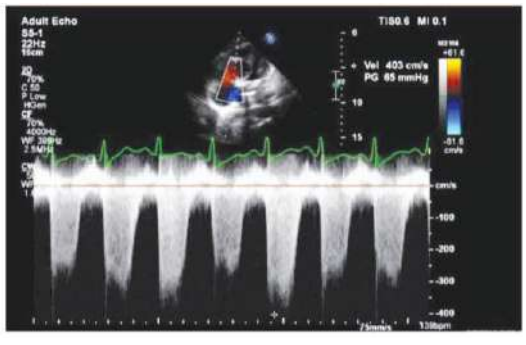
Echocardiography parameters were as follows: (Table 06)

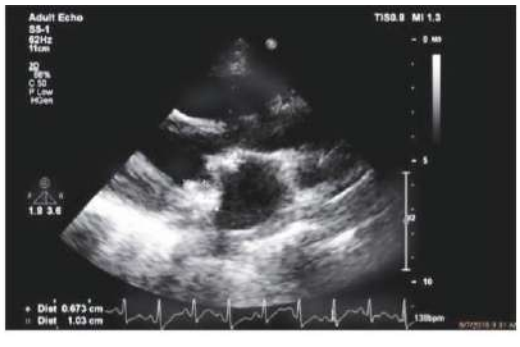
	Prior to thrombolysis.	After the thrombolysis.	Follow up in 6 months.
TR PG	65mmHg	20mmHg	18mmHg
MV mean PG	36mmHg	9mmHg	7mmHg
MV peak PG	53mmHg	13mmHg	10mmHg
Doppler mitral valve area		2cm2	2.12cm2
Aortic valve	Normal	Normal	Normal
Findings	Prosthetic mitral Valve thrombosis, Two thrombi noted attached to mitral valve (8 ×4mm, 7× 6mm)	No visible thrombus	Normal functioning prosthetic mitral valve

Echo images prior to thrombolysis. (Case number 03)



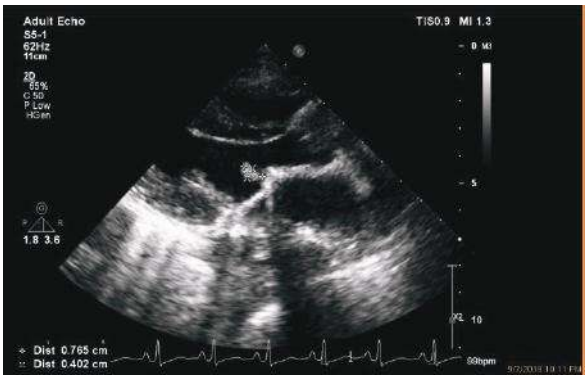


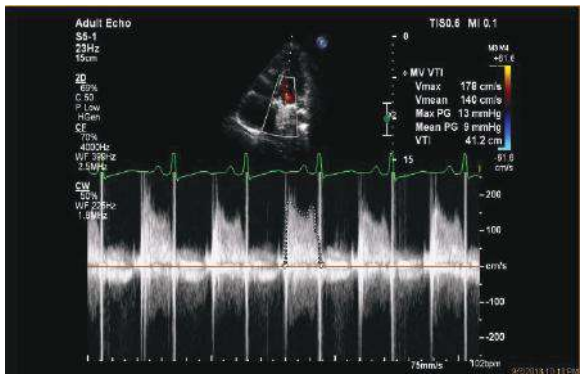


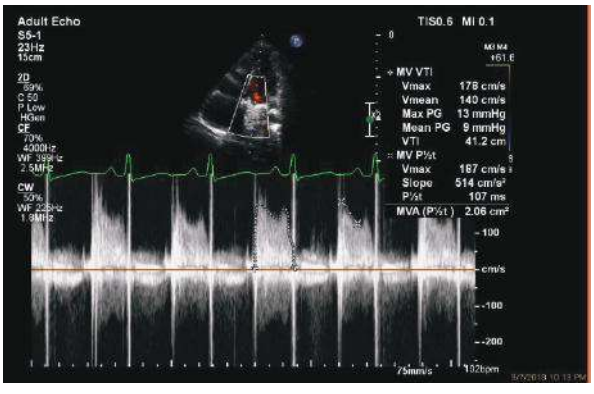


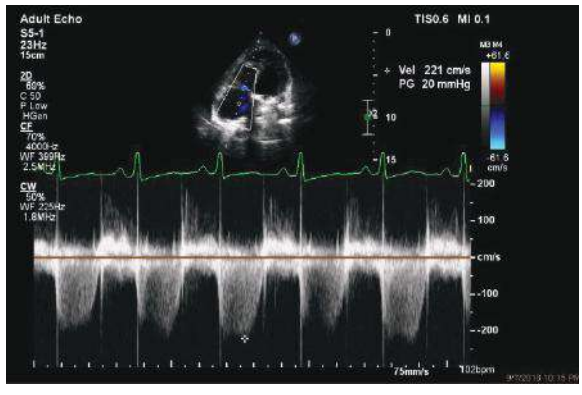
Case Report

Echo images after the thrombolysis

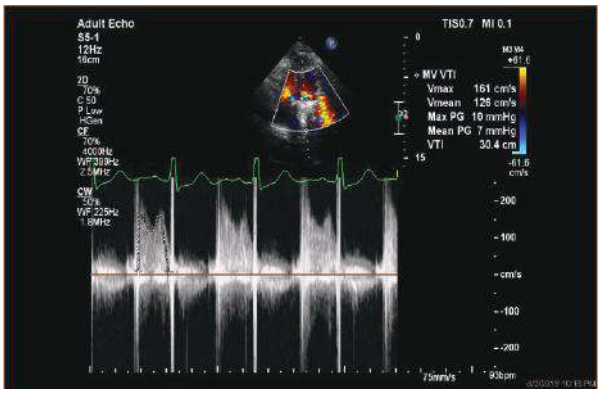


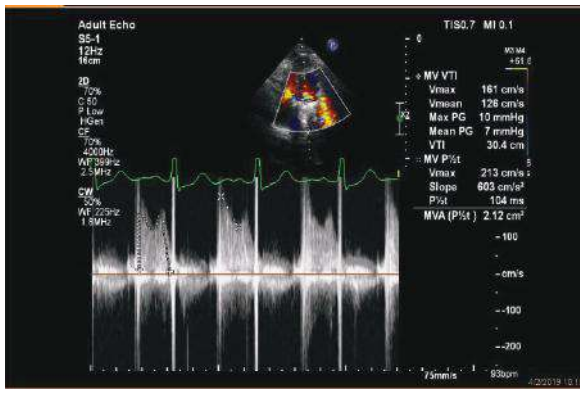






Follow up in 6 months.





Discussion

Prosthetic valve thrombosis is a preventable disease if correct anticoagulation is carried out. All the above patients suffered either due to patient factors or mismanagement at follow up clinics.

Prosthetic heart valve related complications in pregnancy has become a common problem in the child bearing age group. Guidelines have suggested that if the warfarin requirement is more than 5mg per day it is advisable to change to enoxaparin or heparin during first trimester to prevent warfarin related embryopathy. If the patient is given enoxaparin, it is advised to monitor factor Xa levels. However in our set up, this facility is not available. If the patient is given enoxaparin, it is advised to give a weight adjusted dosage with 1.5mg per kilogram daily or 1mg per kilogram twice daily.

In case number 02, the patient was given an inadequate dose of enoxaparin which led to the prosthetic valve thrombosis. She made a complete recovery after thrombolysis with alteplase and she delivered a healthy baby.

The other two patients had valve thrombosis as a result of inadequate anticoagulation with warfarin. This highlights the importance of proper follow up of patients on warfarin therapy with regular INR assays. All the above patients presented with NYHA class III-IV dyspnea.

Prosthetic valve thrombosis is suspected on detecting poor leaflet motion with a high trans-mitral gradient during echocardiography. Sometimes echocardiography clearly visualizes a thrombus. Pannus formation is an important differential diagnosis. The duration of illness helps to differentiate the above two conditions. All of our patients had acute presentations with typical echocardiography and TOE features suggestive of valve thrombosis.

Right sided mechanical heart valves and mechanical mitral valves have an increased risk of valve thrombosis due to low flow circulation when compared to mechanical aortic valves. Due to this reason INR is kept at a higher level in patients with mechanical right sided and mitral valves.

NYHA Class III-IV symptoms, large thrombus (more than $1cm^2$), mobile thrombus (more than $0.3cm^2$), pannus formation or concurrent presence of cardiac disease are indications for open heart surgery with thrombectomy or for redo valve replacement.

Class I-II symptoms, small thrombus (less than $1cm^2$) or mobile thrombus (less than $0.3cm^2$) are indications for thrombolysis. All of the above patients had indications for surgery, though they underwent thrombolysis. They all had successful results without any complications. Following thrombolysis all patients were given heparin to achieve an APTT of 1.5 – 2.0.

Concurrently warfarin was started, with aspirin 100mg daily. They were all given proper follow up with regular INR monitoring and showed well-functioning valves 6 months after the event.

Conflicts of interests: None

References

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2. *Whitlcok RP, Sun JC, Fremes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis. 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e576S.*
3. *Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63:e57.*

Editorial comment

These case scenarios are very relevant for cardiologists in Sri Lanka where facilities for re-operation are restricted. Conservative management may have to be considered even though not in accordance with standard guidelines.

Case report

Transradial rotablation in a patient with an acute ST segment elevation myocardial infarction: a case report.

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Abstract

A 68-year-old gentleman with type II diabetes mellitus was admitted to our unit following acute inferior ST elevation myocardial infarction (STEMI). Due to ongoing ischemic symptoms, he underwent emergency trans radial coronary angiography. His culprit right coronary artery (RCA) was heavily calcified with severe stenosis in the proximal segment. Therefore, rotational atherectomy was performed for debulking, after unsuccessful attempts with balloon catheters, including a cutting balloon. A drug eluting stent was deployed in the RCA from the ostium of the RCA. Patient improved remarkably after the procedure and he was discharged in four days. The case was special because of the high risk involved in the procedure.
Keywords: Inferior STEMI, Calcific proximal RCA, Rotablation, Primary PCI

Case report

A 68-year-old man was brought to our primary percutaneous coronary intervention service with chest pain and inferior segment ST-elevation on his electrocardiogram (ECG). He was an ex-smoker and his past medical history only included diabetes mellitus of ten years duration for which he was on gliclazide 80mg twice a day and Metformin 500mg three times a day. On arrival to the catheterization laboratory, he was alert, orientated, and breathing spontaneously. His blood pressure was 90/60 mmHg. His ECG showed a ventricular rate of 64/min and 5 mm ST-elevation in inferior leads, lead III more than lead II. He was loaded with oral aspirin 300 mg and clopidogrel 600 mg by the emergency therapy unit before arriving to our unit.

Coronary angiogram of the right coronary artery was performed via right radial access with 6 French sheath and 5F diagnostic catheter. This showed 99% occlusion of right coronary artery (RCA) at proximal segment with calcification. Right coronary artery was engaged with 6 French Judkins right 3.5 (JR3.5) guiding catheter. RCA lesion was crossed with ASAHI SION guide wire. Lesion predilated with MOZEC 2.5x14mm compliant balloon at 12 atm. At this time ST segments came down and patient felt comfortable. Due to the tight calcific nature of the lesion we planned to intervene it later once the acute condition is settled and went ahead with coronary angiogram of the left coronary artery at which time patient again developed chest pain and ST segments in the inferior ECG leads elevated.

The 6 French sheath was exchanged to 7 French sheath and the right coronary artery was again engaged with 7French Judkins right 3.5 (JR3.5) guiding catheter. RCA lesion was crossed with ASAHI SION guide wire. Lesion predilated with MOZEC 2.5x14mm compliant balloon at 12 atm and SPRINTER 3x9mm no-compliant balloon at 14 atm. Proximal calcified lesion tried to balloon dilated with FIEXTOME 3x10mm cutting balloon at 12 atm, but the balloon ruptured.

Then RCA lesion crossed with ROTA Link plus rota wire. Proximal RCA lesion rotablated with ROTA Link 1.5mm burr at 180000rpm.under a temporary pacemaker cover. Rota wire was exchanged to ASAHI SION guide wire. RCA lesion was stented with PROMUS ELEMENT 2.75x16mm drug eluting stent (DES) at 16 atm from ostium of the RCA. Stent post dilated with MOZEC 3.5x8mm HPB at 12– 22 atm flaring the ostium of the RCA.

Post-procedure angiogram revealed excellent angiographic results with TIMI III flow in RCA and branches. Patient was pain free and the ST segment elevation in the ECG resolved.

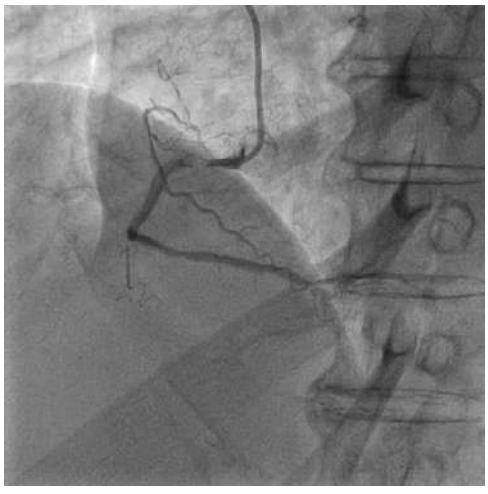

Figure 01. Right coronary artery angiogram showing 99% lesion at the proximal right coronary artery.

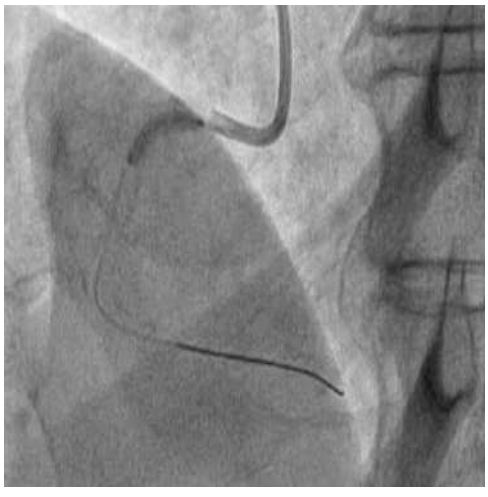

Figure 02. Balloon dilatation of the RCA lesion with MOZEC 2.5x14mm compliant balloon at 12 atm.

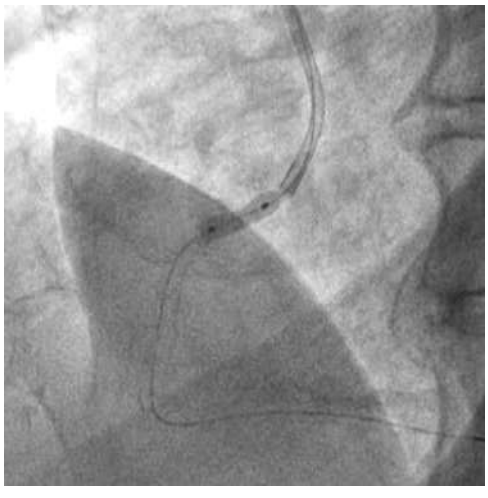

Figure 03. Balloon dilatation of the RCA lesion with V SPRINTER 3x9mm non- compliant balloon at 14 atm.

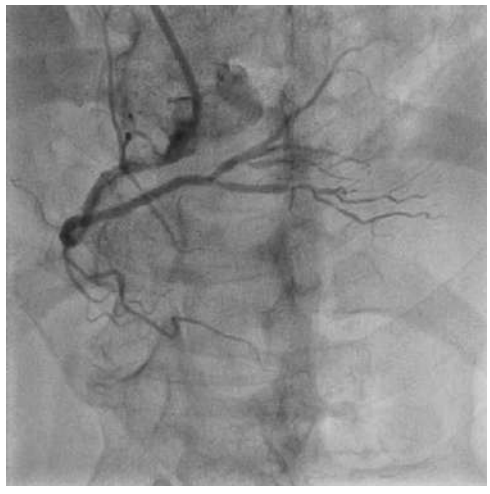

Figure 04. Coronary angiogram of the right coronary artery following balloon dilatations.

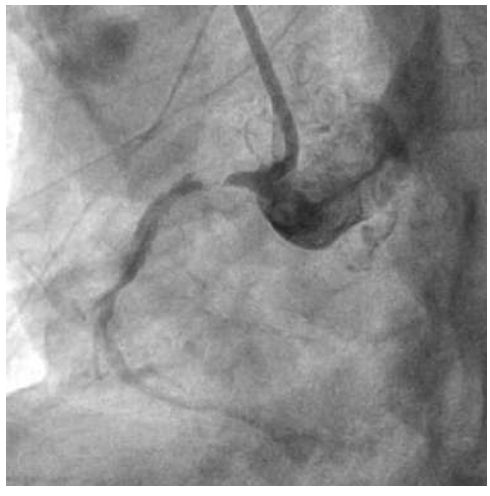

Figure 05. Recoiling of the lesion following initial balloon dilatations.

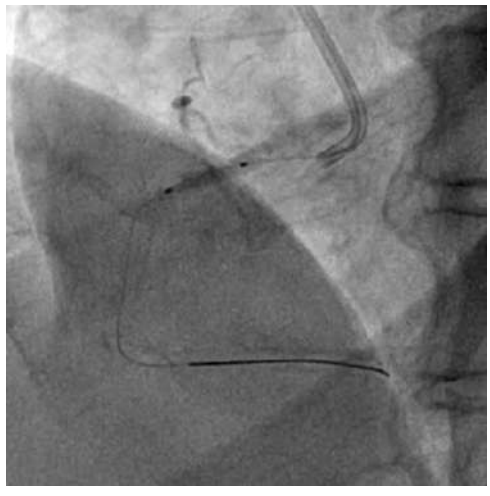

Figure 06. Dilatation of the RCA lesion with a FIEXTOME 3x10mm cutting balloon at 12 atm.

Case Report

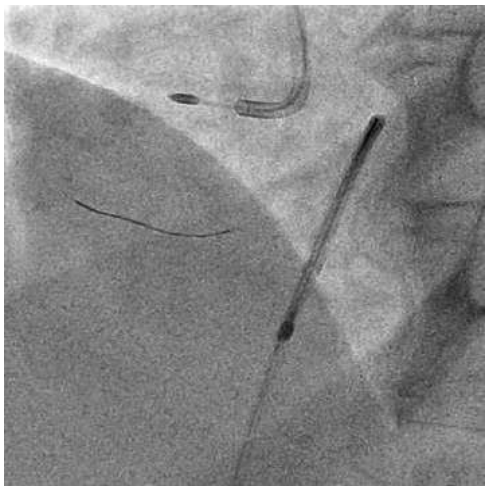

Figure 07. Rotablation of the lesion with ROTA Link 1.5mm burr at 180000rpm.A temporary pacemaker is in situ.

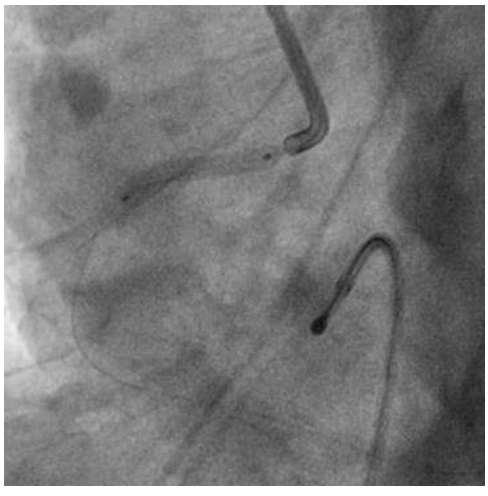

Figure 08. Stenting the RCA lesion with PROMUS ELEMENT 2.75x16mm drug eluting stent (DES).

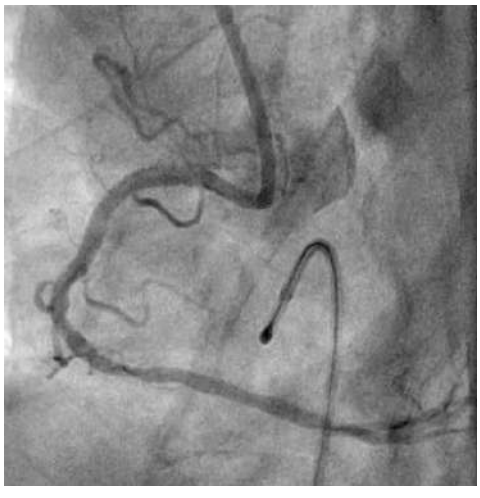

Figure 09. Post- stenting coronary angiogram of the RCA showing excellent results.

Discussion

Rotational atherectomy is relatively contraindicated in the setting of acute coronary thrombosis such as STEMI because of the risk of potential platelet activation by the rotablator. The manufacturer advices using rotablation at least 2 to 4 weeks after the use of thrombolytics in STEMI [1]. However, there are case reports of Rotablation in the situation of acute ST segment elevation myocardial infarction with final procedure success [1,2]. Initially we thought of avoiding Rotablation and stenting in the acute setting, but it became mandatory as initial balloon dilatation was a temporary success and the attempts to dilate the lesion with non-compliant balloon, a cutting balloon were unsuccessful. In this case Rotablation carried an additional risk due to the very proximal nature of the lesion to the coronary artery ostium.

Conflicts of interests: None

References

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Case Report

5 year outcome of double rotablation of unprotected left main/LAD/Lcx with culotte stenting in an 84 year old female- seeing beyond the Syntax scores in real world patients.

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Abstract

Unprotected left main stem coronary intervention in the presence of severe calcification in octogenarians with comorbidities and acute coronary syndromes is a dilemma, where the existing evidence base for outcomes from large randomized controlled trials such as Syntax (dealing with younger patients who have stable disease) does not cover these clinical situations. Despite the assumption of poor outcomes with PCI than surgery, we present a case that clearly defies that belief, of an 84-year-old Sri Lankan lady who underwent double rotablation assisted bifurcation PTCA of Left main-LAD-Lcx coronaries with severely calcific >99% stenosis (Medina 1,1,1) 5 years ago. She was followed up for > 5 years, where at the age of 89 years, has remained completely free of symptoms and recurrent events, with a good quality of life and independence, despite presence of diabetes and other comorbidities. This outcome may suggest, that in centers with expert operators, complex PCI should not be denied to patients due to perceived fear of complications based on advanced age and prohibitive coronary anatomy. Complex PCI, in this group may sometimes represent a better treatment option than surgery, which carries a higher morbidity and risk than PCI.

Keywords: Unprotected LM disease, Culotte stenting, Octogenarian

Introduction

Severe calcific left main coronary disease is not uncommon in the elderly population and this is usually an indication for revascularization with CABG, due to the perceived beneficial impact on survival, following the results of Syntax trial [(1)]. The outcome benefit is pronounced for diabetic subpopulation and those with higher Syntax scores [(2)]. The Excel clinical trial [(3)], which relates to PCI with newer generation DES, has shed more information on unprotected left main stenting compared with CABG, with non-inferior outcomes at 3 years, compared to data reported by older generation Syntax trial [(4)].

However, these clinical trials have excluded many types of patients that are encountered by us on a daily basis in our clinical practice. Clinicians make decisions based on trials that sometimes do not directly appear applicable to the trials. Patients with acute coronary syndromes, impaired LV function, octogenarians (N.B. average age of above trials were ~ 65 yrs.), prior coronary disease or surgery/PCI, Asians with less medical fitness and different comorbidities, small distal coronaries not suitable for grafts and calcification upstream, were clearly exclusions from these trials. Morbidity and mortality is expected to be higher in Sri Lankans with a lower life expectancy compared to the west. However, outcomes in high risk coronary interventions with rotablation in unprotected left main in octogenarians with long term follow up is rarely reported [(5)] and is generally done in very low volumes in Sri Lanka.

Therefore, we aim to highlight the five year follow up of an 84 year old diabetic female who underwent a complex left main intervention.

Clinical Summary

An 84 year old lady with poorly controlled diabetes and recent onset chest tightness and resting anterolateral T wave inversion (Cardiac Troponin I negative) with intermittent frequent ventricular ectopy was investigated. Left ventricular function was preserved with EF>55% with no resting RWMA on echocardiography. Coronary angiography demonstrated critical 99% stenosis of a heavily calcified distal left main stem, with further proximal /ostial disease of LAD and Lcx (Image 1). Right coronary artery was dominant and free of significant disease. Calculated anatomical syntax score was 25; despite this strictly being out of the remit of syntax population, it would suggest that in this diabetic patient, a better chance of disease free survival with CABG. However, with a calculated Euro score of >25.7% and following a comprehensive cardiac surgical assessment, a decision not to proceed to CABG was undertaken. Instead, patient consented to a double rotablation assisted PCI following discussion of options.

Case Report

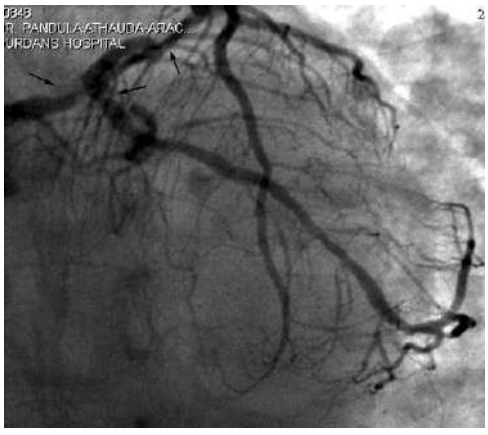

Image 1

Procedural Summary

Presence of heavy calcification in a Medina 1, 1, 1 distribution (see image1) meant that two sequential rotablations of left main to LAD or Lcx (see images 2 and 3), without protection of the side branch at each passage, had to be carried out through the left main. Adequate debulking required a minimum of a 1.75 mm burr, and a need for simultaneous final kissing balloons desired a 7 French femoral access and guide catheters in a small elderly female.

A second femoral access was established for elective intra-aortic balloon counter pulsation during the procedure, in the setting of arrhythmia and the risk of loss of flow during simultaneous kissing inflations to a large area of myocardium, albeit, currently the data to support this approach is being debated. The intra procedural steps and findings are illustrated with images. Successful double rotablation and culotte stenting (Xience DES) of left main-Lcx-LAD and extension of LAD stent with another distal overlap, was performed with final simultaneous kissing balloon inflations and optimal stent expansion (see image 4). There were no complications and patient could be mobilized in 12 hours.

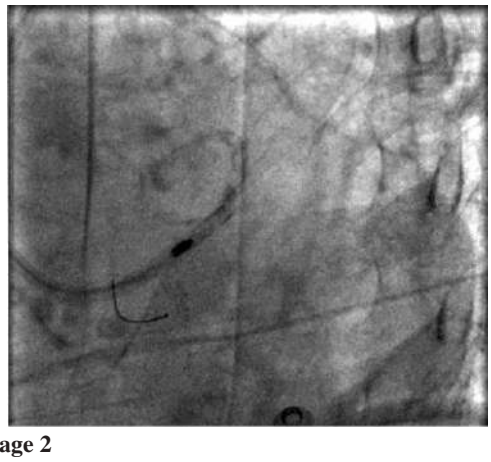

Image 2

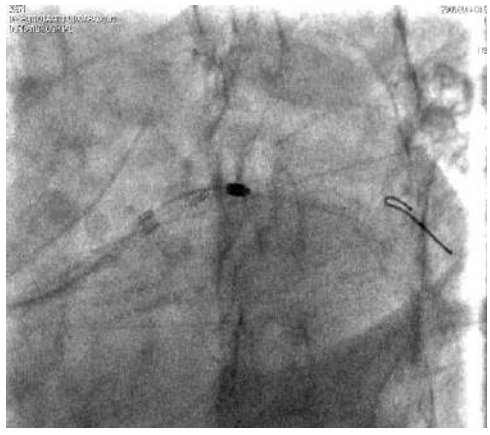

Image 3

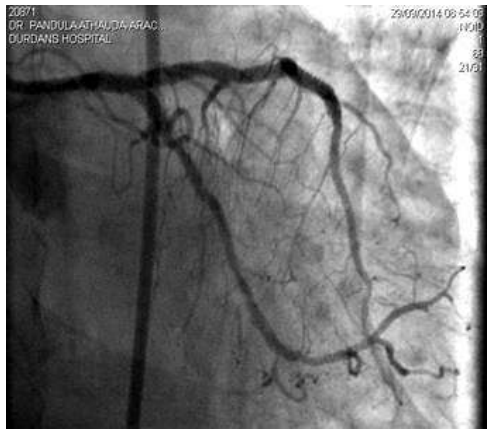

Image 4

Clinical progress

Patient was placed on aspirin and clopidogrel for one year and thereafter on single antiplatelet agent. Functional status of patient improved substantially along with diabetic control. The ventricular ectopy disappeared post PCI. She was able to travel overseas and able to walk briskly and lead an active life. She had no bleeding or neurological events.

Five years later, currently at the age of 89 years, she is alive and active, with no angina, good LVEF >55%, no arrhythmia, no cardiovascular events and not needed a single hospital admission for her cardiac disease.

Discussion

The Syntax II trial provided improvements to the syntax model by addition of clinical variables to predict who may benefit most from PCI or CABG [6]. In our patient, Syntax II scores were as follows; for PCI SYNTAX Score II: 45.6~ PCI predicted 4 Year mortality~23.1 %; for CABG SYNTAX Score II: 41.5 ~ CABG predicted 4 Year mortality: 16.9 %. It is also worth noting that, according to original Syntax data in diabetic patients in the second tertile of Syntax score,

5-year event rates were stated to be significantly higher for PCI vs CABG for MACCE (PCI: 46.5% vs CABG: 29.0%; P < 0.001) [7] and the incidence of repeat revascularization (PCI: 35.3% vs CABG: 14.6%; P < 0.001). These data, on superficial examination favors surgical revascularization.

But, even in countries such as USA, surgical morbidity in octogenarians may be as high as 51% [8], which is a substantial concern; this is in addition to the high perioperative mortality rates predicted by Euroscore II.

The option of conservative medical management is sometimes adopted in this age groups. However, in those aged 65 years and above, who had untreated left main or 3 vessel coronary disease, the unadjusted all-cause 3-year Kaplan–Meier MACE-free survival curves, suggest a mortality in excess of 40%, and significant MACCE [9]. With advancing age over 80 years, in Sri Lankan patients with critical left main disease, these values may approach nearly 100%, although no data exists at present. Indeed, the risk of death from any cause over the age of 80 years is also substantial.

Hence, treated or untreated, possibility poor outcome was generally expected, but our 89 years old patient, by agreeing to PCI at 84 years, has had an excellent clinical outcome both in the short term and long term, despite the advancing age and comorbidities with the use of double rotablation and Left main PTCA.

Therefore, we believe, if performed by suitably capable operators, difficult cases in high risk settings, can achieve good outcomes and no contemporary trial data can predict the individual outcomes, which of course must be carefully analyzed by individual expert, taking all factors into consideration. Cases such as these, must be collated to generate data for future trials in Sri Lanka in these difficult subsets of patients.

Conflicts of interests: None

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Case Report

A rare case of an allergic vasospastic acute coronary syndrome (Kounis Syndrome) following anaphylaxis due to metronidazole.

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Abstract

We report a case of a 33-year-old previously healthy young lady with a background history of atopy and allergy, presenting in anaphylactic shock following the administration of metronidazole after abdominal wall surgery. She was resuscitated after three cycles of cardiopulmonary resuscitation. Subsequently she developed features of cardiac failure and initial cardiac evaluation revealed ECG and 2DEcho-cardiographic evidence of anterior myocardial ischemia, severe systolic dysfunction and global hypokinesia of the heart with an ejection fraction of 35%. She was managed with inotropic support, diuretics, antianginals, antithrombotic and anticoagulants. Further evaluation with a coronary angiogram revealed normal patent coronary arteries. A myocardial perfusion scan showed no abnormal tracer areas. Serial follow up echo cardiograms demonstrated improvement of systolic function and improvement of ejection fraction with symptomatic treatment.

Kounis syndrome is described as a separate disease entity which result in acute coronary syndrome following type 1 hypersensitivity reactions with mast cell activation and allergic myocardial infarction. The patient recovered well with the treatment and was asymptomatic with normal cardiac function at her three months follow up. She was referred to the immunology clinic for further evaluation of her immunologic status and possible desensitization.

Keywords: Allergic vasospastic angina, Kounis syndrome, Mast cell activation, Allergic myocardial infarction.

Introduction

Anaphylaxis is one of the most dreaded, acute, life threatening medical conditions which warrant immediate medical attention. It has a unified worldwide distribution with any individual having an equal chance of developing this condition with prior sensitization. The basic pathology of this condition revolves around the exposure to a potential allergen which binds to immunoglobulin E (IgE). This results in immediate activation of mast cells and basophils which release several chemical mediators to the systemic circulation(1).The physiological response to the mediator released, results in smooth muscle contraction, vasodilation and increase in the vascular permeability which brings about numerous effects on different organ systems of the body.

There will be generalized body swelling mainly involving the periorbital regions and lips. Cutaneous manifestations will result in generalized urticarial rashes and pruritus with redness and erythema of the skin. The mast cell mediators mainly Interleukin 4(IL-4) and Interleukin 13(IL-13) will act on the bronchial tree causing smooth muscle contractions and increase in mucus production this results in severe Broncho-constriction and increased secretions resulting in acute respiratory distress(2).

Numerous cardiovascular effects have been described in relation to anaphylaxis. The major effect is hypotension which can sometimes be severe and refractory. Increase in capillary permeability, reduction in the vascular tone and reduction in peripheral resistance all contribute to the development of hypotension. Other than hypotension the other recognized effects include tachycardia with dangerous arrhythmias such as ventricular fibrillation, leading to cardiac failure and rarely myocardial infarctions following intense coronary vascular spasms.

Kounis syndrome is described as a separate disease entity which result in acute coronary events following type 1 hypersensitivity reactions. A variable clinical spectrum has been described which include acute coronary syndrome, unstable angina to acute myocardial infarction and cardiac failure as well as acute stent thrombosis (3).

Clinical presentation

A 32-year-old, previously healthy lady, a mother of two children underwent a periumbilical herniotomy and mesh repair which had developed after her second pregnancy. This was decided by her surgeon after a consultation at the local hospital, since she was becoming symptomatic. She had a background history of atopy with childhood asthma and a history of allergy to ciprofloxacin and tomatoes.

She also gave an interesting history of generalized body itching and urticarial symptoms following exposure to rain water. She never reported any similar symptoms to well or tap water. Although she had several allergic reactions to multiple food and drugs there was no previous history of anaphylaxis or anaphylactic shock upon exposure to any of the allergens. She was never referred to an immunologist for evaluation of her immune status. She was asymptomatic pre-operatively and anaesthetic evaluation revealed no abnormalities in her pre-op investigations.

Immediate post-operative period was uneventful, and she had made a smooth recovery from spinal anaesthesia. She was prescribed intravenous cefuroxime and metronidazole as post-operative antibiotic cover. The nursing officer on duty gave the first dose of metronidazole 500mg during her rounds and within a couple of minutes of starting the drug infusion the patient developed sweating and complained of difficulty in breathing and shouted with a feeling of impending doom. By then she had not received cefuroxime or any other oral medication. Within seconds the ward doctor who was on call was summoned and he immediately stopped the drug infusion and connected the patient to a monitor. Within few minutes patient complained of generalized body itching and light-headedness and was finding it difficult to breath. She was haemodynamically unstable and had a peripheral oxygen saturation of 88% and a blood pressure of 80/62 mmHg.

She was immediately put on high flow oxygen and started on a free-flowing normal saline drip. She was given intramuscular adrenaline, intravenous hydrocortisone and intravenous chlorphenaramine. Her haemodynamic status did not improve with the medication and she went into an acute cardiopulmonary arrest within a couple of minutes. A cardiac call had been sent and the medical team started cardiopulmonary resuscitation (CPR). She was given 3 cycles of CPR and on the third cycle her circulation returned with a palpable weak pulse. The cardiac monitor revealed a ventricular tachycardia of over 220 beats per minute (bpm). She was immediately cardioverted with a synchronized DC shock.

She was commenced on an intravenous amiodarone infusion and started on immediate post resuscitation intensive care and was managed in the intensive care unit (ICU).

She was supported with inotropes with intravenous noradrenaline and dopamine infusions to maintain the mean arterial pressure above 70mmHg. Her ECG showed a sinus rhythm with widespread T inversions in leads L1, L11, AVF, aVL and V2-V6. Post resuscitation troponin I was 32mg/dl. 2D Echocardiogram demonstrated evidence of global hypokinesia with severe left ventricular systolic and diastolic dysfunction with an ejection fraction of 35%. There was echocardiographic evidence of a possible apical clot. Her full blood count demonstrated a white cell count of $13x10^3/\mu L$ with neutrophil count of 83% and lymphocytes of 14% with no eosinophilia. Erythrocyte sedimentation rate and C-reactive protein were in the normal range. Troponin I was initially 32ng/ml and Brain Natriuretic Peptide (BNP) were above 1500pg/ml, aspartate transaminase (AST) was 310mg/dl and alanine transaminase (ALT) was 287 mg/dl. Renal function tests, coagulation profile and serum electrolytes were all within the normal range. Ultrasound examination of abdomen showed no evidence of intra-abdominal masses or organomegaly.

The patient was managed as a case of congestive cardiac failure with severe LV dysfunction with low ejection fraction secondary to possible myocardial infarction and coronary ischemia. She was continued with subcutaneous enoxaparin 60mg twice daily (bd) and warfarin daily with regular monitoring of her INR. Inotropic support was continued until her parameters improved. All antibiotics were omitted for the time being and the surgical site was monitored by the surgical team for the development of any surgical site infections. Her clinical parameters improved, and she was started on captopril 6.25mg tds and oral digoxin 0.025micgrms daily via nasogastric tube (NG). Amiodarone infusion was omitted. Inotropic support was tailed off and she was extubated on post day 3 of resuscitation. She was transferred to, the Cardiology Unit National hospital of Sri Lanka, Colombo for further management and evaluation of her cardiac status. She was off inotropic support at the time of transfer. She underwent further investigations which included a coronary angiogram. Adequate precautions were taken before giving intravenous contrast and she was kept on steroid cover. The angiogram did not show any significant narrowing's or abnormalities in the coronary vasculature. Epicardial coronary vessels were normal and there were TIMI 3 flow in all three coronaries.

A myocardial perfusion scan was performed to look for areas of nonviable myocardium and infarctions which did not show any such areas at the time of the scan which was around 4 weeks after the event. The possibility of vasospastic angina leading to myocardial ischemia with secondary heart failure was entertained. Serial mast cell tryptase levels were not done since it was not routinely available in the local setting.

She was continued on warfarin, titrated to maintain an International Normalizing Ratio (INR) between 2-3 and appropriate heart failure treatment. The metabolic screening was negative for impaired fasting glucose and dyslipidaemia and thyroid diseases. A thrombophilia screening was negative for protein C and S deficiency and screening for antiphospholipid syndrome was negative.

A referral to the immunologist was made to evaluate the immunological status of the patient. C1 esterase inhibitor levels were checked to exclude mast cell mediated angio-oedema. It was discussed with the patient regarding the risks of desensitization. Considering the degree of the severity of the anaphylactic episode the patient opted for a preventative approach and agreed to a plan of being vigilant about the allergens and avoidance of such exposure. She was also prescribed an epi-pen to be kept with her always and was educated on self-use.

Her repeat echocardiogram before discharge demonstrated an improvement of systolic and diastolic functions of the heart and the ejection fraction had improved up to 45%. There was no evidence of an apical clot. She was asymptomatic at the time of discharge. Follow up echocardiogram at three months demonstrated all most normal LV functions. All her medications including warfarin was omitted and the patient was advised to attend the clinic for follow up.

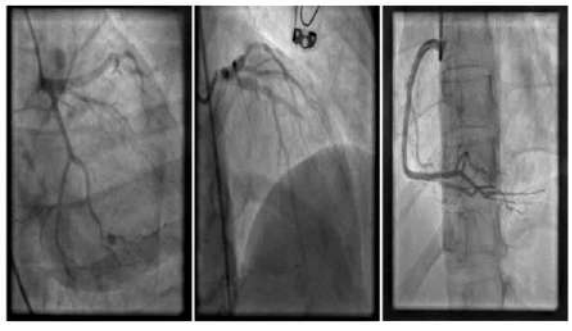

Figure 3.1: angiographic images showing left and right normal coronary arteries

Discussion

Vasospastic angina which was previously referred to as Prinz metal angina is a rare clinical entity which describe coronary vasospasms which result in clinical symptoms of angina and associated changes in the ECG as well as cardiac biomarkers with normal patent coronary arteries in angiographic studies[4]. This rarely results in myocardial ischemia with permanent myocardial damage. A rare entity of allergic vasospastic angina has also been described as a separate clinical entity. A miniature swine model has been used to understand the pathogenesis of coronary spasms and it is thought to be related to various anaphylactoid mediators resulting in constriction of the coronary arteries [5]. It is believed that histamine plays a major role in coronary vasospasms but some of the autopsy studies show infiltration of the myocardium by mast cells [6].

Kounis described the concept of allergic angina where he described the possible pathological pathways for coronary vasospasm. He further elaborated several possible clinical entities which included allergic myocardial infarction as well as anaphylaxis induced stent thrombosis. The current hypothesis has limited analytical data since all of the described entities are based on case reports and observations. It is believed that pro inflammatory mediators such as histamine, arachidonic acid, and several other chemokines are activated in both anaphylaxis as well as non-allergic myocardial infarctions. There is developing evidence that mast cells may play a role in the pathogenesis of acute plaque rupture and also reflex vasospasms in acute coronary events. Consideration of mast cell stabilizers may be promising in the near future to prevent acute coronary events [7].

In this patient, other possibilities for this presentation could be due to anaphylaxis induced severe hypotension causing inadequate coronary circulation resulting in myocardial ischemia. But this would normally result in unstable angina; epicardial arteries are not usually compromised unless there is an occlusion or spasms [8]. Since this patient had an acute stress episode the possibility of stress induced cardiomyopathy (Takotsubo) should be considered as a differential diagnosis. It has almost a similar presentation and occur mostly in post-menopausal age group following intense stress which has also been reported following anaphylaxis [9]. This is thought to be related to the intense catecholamine surge which result in intense vasospasms.

The classic echocardiographic findings describe systolic apical ballooning of the left ventricle which was not seen in this patient. The classical findings of Takotsubo are usually seen in eighty percent of patients. Other possible mimickers are pheochromocytoma and myocarditis both of which can present very rarely with similar manifestations, she has been healthy prior to the episode, and her pre-op evaluation being normal and both the conditions are unlikely in this situation.

Anaphylaxis is one of the most serious acute life-threatening conditions which the public needs to be made aware of. Proper advice and education should be given to individuals who are at risk to develop this and need to be supplied with emergency medication such as self-injectable adrenaline. Various antibiotics have been identified as potential allergens. The mortality rate from anaphylaxis is around 0.5-2% but in Sri Lanka it is estimated to be between 10-20% which is much higher than the global prevalence. Most describe penicillin, cephalosporin and sulphur drugs as the common allergens in anaphylaxis [10]. Metronidazole is a bactericidal antibiotic which mainly acts against anaerobic bacteria and is widely used in post-surgical procedures. Although any antibiotic could act as an allergen, anaphylaxis to metronidazole is rarely reported. It highlights the importance of being vigilant about use of any antibiotic rationally in a previously susceptible individual. Although not commonly reported, numerous case reports have been published globally but hardly in the context of Sri Lanka and this could be the first case of vasospastic coronary syndrome to metronidazole reported in Sri Lanka.

Specific treatment of vasospastic angina is not properly studied and understood due to insufficient data pertaining to the number of patients reported. It is considered as a variation of stress induced cardiomyopathy therefore and the treatment is considered almost similar to the latter. It is thought to be a transient phenomenon where prompt treatment of anaphylaxis and supportive care following the antecedent incident will result in resolution of symptoms and complete recovery of the patient.

Patients who develop complications such as acute heart failure or shock require more aggressive therapy. The treatment suggested is in accordance with the standard protocols and guidelines of heart failure and shock.

Anticoagulation is recommended for a minimum of three months for patients having evidence of intracardiac thrombus which is a grade 1B recommendation [11]. The duration is modified according to the response rate and the resolution of the thrombus.

The mortality rates are said to be around 4% in the acute setting. The patients who survive the acute episode will generally make a full recovery. Usually the systolic dysfunction returns to normal within 6 weeks. The rate of recurrence of a similar episode is so far unknown due to lack of data.

The use of antibiotics in patients with atopy and allergy should be done with utmost vigilance. Occurrence of vasospastic angina and myocardial infarctions following anaphylaxis should be reported and appreciated as a separate clinical entity and needs further evaluation to understand at risk individuals and develop newer treatment modalities.

Conflicts of interests: None

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Case Report

Allergic Acute Coronary Syndrome (Kounis Syndrome) during Coronary Angiography: A Case Series.

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Abstract

Kounis Syndrome is the occurrence of Acute Coronary Syndrome (ACS) precipitated by an anaphylactic reaction. This article reviews two such cases which occurred during coronary angiography, as evidenced by coronary artery vasospasm and ST segment elevation secondary to contrast dye exposure. The paradoxical occurrence of coronary artery vasospasm concurrently with peripheral vasodilation makes the management of this condition complicated. This article also outlines the current evidence available for management of Kounis Syndrome.
Keywords: Allergic vasospastic angina, Kounis syndrome, Mast cell activation, Tryptase, Allergic myocardial infarction. STEMI

Introduction

Kounis Syndrome is the occurrence of Acute Coronary Syndrome (ACS) precipitated by an anaphylactic reaction [1]. A few cases of Kounis Syndrome (KS) have been documented in patients undergoing Coronary Angiography (CA), with occurrence of the syndrome likely remaining under reported [3,4]. Two varieties of KS have been described, with classification based on the presence or absence of coronary artery disease prior to the \episode [5].

Type 1 Kounis Syndrome is the occurrence of an ACS secondary to an allergic reaction in a patient with normal coronary arteries [5]. In Type 1 KS it is thought that ACS occurs due to coronary vasospasm, secondary to an inflammatory cascade [6]. Elevation of the plasma histamine concentration in the coronary circulation has been observed during Prinzmetal Angina, and this has been postulated to be a potential underlying mechanism of vasospasm in the setting of anaphylaxis [7].

In Type 2 Kounis Syndrome, ACS secondary to an allergic reaction occurs in patients with documented coronary artery disease [5]. In these patients it is hypothesized that a combination of atheromatous plaque erosion, and thrombus secondary to inflammation and vasospasm, is responsible for symptoms [5]. This pathogenesis is supported by autopsies which have shown mast cells, which are integral to the pathogenesis of type I hypersensitivity reactions, present in ruptured atheromatous plaques post mortem in patients with vasospastic angina and sudden death post anaphylaxis [8].

Case 1

A 52 year old male with a background of hypertension was transferred from a regional hospital for a semi-elective CA following an electrically positive Exercise Stress Test (EST). He had never been exposed to iodine contrast in the past and Iopamidol was used peri procedurally. He was found to have triple vessel disease, with a 90% stenosis of the left circumflex coronary artery (LCx).

Approximately 20 minutes after the initial injection of contrast dye, he became tachypnoeic, tachycardic and severely hypotensive. Electrocardiogram revealed new ST-segment elevation in V1-V2 and repeat CA showed complete occlusion of the LCx without any evidence of dissection or perforation. Subsequently two drug eluting stents (DES) were placed with good results, leading to a resolution of the patient's chest pain and ST elevation. 10 minutes later, while in the recovery bay, he experienced stridor, wheezing and developed severe angioedema. Intravenous adrenalin and hydrocortisone were administered. He was intubated, ventilated and transferred to the intensive care unit (ICU). Serum Tryptase was 62.7 ug/L (RR< 13.5 ug/L), in keeping with an anaphylactic reaction. He was extubated the following day and discharged three days later with full resolution of his symptoms.

Case Report

Case 2

A second case of KS during CA was seen in a 61 year old male with a background of hypertension presenting with posterior ST elevation myocardial infarction (STEMI). CA revealed a thrombotic occlusion in the posterolateral (PL) branch of the right coronary artery (RCA), along with a 60% stenosis of the mid left anterior descending artery (LAD). During attempted angioplasty the RCA was found to be completely occluded at the mid-level with an increase in ST-segment elevation. The patient subsequently developed complete heart block with hypotension, and was given metaraminol, atropine, intracoronary glyceryl trinitrate (GTN) and normal saline. An intra-aortic balloon pump (IABP) was inserted. The procedure was abandoned, and his ST segments normalized. An echocardiogram revealed normal left ventricular (LV) size and function and impaired RV systolic function. He was transferred to the intensive care unit, stabilized with vasopressors and was successfully discharged home several days later.

Two years later the same patient was referred for elective CA to investigate chest pain and a positive EST. During CA, the RCA and its PL branch were both patent, with progression of the LAD lesion to 80% stenosis. During preparation for angioplasty he developed chest pain, profound hypotension, angioedema, wheeze and a body rash with inferior ST segment elevation. The RCA was injected again, and this time, was found to be completely occluded. An anaphylactic reaction was suspected for which 1 mg of adrenaline, 100 mg hydrocortisone, and 25 mg promethazine were all given intravenously, along with intracoronary GTN. The ST segment elevation resolved, and the patient stabilized and maintained a patent airway. The procedure was abandoned, and he was transferred to the Coronary Care Unit for further observation. He was much improved the next day and discharged on oral prednisolone, promethazine and ranitidine.

Discussion

In patients undergoing CA who rapidly become haemodynamically unstable, with associated new ischemic symptoms and ECG changes, it is important that along with procedure related complications, such as coronary artery dissection, that an anaphylactic aetiology is also considered [9]. As seen in the second case, Kounis Syndrome can present without signs typically associated with anaphylaxis, which can cloud the diagnosis.

Although not always present, other allergic symptoms such as angioedema, respiratory distress, rash and gastrointestinal involvement can also occur [9], as demonstrated in the cases above. Having a high clinical suspicion for allergy to contrast dye or other medications delivered during CA, the possible resulting cardiac and systemic effects should remain at the forefront of a clinician's mind. The recognition that the patient is in fact experiencing both distributive shock, associated with the anaphylaxis, and a cardiogenic shock due coronary vasospasm, allows for targeted resuscitation to be delivered in a timely manner.

Management

The paradoxical occurrence of coronary artery vasospasm concurrently with peripheral vasodilation found in KS can make management challenging. There are currently no treatment guidelines regarding its management. However recommendations in previously published literature involve a combination of evidence-based treatments for both anaphylaxis and ACS, tailored to the individual patient [11].

The use of antihistamines (H1 and H2) and corticosteroids is thought to be beneficial and postulated to have a role in medium term management of anaphylaxis [11]. A meta-analysis of the use of glucocorticoids in acute myocardial infarction found them safe, with modest benefits [12]. It should be noted however that Cochrane reviews on the issue of H1 antihistamines and steroids in anaphylaxis have not shown any proven benefit in an acute setting [4,13]. The role of adrenalin is obviously controversial in patients with active vasospasm and myocardial ischemia, as adrenalin has been documented to cause vasospasm, ischemia, prolonged QT-interval, arrhythmias and cardiac arrest [11]. However, in patients with severe anaphylactic shock refractory to intravenous fluids and inotropes, as in the cases above, adrenalin should be considered [11]. Conversely, the interventions required to relieve coronary artery spasm, such as nitrates and calcium channel blockers, will decrease systemic vascular resistance [11]. The injection of GTN directly into the coronary arteries of the second case likely allowed for a local vasodilatory effect with minimal systemic response. Treatment with standard ACS medications should be reserved for those with Type 2 KS [11].

If further CA is required, pre-treatment with diphenhydramine, corticosteroids and the use of non-ionic contrast media in patients with previous reactions has been shown to significantly reduce the rate of recurrent reaction [9]. Some success has also been demonstrated with Gadolinium-based contrast in patients with severe iodine allergy [14].

Conflicts of interests: None

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Editorial comment

In this issue of the journal, we publish two papers on the Kounis syndrome. It is suspected that Kounis syndrome is under diagnosed in Sri Lanka due to inadequate knowledge of this clinical entity amongst the medical professionals.

Anecdotal descriptions of this syndrome surface from time to time mainly focusing on young people who develop heart attacks after insect bites and vaccinations.

The variants of Kounis Syndrome are well described in the literature.

In type I, the coronary arteries are normal. The allergic reaction causes coronary arterial spasm leading to myocardial ischaemia which can range from an acute coronary syndrome of low risk to a full blown myocardial infarction.

In type II, the coronary tree does have atheromatous plaques which are clinically quiescent. The allergic reaction causing a spasm at these sites leads to plaque erosion or rupture followed by formation of an occlusive thrombus.

Type III occurs within the domain of coronary stents. The allergic reaction initiates a thrombotic process with the formation of an in-stent thrombus rich in eosinophils and mast cells. The allergy trigger could be a component of the coronary stent or the anti-proliferative drug coating.

Whenever Kounis syndrome is diagnosed, it is of clinical relevance to categorize the reaction into one of the three types. This is because the treatment lines would have different emphasis in the different Kounis syndrome types.

In type I, the allergic event must be treated with adrenaline, steroids, HI and H2 receptor blockers.

In type II, in addition to treating the allergic cascade, nitrates and a calcium channel blocker should be used as needed. Beta blockers may lead to unopposed alpha effects which would promote coronary spasm and are best avoided.

In type III, interventions to stabilize mast cells need to be added to the therapeutic regime.

It is hoped that the exposure given to Kounis Syndrome in this journal would have a positive impact on the better clinical recognition and management of this condition.

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Additionally, patients suffering from anxious and depressive disorders are more likely to have increased activity of sympathetic nervous system [23] and subsequently catecholamine overload [23, 25].

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File formats which are accepted for submission include Microsoft word (DOC, DOCX).

In regard to preparing figures, please follow the formatting instructions below.

- Figures should be provided embedded *in the main manuscript file in the correct position*.
- Figures should **ALSO** be provided as separate files (not embedded in the main manuscript file).
- Each figure of a manuscript should be submitted with acceptable quality.
- Tables should submitted included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.

- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order along with an appropriate title.
- Figure titles (max 20 words) and legends (max 200 words) should be provided in the main manuscript, and also in the graphic file.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration.
- Individual figure files should be within 5 MB if *possible*. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
- Please note that it is the responsibility of the author(s) to obtain permission and consent where and when relevant.

When creating and including tables please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Table titles (max 20 words) should be included above the table, and legends (max 200 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used.

We hope these instructions are simple and easy to follow and look forward to your submission for our next issue.

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