Review

Diagnosis, evaluation and treatment of resistant hypertension

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Abstract

Resistant hypertension could be defined as blood pressure that remains elevated despite being treated with 3 anti-hypertensives of which one is a diuretic at maximum tolerable dose. It is an important global health issue associated with morbidity and mortality. It is a relatively common clinical problem. It is commonly associated with old age, obesity, sleep apnoea, and chronic kidney disease. A number of pathophysiological mechanisms are involved in resistant hypertension. Imbalance in sympathetic nervous system and renin-angiotensin system, excess sodium intake, disturbances between vasoconstrictors and vasodilators and wall resistance are other mechanisms involved in the pathogenesis. In the management life style modification such as weight loss, exercise and salt restriction has to be strictly enforced. If underlying cause is found it has to be treated. The initial preferred multidrug regime includes a diuretic, angiotensin - converting enzyme inhibitor or angiotensin II receptor blockers and long-acting calcium channel blockers. If this initial optimization of drugs is not effective a mineralocorticoid receptor antagonists can be added. Despite the use of several antihypertensive agents, a substantial proportion of patients with resistant hypertension remain uncontrolled. This has necessitated the testing of devices in the treatment of resistant hypertension. Two new approaches, carotid Baroreflex Activation Therapy and renal sympathetic denervation have shown some promise in the preliminary studies.

Introduction

Resistant hypertension (RHYT) is an important global health problem. It is associated with severe target organ damage. Patients with RHYT usually have a combination of other co-morbid conditions such as obesity, diabetes and chronic kidney disease that further elevate the risks of morbidity and mortality [1]. Resistant hypertension (RHYT) could be defined as blood pressure (BP) that remains elevated above 140/90 in patients under the age of 60 or above 150/90 in patients above 60 years of age despite being treated with 3 antihypertensives of which one is a diuretic at maximum tolerable dose. The term resistant hypertension is also applicable to patients whose blood pressure control is achieved by using 4 or more antihypertensives[2,3].

Epidemiology

The prevalence of RHYT varies depending on the nature of study and the diagnostic criteria used. The prevalence ranges from about 5 to 50 % in various cohorts. The initial studies reporting on the prevalence of RHYT individuals with pseudo resistance also were included due to lack of comprehensive workups. In some cases the treatment regime did not have a diuretic[4,5]

Prevalence of RHYT based on trial data in which participants are aggressively titrated to reach target BP, has been 20% to 50% [4]

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), found that 35% of the previously untreated subjects and 50% of the previously treated subjects had resistant hypertension, after a 5 year follow-up[6]. In the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial(ALLHAT), 34% of subjects BP remained >140/90 mm Hg on an average of 2 medications and 27% of participants needed 3 or more medications after approximately 5 years of follow-up.[5]

The epidemiological studies show a low prevalence of RHYT. A US National Health and Nutrition Examination Survey data suggests that among hypertensive adults 13% have RHYT[7].

In a recent Spanish Ambulatory Blood Pressure Monitoring (ABPM) Registry study the prevalence of RHYT was found to be 12.2%. However when ABPM was done 7.6% were found to be having true RHYT[8].

Daugherty et al studied over 200,000 patients who were newly diagnosed with hypertension and showed an incidence rate for RHYT of 1.9%. Approximately 21% were found to be needing 3 or more medications during follow-up[9].

A recent study done in Korea using ABPM registry data highlighted the difference between the RHYT incidences using daytime / night time BP criteria. This finding is important as night blood pressure is a better predictor of cardio vascular events[10].

At present, the available literature on the prevalence of RHYT shows inconsistencies in methodology and definition of RHYT. A meta analysis conducted on the prevalence of RHYT clearly stated the need for homogeneous methodologies and uniformity in defining RHYT [11].

Diagnosis of RHYT

Uncontrolled hypertension can be classified into 4 types

1.Pseudo resistant hypertension
2.RHYT with white coat effect
3.Secondary resistant hypertension
4.Primary resistant hypertension

Pseudo resistant hypertension

Pseudo resistance could result from factors related to patient, physician, and drugs.

Poor compliance to medication has been recognized as an important cause for uncontrolled hypertension (UH). It is the main reason for pseudo resistant hypertension, repeated hospital admissions and correlates with poor cardiovascular outcomes[12]. Testing for non-adherence should become a part of routine clinical practice in diagnosing RHYT.

Clinical inertia is an important factor contributing to UH. Clinical inertia is said to exist when a medical provider fails to initiate or intensify therapy when treatment goals are unmet.[13] Recent studies have identified clinical inertia as a key intervention target for improving BP control [14]. In addition "diagnostic inertia" – the failure to consider the underlying cause of the hypertension in a patient who is not responding to usual therapy also needs to be considered[15].Faulty technique used in BP measurement is also an important factor contributing to pseudo resistance.

White coat effect

White coat effect can be defined as recording of higher than normal BP when measured in the medical environment, but with normal 24-hour or day time BP when measured with ABPM in patients who are treated with 3 or more antihypertensives of which one is a diuretic.

When patients with UH are subjected to ABPM one third of patients will show normal BP levels. In a carefully conducted Spanish study 12.2% had UH. When these subjects with apparent RHYT underwent ABPM 37.5% had relatively normal 24-hour BP[16].

The differences in the prevalence of white-coat effect among various RHYT studies are attributable to the criteria used to interpret ambulatory blood pressure recording. Among the various time periods used in interpreting ABPM nocturnal BP is the best prognostic indicator for cardiovascular events.

As the clinical features are not very helpful in distinguishing between true resistance and white-coat effect, ABPM must be applied as a diagnostic tool in the investigation of RHYT.

Secondary resistant hypertension

Patients with RHYT are much more likely to have an underlying cause for hypertension[2]. Primary aldosteronism (PA), Obstructive Sleep Apnoea (OSA) and renal diseases are commonly associated with RHYT.

Endocrine causes

Primary aldosteronism (PA) is recognised as an important cause of RHYT. Small scale studies have reported a prevalence rate of PA around 20%. A study that evaluated 2032 patients with RHYT reported that 21% of patients with high aldosterone to renin ratio combined with high aldosterone levels. However, only 50% of them were confirmed to be having PA by salt suppression tests[17]

Renal disease

Target BP for patients with renal impairment and proteinuria are lower than that of the other patients with hypertension. The prevalence of RHYT among patients with renal impairment is over 50 % [18]. Renovascular hypertension is also an important cause of secondary RHYT. A study by Pedrosa et al, found renal artery stenosis (RAS) in 2.4% and parenchymal disease in 1.6%.[19]

Obstructive Sleep Apnoea

The pathogenesis of elevated BP in patients with OSA is multi factorial. Increase in sympathetic out flow, increase peripheral resistance, tissue

hypoxia, higher cardiac output, fluid retention, effects of increased aldosterone levels are possible mechanisms for RHYT in OSA[20].

A study by Pedrosa et al on 71 patients with RHYT demonstrated a 64% prevalence of OSA[19]. A Spanish study on 62 RHYT patients reported a 90% prevalence of OSA. Under strict diagnostic criteria the prevalence was reduced to 70%, thus illustrating the importance of accurate and homogeneous definition of OSA[21]. OSA has shown strong and independent association with RHYT [22].

Drug and dietary factors in RHYT

The most common drugs causing hypertension are Non-Steroidal Anti Inflammatory Drugs (NSAIDs). In 265 patients with RHYT, treatment resistance was drug-related in 36% of the cases, with NSAIDs being responsible in 88%.

The effect of NSAIDs on BP is more pronounced in patients with reduced kidney function [18]. Sympathomimetic agents, oral contraceptives, glucocorticoids, anabolic steroids, erythropoietin, and cyclosporine are some commonly used drugs that can interfere with BP control.

Use of illicit drugs and excess alcohol consumption are also known to interfere with BP control. Drug may interfere with pharmacokinetics pharmacodynamics or absorption of anti-hypertensive agents. They may also interfere by altering volume homeostasis [23].

Excess dietary salt intake also causes secondary RHYT. A study by Pimenta *et al*, demonstrated that excessive salt intake may interfere with BP control in patients with RHYT [24] The BP control achieved by salt restriction in RHYT was larger than reductions observed in cohorts of general hypertensive subjects.

Primary resistant hypertension

A study by Pedrosa et al in 125 patients with RHYT, OSA was found in 64.0%, followed by PA (5.6%), RAS (2.4%), renal parenchymal disease (1.6%), oral contraceptives (1.6%), and thyroid disorders (0.8%). The balance 34.4%, had no secondary cause to account for hypertension [19].

This group of patients who do not have associated conditions could be regarded as having primary RHYT. However some of these patients may have elevated aldsoterone levels and some degree of sleep apnoea which will not meet the diagnostic criteria of the secondary condition.

Pathophysiology of RHYT

A number of pathophysiological mechanisms are involved in RHYT. Imbalance in sympathetic nervous system (SNS) and renin-angiotensin system appears to play an important role.

Excess sodium intake, disturbances between vasoconstrictors and vasodilators and wall resistance are other mechanisms involved in RHYT.

Many secondary causes for RHYT are associated with SNS imbalance. Older age, high baseline BP, obesity, excessive dietary salt ingestion, OSA, increased aldosterone level and chronic kidney disease are closely associated with activation of SNS[2].

Old age is associated with high prevalence of RHYT. Studies have shown that SNS activity increases with age and that it is closely associated with high BP[25]. Arterial stiffening which is a feature of increasing age may contribute to treatment resistance, in addition to being a contributor to pseudo-resistant hypertension.

Obesity is a common feature in patients with RHYT. Increased SNS activity, insulin resistance, impaired sodium excretion, increases in aldosterone sensitivity and OSA may be potential mechanisms interfering with BP control in obesity[26]

The mechanism by which excess salt intake leads to RHYT has not been studied in detail. Excess salt intake leads to volume expansion and increases the number of mineralocorticoid receptors or the activation of these receptors independent of aldosterone mechanism may contribute to RHYT[27].

Obstructive sleep apnoea produces RHYT through many possible mechanisms. This includes increased levels of vasoconstrictors, vascular stiffening, endothelial dysfunction, activation of the renin-angiotensin system, oxidative stress and sympathetic hyperactivity[28].

In 20% of patients with RHYT aldosterone excess is the main pathophysiological factor involved in producing RHYT. Aldosterone's antinatriuretic effect may partially be responsible for RHYT. Recent research has identified the role of extra renal amiloride-sensitive sodium channels and mineralocorticoid receptors (MR) in controlling BP. Other effects of aldosterone on vascular cells include inflammation, fibrosis, hypertrophic remodeling, endothelial stiffening, and oxidative stress which also contribute to the pathophysiology of RHYT[29].

Kidney plays a central role in hypertension. In a normal subject elevation of BP would lead to pressure natriuresis which increases sodium and water excretion, thereby reducing BP. Patients with hypertension have blunted pressure natriuresis with resultant increase in extracellular fluid volume. In addition, activation of the renin-angiotensin-aldosterone system, increased renal SNS activity and increased sodium reabsorption also contribute to RHYT[30].

Evaluation of patients suspected of having resistant hypertension

Identification of pseudo resistance is an important step in the diagnostic approach in RHYT. After excluding pseudo resistant hypertension it is recommended that a 24 hour ABPM be performed in patients with RHYT after causes of pseudo resistance have been ruled out.

Clinically RHYT can be suspected when a patient with UH does not have evidence of target organ damage.

The ABPM recording will also be useful in classifying the hypertension pattern which has prognostic significance. This classification can also help to organize optimal chronotherapy[31].

At present there is no consensus on the criteria used to diagnose white coat RHYT. Some studies have used day time BP and some have used average 24 hour BP.

After performing the ABPM we will be able to identify patients with "True RHYT". This will include both primary and secondary RHYT. A detailed history and examination of this group of patients would be helpful in identifying secondary causes of hypertension.

PA is a common secondary cause of RHYT. Hence, testing for PA should be considered in patients with RHYT. The well established initial test for PA is the morning plasma Aldosterone-to-Renin Ratio (ARR). An increased ARR is not diagnostic of PA by itself and warrants further confirmatory testing.

In patients who have a suggestive history testing for OSA should be considered. Though OSA is suspected from the clinical features a study on patients with RHYT showed that 83% of OSA patients were unsuspected and were identified on the basis of polysomnogram results [32]. This study makes a strong case to consider polysomnogram in all patients with RHYT. Renal paranchimal disease and reno-vascuar diseases also need to be investigated as they are common causes of secondary RHYT.

Chronic renal failure can be easily diagnosed by basic investigations and imaging. Renal artery stenosis is suspected in elderly patients with RHYT. Flash pulmonary oedema and deteriorating renal function with ACE inhibitors may give a clue to the diagnosis. Renal arterial imaging will confirm the diagnosis.

There are other rare causes for secondary hypertension which may present as RHYT. In cases where the index of suspicion of a secondary cause is high, detailed investigations for a secondary cause should be carried out.

Treatment

Life style modification

In a randomised cross-over study in patients with RHYT, low salt intake (2.8 g) was shown to reduce BP by 23/9 mmHg compared to high salt intake (14 g) [33]. The current recommended total intake of sodium is 2400 mg /day (6 g or one teaspoon of salt) [3]. Some rare forms of salt sensitive hypertension are known to present as RHYT which also responds to low salt intake[34].

In obese patients, weight loss and physical activity are known to promote BP control[5] For every kilogram of weight lost there will be 0.3–1.0 mmHg BP drop[35]. Weight loss also decreases sympathetic activation, plasma renin activity and aldosterone levels. However, recent studies have suggested that BP reduction achieved through weight loss may not be sustained even if weight loss is sustained[36]. Daily aerobic exercise for 30 to 45 minutes per day is recommended for patients with hypertension[37].

A study on the effect of exercise in patients with RHYT showed a day time BP reduction of 6±12 and 3±7 mm Hg, systolic and diastolic respectively. Physical exercise was able to decrease BP even in subjects with low response to drug therapy[38]. Excess alcohol intake is associated with UH. However mild to moderate alcohol intake has been associated with reduction in cardiovascular events in many observational studies. A systematic review of alcohol intervention studies showed that alcohol restriction reduced systolic and diastolic BP by 2.7 mm Hg and 1.4 mm Hg, respectively[39].

Optimizing of drug therapy

At the outset it is important to go through all the medications the patient is on. Medications that may interfere with BP should be avoided or withdrawn. Most often patients with UH are on suboptimal medical regimens [40]. Alterations in the pharmacological treatment should begin with optimization of diuretic use. Diuretics use has been shown to decline significantly after a year's follow-up [41].

Studies have shown that optimizing diuretics was the most common method of improving BP control in RHYT[42]. Optimizing drug therapy was done frequently by adding a diuretic, increasing the dose of the diuretic or changing the diuretic based on renal function.

Chlorthalidone, a thiazide like diuretic, has a steady long duration of effect[43]. It is twice as potent hypotensive agent as hydrochlorothiazide. Chlorthalidone is effective in salt-sensitive hypertensives.

It controls night time blood pressure better than hydrochlorothiazide[44]. Chlothalidone is recommended as the preferred diuretic in the treatment of RHYT[4].

A thiazide-like diuretic indapamide, has greater antihypertensive efficacy than hydrochlorothiazide[45]. When fluid overload is likely, as in mild renal impairment addition of furosemide may be useful.

Renin–angiotensin system plays a central role in the pathogenesis of RHYT. Hence ACE inhibitors should be used in the RHYT regime. Studies have shown that a combination of ACE inhibitors and calcium channel blockers (CCB) to be better than ACE inhibitors and thiazide diuretics in reducing cardiovascular morbidity and mortality in patients with hypertension [46]. An alternate combination of ARB and CCB has also been show to be effective in RHYT[47]. Thus, ACEi or ARB and CCB could be the rational choice to be included in the initial regimen of RHYT.

The optimal drug combination will also be influenced by the clinical profile of the patient. For instance, use of a ACE inhibitor is recommended in patients with diabetes mellitus, heart failure, ischaemic heart disease, chronic kidney disease, high cardiovascular risk and stroke[3].

Currently fixed-dose combinations of 2 antihypertensive agents in a single tablet are generally preferred to improve compliance[48]. The timing of drug administration is also important in BP control. Switching one of 3 or more medications from morning to night time administration can control BP in 20% of patients[49]

Patients who still remain uncontrolled should be started on the 4th RHYT drug. The role of mineral corticoid receptor(MR) antagonists in RHYT has been demonstrated in many studies. The follow-up study of the Anglo-Scandinavian Cardiac Outcomes Trial showed BP drop by 22/10mm Hg with spironolactone[50]. A double blind placebo controlled trial of spironolactone showed 10mm Hg BP drop compared with placebo in patients with RHYT[51]. The effect of spiranolactone in RHYT is multi factorial.

The dose of spironolactone used in these studies is not adequate to completely block the renal effects of aldosterone. Hence their efficacy may be due to its effect on vascular tissue and other mechanisms[52].

A more selective MR antagonist, eplerenone is an alternative if breast tenderness or menstrual irregularities are encountered with spironolactone[53]. Amiloride, is a useful alternative to spiranolactone and can be used in combination with spironolactone

Beta blockers are a rational choice in patients with evidence of sympathetic over activity. Lipid soluble beta blockers with multiple actions such as propranalol may be beneficial in the treatment of RHYT[54]. Some beta blockers have shown some benefit in patients with OSA [55]. Alpha blockers, vasodilators and centrally acting drugs also can be used. However there is no data to prove their efficacy in the treatment of RHYT.

Newer antihypertensive agents e.g., endothelin receptor blockers, aldosterone synthase inhibitors, and neprilysin inhibitors are being tested. Darusentan, a endothelin receptor blocker was effective in reducing BP in RHYT. However, adverse effects especially fluid retention and deterioration of renal function are significant problems[56].

Further studies are needed to clarify the place of newer agents in the treatment of RHYT.

Treatment of secondary RHT

Secondary causes of RHYT may need specific treatment depending on the cause. Delving into the specific treatment of individual secondary cause is beyond the scope of this article. However, OSA being a common secondary cause of RHYT, it merits consideration of its specific treatment in relation to BP.

Continuous positive airway pressure (CPAP) is considered the treatment of choice for patients with OSA.

However, the long-term benefit of CPAP in reducing BP is modest ranging from 1.38 mmHg to 2.46 mmHg[57]. Some studies have emphasized the need for long CPAP to show significant sustained effect on BP. Longer duration of application of CPAP per day is also known to determine the degree of BP reduction[58]. All these findings point towards a complex relationship between CPAP treatment and BP response in OSA patients with RHYT.

OSA is also associated with SNS over activity and elevated aldosterone levels. Hence these patients are likely to benefit from the use of spiranolactone and beta blockers.

Device based therapy in RHYT

Despite the use of several antihypertensive agents, a substantial proportion of RHYT patients remain uncontrolled.

This has necessitated the testing of devices in the treatment of RHYT.

The main target of device based therapy in RHYT is the sympathetic nervous system. Two new approaches, carotid Baroreflex Activation Therapy (BAT) and renal sympathetic denervation (RDN) have shown some promise in preliminary studies.

The RDN is a procedure that achieves selective renal sympathectomy via an endovascular approach. This approach showed promising results in the initial studies. However a blinded randomised study of renal denervation failed to show any benefit over sham procedure in patients with RHYT [59]. The BAT delivers electrical stimulation to carotid baroreceptors to modulate sympathovagal balance. The Rheos Pivotal Trial a double-blind, randomized, prospective, sham-controlled trial showed that BAT can safely reduce blood pressure in patients with RHYT in the long run[60].

Recently Peter W. de Leeuw et al have reported on the long-term efficacy and safety of BAT. In this study after 5-6 year follow-up, office systolic pressure fell by 35 mm Hg ($P<0.0001$), whereas office diastolic pressure dropped by 18 mm Hg ($P<0.0001$). In ≈25% of patients, it was possible to reduce the number of medications. This study has demonstrated clear long term benefit from BAT [61].

Conclusion

Resistant hypertension is an important global health issue. The epidemiology of RHYT needs to be studied in detail. Further studies are needed to understand the pathophysiology of RHYT. Newer drugs and devices have to undergo systematic evaluation and head to head comparison with older drugs to ascertain their role in the treatment of RHYT.

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Review

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Review

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