Givinostat for diastolic dysfunction

Histones are proteins which are present in the cell nucleus, helping to package nuclear DNA into nucleosomes. Tails of histones protrude out of the nucleosome core and are susceptible to acetylation and deacetylation. These processes are thought to be important in gene regulation.

Data published in Science translational medicine in March 2018[1] claims a role for histone deacetylase activity on diastolic dysfunction via a nongenomic mechanism.

The acetylation of myofibrils altered relaxation but not contraction of the myocardium which opened up a therapeutic target for treating diastolic dysfunction. Hence the authors postulated that histone deacetylase inhibitors could prevent diastolic dysfunction.

In a rodent model with hypertension and age related diastolic dysfunction, histone deacetylase inhibition produced beneficial effects.

The molecule givinostat is a histone deacetylase inhibitor. This agent has given satisfactory results in a murine model with HFpEF. Human clinical trials need to be performed in the future.

Givinostat could be a valuable drug for diastolic dysfunction. At present it is designated as an orphan drug used for polycythaemia rubra vera and juvenile idiopathic arthritis.

Optogenetic termination of ventricular arrhythmias

Optogenetics is a novel technique which utilizes light to control activation of living cells. The cells have to be genetically modified to produce a light sensitive opsonin on ionic channels which are then activated by a light source.

Researchers in the Netherlands injected cardio tropic adeno associated virus (AAV) vectors which encoded channelrhodopsin which was red activable (reaChR) into wistar rats[2]. The hearts were then harvested and perfused on a Langendorff apparatus. By the application of a depolarizing or hyperpolarizing photocurrent, these newly induced channels could be activated. In these rats, optical pacing was achieved by using 470nm LED light.

Ventricular tachyarrhythmias (VT) were then induced by electrical currents. The VT s were optogenetically terminated using 1000nm light pulses.

Optogenetic intervention could well be a treatment modality for arrhythmias in the future which could be less distressful for the patient than current methods with electric shocks.

suPAR as a predictor of renal dysfunction

suPAR is an acronym referring to Soluble Urokinase-type Plasminogen Activator Receptor. uPAR is the receptor for urokinase (urokinase-type plasminogen activator) which is a membrane bound protein. The membrane bound uPAR when cleaved is released as a soluble molecule into the circulating blood stream.

The serum concentration of suPAR is an acceptable biomarker for inflammatory and immune system activation. suPAR levels are elevated in SIRS, cancer, coronary disease, type 2 diabetes, HIV and seem to be associated with mortality too. It has been suggested as a marker of aggressive disease.

In March 2018 the ACC scientific session newspaper published the findings from a team at Emory University school of Medicine in Atlanta[3], which showed that suPAR was strongly predictive of a decline in renal function in patients with cardiovascular disease.
suPAR is thought to be the first biomarker which can predict renal dysfunction in heart patients. S Creatinine and micro albuminuria, it must be remembered, rise only after renal injury. Patients who have very high levels of suPAR also have a high incidence of renal dysfunction. The investigators postulate that prolonged exposure to high suPAR concentrations result in renal dysfunction.

Two other pieces of research are relevant in this context. The first is the association between suPAR and focal segmental glomerulosclerosis. The second is the benefit of monoclonal antibodies against suPAR in renal injury in animal models.

This research is important for cardiologists when dealing with patients with renal dysfunction suffering from ischaemic heart disease and heart failure requiring contrast based intervention which is potentially nephrotoxic.

References