
Sympathetic activation and malignant ventricular arrhythmias: a molecular link?

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The past two decades have seen a wealth of data supporting a central role for the neurohormonal system in the pathophysiology of human heart failure[1]. Much attention has focused on the sympathetic nervous system. In the acute setting, when circulatory integrity is threatened (e.g. acute myocardial infarction), activation of the sympathetic nervous system is an essential response helping to maintain tissue perfusion through actions on the heart, the vasculature and the kidneys. In contrast, prolonged activation of the sympathetic system has deleterious effects on haemodynamics (sodium and water retention, enhanced afterload) and on the heart itself (remodelling, fibrosis). It is also believed that sympathetic overactivity may provoke malignant ventricular arrhythmias, a potential cause of sudden death in this group of patients.

In view of the adverse consequences of prolonged sympathetic activation it might be anticipated that measurement of plasma levels of catecholamines would provide valuable prognostic data and even facilitate the tailoring of therapy in chronic heart failure. Indeed, elevated plasma levels of norepinephrine are associated with an impaired prognosis in patients with chronic heart failure[2,3]. Cardiac cachexia, a wasting condition that occurs in a significant percentage of patients with chronic heart failure, is associated with a particularly poor prognosis[4].

Resting plasma catecholamine levels are more closely related to the presence of cardiac cachexia, as compared with other conventional markers of disease severity such as peak oxygen consumption, left ventricular ejection fraction, and New York Heart Association classification[5]. Despite these findings, drugs that reduce plasma catecholamine levels are not necessarily associated with an improved prognosis[reviewed in 3], suggesting that the mechanisms involved in blunting the effects of the sympathetic nervous system are much more complex. Catecholamines not only act as hormones when released from the adrenal medulla, but also as neurotransmitters when they are also released into the synaptic cleft. Only a small proportion of catecholamines released at the synapse spill over into the circulation. Therefore, plasma concentrations of norepinephrine and epinephrine may significantly underestimate the local/regional catecholamine concentration. Activation of the sympathetic nervous system is also manifest in several different ways. Whilst the effects of sympathetic activation within the cardiorespiratory system can be assessed indirectly by analysis of heart rate variability and reflex responses for the arterial baroreflexes[6,7], local effects are probably of at least equal importance. Cardiac sympathetic nervous activity can be determined from assessment of norepinephrine spillover, whilst cardiac norepinephrine stores can be estimated using radioisotope dilution methodology. Using these techniques a recent study has shown that cardiac sympathetic...
nervous activity may influence the mode of death in patients with heart failure\textsuperscript{[6]}. High cardiac sympathetic activity (with high cardiac norepinephrine stores) appears to be a risk factor for sudden cardiac death, whereas death from progressive heart failure is associated with high cardiac sympathetic turnover but depleted stores. This led to the speculation that in patients with large cardiac catecholamine stores, acute sympathetic stimulation may result in surges of norepinephrine release thereby increasing the risk of lethal arrhythmias.

Despite greater insight into the pathophysiological importance of the sympathetic nervous system in patients with chronic heart failure, the cellular mechanisms involved have remained somewhat more elusive. In this issue, Schillinger and colleagues\textsuperscript{[9]} provide a plausible molecular explanation as to how sympathetic nervous activation might result in the generation of malignant ventricular arrhythmias. They measured the levels of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger and sarcoplasmic reticulum (SR)-Ca\textsuperscript{2+}-ATPase in left ventricular myocardium obtained from patients with end-stage heart failure undergoing transplantation and in non-failing myocardium obtained from brain dead organ donors. Abnormal expression of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger and SR-Ca\textsuperscript{2+}-ATPase are thought to contribute to alterations in excitation-contraction coupling and subsequent impairment of ventricular function characteristic of human heart failure. In addition, as a consequence of electrogenic effects, the authors’ hypothesized that increased Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger expression might be associated with increased ventricular arrhythmias. They found that levels of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger protein were increased (56\%) and SR-Ca\textsuperscript{2+} ATPase levels were decreased (20\%) in failing myocardium as compared with normal heart tissue ($P<0.05$). In addition, a significant positive correlation was found between Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger levels and plasma levels of norepinephrine ($r=0.64$, $P<0.01$). No relationship was found between SR-Ca\textsuperscript{2+}-ATPase levels and any of the measured plasma hormones or cytokines.

Despite potential difficulties in extrapolating plasma levels of catecholamines to actual local cardiac sympathetic activity, plasma norepinephrine was the only neurohormonal parameter that correlated with Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger levels. Whilst it is still feasible that both these parameters are merely markers of heart failure severity (levels of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger protein were also negatively correlated with fractional shortening, $r=-0.56$, $P<0.05$), a distinct relationship does appear to exist between them. The authors’ present additional data from animal studies that adds further support towards a mechanistic interaction, with catecholamines providing the stimulus for enhanced Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger expression.

Schillinger and colleagues also examined the association between Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger expression and plasma norepinephrine levels and the prevalence of ventricular arrhythmias, determined from recent Holter electrocardiograms. Patients with sustained or non-sustained ventricular tachycardia ($\geq 3$ consecutive beats, Lown class IVb) had significantly higher levels of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger protein and plasma norepinephrine, as compared with patients with a maximum of two consecutive ventricular beats (Lown class 0–IVa). The authors’ concluded that sympathetic activation might enhance the expression of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger in end-stage heart failure, which in turn, as a sequelae of electrogenic effects, could favour the development of malignant arrhythmias. Whilst it is not yet possible to confirm a direct causal link between increased expression of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger protein and ventricular arrhythmias, this hypothesis certainly has interesting qualities and requires further evaluation.

Another important issue raised by this study is how documented, potentially life-threatening arrhythmias, such as sustained or non-sustained ventricular tachycardia, relate to the mode of death in patients with heart failure. The exact mechanism of ‘sudden cardiac death’ is difficult to determine and whilst it has commonly been attributed to lethal cardiac arrhythmias it is well recognized that acute ischaemic events contribute significantly\textsuperscript{[10]}. Even without fatal consequences the development of ventricular arrhythmias is detrimental, often undermining the optimal therapeutic management of patients with severe heart failure. For example, inotropic support with dobutamine (a $\beta$-receptor agonist) is often limited by the development of arrhythmias. Nesiritide, a recombinant form of human brain natriuretic peptide, has been shown to improve haemodynamic function (without an associated reflex tachycardia) and clinical status in patients with decompensated heart failure\textsuperscript{[11]}. Improvements in clinical status seen with nesiritide are similar to those obtained with dobutamine. However, nesiritide therapy is associated with a lower incidence of serious ventricular arrhythmias when compared to dobutamine\textsuperscript{[12]}. It is conceivable that this may relate to documented biological properties of natriuretic peptides, such as suppression of the sympathetic nervous system and interactions with baroreceptor control of the circulation\textsuperscript{[13]}. It would be of great interest to compare the effects of different pharmacological agents, including nesiritide and dobutamine, on myocardial Na\textsuperscript{+}-Ca\textsuperscript{2+}-exchanger protein levels to establish whether alterations in their expression correlates with the clinical differences.
Whilst contributing to our understanding of the pathophysiology of chronic heart failure, the study by Schillinger and colleagues[9] also highlights the increasingly recognized heterogeneous nature of this disorder. Improved insights into the molecular mechanisms involved in, for example, the genesis of lethal arrhythmias or the detrimental effects of sympathetic activation is essential and may facilitate the development of novel therapies. With the increasing complexity of available interventions in the management of chronic heart failure it is, however, likely that not all therapies will be applicable to each individual patient. In this respect patient profiling and targeted therapy is an appealing goal[14,15]. Whilst this might begin with neurohormonal and cytokine assessment, more detailed evaluation at the cellular/molecular level may also be required.

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References

Exercise-related syncope: are athletes different from sedentary subjects?

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Syncope seldom occurs during effort. For example, in one recent study[11], syncope during effort was reported in only 17 (5%) of 341 patients referred to three Syncope Units for evaluation of unexplained syncope. In the patients with structural heart disease, syncope during effort was a significant predictor of a cardiac cause of syncope (with an odds ratio of 3:1) with a specificity of 96%[11]. In other words, in the patients with structural heart disease the occurrence