Review Paper

DISTURBED autonomic nervous 'balance' of the sympathetic nervous and vagal outflows to the heart potentiates the experimental development of ventricular arrhythmias in laboratory animals. For some time the best evidence for the occurrence of a similar phenomenon in humans was provided by the long QT interval syndrome, sufferers of which are very prone to develop serious ventricular arrhythmias and in whom evidence exists of abnormal anatomy and function of the cardiac sympathetic nerves. Recently the case for disturbed autonomic function causing clinical arrhythmias has become more broadly based. Reduced baroreflex sensitivity after myocardial infarction, and low heart rate variability, both of which rest largely on vagal underactivity, have been shown to be associated with substantially increased risk of subsequent sudden death. A second observation is that patients having recovered from unexpected ventricular tachycardia or ventricular fibrillation have markedly increased cardiac sympathetic activity compared with appropriate reference groups, based on measurements of the rate of spillover of the sympathetic neurotransmitter, noradrenaline, from the heart to plasma. These clinical findings support a role for cardiac autonomic dysfunction, specifically sympathetic activation and vagal withdrawal, in arrhythmogenesis. These observations are timely, given the recent demonstration that most conventional anti-arrhythmics are of little benefit in preventing sudden death. A reappraisal of the anti-arrhythmic activity of &-adrenergic blocking drugs, and evaluation of potential benefits of other pharmacological and non-pharmacological means of favourably altering cardiac autonomic function is now needed.

Key words: Sympathetic nervous system, Noradrenaline, Vagus nerve, Long QT interval syndrome, Arterial baroreflex, heart rate variability, Mental stress

Since antiquity it has been held that acute and severe mental distress can cause sudden death. Of late, medical evidence has emerged to support the medical folklore, although adding the proviso that when this event occurs it is usually in those with structurally abnormal or diseased hearts. The autonomic nerves of the heart are seen as providing the mediating mechanism.

The heart is innervated by both the sympathetic and the parasympathetic nervous systems. Parasympathetic innervation is through the vagus. The cardiac sympathetic innervation is complex, showing considerable asymmetry. On the right side, the sympathetic nerves to the heart arise predominantly from the right middle cervical ganglion, with a small cardiac branch from the right stellate ganglion. On the left side, cardiac sympathetic innervation through the stellate ganglion is more prominent than on the right, but the chief sympathetic supply is from the left middle cervical ganglion. The atria are more densely innervated by sympathetic fibres than the ventricles and it is the sinoatrial node and the atrioventricular node which receive the richest supply. A disproportionate number of the sympathetic fibres destined for the sinoatrial node arise from the right side, while the atrioventricular node receives a preponderance of left-sided sympathetic fibres.

Electrophysiological studies underscore the importance of the autonomic nerves of the heart in determining cardiac electrical stability. Sympathetic activation has the proarrhythmic effects of reducing ventricular refractoriness and fibrillation thresholds, and generating after depolarizations, while the vagus is protective in these respects. Experimental studies in laboratory animals directly support the importance of neural, and behavioural, processes in arrhythmia development.

The clinical evidence that cardiac sympathetic activation has an important role in humans is more circumstantial. Central to our clinical understanding of the importance of the cardiac sympathetic outflow in arrhythmogenesis are studies on the long QT interval syndrome, this inherited disorder having been termed by Zipes 'a Rosetta stone for sympathetic related ventricular arrhythmias'. Patients with this condition have abnormally long ventricular repolarization, which predisposes to the development of ventricular tachyarrhythmias (typically the torsade de pointes form of ventricular
tachycardia) and sudden death (Fig. 1). The immediate precipitant of the arrhythmia is very commonly a stimulus causing sympathetic activation, such as a loud noise or an emotional upset. Although the underlying genetic mechanism is disputed, the widely held view is that there is a developmental abnormality of cardiac innervation affecting electrical conduction and repolarization in the heart, deriving from the normal asymmetry of cardiac sympathetic innervation described above, with over-representation of innervation from the left stellate and middle cervical ganglia, and under-representation of right-sided innervation. Anti-adrenergic measures, either \( \beta \)-adrenergic blocking drugs, or in resistant cases left stellate ganglionectomy, are usually very effective in suppressing the disordered rhythm and in preventing syncopal attacks and sudden death.

The applicability of the evidence incriminating sympathetic nervous activation in the development of ventricular tachyarrhythmias, drawn from studies in the long QT interval syndrome, to the wider population of patients at risk, typically those with existing coronary artery disease and left ventricular dysfunction, is uncertain. A central difficulty here, only recently rectified, has been the lack of reliable measures of human cardiac sympathetic function. Methods recently developed for assessing the function of the cardiac autonomic nerves include measurement of the rate of spillover of noradrenaline from the sympathetic nerves of the heart, testing of arterial baroreflex sensitivity, which rests in large measure on vagal function and the use of sophisticated mathematical partitioning or power spectral analysis to separately detect components of heart rate variability determined primarily by sympathetic and by vagal influences respectively. In the assessment of cardiac sympathetic nervous function from noradrenaline spillover measurements, radiolabelled noradrenaline is infused intravenously and arterial and coronary sinus blood sampled. The release of noradrenaline to plasma from the sympathetic nerves of the heart is quantified from the degree of dilution of the tracer by unlabelled noradrenaline in passage through the heart, measured in coronary sinus plasma. In the testing of arterial baroreflex sensitivity, baroreflex curves are constructed which relate blood pressure changes induced by the intravenous administration of blood pressure-raising and lowering drugs to the magnitude of the reflexly produced changes in heart rate. With power spectral analysis of circulatory rhythms, the individual, superimposed rhythms produced cyclic variation in heart rate or arterial pressure can be separated and measured. Heart rate variability is largely attributable to the influence of the autonomic nervous system. High-frequency (approximately 0.3 Hz) and low-frequency (approximately 0.1 Hz) components of heart rate variability can be detected. The high-frequency component is linked to respiration, and is associated in particular with vagal influences and abolished by atropinization. The low-frequency variability is largely derived from the cardiac sympathetic nerves, and is reduced by \( \beta \)-adrenergic blockade. These methods for the clinical testing of cardiac autonomic function have now been applied to the study of arrhythmogenesis, with some interesting early results.

One finding is that the presence of reduced baroreflex sensitivity, particularly in the recovery period after myocardial infarction, predicts the development of ventricular arrhythmias and sudden death. Reduced heart rate variability carries similar predictive power. Although the interpretation of these findings is not straightforward, the inference drawn is that a reduction in vagal activity, in the setting of coronary artery disease, has predisposed to the development of the ventricular arrhythmias. Recommendations have been made that autonomic testing of this type perhaps be performed routinely after myocardial infarction, to help in prognostication and medical management.

In another recent study, performed on patients successfully resuscitated from an episode of ventricular tachycardia or ventricular fibrillation occurring outside hospital and tested some days later when they were haemodynamically stable, markedly increased spillover of noradrenaline from the heart, indicative of the activation of the cardiac sympathetic nerves, was detected (Fig. 2). A reference population of patients without arrhythmias, studied during coronary angiography, had normal sympathetic nervous function. The sympathetic nervous stimulation present in arrhythmia patients was highly selective for the sympathetic nerves of the heart. Although the cardiac sympathetic activation appeared to be due in part to the presence of depressed left ventricular function, attributable to coronary artery disease, other mechanisms, perhaps behavioural, may have been contributing. It is well established, for example, that mental stress, applied in a laboratory