Role of sympathoadrenergic mechanisms in arrhythmogenesis

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Received 31 May 1999; accepted 31 May 1999

See article by Guo et al. ([1], pages 930–938) in this issue.

Ventricular arrhythmias occur frequently following acute myocardial infarction, during reperfusion and in heart failure. They are the likely major cause of sudden cardiac death in the majority of instances and as such represent a continuing and major cardiac health problem. The role of the sympathetic nervous system (SNS) in the genesis of arrhythmias under these conditions has been extensively studied for many years. Nevertheless, the importance of SNS activation in arrhythmogenesis remains controversial. This is again apparent in the current issue of Cardiovascular Research, where the findings from two papers with apparently contradictory interpretations are presented [1,2].

Numerous experimental approaches have been applied to manipulate the activity of the SNS, from denervation and catecholamine depletion to cardiac sympathetic nerve stimulation or treatment with adrenergic agonists. These studies have been reviewed thoroughly [3–7]. Several lines of evidence have suggested an important or perhaps even pivotal role for SNS activation in initiating arrhythmias following myocardial infarction, reperfusion or heart failure. Thus both high levels of circulating catecholamines as well as increased cardiac noradrenaline (NA) spillover [8], increased sympathetic nerve firing rates and suppressed baroreflex sensitivity are all associated with increased incidences of arrhythmias and mortality [5]. β-blockers have been shown to be particularly beneficial in reducing cardiac mortality following myocardial infarction or heart failure, although evidence that their mechanism is by an anti-arrhythmic effect is less clear cut. There is strong evidence that ventricular fibrillation and sudden cardiac death may be triggered in some patients by psychologic stressors [9,10]. Activation of sympathetic nerves, especially stimulation of the left cervicothoracic stellate ganglion, induces ventricular arrhythmias under conditions of ischaemia, infarction and heart failure [2,4]. Transgenic mice with cardiac specific overexpression of Gsα have increased incidence of arrhythmias and mortality [11]. The importance of locally mediated release of NA, with subsequent activation of α1-adrenoceptors, in ischaemia-reperfusion arrhythmias has been thoroughly investigated [12,13] and a good correlation between the quantity of NA release or the extent of α-AR activation and the severity of arrhythmias has been reported [12,14,15].

There are, however, a number of studies implying the opposite, namely that activation of SNS is not an important or necessary antecedent of arrhythmias [3,16]. Walker et al. have presented an elegant and novel approach to address the role of SNS under conditions of myocardial ischaemia and infarction [1]. They firstly transplanted rat hearts into the abdominal aorta of host rats and then, at various time points (1 h, 2, 5 and 10 days) after transplantation, subjected both donor and native hearts to regional ischaemia. Thus, the paired donor and native hearts were under identical hormonal and circulatory conditions but with a crucial difference in that only the native, but not the donor heart, was sympathetically innervated. They hypothesized that any difference in arrhythmia incidence between donor and native hearts could then be attributed to the presence of an intact innervation only to the native heart. However, their findings clearly show that both hearts experienced similar incidence of arrhythmias [1].

There are several issues which need to be considered in relation to their model. First, the model does closely resemble the situation in cardiac transplantation with the exception that the transplanted rat heart did not perform significant external work. The lack of the autonomic control was demonstrated by unchanged heart rate following alterations in blood pressure or with ganglion blockade. The NA content in the heart was not measured but it is likely to be small at least at the 10-day period. It is known that three days after chemical sympathectomy NA content is only 7% of normal value [6]. Second, the development of adrenoceptor supersensitivity in the trans-
planted heart was demonstrated clearly with enhanced heart rate responses to NA or propranolol (at Day 10) [1]. As denervation sensitization increases the arrhythmia susceptibility [6], it is thus possible that, in the presence of receptor supersensitivity, adrenergic activation occurs by either increase in circulating catecholamines and possibly local release of residual NA, which might still have been sufficient to contribute to arrhythmia development. Third, considering a lower workload and the resultant energy expenditure in transplanted hearts, a lower arrhythmia incidence during ischemia was expected but this was not observed.

Controversy over the role of the SNS is partly due to difficulty in manipulating the activity of the SNS, particularly in eliminating its influence. The arrhythmogenic outcome of SNS activation has been demonstrated in the majority of studies inducing nerve activation by either electric stimulation or other means [2,4,6,7]. There is evidence that in hearts subjected to infarction or failure, sympathetic nerve stimulation results in heterogeneous, rather than a homogenous, adrenergic activation, which is more arrhythmogenic [2,6,17]. Although it has been shown that co-transmitters, such as neuropeptide Y, have significant electrophysiological actions [18,19], the potential synergistic effects of NA and co-transmitters on perturbations in electrophysiology under pathological conditions has been little studied. While neuronally mediated NA release can be prevented by acute sympathectomy, local release of NA can still trigger arrhythmias during ischemia and reperfusion [12,13]. As discussed above, chronic denervation is confounded by the post-junctional supersensitivity of adrenoceptors and signal pathway.

It is generally agreed that structural cardiac abnormalities (ischemia and infarct, cardiomyopathy, hypertrophy, ventricular remodeling) provide substrates on which a triggering mechanism operates to initiate arrhythmias [2,7,20]. Events like SNS activation, endocrine disturbances, abnormalities in electrolytes, haemodynamic alterations, drug toxicity and ectopic beats, may function as arrhythmic triggers. Thus, multiple mechanisms and signaling pathways are involved in the generation of ventricular arrhythmias under pathological conditions. This view may also be indicated by more potent efficacy of some anti-arrhythmic drugs with multiple effects, such as amiodarone. Because of such redundancy of arrhythmogenic pathways, it is expected that a near complete blockade of one system can not fully stop the onset of such event. This argues against the validity of denervation or catecholamine depletion as tools to support or refute the importance of SNS activation in arrhythmia development. One example could be the altered myocardial metabolism that follows denervation or catecholamine depletion with glycogen storage increased by several fold [21]. Thus, during subsequent ischemia-reperfusion an enhanced and maintained glycolysis would occur leading to more pronounced intracellular acidosis, Na\(^+\)/H\(^+\) and Na\(^+\)/Ca\(^{2+}\) exchanges, and increased susceptibility to arrhythmias [22–24].

It may be useful to consider the attributes of an ‘ideal’ experiment needed to establish the importance of sympatheadrenergic activation in the genesis of arrhythmias. The intervention should affect all SNS signal transduction pathways (i.e. not only these mediated by \(\beta\)- or \(\alpha\)-adrenoceptors) but without producing confounding changes in alternative pathways which can ultimately lead to arrhythmia development. The intervention should be cardiac specific and should inhibit responses to local activation of nerves as well as that in response to neural reflex activity. The arrhythmias should be either initiated or abolished (or at least substantially reduced) by manipulating SNS activity and signal pathway at a time immediately preceding the onset of arrhythmias. Whilst at the present time there seems not prospect of such an ‘ideal experiment’ being conducted, its features can be used as a yardstick against which actual experimental setting may be measured. With the progress in the transgenic techniques, mouse cardiophysiolo and induced models of myocardial infarction and heart failure, it is likely that the use of mouse lines, with the SNS and adrenergic signal pathways enhanced or abolished, may be a novel approach to address this question, although the severity of arrhythmias appears to be lower in the mouse compared to other species [25]. The mouse lines of potential use may include cardiac specific overexpression or deletion of nerve growth factor which determines the extent of sympathetic innervation and the catecholamine content in the heart, and of \(\alpha\)- and \(\beta\)-adrenoceptors [26–30].

### References


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