Editorial

Are the arrhythmias due to myocardial ischaemia and infarction dependent upon the sympathetic system?

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Received 3 June 1999; accepted 3 June 1999

See article by Du et al. ([10], pages 919–929) in this issue.

Many studies have implicated the sympathetic nervous system as being of importance in the genesis of the arrhythmias induced by myocardial ischaemia and infarction [1]. This can involve increased activity in the sympathetic system or the local release of norepinephrine from sympathetic nerve endings exposed to the extracellular conditions that occur in ischaemic tissue. Evidence to support the role of the sympathetic nervous system has included the use of drugs to modify the system or extirpation of nerves, but rarely mimics or increases sympathetic activity. It has to be remembered that, regardless of the manner in which evidence is accumulated, activation of the sympathetic system is always arrhythmogenic and that this in itself exacerbates or even triggers arrhythmias due to other causes, and will reveal any underlying tendency for arrhythmias.

Despite a large number of experiments, the available evidence both supports and denies the importance of the sympathetic system. Some of the contradictions may arise from the methods or species used, or whether the pathological condition being considered is ischaemia, infarction, or reperfusion following a period of ischaemia. The latter is a distinct condition in which the mechanisms inducing arrhythmias may be very different. Furthermore, species may be an important factor. In some species (e.g. rats, rabbits, pigs), occlusion of a coronary artery results in complete ischaemia in the area downstream of the site of occlusion since, in such species, coronary arteries are true end arteries, i.e. they do not have coronary collateral arteries. In other species (e.g. dog, guinea pig), the occurrence of collateral arteries results in non-uniform ischaemia or even only partial ischaemia [2]. Such differing levels of ischaemia could have different sensitivities to possible arrhythmogenic influences of the sympathetic system.

In the following examination of the possible arrhythmogenic importance of the sympathetic system, we have chosen to consider only evidence obtained in the rat and will differentiate between conditions of ischaemia and those of infarction. Arrhythmias arising from reperfusion are not considered. The necessity of differentiating between ischaemia and infarction cannot be overstated since there may be great differences between the two. For purposes of differentiation, we consider ischaemia to occur in the early period after loss of blood flow, before heart cells are irreversibly injured. Infarction is when the majority of cells are irreversibly injured or dead. It has to be recognised that an infarction zone contains a small percentage of injured but surviving cells.

Within the above definitions, we can consider the evidence in rat hearts, both in vitro and in vivo, for a role for the sympathetic system in causing arrhythmias due to ischaemia and infarction.

We will first consider the evidence for involvement of the sympathetic system in the genesis of arrhythmias due to ischaemia in vivo. The evidence can be divided into that obtained with drugs and that with surgical denervation [3]. Beta-blockers have been shown in many studies to reduce arrhythmias following induction of ischaemia in anaesthetised rats. However, such protection was not seen in conscious rats [4]. This apparent paradox may be resolved by studies which show that the protective effect of beta-blockers in anaesthetised rats is due to an indirect action in which beta blockade in non-cardiac tissue allows for a rise, from depressed levels, of serum potassium and it is this
that prevents the occurrence of arrhythmias [5]. A rise in serum potassium with beta-blocker treatment is not seen in conscious animals since it is a secondary consequence of acute surgery and anaesthesia.

When the activity of the sympathetic system is blocked by various drugs, including the classical blocker of neuronal sodium channels, tetrodotoxin, no antiarrhythmic effects is seen against ischaemia-induced arrhythmias [6]. Nerve blockade in vivo is analogous to the situation when isolated hearts are subjected to coronary occlusion; the arrhythmias that occur are identical to those seen in intact hearts [7,8].

A final piece of evidence is the study reported in this issue of the journal [9] in which transplanted hearts were subject to myocardial ischaemia. It was found that arrhythmias in transplanted hearts were very similar to those occurring in normal innervated hearts, regardless of the age of the transplant and the degree of degeneration of the nervous system.

It is difficult to conclude from such studies that the sympathetic nervous system plays a direct role in the genesis of ischaemia-induced arrhythmias in rat hearts. The situation with respect to infarction may be different. Another study reported in this issue of the journal [10] appears to show, quite unequivocally, that, in isolated hearts studied in situ, arrhythmias associated with infarction have sympathetic dependence. In the elegant and detailed study reported in this issue of the journal, Du et al. [10] were able to show, consistently, that stimulation of cardiac sympathetic nerves induced arrhythmias in perfused infarcted rat hearts in situ. The incidence and severity of such arrhythmias depended upon infarct size, gender and perfusate potassium concentration, and were abolished by beta-blockers. The authors argued persuasively that activation of the sympathetic system acted as a trigger on the preexisting substrate (the infarct). A trigger role for the sympathetic system in infarction has been suggested by many other studies in other species and inferentially in man [11].

The authors also report a relationship between infarct, or ischaemic, zone size and arrhythmias. This is not surprising since, if there is no damage, there are no arrhythmias, while a graded relationship is to be expected. In ischaemia, the relationship is a square root one [3], suggesting that the surface area of the zone is critical, while in infarction, it appears to be the infarct volume that is critical. Such similarities between ischaemia and infarction are suggestive of a similar mechanism. It should also be noted that the evidence relating sympathetic activity to arrhythmias in ischaemia is incomplete in that, while a variety of procedures, drugs, surgery, etc. have been used to probe the role of the sympathetic system, the sympathetic system has still not been directly activated. What is needed is a repeat of experiments by Du et al. [10] using sympathetic stimulation in the presence of ischaemia.

In speculating on the different roles for the sympathetic system in infarction and ischaemia, it may be of importance to remember that, in the presence of the powerful stimulus of ischaemia, the addition of an arrhythmogenic stimulus of sympathetic activity would have only an additive effect or no effect. However, in the presence of the limited arrhythmogenic stimulus of infarction, sympathetic stimulation may well have a synergistic effect. This speculation could be specifically tested by using the Du et al. [10] technique and rats with various sizes of ischaemic zone.

In conclusion, with a few additional experiments, it should be possible to unequivocally describe the importance of the sympathetic system in exacerbating or inducing arrhythmias in rat hearts under the separate conditions of ischaemia and infarction. It is assumed that such findings would be relevant to other species, and perhaps to man.

Acknowledgements

The editors gratefully acknowledge the help of Mrs. Y. Zwiers in the final preparation of the manuscript.

References