Editorial Comment

Ischemic Modulation of Cardiac Autonomic Innervation*

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Numerous studies in experimental animals have established the importance of the autonomic nervous system in the genesis of a wide variety of cardiac arrhythmias. The most compelling clinical data supporting the role of sympathetic innervation in ischemia-related arrhythmias come from the studies demonstrating a reduction in total and sudden cardiac death in patients treated with a beta-adrenoceptor antagonist after myocardial infarction. How beta-adrenoceptor blockers reduce the death rate is not yet clear.

The present study. The article by Dae et al. (1) takes us one step closer to understanding mechanisms of sympathetically mediated arrhythmias by employing a technique to study cardiac sympathetic innervation. Metaiodobenzylguanidine (MIBG), a guanethidine analogue developed at the University of Michigan and used initially to identify adrenal tissue in patients with pheochromocytoma (2), can be employed to image cardiac sympathetic nerves and detect whether sympathetic terminals are present and take up MIBG normally (3,4). A defect in the MIBG cardiac scintigram in an area that simultaneously shows a normal thallium-201 image outlines viable myocardium with normal blood flow and normal cellular function, at least for thallium-201 uptake, but absent or diminished MIBG uptake. The latter is due to reduced or absent cardiac sympathetic nerve terminals, that is, postganglionic cardiac sympathetic denervation.

Effects of ischemia and infarction on cardiac autonomic innervation. These effects have been studied for some years and provide the underpinnings for our knowledge of the MIBG response (5). Knowing the intracardiac routes of autonomic neural innervation allows one to predict the different effects produced by a subendocardial versus a transmural lesion. Afferent and efferent vagal fibers in the dog cross the atrioventricular (AV) groove in the superficial subepicardium and then enter the myocardium where they are located in the subendocardium, penetrating upward to innervate the epicardium. They can be interrupted by an epicardial lesion (epicardial phenol application, surgical dissection at the AV groove) or by an endocardial lesion (subendocardial ischemia or infarction) within the ventricle. In contrast, sympathetic afferent and efferent fibers are located in the superficial subepicardium throughout their course, primarily in the periadventitia of the coronary arteries, diving intramurally to innervate the endocardium. They can be interrupted by epicardial lesions at the AV groove and within the ventricle. Therefore, transmural myocardial ischemia or infarction that involves the subepicardium will interrupt “downstream” efferent sympathetic innervation. In contrast, subendocardial ischemia or infarction spares the subepicardium and sympathetic nerves, but interrupts the vagus. Although sympathetic responsiveness in the surviving subepicardial shell overlying a subendocardial infarction is reduced to some degree (6), intact sympathetic innervation with vagal denervation can create a heart prone to developing arrhythmias (7). The present study of Dae et al. (1) using MIBG scintigraphy confirms some of the different efferent sympathetic denervation patterns produced by nontransmural and transmural infarction.

It is important to stress that ischemic-neural interaction is dynamic and changing. One MIBG thallium-201 scan creates a static, snapshot view of potentially evolving pathophysiology (5). For example, acute myocardial ischemia initially causes functional neural denervation, probably related to accumulation of ischemic catabolites in the myocardium in which the nerve axons lie. Resumption of coronary flow restores these early, reversible neural responses. More permanent denervation takes hours of ischemia to establish. But even after anatomic disruption of nerve axons with more permanent denervation has occurred, a new phenomenon is observed, that of denervation supersensitivity. Denervation supersensitivity creates an area of myocardium that responds in an exaggerated fashion to catecholamines. Such a response appears to generate an arrhythmogenic state that is eliminated by beta-adrenoceptor blockers (5) and may also provide a substrate for heterogeneous drug actions on the heart and a possible cause of proarhythmia (8). Finally, after 12 to 14 weeks, reinnervation occurs and the MIBG defect normalizes. Interestingly, and as yet unexplained, supersensitivity persists despite reinnervation (5). Some of these sympathetic patterns have been documented in patients with coronary artery and other forms of heart disease (4).

Clinical implications. The clinical importance in the pathogenesis of ventricular arrhythmias, especially sudden cardiac death, of the regional sympathetic denervation patterns shown in the canine studies described and in the MIBG scintigrams in humans (4) has not yet been established. It should be a priority for future research. Such a link, if forged, will provide insight into sympathetically responsible
mechanisms causing sudden cardiac death and may permit
development of more specifically directed antiarrhythmic
therapy (9). For example, speeding the process of reinner-
vation or preventing the initial denervation may prove to
have an antiarrhythmic effect. If the connection between
regional sympathetic denervation and arrhythmias cannot be
established, then cardiac MIBG scintigraphy will be an
interesting but perhaps not clinically useful tool. I am betting
on the former possibility and anticipate that studies like
those by Dae et al. (1) will yield important insights into these
mechanisms.

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