Neurally Mediated Hypotension and Bradycardia: Which Nerves? How Mediated?*

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The present study. In this issue of the Journal (1), investigators from the University of Minnesota report the third in a series of studies focusing on the phenomenon of "neurally mediated syncope." In the present study, six patients (Group I) who presented with "cardiovascular collapse apparently associated with cardiac asystole" underwent head-up tilt testing before and during infusion of isoproterenol, as reported previously (2), after a negative electrophysiologic study. The responses of these patients were compared with those of two groups of age- and gender-matched control patients. Group II comprised patients with a history of syncope (but without a history of asystole) and a negative electrophysiologic study. Group III comprised patients with recurrent syncope and findings at electrophysiologic study sufficient to explain their clinical presentations. All patients in Groups I and II developed hypotension and bradycardia with head-up tilt alone or with head-up tilt during isoproterenol infusion. Such a response was not seen in Group III patients.

These investigators (2,3) have shown previously that hypotension and bradycardia can be provoked in a substantial proportion of patients with unexplained syncope and nondiagnostic findings at electrophysiologic study. The patients described in the present study differ from those reported previously primarily in the severity of their presenting symptoms as well as in their responses to the tilt/isoproterenol test. Therefore, the present study extends the spectrum of the clinical and laboratory manifestations of "neurally mediated syncope" described previously by these investigators (2,3) and Waxman and colleagues (4).

Mechanisms that mediate the spontaneous or provoked episodes of hypotension and bradycardia. These mechanisms are unclear. It has been hypothesized that exaggerated discharge of ventricular mechanoreceptors with vagal afferents is induced by vigorous myocardial contraction around a small ventricular chamber and that this produces sympathoinhibition and vagal parasympathetic cholinergic discharge. Indirect support for this hypothesis in humans comes from the observations that pretreatment with propranolol (4), metoprolol (5) or disopyramide (6) prevents or attenuates spontaneous and inducible hypotension and bradycardia. Among other effects, these medications impair ventricular contractility and attenuate the discharge of ventricular mechanoreceptors.

In cats and rats, reduction in cardiac filling pressures produced by hemorrhage causes sympathoinhibition and bradycardia that is prevented by interruption of vagal afferent impulses from cardiopulmonary sensory receptors (7,8). These sympathoinhibitory and bradycardic responses are also inhibited in rats by blockade of serotonin synthesis with p-chloro-phenylalanine or serotonin receptors with methysergide (9). In dogs, however, neither vagotomy nor sinoaortic denervation (which interrupts input from arterial baroreceptors) prevents sympathoinhibition during substantial hemorrhage (10). Thus, there appears to be interspecies variability in the mechanism of this response and other mechanisms, such as serotonergic and opioid pathways, in addition to ventricular baroreceptors with vagal afferents may be involved. In this regard, it is also worth noting that sympathetic stimulation may increase the discharge of inhibitory arterial as well as ventricular baroreceptors (11). Therefore, consideration should be given to a possible role for paradoxical activation of both arterial and ventricular baroreceptors in the hypotensive and bradycardic responses to tilt/isoproterenol testing.

Vasodepressor and bradycardic mechanisms in humans. In humans, sudden, inappropriate slowing of heart rate after an initial tachycardia has been reported during significant hemorrhage, a response similar to that described during tilt/isoproterenol testing (12). In addition, inappropriate sinus slowing has also been reported in some patients during hemodynamically unstable ventricular tachycardia (13). This raises the intriguing possibility that reflex vasodepressor and bradycardic mechanisms may be important in initiating cardiovascular collapse in some patients with ventricular tachycardia. In large part because of the constraints of human investigation, the roles of sinoaortic and ventricular mechanoreceptors in mediating these responses in humans have not been clarified. Induction of hypotension and (native) sinus bradycardia in heart transplant recipients with orthostatic stress or during the tilt/isoproterenol test suggests that activation of cardiac mechanoreflexes is not the sole mechanism mediating these responses because ortho-
topic cardiac transplantation results in ventricular denervation (deafferentation).

The tilt/isoproterenol test to induce bradycardia and hypotension. The specificity and reproducibility of the tilt/isoproterenol test for the induction of bradycardia and hypotension in this study (1) and previous studies (2,3) by these investigators have not been fully examined. It is possible that fear or anxiety provoked by the laboratory environment (14) and intravascular instrumentation may have contributed to the development of syncope in patients prone to vasodepressor reactions. A large study (15) of Air Force pilots and navigators showed that syncopal reactions were much more frequent during tilt when subjects underwent invasive (as opposed to noninvasive) hemodynamic monitoring. Sham studies in which 1) venous pooling during tilt is prevented by inflation of thigh cuffs, and 2) vehicle is infused in lieu of isoproterenol would help define further the mechanism of alternative inotropic agents such as dobutamine that have groups of investigators (1-4). Further investigation should be directed toward elucidating the mechanisms of these reactions.

Implications. A final important question that persists is how do these patients differ physiologically from other patients and normal subjects? Do they have exaggerated cardiac mechanoreflexes as described in young athletes (16) and patients with borderline hypertension (17)? Do they have abnormally increased number of beta-receptors that could lead to heightened sensitivity to endogenous or exogenous catecholamines? And, finally, as suggested previously by Abboud (14), might these patients have an abnormality in the ionic mechanisms that control the discharge of mechanically sensitive receptors in the ventricle?

The clinical characteristics of inducible hypotension and bradycardia have now been reproducibly reported by two groups of investigators (1-4). Further investigation should be directed toward elucidating the mechanisms of these responses and their therapeutic implications in patients with unexplained syncope.

References