Editorial Comments

Baroreflex Impairment and Sudden Death After Myocardial Infarction

Robert F. Rea, MD, James B. Martins, MD, and Allyn L. Mark, MD

In the last 50 years, investigators have produced convincing evidence that sympathetic and parasympathetic mechanisms are important in predisposing the ischemic heart to malignant ventricular arrhythmias. In this issue, Schwartz and his colleagues in Italy and Oklahoma present two studies that extend their previous investigations into the role of the autonomic nervous system in the pathogenesis of sudden cardiac death (SCD).

See p 816 and p 969

These investigators present data from animal experiments and from a clinical study focusing on the role of impaired arterial baroreflexes in mortality after myocardial infarction (MI). It is worthwhile to consider these articles both individually and together as they relate to the problem of SCD.

In the clinical study, La Rovere et al measured baroreflex control of heart rate 4 weeks after a first MI in 78 men. During a follow-up of 24 months, there were six cardiovascular deaths, of which four were sudden. The baroreflex slope relating change of heart rate to change of systolic pressure was significantly greater in survivors than in nonsurvivors.

In the animal study, Schwartz et al measured baroreflex control of heart rate in 192 dogs 4–5 weeks after an anterior wall MI produced by anterior descending coronary artery ligation. Subsequently, during transient circumflex coronary artery occlusion performed during treadmill exercise (acute inferior ischemia in the setting of a chronic anterior MI), 106 dogs suffered ventricular fibrillation (VF). The baroreflex slope was significantly lower in dogs susceptible to VF than in dogs resistant to VF. Interestingly, animals susceptible to VF (and those dying spontaneously after MI) had reduced baroreflex slopes even before coronary ligation when compared with other animals.

Taken together, these observations suggest an important relation between impairment of arterial baroreflexes and mortality after MI.

There is a sound physiological basis for the central hypothesis of these studies. Afferent impulses originating in arterial baroreceptors project to the central nervous system to inhibit sympathetic nerve activity and activate parasympathetic vagal neural influences on the heart. Attenuation of baroreceptor reflexes could result in enhanced sympathetic activity and reduced vagal parasympathetic cardiac outflow, a physiological condition that has been associated with the emergence of ventricular arrhythmias in the presence of ischemia. However, the mechanism by which autonomic inputs modify susceptibility to ventricular arrhythmias is not simply a matter of generalized sympathetic and parasympathetic tone and predominance. MI may produce regional and local changes in cardiac autonomic influences that predispose to ventricular arrhythmias. With transmural infarction, sympathetic innervation to viable myocardium distal to the site of infarction may be interrupted and thereby promote regional sympathetic imbalance in the ventricle. With nontransmural infarction, parasympathetic innervation in a viable epicardial rim may be disrupted while sympathetic innervation is preserved. This can produce a localized sympathetic-parasympathetic imbalance that promotes ventricular arrhythmias. Thus, there are multiple mechanisms and sites whereby alterations in autonomic influences may affect the propensity for ventricular arrhythmias in ischemic heart disease. The issue and controversy raised by Schwartz and colleagues is whether baroreflex impairment is an independent marker and mechanism of the autonomic contribution to SCD in patients with coronary heart disease.

In the study by La Rovere et al, several important questions persist. First, is a depressed baroreflex slope an independent predictor of mortality after MI in humans? Five of the six deceased patients had other risk factors predicting mortality after MI, namely, reduced left ventricular ejection fraction and/or multivessel coronary disease. A stepwise multivariate analysis of established and proposed risk factors might have helped to determine if a depressed baroreflex slope was a predictor of SCD after MI independent of other recognized risk factors. Second, how did concurrent medical treatment affect mortality? Drugs known to affect baroreflexes and autonomic effects on the heart were used in many patients. Third, was the number...
of patients and deaths sufficient to provide adequate statistical power?

The animal studies strengthen the case for an association between attenuated baroreflexes and SCD. It was shown that myocardial infarction depressed baroreflex control of heart rate and that the baroreflex slope was lower in dogs susceptible to VF. In addition, a reduced baroreflex slope before coronary ligation was associated with spontaneous death during coronary ligation and subsequent susceptibility to VF. Furthermore, in a previous study, these investigators demonstrated that an increase in baroreflex sensitivity produced by endurance exercise training was associated with reduced susceptibility to VF in this model of acute ischemia and chronic MI.10

Despite the strengths and the Herculean proportions of the animal study, several caveats are warranted. First, is a depressed baroreflex slope an independent marker and contributor to SCD in this experimental model or is it simply a correlate of other markers or mechanisms? Further studies of the role of baroreflex impairment in this animal model should include systematic assessment of infarct size, risk area of the circumflex vessel, ventricular function, and the electrophysiological substrate for ventricular arrhythmias. Second, in a previous related study, animals with higher baroreflex slopes and resistance to VF had significant reductions in heart rate during circumflex occlusion, whereas animals susceptible to VF did not.11 This suggests that animals resistant to VF may have had greater activation of the Bezold-Jarisch reflex during circumflex occlusion (inferior ischemia) compared with animals susceptible to VF.12 The Bezold-Jarisch reflex originates in sensory receptors in the heart, particularly in the inferoposterior wall of the left ventricle. Activation of this reflex during infaroposterior ischemia triggers parasympathetic activation, bradycardia, and sympathetic withdrawal. Thus, this reflex might also protect against ventricular arrhythmias during acute myocardial ischemia. Although there are interactions of arterial baroreflexes and the Bezold-Jarisch reflex, they are distinct reflexes. In the context of the present study in dogs with anterior infarction and inferior ischemia, it is difficult to distinguish the possible role of cardiac sensory receptors (Bezold-Jarisch reflex) from that of arterial baroreceptors in mediating the resistance to VF. The consideration of a role for the Bezold-Jarisch in the resistance to VF also has implications for the relevance of the animal model used in these studies. This model involves anterior infarction and inferior ischemia. The Bezold-Jarisch reflex is engaged primarily during inferior ischemia and to a much lesser extent during anterior ischemia. Consequently, it would be interesting to know if the observations in the present studies also extend to a model of inferior infarction with anterior ischemia. Third, it is now recognized that studies of parasympathetic control of heart rate with the phenylephrine technique may not pertain to sympathetic control. Sympathetic regulation may be preserved at a time when parasympathetic control of heart rate is impaired.13 Finally, the arterial baroreflex is not a static mechanism but instead exhibits dynamic resetting in threshold, set point and gain. Thus, one should be cautious in extrapolating from measurements of the baroreflex in the resting state to conclusions regarding the role of the baroreflex during exercise and ischemia.

A final point relates to the relevance of the experimental model (acute ischemia superimposed on chronic infarction) to human disease. The pathophysiological setting of SCD in patients with coronary artery disease is unquestionably more diverse than that in the animal studies presented here and includes at least the following three possibilities: 1) acute ischemia in the presence of chronic MI, 2) acute ischemia in the absence of chronic MI, and 3) chronic MI with a fixed and provocative electrophysiological substrate for malignant ventricular arrhythmias in the absence of acute ischemia. Studies of survivors of SCD unassociated with acute MI have suggested that up to two thirds of patients have sustained ventricular arrhythmias inducible with programmed ventricular stimulation, presumably in the absence of acute ischemia.14 Thus, the conclusions based on the present experimental model may not be relevant to the majority of patients at risk for SCD.

Autonomic influences on both acute and chronic substrates are unquestionably important in the predisposition to ventricular arrhythmias and may be modulated in potentially beneficial ways by drug and nondrug therapies. Further investigation into the markers and mechanisms of these influences is clearly needed. We believe, however, that it is premature to suggest that an analysis of baroreflex sensitivity in patients with chronic ischemic heart disease provides novel and independent information about the risk for sudden death.

References

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R F Rea, J B Martins and A L Mark

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