Therapeutic indications for $\beta$-adrenergic blockade expand apace. Large trials have established beyond argument a central role for $\beta$-blockers in treatment of patients recovering from acute myocardial infarctions [1]. This year, two new studies [2,3] established the benefit of $\beta$-blockers in treatment of patients with chronic congestive heart failure.

$\beta$-Adrenergic blocking drugs exert their benefits in a variety of ways. In angina patients, they reduce ongoing myocardial ischaemia [4]. In post-infarction patients, they prevent early myocardial rupture [5] and reinfarction [1]. In heart failure patients, they improve left ventricular function and retard the progression of myocardial dysfunction [2,3].

One of the more intriguing and important effects of $\beta$-blockers is that they prevent ventricular fibrillation and sudden cardiac death [2,3,6]. Prevention of sudden death is intriguing because $\beta$-blockers exert little effect on less serious ventricular dysrhythmias [6], and it is important because sudden cardiac death is the largest single cause of death in developed countries. Mechanisms responsible for prevention of sudden death by $\beta$-blockers are not well understood.

$\beta$-Adrenergic blocking drugs are diverse. They may or may not have intrinsic sympathomimetic or vasodilator activity, and they may or may not be cardioselective. In this issue of Clinical Science, Vaile and his group at the University of Birmingham, U.K. [7] report their study of another attribute of $\beta$-blockers, i.e. lipophilicity. They compared the effects of a lipophilic $\beta$-blocker, metoprolol, with those of a hydrophilic $\beta$-blocker, atenolol, on heart rate variability in healthy men.

Vaile's study [7] is noteworthy in several respects. First, this extensive report is based on only one measurement: the intervals between electrocardiographic R waves. Nonetheless, the study is ingenious and extraordinarily well designed, with double-blind, placebo control, and crossover features. Secondly, the article focuses on a property of $\beta$-blockers that has long been recognized [8] but little appreciated, that they enhance vagal effects. Thirdly, the study draws attention to an aspect of vagal physiology which is almost universally ignored: the abrupt cardioacceleration that occurs when vagal restraint is withdrawn.

Vaile et al. [7] tested the hypothesis that lipophilic $\beta$-blockers enhance vagal influences more than hydrophilic $\beta$-blockers. There are several reasons why it was important to test this hypothesis. Published evidence suggests that sudden cardiac death is prevented by lipophilic $\beta$-blockers [2,3,6], which readily cross the blood-brain barrier, but not by hydrophilic $\beta$-blockers, which do not readily gain entrance to the central nervous system [9]. $\beta$-Blockers can prevent sudden death, when they are injected directly into the central nervous system [10]. Moreover, there is some evidence that systemically administered $\beta$-blockers do exert their beneficial effects by increasing vagal–cardiac nerve traffic emanating from the medulla. [However, much of this evidence (Vaile’s references [10,34,37]) is difficult to evaluate because it is published only in abstract form.]

The results of Vaile’s study [7], and results of research published earlier [11], do not support the hypothesis that $\beta$-adrenergic blocking drugs enhance vagal effects through influences exerted within the central nervous system. In general, Vaile’s study shows that metoprolol and atenolol increase fluxes of the level of vagal restraint, both augmentation and withdrawal, similarly. However, these results do not diminish the possibility that $\beta$-blockers prevent sudden cardiac death, in part by enhancing vagal influences.

It is abundantly clear that subnormal levels of vagal–cardiac nerve traffic [12] or vagal baroreflex gain [13,14] constitute risk factors for cardiac mortality. It is less clear how loss of vagal influences promotes sudden death, and how restoration of vagal influences protects against it [15]. Although vagal stimuli alter human ventricular electrophysiological properties, such effects are extremely small [16]. Thus, subnormal levels of vagal restraint may merely be markers for serious underlying cardiac disease.

This seems unlikely; it is more likely that cardiac patients have derangements of both vagal and sympathetic mechanisms, and that these derangements in some way feed into the pathophysiology of sudden cardiac death. I provide one example of how this might happen. The majority of people who die while wearing Holter monitors have terminal ventricular fibrillation, which is usually preceded by ventricular premature beats or ventricular tachycardia [17]. We and others have studied autonomic responses to rhythms that precede ventricular fibrillation. Huikuri et al. [18] recorded atrial electrograms, and showed that patients who have major autonomically mediated increases of their sinus rates during ventricular tachycardia tolerate the tachycardia well, and do not require cardioversion. We [19] showed that patients who mount large sympathetic nerve responses to the hypotension that occurs at the beginning of ventricular tachycardia restore their systemic (and
coronary) arterial pressure much more rapidly than patients whose sympathetic responses to hypotension are blunted. This year, Hamdan et al. [20] confirmed this observation and extended it by showing that the gains of both vagal and sympathetic baroreflex responses predict the speed of recovery of arterial pressure during ventricular tachycardia, simulated by rapid ventricular pacing.

The early cardioacceleration component of the haemodynamic response to abrupt hypotension is mediated by withdrawal of vagal restraint. Vaile et al. [7] report that β-blockers augment this abrupt cardioacceleration. This is a provocative observation. It may not be far-fetched to speculate that β-blockers protect against sudden cardiac death in part by enhancing recovery of arterial pressure during rapid rhythms known to precede ventricular fibrillation.

D. L. ECKBERG

Hunter Holmes McGuire Department of Veterans Affairs Medical Center and Medical College of Virginia, Richmond, VA 23249, U.S.A.

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REFERENCES