Beta-Blockade for Mitral Regurgitation

Could the Management of Valvular Heart Disease Actually Be Moving Into the 21st Century?*

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Severe valvular heart disease comprises a group of lesions that impose a hemodynamic burden on potentially all 4 cardiac chambers. This burden is eventually fatal if left untreated by timely valve repair or valve replacement. However, defining the word timely is fraught with uncertainty. Ideally, the procedure should occur early enough to spare the patient from irreversible left or right ventricular (and atrial) dysfunction, or both, and certainly from sudden death, but should be delayed long enough to reduce time-dependent complications inherent to valve prostheses if valve repair is impossible to perform. Remarkably, in 2012, in the midst of a wealth of scientific tools available in other medical realms, deciding on the “golden moment” for valvular intervention rests on tools that are at least 50 years old: the presence of cardiac symptoms, increased heart size, ejection performance, evidence of pulmonary hypertension, or a combination thereof (1). To be sure, modern imaging techniques can give us precise measurements of lesion severity, of the size and function of the cardiac chambers, of pulmonary pressure, and of regional and global wall motion.

In turn, these data form the current basis for timing mechanical intervention. In modern practice, these markers have been reasonably satisfactory guides, judging from the fact that outcomes are good when there is adherence to guidelines using these parameters (2,3). Unfortunately, by using symptoms, chamber size, and chamber function to judge the timing of mechanical intervention, we are looking only at the end result of the pathological processes put into motion by the hemodynamic overload present in all valvular lesions. Obviously, to come to the point where symptoms or changes, or both, in cardiac geometry and wall motion have developed, a series of biological systems must have been activated or perturbed. This concept potentially presents an alternative strategy to the timing of mechanical intervention. Instead of waiting for the end result of the pathological features of valvular heart disease, we could intervene earlier if we knew that the presence of specific biological events meant a nearly inevitable progression to the parameters we now use to judge interventional timing.

The study by Ahmed et al. (4) in this issue of the Journal gives support for such an approach. It provides yet additional evidence the adrenergic nervous system becomes engaged as a support mechanism in mitral regurgitation (MR) fairly early in the course of disease, before other thresholds indicating the need for surgery are crossed, and that beta adrenergic blockade may be beneficial by preventing the damage done by adrenergic overactivation. It has been known for a long time that MR begets increased sympathetic activity (5–8). Catecholamines are increased both in the experimental animal and in humans with MR. In the dog, beta-blockade restores depressed contractility resulting from MR and restores the loss of contractile elements seen in this model, strongly suggesting a cause-and-effect relationship between catecholamine excess and myocardial injury (8). It is also known that contractility improves in humans after surgery for MR and that this improvement is associated with a reduction in catecholamines (5,6). In turn, the data from Ahmed et al. (4) support previous observations that patients with MR receiving beta blockers have a better outcome than those not receiving them, regardless of the presence of hypertension or coronary artery disease (9). In patients randomized to receive metoprolol, ejection fraction remained unchanged, whereas it declined in placebo-treated patients. Although the foibles of ejection fraction in measuring function in MR are well known, that end-systolic volume tended to increase without a change in load in the placebo group suggests that contractility declined in those patients and that this decline may have been mitigated by beta-blockade. Taken as a whole, the data suggest a reasonable hypothesis regarding the pathophysiology of MR. As MR leads to reduced forward cardiac output, the adrenergic nervous system acts reflexively to support the circulation. In turn, persistent sympathetic activity leads to myocardial damage and eventual heart failure. We detect the end products of this scenario when we observe the onset of symptoms and objective evidence of cardiac dysfunction. These data set the stage for a large randomized clinical trial to determine whether beta-blockade would be a useful therapy in temporizing the need for surgery in MR patients.

However, the impact of the current study may go well beyond the potential for treating MR medically. Suppose

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that, instead of or in addition to periodic examinations of cardiac and mitral valve function, we also measured catecholamines or perhaps a surrogate such as heart rate variability, and suppose that we found that after the adrenergic nervous system reached a certain level of activity, eventual cardiac deterioration was almost inevitable. This may provide a simpler way to time surgery more accurately and earlier before ventricular structural changes occur. Or, if not the adrenergic nervous system, other biological changes in MR must be occurring and could be tracked. For the heart to enlarge, there must be a change in connective tissues supporting the myocardium, and these changes almost surely rely on activation and deactivation of matrix metalloproteinases, which also could be measured, yielding yet another potential method for timing surgery (10–12). Alternatively, in the experimental model of MR in the dog and in papillary muscles of MR patients, there is an eventual loss of contractile elements (13,14). Thus, tracking ultrasensitive troponin levels may detect the early occurrence of these events before overt left ventricular dysfunction develops. In addition, in human MR, calcium handling is altered, and early detection of these changes also may give insight into future developments (15). Or, there may be a host of systemic perturbations that we have yet to consider.

Since the time of the ancients, man has been fascinated with the movement of the heart, and in the 21st century, we have developed incredibly sophisticated machines to detect and measure this movement. Impairment of this motion together with changes in cardiac geometry are the manifestations of advanced pathological processes that already have injured the myocardium and have impaired its function. The current study by Ahmed et al. (4) suggests that biological perturbation occurs well before changes in ejection performance. If we can measure such changes simply and inexpensively, we may to to advance the understanding and management of valvular heart disease from watching the heart move to detecting the processes that impair function while using those tools to time better or even delay the need for mechanical intervention.

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