Left Ventricular Structure and Function in Aortic Valve Disease

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Changes in left ventricular volume, mass, and systolic performance that develop after valve replacement for chronic aortic valve disease have for years provided clinical insights into the effects of severe pressure or volume overload on the human left ventricle. These changes in left ventricular structure and function after operation also have important implications regarding postoperative prognosis, especially in patients with evidence of preoperative left ventricular dysfunction.

In the majority of such patients, systolic function is reversibly depressed, the depression being related to the long-standing pressure or volume overload; aortic valve replacement in these patients results in substantial regression of hypertrophy and improvement in systolic function. However, in a subgroup of patients, more commonly those with pure or predominant aortic regurgitation, left ventricular dysfunction reflects irreversible myocardial changes in addition to altered ventricular loading and is not reversed by operation. These patients with persistent ventricular dysfunction after operation have a poor outcome with regard to symptoms and survival. The preoperative identification of patients with these irreversible myocardial changes on the basis of standard measures of left ventricular volume, hypertrophy, and function has proven to be problematic and elusive.

Numerous studies over the past 2 decades have addressed the alterations in left ventricular wall stress, hypertrophy, dilatation, and systolic function that develop in the course of aortic stenosis or regurgitation as well as those alterations that occur in response to aortic valve replacement. Few studies, however, have focused on the alterations in myocardial cellular structure that underlie these preoperative and postoperative changes or on the cellular abnormalities that may signify irreversible ventricular dysfunction. The study of Krayenbuehl and associates in this issue is an important contribution that provides new insights into the structural adaptations of the myocardium to chronic pressure or volume overload in aortic valve disease and into the long-term structural remodeling that develops in response to reduction of myocardial overload by valve replacement. Their data also indicate that simple morphometric indexes of preoperative myocardial structure and cellular hypertrophy may not be sufficient to predict postoperative left ventricular function.

Regarding the preoperative morphometric measurements of Krayenbuehl et al., the findings of myocardial cellular hypertrophy with relative and absolute increases in interstitial connective tissue content in patients with chronic aortic stenosis or regurgitation are certainly not new and confirm previous observations. However, the significant inverse correlation between muscle fiber diameter and both left ventricular ejection fraction and peak velocity of contractile element shortening is a unique observation relating the degree of cellular hypertrophy to ventricular contractile performance. In contrast, there was no such relation between extent of interstitial fibrosis and ejection fraction. As noted by the investigators, the relatively weak correlation between muscle fiber diameter and ejection fraction might be explained by the many other factors, particularly ventricular loading, that influence ejection fraction, although one may equally argue that these loading conditions are also the inciting stimuli responsible for the development of cellular hypertrophy. Factors other than cellular hypertrophy may explain the relatively weak and inverse relation between muscle fiber diameter and systolic function. Myocardial degeneration may represent the end stage of severe hypertrophy and may result when the protein synthetic mechanisms of the cardiac cell are exhausted. Degenerated cells would be expected to have reduced contractile performance. Although the normal preoperative volume fraction of myofibrils in the patients studied by Krayenbuehl et al. is evidence against cellular degeneration, other ultrastructural characteristics of degeneration, such as proliferation of sarcoplasmic reticulum or mitochondria and basement membrane thickening, were not assessed.

The serial postoperative structural changes reported by Krayenbuehl and coworkers are also of interest. In concert with significant decreases in

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left ventricular mass index and wall thickness, muscle fiber diameter decreased significantly at the intermediate (9–25 month) postoperative study, both in patients with aortic stenosis and in those with aortic regurgitation, and did not further change at the late (41–99 month) postoperative reevaluation. In contrast, myocardial fibrous content, which decreased by the time of the intermediate study only in patients with aortic regurgitation, decreased significantly in both aortic stenosis and aortic regurgitation at the late evaluation. By placing these data in the context of previous clinical observations, it appears that the substantial reductions in left ventricular mass that occur within the initial 1 to 1.5 years of aortic valve replacement,9–18 and the associated increases in ventricular ejection performance,10,12,17–22 are mediated during this time period by a significant decrease in the size of muscle fibers and, in the case of aortic regurgitation, a simultaneous decrease in myocardial fibrous content. In comparison, the late postoperative changes in left ventricular mass, filling pressures, and systolic function,16,23,24 which are of considerably smaller magnitude than those occurring early after operation, are associated primarily with regression of myocardial fibrous tissue.

However, it is also apparent from the data of Krayenbuehl et al2 that resolution of hypertrophy at the cellular level may be incomplete even many years after aortic valve replacement. Despite significant decreases in muscle fiber diameter and fibrous content at the late postoperative study compared with preoperative values and despite reduction of macroscopic left ventricular mass index to the normal range in most patients, late postoperative measures of muscle fiber diameter and relative interstitial fibrosis remained elevated. An additional and unexpected morphometric finding identified by Krayenbuehl and coworkers during the late postoperative period is a reduction in the volume fraction of myofibrils, the significance of which, as recognized by these investigators, cannot be fully explained at present. Of importance, on the basis of their data, this does not appear to be associated with impaired contractile function and thus does not appear to represent cellular degeneration. However, partly as a result of this finding, coupled with slight increases in left ventricular systolic pressure related to the prosthetic valve, calculation of myofibrillar systolic wall stress yielded elevated values, which can be viewed as evidence for persistent systolic overloading at the myofibrillar level.

Regarding the preoperative prediction of postoperative left ventricular function, Krayenbuehl and coworkers2 observed that the preoperative ejection fraction, but not the preoperative myocardial cellular structure, was related to the late postoperative functional outcome. These findings support numerous previous observations that ejection phase indexes of ventricular function are sensitive preoperative measures in identifying patients at risk of irreversible left ventricular dysfunction, heart failure, or death after aortic valve replacement.17,24–34 The load dependence of ejection fraction and the related problems with its use as a measure of left ventricular contractile state are well known, but the study of Krayenbuehl et al2 is further evidence of the clinical value of this index of systolic function in aortic valve disease. However, it is also quite clear that ejection fraction alone is not sufficient in the characterization of patients or in predicting postoperative prognosis because many patients with depressed ejection fraction do well after operation and, especially in aortic stenosis, manifest substantial increases and normalization of ejection fraction after operation.10–13,16–22,24 Other objective measures are needed, and the study of preoperative cellular changes associated with postoperative left ventricular dysfunction may be the basis for such criteria. It is disheartening that the myocardial cellular changes measured by Krayenbuehl et al2 were not predictive of postoperative left ventricular function even though muscle fiber diameter correlated with preoperative ejection fraction and preoperative ejection fraction was predictive of postoperative functional outcome. The inability of muscle fiber diameter or other indexes of cellular structure to predict postoperative outcome may reflect the small numbers of patients undergoing late evaluations (a limitation of their study, but an understandable one, given the methodology) and the fact that in these patients systolic function was not changed by operation.

This lack of change in systolic function after operation is perhaps the most noteworthy unexpected finding of Krayenbuehl and associates,2 especially in light of the significant postoperative decreases in left ventricular mass, end-diastolic volume, peak wall stress, and (in patients with aortic stenosis) systolic pressure. The overwhelming experience of numerous previous investigators,10,12,17,19,20,22,35 including Krayenbuehl and associates themselves in a larger series of patients,18,23 indicates that a significant increase in ejection fraction would be expected after valve replacement in patients with either aortic stenosis or regurgitation but to a greater extent in aortic stenosis.10,20,22 This increase in ejection fraction may continue through the long-term postoperative course.23,24 The lack of increase in indexes of systolic function in the study of Krayenbuehl and colleagues,2 early or late after operation, may again reflect the small numbers of patients undergoing late evaluation or other patient selection factors. Of note, most patients studied by Krayenbuehl et al2 appear to have had normal preoperative ejection fraction, and these patients may be less likely to manifest postoperative changes than those with subnormal ejection fraction.9,18,20,36 If only a small number of patients with depressed left ventricular function were studied, then there would not only be a reduced likelihood of observing significant increases in ejection fraction, but of greater importance, there would also be less likelihood of including patients with
persistent ventricular dysfunction and, thus, of being able to study the cellular markers of irreversible myocardial disease. Maron et al have shown that ultrastructural evidence of cellular degeneration in left ventricular hypertrophy stemming from aortic valve disease is a common finding in aortic regurgitation but not in aortic stenosis. These ultrastructural cellular changes may provide a key to the clinical observation that persistent left ventricular dysfunction after operation is a more common occurrence in aortic regurgitation than in aortic stenosis. A larger series of patients with aortic regurgitation and left ventricular dysfunction studied with preoperative myocardial biopsies would be useful to evaluate the role of morphometric studies in the characterization of such patients and in the prediction of subsequent postoperative outcome.

References


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