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EDITORIAL REVIEWS

Surgical Outcome in Chronic Aortic Regurgitation: A Physiologic Framework for Assessing Preoperative Predictors*

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Nearly 30 years after the first valve replacement for aortic regurgitation, we are still searching for reliable markers for correct timing of surgery (1,2). The report by Carabello and associates in this issue of the Journal (3) maintains that abnormalities in left ventricular contractility are the predominant substrate for poor surgical outcome in patients with chronic aortic regurgitation. Thus, our goal continues to be valve replacement late enough in the course of the disease to justify the surgical risk yet early enough to avoid irreversible damage to the left ventricular contractile mechanism. For years, accomplishment of this goal has been thwarted by the complex interaction of changes in preload, afterload and contractility that are characteristic of chronic aortic regurgitation. It is clear that the *ideal preoperative predictor* of surgical outcome in chronic aortic regurgitation must be load and heart rate independent as well as highly sensitive to left ventricular contractile state. The following discussion explores the physiologic rationale as well as inherent limitations of the most commonly used preoperative predictors of postoperative course in patients with chronic aortic regurgitation. In each case, comparisons with the "ideal predictor" will be made.

Regurgitant Volume and Regurgitant Fraction

Previous studies. Aortic root contrast cineangiography is used for the rough estimation of the severity of aortic regurgitation. Left ventricular cardiac output and effective forward cardiac output can provide a more quantitative assessment of regurgitant volume and regurgitant fraction. Recently, these data have been acquired using noninvasive techniques such as pulsed and continuous wave Doppler echocardiography (4–6), Doppler color flow mapping (7,8) and radionuclide angiography (9,10).

Comments. Left ventricular and peripheral vascular hemodynamic conditions are major determinants of aortic regurgitant volume and regurgitant fraction. The most important physiologic factors affecting severity of aortic regurgitation include: 1) regurgitant orifice size; 2) aortic diastolic blood pressure; 3) left ventricular diastolic pressure and chamber compliance; and 4) length of diastole (11–13). It is important to note that regurgitant volume and fraction are poor predictors of surgical outcome for aortic valve replacement, in large part because they do not reflect left ventricular contractility or intrinsic myofibrillar function (14–16). For example, with increased heart rates, the regurgitant volume per beat decreases, particularly in patients with severe regurgitation (9,11). Peripheral vasodilators such as nitroprusside and hydralazine can also reduce the regurgitant fraction while increasing forward cardiac output (10).

End-Diastolic Indexes

Previous studies. The physiologic response to chronic moderate to severe aortic regurgitation is ventricular dilation at end-diastole associated with an increase in left ventricle wall mass, which helps maintain normal end-diastolic wall thickness and the end-diastolic wall thickness to chamber dimension ratio (17,18). End-diastolic wall stress (the product of end-diastolic pressure and dimension divided by wall thickness) is the best measure of the load acting to stretch left ventricular fibers at end-diastole (preload) (19). However, in the clinical setting, left ventricular end-diastolic volume (dimension) or pressure, or both, rather than end-diastolic wall stress, has been used as an estimate of true end-diastolic fiber load. In our study (14) of chronic aortic regurgitation, preoperative end-diastolic volume index demonstrated only a fair predictive value for postoperative ventricular performance. The same was true for left ventricular end-diastolic dimension in previously reported studies (20,21). Our study (14) also demonstrated a poor correlation between preoperative left ventricle end-diastolic pressure and the patient's postoperative course. Some patients with normal preoperative end-diastolic pressure (<14 mm Hg) had abnormal postoperative left ventricular function, whereas others with markedly abnormal preoperative end-diastolic pressure (>20 mm Hg) had normal postoperative left ventricular function. Other authors (22,23) reported similar findings.

Comments. The Frank-Starling phenomenon, described in the early 1900s, emphasizes the fact that left ventricular stroke volume is highly dependent on end-diastolic fiber

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load (24). Clinically, end-diastolic fiber load (preload) in aortic regurgitation is determined by 1) chamber stiffness; 2) myocardial contractility; 3) intravascular blood volume and its distribution; 4) atrial contribution to left ventricular filling; 5) right ventricular-left ventricular interaction; 6) intrapericardial and intrathoracic pressures; and 7) systemic venous capacitance. These confounding variables mask the status of left ventricular contractility and, again, it is not surprising that the end-diastolic indexes of left ventricular performance are insensitive predictors of postoperative clinical course.

Ejection Phase Indexes of Overall Left Ventricular Performance

Rest Data

Previous studies. Forman et al. (22) suggested that left ventricular ejection fraction was useful in the timing of aortic valve replacement in aortic regurgitation based on the observation that patients with an ejection fraction <0.50 had a significantly poorer 3 year survival rate (64 ± 10%) than did patients with an ejection fraction ≥0.50 (91 ± 8%, $p < 0.02$). Greves et al. (25) reached a similar conclusion. Other studies (20,26,27) have also noted that left ventricular ejection fraction at rest or echocardiographically determined percent fractional shortening correlated well with risk of death or persistent left ventricular dysfunction after aortic valve replacement. Many studies (14–16,28–30), however, found rest ejection fractions to be an unreliable measure of myocardial contractility.

Comments. Overall left ventricular performance, as measured by ejection fraction or percent fractional shortening, reflects the interdependence of preload, afterload, heart rate and contractile state. In aortic regurgitation, left ventricular end-diastolic fiber load is significantly increased, as are end-diastolic volume and stroke volume (19). The resultant left ventricular ejection fraction can be maintained within the normal range even if myocardial contractility is depressed. This inability to distinguish between changes in contractile state and altered myocardial load is an important limitation of all ejection phase indexes of ventricular performance. Superimposed on this problem is the effect of the interaction between systolic and diastolic events in the cardiac cycle. For example, in a patient with moderate to severe aortic regurgitation, preload, and subsequently ejection fraction, will vary depending on heart rate despite constancy of left ventricular contractile state (9,11). Disparate results using ejection phase indexes are therefore expected.

Exercise Response

Previous studies. The left ventricular ejection fraction response to exercise has been used for almost a decade as a measure of functional reserve in patients with chronic aortic regurgitation (11,15,16,26–28,30–34). Indeed, it has been suggested that failure to augment ejection fraction during exercise may be an early harbinger of myocardial dysfunction. Borer et al. (30) reported that 19% of their patients with severe aortic regurgitation had a subnormal ejection fraction at rest and 67% had an abnormal ejection fraction response to supine bicycle exercise; they concluded that the ejection fraction response during exercise was "a sensitive and potentially useful clinical index of the functional status of the left ventricle in patients with aortic regurgitation." Others reached similar conclusions in symptomatic (16,32) and asymptomatic patients (15,33). In contrast to these findings, Gee et al. (28) reported an excellent postoperative course in 23 patients despite a decrease in preoperative exercise ejection fraction in 91% of their patients. At a mean follow-up of 30 months, no patient had died of left ventricular dysfunction nor had any patient demonstrated symptoms of congestive heart failure. Finally, Bonow et al. (26) reported on long-term follow-up in 80 patients who underwent valve replacement for aortic regurgitation, the majority having a normal ejection fraction at rest and a decrease in ejection fraction with exercise. Survival was excellent. Neither the value of the exercise ejection fraction nor the magnitude of the ejection fraction response to exercise predicted which patients with subnormal ejection fraction at rest were at risk of death or persistent ventricular dysfunction after operation. Thus, the ejection fraction response to exercise failed to provide "meaningful information regarding postoperative prognosis over the initial five to seven years after aortic valve replacement."

Comments. Despite its widespread use and popularity, the left ventricular ejection fraction response to exercise appears to have limited predictive value as a marker for postoperative course in chronic aortic regurgitation. This reflects the inability of the technique to distinguish between ejection fraction changes due to altered loading conditions and those due to left ventricular contractile abnormalities. This limitation is further compounded by the complexity of acute circulatory events that occur with dynamic exercise. These include: 1) peripheral vasodilation in exercising muscles; 2) increases in sympathetic tone to the heart; 3) release of catecholamines from the adrenal medulla; 4) alterations in systemic venous capacitance leading to maintenance of venous return and ventricular preload; and 5) augmentation of heart rate in association with a marked decreased in the length of the diastolic portion of the cardiac cycle. Derangements of any one of these mechanisms can result in failure to increase ejection fraction without implicating a depression in myocardial contractility.

In addition, the criteria for the "normal" ejection fraction response to exercise have been defined in subjects without ventricular volume overload or valvular regurgitation. It is conceptually inappropriate to expect a highly load-dependent ejection phase index such as ejection fraction to

respond to dynamic exercise in a similar manner in normal subjects and in patients with chronically altered left ventricular loading conditions. This is well illustrated in patients with aortic regurgitation, in whom exercise-induced tachycardia markedly reduces the duration of diastole, which reduces the duration and absolute value of the aortic regurgitant volume per beat (11,27). The ventricle, which is volume overloaded before exercise, becomes relatively "preload deficient" during exercise. The preload-augmented ejection fraction present at rest frequently falls with exercise, reflecting an acute change in left ventricle loading conditions rather than diminished contractile reserve. This helps to explain the very high incidence of abnormal ejection fraction response to exercise seen in nearly all studies of aortic regurgitation regardless of the age, functional class or rest ejection fraction of the patient group. Thus, the multiplicity of factors operating simultaneously in the exercising patient with aortic regurgitation results in too many discordantly changing variables to allow the ejection fraction response to exercise to be clinically reliable as a measure of ventricular contractile reserve.

End-Systolic Indexes

Volume or Dimension

Previous studies. The left ventricular fiber length at end-systole closely reflects the contractile performance of the myocardium because it is virtually independent of preload and varies with afterload. End-systolic volume (dimension) then becomes attractive as an index for assessing left ventricular contractility in patients with chronic aortic regurgitation (10,14,20,21,35–37). In 41 patients with chronic left ventricular volume overload, we (14) found that all patients with a normal preoperative left ventricular end-systolic volume index demonstrated normal left ventricular function postoperatively. In the subset of patients with aortic regurgitation, a marked increased in end-systolic volume index ($\geq$90 ml/m^2) predicted high perioperative mortality and residual left ventricle dysfunction. Henry et al. (20) used echocardiography to study symptomatic patients undergoing aortic valve replacement for isolated aortic regurgitation. Preoperative left ventricular end-systolic dimension >55 mm and fractional shortening <25% identified a group in which 69% of patients died either at operation or subsequently from congestive heart failure. In contrast, only 6% of patients with left ventricular end-systolic dimension <55 mm died at operation or had subsequent heart failure. Similarly, Kumpuris et al. (36) reported that end-systolic dimensions $\geq$50 mm were predictive of irreversible cardiac dilation. Bonow et al. (26) also found that preoperative rest end-systolic dimension was highly correlated with subsequent long-term survival.

The study by Carabello et al. (3) in this issue of the Journal further corroborates these findings by noting that there was a significant correlation between preoperative end-systolic dimension and postoperative left ventricular ejection fraction. This study emphasizes that recent advances in operative techniques and myocardial preservation may necessitate revision of the end-systolic volume (dimension) guidelines for surgical intervention in chronic aortic regurgitation. In contrast to these studies, Fioretti et al. (37) found that a preoperative end-systolic dimension $\geq$55 mm did not preclude successful aortic valve replacement, as judged by long-term survival, symptomatic relief and normalization of left ventricle dimension. Daniel et al. (38), in their retrospective study of 84 patients who had undergone aortic valve replacement for isolated aortic regurgitation, found a "weak association without useful positive predictive value" between preoperative end-systolic dimension $\geq$55 mm and postoperative death.

Comments. Left ventricular end-systolic volume (dimension) is independent of preload and varies directly with contractile state and afterload (39,40). In the clinical studies of aortic regurgitation that used these indexes, it was assumed that ventricular afterload was a relatively noncontributory factor to end-systolic volume (dimension). This neglects the fact that increased end-systolic fiber length may be due to depressed inotropic state of individual sarcomeres or an excessively high level of left ventricular afterload resulting from increased chamber size and pressure, or both. If a contractile abnormality is present, poor postoperative outcome would be expected. However, if a systolic load mismatch is present, relief of the left ventricular volume overload may allow a more favorable outcome than would be predicted only by analysis of end-systolic volume (dimension). This issue can be addressed only if, in addition to left ventricular preload, one eliminates afterload as a confounding variable.

Pressure-Volume Relation

Previous studies. In an attempt to incorporate afterload into the analysis of left ventricular performance, some investigators have turned to the end-systolic pressure-volume relation. The slope of this relation, which is usually determined using a pharmacologic challenge, is independent of preload, incorporates afterload and is a sensitive measure of contractility. Most clinical investigators have substituted peak systolic pressure for end-systolic pressure to simplify determination of the end-systolic pressure-volume slope. Using this approach, Schuler et al. (41) concluded that there was a subset of patients with normal left ventricular ejection fraction at rest who demonstrated decreased peak systolic pressure–end-systolic volume slopes consistent with marked depression of myocardial contractility. These same patients had a decreased ejection fraction response to dynamic exercise. Shen et al. (29) also demonstrated abnormal pres-

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sure-volume slopes in patients with moderate to severe aortic regurgitation despite the absence of symptoms and the presence of normal ejection fraction at rest. Iskandrian et al. (34,42) further simplified the end-systolic pressure-volume slope concept into a peak systolic pressure/end-systolic volume ratio generated from a single point at rest. When this index was used, most patients with moderate or severe aortic regurgitation had abnormalities either at rest or during exercise. This occurred in many patients despite normal ejection fraction at rest and during exercise.

Comments. The concept of end-systolic pressure-volume slope as a load independent measure of left ventricular contractility is an exciting one, especially in patients with aortic regurgitation. However, the simplifications used to study such patients are highly suspect. The substitution of peak systolic for end-systolic pressure assumes that the relation between these two pressures is always constant. This is not the case when one considers the effects of pharmacologic interventions or dynamic exercise on such important hemodynamic variables as: 1) the timing and rate of left ventricular peak ejection; 2) the volume of aortic regurgitant flow; and 3) the velocity as well as the amplitude of reflected waves from the periphery. The further simplification of using the peak systolic pressure/end-systolic volume ratio as a contractility index is even less physiologically justified. This ratio, which is highly afterload dependent, can be considered a pressure-volume slope generated from a single point with its regression line always passing through the origin of the pressure and volume axes. This is rarely the case for true end-systolic pressure-volume regression lines. Finally, the end-systolic pressure-volume relation can be thought of as a force-length relation. In an abnormally shaped, hypertrophied ventricle (as seen in aortic regurgitation), the force variable is better measured as wall stress. This has the advantage of taking ventricular dimensions, shape, wall thickness and pressure into account when quantifying left ventricular forces acting on the myocardium. It also allows more appropriate comparisons between ventricles of different size and wall thickness.

Wall Stress-Volume and Wall Stress-Shortening Relations

Previous studies. Left ventricular afterload can be thought of as the force opposing fiber shortening after the onset of ejection. It has been shown (43,44) that it is the wall stress at end-systole rather than the wall stress during the course of ventricular ejection that most closely determines the extent and mean velocity of left ventricle fiber shortening for a given contractile state. As such, it is the end-systolic wall stress that determines end-systolic volume and dimension in patients with chronic aortic regurgitation. Wisenbaugh et al. (45,46) used simultaneous left ventricular cineangiography and micromanometry to determine end-systolic wall stress in 16 patients with aortic regurgitation. In this group, ejection fraction at rest was depressed (0.53 ± 0.13, $p < 0.05$ versus that in normal subjects) at a time when end-systolic wall stress was 32% higher than normal. In 12 of the 16 patients, the relation between end-systolic wall stress and ejection fraction fell below the 95% prediction limit of the linear inverse relation between ejection fraction and end-systolic wall stress for normal subjects. Thus, it appeared that afterload mismatch alone did not fully account for the magnitude of left ventricular dysfunction noted in their patients. Similar conclusions were reached by other investigators (47–49). The study of Greenberg et al. (50) extended these concepts to include dynamic exercise. In 20 patients with aortic regurgitation, they found normal left ventricular

Table 1. Physiologic Framework for Assessing Preoperative Predictors of Surgical Outcome in Chronic Aortic Regurgitation

	Preload	Afterload	HR	Contractility
Severity of AR				
Regurgitant volume	+	+	+	0
Regurgitant fraction	+	+	+	0
End-diastolic indexes				
Volume (dimension)	+	+	+	+/0
Pressure	+	+	+	+/0
Ejection phase indexes				
Rest data	+	+	+	+
Exercise response	+	+	+	+
End-systolic indexes				
Volume (dimension)	0	+	+/0	+
Pressure-volume slope	0	0	+/0	+
Wall stress/volume ratio	0	+	0	+
Wall stress-EF relation	+	0	+	+
Wall stress-Vcf_c relation	0	0	0	+

AR = aortic regurgitation; EF = ejection fraction; HR = heart rate; Vcf_c = rate-corrected velocity of fiber shortening; + = dependent; 0 = independent.

ejection fraction at rest in conjunction with high levels of end-systolic wall stress at rest. These patients exhibited a drop in ejection fraction with exercise at a time when hemodynamic findings were suggestive of exercise-induced afterload excess. Thus, depending on the patient group studied, abnormalities in left ventricular end-systolic wall stress can have varying degrees of effect on end-systolic volume (dimension) or overall left ventricular shortening characteristics.

Comments. Most of the studies of left ventricular afterload in patients with aortic regurgitation have related end-systolic wall stress to load-dependent ejection phase indexes (that is, ejection fraction [45–47,49,50] and percent fractional shortening [48]). Although this approach eliminates problems with afterload, it does not address the effect of preload augmentation on overall left ventricular performance. Carabello et al. (51) have previously suggested that the single point ratio between end-systolic wall stress and end-systolic volume is an easily obtained, load-independent index of left ventricular contractility that circumvents this problem. However, it is now known that this simple ratio changes directly with alterations in left ventricular afterload, and is therefore of limited clinical utility as a measure of contractile state. This problem could potentially be overcome if the end-systolic wall stress-volume relation were determined over a wide range of afterload conditions induced with a pharmacologic intervention. In this manner, afterload could be incorporated directly into the analysis of the data.

A promising contractility index that has not yet been studied in patients with aortic regurgitation is the relation between end-systolic wall stress and the rate-corrected velocity of left ventricular fiber shortening (52,53). This index, which can be determined using totally noninvasive techniques, is preload and heart rate independent and incorporates afterload. It has been successfully used to distinguish load alterations from contractile abnormalities in patients with chronic left ventricular pressure overload (valvular aortic stenosis and coarctation of the aorta) (54), chronic volume overload (renal failure with arteriovenous fistula for hemodialysis) (55) and dilated cardiomyopathy (56).

Conclusions

Table 1 presents a physiologic framework for assessing left ventricular performance in chronic aorta regurgitation. Each preoperative predictor is correlated with its dependency on preload, afterload, heart rate and contractility. It is evident that the end-systolic indexes come closest to the ideal index because they are least dependent on load and heart rate and remain sensitive to contractile state. These end-systolic indexes, when properly determined, should allow us to accomplish our goal of sending patients to surgery "late enough in the course of their disease to justify the surgical risk, yet early enough to avoid irreversible damage to the left ventricular contractile mechanism."

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