MANAGEMENT OF THE PATIENT WITH CHRONIC AORTIC REGURGITATION

MEDICAL GRAND ROUNDS

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February 4, 1982

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Introduction

The most difficult decision in the management of the patient with chronic aortic regurgitation is whether an artificial valve should be placed, and if so, when. The guidelines for this decision have never been clear, (1,2) however the decision has become even more difficult in the last few years because of the accumulation of many studies. While these studies have added to our knowledge of the problem, they have also led to much advice, some of which seems to be contradictory. In this discussion I will review the pathophysiology of chronic aortic regurgitation, the methods that are available to measure the pathophysiologic changes, and the results to be expected from surgery. I will try to reconcile the differing viewpoints which are based on different approaches to the problem, and will suggest an approach based on an analysis of the evidence. This review is about chronic aortic regurgitation, and many of the results and suggestions do not pertain to acute regurgitation.

The current concept of the problem is most easily presented graphically as a plot of survival expectancy versus time, as illustrated in Figure 1.

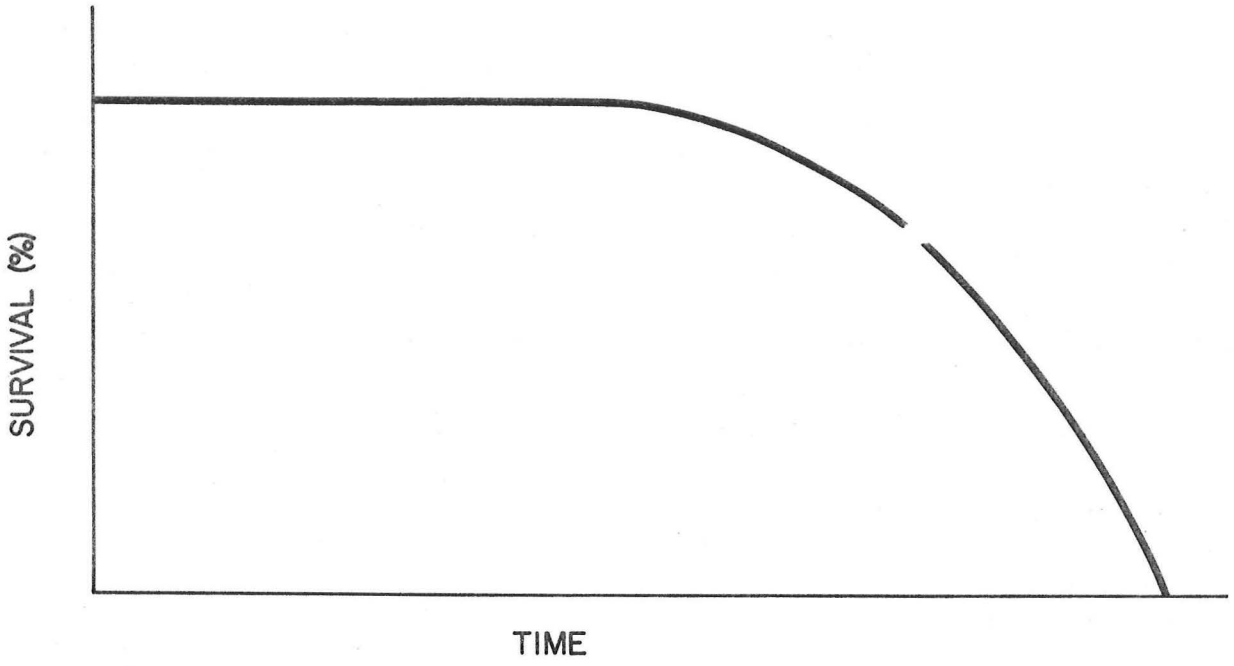

Figure 1.

This type of survival curve was initially developed from studies of the natural history of aortic regurgitation which were done before valve surgery and techniques to measure ventricular function were developed. These studies showed that patients with clinically apparent severe regurgitation had a latency period of years before symptoms developed, and then had several more years before they deteriorated further. Intuitively it would seem that the pathophysiologic equivalent of this curve would be a progressive worsening of the severity of the regurgitation until the left ventricle was unable to compensate further, after which hemodynamic deterioration would occur. Under this concept the ventricle that was present would be functioning normally, but it would just not be large enough to handle the increased volume of blood. However as good techniques to measure ventricular function became available, several facts became apparent. The first was that in some patients ventricular function was abnormal and furthermore that the presence and severity of this ventricular dysfunction was not highly dependent on the amount of regurgitation. By the time that the techniques to measure ventricular function were available, surgery was already an accepted form of therapy. Therefore the natural history of patients with aortic regurgitation relative to their ventricular function was never well studied, however it was soon realized that the course of patients after surgery was highly dependent on their ventricular function before surgery. Consequently a parallel, but worse, prognosis relative to ventricular function was assumed for patients should they not be operated upon. This train of thought led to the present popular concept that the position of a patient on the survival versus time curve is chiefly dependent on his ventricular function. This concept, combined with the earlier clinical studies which showed that patients with aortic regurgitation may tolerate the lesion well for years, led to the further concept that the course of patients with aortic regurgitation is to initially have good ventricular function and do well. Then, after a variable period of time, the volume overload will cause ventricular dysfunction, which may be irreversible by surgery. Consequently both medical and surgical prognosis worsens at this time. It should be emphasized that this assumed course for individual patients over long periods of time, and especially the relationship of this course to ventricular function, is chiefly derived from studies of many patients over short periods of time. Consequently, this proposed course is at present conjectural and may not be the course of all patients.

If it is accepted that patients with aortic regurgitation progress from good to poor ventricular function, and that their medical and surgical prognosis depends on their ventricular function, then a difficult dilemma becomes apparent. This dilemma is when to operate as shown in Figure 2.

If the patient is operated upon when ventricular function is good, he is hopefully spared the danger of irreversibly damaging his ventricle. However he is then confronted with the risks of operation and an artificial valve early. On the other hand if surgery is delayed until late, the risk of operation and an artificial valve is delayed, but the prognosis associated with the poorly functioning ventricle is worse. Therefore the question of when to operate is a balancing of the different risks. This balance may be different for different patients(3). Refinement of the decision making process is presently thought to depend on two factors. The first is a better understanding of the course in unoperated patients. This will be difficult to

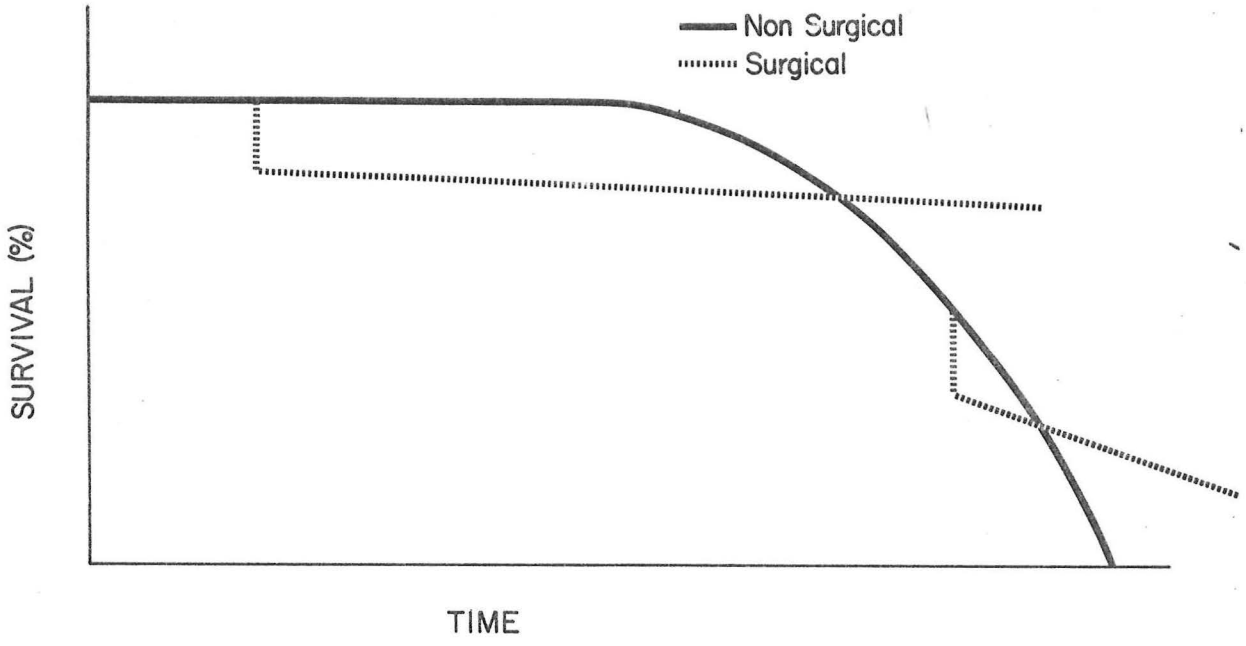

Figure 2.

achieve because of the present reluctance to withhold surgery. The second is continued development of techniques to measure ventricular function and a better understanding of the ability of these techniques to predict where a given patient is on the survival curve.

Important Hemodynamic Variables

The important hemodynamic variables which can be measured in the patient with aortic regurgitation are listed in Table 1. Volume measurements are listed on the left and the analogous single dimensional measurements are listed on the right. Stroke volume measurements are sometimes alternately presented as flow/min. This measurement is calculated by multiplying the stroke volume by heart rate. The technique used to obtain the measurement is marked by an (x).

Table 1.

Volume	Cath	RN	Single Dimension	Cath	Echo
End Diastolic Volume	x	x	End Diastolic Diameter	x	x
End Systolic Volume	x	x	End Systolic Diameter	x	x
Ventricular Stroke Volume	x	x			
Peripheral Stroke Volume	x				
Regurgitant Stroke Volume	x	?			
Ejection Fraction	x	x	Fractional Shortening	x	x
Mass	x		Wall Thickness	x	x

The diameter of the ventricle at end diastole and end systole is analogous to the volumes at these times. Ventricular stroke volume is the difference between end diastolic and end systolic volume. Although regression equations have been calculated to determine stroke volume from ventricular diameters, this is generally not considered accurate enough for quantitation in the presence of aortic regurgitation. The ventricular stroke volume is further divided into that portion which goes forward to the periphery of the body, which is called the peripheral stroke volume, and that portion which is regurgitated backward to the ventricle, which is called the regurgitant stroke volume. These stroke volumes are illustrated in Figure 3. For comparative purposes ventricular volumes are frequently normalized to their volume index by dividing the absolute volume by the patient's body surface area in m^2. The average body surface area is 1.7 m^2. The ventricular stroke volume, peripheral stroke volume, and regurgitant stroke volume are combined in three different ways to express the amount of regurgitation. A statement of the absolute amounts of each of the stroke volumes is the method of expression which is easiest to understand and least subject to misinterpretation. A second method of expression is the stroke volume ratio which is defined as the regurgitant stroke volume/peripheral stroke volume. This method is used in radionuclide work for reasons which will be explained later. The third method of expression is the regurgitant fraction which is defined as the regurgitant stroke volume/ventricular stroke volume. It is important to realize that the regurgitant fraction is not linearly related to the absolute values or the stroke volume ratio. The regurgitant fraction is equal to (stroke volume ratio -1)/stroke volume ratio. The graphical representation of this relationship is shown in Figure 4. The importance of understanding the commonly used regurgitant fraction is that when one is accustomed to linear relationships, the regurgitant fraction seems to over-estimate small amounts of regurgitation and underestimate large amounts.

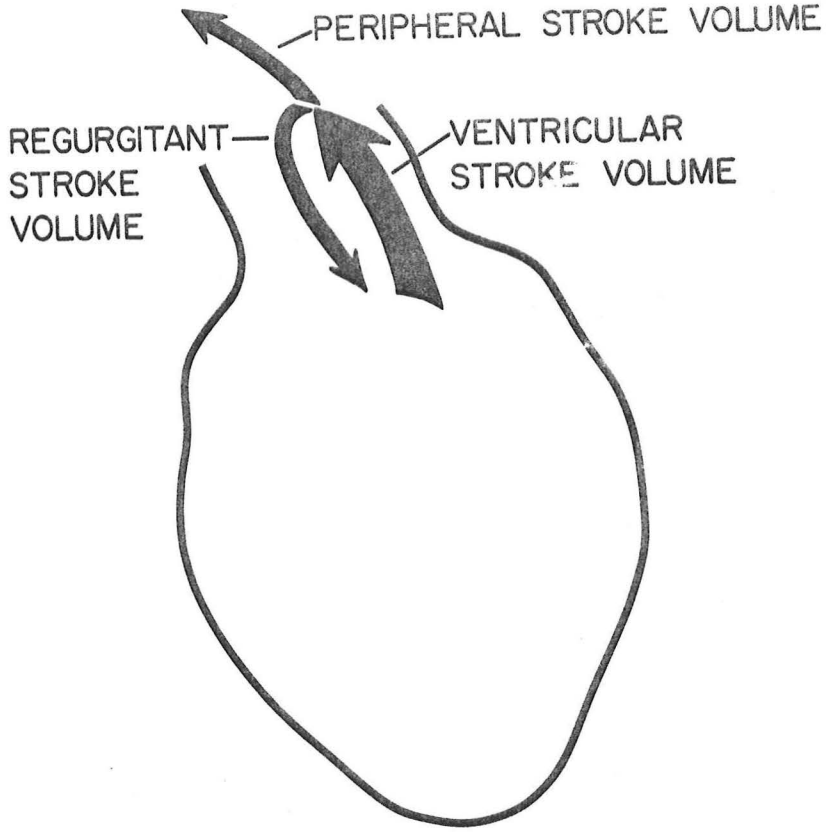

Figure 3

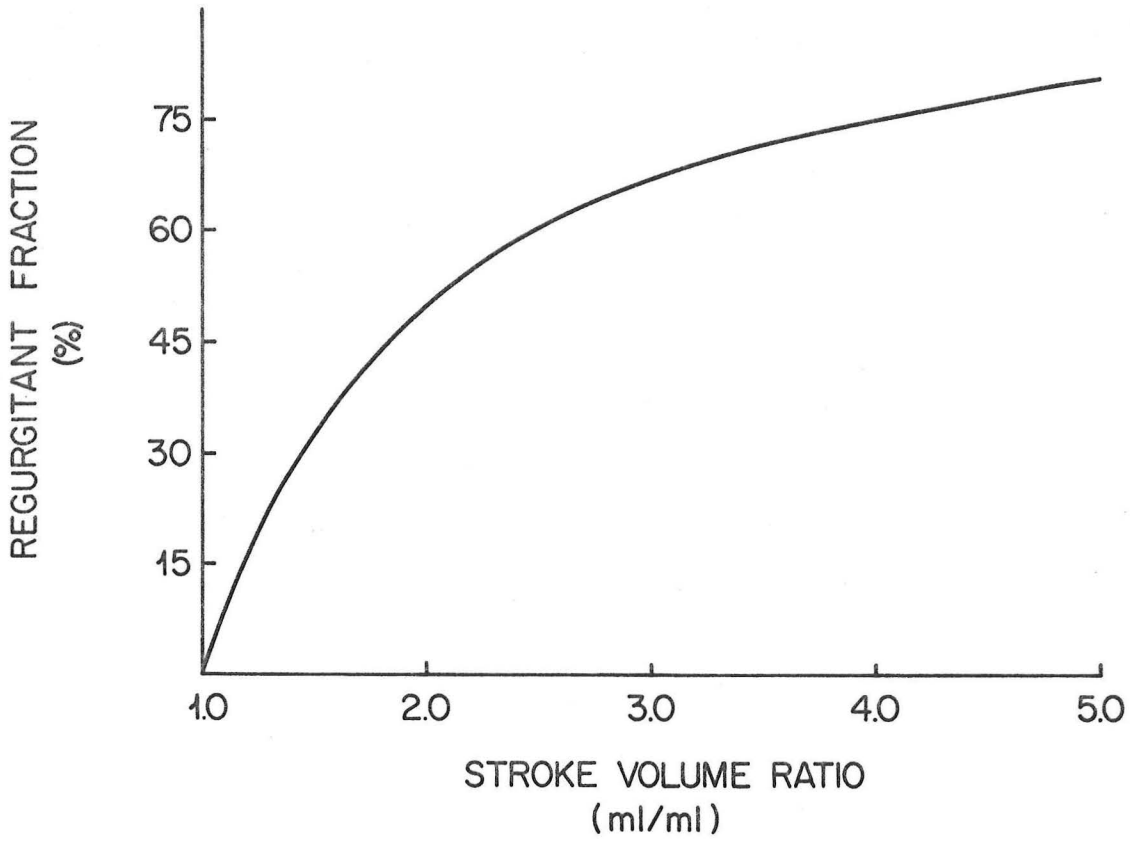

Figure 4

The ejection fraction is defined as the stroke volume/end diastolic volume, as illustrated in Figure 5. Stated another way, it is the fraction

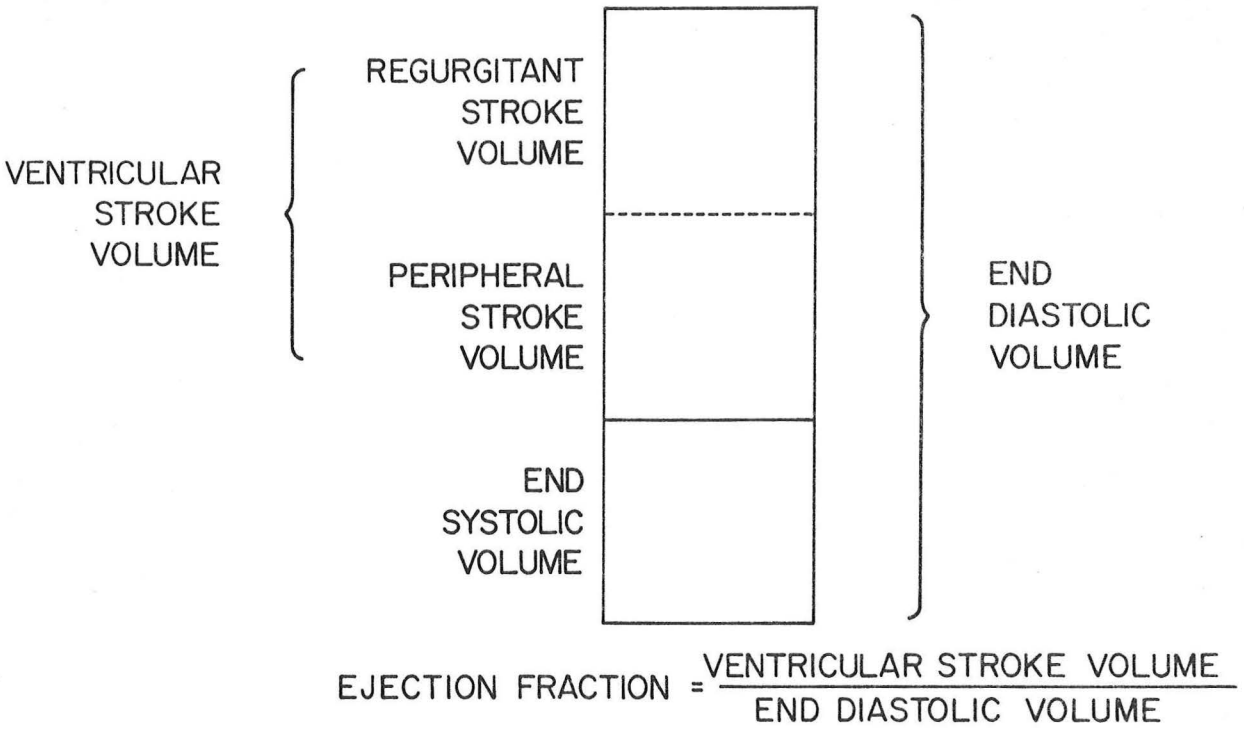

Figure 5.

of blood ejected from the ventricle with each beat. The ejection fraction can be envisioned as the cubic equivalent of the fractional shortening of the ventricular diameter. The ejection fraction is mathematically also a function of the relationship between ventricular stroke volume and end systolic volume. Wall thickness is used in conjunction with the ventricular radius (calculated by halving the diameter) to derive the radius/wall thickness (R/T) ratio. This ratio is used to approximate wall stress by the formula which states that wall stress $\cong$ ventricular pressure x R/T. Wall stress is important since it is the practical measurement which most closely approximates the tension actually faced by the fiber in the ventricular wall. The R/T ratio and its analogous volume/mass ratio also are measures of the appropriateness of ventricular hypertrophy relative to the dilatation of the chamber.

Approximate normal values are shown in Table 2 (4-11). Values may deviate due to technique and laboratory.

Table 2

Measurement	Normal	Range
End diastolic volume index (m/m^2)	70-78	<100-110
End systolic volume index (ml/m^2)	20-24	<36-45
Ventricular stroke volume index (ml/m^2)	45-51	19-31 to 71-76
Ejection fraction (vol/vol)	.64-.72	.50-.56 to .78-.88
Mass index (gm/m^2)	83-100	60 to 124
End diastolic diameter (mm)	46-48	40 to 52
End systolic diameter (mm)	28	22 to 34
Fractional shortening (%)	34-38	25-30 to 43-46
Radius/wall thickness (mm/mm)	3.0	1.6 to 4.4

Methods to Measure Hemodynamic Variables

Catheterization. Cardiac catheterization is necessary to measure peripheral stroke volume accurately, however only right heart catheterization is needed. The Fick or indicator dilution (usually either thermal or indocyanine green) techniques are used for this measurement. These techniques are usually accurate to about 10% (4). Left heart catheterization is necessary for supravalvular aortography to assess the presence and severity of aortic regurgitation. Supravalvular aortography is very sensitive and specific in determining the presence or absence of regurgitation. However its value in making this qualitative diagnosis is not great except in unusual circumstances, because the bedside evaluation is usually adequate for making the diagnosis. The aortographic assessment of the severity of regurgitation is only broadly correlated with the more quantitative techniques of quantitative ventriculography and catheter tip velocitometry. (12,13). These correlations show that the aortographic assessment in individual patients is frequently in error, and that aortography generally tends to overestimate the severity of regurgitation.

The determination of end diastolic and end systolic volumes are the basic measurements from which the ventricular stroke volume and regurgitant stroke volume are derived. Ventriculography done at the time of catheterization is generally considered the standard against which other techniques are evaluated. However this technique itself has never been adequately evaluated *in vivo* because of the lack of an independent standard against which to judge it. Using the technique, ventricular volume is calculated by angiographically determining the three perpendicular radii of the ventricle and then using them in the formula for the volume of an ellipsoid. There are two major

problem areas which contribute to inaccuracy of the technique. The first is that the shape of the ventricle may differ from the shape of an ellipsoid. This factor is frequently commented upon in critical reviews, but is probably not as severe as indicated. For instance using the ellipsoid formula to calculate the volume of a cylinder results in an error of only 3% and using it to calculate the area of a cone results in an error of about 20%. The more important problem leading to error in volume calculations is the error in correcting for x-ray magnification. To correct for this, the position of the ventricle within the chest must be estimated. At standard cath lab distances, the error in volume resulting from each 1 cm error in estimation of heart position is about 6%. Because ejection fraction is a ratio of volumes which would be affected equally by an error in x-ray magnification, the ejection fraction is theoretically not subject to this error. Biplane cineventriculography decreases the inaccuracy caused by each of these problems. In studies comparing the calculated volume to true volume in *in vitro* models, the correlation coefficient is .99 and the standard error of estimate is 8 ml. (7,14). The correlation is obviously not as good for the *in vivo* situation, but there are no studies of this correlation. However the ventricular stroke volume determined by the ventriculographic method has been compared to the peripheral stroke volume determined by the Fick method in patients without regurgitation in whom the two volumes should be identical. This study showed a correlation coefficient of .97 and a standard error of estimate (SEE) of 6 ml. (13). Reproducibility of angiographic values have not been well evaluated. However one sobering study showed that when ventriculographic measurements were repeated in a group of patients several days apart, the standard error of estimate of the ejection fraction was .10 and the SEE of the ventricular volume was 9-19 ml. (15). Thus this study, which included the effect of physiological and technical variation would indicate that the ejection fraction would have to change over about .20 before the change could be accepted as true change with 95% confidence. My opinion is that this SEE is inappropriately large, but I have no data to counter it. Wall thickness can be measured at the time of ventriculography and used for calculations of wall stress, radius/thickness ratio, and mass/volume ratio.

Radionuclide Scintigraphy. Radionuclide scintigraphic measurements of the left ventricle are made by either analyzing the first pass of a radioactive bolus as it passes through the cardiac chambers or by analyzing the radioactivity in the ventricle after the radionuclide has equilibrated in the blood pool. Both methods are equally accurate for the determination of ejection fraction, (16) but only the blood pool technique is suitable for the determination of ventricular volume. The principle of the determination of ejection fraction is simply that the volume of blood in the chamber throughout the cardiac cycle is proportional to the number of radioactive counts in the ventricle. (17-19). Since only relative changes in volume are measured, the attenuation of counts through the chest wall is not an important factor as it is with determining absolute volume. However two sources of error must still be considered. The first is correction for background counts which amount to about 35% of the radiation coming from the area of the ventricle. (20). Depending on the method of correction for background, the mean ejection fraction could be varied from 45% to 90% in one study. (21). The second source of error is the drawing of the region of interest from which the camera is to extract counts. In one study the technique of drawing this region of interest could

vary the mean ejection fraction from 45% to 67%. (21). Comparison of the radionuclide technique to the angiographic technique for determining ejection fraction yields correlation coefficients of .84 to .94. (16,18,21,22). Unfortunately standard error of estimates were not given. Reproducibility, determined by repeating studies on sequential days, shows that the ejection fraction varies by an average of 4.4% from day to day. (20). Although these studies do not allow a precise estimate of accuracy and reproducibility, it is generally considered that with strict attention to detail, the radionuclide technique of measuring the ejection fraction is both accurate and reproducible.

The determination of absolute ventricular volumes is based on the principle that if the concentration of radioactive counts/ml of blood is known, then the ventricular volume can be determined by measuring the counts within the ventricle. (23,24). The technique has the same sources of error that are present with determination of the ejection fraction plus the problem of attenuation of counts as they pass through the chest wall. The attenuation coefficient averages about .20 (24-26) which means that the calculated and actual volume vary by a factor of 5x. In two centers, this attenuation coefficient is assumed to be constant in all patients (23,24), while in another center the attenuation coefficient is uniquely calculated for each patient based on chest geometry and was found to vary from .14-.38 (26). This individual calculation of attenuation coefficient did not improve the correlation coefficients, however. In spite of the problem with attenuation, the radionuclide method measures volumes accurately. When compared with angiography, the correlation coefficient ranged from .94-.98, while the standard error of estimates ranged from 15-36. (24,26).

The amount of regurgitation can be quantitated noninvasively by a clever use of radionuclide gated cardiac blood pool imaging. (27-31). This technique is based on the premise that after radionuclides are evenly distributed throughout the blood the volume of a chamber is proportional to the counts coming from the chamber. Therefore the change in counts from diastole to systole is proportional to the stroke volume. If right ventricular regurgitation or shunting is not present, then the change in right ventricular counts is proportional to the peripheral stroke volume. Since the change in left ventricular counts is proportional to left ventricular stroke volume, the ratio of change in left ventricular counts/change in right ventricular counts is the stroke volume ratio, previously defined as ventricular stroke volume/peripheral stroke volume. This radionuclide technique is not adequate for diagnosing the presence of small amounts of regurgitation, as its sensitivity is 91%, but its specificity is only 73%. (27,28). However it is generally adequate to measure the amount of regurgitation. Correlation coefficients range from .85-.95 (standard error of estimates not given) when compared to angiography. The technique has decreased accuracy in the presence of poor ventricular function, mitral valve prolapse, and arrhythmias. (28).

Echocardiography. Conventional m-mode echocardiography measures ventricular dimensions by the reflection of echoes from an "ice-pick" beam of sound. Thus an echocardiogram measures one dimension of the 3-dimensional ventricle. This one dimensional view and the difficulty of defining endocardial surfaces are the chief limitations of echo. Calibration is more accurate than other techniques because dimensional measurement depends on the speed of sound in tissue, which

is constant. The basic echocardiographic measurements are the end diastolic diameter, end systolic diameter, and the percentage change in diameter, which is derived from the first two measurements. These measurements are analogous to the end diastolic volume, end systolic volume, and ejection fraction. Generally the end diastolic diameter is more accurately measured than the end systolic diameter. Echo measurements are considerably less accurate in the volume overloaded ventricle than the normal ventricle. (32-34). Consequently only measurements in the volume overloaded ventricle will be considered subsequently. The end diastolic diameter correlates only moderately well with either angiographic end diastolic diameter or volume with r values of .60-.80. (33,34). However end systolic diameter correlates poorly with r values of .58-.64. (33,34). Consequently the echo percent change in diameter correlates poorly with either the angiographically determined percent change in diameter or the ejection fraction with r values of .29-.53. Reproducibility of echo measurements in patients with volume overload are somewhat better than would be expected from the absolute correlations. Changes in measurements should be considered real with 95% confidence if the end diastolic diameter changes over .3-.4 cm, end systolic diameter changes over .6cm, and the percent change in diameter changes over 6-9 percentage units. (35,36). The serial echocardiographic assessment of patients after either aortic or mitral valve surgery is of questionable validity since 91% of aortic valve replacement patients develop septal asynergy in the postoperative period. (37). Two dimensional echocardiography may eventually improve the ability of echo to measure ventricular function. Studies in patients without volume overload appear promising. (38-41). However studies of patients with volume overload remain to be done.

M-mode echocardiography can be used to determine the ventricular radius/wall thickness (R/T)ratio. The methodologic limitations must be appreciated however. A change of 2 mm in ventricular diameter is generally considered necessary to accept the change as real. (9). If a patient has a radius of 3.5 cm and a wall thickness of 1.0 cm, his R/T ratio is 3.5. A change in the echo interpretation of where the endocardial surface is of 1 mm in either direction would result in an R/T ratio of either 3.1 or 4.0.

Intravenous Digital Angiography. The new technique of digital angiography is probably going to be used widely in the near future. The principle of this technique is that a fluoroscopic image of the heart is stored in a computer before any contrast media is injected into the patient. Then contrast media is injected and while the contrast is in the left ventricle, a fluoroscopic study of the heart is recorded. The computer then substracts the initial image from the study done with contrast media. This results in a dramatic enhancement of the image. The enhancement is usually sufficient to provide usable ventriculographic information with only an intravenous injection of contrast. The ventriculographic information will be analyzed with techniques now used for ventriculography after intraventricular injection.

Summary of Techniques. Hemodynamic measurements in the patient with aortic regurgitation can now be made with catheterization, radionuclide, and echocardiographic techniques; and possibly soon with intravenous angiographic techniques. These techniques can be combined to give serial and then definitive evaluation of the hemodynamic condition. Catheterization with angiography is

the most trusted method of evaluation. This is partly because pressure can be measured and other lesions can be studied. However it is also because there is a lot of experience behind catheterization and confidence is engendered when the pathophysiology can be "seen" with angiography. However radionuclide scintigraphic measurements are proving quite reliable in experienced hands. Echocardiography has limitations, especially in the volume overload state, and is definitely not the method of choice for evaluating patients with aortic regurgitation. However it is important because many studies have been done with it, apparently because of its ease of application.

It must be emphasized however how much these methods depend on the technical quality of the lab and the skill of the operator. Unless these factors are known to be good, no measurements can be trusted.

Interrelationship of Hemodynamic Variables

As shown in Figure 6, the end diastolic volume is composed of the end systolic volume and ventricular stroke volume. The ventricular stroke volume is composed of the peripheral stroke volume and the regurgitant stroke volume. The ejection fraction is the ratio of ventricular stroke volume/end diastolic volume. The ejection fraction is also a function of the relationship between the ventricular stroke volume and the end systolic volume.

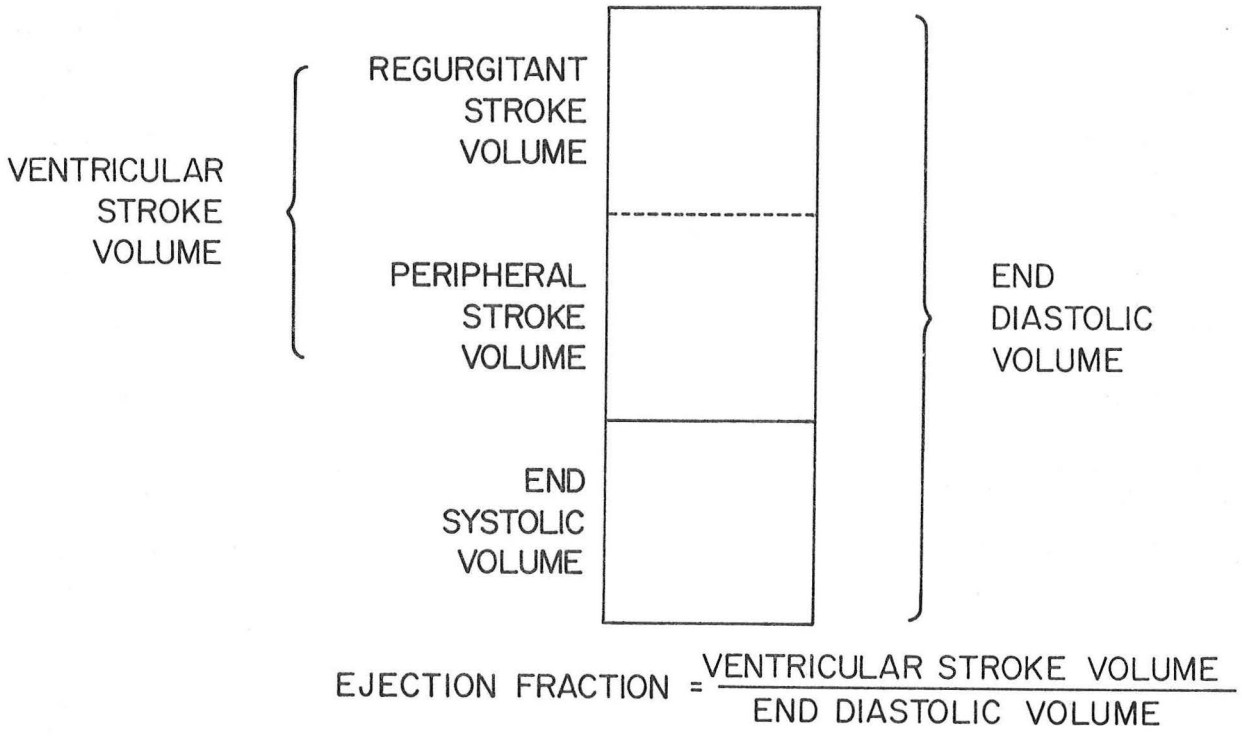

Figure 6

To most easily understand the interrelationship of these variables in patients at different stages of aortic regurgitation, it is helpful to construct a graph which shows all variables at one time, as shown in Figure 7. This basic graph will be repeated several times throughout the discussion with different sets of data. On this graph the horizontal axis represents the end systolic

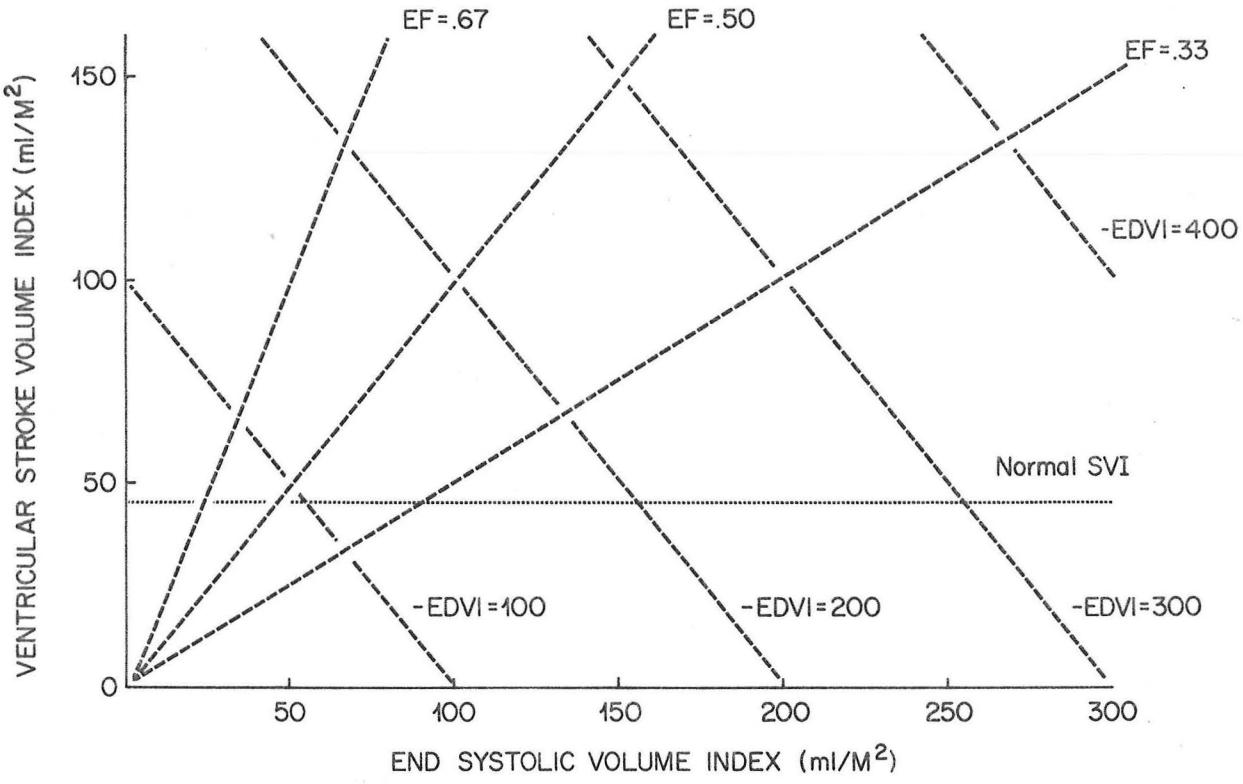

Figure 7

volume index (actual end systolic volume/body surface area measured in m^2). The vertical axis represents the ventricular stroke volume index. The average normal peripheral stroke volume index is 45 ml/m^2 and has a range of about 30-70 ml/m^2. This value is indicated by the horizontal dotted line. Since in the presence of regurgitation, the ventricular stroke volume is composed of the peripheral stroke volume and the regurgitant stroke volume, this horizontal dotted line at 45 ml/m^2 approximately divides the ventricular stroke volume index (on the vertical axis) into the peripheral stroke volume index below the line and the regurgitant stroke volume index above the line. The end diastolic volume index is the sum of the end systolic volume index on the horizontal axis and the ventricular stroke volume index on the vertical axis. The end diastolic volume index is therefore represented by the diagonal dotted lines running from the upper left to the lower right. The upper limit

of the normal end diastolic volume index is 100 ml/m^2, represented by the lowest end diastolic volume index line. Ejection fraction is defined by the ratio of ventricular stroke volume index/end diastolic volume index, but is also determined by the relationship of the ventricular stroke volume index and the end systolic volume index. Therefore the ejection fraction is represented by the diagonal dotted lines running from the lower left to the upper right. The uppermost line represents an ejection fraction of .67 which is the average normal value, and the middle line represents an ejection fraction of .50 which is the lower limit of normal. The lowest line represents an ejection fraction of .33 which is a moderately low value.

Physiology of Early Regurgitation

An approximate simplifying concept which helps explain many of the immediate hemodynamic changes which occur after the onset of aortic regurgitation is that the end systolic volume is determined by the systolic pressure and ventricular contractility while the end diastolic volume is determined by the volume load presented to the ventricle during diastole. (42-45). Therefore immediately after the onset of regurgitation the volume load on the ventricle increases which makes the end diastolic volume increase. Since contractility and systolic pressure do not change, the end systolic volume stays constant. (46). Because end diastolic volume increases while end systolic volume stays constant, the ventricular stroke volume increases. This change in volumes is graphically shown below by a move from point A to point B on the graph in Figure 8. The graph is the same graph as shown previously.

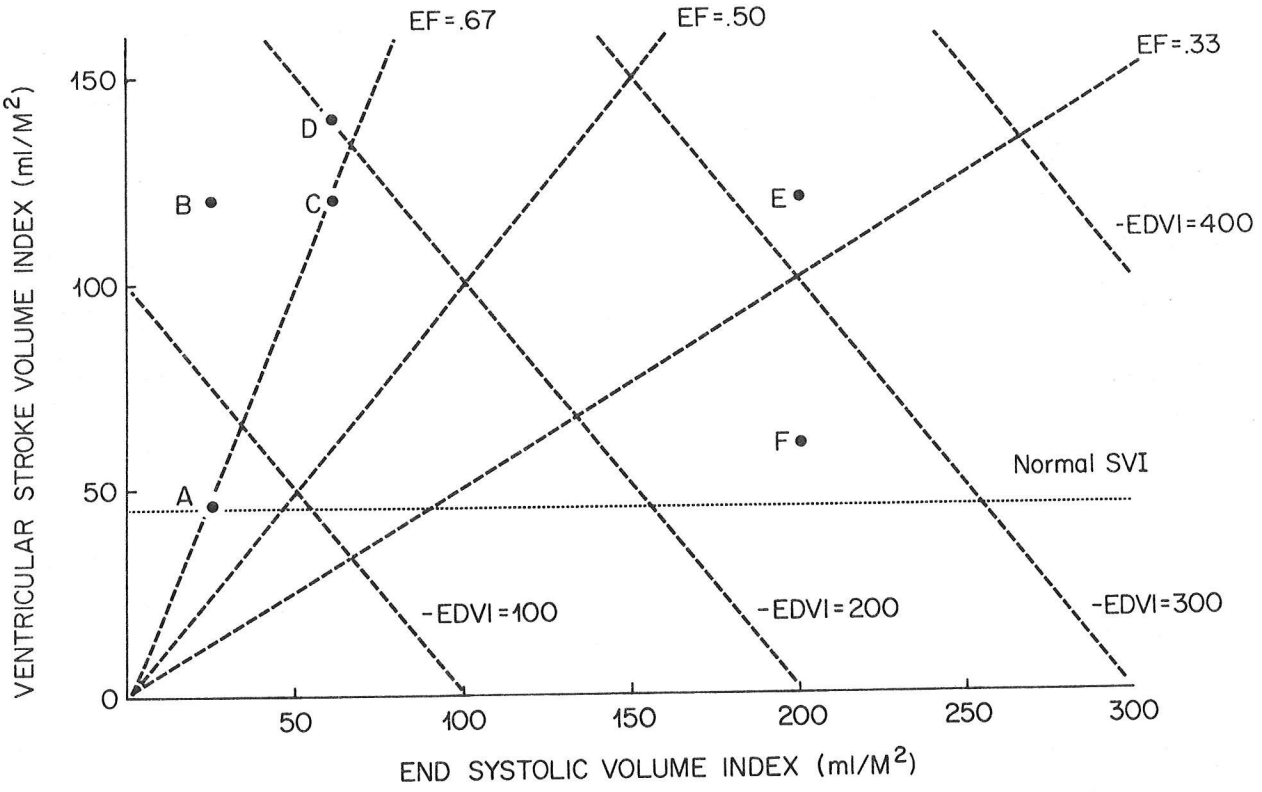

Figure 8

Since the ventricular stroke volume index increases from point A to point B, while the end systolic volume index stays constant, the ejection fraction is increased. This is an important point regarding how to measure ventricular contractility. In this example the ejection fraction increased without a change in contractility. The ability of the ventricle to compensate for regurgitation in this acute manner is limited. The pressure-volume relationship of the normal ventricle is such that at an end diastolic pressure of 30 mmHg, the end diastolic volume index has increased to only about $100ml/m^2$ from its normal value of $70ml/m^2$. (47). Thus the ventricular stroke volume index has increased from about 45 ml/m^2 to about $75ml/m^2$, which is considerably less than the ventricular stroke volume index frequently seen in chronic aortic regurgitation. If the volume load acutely presented to the ventricle is greater than the values mentioned, the diastolic pressures rise excessively and pulmonary edema occurs. Thus acute aortic regurgitation causes symptoms at a relatively low volume of regurgitation.

Physiology of Chronic Regurgitation

Over a period of time, the ventricle responds to a volume overload with its chronic adaptive mechanism. The effect of this mechanism is shown in Figure 9 which schematically depicts a normal ventricle on the left, an acutely overloaded ventricle in the middle, and a chronically overloaded ventricle on the right.

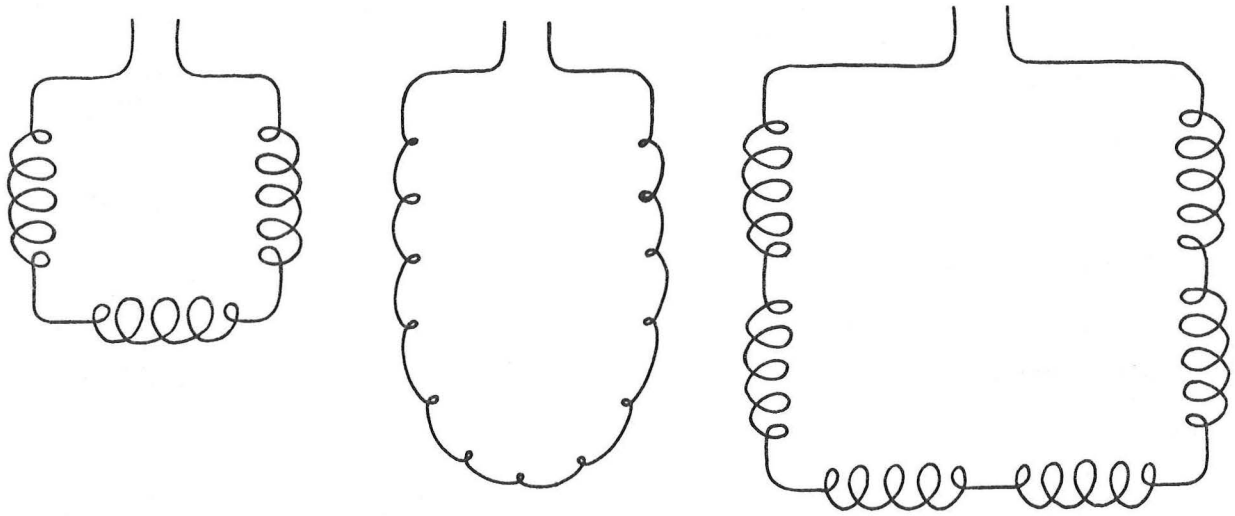

Figure 9

The effective result of chronic adaptation to volume overload is that more sarcomeres, each of normal length, surround the ventricle. Thus in the middle panel of Figure 9, the ventricle is responding to the acute volume overload by stretching its sarcomeres while in the right panel the ventricle is even larger while none of its sarcomeres are stretched. Whether sarcomeres actually serially replicate or not is uncertain, but there is considerable evidence to support the effective result.

In dogs with a wide range of baseline ventricular volumes, in whom the diastolic pressure is then varied over a wide range, the length of the sarcomeres correlate with the diastolic pressure. (48-51). In patients with chronic regurgitation, diastolic pressures are frequently only mildly elevated, implying minimal stretching of sarcomeres, while volumes average about 3x normal. (52-58). In dogs instrumented so that ventricular pressure and volume could be measured chronically after volume overload was created, the diastolic volume and circumference of the ventricle at a uniform diastolic pressure increased over a period of weeks. (59-61). Importantly, the relative systolic shortening of the ventricular circumference and the sarcomere length of these animals remained constant, even while the diastolic volume and circumference increased. (59,61-63). Although the methodology was not as well controlled as in the animal studies, human biopsy and autopsy studies have shown no significant difference between sarcomere lengths in normal and volume overloaded ventricles. (64-67). The actual mechanism by which this apparent serial replication occurs is not clear. It may occur by simple end to end replication of sarcomeres, by some form of realignment of muscle bundles, (64,65) or by "slippage" of sarcomeres within the fiber. (61,63,68).

Wall stress is the best practical estimate of the force which the in situ myocardial fiber must generate to develop ventricular pressure. Wall stress is approximated by the formula:

$$\text{Wall Stress} = \text{Pressure} \times (\text{Ventricular Radius}/\text{Wall Thickness})$$

Consequently as the ventricle enlarges, its wall stress would increase unless wall thickness increased. Clinical studies have shown that the wall thickness does increase in the volume overloaded ventricle so that the ventricular radius/wall thickness ratio stays constant. (69,70). This increase in wall thickness is achieved by an apparent parallel replication of sarcomeres.

Therefore the mass of the volume overloaded ventricle increases due to an apparent serial and parallel replication of sarcomeres. The normal left ventricular mass is $100 gm/m^2$, and in studies of patients with chronic aortic regurgitation, the mass averages $141-240 gm/m^2$. (53-54,56-58). While it is clear that the number of sarcomeres increases, it is less clear whether the number of myocardial cells increases. The myocardial cells clearly increase in size, but whether this increase in cell size accounts for all of the hypertrophy is uncertain. (64,65,71-73).

If the ventricle compensates for chronic volume overload by effectively increasing the number of sarcomeres in series, then when each sarcomere contracts to the same end systolic length as it did prior to the onset of volume overload, the ventricular and systolic volume will be larger. As this occurs, the

ejection fraction will return to the value that it was before the onset of volume overload. This is represented by a move from point B to point C on the graph in Figure 8. The meaning of an increase in the end systolic volume is frequently a matter of controversy. Some authors advocate the end systolic volume index as an excellent measure of ventricular contractility because of its independence from preload, (74-76) however this viewpoint neglects the dependence of the end systolic volume index on hypertrophy. The ejection fraction, on the other hand, is dependent on preload, but tends to be independent of hypertrophy. An absolute confidence in either the end systolic volume index or the ejection fraction as a measure of contractility is not appropriate since most patients probably compensate for their volume overload both by the acute preload and chronic hypertrophy mechanisms. The only way to be certain of which contractility measure to use would be to know the in situ sarcomere length, which of course is impossible.

The controversy about whether to use the end systolic volume index or the ejection fraction as a basis for decision making leaves the clinician in a quandry however, as shown on the graph in Figure 10. On this graph, the hemodynamic values of 57 patients with chronic aortic regurgitation are plotted. These patients represent a composite of five studies of the hemodynamics of chronic aortic regurgitation. (54-58). On this graph only the

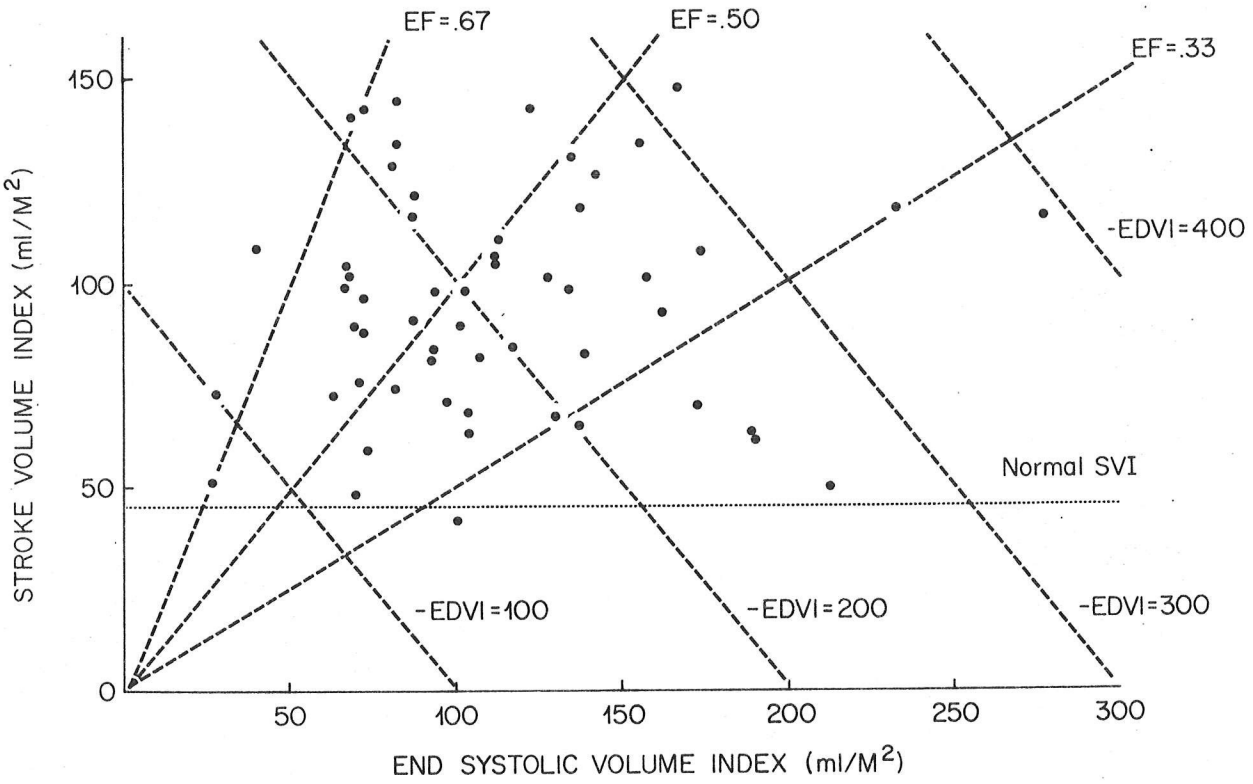

Figure 10

preoperative values are plotted, however all of the patients had successful valve surgery and were recatheterized after the operation. As such, they are a biased population, however they are probably representative enough to illustrate the relevant pathophysiology. Their postoperative data will be presented later. On this graph a number of patients would be classified in a contradictory category if the criteria of end systolic volume index > 60ml/M^2 (77) or ejection fraction <.50 were used to judge the presence of ventricular dysfunction.

Natural History

Patients with clinically severe aortic regurgitation have a surprisingly good prognosis. Studies done before the development of good valvular surgery have shown that after the development of clinically severe regurgitation the average 10 year survival is 50-60%, and the 20 year survival is 45%. (78,79). After the onset of symptoms the average survival is 5-6 years. (80,81). Symptoms usually consist of fatigue and dyspnea, and peripheral edema usually occurs late. (80). Death is usually associated with chest x-ray or electrocardiographic evidence of severe ventricular enlargement. (82,83). The hemodynamic basis for the deterioration in the clinical course of the patients in these early natural history studies is uncertain since the patients were not well studied hemodynamically.

Development of Heart Failure

The hemodynamic course that patients with significant aortic regurgitation follow is not known with certainty, but if the disease progresses two basic courses are probable. One course is that the severity of regurgitation worsens and the other is that ventricular function worsens. The first course is illustrated by a move from point C to point D on the graph in Figure 8. In this case the ventricular stroke volume increases because of an increase in the regurgitant stroke volume, but the end systolic volume stays constant because ventricular contractility is unchanged. The second course is illustrated by a move from point C to point E. In this case the ventricular stroke volume stays constant, but the end systolic volume increases because of a decrease in ventricular contractility. In both cases the end diastolic volume increases to compensate for either the increasing ventricular stroke volume or increasing end systolic volume. When the volume load on the ventricle during diastole is higher than it can accommodate without increasing diastolic pressure beyond tolerable levels, clinical decompensation ensues. Since in both cases congestive failure symptoms occur and the chest x-ray and electrocardiogram indicate a large ventricle, early clinical studies and anecdotes are of little help in determining which hemodynamic course was most common. Recently, echocardiographic studies indicate that decreasing ventricular function is probably the major cause of symptoms (36,84), however these are not large or definitive studies. Probably both mechanisms and a combination of both are operative in different patients.

The cause of the deterioration of ventricular function in chronic regurgitation is not known, but several possibilities have been suggested. None of these possibilities have been substantiated well enough to gain general

acceptance. There is some evidence that calcium transport by the sarcoplasmic reticulum may not be occurring properly, but little other biochemical abnormality has been found. (85,86). Disruption of the ultrastructure, including misalignment of sarcomeres and hyperconvolution of the intercalated discs, has been noted by some investigators, (68,71) but not commonly mentioned in other studies. An alteration of the macroscopic alignment of the ventricular muscle bundles has been suggested, but in limited studies this alignment appears to remain normal. (73,87). Minor increases in myocardial fibrosis are present, (72,73) but the degree of fibrosis does not correlate with the ventricular function. (71).

A controversial but popular theory for the cause of dysfunction is that the hypertrophied myocardium outgrows its blood supply. In 1960 Linzbach stated that the number of capillaries and fibers increase with hypertrophy, and therefore the diffusion distance from capillary to sarcomere does not increase. (65). This position has been widely quoted. However other evidence indicates that the number of capillaries does not increase and that hypertrophy is chiefly accomplished by an increase in fiber size. (73,88,89). Thus the diffusion distance between capillary and sarcomere would increase to a distance that oxygen transport would be hindered. (89). Another possible factor influencing coronary flow is the decreased diastolic pressure in patients with aortic regurgitation. (90). The adequacy of coronary blood flow in experimental models is often determined by measuring the coronary flow both at rest and after temporary occlusion of the vessel. The flow after occlusion is termed the reactive hyperemic flow and is usually several times the resting flow. Actual measurement of coronary flow in the dog with volume overload hypertrophy shows that the resting coronary flow to the ventricle increases with hypertrophy proportional to the increase in mass, but the reactive hyperemic flow to the ventricle stays constant. Thus resting flow per gram of myocardium stays constant, but the maximum hyperemic flow per gram decreases. (91).

Finally there is evidence to suggest that diminished ventricular function may be secondary to an inadequate hypertrophy of the myocardial mass. (5,8,9,66). Inadequate hypertrophy would be indicated by a high radius/thickness (R/T) ratio. Since stress is approximated by pressure x R/T, a high R/T would lead to a higher than normal stress, which is the best estimate of the load actually faced by the in situ fiber.

Heart Failure with Low Stroke Volume

In addition to the patients who manifest symptoms of failure at points D and E on the graph in Figure 8, there is another important group of patients represented by point F. These patients are best characterized by a high end systolic volume index (or the analogous end systolic diameter), a low ejection fraction, and a low ventricular stroke volume index compared to most patients with aortic regurgitation. Because the ventricular stroke index is low, the regurgitant stroke volume index is also low, and consequently the severity of the regurgitation is less than in most patients with regurgitation. This group of patients has generally not been identified specifically as a low regurgitant stroke volume group, but has generally been included as part of the low ejection fraction or high end systolic volume group. This lack of identification is probably due to several factors. Many catheterization

laboratories do not quantitate the amount of regurgitation. Furthermore the most common method of estimating the amount of regurgitation is by supravalvular angiography. This technique tends to overestimate the amount of regurgitation, especially in the presence of a low ejection fraction. (12,13). In addition many studies characterize patients in terms of only one variable. Characterizing the group in terms of only a diminished ejection fraction or an increased end systolic volume index would allow overlap with other patients. However it is clear that a markedly depressed ejection fraction is incompatible with significant aortic regurgitation unless the end diastolic and end systolic volumes are very large.

An important unanswered question is how do the patients at point F arrive at that point on the graph? Did these patients follow the usually accepted course of a period of long standing severe regurgitation followed by the onset of ventricular dysfunction, or did they develop ventricular dysfunction for some other reason and only incidentally have regurgitation? There are no longitudinal studies to answer this, consequently speculative logic must be used. If the ventricular stroke volume is not high in these patients at the time of ventricular dysfunction,could it ever have been higher? The determinants of the regurgitant stroke volume are the diastolic pressure gradient across the valve, size of the regurgitant orifice, and diastolic time. It seems unreasonable that any of these variables would have changed enough to decrease the regurgitant stroke volume significantly. Thus although certainly not proven, there is good evidence to indicate that these patients do not have ventricular dysfunction secondary to severe aortic regurgitation. The possible etiology of the ventricular dysfunction would seem to be either that they responded in an unusually severe way to mild regurgitation, or that the ventricular dysfunction and regurgitation are just coincidental. It is interesting to speculate that this group of patients may be the basis for the now often quoted clinical dictum that the patient with regurgitation may already have diminished ventricular function when he first develops symptoms.

Importance of Heart Failure

Patients with chronic aortic regurgitation who die without having surgery almost all die because of heart failure while arrhythmias play a secondary role. (82). However most patients with aortic regurgitation undergo surgery prior to a cardiac related death. Although operative mortality ranged up to 20% several years ago, (77,92,93) the mortality is now about 5% in most centers. (58,82,84,94-96). With mortality rates this low it is difficult to define predictors of risk, but poor ventricular function probably does increase the risk. (58,82,95,97,98,99). One group has suggested that patients with an end systolic volume index above 60ml/m^2 have an increased risk, but their data is not statistically significant. (77). Patients who die in the period from several days to several years after surgery generally do so from heart failure, arrhythmias, valve dysfunction, or a combination of less frequent causes. Although in the past, frequently over half of the patients would die from valve dysfunction, this problem is much less frequent today because of better valves and more experience in handling valve problems. Heart failure is responsible for an average of about ½ of all late post-operative deaths with a range of 0-86% in different studies. (58,82,94-99). Sudden death is responsible for a surprisingly high average of about ¼ of

all late postoperative deaths with a range of 0-40%. (58,82,95,97-99). Patients who die suddenly after surgery frequently are in heart failure or have clinically apparent ectopy. (100). Thus in some patients heart failure is not cured by surgery and these patients are at high risk of death.

As would be expected, preoperative measures of ventricular function predict survival as shown in Table 3.

Table 3.

Ejection Fraction	>.50=94%	vs. < .50=64%	at 3 years (94)
Ejection Fraction	>.45=87%	vs. < .45=54%	at 5 years (95)
Ejection Fraction	>.45=94%	vs. < .45=80%	at 6 years (99)
Fractional Shortening	>.25=94%	vs. < .25=31%	at 4 years (101)
Fractional Shortening	>.35=100%	vs. < .30=85%	at 4 years (102)
End Systolic Diameter	< 55=94%	vs. > 55=31%	at 4 years (101)

Thus again the clinician finds himself in a quandry. The above measures seem to separate patients into two groups. The first group are patients who do well after surgery, but may have done well without surgery, and therefore are patients in whom surgery may not yet be indicated. The second group are patients who do poorly after surgery and presumably would have done poorly without surgery. To recommend surgery is not totally satisfying for either group.

To try to solve this dilemma further, answers to several questions must be attempted. The first is how often patients with significant aortic regurgitation progress to ventricular dysfunction. The next question is whether the dysfunction that occurs as a sequelae to significant aortic regurgitation is reversible or not. Then, since some patients are known to have persistent ventricular dysfunction after successful valve surgery, the question that was addressed earlier must be readdressed. That question was whether all patients with ventricular dysfunction and aortic regurgitation developed the dysfunction as a result of the regurgitation. If the dysfunction did not develop as a result of the regurgitation, then it seems reasonable to not expect surgery to reverse the dysfunction.

One popular approach is to assume that patients with significant aortic regurgitation do progress to a stage of irreversible ventricular dysfunction and that identification of a stage in these patients' course just prior to the onset of ventricular dysfunction would allow the optimal timing of surgery. To do this, ventricular function has been measured during the stress of either exercise or an iatrogenic increase in afterload. (103-106). The principle is that whereas dysfunction may not be present at rest, the stress would bring out latent dysfunction and thereby identify a stage prior to the onset of dysfunction at rest. Measurement of ejection fraction at rest and exercise is a much discussed approach, however the ejection fraction is sensitive to changes in preload, and the increased heart rate during exercise may change

preload markedly in patients with aortic regurgitation. (107,108). Consequently Dehmer et al have measured both ejection fraction and absolute volumes in patients before and after regurgitation. (103). In some patients, especially those with large resting volumes, the end systolic volume increases with exercise, as opposed to the normal response which is for the end systolic volume to decrease. The significant of this observation is now being investigated.

Hemodynamic Effect of Surgery

The one certain hemodynamic result of successful aortic valve surgery is that it eliminates the regurgitant stroke volume, and thereby decreases the ventricular stroke volume to the value of the peripheral stroke volume. Mathematically this decrease in the ventricular stroke volume must be due to either a decrease in end diastolic volume or an increase in end systolic volume. Overall the decrease in ventricular stroke volume in the immediate postoperative period is accompanied by a marked decrease in end diastolic volume with only a minimal or even decrease in the end systolic volume.(109). In the following 1-2 years, both the end diastolic and end systolic volume decrease even further. (54,109). Overall the volumes decrease to about 50-60% of their preoperative values and approach the normal range. (54,109).

The hemodynamic changes in individual patients will be presented based on the data of the 57 patients which were published in the five articles of pre and postoperative hemodynamic values. (54-58). These patients were catheterized an average of 11 months after surgery. In Figure 11 the individual decrease in the end diastolic volume index relative to the decrease in the ventricular stroke volume index is shown. Importantly the decrease in end diastolic volume index is dependent on the decrease in ventricular stroke volume index. Furthermore the absolute decrease in end diastolic volume index is considerably greater than just the decrease in ventricular stroke volume index.

After the end diastolic volume decreases, the end systolic volume also decreases. As shown in Figure 12, the magnitude of decrease in the end systolic volume index is dependent on the magnitude of decrease in the end diastolic volume index.

Thus the decrease in the ventricular stroke volume caused by valve surgery seems to set into motion a chain of events which results in a regression of both the diastolic and systolic ventricular volumes back toward normal. The decrease in the end systolic volume index after surgery is subject to the same controversial considerations that were apparent when the end systolic volume index increased in response to the initial development of aortic regurgitation, only in reverse. Thus the decrease of the end systolic volume after surgery can be interpreted as either an increase in contractility or as a regression of the apparent serial hypertrophy of sarcomeres. Since mass decreases (approximately proportional to the decrease in end diastolic volume, r .57), the number of sarcomeres in the ventricle must decrease.

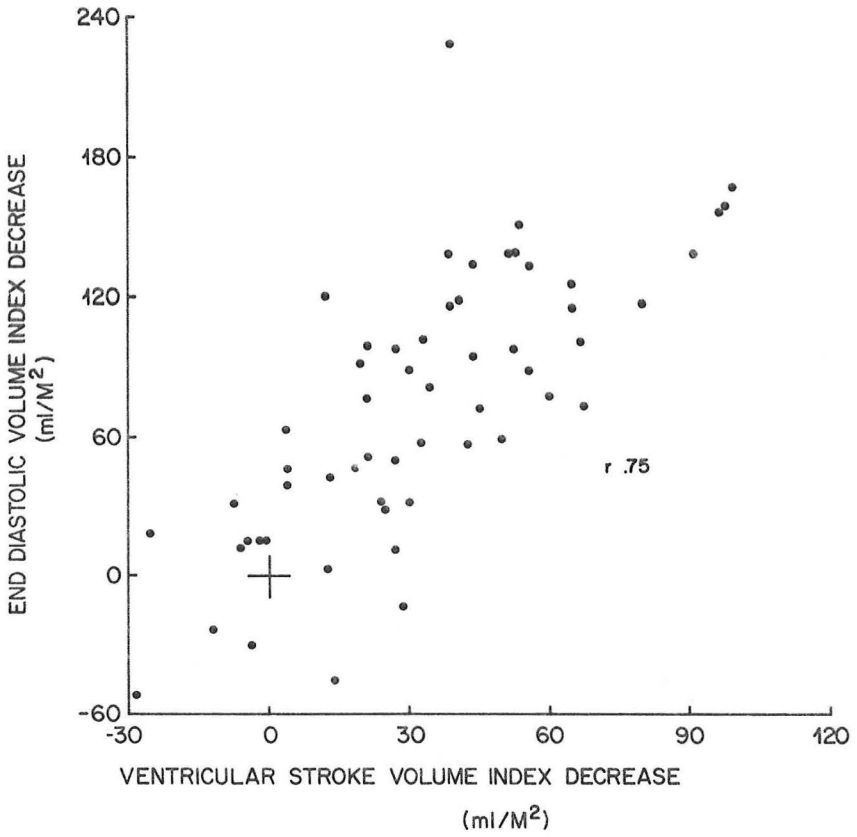

Figure 11

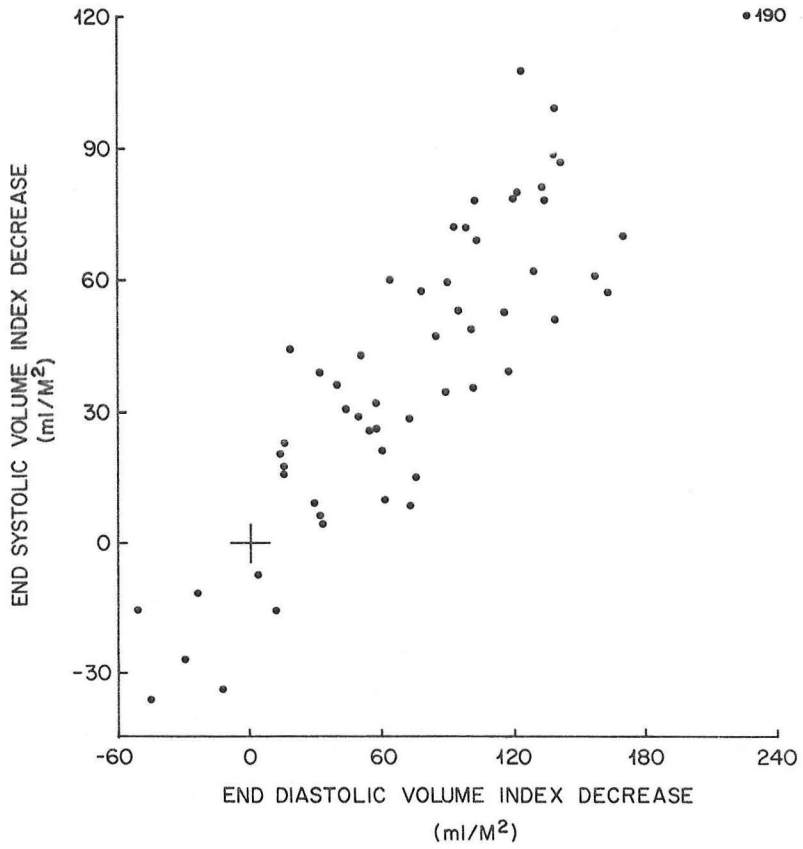

Figure 12

Since the magnitude of regression of the ventricular volumes seems to depend on the magnitude of the decrease in ventricular stroke volume, and the magnitude of the decrease in ventricular stroke volume would logically depend on the magnitude of the ventricular stroke volume prior to surgery, it would seem logical that the patients who do not have a regression of volumes after surgery would be the patients who had a low regurgitant stroke volume index and consequently a low ventricular stroke volume index prior to surgery. The graph in Figure 13 presents evidence for this reasoning. The graph is the same graph shown previously with the preoperative hemodynamic values of the same 57 patients. However this time, the patients whose end diastolic volumes decreased less than 20% are marked. Notice that many of the patients whose ventricular volumes failed to decrease have a low ventricular stroke volume index, high end systolic volume index, and a low ejection fraction. These are the same patients in whom doubt was raised earlier in the discussion as to whether their ventricular dysfunction resulted from significant aortic regurgitation in the first place.

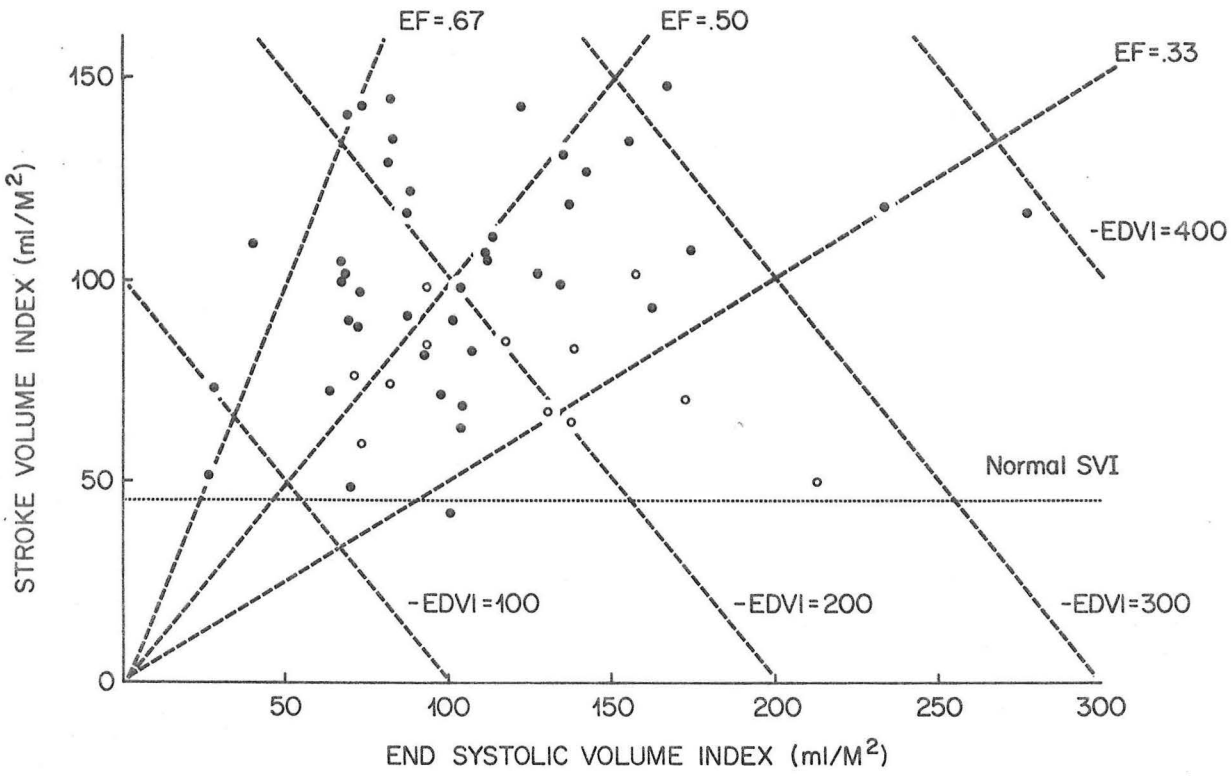

Figure 13

Judging the Beneficial Effect of Surgery

When attempting to show the hemodynamic effect of surgery, it is common to compare the ejection fraction before and after surgery. Another method to show a hemodynamic effect is to compare the ventricular volumes before and after surgery. Use of these two methods in the same patient may lead to different interpretations of the effect of surgery.

The presurgical ejection fraction is compared to the postsurgical ejection fraction for the 57 patients on the graph in Figure 14. The graph shows a good correlation between the ejection fraction before and after surgery. Superficially this graph could be interpreted as demonstrating

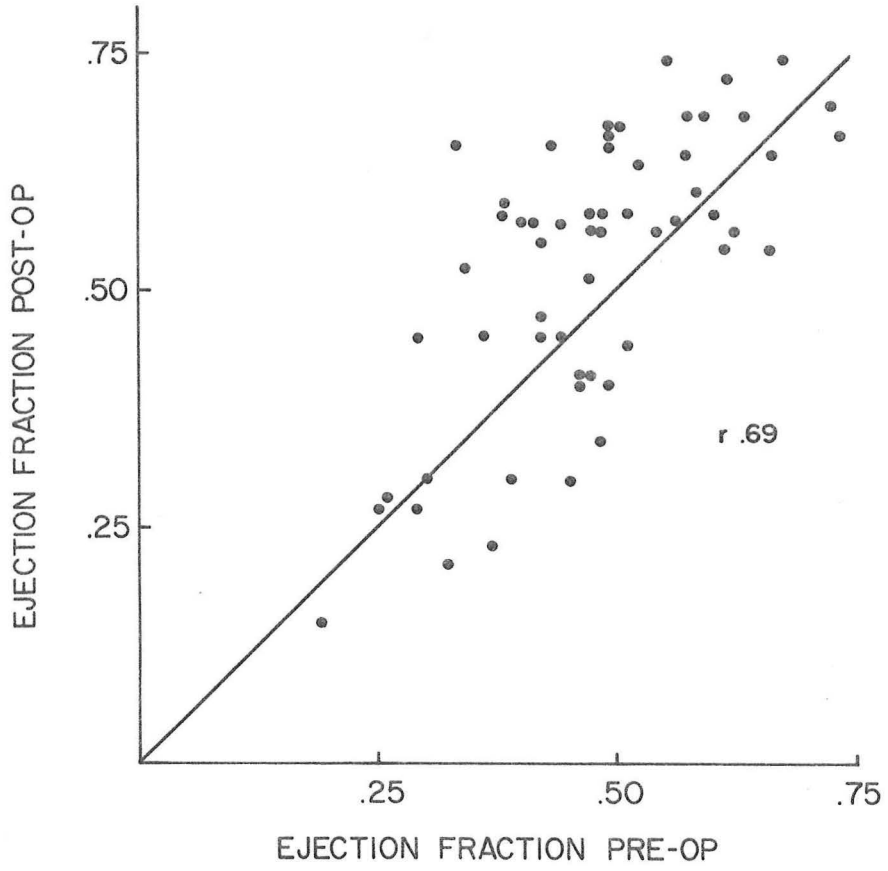

Figure 14

that surgery had only a small effect on the hemodynamic situation. However the ejection fraction is a ratio and is determined by the relationship between the ventricular stroke volume and the end systolic volume. Therefore a lack of change in the ejection fraction could result from the widely divergent hemodynamic situations of either no change in the ventricular stroke volume and end systolic volume or a major change in the ventricular stroke volume with a proportional change in the end systolic volume. Thus on the graph in Figure 15 it can be seen that the ventricular stroke volume and the end systolic volume do change in all combinations. Another way of assessing the

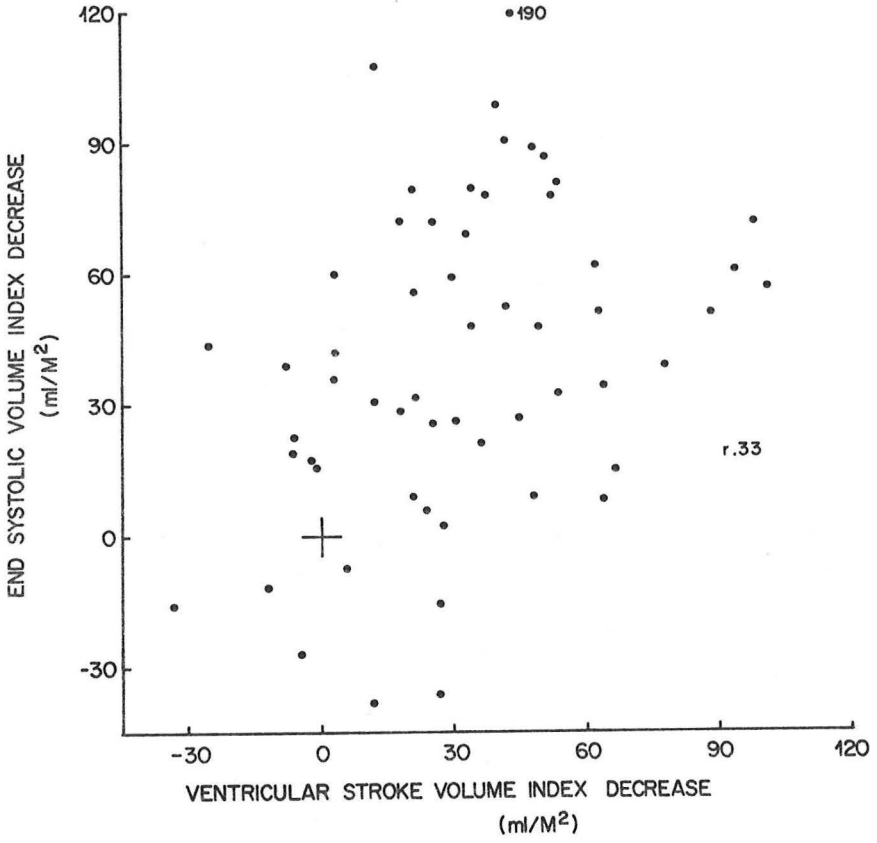

Figure 15

utility of the ejection fraction is to compare a group of patients in whom the ejection fraction increased with surgery, i.e. ventricular function could be said to improve, to a group of patients in whom the ejection fraction decreased, i.e. ventricular function could be said to deteriorate. This was done for the group of 57 patients on the graph in Figure 16. Twenty patients had a decrease or no change in ejection fraction and 37 patients had an increase in ejection fraction. Notice that there was not a dramatic difference in the mean pre and post surgical volumes of these patients. The only major difference was that the group with a decreased ejection fraction failed to decrease their end systolic volume index after surgery as much as the other group.

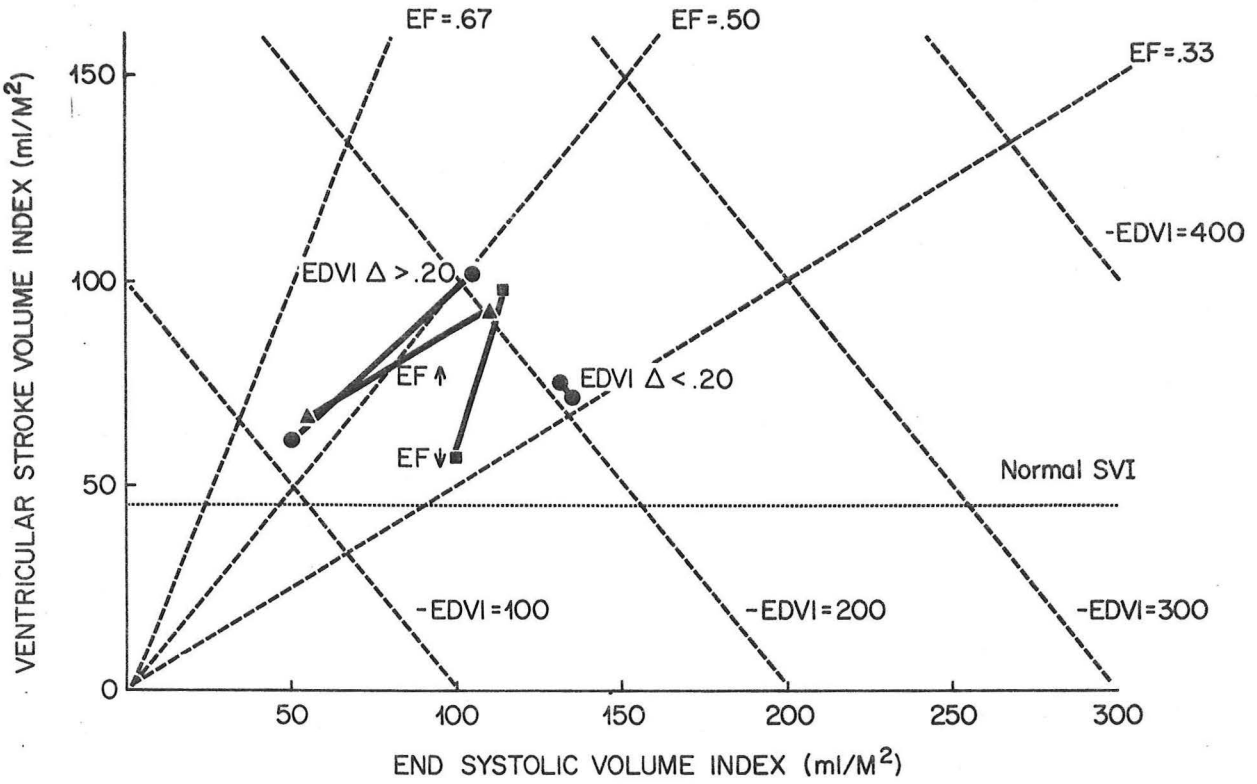

Figure 16

On the other hand, separation of the 57 patients into two groups based on whether their end diastolic volume decreased by more or less than 20% yields a more striking difference in the mean volumes. (Figure 16). There were 14 patients who did not decrease their end diastolic volume over 20% and 43 who did. Notice the minimal change in the ventricular stroke volume index and end systolic volume index in one group and the marked change in the other. In the group in which the end diastolic volume index changed, the end diastolic volume index almost becomes normal. (110 ml/m^2, normal <100ml/m^2). Interestingly the ejection fraction remained at 37 in the group with no change in mean volumes, and only increased from 51 to 57 in the group with the marked change in volumes.

A failure of surgery to decrease the end diastolic diameter (analogous to the end diastolic volume) is highly predictive of post surgical congestive heart failure and late mortality. (8,35,110-112). Thus although a knowledge of all of the hemodynamic changes caused by surgery are helpful for predicting the course in an individual patient, the change or lack of change in the end diastolic volume or diameter is the most predictive of the future course.

Summary

Two points need to be reemphasized. First this discussion has considered chronic aortic regurgitation, not acute regurgitation. The hemodynamic implications, goals of therapy, and recommended therapy are significantly different in the two conditions. Second the discussion and recommendations have assumed accurate measurements. The quality of a laboratory should not be assumed without question.

Patients with chronic aortic regurgitation can be hemodynamically characterized by several different variables. Patients with a high regurgitant stroke volume tend to have either a normal or only mildly diminished ejection fraction with a variable end systolic volume. In these patients clinical deterioration is sometimes accompanied by a decrease in ventricular function. However surgery tends to reverse this dysfunction, induces a regression of ventricular volumes, and produces a good clinical result. Patients with a low regurgitant stroke volume tend to have a more severely diminished ejection fraction with a variable end systolic volume. Although it is unclear why these patients have diminished ventricular function, there is reason to believe that the diminished ventricular function did not occur as a result of severe regurgitation. Surgery gives these patients some temporary relief by eliminating the small amount of regurgitation, but frequently does not improve ventricular function nor induce a regression of ventricular volumes. Consequently the long term outlook is generally poor.

The question of whether longstanding severe aortic regurgitation leads to irreversible depression of ventricular function has not been answered. Although it is most widely held that it does, there is no good evidence to support the concept. There are no longitudinal studies to support the concept, and at least in the available studies, surgical elimination of a high regurgitant stroke volume seems to always induce a regression of the high ventricular volumes.

The recommended management of patients with chronic aortic regurgitation can be based on a combination of clinical symptomatology and hemodynamic status. The symptomatic patient with a large regurgitant stroke volume should have surgery. Good short and long term results should be expected. The symptomatic patient with a small regurgitant stroke volume should also probably have surgery. Some short term relief is likely, but long term results are doubtful. There is little disagreement in these recommendations. The controversy generally occurs in the management of the asymptomatic or minimally symptomatic patient. The reason for this controversy is the uncertainty as to whether irreversible changes to the ventricle can occur before operation can be justified on the basis of symptoms. At present

I believe that the evidence indicates that regurgitation does not cause irreversible dysfunction often enough to justify prophylactic surgery. Others disagree with this view. Since neither approach is known to be best, it seems prudent at present to follow patients with significant regurgitation closely if surgery is not performed. Radionuclide scintigraphy seems most suitable for these serial evaluations. If the approach of prophylactic surgery is desired; the aggressive guideline of operating on patients with an end systolic volume index over 60ml/m^2, the conservative guideline of operating on patients with an end systolic diameter over 50-55 mm, or the moderate guideline of operating on patients with an ejection fraction below 50% or when the exercise ejection fraction falls have all been suggested.

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