Coronary Blood Flow in Dogs With Contractile Dysfunction Due to Experimental Volume Overload

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Background. **Abnormalities in coronary blood flow are responsible for stress-induced reductions in contractile function in pressure overload hypertrophy. Less is known about coronary blood flow in volume overload. In this study, we tested the hypothesis that coronary blood flow abnormalities were responsible for contractile abnormalities in experimental volume overload hypertrophy.**

Methods and Results. **We examined coronary blood flow at rest and during pacing in seven dogs with contractile dysfunction secondary to chronic experimental mitral regurgitation (average regurgitant fraction at 3 months, 0.58±0.05). After 3 months of mitral regurgitation, left ventricular mass had increased from 92±8 g at baseline to 118±10 g ($p<0.002$). The slope of the end-ejection stress–volume relation, one of our indexes used to estimate contractile function, had fallen from 5.4±0.3 at baseline to 3.0±0.3 at 3 months of mitral regurgitation ($p<0.001$). In the mitral regurgitation dogs, coronary blood flow at rest was similar to that of control dogs (endocardial blood flow: control dogs, 1.33±0.12 ml/min/g; mitral regurgitation dogs, 1.16 ml/min/g, p=NS; epicardial blood flow at rest: control dogs, 1.30±0.16 ml/min/g; mitral regurgitation dogs 1.13±0.2 ml/min/g, p=NS). With pacing-induced stress, coronary blood flow increased appropriately in control and mitral regurgitation dogs. Ultrasonic dimension gauges placed in the endocardium and epicardium demonstrated no further deterioration in ventricular function during pacing in the mitral regurgitation dogs. In a separate group of five control dogs and five dogs with mitral regurgitation and left ventricular dysfunction, coronary blood flow was examined in the conscious closed-chest state at rest, during adenosine infusion, and during rapid atrial pacing (240 beats/min). Blood flow increased similarly in both groups during pacing and adenosine infusion.**

Conclusions. **We conclude that in dogs with mitral regurgitation that have developed contractile dysfunction, abnormalities in coronary blood flow do not explain the resting contractile dysfunction. Furthermore, studies during pacing-induced stress and coronary vasodilation with adenosine demonstrate that substantial coronary blood flow reserve is present in this type of volume overload hypertrophy. (*Circulation* 1991;83:1063–1075)**

Long-standing pressure or volume overload on the left ventricle eventually results in left ventricular dysfunction and congestive heart failure. The mechanism by which hemodynamic overload causes muscle dysfunction is unknown. Inadequate coronary blood flow has been postulated as one cause of the left ventricular dysfunction present in overloaded states. Coronary blood flow has been extensively studied in pressure overload and has been clearly found to be abnormal.[1] In pressure overload, coronary blood flow reserve is greatly diminished.[2,3] Furthermore, coronary blood flow to the subendocardium at rest or with stress is also clearly reduced.[4–6] In recent studies, these abnormalities of subendocardial blood flow in pressure overload were found to correlate well with an observed reduction in global[7] or subendocardial contractile function during pacing stress in aortic-banded dogs.[8] Thus, coronary blood flow abnormalities are, in part, responsible for left

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ventricular dysfunction found in pressure overload hypertrophy especially during stress.

Coronary blood flow abnormalities in volume overload hypertrophy produced by mitral regurgitation are not as well defined as those for pressure overload, although abnormalities in coronary blood flow in mitral regurgitation have been reported.[9] Whether these abnormalities are responsible for left ventricular dysfunction present in volume overload is unknown. The following study was performed to test the hypothesis that coronary blood flow abnormalities, if present, would cause the left ventricular dysfunction occurring in experimental volume overload hypertrophy.

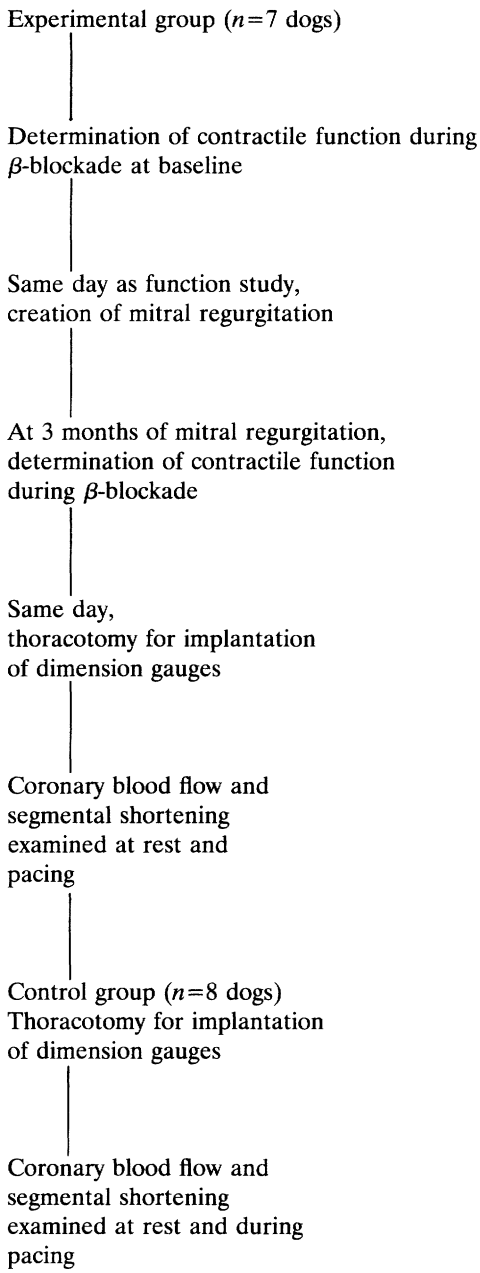
Methods

Study Design

Seven dogs with severe chronic mitral regurgitation that had developed left ventricular dysfunction were the initial subjects of this study (initial group). Left ventricular function was estimated before the creation of mitral regurgitation and again after severe mitral regurgitation had been present for 3 months. Thus, with respect to contractile function, each animal served as its own control. Contractile function was studied at baseline and again at 3 months during β-adrenergic receptor blockade. β-Blockade was used to remove β-adrenergic influences that might have altered contractile state separately from intrinsic contractile function. Contractile state was estimated from the slope of the end-ejection stress–volume relation (EESVR),[10] from this relation corrected for the development of cardiac hypertrophy by multiplying the slope by left ventricular mass and also by end-diastolic volume, and from assessment of end-systolic stiffness.[11,12] Coronary blood flow was studied in these animals and in eight control dogs with the microsphere technique at rest and during rapid atrial pacing. To assess whether abnormalities in coronary blood flow worsened left ventricular function during stress, we obtained measurements of regional coronary blood flow simultaneously with ultrasonic measurement of subendocardial and subepicardial segmental shortening[13] at rest and during pacing in the animals with mitral regurgitation and in the controls (Figure 1).

The above studies were performed in the open-chest anesthetized animal in which thoracotomy was performed to instrument the animals with sonomicrometers. Determination of coronary blood flow in the anesthetized state has well-known limitations.[14] Therefore, we also measured coronary blood flow in 10 additional animals (five control dogs and five dogs with chronic mitral regurgitation and left ventricular dysfunction) studied in the closed-chest conscious state. In these animals, coronary blood flow reserve was more extensively studied at more rapid atrial pacing rates (tolerated in the closed-chest state) and during maximum coronary vasodilation produced by adenosine infusion, 1.06 mg/kg/min.[4] In the second group of experiments, the animals with mitral regurgitation had mitral regurgitation similar in severity to that of the first group of experiments (regurgitant fraction, 0.63±0.04). Coronary blood flow and left ventricular function were measured in a fashion identical to the previous experiments.

FIGURE 1. *Diagram of Study Protocol.*



Determination of Global Ventricular Function

Intact ventricular function is difficult to estimate in severe mitral regurgitation because of loading changes that make ejection phase indexes difficult to interpret.[15–17] We examined contractile function in this study with the EESVR as an index of contractile function, which is relatively load independent.[10] The data used to develop this relation were obtained from multiple variably loaded beats produced during a

single ventriculogram recorded with cineangiography and simultaneous high-fidelity recordings of left ventricular and aortic pressures.[10,18] The multiple variably loaded beats were created by inflation of a balloon in the inferior vena cava followed by deflation of the balloon. By performing left ventriculography during balloon deflation, we recorded a stepwise increase in left ventricular volume, pressure, and stress from which the EESVR was developed. We recognize that end ejection and end systole are not equivalent, particularly in mitral regurgitation. As in previous studies, we chose these end points because of their accuracy and reproducibility from subject to subject[10] and from beat to beat.

The eccentric hypertrophy that occurs in volume overload increases left ventricular volume, which decreases the slope of the end-systolic stress–volume relation (EESVR) whether or not contractile function has been depressed.[19,20] Correction of end-systolic indexes by multiplying by end-diastolic volume or by left ventricular mass has been proposed, and we used both corrections in this study.[21] The initial slope of the relation was multiplied by the initial mass and in a separate calculation also by initial end-diastolic volume. The corrected slopes were then compared with the corrected slopes at 3 months.

Recently, end-systolic stiffness derived from ventricular stress–strain analysis was also used to measure contractile function.[11,12] This method is independent of cardiac size—a potential advantage over the EESVR. The method is load independent and is sensitive to changes in contractile state.[12] Its derivation from stress and the natural log of the reciprocal of wall thickness (1/H, an expression of strain) is presented in Appendix 1. End-systolic stiffness was calculated from the ventriculographic and pressure data identical to those used to calculate the EESVR at baseline and at 3 months.

Initial Study: Instrumentation, Examination of Global Ventricular Function, and Creation of Mitral Regurgitation

Seven healthy parasite-free mongrel dogs weighing 20–30 kg were anesthetized with a mixture of droperidol–fentanyl (0.15 ml/kg i.m.). The animals then breathed spontaneously through a rebreathing apparatus, inhaling a 3:1 mixture of nitrous oxide to oxygen. This combination of droperidol–fentanyl–nitrous oxide has had little effect on contractile function.[22] After anesthesia was induced, a cutdown was performed to expose the left carotid artery and left external jugular vein. A thermodilution Swan–Ganz catheter was advanced from the left jugular vein to the pulmonary artery. A 20-mm balloon catheter was inserted through this same vessel into the inferior vena cava and was used to alter venous return and, thus, to alter ventricular loading conditions to produce the variably loaded beats for the construction of the EESVR. A 5F pigtail catheter was introduced into the left carotid artery, advanced to the left ventricle, and connected to a mercury-calibrated transducer. A double micromanometer transducer catheter was advanced from the same artery so that one transducer was positioned in the left ventricle while the second transducer was above the aortic valve in the ascending aorta. At this time, β-blockade was induced by infusing a loading dose of esmolol (0.5 mg/kg/min × minutes), followed by a continuous infusion at a dose of 0.3 mg/kg/min. Pressures were recorded, and cardiac output determinations were made in triplicate. Baseline ventriculography was performed in the 30° right anterior oblique position at 60 frames/sec by injecting nonionic radiographic contrast at 10 ml/sec for 1.5 seconds. The ventriculogram, thus obtained, was used to calculate resting ejection fraction and also resting left ventricular mass and volume to be used later in correcting the EESVR. After a 10-minute recovery period, the inferior vena cava balloon was inflated. Care was taken so that aortic diastolic pressure was not less than 50 mm Hg to ensure that coronary blood flow was not compromised.[23] Deflation of the balloon produced a stepwise increase in left ventricular pressure during which a second ventriculogram was obtained with 6 ml contrast administered per second for 4–5 seconds.[10,18] After this second ventriculogram, the Millar (Millar Instruments, Houston) and pigtail catheters were removed and a 30-cm 8F sheath was inserted into the left carotid artery and guided under fluoroscopy into the left ventricle. With methods previously described, a urologic calculus removal forceps was introduced into the left ventricle to grasp chordae tendineae, forcible retraction of which produced mitral regurgitation.[10,24]

Final Study for Open-Chest Animals: Instrumentation and Examination of Global Ventricular Function, Coronary Blood Flow, and Regional Myocardial Function

After mitral regurgitation had been present for 3 months, the animals were returned to the catheterization laboratory. Anesthesia, instrumentation, and β-blockade were identical to those in the baseline study. An initial ventriculogram was obtained to determine the volumes needed to calculate regurgitant fraction and to determine end-diastolic volume and mass for corrections of EESVR. A second ventriculogram was obtained during which the inferior vena cava balloon technique was again used to develop the beats needed to examine the EESVR at 3 months. After completion of this ventriculogram, the animal was connected to a Harvard respirator (Harvard Apparatus, South Natick, Mass.), and a deeper plane of anesthesia was induced by the addition of 1% isoflurane to the inhalatory mixture. A left thoracotomy was performed, and the left ventricle was suspended in a pericardial cradle. The circumflex coronary artery was exposed distal to the bifurcation with the left anterior descending artery. Two pairs of ultrasonic dimension gauges were placed in the myocardium in the region supplied by the circumflex coronary artery to measure dimensions of subendocardial and subepicardial segments. The suben-

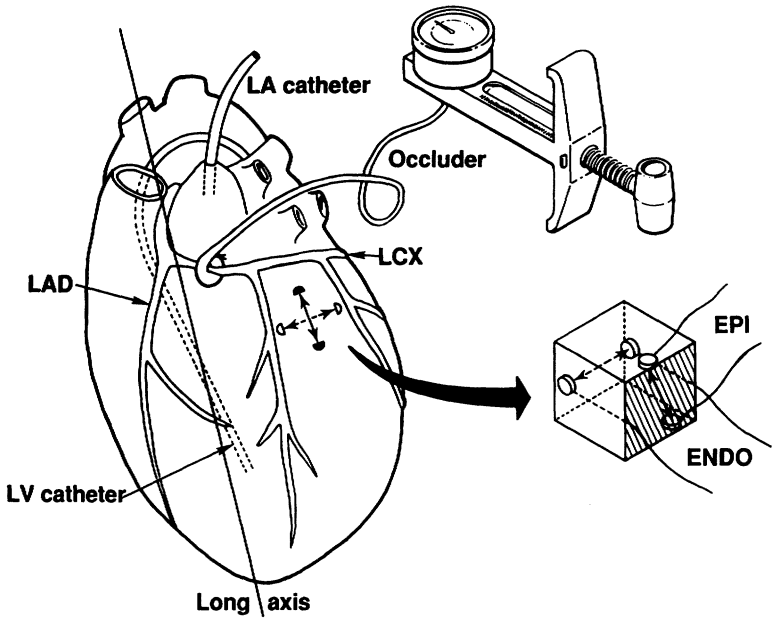


FIGURE 2. *Diagram of instrumentation for the final study. ENDO, endocardial dimension gauge placement; EPI, epicardial dimension gauge placement; LA, left atrium; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LV, left ventricle.*

docardial gauges were placed perpendicular to the long axis of the ventricle and, thus, parallel to the direction of circumferential fiber orientation. The epicardial gauges were oriented in the direction of the epicardial surface fibers that run obliquely across the surface of the ventricle at an angle of approximately 50° to the circumferential plane (Figure 2).[13] A catheter was then placed in the left atrium for the purpose of injecting microspheres. A pigtail catheter was placed in the descending aorta for blood sampling during microsphere injection. An inflatable cuff occluder was placed around the circumflex coronary artery. This occluder was used to cause a partial and then a total coronary occlusion to demonstrate that if pacing-induced coronary blood flow abnormalities caused ischemia, ischemic segmental myocardial dysfunction could be detected by our instrumentation (Figure 3). In every animal, partial circumflex coronary occlusion produced a degree of obstruction that diminished subendocardial shortening while subepicardial shortening remained normal (Figure 3). Further inflation of the cuff produced total, brief circumflex occlusion that resulted in severe depression of both subendocardial and epicardial shortening that returned to baseline conditions after release of the occlusion. The cuff occluder was then removed from the artery. Subendocardial and epicardial coronary blood flows were measured simultaneously with subendocardial and epicardial dimensional shortening first at rest and then during stress produced by rapid atrial pacing (200 beats/min). Regional myocardial blood flow was measured by injecting approximately 3 million previously sonicated carbonized microspheres labeled with gamma-emitting radionuclides, cesium-141 or ruthenium-103 into the left atrium. Beginning 30 seconds before injection and continuing for 2 minutes after injection, a reference sample of arterial blood was withdrawn from the aortic catheter at a constant rate of 7.75 ml/min. At the end of this experiment, the dogs were killed by removal of the heart under anesthesia. The left ventricle was dissected from the rest of the heart, weighed, and fixed in 10% buffered formalin for at least 3 days. It was then sectioned for scintigraphic counting as described previously.[8,25] Myocardial and blood reference samples were analyzed in a gamma multichannel analyzer. Radioisotope counts were corrected for background and for overlapping counts contributed by the accompanying isotope.

Final Study for Closed-Chest Animals: Instrumentation and Examination of Global Ventricular Function and Coronary Blood Flow

In the final study for closed-chest animals, five additional dogs with chronic mitral regurgitation (created in a fashion identical to that of the first group) underwent determination of contractile function at baseline and after 3 months of mitral regurgitation in a fashion identical to that of the above group, except that this group was only lightly sedated with sufentanil (0.1 μg/kg/min). No thoracotomy was performed. Catheters were inserted percutaneously after local anesthesia by infiltration with lidocaine. Left atrial catheterization was achieved by advancing a 5F pigtail catheter from the femoral artery to the left ventricle then retrograde across the mitral valve. β-Blockade used during the determination of contractile function was then discontinued. Thirty minutes after completing the esmolol infusion, coronary blood flow was measured with microspheres in control animals and animals with mitral regurgitation at rest, during atrial pacing at 240 beats/min, and during adenosine infusion (1.06 mg/kg/min), which is a dose that causes maximum coronary vasodilation.[4] A third

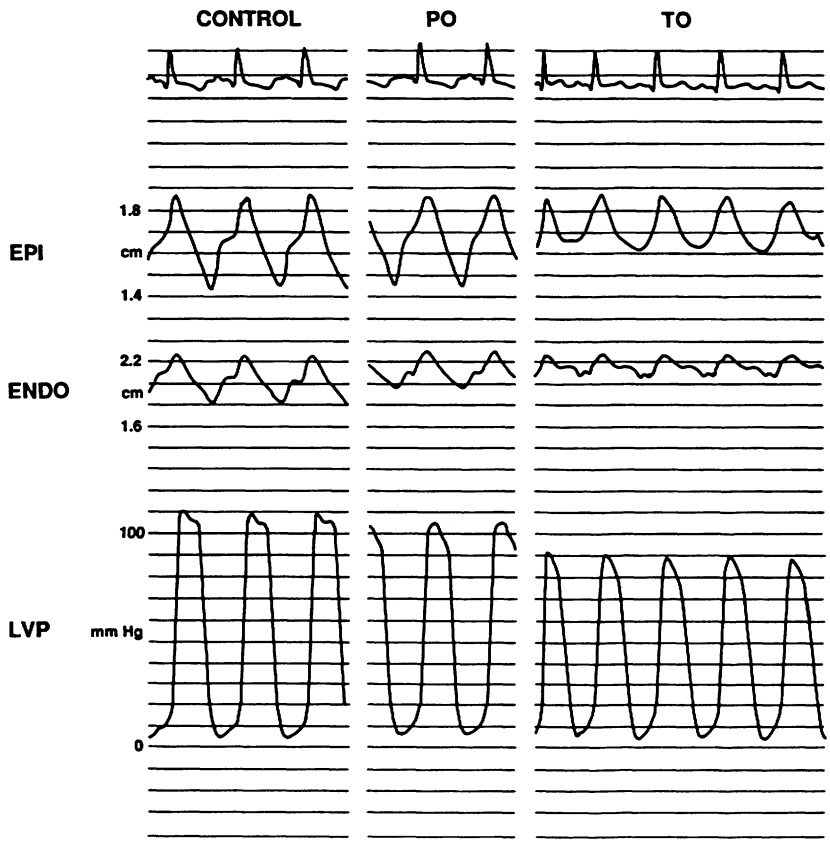


FIGURE 3. *Tracings of segmental function during ischemia. Endocardial (ENDO), epicardial (EPI), and left ventricular pressure (LVP) during partial occlusion (PO) and total occlusion (TO) of the circumflex coronary artery. During partial occlusion, endocardial segmental shortening is diminished, whereas epicardial shortening remains at control levels. During total occlusion, endocardial and epicardial shortening cease, and wall motion is paradoxic.*

microsphere labeled with the gamma-emitting radioisotope chromium-51 was used to obtain coronary blood flow in the third experimental condition.

Calculations

Left ventricular volumes were calculated with the area–length method. Left ventricular mass was calculated from angiographic images at the baseline study and at 3 months by the method of Rackley et al.[26] Actual left ventricular mass was also weighed after death at 3 months. A good correlation was found between angiographically measured mass and weighed mass at 3 months (r=0.96). Because mass determination requires volume determination, this close agreement between actual and angiographic mass, as in our previous studies,[10,18] supports our ability to accurately measure cardiac volumes angiographically. End-diastolic volume was taken from the frame with the largest left ventricular volume. End-systolic volume was taken as the smallest angiographic volume. We recognize that end-systolic volume and end-ejection volume may not be identical in mitral regurgitation. We refer to end-ejection volume because of its exact definition and reproducibility.[10] End-ejection wall stress was calculated with Mirsky's method.[27] Wall thickness was measured at the mid-anterior wall in diastole. Wall thickness for subsequent frames was calculated from end-diastolic thickness and the amount of systolic shortening under the assumption that cardiac mass remains constant during one cardiac cycle.[28] Coronary blood flow (QM) was calculated as QM=QR × CM/CR, where QR is reference blood flow (7.75 ml/min), CM is gamma counts per minute from the myocardial specimen, and CR is counts per minute from the reference blood specimen. Blood flows were divided by the sample weights and were expressed as milliliters per minute per gram of myocardium.

Data Analysis and Statistics

Pressure, cardiac output, and volumetric measurements; angiographic cardiac mass; EESVR; corrected EESVR; and systolic stiffness constant were compared at baseline and at 3 months by a paired t test. Subendocardial and subepicardial coronary blood flows and subendocardial and subepicardial shortening fractions were compared at rest and during pacing by analysis of variance followed by a t test when the analysis found significant differences. The linear correlation between angiographic cardiac mass and weighed cardiac mass was made with the least-squares method. The relation between stress and volume was assumed to be linear in the physiological range of these studies[29] and was obtained by linear regression analysis. All plots of stress to volume at baseline and after mitral regurgitation had a good correlation $r \geq 0.95$. Derivation of the end-systolic stiffness constant (k) was made with curvilinear fit of

TABLE 1. Hemodynamic and Volumetric Data: Initial Group

	Baseline	MR_3	$<p$
EDV (co)	73±6	105±8	0.01
LVM (g)	92±8	118±10	0.002
PCW (mm Hg)	9±1	22±3	0.02
FSV (cc)	44±7	26±2	0.01

Values are mean±SEM.
MR_3, 3 months of mitral regurgitation; EDV, end-diastolic volume; LVM, left ventricular mass; PCW, pulmonary capillary wedge pressure; FSV, forward stroke volume.

stress to the natural log of the reciprocal of wall thickness, ln(1/H), expressed as $\sigma = Ce^{kln}(1/H)$, where k is the exponential constant relating stress to ln(1/H) (the expression of strain).[12] Dispersion from the mean is noted by standard error of the mean.

Results

Initial Studies

At 3 months, all dogs had severe mitral regurgitation with an average regurgitant fraction of 0.58±0.05. Table 1 lists hemodynamic and volumetric parameters at baseline and after 3 months of mitral regurgitation. End-diastolic volume, left ventricular mass, and pulmonary capillary wedge pressure were all significantly increased at 3 months. Forward stroke volume was severely decreased.

Parameters of Contractile Function

As in our previous study, at 3 months of mitral regurgitation, contractile function was depressed. At baseline, ejection fraction was 0.55±0.04; ejection fraction increased with acute mitral regurgitation to 0.67±0.02, probably because of the favorable changes in loading conditions produced by acute mitral regurgitation. However, by 3 months of mitral regurgitation, ejection fraction was depressed compared with the acute state (when similar loading conditions were present) and was 0.59±0.02 ($p<0.01$). An example of the EESVR obtained at baseline and at 3 months for one animal is shown in Figure 4. The slope of the EESVR for the group was severely depressed at 3 months (Figure 5). When EESVR was corrected for the presence of ventricular hypertrophy by multiplying by either end-diastolic volume or by left ventricular mass, the corrected relation still indicated that contractile function was depressed at 3 months (Table 2). The end-systolic stiffness constant also decreased from 3.74±0.32 to 2.70±0.20 ($p<0.01$).

Coronary Blood Flow at Rest and During Rapid Atrial Pacing

Coronary blood flow was similar at rest in control and mitral regurgitation dogs (Figure 6). During rapid atrial pacing, both groups of dogs had a significant and similar increase in epicardial and endocardial coronary blood flow. Endocardial and epicardial shortening fraction did not change during rapid atrial pacing (Figure 6). Hemodynamic parameters before and during pacing are shown in Table 3. No differences in systolic blood pressure, diastolic blood pressure, or rate–pressure product existed between the control group and the mitral regurgitation group at rest or during pacing. During pacing, heart rate and rate–pressure product increased similarly in both groups. No differences in the ratio of subendocardial to epicardial coronary blood flow were found between groups (control versus mitral regurgitation) or between states (resting versus pacing): control dogs at baseline, 1.05±0.05; mitral regurgitation dogs at baseline, 0.98±0.09; control dogs at pacing, 1.05±0.14; and mitral regurgitation dogs at pacing, 0.90±0.08.

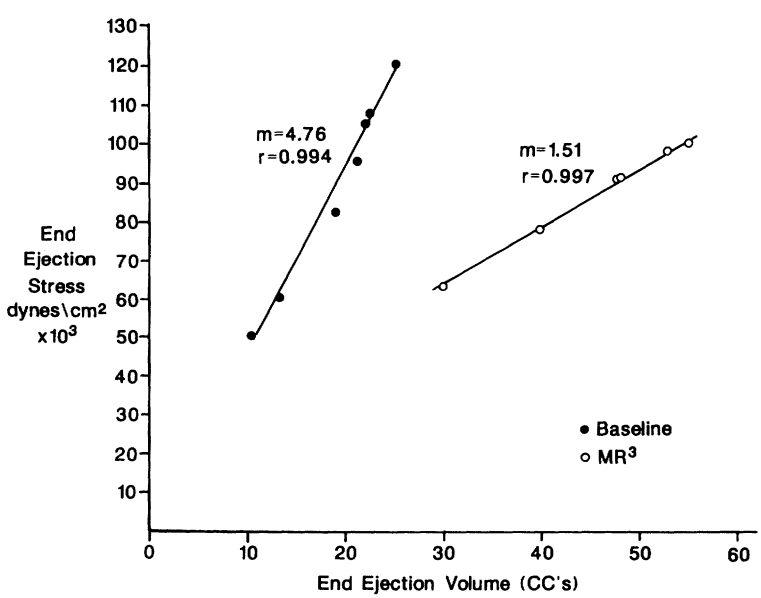


FIGURE 4. *Plot of end-ejection stress–volume relation for one subject at baseline and after 3 months of mitral regurgitation (MR_3). Slope of MR_3 is severely depressed compared with that of baseline.*

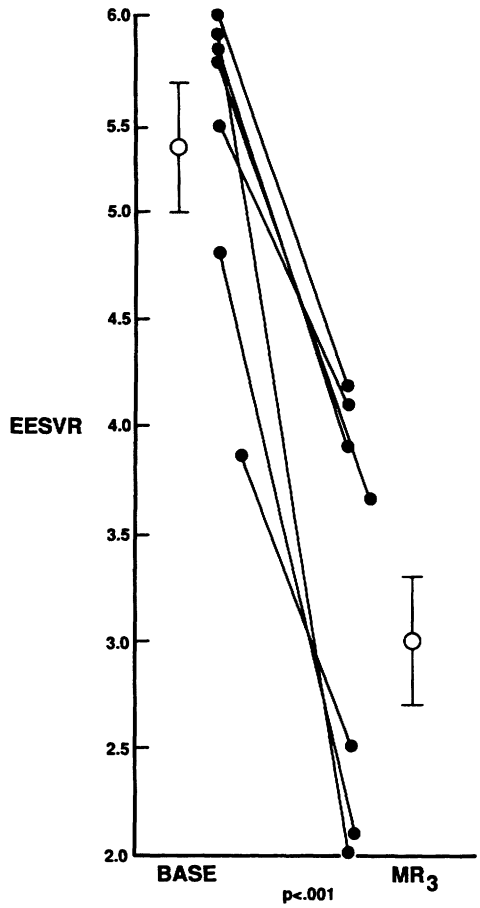


FIGURE 5. *Plot of contractile function in the initial group with mitral regurgitation. Contractile function as approximated by the slope of the end-ejection stress–volume relation (EESVR) is shown at baseline (BASE) and after 3 months of mitral regurgitation (MR_3). All dogs had a substantial decrease in the slope of the EESVR at 3 months.*

Closed-Chest Studies

The regurgitant fraction for the second group of mitral regurgitation dogs was 0.63±0.04. As demonstrated in Table 4, end-diastolic volume and left ventricular mass were substantially increased after 3 months of mitral regurgitation. As with the first group of dogs, EESVR, corrected EESVR, and the end-systolic stiffness constant were significantly depressed after 3 months of mitral regurgitation. Coronary blood flow data are shown in Table 5. Endocardial and epicardial coronary blood flows increased significantly in the control and the mitral regurgitation groups both with pacing and with adenosine infusion. However, no differences were found between groups at each of the three states in which coronary blood flow is measured.

TABLE 2. Parameters of Contractile Function: Initial Group

	Baseline	MR_3	$<p$
EESVR	5.4±0.3	3.0±0.3	0.001
$EESVR_m$	488±39	374±47	0.05
$EESVR_v$	383±18	311±13	0.05
k	3.74±0.32	2.70±0.20	0.01

Values are mean±SEM.

MR_3, 3 months of mitral regurgitation; EESVR, slope of end-ejection stress–volume relation; $EESVR_m$, slope of end-rejection stress–volume relation corrected by multiplying EESVR by left ventricular mass; $EESVR_v$, slope of end-ejection stress–volume relation corrected by multiplying by end-diastolic volume; k, the end-systolic stiffness constant.

Discussion

A major finding of this study was that dogs with left ventricular dysfunction secondary to chronic mitral regurgitation had normal coronary blood flow at rest. Because coronary blood flow was normal at rest, the abnormality in resting contractile function that we observed in animals with mitral regurgitation probably cannot be explained by existing abnormalities in coronary blood flow. Furthermore, during rapid atrial pacing, coronary blood flow increased in mitral regurgitation dogs in a fashion similar to that in control dogs. Unlike pacing-induced changes previously reported in animals with pressure overload,[7,8] there was adequate coronary blood flow reserve to maintain endocardial and epicardial shortening at baseline levels. In our first group of studies, we used an open-chest model (to insert sonomicrometers) to examine the correlation between coronary blood flow and segmental function during stress. However, the open-chest anesthetized models have well-known limitations in the examination of coronary blood flow.[14] Therefore, in a separate set of closed-chest experiments, we examined coronary blood flow at a faster pacing rate (not tolerated in the open-chest condition) and also during adenosine infusion. These studies confirmed that substantial coronary blood flow reserve existed in the mitral regurgitation dogs and that, in fact, this reserve was similar to that found in control dogs. Because we observed additional coronary blood flow reserve, coronary blood flow abnormalities are even less likely to explain the resting contractile dysfunction present in the dogs with volume overload.[30]

Contractile Dysfunction in Mitral Regurgitation

A central premise of this study is that our dogs with chronic mitral regurgitation had developed contractile dysfunction after 3 months of chronic mitral regurgitation. Contractile function was studied during β-blockade at baseline and at 3 months of mitral regurgitation to ensure that β-adrenergic reflexes did not obscure reductions in intrinsic contractile function. To examine contractile function in mitral regurgitation, an index must be used that accounts for the significant changes in loading.[31] We examined contractile function with the EESVR as previously reported.[10] This relation is relatively independent of preload and accounts for afterload in its expression. This measure of contractile function was greatly depressed at 3 months. However, we recognize that the EESVR is not only dependent on contractile function but also on ventricular size.[19–21] Thus, the

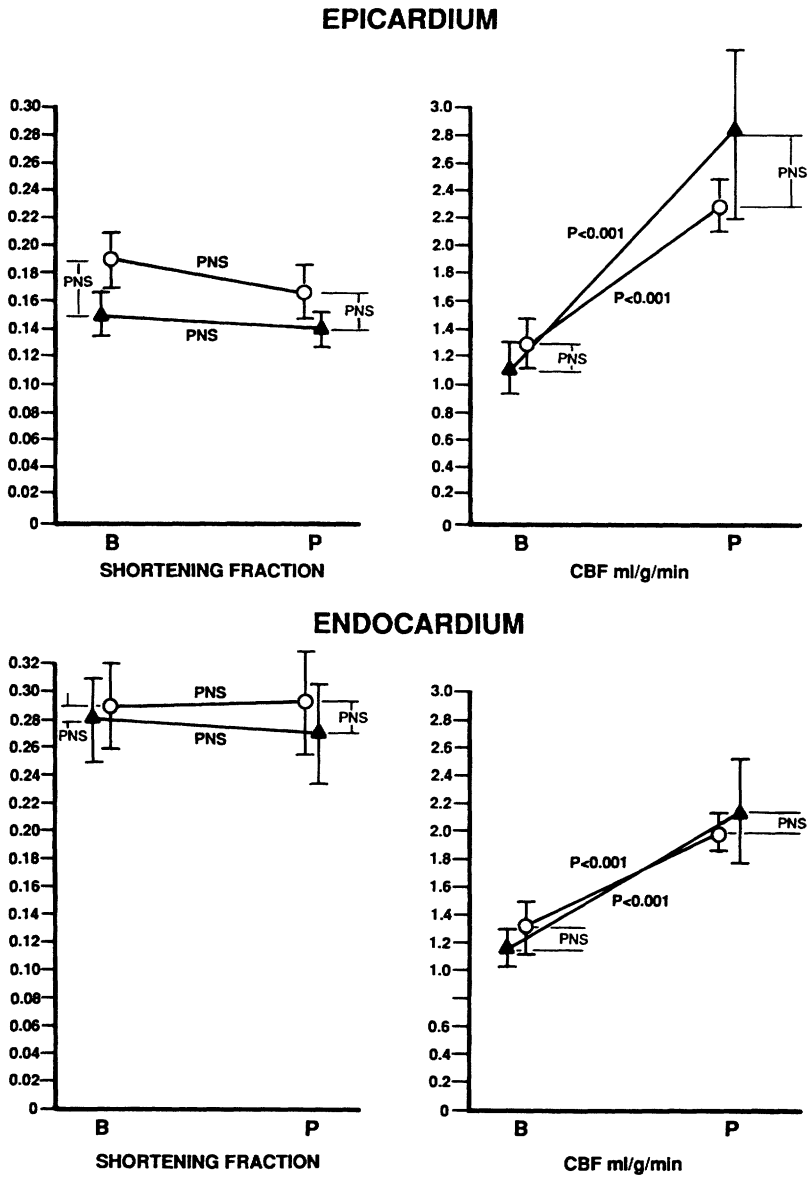


FIGURE 6. *Plots of shortening fraction and coronary blood flow at rest and during pacing. Epicardial and endocardial shortening fraction and coronary blood flow (CBF) are shown at baseline (B) and during rapid atrial pacing (P). Shortening fraction did not deteriorate in control (▲) or mitral regurgitation (○) dogs during rapid atrial pacing. Coronary blood flow increased similarly during rapid atrial pacing in both groups of dogs.*

EESVR could have been depressed at 3 months either because sarcomere function was abnormal (depressed contractile function) or because more normally functioning sarcomeres caused the ventricle to be bigger at end systole than before the creation of mitral regurgitation. Corrections for this relation by multiplying by either mass or volume have been proposed. We performed both corrections and found that both still indicated a significant depression in contractile function at 3 months. In addition, we examined end-systolic stiffness determined from the relation of stress to the natural log of the reciprocal

TABLE 3. Hemodynamics Before and After Pacing: Initial Group

	Control		MR_3	
	Baseline	Pacing	Baseline	Pacing
HR (beats/min)	125±2	201±7*	121±7	206±3*
Systolic BP (mm Hg)	104±3	101±3	96±3	91±4
Diastolic BP (mm Hg)	65±3	66±3	69±3	65±2
RPP	$1.31\pm0.1\times10^4$	$2.03\pm0.1\times10^{4*}$	$1.16\pm0.2\times10^4$	$1.87\pm0.3\times10^{4*}$

Values are mean±SEM.
MR_3, dogs with mitral regurgitation for 3 months; HR, heart rate; BP, blood pressure; RPP, rate–pressure product.
*$p<0.001$ vs. baseline. No differences existed in any parameters between groups at baseline or pacing.

TABLE 4. Volumetric and Contractile Data: Second Group (Closed-Chest Dogs)

	Baseline	MR_3	*p*
EDV (cc)	82.2±3.1	137.6±13.6	0.02
LVM (g)	112.6±3.5	154.0±5.8	0.001
EESVR	4.92±0.5	1.7±0.25	0.01
$EESVR_m$	548±51	261±38	0.02
k	4.57±0.55	2.25±0.60	0.01

Values are mean±SEM.

MR_3, 3 months of mitral regurgitation; EDV, end-diastolic volume; LVM, left ventricular mass; EESVR, slope of the end-ejection stress–volume relation; $EESVR_m$, slope of end-ejection stress–volume relation corrected for mass; k, the end-systolic stiffness constant.

of wall thickness, ln(1/H) (an expression of strain) in our dogs with mitral regurgitation.[12] This relation is size and load independent and is sensitive to changes in inotropic state.[12] This index also showed depression of contractile state in both groups of dogs after 3 months of mitral regurgitation. Even ejection fraction enhanced by favorable loading conditions was depressed at 3 months compared with the acute state. Thus, as in our previous study of a different group of animals,[10] all data indicate that the mitral regurgitation animals had contractile dysfunction at 3 months. Furthermore, in a recent study from our laboratories, our measures of intact ventricular function correlated well with the contractile function of isolated myocytes taken from the same hearts.[32] That an independent laboratory unaware of our results, using entirely different methods to analyze myocardial function, found results similar to ours tends to substantiate our methods for measuring contractile function.

Relation of Our Study to Other Studies of Coronary Blood Flow in Ventricular Hypertrophy

Coronary blood flow has been extensively studied in pressure overload hypertrophy.[1] Although coronary blood flow may be normal at rest, nearly all studies demonstrate that during stress with exercise or pacing or during coronary vasodilation with adenosine there is significant subendocardial underperfusion in pressure overload hypertrophy.[4–8,33–35] We recently reported that abnormalities in subendocardial blood flow in pressure overload hypertrophy were specifically associated with contractile abnormalities isolated to the subendocardium.[8]

Coronary blood flow has been less thoroughly studied in volume overload. Recent studies in aortic regurgitation demonstrated reduced coronary blood flow reserve in patients with this disease.[36] An arteriovenous fistula model of volume overload produced abnormal endocardial blood flow during vasodilatation with adenosine.[37] However, because acute closure of the fistula resulted in normalization of coronary blood flow, the investigators concluded that hemodynamic abnormalities created by the fistula, rather than the hypertrophy, were responsible for the coronary blood flow abnormalities during shortening. Most other studies of volume overload produced by an arteriovenous fistula found relatively normal coronary blood flow,[38–40] although in one study,[41] blood flow reserve was decreased. It should be emphasized, however, that the pathophysiological states represented above are states of combined pressure and volume overload in which the additional volume is ejected into the high pressure of the aorta.[10,42] Conversely, in mitral regurgitation, the additional volume pumped by the left ventricle is expelled into the low-pressure left atrium, and thus, mitral regurgitation represents low-pressure ("pure") volume overload.[10] We are aware of only one study that has examined coronary blood flow in mitral regurgitation, and that study did find a modest reduction in coronary blood flow reserve with the use of brief coronary artery occlusion in the anesthetized state during cardiac surgery. In our study in the closed-chest conscious state with adenosine, we found no difference between maximum coronary blood flow in control dogs and in mitral regurgitation dogs. The differences between these studies may reflect the method used to measure coronary reserve and the state of the subjects at the time of experimentation.

Previous studies suggested that the degree of abnormality in coronary blood flow is related to the amount of hypertrophy present.[43] In this regard, it is not surprising that no serious abnormality in coronary blood flow during rest or during pacing was observed in our animals with mitral regurgitation because only a 30% increase in cardiac mass was observed compared with 75–100% cardiac hypertro-

TABLE 5. Coronary Blood Flow: Second Group (Closed-Chest Dogs)

	Baseline		Pacing (240 beats/min)		Adenosine	
	Control	MR_3	Control	MR_3	Control	MR_3
ENDO CBF ml/min/g	1.4±0.12	0.94±0.10	1.95±0.22*	1.74±0.23*	4.3±0.62*†	4.32±0.30*†
EPI CBF ml/min/g	1.03±0.10	0.82±0.06	1.62±0.17*	1.64±0.29*	5.32±0.38*†	4.2±0.24*†
ENDO/EPI	1.39±0.11	1.15±0.05	1.23±0.07	1.09±0.05	0.81±0.09	1.03±0.02
RPP	15.2±2.48	10.7±0.49	32.1±5.8*	25.5±1.6*	13.6±2.4†	11.0±1.0†

Values are mean±SEM.

MR_3, 3 months of mitral regurgitation; ENDO CBF, endocardial coronary blood flow; EPI CBF, epicardial coronary blood flow; RPP, rate–pressure product.

*$p<0.05$ vs. baseline; †$p<0.05$ vs. pacing.

phy present in pressure overload models. Although more severe hypertrophy in mitral regurgitation may be associated with coronary blood flow abnormalities, this point is not germane to the current study. A contractile abnormality was present in this study, and this abnormality was not explained by abnormalities in coronary blood flow.

Limitations

In the examination of contractile function, we defined the end-systolic afterload–volume relation with definable and reproducible markers of both end-systolic pressure (from which end-systolic stress was calculated) and end-systolic volume. We recognize that neither the dicrotic notch nor the minimum volume may actually represent end systole, especially in mitral regurgitation. However, our definitions of dicrotic notch stress and end-ejection volume would have matched higher stress (higher than present at minimum volume) with a volume lower than true end systole during mitral regurgitation than in the baseline state. This would have tended to increase the slope of the EESVR, making the presence of contractile dysfunction harder to prove.

Last, if our method of creating mitral regurgitation caused acute damage to the ventricle, contractile dysfunction unrelated to coronary blood flow could have occurred. However, we have demonstrated that the contractile dysfunction that occurs with this model is not acute but rather develops chronically, probably as the hypertrophic process develops.[10]

Conclusion

Chronic volume overload produced by our model of mitral regurgitation produces contractile dysfunction. This contractile dysfunction was present when coronary blood flow was normal. Stress did not produce abnormalities in endocardial or epicardial blood flow nor in segmental endocardial or epicardial shortening. Thus, it is extremely unlikely that abnormalities in coronary blood flow were responsible for the contractile dysfunction we observed.

Appendix: Derivation of the Constant of End-Systolic Stiffness*

Strain is defined as the deformation of a material caused by application of a force. It is usually expressed in relation to an unstressed dimension, $\ln(l/l_0)$, or area $\ln(A/A_0)$ and is a dimensionless property. We make the assumption that the myocardium is incompressible.[44,45] As such, it has a constant volume equal to its area (A) multiplied by its thickness (H). Thus, changes in area are reflected by changes in thickness. As noted above, areal strain is defined as $\ln(A/A_0)$. Assuming that the myocardium is incompressible, $\ln(A/A_0)$ can be substituted for by $\ln(1/H/1/H_0)$ or $\ln(H_0/H)$. Myocardial stiffness is described mathematically as the change in stress ($d\sigma$) divided by the change in strain ($d\epsilon$) $-d\sigma/d\epsilon$. By altering stress (σ), one alters strain, thereby deriving the σ–$d\sigma/d\epsilon$ relation (myocardial stiffness), which should reflect contractile state. Because the slope of the σ–$d\sigma/d\epsilon$ relation is defined by increments in σ and $d\sigma/d\epsilon$, extrapolation to zero strain to define the slope is unnecessary. This allows our second central assumption, that $\ln(H_0/H)$ can be substituted by $\ln(1/H)$ as the expression of strain in our stress–strain relation. The stress–strain relation is curvilinear[12] and is expressed as $\sigma = Ce^{k\ln(1/H)}$, where σ is stress, c is a constant, and k is the exponential constant. The constant k reflects myocardial stiffness, k_{SM}, and thus, reflects the inotropic state.

Theoretical Background

The σ–$\ln(1/H)$ relation is based on previous studies calculating regional work of the ventricle.[46–50]

Calculation of Regional Work

The mechanical work done by a region of interest of the ventricular wall is the area under the tension–area curve given by the formula

$$RW = -\int T da \qquad (1)$$

where RW is regional work, T is the isotropic wall tension, A is the area of a regional midwall layer of the ventricle, and the integral is obtained during a cardiac cycle. Tension is pressure (P) multiplied by radius (r); thus, tension multiplied by area is $(P\times r)\times r^2 = P\times r^3$ (r^3 has the same units as volume) $\approx P\times V$, which is the more familiar expression of stroke work. The accuracy of regional work calculated by this method was validated by Goto et al[51] in the excised cross-circulated heart with a volume servopump system.

In an ellipsoid model of the left ventricle, tension calculated at the equator is defined as

$$T = 1/2(T_\theta + T_\phi) \qquad (2)$$

where T is tension, T_θ and T_ϕ are the circumferential and meridional components, respectively, of wall tension at the equator. A relation between T_θ and T_ϕ is given by Laplace's law:

$$P = \frac{T_\theta}{r} + \frac{T_\phi}{R} \qquad (3)$$

where r and R are the minor and major radii of curvature, respectively, of the endocardial surface, and P is ventricular pressure. The equilibrium of the forces at the equator in the direction of the long axis yields

$$T_\phi = \frac{rP}{2} \qquad (4)$$

*Condensed from Nakano et al.[12]

From Equations 3 and 4

$$T_\theta = r\left(P - \frac{T_\phi}{R}\right) = \left(1 - \frac{r}{2R}\right)Pr \qquad (5)$$

where a is the major radius, and b is the minor radius; r=b and $R=a^2/b$. Thus,

$$T_\phi = \frac{bP}{2} \qquad (6)$$

Substituting for r and R in Equation 5,

$$T_\theta = \left(1 - \frac{b^2}{2a^2}\right)bP \qquad (7)$$

Therefore, T is expressed as[13]

$$T = \frac{T_\theta + T_\phi}{2} = \frac{1}{2}\left(\frac{bP}{2} + \left[1 - \frac{b^2}{2a^2}\right]bP\right) = \frac{Pb}{2}\left(\frac{3}{2} - \frac{b^2}{2a^2}\right) \qquad (8)$$

Because T is isotropic in the plane perpendicular to radius, it takes the same value for every direction perpendicular to a radius through a point in the ventricular wall.

Normalization of Regional Work to a Unit Volume of Myocardium

Because larger areas of interest of the myocardium can produce more work than smaller areas of interest, it is necessary to normalize regional work to a unit volume of myocardium to compare areas of interest.[47,48]

Given an imaginary section of myocardium that has a volume Vm, Vm equals the product of area (A) and wall thickness (H), measured along a straight line perpendicular to the epicardial surface and passing through a selected point of the section:

$$Vm = A \times H \qquad (9)$$

Because the myocardium is incompressible, Vm is constant. If examination of regional work (RW) per unit volume (Vm) of myocardium (RWM) is desired, RW is divided by Vm (RW/Vm), which results in RW/AH. Thus, RWM=RW/AH. Recall Equation 1 $RW = -\int T dA$. Thus,

$$RWM = \left(-\int T dA\right)/AH$$

$$= -\int (T/H)(dA/A)$$

$$= -\int (T/H)(d\ln A) \qquad (10)$$

Tension (T) divided by thickness (H) is equal to wall stress (σ). Thus,

$$RWM = -\int \sigma d\ln A \qquad (11)$$

This equation describes the area surrounded by the σ–lnA loop. The formula for calculating stress (σ) is derived by dividing tension (equation 8) by thickness:

$$\sigma = \frac{Pb}{2}\left(\frac{3}{2} - \frac{b^2}{2a^2}\right)/H \times 1{,}332 \text{ dynes/cm}^2 \qquad (12)$$

Meaning of lnA and Definition of Area Strain

The change in lnA(dlnA), or dA/A, in the σ–lnA relation expresses a relative change in area (incremental area strain). Total area strain (ϵ_t) is given by

$$\epsilon_t = \int_{A_0}^{A} dA/A = \ln A - \ln A_0 = \ln(A/A_0)$$

where A_0 is the area corresponding to a state of zero stress. Definition of unstressed area (A_0) is required to obtain the complete stress–strain relation extrapolated to the x axis. However, A_0 is not required in the analysis of the stiffness–stress ($d\sigma/d\epsilon$–σ) relation. As noted above, myocardial stiffness is defined as the change in stress ($d\sigma$) divided by the change in strain $d\epsilon$–$d\sigma/d\epsilon$. This relation only examines incremental changes in stress and strain to define its slope. Thus, extrapolation to A_0 is unnecessary. Therefore, stiffness ($d\sigma/d\epsilon$) is identical with either definition of strain: lnA or $\ln(A/A_0)$. Thus, A_0 can be omitted, and area strain is defined as

$$\epsilon = \ln A \qquad (13)$$

Use of Reciprocal Wall Thickness Instead of Area

Unfortunately, changes in a regional area of interest of the myocardium are difficult to measure. Conversely, wall thickness and changes in wall thickness are easy to measure by conventional echocardiographic or cineangiographic methods. Thus, substitution of thickness (H) for area (A), if possible, would increase the applicability of the method. The following explains how wall thickness can be substituted for area in strain analysis. The myocardium is incompressible.[44,45] Thus, the volume of the region of interest (Vm) is constant, even though A and H vary throughout the cardiac cycle. From Equation 9, A=Vm/H, then

$$\ln A = \ln(Vm/H) = \ln Vm + \ln(1/H)$$

Because Vm is constant, $d(\ln A) = d\ln(1/H)$. Thus, one can substitute ln(1/H) for lnA because ln(1/H) represents strain in the stress–strain relation.

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