Changes in Diastolic Stiffness and Tone of the Left Ventricle During Angina Pectoris

By William H. Barry, M.D., Jeff Z. Brooker, M.D., Edwin L. Alderman, M.D., and Donald C. Harrison, M.D.

SUMMARY
Reported elevations of left ventricular filling pressures during angina suggest increased myocardial stiffness. Both left ventricular beginning- and end-diastolic pressures and volumes were measured in seven patients before, during, and after angina induced by atrial pacing. During nine episodes of angina, mean end-diastolic pressure rose from 12 to 29 mm Hg and ejection fraction fell from 0.47 to 0.37. Logarithms of beginning and end-diastolic pressures were plotted against the corresponding volumes for each angiogram. During angina, there was a marked increase in beginning as well as end-diastolic stiffness of the ventricle. These changes, which were reversible with resolution of angina, may be due to sustained contraction or failure of relaxation of a portion of the left ventricular myocardium during angina pectoris.

Additional Indexing Words:
- Diastolic pressure
- Left ventricular pressure-volume ratio
- Left ventricular compliance
- Myocardial tension

Myocardial function
- Ischemic heart disease
- Coronary artery disease
- Hemodynamic effects of angina

FILLING Pressures of the left ventricle may rise abruptly during angina pectoris induced by exercise or atrial pacing. There has been speculation as to whether this phenomenon is due to an increase in diastolic volume resulting from classical "heart failure," or whether it is due to a change in ventricular compliance during ischemia. In support of the heart failure theory, it has been shown that ventricular ejection fraction decreases during angina. On the other hand, Dwyer demonstrated that the ratio of end-diastolic pressure to end-diastolic volume increased during angina, suggesting a major increase in the end-diastolic stiffness of the ventricle. These findings imply that increases in diastolic pressures during angina may be due both to increases in diastolic volumes and an increase in ventricular stiffness. Measurement of a single pressure-volume ratio, however, does not adequately define the diastolic pressure-volume relationship of the ventricle, and it is not possible to separate these mechanisms adequately from the results of prior studies.

Studies of myocardial stiffness utilizing both isolated muscle strips and intact canine ventricle preparations have been performed. Data from these studies indicate that both static (elastic) and dynamic (elastic + viscous + inertial) myocardial stiffness are linearly related to myocardial stress, or intraventricular pressure. Thus, in theory, it is possible to study these factors in patients who have transient ischemia. The results of our observations in nine patients are presented.

Theory
Both the static and dynamic stiffness coefficient appear to be essentially unchanged throughout the cardiac cycle. Thus, for the intact ventricle, \( \frac{dP}{dV} = kP + C \), where \( P \) = left ventricular pressure, \( V \) = left ventricular volume, \( \frac{dP}{dV} \) is ventricular stiffness, \( k \) the stiffness coefficient, and \( C \) the \( \frac{dP}{dV} \) at 0 pressure. \( C \) is small and has been assumed to be negligible at physiological filling pressures and volumes. Thus, \( \frac{dP}{dV} = kP \).
rearranging gives $\frac{dP}{P} = kdV$; and integration yields $P = kv + b$, where $b$ is a constant of integration.

According to Gaasch et al.,7 the diastolic pressure-volume relationship for the left ventricle therefore may be represented as a straight line on a plot of $\log P$ against $V$, with a slope $k$ and a $\log P$ intercept $b$. A minimum of two points of pressure and volume would then be necessary to define these constants. However, there are no data available which show that the diastolic log $P$-$V$ relationship in the diseased human heart is linear. Dodge et al.12 have presented simultaneous diastolic pressure-volume data obtained from patients with rheumatic heart disease. Analysis of these data shows that the diastolic log $P$-$V$ relationship can be reasonably well fitted by a straight line in seven of nine patients, whereas in two of nine the relationship was quite curvilinear. There are no such data on patients with ischemic heart disease. It is likely that during the usual rates of ventricular filling, $k$ is determined primarily by elastic elements, with only minimal influences by viscous and inertial components.13 The critical frequency range14 for the human ventricle is important in these observations but again, this has not yet been defined, nor has the value of $C$.

We have determined beginning- and end-diastolic pressures and volumes in patients with coronary artery disease before, during, and after recovery from angina induced by atrial pacing. We have assumed that the diastolic compliance of the left ventricle in patients with coronary artery disease may be represented as a first order approximation by a linear plot of $\log P$ versus $V$, and thus determined by two log $P$-$V$ points. From these data the effects of angina on values of $k$ and $b$ were calculated. The results indicate that a major effect of myocardial ischemia accompanying angina pectoris is to shift the diastolic log pressure-volume relationship of the left ventricle upward, in this analysis apparent as an increase in $b$. We believe that these findings suggest that there is a marked increase in left ventricular diastolic "tone" during angina, possibly due to sustained contraction of a portion of ischemic myocardium.

Methods

Patient Selection

Nine patients were selected from those scheduled for cardiac catheterization, left ventricular angiography, and coronary arteriography as part of a diagnostic evaluation for suspected coronary artery disease. Patients with a history of significant hypertension or evidence of valvular heart disease, marked cardiomegaly, or left ventricular aneurysm were excluded. Informed consent was obtained for the procedure in all cases. The catheterization and left ventricular angiography were performed as one procedure, and the coronary arteriography was performed on the subsequent day.

Hemodynamic Measurements

Cardiac catheterization was performed with patients in a fasting state, with 100 mg of oral secobarbital as premedication. A Courmand wedge catheter was inserted into the pulmonary artery via the right brachial vein, and a No. 6 bipolar pacing catheter was inserted via a sheath in the left femoral vein, with the tip positioned against the right atrial wall. A 6.7 French pigtail angiocatheter (Cook) was inserted in the left femoral artery percutaneously, using the Seldinger technique. Pressures were recorded through the fluid-filled angiocatheter connected with either a Statham P23Db transducer, or a Micron MP15 pressure transducer. The Statham pressures were electronically filtered at 12 Hz; the pressures recorded using the Micron system were hydraulically filtered with a tuned connecting system which gave a linear amplitude response to 15 Hz. Cardiac output determinations were made from dye curves obtained by injecting indocyanine green (Cardio-Green) dye in the pulmonary artery and sampling from the left ventricle.

Left Ventricular Angiograms and Volume Determinations

Phased injections of 8–12 cc of ditrizoate meglumine (Renografin 76) were made through the angiocatheter using an "R" wave triggered ENSCO injector. Injections were timed to occur 0.10 sec after the "R" wave and were completed in 0.5 sec using 750 lb/sq in pressure. These injections rarely caused ventricular premature contractions, probably because the initial portion of the injection occurred during the refractory period of the ventricle. The ventricle was adequately opacified for a single cardiac cycle from the end-diastole which followed the injection, through the succeeding systole. The "single cycle" angiogram was recorded and stored on a 15 frame/sec video disc, and subsequently displayed on a TV monitor. The end-diastolic and beginning-diastolic (end-systolic) chamber outlines were traced with a light-pen and volumes calculated on-line by a digital computer using the area-length method. Angiograms were performed in PA or shallow right anterior oblique (RAO) projections, and the position was kept constant in each individual patient during the procedure. Distances of the heart from the anterior chest wall were determined echographically, and corrections made for magnification due to nonparallel X-ray beams and applied to calculations of ventricular volumes.16 This video system has been found to give accuracy and reproducibility equal to conventional single-plane cine volume angiograms.16 An important advantage for this study was that this technique permitted multiple angiograms in close time sequence with minimal hemodynamic alteration caused by the injection of contrast material.

Experimental Procedure

After placement of catheters, an indicator dye dilution cardiac output was performed at the resting heart rate. The LV pressure was then recorded at high and low gain during quiet respiration. Immediately after recording pressures, the angiocatheter was filled with contrast and a single-cycle angiogram performed. The catheter was flushed with dextrose and water and pressures recorded within 15–30 sec after the angiogram. The heart rate was then increased by atrial

Circulation, Volume XLIX, February 1974
pacing at 20 beats/min above the resting heart rate, and after one minute the sequence of pressure measurement, left ventricular angiogram, pressure measurement repeated. Angina was then induced by rapid atrial pacing at a rate of 130–150 beats per minute. When definite angina was produced, pacing was abruptly stopped, with immediate return of heart rate to control. Withing one minute, the sequence of pressure measurement, angiogram, pressure measurement was repeated at a time when the patient still experienced angina and ST segment depression was still present. Following recovery from angina, rapid atrial pacing was then performed again to give the same level of intensity of angina, and the rate of pacing abruptly decreased to 20 beats/min above the resting heart rate, and the measurement sequence repeated. The pacing was then stopped and another indicator dilution output was performed during angina. After recovery from angina, which was complete within 5 to 15 minutes, as judged by absence of pain and return of hemodynamic parameters to control values, pressures and volumes were determined again at resting heart rate and while pacing at 20 beats/min above the resting heart rate. Thus, pressure-volume data were obtained before, during, and after recovery from angina at comparable heart rates. In some patients, mild angina occurred while pacing at 20 beats/min above the resting rate. In these patients, only resting heart rate measurements were performed.

Analysis of Data

After each study, single-beat angiograms stored on the video disc were analyzed for beginning- and end-diastolic volumes. The end-diastolic frame was marked by a radiopaque mechanical event marker (Electronics for Medicine), triggered by the "R" wave of the electrocardiogram which was positioned in the radiographic field at the time of the angiogram. The beginning-diastolic (end-systolic) frame was identified visually as the smallest ventricular volume. Each end-diastolic and beginning-diastolic ventricular outline was traced three times, and the average value of these tracings taken as the ventricular volume. The ejection fraction was calculated from these volumes.

Left ventricular beginning- and end-diastolic and peak systolic pressures were measured and averaged over two respiratory cycles. Beginning-diastolic pressure was taken as the nadir of the diastolic pressure in early diastole, and end-diastolic as the inflection point on the pressure curve after the "A" wave. It should be noted that beginning-diastolic pressure defined in this way does not correspond exactly to beginning-diastolic volume defined by the smallest ventricular volume. This is because the ventricular volume increases a small amount while the ventricular pressure continues to fall after opening of the mitral valve. For pressure volume analysis, the pressures recorded immediately prior to the angiogram were used. No angiograms were accepted if extrasystoles were produced by the injection. All patients were in sinus rhythm during these studies.

The data were statistically analyzed with a paired t-test, each patient serving as his own control.

Results

Of the nine patients studied, seven had marked rises in end-diastolic pressure during the immediate post-pacing period following the onset of angina pectoris. These seven patients all had severe multivessel coronary disease, with greater than 80% stenotic lesions demonstrated angiographically. Treadmill exercise tests were done in six of these seven patients, and all showed ischemic ST depression. Nine technically satisfactory sequences of data were obtained before, during, and after recovery from angina in these seven patients. These data are listed in table 1.

Hemodynamic Effects of Angina

The hemodynamic consequences of angina have been well documented in recent literature1, 2, 4 and were also observed in this group of patients. There was a 140% increase in end-diastolic pressure, from 12 to 29 mm Hg, a 13% increase in peak systolic pressure, and a 21% decrease in ejection fraction with no significant change in cardiac output. The average ejection fraction in this group of patients was well below normal, indicating the severe degree of coronary artery disease as documented by coronary arteriography.

Effects of Angina on Pressure–Volume Relationship

An example of the striking effect of angina on pressure-volume relationship is shown in figures 1 and 2. In this patient, the onset of angina was associated with a marked rise in end- and beginning-diastolic pressures (fig. 1), associated with an increase in beginning and end-diastolic volumes and a decreased ejection fraction. The result of these changes on the log pressure-volume relationship is shown as an upward displacement of the b intercept and a slight decrease in k (fig. 2). The data for all seven patients who developed a rise in end-diastolic pressure with angina are shown graphically in figures 3 and 4. These changes were highly reversible with resolution of angina.

Accuracy of Volume Measurements

With angiographic determination of beginning-diastolic volumes, there is a tendency to underestimate the ventricular volume because of inadequate opacification of intertrabecular spaces by contrast material.7 This distortion might be expected to be even greater using small volumes of contrast material, as was done in this particular study. This would lead to overestimation of the stroke volume and ejection fraction. This probably accounts for the fact that the cardiac outputs determined from
Changes in Hemodynamic Parameters During Angina

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Heart rate (beats/min)</th>
<th>EDP (mm Hg)</th>
<th>BDP (mm Hg)</th>
<th>EDV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BA A RFA</td>
<td>BA A RFA</td>
<td>BA A RFA</td>
<td>BA A</td>
</tr>
<tr>
<td>C.T.</td>
<td>62/M</td>
<td>74 79 81</td>
<td>14 22 18</td>
<td>8 14 10</td>
<td>128 126</td>
</tr>
<tr>
<td>H.K.</td>
<td>58/M</td>
<td>94 102 100</td>
<td>11 25 10</td>
<td>8 20 8</td>
<td>303 329</td>
</tr>
<tr>
<td>J.T.</td>
<td>49/M</td>
<td>68 70 69</td>
<td>12 24 5</td>
<td>5 14 2</td>
<td>195 222</td>
</tr>
<tr>
<td>V.K.</td>
<td>61/F</td>
<td>86 95 85</td>
<td>8 24 7</td>
<td>2 10 2</td>
<td>69 70</td>
</tr>
<tr>
<td>E.M.</td>
<td>59/F</td>
<td>65 81 68</td>
<td>11 37 15</td>
<td>7 31 8</td>
<td>173 187</td>
</tr>
<tr>
<td>K.H.</td>
<td>52/M</td>
<td>60 85 81</td>
<td>17 36 13</td>
<td>8 24 6</td>
<td>296 302</td>
</tr>
<tr>
<td>M.W.</td>
<td>58/M</td>
<td>65 68 71</td>
<td>8 31 6</td>
<td>4 21 3</td>
<td>170 165</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>76 85 82</td>
<td>12.2 29.3 10.4</td>
<td>6.3 19.6 5.4</td>
<td>198 208</td>
</tr>
<tr>
<td>± SEM</td>
<td>± 4</td>
<td>± 4</td>
<td>± 1.4</td>
<td>± 1.9</td>
<td>± 0.8</td>
</tr>
</tbody>
</table>

Abbreviations: EDP = end-diastolic pressure; BDP = beginning-diastolic pressure; EDV = end-diastolic volume; BDV = beginning-diastolic volume; BA = before angina; A = during angina; RFA = recovery from angina.

*Pacing at approximately 20/min above resting heart rate.
†P < 0.05; †P < 0.01. (Paired t-test, BA vs. A)

the product of the angiographic stroke volume and the heart rate were, on the whole, higher than those determined in seven patients by dye dilution methods, by 0.45 ± 0.40 L/min. Figure 5 shows the relationship of angiographic stroke volume with stroke volume determined from an indicator dilution cardiac output at the same heart rate in a group of patients with coronary artery disease, including those described in this report. Difficulties in determination of absolute values of ventricular volume are always present in angiographic studies. This is particularly true in patients with coronary artery disease, where assumptions of geometric symmetry are probably in error. However, our main purpose was to determine relative changes in volume occurring in each individual patient during angina, rather than to compare absolute volumes in one patient with another.

Records demonstrating changes in left ventricular pressure and an ECG tracing of a patient before angina, during angina and after recovery from angina. Angina in this patient was produced by a brief period of atrial pacing at 140/min, and the heart rate maintained at approximately 95/min during pressure recording. The beginning- and end-diastolic pressure (BDP and EDP, respectively) and corresponding ventricular volumes (BDV and EDV respectively), are noted below each condition.

Circulation, Volume XLIX, February 1974
Effect of Contrast Material on Pressure-Volume Relationship

The possible effects of the small amount of contrast material used in each angiogram was of concern because of the documented effects of contrast material on ventricular function. The averages of end-diastolic pressure before and immediately after the angiograms were performed in these studies are shown in figure 6. These data, plus the results of four sequences in two patients who had no sustained end-diastolic pressure elevation at the time of angina, suggest that the effects of contrast in these patients were small.

Discussion

Possible Mechanisms of Changes in Ventricular Stiffness

Our results show that during angina in some patients there is a marked increase in beginning-diastolic stiffness as well as end-diastolic stiffness. This is manifest by an increase in b, or an upward displacement of the entire diastolic P-V curve. That
the increase in beginning diastolic stiffness may be more marked than end-diastolic stiffness is indicated by a decrease in the slope k, although without proof that the log P-V relationship is linear this is difficult to interpret. Regardless of the true shape of the diastolic log P-V relationship, it seems likely that it is displaced upward during angina. Of primary concern, then, is what this change could represent physiologically.

When log tension is plotted against length for a cat papillary muscle at rest and during contraction (fig. 7), it is demonstrated that during contraction there is an increase in b and a decrease in k relative to the resting plot. The resting log tension-length plot of the isolated muscle is analogous to the diastolic log pressure-volume plot of an intact ventricle. Thus, our data may be interpreted as indicating a sustained contraction, or a failure of relaxation, of a portion of the left ventricular myocardium during angina pectoris.

That ventricular diastolic tone varies due to changes in sustained tension generation by myofilaments has been considered by a number of
investigators. The general consensus has been as stated by Meeks in 1927: "Convincing experimental evidence has not yet been presented that the tone of the mammalian ventricle is capable of changing under conditions that may be considered physiological." Indeed, it is only under extreme, unphysiological conditions that hypoxia may induce contracture in certain isolated cardiac and vascular smooth muscle preparations. However, Cooley has recently brought attention to the phenomenon of "ischemic contracture" of the human heart which occurs rarely following cardiopulmonary bypass surgical procedures. A similar phenomenon has been noted in the canine heart. It is possible that during myocardial ischemia and hypoxia associated with angina, a similar "contracture" or failure of relaxation occurs in the affected segment of myocardium. Such a local contracture might account for local hypokinesis of left ventricular wall which has been described during angina; such a wall segment would be expected to expand less in diastole and contract less in systole. In addition, the findings reported by Zaret and Masri of a decrease in myocardial blood flow to an ischemic area during angina may also be due to a local contracture: increased intramyocardial wall pressure during contracture would be expected to reduce blood flow by compression of small penetrating arteries.

The mechanism whereby ischemia or hypoxia produces myocardial contracture is not well defined. Katz has suggested that the response of a muscle to ischemia-hypoxia might depend on the intracellular levels of adenosine triphosphate (ATP) present during hypoxia. In a setting of chronic ischemia with depleted ATP stores, an acute ischemic insult may result in contracture, or failure of relaxation. This could explain why patients with severe coronary artery disease and chronically ischemic portions of myocardium might develop segmental myocardial contracture during acute relative ischemia induced by rises in myocardial oxygen demand. However, if acute ischemia occurs in a muscle with normal ATP stores, a failure of contraction is proposed to result. Thus, during angina or myocardial infarction, the effect of acute ischemia on the myocardium might be expected to involve both of these responses, in varying degrees.

The average values obtained in our study for the stiffness coefficient k in patients with coronary artery disease agree closely with those obtained by a different method by Diamond and Forrester. Relative to normal values, the stiffness coefficient has been found to be decreased in dogs after experimental acute infarction, and with acute hypoxia. It is increased in patients with coronary artery disease, in the recovery stages of myocardial infarction, and in dogs with healed myocardial infarction. The acute and chronic changes in the left ventricular stiffness coefficient may be due to such factors as anatomic disruption of myofibrils, cellular infiltration and tissue edema, and myocardial fibrosis. From our data, however, it seems that during angina reversible changes in k are more important than changes in k in affecting filling pressures. It is important to note that ventricular stiffness, dP/dV, is defined as k × P. During angina, although changes in k are apparently minor, the large increase in P, due possibly to active generation of tension by contracted fibers, results in a net increase in diastolic stiffness.

Effect of Stiffness Change on Ventricular Function

Parker et al. have shown that during angina the ventricle performs less stroke work for a given
diastolic filling pressure. This results in a depressed ventricular function curve, which has been attributed to a decrease in ventricular contractility. However, the stroke work performed for a given end-diastolic fiber length, or end-diastolic volume, gives a more precise characterization of ventricular contractility. As Sarnoff and Berglund have observed, if a change in compliance occurs during an intervention, relating stroke work to end-diastolic pressure rather than end-diastolic volume may give misleading indications of the effect of that intervention on ventricular contractility.

These observations are relevant to assessment of ventricular function in patients with coronary artery disease. Since diastolic stiffness increases during angina, the depression of ventricular function, stroke work/EDP, which has been observed is due to an increase in stiffness of the ventricle, as well as a probable decrease in ventricular contractility, (stroke work/EDV). The relative importance of these factors needs further study.

**Technical Considerations**

Studies of pressure-volume relationships in the intact human ventricle are difficult to perform, and a number of technical problems still exist which we have not altogether adequately solved.

First, improvement in accuracy of ventricular volume determination can hopefully be obtained by the use of more efficient image-intensification, and higher speed video disc capability, because the use of larger volumes of contrast material for studies such as this is not possible. Biplane systems may be of considerable help in studying patients with asymmetrically contracting ventricles, as are found in coronary heart disease.

Second, more accurate simultaneous pressure measurements are required. The initial diastolic pressure is difficult to measure accurately with fluid-filled catheters if any resonance in the system is present. Another difficulty with using early diastolic pressures to determine compliance is that delayed relaxation of myocardial segments may affect this portion of diastole, particularly after recovery from angina, resulting in a nonlinear diastolic log P-V relationship. Multiple pressure-volume measurements in diastole would permit better definition of this phenomenon. Manometer-tipped angiocatheters will make it possible to overcome these difficulties.

Recognizing the importance of these factors, we present these data as an initial study in a difficult area. From our data it seems clear that compliance alterations during angina affect both beginning- and end-diastole. Future studies will hopefully demonstrate more subtle changes in the entire diastolic log P-V relationship, as well as define mechanisms whereby changes in ventricular stiffness can be related to insufficient coronary blood flow.

**Conclusions**

This study indicates that in patients with angina, elevated filling pressures may reflect an increase in diastolic “tone” possibly due to contraction of a portion of ventricular myocardium, as well as classical “heart failure” with increased diastolic volumes and secondarily elevated filling pressures.

Elucidation of the mechanisms of left ventricular dysfunction induced by myocardial ischemia has become more important with the development of techniques for coronary artery surgery. Such mechanisms need to be understood if adequate preoperative evaluation and postoperative assessment of surgical results are to be made. Swan et al. have observed that stiffness coefficient, k, of the ventricle may vary in disease states, producing significant hemodynamic consequences. Our results suggest that, in addition, significant changes in diastolic tone occur in heart disease. These distinctions may have important ramifications regarding therapy and need to be better defined.

**References**


*Circulation, Volume XLIX, February 1974*
LV DIASTOLIC STIFFNESS & TONE IN ANGINA

17. Davilla JC, Sanmarco ME: An analysis of the fit of mathematical models applicable to the measurement of left ventricular volume. Am J Cardiol 18: 31, 1966
Changes in Diastolic Stiffness and Tone of the Left Ventricle During Angina Pectoris
WILLIAM H. BARRY, JEFF Z. BROOKER, EDWIN L. ALDERMAN and DONALD C. HARRISON

_Circulation_. 1974;49:255-263
doi: 10.1161/01.CIR.49.2.255

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/49/2/255

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at: http://circ.ahajournals.org//subscriptions/