Increased Regional Myocardial Stiffness of the Left Ventricle During Pacing-induced Angina in Man

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SUMMARY The left ventricular diastolic pressure-volume relationship shifts upward during angina, but why this happens is not known. To assess regional myocardial stiffness, we studied 12 patients who had coronary artery disease using simultaneous left ventricular micromanometer pressure recording and M-mode echocardiography before and during angina induced by pacing tachycardia. All patients had two- or three-vessel coronary artery disease that involved the posterior left ventricular wall circulation and had positive pacing stress tests, i.e., development of angina and a post-pacing rise in left ventricular end-diastolic pressure (15 ± 3 to 31 ± 6 mm Hg, \( p < 0.001 \)). A marked upward shift in the relationship between the diastolic left ventricular pressure and the posterior wall thickness (h) occurred after pacing tachycardia, but the change in left ventricular posterior wall end-diastolic thickness was minimal (8.9 ± 2.1 to 9.2 ± 2.1 mm, NS). After pacing, the peak rate of left ventricular posterior wall thinning decreased (82 ± 37 to 48 ± 27 mm/sec, \( p < 0.005 \)) and the time constant of relaxation derived from the best exponential fit to the isovolumic left ventricular pressure decay increased (49 ± 5 to 58 ± 7 msec, \( p < 0.001 \)). Diastolic active left ventricular pressure decay, extrapolated from the exponential fit, was subtracted from the measured left ventricular pressure (which is equal in magnitude but opposite in sign to the radial stress at the endocardium) to calculate residual left ventricular pressure (\( P_R \)) and hence residual stress (\( \sigma_R = -P_R \)). A radial stiffness modulus (\( E_R \)) was determined by the slope of the \( P_R \) vs log h plots before and after pacing. Over the same range of residual radial stress (\( \sigma_R \)), \( E_R \) was always higher during pacing-induced angina, indicating increased residual myocardial stiffness. Increased myocardial stiffness in addition to a decreased rate of wall thinning and slow active pressure decay contribute to the upward shift in left ventricular pressure-wall thickness and pressure-volume relationships during pacing-induced angina.

DURING pacing-induced angina in patients with coronary artery disease, the left ventricular pressure-volume relationships shift upward during diastole.1-6 The mechanisms by which these acute changes take place are not well understood and have been the subject of controversy.8, 9 Potential mechanisms include changes in the heart's geometry,10-12 persistent interaction of some contractile elements within the ischemic myocardium throughout diastole,13 interaction between the two ventricles,14 changes in intrapericardial pressure15, 9 and alterations in passive myocardial properties.14-18

The shifts in left ventricular diastolic pressure-volume relationships have been reproduced in dogs with coronary stenoses in the absence of the pericardium and at comparable right ventricular filling pressures.19, 20 Thus, a major role for either the pericardium or the right ventricle in causing these shifts seems unlikely. Also, recent evidence shows that in an isolated canine heart model, left ventricular diastolic pressures are significantly altered by changes in the right ventricle only at very high levels of right ventricular end-diastolic pressure.21

The effects of dyssynergistic contraction on diastolic pressure might be expected only during the early part of diastole, whereas the changes observed with pacing-induced angina last throughout diastole. Such dyssynergistic contraction would be likely to result in delayed relaxation and prolongation of the time constant of relaxation.22 This delayed relaxation could persist so as to constitute incomplete relaxation with persistent interaction of some contractile elements in the ischemic myocardium throughout diastole.13 The differentiation between slow or incomplete relaxation and alterations in "passive" myocardial properties is difficult both conceptually and in practice, because the "passive" properties are likely to depend to some extent on the underlying level of interaction between contractile elements.

We assessed regional diastolic properties of the left ventricular myocardium by examining the relationship between diastolic pressure and wall thickness during ventricular filling. We also attempted to assess regional myocardial stiffness by calculating a radial stiffness-stress relationship for the ischemic segment.

Methods

Twelve patients (ages 34–63 years, mean 51 years) undergoing diagnostic cardiac catheterization for in-
vestigation of coronary artery disease were studied. Patients with overt congestive failure, left main coronary artery disease or unstable angina were excluded from the study. All patients gave informed consent to participate in the study, and no complication occurred as a result of the study.

After routine diagnostic cardiac catheterization, including left ventriculography and coronary arteriography, a pacing stress test was performed. Systemic arterial pressure was measured with a fluid-filled catheter system and strain-gauge transducers and referenced to atmosphere at the midchest level. Left ventricular pressure was recorded with a micromanometer-tip catheter (Millar Instruments) calibrated externally against a mercury reference and matched simultaneously against luminal pressure. The paper speed was 100 mm/sec. The first derivative of the left ventricular pressure recording (dP/dt) was derived from the high-fidelity pressure signal by electronic differentiation. A pacing catheter was advanced to the apex of the right ventricle for right ventricular pacing to ensure capture and to avoid the problem of Wenckebach atioventricular block at faster heart rates.

Echocardiography was performed using a phased-array 80\(^\circ\) sector scanner (Irex) with a 2.25-MHz transducer. The transducer was placed in the third or fourth interspace at the left sternal edge and a short-axis view of the left ventricle at the level of the papillary muscles or mitral valve was obtained. The M-mode cursor was positioned centrally in the two-dimensional image and the derived M-mode image was recorded on photographic paper with a strip-chart recorder at a paper speed of 50 mm/sec. Synchronization markers were recorded simultaneously on both pressure recordings and echocardiographic recordings to facilitate subsequent matching of pressure and echocardiographic data. In four patients, satisfactory M-mode recordings could not be obtained using the two-dimensional transducer and a standard 2.25-MHz M-mode transducer was used instead.

After simultaneous pressure and echocardiographic baseline recordings were recorded, right ventricular pacing was commenced at 90 beats/min and increased by approximately 20 beats/min every 2 minutes until typical angina pectoris occurred. Pacing was continued for 60 seconds at the heart rate that provoked angina pectoris and then abruptly discontinued. Pressures and simultaneous echocardiograms were recorded immediately before cessation of pacing and for at least 1 minute after pacing, until left ventricular diastolic pressure had returned to the baseline level.

Data Analysis

M-mode echocardiograms were digitized throughout a cardiac cycle before pacing (control) and between 5 and 10 seconds after termination of pacing, using a sonic pen digitizer (Scientific Accessories Corporation) interfaced with a computer (Tektronix 4051) and magnetic disc storage file system (Tektronix 4097). Coordinates were recorded every 5 msec. For all 12 patients, the posterior wall endocardial and epicardial echoes were satisfactorily digitized and posterior wall thickness was computed every 5 msec throughout the cardiac cycle. A sixth-order polynomial was fitted to the posterior wall thickness-time data points from the time of peak thickness to give peak rates of left ventricular posterior wall thinning, as previously described. The percent thickening of the posterior wall was calculated from the formula:

\[
\text{ESh} = \frac{\text{EDh} - \text{EDh}}{\text{EDh}} \times 100
\]

where ESh = peak systolic thickness and EDh = end-diastolic thickness.

The left ventricular pressure trace was digitized from the time of peak negative dP/dt to the end of diastole for the same cardiac cycles for which the echocardiograms were analyzed before and after pacing. The left ventricular isovolumic relaxation period was assumed to be the period from peak negative dP/dt to the time at which left ventricular pressure fell to 5 mm Hg above left ventricular end-diastolic pressure (LVEDP). Using the method described by Weiss et al., a time constant of relaxation (T) was derived by computing a best exponential fit to the pressure data points during this isovolumic relaxation period:

\[
P_{e} = P_{o} e^{-\nu T}
\]

where \(P_{e}\) = left ventricular pressure (exponential fit pressure), \(P_{o}\) = left ventricular pressure at the time of peak negative dP/dt, and \(t =\) time (sec).

If the best exponential fit to the measured pressure data has a high correlation coefficient \((r > 0.99)\), the derived exponential curve can be considered to represent the exponential decay of active pressure. Since this correlation coefficient was always greater than 0.99 in this study, derivation of a time constant from a polynomial fit to the pressure data or from the slope of a plot of pressure against dP/dt was considered unnecessary.

Beginning with the nominal instant of mitral valve opening (5 mm Hg above LVEDP), the rate of decline of the pressure that is actually measured \((P_{m})\) is less than the rate given by the exponential fit \((P_{e})\). This relationship is explained by considering that in the filling ventricle the measured pressure \((P_{m})\) reflects not only the ongoing relaxation process, but also the simultaneous pressure increase associated with the filling of the chamber. A net “residual” diastolic filling pressure \((P_{r})\) may be defined as the difference between the measured pressure \((P_{m})\) and the value of the exponential relaxation pressure \((P_{e})\) that would apply if the ventricle continued to relax according to equation (2) above.

Evaluation of Radial Stiffness \((E_{r})\)

To assess myocardial properties as distinct from ventricular chamber properties, analysis of wall stress and strain is required. Measurement of circumferential and meridional stress requires assumptions of
TABLE 1. Clinical, Hemodynamic and Echocardiographic Data

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<th>Pt</th>
<th>Age (years)</th>
<th>LAD</th>
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<th>CX</th>
<th>RCA</th>
<th>LVSP (mm Hg)</th>
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Abbreviations: LAD = left anterior descending coronary artery; DIAG = diagonal branch of LAD; CX = circumflex or circumflex marginal; RCA = right coronary artery; LVSP = left ventricular systolic pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; PW = left ventricular posterior wall; T = time constant of relaxation; ER = radial stiffness modulus; LVEDP = left ventricular end-diastolic pressure.

symmetry or knowledge of radii of curvature, which cannot be readily ascertained in the regionally ischemic ventricle. However, radial stress and strain can be approximated for the ischemic segment if instantaneous pressure and wall thickness are known, for radial stress at the endocardium is equal in magnitude and opposite in sign to the intracavitary pressure, and the incremental radial strain (Δε_r) can be derived from the expression

\[ \Delta \varepsilon_r = \Delta h/h = \Delta \log h \]  

where \( h \) = left ventricular posterior wall thickness and \( \log h \) = natural logarithm of \( h \).

The computed "residual" pressure (P_r) can therefore be used as a measure of "residual" radial stress (σ_r) and a radial stiffness modulus (E_r) can be derived from the incremental "residual" radial stress (Δσ_r) and the incremental radial strain (Δε_r) relationship by the formula

\[ E_r = \Delta \sigma_r/\Delta \varepsilon_r = \Delta \sigma_r/(\Delta h/h) = \Delta \sigma_r/(\Delta \log h) = -\Delta P_r/(\Delta \log h). \]  

Because the effects of active relaxation after mitral valve opening are taken into account in this analysis, the radial stiffness modulus (E_r) is derived from data obtained during the entire diastolic filling period rather than from only the period of diastole after the time of minimum diastolic pressure. As a result, values of E_r may be compared at equivalent levels of "residual" radial stress (σ_r), even when LVEDPs are widely different, as is the case during pacing-induced angina.

Statistical Analysis

The statistical significance of differences between data before and after pacing (means ± sd) was calculated by t test from the paired data.

Results

All patients had two- or three-vessel coronary artery disease (table 1) and all experienced their typical angina pectoris during pacing tachycardia (range 130–160 beats/min, mean 142 beats/min). All patients had coronary artery disease that compromised the circulation to the posterior wall. All except one patient had total occlusion or greater than 80% diameter stenosis of the right coronary artery. The exceptional patient had a 40% stenosis of the right coronary artery and 60% stenosis of a large circumflex marginal branch. Ten patients had significant lesions (> 50%) in the circumflex system (main circumflex or circumflex marginal branches) in addition to severe right coronary artery lesions.

All patients had a postpacing rise in LVEDP (15 ± 3 mm Hg to 31 ± 6 mm Hg, p < 0.001). This increase was associated with a decrease in the peak rate of left ventricular posterior wall thinning in diastole and prolongation of the time constant of relaxation (table 1).

Control and postpacing M-mode echocardiograms and pressure tracings are shown in figure 1. Diastolic pressure was elevated throughout filling. The changes in posterior wall thickness during a single cycle before and during angina are shown in figure 2. During angina after pacing, there was a clear reduction in the rate of posterior wall thinning. There was also a reduction in the percent systolic thickening of the left ventricular posterior wall, and in 10 patients peak thickening occurred earlier in systole relative to the preceding QRS complex during angina than under control conditions.
TABLE 1. (Continued)

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<th>PW thinning (%)</th>
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(continued) Although systolic wall thickening was diminished, especially during the latter part of systole (fig. 2), it occurred in every patient during ischemia; in no case did the posterior wall thin during systole. The absence of systolic wall thinning indicates that the paradoxical systolic expansion or bulge seen during ischemia due to coronary occlusion (in which systolic thinning regularly occurs) did not occur in the type of myocardial ischemia (pacing-induced angina) studied in this investigation.

Plots of left ventricular pressure against posterior wall thickness in four representative patients are shown in figure 3. There was a consistent upward shift in this relationship during pacing-induced angina, with a higher left ventricular diastolic pressure at any value of wall thickness during ventricular filling in all 12 patients.

In figure 4, measured diastolic left ventricular pressure ($P_d$), the exponential fit pressure ($P_f$), and the residual pressure ($P_r = P_d - P_f$) are plotted against time for control and postpacing conditions. Residual pressure ($P_r$) is plotted against log $h$ in figure 5 for control and postpacing conditions. The radial stiffness modulus ($E_k = \text{negative slope of the } P_r - \log h \text{ plot}$) was evaluated at a common residual pressure level of 4 mm Hg. This slope was obtained by linear regression analysis over the approximate range of 2–6 mm Hg before and after pacing, and increased in all patients during pacing-induced angina (table 1). In most patients this slope was increased throughout the entire range of common residual pressure during angina (fig. 5). This postpacing increase in $E_k$ indicates increased myocardial stiffness during angina at equivalent levels of radial stress.

**Figure 1.** Control and postpacing M-mode echocardiograms and pressure recordings for patient 6. The paper speed for the pressure recordings was twice that for the echocardiograms. Angina occurred during pacing tachycardia and persisted for at least 30 seconds into the postpacing period. During angina there was a clear reduction in the rate of posterior wall thinning and substantial rise in left ventricular pressure throughout diastole. IVS = interventricular septum; End = left ventricular posterior wall endocardium; Epi = left ventricular posterior wall epicardium.
During ischemic segment thinning from systolic wall thickening, particularly during angina, the rate of thinning of the ischemic segment in early diastole was substantially diminished (41% reduction in peak rate of posterior wall thinning). This is consistent with slowed relaxation in the ischemic myocardium and is similar to the observation of Mason and co-workers during exercise-induced angina in patients with coronary artery disease.

The methods we used to analyze the echocardiograms in the study have been established. Single end-systolic or end-diastolic echocardiographic measurements of wall thickness have been used in conjunction with hemodynamic measurements to study the role of wall thickness as a determinant of left ventricular diastolic stiffness. In this study, analysis of echocardiographic wall thickness measurements throughout a cardiac cycle was combined with high-fidelity hemodynamic measurements and with an established method for evaluating left ventricular relaxation, allowing analysis of the relationship between left ventricular pressure and regional posterior wall thickness throughout diastole, at rest and with pacing-induced angina.

These changes in regional myocardial diastolic function during angina have not been described. Previous studies have shown an upward shift in the relationship between intracavitary left ventricular pressure and left ventricular volume during pacing-induced angina in man, and with pacing tachycardia in dogs with coronary stenoses.

From the simultaneous thickness and pressure data, we derived a radial stiffness modulus (E_r) using a new method.

**Discussion**

Using a combined echocardiographic and hemodynamic technique, we found an upward shift in left ventricular pressure-posterior wall thickness relationships during angina induced by pacing tachycardia in patients with severe coronary artery disease. The increase in LVEDP during angina (15 ± 3 mm Hg to 31 ± 6 mm Hg) occurred without any change in end-diastolic thickness of the ischemic posterior wall. This observation suggests a decrease in distensibility of the ischemic segment at end-diastole, because a higher diastolic pressure would be expected to cause stretching of the ischemic segment and wall thinning if the material properties of the segment were unchanged. That the ischemic segment is exhibiting a decreased distensibility is supported by the upward shift in the diastolic pressure-wall thickness plots during angina (fig. 3). Previous studies that showed an upward shift in the diastolic pressure-volume plot during angina were consistent with decreased chamber distensibility; the shift in pressure-wall thickness plots observed in the present study is consistent with altered distensibility of a region of the ventricular chamber.

In addition to the increase in diastolic pressure relative to wall thickness, the rate of thinning of the ischemic segment to early diastole was substantially diminished (41% reduction in peak rate of posterior wall thinning). This is consistent with slowed relaxation in the ischemic myocardium and is similar to the observation of Mason and co-workers during exercise-induced angina in patients with coronary artery disease.

**Figure 2.** The changes in left ventricular posterior wall thickness during a single cardiac cycle under control conditions and during angina induced by pacing tachycardia in patient 6. During angina there was a reduction in the peak rate of posterior wall thinning from 70 mm/sec to 37 mm/sec. There was also a reduction in systolic wall thickening, particularly during the latter part of systole.

**Figure 3.** Plots of left ventricular pressure against posterior wall thickness from the onset of mitral valve opening to end-diastole in patients 1, 5, 6 and 8 during the control state and during angina in the postpacing period. In all patients, a similar upward shift in this relationship was observed during angina, and left ventricular pressure was higher at any value of wall thickness.
approach to the assessment of regional myocardial stiffness and a modification of the mathematical model applied by Pasipoularides and co-workers in man\textsuperscript{34} and by Paulus and co-workers in dogs.\textsuperscript{35} This stiffness modulus has been found to be increased during angina induced by pacing tachycardia.

A distinction must be made between ventricular stiffness (dP/dV), which refers to the distensibility of the left ventricle as a structure,\textsuperscript{6, 30, 31, 36-40} and myocardial stiffness (dε/dε), which reflects the material properties of the myocardium per se.\textsuperscript{16} Problems associated with the analyses of pressure-volume and stress-strain relationships have been discussed.\textsuperscript{17, 25} We assessed the changes in the material properties of a single ischemic region of the left ventricular myocardium during pacing-induced angina. The echocardiographic techniques we used precluded study of more than one area at a time. The issue of ischemia, or lack of ischemia, at a distance from the region of myocardium studied affecting the function of this region cannot, therefore, be addressed in this investigation.

Difficulties in assessing global myocardial stiffness, can be overcome by assessing regional myocardial function and stiffness in dogs using ultrasonic crystals implanted in the myocardium to measure either segment length changes\textsuperscript{20, 42} or wall thickness changes.\textsuperscript{35, 32-44} Using metal clips to produce fixed coronary stenoses on the left anterior descending and circumflex coronary arteries in anesthetized dogs, Paulus and co-workers demonstrated an upward shift in both pressure-segment length\textsuperscript{35} and pressure-wall thickness relationships\textsuperscript{35} during pacing-induced ischemia. An analysis of radial stiffness-stress relationships similar to that used in the present study showed that a radial stiffness modulus (E\textsubscript{r}) derived from radial stress-wall thickness plots was increased during pacing-induced ischemia in dogs with coronary stenosis.\textsuperscript{35}

The validity of this radial stiffness modulus as an index of myocardial stiffness depends on the important assumption that after the period of isovolumic relaxation active pressure continues to decay exponentially toward zero. The exponential nature of isovolumic relaxation has been described by Weiss et al.\textsuperscript{22} They proposed that after mitral valve opening, active myofilament interaction continues to decay in the same manner. There is some evidence that if filling is prevented, the left ventricle continues to relax exponentially, although left ventricular pressure may decline to negative values rather than to zero.\textsuperscript{45} This is likely to be important only when the measured pressure is very low or negative during the early part of diastole, as in some cases of mitral stenosis. However, with the onset of filling at the time of mitral valve opening, the process of active relaxation may be modified and may deviate from its initial exponential decay. Clearly, such a possibility is very difficult to test adequately, and for the purposes of this study, active pressure was assumed to continue to decay exponentially after mitral valve opening. Justification for the subtraction of the extrapolated exponential pressure (P\textsubscript{e}) from the measured pressure (P\textsubscript{w}) to give residual pressure (P\textsubscript{r}) depends on the fact that during the early part of diastole cavity pressure (P\textsubscript{c}) is falling in the presence of increasing

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{The measured diastolic left ventricular pressure (P\textsubscript{w}), the exponential fit relaxation pressure (P\textsubscript{e}), and the residual pressure (P\textsubscript{r}) are plotted against time from the time of peak negative dP/dt to end-diastole for patient 6 under control and post-pacing conditions.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Residual pressure (P\textsubscript{r}) is plotted against log h (natural logarithm of the left ventricular posterior wall thickness) under control and post-pacing conditions for patient 1 from the time of mitral valve opening to end-diastole. The radial stiffness modulus (E\textsubscript{r}) at any level of radial stress (σ\textsubscript{r} = −P\textsubscript{r}) is defined by the expression E\textsubscript{r} = Δσ\textsubscript{r}/Δε\textsubscript{r} = −ΔP\textsubscript{r}/Δ(log h), which is the slope of the P\textsubscript{r} vs log h plot at that value of P\textsubscript{r}. This slope is clearly steeper at common levels of stress below the end-diastolic pressure under control conditions (17 mm Hg). An increase in the slope (E\textsubscript{r}) of this plot was observed for all patients at common levels of radial stress.}
\end{figure}
cavity dimensions and therefore cannot be a purely “passive” pressure.

The postspacing rise in the radial stiffness modulus (E_r) in our study suggests an increase in regional myocardial stiffness during the myocardial ischemia of angina pectoris. The cause of an increase in myocardial stiffness induced by this type of ischemia cannot be determined from the present experiments. Other data support the concept that persistence of cross bridges in the ischemic myocardium throughout diastole is responsible for the rise in diastolic resistance to filling.11,20 Such persistent interaction between contractile elements could result from impaired calcium sequestration by an ATP-deficient sarcoplasmic reticulum20, 46, 47 or increased net calcium influx.48

This study suggests that there is an increase in underlying “residual” myocardial stiffness in ischemic myocardium independent of the slowed active relaxation that undoubtedly occurs. Several components may contribute to “residual” pressure, including the effects of tissue turgor and incomplete dissociation of myofilaments.20 This increase in stiffness is associated with a decreased peak rate of posterior wall thinning in diastole. Other mechanisms may also play a part in causing the upward shift in pressure-volume relationships during angina. Experimental studies11 indicate that the pericardium and right ventricle do not play an important part in this phenomenon. However, the role of dyssynergistic contraction and relaxation needs to be assessed further. The time course of posterior wall thickening was only minimally altered during ischemia in this study (fig. 2). There was no systolic wall thinning, as would be expected with ischemia due to coronary occlusion, where the ischemic segment shows paradoxical systolic lengthening and bulging.10, 11, 44

Thus, our findings do not support systolic stretching and diastolic recoil of the ischemic segment as the mechanism for the increased left ventricular diastolic pressure during angina.

References

34. Pasipoularides A, Misky I, Hess OM, Krayenbuehl HP: Muscle
Effect of Rate on Left Ventricular Volumes and Ejection Fraction During Chronic Ventricular Pacing

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SUMMARY Resting left ventricular (LV) function was evaluated in 22 patients with permanent ventricular pacemakers. LV ejection fraction and volume indexes were determined by gated blood pool scintigraphy at ventricular pacing rates of 50–100 beats/min. In patients with a normal heart size, increases in pacing rates resulted in significant linear decreases in stroke volume index and ejection fraction. However, end-systolic volume index and cardiac index did not change. Patients with cardiomegaly appeared to respond differently. End-diastolic volume index decreased significantly as the pacing rate was increased from 50 to 100 beats/min. Ejection fraction was significantly reduced only at pacing rates of 90 and 100 beats/min. Mean cardiac index was highest at ventricular pacing rates of 70–90 beats/min. Increases in cardiac index, achieved by increasing the pacing rate, were maintained over a 4.3-month follow-up. Patients with underlying sinus rhythm had a 27% increase in cardiac output in association with an increase in ejection fraction from 55% to 62% when sinus rhythm was compared to ventricular pacing at a rate of 60 beats/min.

These data suggest that patients with cardiomegaly have a narrow range of optimal pacing rates at rest.

PROGRAMMABLE PACEMAKERS are widely available. Pacing rate and other pacemaker functions can be altered easily and noninvasively. Investigations of the role of pacing rate on cardiac function have produced varying results. Many investigations suggest that patients will have little or no change in cardiac output when the ventricular pacing rate is altered. However, Sowton and Samet et al. reported marked increases in cardiac output when pacing rate is increased in selected patients. In addition, there are occasional reports of patients with congestive heart failure and severe bradycardia who have responded favorably to ventricular pacing.

The cardiac response to changes in pacing rate may be related to the degree of cardiac compensation. However, few data are available regarding left ventricular ejection fraction or ventricular volumes during alterations in ventricular pacing rate. This study was undertaken to evaluate resting left ventricular function in patients with chronically implanted ventricular pacemakers and to define alterations that might be produced by changes in pacing rate.
Increased regional myocardial stiffness of the left ventricle during pacing-induced angina in man.
P D Bourdillon, B H Lorell, I Mirsky, W J Paulus, J Wynne and W Grossman

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