Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia

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ABSTRACT Both systolic and diastolic dysfunction have been described during pacing-induced ischemia, but the temporal sequence of systolic and diastic impairment has not been established. Accordingly, 22 patients with coronary artery disease were paced at increasing heart rates and studied with simultaneous hemodynamic monitoring, electrocardiographic recording, and radionuclide ventriculography. In addition, with synchronized left ventricular pressure tracings and radionuclide volume curves, three sequential pressure-volume diagrams were constructed for each patient corresponding to baseline, intermediate, and maximum pacing levels. Eleven patients (group I) demonstrated a nonischemic response to pacing tachycardia without chest pain, significant electrocardiographic changes, or significant rise in left ventricular end-diastolic pressure (LVEDP) in the immediate postpacing period. These patients demonstrated a progressive decrease in LVEDP, end-diastolic volume, and end-systolic volume, no change in cardiac output or left ventricular ejection fraction, and a progressive increase in left ventricular diastolic peak filling rate and the end-systolic pressure-volume ratio. Pressure-volume diagrams shifted progressively leftward and slightly downward, suggesting both an increase in contractility and a mild increase in left ventricular distensibility. The remaining 11 patients (group II) exhibited an ischemic response to pacing tachycardia, with each patient experiencing angina pectoris, demonstrating greater than 1 mm ST segment depression on the electrocardiogram, and exhibiting greater than 5 mm Hg rise in LVEDP immediately after pacing. LVEDP, end-diastolic volume, and end-systolic volume in these patients initially decreased and then subsequently increased during angina, with no change in cardiac output but a decrease in ejection fraction. Left ventricular peak diastolic filling rate and the left ventricular end-systolic pressure-volume ratio both increased at the intermediate pacing rate but fell at maximum pacing. Pressure-volume diagrams for these patients shifted leftward initially, then back to the right, during intermediate and peak pacing levels, often with an upward shift in the diastolic pressure-volume relationship. LVEDP in group II was significantly higher than that in group I at the intermediate pacing level with no difference in end-diastolic or end-systolic volumes, suggesting decreased left ventricular distensibility in these patients before the onset of systolic dysfunction at the maximum pacing level. We conclude that an ischemic response to pacing tachycardia involves both systolic and diastolic dysfunction, with diastolic impairment often preceding systolic depression.


PREVIOUS investigators have described both hemodynamic and left ventricular volume changes in patients who are stressed by atrial-paced tachycardia.

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tachycardia generally manifest no change in cardiac output or ejection fraction and exhibit a fall in left ventricular filling pressure with no significant rise in left ventricular end-diastolic pressure (LVEDP) in the immediate postpacing period. Ventricular volumes in these patients generally decrease as heart rate increases. Patients with coronary artery disease who develop ischemia during pacing tachycardia may also show no change in cardiac output, but generally differ from patients who do not develop ischemia in that they demonstrate a decreased ejection fraction, an increased pulmonary capillary wedge pressure, and either no change or a slight increase in LVEDP at maximum pacing, with a marked rise in LVEDP.
immediately after pacing. In addition, several investigators have reported in these patients a smaller decrease in ventricular volumes as heart rate increases in comparison to patients with nonischemic responses. 4, 6, 14

Although hemodynamic abnormalities associated with pacing-induced ischemia have been studied extensively, speculation has continued over the pathophysiologic mechanisms underlying these changes. In particular, some investigators have stressed a primary role for pacing-induced systolic failure with a decrease in left ventricular ejection fraction and a subsequent increase in ventricular volumes, 1, 6 whereas other investigators have emphasized primary diastolic dysfunction with a decrease in left ventricular distensibility resulting in higher pressures at any given volume during diastolic filling. 5, 7-9 Both of these mechanisms are thought to play a role in producing elevated left ventricular filling pressures during angina precipitated by pacing tachycardia, but prior studies have not been able to assess the relative contributions of systolic and diastolic dysfunction in producing hemodynamic abnormalities, nor has the temporal sequence of systolic and diastolic impairment been determined.

Prior attempts to assess simultaneously systolic and diastolic performance during pacing tachycardia have been hindered by technical difficulties associated with serial pressure-volume analyses at different pacing rates. Recently, radionuclide ventriculography in conjunction with left ventricular pressure recordings has been proposed as a means of assessing pressure-volume relations throughout the cardiac cycle and has been used in the construction of accurate and reproducible pressure-volume diagrams. 15, 16 A marked advantage of this technique is that multiple measurements of left ventricular volume can be made without effect on left ventricular function and without risk to the patient. With this method, the purpose of the present study was to assess simultaneously systolic and diastolic function in 22 patients with coronary artery disease stressed with incremental atrial pacing at the time of cardiac catheterization. In particular, it was our goal to differentiate systolic and diastolic effects during pacing ischemia and to determine which effect came first.

Methods

Study group. Atrial pacing with simultaneous hemodynamic monitoring and radionuclide ventriculography was conducted at the time of cardiac catheterization in 22 patients. The group consisted of 15 men and seven women with a mean age of 59 years. All patients were referred to the Beth Israel Hospital for evaluation of chest pain and were being treated with a combination of long-acting nitrates (17/22), /β-blockers (14/22), and/or calcium blockers (13/22). All medications were continued up until the time of cardiac catheterization. Prior myocardial infarction had been documented in nine of the 22 patients. None of the patients at the time of the study had evidence of acute myocardial infarction, unstable angina pectoris, congestive heart failure, ventricular ectopy, valvular disease, or cardiomyopathy. All patients gave written consent after being informed of the potential risks involved. There were no complications as a result of this study.

Cardiac catheterization and coronary angiography. Coronary angiography was performed in all patients with standard techniques. Left ventriculography was performed with a pigtail catheter, and simultaneous biplane cine recordings were made in the right and left anterior oblique projections. Right heart catheterization was performed in all patients with a flow-directed thermodilution catheter (Mansfield Scientific, Inc., Mansfield, MA), which was inserted percutaneously into the right femoral vein and advanced to the pulmonary artery. Systemic pressures were measured with a percutaneously placed radial arterial cannula.

Left ventricular pressures were obtained from a fluid-filled left ventricular catheter in 16 patients and from high-fidelity micromanometer catheters (Millar Instruments, Houston) in the remaining six patients. Pressures from the fluid-filled catheters were measured with a P-50 Micron pressure transducer attached directly to a manifold, which was connected to the proximal hub of the intracardiac catheter without intervening tubing. The frequency response of this system has been described previously from our laboratory 17 and is flat ± 5% to greater than 20 Hz. Recordings were inscribed with a Honeywell–Electronics for Medicine recorder (VR-12). Left ventricular end-diastolic pressure was measured at the peak of the R wave on the electrocardiogram.

Atrial pacing protocol. After the completion of coronary angiography and left ventriculography, a bipolar, flared pacing catheter (Atri-pace Flare; Mansfield Scientific) was placed within the right atrium via a percutaneous puncture of the left femoral vein. When a satisfactory pacing threshold had been achieved, the pacing rate was increased rapidly until atrioventricular block occurred. If the patient developed atrioventricular block at a rate less than 85% of age-predicted maximum heart rate, 1 mg of atropine was administered. Seven of the 22 study patients were subsequently pretreated with atropine. The target pacing rate was the highest rate that could be achieved up to 85% of age-predicted maximum heart rate.

In all but two patients, the maximum heart rate was between 115 and 160 beats/min, and the intermediate heart rate was therefore set at a level between 100 and 120 beats/min. Approximately 30 min after the completion of left ventriculography, baseline pressure and cardiac output measurements were made and a baseline radionuclide scan was obtained (see below). Pressures were recorded from the pulmonary capillary wedge position, systemic artery, and the left ventricle. Four thermodilution cardiac output measurements were made and averaged.

Atrial pacing was subsequently conducted at an intermediate and maximum or target heart rate. The intermediate heart rate was approximately midway between baseline and maximum heart rate, usually at approximately 110 beats/min. The maximum heart rate was determined by the onset of marked angina pectoris, the onset of atrioventricular block, or the achievement of 85% of maximum age-predicted heart rate. At each pacing rate, repeat measurements of pressure and cardiac output were made and a repeat radionuclide scan was obtained. Subsequently, pacing was terminated abruptly with continuous monitoring of LVEDP. Group II patients who developed angina at the maximum paced rate were not given nitroglycerin until completion of the pacing study.
A 12-lead electrocardiogram was obtained in the prepacing baseline period, just before the discontinuation of pacing, and immediately after pacing.

**Gated blood pool scintigraphy**

*Acquisition.* Acquisition of radionuclide studies was begun approximately 30 min after the contrast ventriculogram during the prepacing baseline period. In all patients, heart rate, left ventricular pressure, and pulmonary capillary wedge pressure had returned to their precontrast levels. Each patient was injected with 0.75 GBq (20 mCi) of autologous red blood cells labeled with technetium-99m. The in vitro technique was used for labeling. After the baseline scan, repeat scans were obtained at the intermediate and maximum pacing rates.

All radionuclide studies were acquired with the patients in the supine position using a mobile Anger camera computer system (Technicare 410 with on-board VIP computer system). Each gated cardiac blood pool study was obtained with a 30 degree slant-hole collimator to obtain cephalic angulation in the modified left anterior oblique view. The degree of obliquity was between 35 and 45 degrees and was individualized in each patient to best visualize the septum. During the multiple gated studies that were obtained, neither the patient nor the camera were moved between studies.

The gated cardiac blood scans were obtained with a 64 × 64 matrix for the full field of view (200 cm). Thirty-two frames per RR interval were acquired. Minimum acquisition time was 3 min, although most studies were acquired for 5 min. The time of each gated study was recorded and a blood sample was obtained at the midpoint of each study.

*Analysis.* For each gated study, a left and right ventricular count rate (volume) vs time curve was obtained with an operator-drawn, fixed left ventricular region of interest and an operator-drawn, fixed, truncated right ventricular region of interest. The operator used the end-diastolic image to identify the septal borders of the ventricles and the stroke volume image to identify the atrioventricular and free wall borders of the heart. In patients with left ventricular dysfunction, the end-diastolic image was used to confirm the boundaries of the free wall of the ventricle. For the right ventricle, a horizontal line from the pulmonary outflow tract to the right ventricular free wall was used to separate the atrioventricular structures. Background was derived from computer-generated regions of interest and was assumed to be constant both spatially and temporally.

Since three left ventricular volume vs time curves were obtained in each patient, the relative change in end-diastolic volume between studies was determined by correcting the end-diastolic counts in each curve for acquisition time, physical decay, and biological clearance. Acquisition time for each end-diastolic frame was calculated by multiplying the frame duration (RR interval/number of frames) by the number of cardiac cycles collected. Loss of counts due to physical decay was calculated with the time at which each study was acquired. Biological clearance of the tracer was calculated by measuring the changes in the counts obtained in a well counter of 100 μl sample of blood obtained at the midpoint of each study.

Left ventricular peak filling rates in each patient were assessed by fitting a third-order polynomial to the rapid diastolic portion of the time–activity curve using a least squares technique and were computed in left ventricular counts per second; values were normalized for the number of left ventricular counts at end-diastole and expressed as end-diastolic counts per second (EDV/sec).

A square wave that indicated the time at which the gamma camera’s computer system detected the patient’s R wave on the electrocardiogram was transmitted to the Electronics for Medicine recorder to synchronize the radionuclide volumes with the left ventricular pressure tracings.

**Generation of left ventricular pressure-volume diagrams.** Radionuclide pressure-volume diagrams were recorded during the initial gated blood pool study and on all subsequent radionuclide studies by means of a method previously described from our laboratory. At the midpoint of each modified left anterior oblique scan, left ventricular pressures were recorded at rapid paper speed. A minimum of six left ventricular pressure curves representing the range of pressures on both sides of midinspiration or midexpiration were digitized and averaged by a Tektronix 4052 computer. The average left ventricular pressure curve and gated blood pool volume curve were synchronized to end-diastole (defined by the peak of the R wave on the electrocardiogram) and digitized, and pressure-volume diagrams were subsequently plotted from 32 pressure-volume coordinates throughout the cardiac cycle. Absolute volumes were determined for each pressure-volume diagram by assigning the left ventricular angiographic end-diastolic volume to the baseline pressure-volume diagram, with all subsequent absolute end-diastolic and end-systolic volumes determined from the previously calculated relative changes in end-diastolic volumes and from radionuclide ejection fractions.

**Right ventricular pressure-volume relationships.** In eight of the 22 patients, right ventricular pressures and radionuclide volumes were also measured during pacing tachycardia. Right ventricular pressures were measured with a specially constructed, flow-directed balloon catheter with right atrial, right ventricular, and pulmonary arterial ports (Mansfield Scientific). The right ventricular lumen has a diameter of 0.9 mm and a frequency that is satisfactory to 25 Hz. Pacing was discontinued in each of these patients with simultaneous measurement of left and right ventricular end-diastolic pressure. Absolute right ventricular end-diastolic volumes were determined by calculating the ratio of thermodilution stroke volume to right ventricular radionuclide ejection fraction at each pacing level.

**Statistics.** The degree of coronary stenosis was evaluated subjectively by two separate observers and estimated with the greatest degree of diameter narrowing in any projection. A 50% or greater reduction of lumen diameter in any one view was considered to have hemodynamic significance.

After pacing was stopped, LVEDP was measured by averaging beats numbered 5 through 15 after the last paced beat.

The left ventricular end-systolic pressure-volume ratio was estimated for each patient at each pacing rate from the ratio of end-systolic pressure (taken at the dicrotic notch on the aortic pressure tracing) divided by the minimum radionuclide volume. All radionuclide scans were analyzed by two observers without knowledge of the coronary anatomy or pacing hemodynamics.

Means and SDs were calculated for all variables. Multiple groups of data were analyzed by analysis of variance. Paired dimensional data were analyzed by either the paired t test or Wilcoxon signed-rank test where appropriate, for parametric and nonparametric distributions. A p value < .05 was considered significant.

**Results**

Ischemic vs nonischemic response to pacing tachycardia. Of the 22 patients enrolled in the study, 11 were judged to have a nonischemic response to pacing tachycardia. None of these patients experienced chest pain or significant electrocardiographic changes at maximum pacing rates; all exhibited a progressive decrease in pulmonary capillary wedge pressure and LVEDP during intermediate and maximum pacing rates, and none...
experienced a significant elevation (>5 mm Hg) of LVEDP in the immediate postpacing period. These 11 patients constitute group I and serve as a control group.

The remaining 11 patients were all judged to have an ischemic response to pacing tachycardia. All 11 patients experienced angina pectoris, demonstrated 1 mm or greater ST segment depression on the electrocardiogram at maximum pacing, and experienced significant elevations in their pulmonary capillary wedge pressure during maximum pacing, and demonstrated greater than 5 mm Hg rise in LVEDP in the immediate postpacing period. These patients constitute group II. None of the group II patients developed angina pectoris or ischemic ST segment shifts at the intermediate pacing rate.

Clinical and angiographic characteristics (table 1). Group I consisted of seven men and four women with a mean age of 60 years. Three of these patients had normal coronary arteries, while the remaining eight had significant coronary artery disease (three had single-vessel right coronary artery disease, three had two-vessel disease, and two had three-vessel disease). Four of these patients had evidence of prior myocardial infarction.

Group II consisted of eight men and three women with a mean age of 57 years. All 11 patients had significant coronary artery disease (one had single-vessel left anterior descending disease, five had two-vessel disease, and five had three-vessel disease). Five of these patients had evidence of prior myocardial infarction.

There was no significant difference between groups I and II with respect to age, sex distribution, history of prior myocardial infarction, or use of specific medications. Similarly, contrast ventriculographic analysis revealed that there was no significant difference in

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CFX = left circumflex artery; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LAD = left anterior descending artery; MI = myocardial infarction; nml = normal; RCA = right coronary artery.
ejection fraction or end-diastolic and end-systolic volume index between the two groups. Results of coronary angiographic and left ventriculographic studies are listed in table 1.

Hemodynamics at rest and in response to pacing tachycardia (tables 2 and 3). Hemodynamic measurements at rest and with pacing tachycardia are summarized for group I patients in table 2 and for group II patients in table 3. Groups I and II did not differ significantly with respect to heart rate, mean arterial pressure, pulmonary capillary wedge pressure, left ventricular pressure, and thermodilution cardiac output in the prepping baseline period. Similarly, at the intermediate and maximum pacing rate, the two groups did not differ

### TABLE 2

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CO = cardiac output (l/min); EDVI = end-diastolic volume index (ml/m²); ESP/VR = end-systolic pressure-volume ratio (mm Hg/ml/m²); ESVI = end-systolic volume index (ml/m²); EF = ejection fraction (%); HR = heart rate (bpm); Int = intermediate pacing; LVP = left ventricular pressure (mm Hg); MAP = mean arterial pressure (mm Hg); Max = maximum pacing; PCW = pulmonary capillary wedge pressure (mm Hg); PFR = peak filling rate (EDV/sec); Post = postpacing; Pre = prepacing.

*aNot measured.*
with respect to heart rate, mean arterial pressure, or thermodilution cardiac output.

LVEDP in group I decreased progressively from prepacing baseline and subsequently returned to its baseline value in the postpacing period (heart rate [HR]1, 9 ± 2 mm Hg; HR2, 5 ± 2 mm Hg; HR3, 4 ± 1 mm Hg; postpacing, 7 ± 4 mm Hg). In group II, LVEDP did not change significantly during intermediate and maximum pacing but rose to a significantly higher level in the postpacing period (HR1, 10 ± 4 mm Hg; HR2, 10 ± 4 mm Hg; HR3, 12 ± 6 mm Hg; postpacing, 18 ± 4 mm Hg; p < .01). Of note, LVEDP in group II was significantly higher than that in group I at both the intermediate and maximum pacing levels (HR2, 10 ± 4 vs 5 ± 2 mm Hg, p < .05; HR3, 12 ± 6 vs 4 ± 1 mm Hg, p < .01).

**TABLE 3**

Hemodynamics and ventricular volumes during pacing tachycardia in group II

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Abbreviations as in table 2.

*p < .05 vs group I.

*p < .01 vs group I.

*Not measured.
Pulmonary capillary wedge pressure in group I likewise decreased progressively from baseline during intermediate and maximum pacing rates (HR1, 7 ± 2 mm Hg; HR2, 6 ± 2 mm Hg; HR3, 5 ± 2 mm Hg). In contrast, group II demonstrated a significant rise in pulmonary capillary wedge pressure during peak pacing (HR1, 7 ± 2 mm Hg; HR2, 7 ± 3 mm Hg; HR3, 14 ± 5 mm Hg; p < .02). At maximum pacing, pulmonary capillary wedge pressure in group II was significantly higher than that in group I (HR3, 14 ± 5 mm Hg vs 5 ± 2 mm Hg; p < .01).

Radionuclide ventriculography at rest and with pacing tachycardia (tables 2 and 3). Radionuclide data for each patient are presented in tables 2 and 3. The correlation between left ventricular ejection fraction determined by contrast ventriculography and the baseline radionuclide scan in all 22 patients was \( r = .91 \). In response to pacing tachycardia, group I demonstrated a progressive decrease in radionuclide end-diastolic and end-systolic volumes. Left ventricular ejection fraction was unchanged at all three heart rates. In contrast, patients in group II demonstrated an initial decrease in radionuclide end-diastolic and end-systolic volumes at the intermediate pacing level, followed by an increase in either end-diastolic volume (HR1, 72 ± 21 ml/m²; HR2, 47 ± 16 ml/m²; HR3, 65 ± 32 ml/m²) and/or end-systolic volume (HR1, 29 ± 20 ml/m²; HR2, 17 ± 9 ml/m²; HR3, 32 ± 28 ml/m²). At maximum pacing, both end-diastolic and end-systolic volumes in group II were significantly higher than those in group I (EDV, 65 ± 25 vs 42 ± 14 ml/m², p < .01; ESV, 32 ± 28 vs 16 ± 11 ml/m², p < .01). Left ventricular ejection fraction at maximum pacing was also significantly lower than at baseline (HR1, 63 ± 17%; HR3, 55 ± 17%; p < .05), whereas the mean ejection fraction was unchanged at the intermediate rate (HR1, 63 ± 17%; HR2, 63 ± 17%).

End-systolic pressure-volume ratio (tables 2 and 3). For group I, the end-systolic pressure-volume ratio showed a progressive increase during intermediate and maximum pacing rates (HR1, 5.8 ± 2.1 mm Hg/ml/m²; HR2, 7.4 ± 3.2 mm Hg/ml/m²; HR3, 9.8 ± 5.4 mm Hg/ml/m²). Group II, in contrast, exhibited an initial increase in the end-systolic pressure-volume ratio during intermediate pacing, with a subsequent fall in the ratio during maximum pacing (HR1, 6.7 ± 4.6 mm Hg/ml/m²; HR2, 9.1 ± 5.6 mm Hg/ml/m²; HR3, 5.9 ± 4.4 mm Hg/ml/m²).

Sequential pressure-volume diagrams (figures 1 and 2). Pressure-volume diagrams for group I shifted progressively to the left and slightly downward during intermediate and maximum pacing rates. Figure 1 shows

**FIGURE 1.** Sequential pressure-volume diagrams for a representative patient (No. 3, group I) with a nonischemic response to pacing tachycardia. Left ventricular pressures were measured with a micromanometer catheter. With pacing, pressure-volume diagrams shifted downward and to the left with an increased end-systolic pressure-volume ratio.

**FIGURE 2.** Pressure-volume loops illustrating a spectrum of responses to progressive pacing in group II patients. A. Response showing predominant diastolic dysfunction (patient 4). B. Response showing decreased followed by increased LVEDP (patient 2). C. Response showing a progressive increase in LVEDP (patient 6).
three sequential pressure-volume loops for a group I patient (No. 3) with normal coronary arteries in whom left ventricular pressure was recorded with a micro-manometer catheter. Included in this figure is an expanded pressure-volume graph in which only the diastolic limbs of the three pressure-volume loops are plotted. None of the group I patients had a progressive upward shift in their pressure volume loops. Except for one patient with a plateau response, all showed a progressive downward shift.

In contrast, five of the 11 group II patients had an upward shift as the heart rate increased from baseline to the intermediate or maximum paced rate. Only one of the group II patients showed a progressive downward shift. Five of the group II patients had a plateau response (patients 1, 3, 8, 9, and 10).

Pressure-volume diagrams for group II initially shifted to the left at the intermediate pacing level, followed by the shift back to the right with the onset of angina. In addition, the diastolic limbs of the sequential pressure-volume loops for these patients failed to show the progressive downward shift with increasing pacing rates, except in one case. Figure 2 shows three sequential pressure-volume diagrams for three representative group II patients illustrating the spectrum of responses in this group. The first series of diagrams were recorded from patient 4, who had a predominant diastolic dysfunction response to pacing. The second series of loops (patient 2) were recorded from a patient with a slight decrease in diastolic pressure at the intermediate pacing rate. This patient then developed an increase in LVEDP at the maximum paced rate together with an upward shift in the diastolic pressure-volume relationship. The third patient (No. 6) had a progressive increase in diastolic pressure as the heart rate increased. The diastolic pressure-volume relationship shifted leftward and upward, consistent with decreased left ventricular diastolic distensibility.

**Diastolic before systolic dysfunction at the intermediate pacing level** (figure 3). Examination of pressure-volume data for groups I and II at the intermediate pacing level shows that there was no significant difference between either end-diastolic or end-systolic volume in the two groups and that both groups had manifested a leftward shift of their pressure-volume diagrams with an increase in their end-systolic pressure-volume ratios. However, LVEDP in group II was significantly higher than that in group I at this pacing level, suggesting that for group II as a whole left ventricular distensibility decreased before the onset of systolic failure. However, as is apparent from examination of table 3, there was heterogeneity of patient response, and in at least one case (patient 7), systolic dysfunction was apparent at the intermediate rate and was simultaneous in onset with diastolic dysfunction.

**Right ventricular pressure-volume relationships (table 4).** Four patients in group I and four patients in group II had sufficient measurements to allow plotting of right ventricular pressure-volume relationships. All showed a progressive decrease in right ventricular end-diastolic pressure and right ventricular end-diastolic volume with pacing tachycardia. No patient demonstrated an increase in right ventricular end-diastolic pressure in the immediate postpacing period. Right ventricular

**FIGURE 3.** LVEDP, end-diastolic volume, end-systolic volume, and end-systolic pressure-volume ratio in groups I and II. LVEDP in group II was significantly higher than that in group I at the intermediate pacing level in spite of no significant difference in end-diastolic and end-systolic volumes and no evidence of a decrease in the end-systolic pressure-volume ratio. The points represent mean values ± SEM.
TABLE 4
Right ventricular pressure-volume relationships

| Group | Prepacing baseline | Intermediate pacing | Maximum pacing | Post-pacing | RVP | SV | EF | RVEDV | RVP | SV | EF | RVEDV | RVP | SV | EF | RVEDV | RVP | SV | EF | RVEDV |
|-------|-------------------|---------------------|----------------|-------------|-----|----|----|-------|-----|----|----|-------|-----|----|----|-------|-----|----|----|-------|-----|----|----|-------|
| I     |                   |                     |                |             |     |    |    |       |     |    |    |       |     |    |    |       |     |    |    |       |     |    |    |       |
| 1     | 26/6              | 65                  | 52             | 125         | 20/2 | 37 | 48 | 100   | 20/2 | 23 | 50 | 46   | 24/3 |     |    |       |     |    |    |       |
| 2     | 25/8              | 93                  | 37             | 251         | 20/6 | 82 | 34 | 241   | 19/6 | 68 | 36 | 188  | 20/6 |     |    |       |     |    |    |       |
| 3     | 28/9              | 92                  | 47             | 196         | 23/7 | 56 | 41 | 136   | 16/4 | 42 | 34 | 123  | 20/8 |     |    |       |     |    |    |       |
| 4     | 26/7              | 61                  | 45             | 135         | 23/4 | 50 | 38 | 131   | 20/4 | 40 | 39 | 102  | 20/4 |     |    |       |     |    |    |       |
| II    |                   |                     |                |             |     |    |    |       |     |    |    |       |     |    |    |       |     |    |    |       |
| 1     |                   |                     |                |             |     |    |    |       |     |    |    |       |     |    |    |       |     |    |    |       |
| 2     | 20/8              | 65                  | 45             | 144         | 18/4 | 45 | 49 | 92    | 20/2 | 33 | 45 | 73   | 20/4 |     |    |       |     |    |    |       |
| 3     | 20/6              | 83                  | 52             | 159         | 20/2 | 75 | 45 | 166   | 28/2 | 61 | 44 | 138  | 32/7 |     |    |       |     |    |    |       |
| 4     | 28/11             | 65                  | 45             | 144         | 24/7 | 61 | 44 | 139   | 30/4 | 51 | 38 | 134  | 28/4 |     |    |       |     |    |    |       |
|       | 25/6              | 89                  | 48             | 185         | 23/4 | 70 | 47 | 149   | 25/2 | 65 | 48 | 135  | 23/4 |     |    |       |     |    |    |       |

EF = right ventricular ejection fraction (%); RVP = right ventricular pressure (mm Hg); RVEDV = right ventricular end-diastolic volume (ml); SV = thermodilution stroke volume.

pressures and volumes are listed for all eight patients in table 4.

Left ventricular peak diastolic filling rates (tables 2 and 3). Left ventricular peak diastolic filling rates in group I rose progressively with incremental increases in heart rate (table 2). In contrast, peak filling rates in group II showed an initial rise at the intermediate pacing level with a subsequent fall at maximum pacing (table 3). In all patients, there was a mild prolongation of the PR interval during intermediate and maximum pacing so that the time of peak filling occurred later in diastole in comparison to the prepacing baseline period; there was no difference, however, between PR prolongation in the two groups.

Discussion

Our findings confirm previously reported results with respect to changes in cardiac output, left ventricular ejection fraction, LVEDP, pulmonary capillary wedge pressure, and ventricular volumes during ischemia induced by pacing tachycardia.1-14 In addition to confirming prior results, however, the simultaneous recording of left ventricular pressures and volumes in this study allows for a more complete analysis of pressure-volume relationships during pacing-induced ischemia than has been previously reported. In particular, we have been able to examine systolic and diastolic effects separately, and the results suggest that diastolic impairment commonly precedes systolic failure.

Systolic function during pacing-tachycardia. Several investigators have reported small inotropic increases in patients20 and dogs21, 22 with increased heart rates, presumably secondary to a Treppe effect, with slight increases in ejection phase indexes at higher heart rates. Controversy has arisen, however, over the fact that most ejection-phase indexes are load dependent and therefore cannot serve as accurate measures of left ventricular contractile state during pacing tachycardia when preload and afterload may be changing.23

As an alternative means of measuring ventricular performance, there has been considerable interest over recent years in the use of the end-systolic pressure-volume relationship. Evidence from both animal24 and human studies25, 26 has suggested that the end-systolic pressure-volume relationship is a load-independent index of left ventricular contractile performance. Results of a recent study using simultaneous radionuclide ventriculography and arterial pressure recordings have documented an increase in the end-systolic pressure-volume ratio during pacing tachycardia, with a smaller increase in the ratio in patients with coronary artery disease who were similarly paced.14 The authors of that study, however, did not measure left ventricular pressure directly and therefore could not assess diastolic function simultaneously.

In the present study, the sequential left ventricular pressure-volume diagrams for all patients in group I showed a progressive leftward shift of the loops (figure 1). Although it is clear that the slope and the volume intercept of the end-systolic lines for these patients have not been defined, the progressive leftward shift of the upper left-hand corner of the pressure-volume diagrams with an increased end-systolic pressure-volume ratio (similar end-systolic pressure, lower end-systolic volume) suggests an increase in contractile state.

Sequential pressure-volume diagrams for group I
can be contrasted with diagrams for patients in group II (figure 2). Similar to the patients with a nonischemic response, group II patients showed an initial leftward shift of their pressure-volume diagram with an increased end-systolic pressure-volume ratio at the intermediate pacing rate. However, unlike those for group I, at maximum pacing rates and with the onset of angina, pressure-volume loops for group II often shifted back to the right and were characterized by a subsequent decrease in their end-systolic ratio. In these patients an initial Treppe effect appeared to be present but was subsequently replaced with evidence of decreased contractility probably secondary to ischemia at a higher heart rate. Five of the group II patients did sustain a moderate fall in ejection fraction, averaging 13%, and one patient demonstrated a marked decrease in ejection fraction at the intermediate paced rate. These decreases in ejection fraction may not represent a decrease in contractility, since end-diastolic volume decreased and ejection fraction is known to be preload dependent. However, the end-systolic pressure-volume ratio did decrease at the intermediate rate in two patients, and this index is believed to be preload independent. Thus some of the group II patients may have had systolic dysfunction at the intermediate paced rate. However, the mean end-systolic pressure-volume ratio of the group II patients increased as the heart rate was increased from baseline to intermediate.

**Diastolic function during pacing tachycardia.** It is notable that five patients in group I demonstrated a progressive downward shift in the diastolic limbs of their pressure-volume diagrams, suggesting a small increase in left ventricular diastolic distensibility during pacing tachycardia (figure 1). Whether this downward shift is related to an increase in myocardial relaxation, an alteration in viscoelastic properties, or a change in diastolic restraint by factors extrinsic to the left ventricle (e.g., right ventricle, pericardium) is not known. Some investigators have documented mild chronotropic increases in parameters of diastolic relaxation such as peak $-dP/dt$ and time constant $T$ in animals, and more recently, the peak rate of posterior wall thinning and change in left ventricular internal dimension in man. In addition, it is clear that in the four group I patients in whom right ventricular pressure-volume relationships were measured, there was a progressive decrease in both right ventricular end-diastolic and end-diastolic volume; such a decrease could potentially affect left ventricular diastolic pressure-volume relations through ventricular interaction and/or secondary to a decrease in constricting effects from an intact pericardium.

In contrast to group I, group II not only failed to demonstrate a progressive downward shift in the diastolic limbs of their pressure-volume diagrams, but often exhibited an upward shift at intermediate and peak pacing levels, suggesting a decrease in distensibility at these heart rates (figure 2). Speculation has continued over the last two decades on whether the increase in diastolic pressures during pacing-induced ischemia is related to a decrease in distensibility or is secondary to systolic failure with increases in ventricular volumes. Examination of sequential ventricular volumes in group II patients reveals that all 11 patients experienced a primary increase in either end-diastolic and/or end-systolic volume at the maximum pacing rate, compared with values at the intermediate pacing rate. In addition, however, it is notable that at the intermediate pacing rate, LVEDP was significantly higher in group II than in group I, even though end-diastolic volume had fallen for both groups (figure 3). Since end-diastolic and end-systolic volumes were not significantly different for these two groups at this pacing rate, it is probable that group II patients had already exhibited a decrease in left ventricular distensibility. Thus, in those patients who manifested an ischemic response to pacing with a significant elevation in LVEDP after pacing, decreased left ventricular diastolic distensibility occurred during pacing.

To determine whether the changes in left ventricular diastolic pressure-volume relationships in group II were related to a primary decrease in left ventricular distensibility or to either the effect of an ischemic right ventricle or a constricting effect of the pericardium, it is necessary to examine both left and right ventricular pressure-volume changes simultaneously. Although right ventricular pressures and volumes were examined in only eight patients (four in group I, four in group II), the decrease in right ventricular pressure and volume that occurred in these patients, as well as the lack of postpacing rise in right ventricular end-diastolic pressure, suggests that the higher LVEDP that occurred at the intermediate pacing rate in the group II patients was related neither to ventricular interaction nor to a constricting effect of the pericardium (since the end-diastolic volumes of both left and right ventricle at intermediate and maximum pacing were significantly below prepacing baseline volumes (tables 3 and 4).

The concept that diastolic dysfunction may precede systolic dysfunction suggests that impaired diastolic performance during pacing tachycardia may not only be the first manifestation of ischemia but may also contribute to further ischemia. For example, impair-

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ment of isovolumetric relaxation with reduction in the rate of decrease of early diastolic wall tension may impede regional antegrade coronary blood flow.

All the patients in this study were receiving various antianginal medications, including β-blockers, nitrates, and/or calcium-channel blockers. It is likely that these drugs had an effect on diastolic compliance and systolic function. We cannot determine whether or not the separation of diastolic from systolic dysfunction would also be seen in patients who are not receiving antianginal medications, although we presume that this separation would be present in these patients.

We began our pacing study 30 min after the completion of angiographic examinations to give the ventricle a chance to recover from the effects of contrast media. We cannot be certain that contrast injection might have affected the function of the stressed ventricle.

The accuracy of radionuclide determinations of left ventricular chamber volumes is fundamentals to many of the conclusions of this study. In this regard, we have previously published our comparison of angiographic and radionuclide volumes, which revealed an excellent correlation (r = .92) between these two measurements.16

Changes in peak filling rates: systolic or diastolic dysfunction? Diastolic peak filling rate has been proposed as a marker of diastolic left ventricular function.31 Examination of peak filling rates from this study reveal a progressive increase in peak filling rate with increases in heart rate in group I in contrast to an initial rise and then fall in peak filling rate in group II. The progressive increase in peak filling rates in group I patients suggests a significant enhancement of diastolic filling during pacing tachycardia, especially since the increased filling rate has occurred in the presence of a decrease in left ventricular filling pressure, which presumably represents the driving force for left ventricular filling. Similarly, the decrease in peak filling rate in group II patients at peak pacing despite similar or higher filling pressures suggests increased resistance to diastolic filling in these patients during angina and is compatible with the decrease in distensibility reflected in the pressure-volume diagrams at this level. In this regard, Bourdillon et al.15 have shown a decrease in the peak rate of posterior wall thinning during regional (posterior) ischemia in patients with pacing-induced angina, and Mason et al.32 had previously demonstrated a similar decrease in regional wall thinning during exercise-induced angina. In Mason’s study, peak wall thinning rate (which may be the myocardial counterpart to peak filling rate) increased progressively with exercise in normal subjects.

In this study, it was notable that there was no change in peak filling rate during intermediate intermediate pacing rates in group II patients, although pressure-volume relationships suggested a decrease in left ventricular distensibility. One possible explanation for this discrepancy is that left ventricular filling pressures in group II patients were elevated and therefore peak filling rates may have been relatively reduced (i.e., peak filling rates should have been higher because of the higher driving pressures). Alternatively, since peak filling rate is derived in terms of end-diastolic volumes per second, one might expect this parameter to be heavily influenced by changes in ejection fraction and end-diastolic volume.33 Thus the progressive increase in peak filling rates in group I and the biphasic response of peak filling rates in group II closely paralleled volume changes in both of these groups of patients. This raises the possibility that peak filling rate may be dependent on both systolic and diastolic function, rather than on diastolic performance alone, although additional studies are needed to clarify this point.

Support for the concept that diastolic function may be more vulnerable to ischemia than systolic function comes from the study of St. John Sutton et al.34 These workers studied the response of papillary muscles to graded hypoxia, and found that as $P_{O_2}$ was decreased from 634 to 34 mm Hg, decreases in maximum relaxation rate were proportionally greater than decreases in maximum contraction rate with intermediate hypoxia, but the proportionality was restored during severe hypoxia. Thus, as relative hypoxia develops in the myocardium distal to a coronary stenosis where $O_2$ consumption is increased by tachycardia, an intermediate state may exist where a primarily diastolic abnormality is manifest.

In conclusion, patients with a nonischemic response to pacing demonstrated a progressive leftward shift of their left ventricular pressure-volume diagrams with an increased end-systolic pressure-volume ratio and a progressive downward shift in their diastolic pressure-volume relationships accompanied by a rise in left ventricular diastolic peak filling rates. In contrast, patients who exhibited ischemia with pacing demonstrated a biphasic shift of their left ventricular pressure-volume diagram with an increased followed by a decreased end-systolic pressure-volume ratio. Peak filling rates in these patients showed a biphasic response that closely paralleled volume changes, whereas left ventricular diastolic pressure-volume relationships indicated a decrease in left ventricular distensibility before the onset of systolic dysfunction. These results suggest that both systolic and diastolic
dysfunction occur during pacing-induced ischemia and that diastolic impairment precedes systolic failure.

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