METHODS

The Pacing Stress Test Reexamined: Correlation of Pacing-Induced Hemodynamic Changes With the Amount of Myocardium at Risk

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To assess the relation between extent of ischemia and the magnitude of hemodynamic changes, 25 patients (5 with normal coronary arteries and 20 with significant coronary obstructive disease) were studied with rapid atrial pacing and thallium scintigraphy at the time of cardiac catheterization. Hemodynamic variables were measured before, during and after maximal pacing. Thallium was injected intravenously during maximal pacing and scans in three standard views were obtained immediately in the catheterization laboratory, with delayed scans obtained 4 hours after the cessation of pacing. The three thallium scans were each subdivided into five segments, and a thallium score was obtained on the basis of the total number of segments that were hypoperfused. Each patient was assigned a total thallium score corresponding to thallium defects at maximal pacing, as well as a redistributed thallium score corresponding to the difference between thallium score at maximal pacing and that 4 hours later.

With pacing, patients with normal coronary arteries demonstrated no significant change in baseline hemodynamic variables, whereas patients with coronary artery disease exhibited a decrease in cardiac index, an increase in systemic vascular resistance, a widening of arteriovenous oxygen difference, an increase in pulmonary capillary wedge pressure and mean pulmonary artery pressure during maximal pacing and an increase in left ventricular end-diastolic pressure immediately after pacing. There was a significant correlation (Spearman rank r = 0.64, p < 0.01) between redistributed thallium score and an increase in left ventricular end-diastolic pressure in the postpacing period. Moreover, there was an even higher correlation (Spearman rank r = 0.90, p < 0.001) between total thallium score and the postpacing increase in end-diastolic pressure.

It is concluded that in patients with coronary artery disease the magnitude of pacing-induced hemodynamic changes reflects both the amount of myocardial tissue at ischemic jeopardy and the total mass of hypoperfused myocardium during maximal pacing stress.

Atrial pacing has been used for more than 15 years as a stress test for precipitating angina pectoris in patients with coronary artery disease (1–8). Sowton et al. (1) were the first to use this technique to measure the anginal threshold

in patients with ischemic heart disease. They demonstrated that pacing-induced angina consistently occurred in a given patient at a particular tension-time index (product of aortic ejection pressure, ejection time and heart rate) and was often associated with increased pulmonary artery mean pressure and pulmonary capillary wedge pressure.

Parker et al. (2) supplemented those initial observations by studying pacing-induced ischemia with left ventricular catheterization. They found that patients with normal coronary arteries demonstrated a decrease in left ventricular end-diastolic pressure during pacing tachycardia. In contrast, patients with coronary artery disease paced to angina did not exhibit this normal decrease and, furthermore, often demonstrated an abrupt increase in left ventricular end-diastolic pressure in the immediate postpacing period.

Although a variety of hemodynamic abnormalities associated with pacing-induced ischemia have been described (1–14), it is uncertain whether the magnitude of these hemo-

dynamic changes reflects quantitatively the amount of myocardium that is ischemic during angina. The development of thallium-201 scintigraphy has provided a method not only for detecting myocardial ischemia (15–30), but also for quantifying the amount of hypoperfused myocardium (22–28). Except at the extremes of coronary blood flow, initial myocardial uptake of thallium-201 has been shown to reflect myocardial perfusion, while redistribution of the radionuclide has been shown to correlate more closely with cellular viability (15,29). Diminished myocardial uptake of thallium-201 has been documented during exercise stress (16–20), during Prinzmetal's angina (30,31), in patients with acute or prior myocardial infarction (22,24–27) and in patients with severe coronary artery disease at rest (32). More recently, there has been evidence that ischemia induced by rapid atrial pacing may be detected and quantified with simultaneous thallium scintigraphy (33–35). In all of these situations, the combination of initial distribution and redistributed thallium images has provided a measure of both the amount of ischemic and infarcted myocardium in a given patient. Accordingly, the present study was undertaken to examine the relation between pacing-induced hemodynamic changes and the extent of myocardial ischemia as quantified by thallium-201 scintigraphy.

Methods

Study group. Twenty-five patients with a clinical diagnosis of angina pectoris underwent atrial pacing with hemodynamic monitoring and thallium scintigraphy at the time of cardiac catheterization. The study group consisted of 19 men and 6 women with a mean age of 55 years (range 34 to 69). On the basis of a prehospitalization clinical evaluation, all 25 patients were believed to have stable angina pectoris and were being treated with long-acting nitrates (18 patients), beta-adrenergic blocking agents (16 patients) or calcium channel blocking agents (3 patients), alone or in combination. All medications were continued until the time of catheterization. Prior myocardial infarction had been documented in 12 of the 25 patients. Two patients had previously undergone coronary artery bypass graft surgery at least 3 years before the time of this study and were being reevaluated because of recurrent chest pain. None of the patients at the time of study had clinical evidence of acute myocardial infarction, unstable angina pectoris, uncompensated congestive heart failure, significant ventricular ectopic rhythm, current valvular disease or cardiomyopathy. All patients gave written informed consent after the proposed study and its risks were described. There were no complications as a result of this investigation.

Cardiac catheterization and angiography. Coronary angiography was performed in all patients using the Judkins technique. Left ventriculography was performed with a pig-tail catheter with simultaneous biplane cine recording in the right and left anterior oblique projections.

A flow-directed Swan-Ganz thermodilution catheter was inserted percutaneously into the right femoral vein and advanced to the pulmonary artery. Pressure measurements were obtained at the inferior vena cava, right atrium, right ventricle, pulmonary artery and pulmonary capillary wedge positions. With the tip of the catheter positioned within the right atrium, simultaneous pressures were obtained in the right atrium and inferior vena cava. Subsequently, inferior vena cava measurements were used as a guide to the right atrial pressure. Systemic arterial pressure was monitored in all patients using a percutaneously placed radial catheter. Left ventricular pressures were obtained from a fluid-filled catheter within the left ventricle. Pressures were measured using P50 Micron pressure transducers attached directly to a manifold connected to the proximal hub of the intravascular catheter without intervening tubing. The frequency response characteristics of this system have been previously reported (36). Recordings were inscribed using a Honeywell Electronics for Medicine recorder (VR-12).

Atrial pacing protocol. After the completion of selective coronary angiography and left ventriculography, a bipolar flared pacing catheter (Atripace I, Mansfield Scientific Inc.) was placed within the right atrium by percutaneous puncture of the left femoral vein. When a satisfactory pacing threshold had been achieved, the pacing rate was increased rapidly until atrioventricular (AV) block occurred. If the patient developed AV block at a rate that was less than 85% of the age-predicted maximal heart rate, 1 mg of atropine was administered intravenously. All patients were subsequently able to be paced to the predicted heart rate or to a lower pacing rate at which angina occurred.

Approximately 30 minutes after the completion of left ventriculography, baseline pressure and cardiac output measurements were made. Pressures were recorded from the inferior vena cava and pulmonary artery, pulmonary capillary wedge position, systemic artery and left ventricle. Four thermodilution cardiac output determinations were made and averaged. Arterial and pulmonary artery blood samples were obtained for determination of a baseline arteriovenous oxygen difference.

Atrial pacing was then initiated at a rate of 80 beats/min and progressively increased by 15 beats/min every 2 minutes until the patient experienced typical and significant chest discomfort (graded by the patient as 5 or more on a scale of 1 to 10) or until a pacing rate greater than 85% of the age-predicted maximal heart rate had been achieved. At the maximal pacing rate, repeat measurements of pressures as well as repeat determinations of cardiac output and arteriovenous oxygen difference were made. Subsequently, the pacing was abruptly terminated with continuous recording of pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and systemic arterial pressure.

Thallium-201 scintigraphy. At the highest pacing rate, 1.5 to 2.0 mCi of thallium-201 was administered intravenously and pacing was subsequently continued for 5 minutes while hemodynamic data were obtained. During exercise-thallium testing, exercise is usually maintained for 30 to 60 seconds after injection of the radionuclide to allow the thallium to reach the myocardium. However, because of the rapid decrease in heart rate after the discontinuation of the pacing stimulus and the subsequent diminution of myocardial oxygen demand, the pacing time after thallium injection was extended to 5 minutes. To determine the time course of thallium distribution during the 5 minute pacing period, arterial blood samples were collected in the first seven patients studied. Samples were obtained at 1, 2, 3, 5, 10, 15 and 20 minutes after the time of intravenous injection. Counts of the blood from all seven patients demonstrated a similar peak and disappearance of thallium from the arterial blood, with arterial activity being highest during the first minute after pacing and subsequently decreasing to approximately one-tenth of the peak level within 5 minutes. Thus, the highest blood activity of thallium occurred well within the 5 minute pacing period (37).

Myocardial imaging was begun in the cardiac catheterization laboratory immediately after the discontinuation of the pacing stimulus. Images were obtained in the supine position and consisted of the anterior view, a 40° modified (30° cephalic) left anterior oblique view and 70° left anterior oblique view. A 37 photo-multiplier tube, Anger type scintillation camera (Technicare series 410) with a slant-hole collimator (Engineering Dynamics Corporation) (38) was used. Images were recorded with a 20% window centered on the mercury X-ray film produced after thallium decay (69 to 80 keV). Images were collected for 6 minutes in each view with a Technicare VIP Computer System and stored on flexible discs for subsequent analysis and photography.

Redistribution images were obtained in the same manner a minimum of 4 hours (range 4 to 6) after the cessation of pacing.

Data analysis. The degree of coronary stenosis was evaluated subjectively by two observers and estimated using the greatest degree of diameter narrowing in any projection.

A 50% or greater reduction in lumen diameter in any one view was considered hemodynamically significant.

After cessation of pacing, left ventricular end-diastolic pressure was measured by averaging beats numbered 5 through 15 after the last paced beat.

Systemic vascular resistance (SVR) was calculated using the following formula:

$$SVR = (\overline{MAP} - \overline{RA}) \times 80/CO,$$

where $\overline{MAP}$, $\overline{RA}$ and CO are mean arterial pressure, mean right atrial pressure and cardiac output, respectively. Right atrial pressure was obtained from the inferior vena cava pressure as previously described.

All thallium scans were interpreted subjectively by three of us without knowledge of coronary anatomy and agreement was by consensus. Thallium scans were quantified by dividing each of the three views (anterior and 40° modified and 70° left anterior oblique) into five segments (Fig. 1). Each of the 15 sections were labeled as being normal or hypoperfused and a thallium score was subsequently obtained by determining the total number of hypoperfused segments. Some decrease in activity in the apical segments due to thinning was accepted as normal. Thallium scores were calculated from each patient's scans at the maximal pacing rate and 4 hours after the cessation of pacing during delayed imaging. Reversible or redistributed defects were quantified by determining the difference between the two thallium scores.

Statistical analysis. Mean and standard deviation were calculated for all variables. Multiple groups of data were analyzed using analysis of variance. Paired dimensional data were analyzed using either the paired t test or Wilcoxon signed-rank test, where appropriate, for parametric and nonparametric distributions. Unpaired dimensional data were analyzed using either the unpaired t test or the Mann-Whitney U test where appropriate. All correlations between hemodynamic, thallium and coronary angiographic data were made using the Spearman's rank correlation. A probability (p) value of less than 0.05 was considered significant.

Figure 1. Interpretation of thallium scans: each segment is rated as being normal (**clear**) or hypoperfused (**stippled**). In the example, the total thallium score is 5 during maximal pacing (max pace), the delayed score is 2 and the redistributed score is 3 (5 minus 2). ANT = anterior; LAO = left anterior oblique.
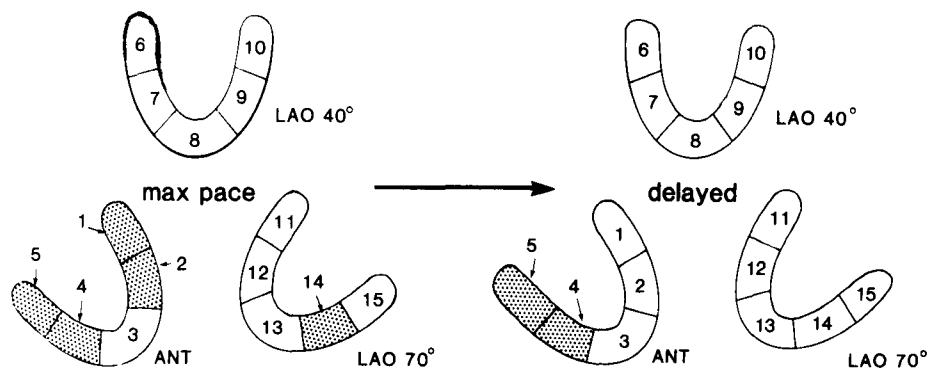
Results

Coronary angiography (Table 1). Five of the 25 patients had nonsignificant coronary artery disease with 4 of them having completely normal coronary artery anatomy and the remaining 1 having only a 25% stenosis in the distal left anterior descending artery. These five patients constitute Group 1 and serve as a normal control group.

The remaining 20 patients had significant coronary obstructions and constitute Group II. Eleven patients of this group had three vessel disease, four had two vessel disease and five had one vessel disease. The two patients who had undergone previous coronary artery bypass grafting (both patients had grafts to the left circumflex and left anterior descending arteries) demonstrated completely patent grafts, but both had progression of coronary artery disease in grafted vessels distal to the sites of the graft anastamoses and in the right coronary artery.

Left ventriculography (Table 1). Analysis of the left ventriculograms revealed that the patients without significant coronary artery disease (Group 1) had a higher left ventricular ejection fraction than the patients with such disease (Group II) (67 ± 4 versus $58 \pm 12\%$, $p < 0.05$). Patients in Group I also had a lower end-diastolic volume index (64 ± 13 versus 76 ± 20 ml/m^2, $p < 0.05$) and end-systolic volume index (21 ± 5 versus 33 ± 19 ml/m^2, $p < 0.02$).

Hemodynamics at rest and in response to pacing tachycardia in Group I (Table 2) and Group II (Table 3). The patients without significant coronary disease (Group I) did not differ significantly from the patients with significant disease (Group II) in any hemodynamic variable in

Table 1. Clinical Characteristics and Angiographic Data in 5 Patients Without (Group I) and 20 Patients With (Group II) Significant Coronary Artery Disease

Patient	Age (yr) & Sex	Prior MI	Prior Surgery	Nitrates	Medications Beta-Blocking Agents	Calcium Blocking Agents
Group I						
1	40M					
2	61M					
3	69F			+	+	
4	42M			+	+	
5	42M			+	+	
Mean ± SD	51 ± 13					
Total		0	0	3	3	0
Group II						
1	61F			+	+	
2	62F			+	+	
3	47M	+		+	+	
4	65M	+		+	+	
5	57M	+		+	+	
6	71M	+				
7	60M	+		+	+	
8	62M	+		+	+	
9	58F			+		
10	34M	+		+		
11	63M			+	+	
12	58F	+		+	+	+
13	41M	+		+		
14	59M	+				
15	46M			+		+
16	54M				+	
17	49M	+		+	+	+
18	59M					
19	61F	+	s/p CABG	+	+	
20	55M		s/p CABG	+	+	
Mean ± SD	56 ± 9					
Total		12	2	15	13	3

*$p < 0.05$ versus Group I; †$p < 0.02$ versus Group I. CABG = coronary artery bypass graft; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; F = female; LAD = left anterior descending artery; LCx = left circumflex artery; M = male; MI = myocardial infarction;

the control period before pacing. In response to pacing, the two groups did not differ significantly with respect to maximal paced heart rate (153 ± 12 versus 146 ± 19 beats/min), systolic blood pressure at maximal pacing (126 ± 10 versus 134 ± 28 mm Hg) or heart rate-blood pressure product (19,228 ± 1,949 versus 19,249 ± 3,191 mm Hg × beats/min).

At maximal pacing, Group I demonstrated no significant change in cardiac index, systemic vascular resistance and arteriovenous oxygen difference (Fig. 2). Group II, however, exhibited a decrease in cardiac index (prepacing 3.1 ± 0.6 liters/min per m², maximal pacing 2.7 ± 0.6 liters/min per m², $p < 0.01$) as well as an increase in systemic vascular resistance (prepacing 1,288 ± 425 dynes·s·cm⁻⁵, maximal pacing 1,517 ± 411 dynes·s·cm⁻⁵, $p < 0.01$) and a widening of arteriovenous oxygen difference (pre-

pacing 42 ± 10 ml/liter, maximal pacing 52 ± 9 ml/liter, $p < 0.01$).

Left ventricular end-diastolic pressure in Group I decreased slightly from the prepacing value during maximal pacing and subsequently returned to its baseline value in the postpacing period (prepacing 14 ± 2 mm Hg, maximal pacing 9 ± 5 mm Hg, postpacing 13 ± 3 mm Hg) (Fig. 3). In Group II, left ventricular end-diastolic pressure did not change significantly during maximal pacing, but did show a significant increase during the postpacing period (prepacing 15 ± 5 mm Hg, postpacing 25 ± 9 mm Hg, $p < 0.01$). End-diastolic pressure at maximal pacing and in the postpacing period was not measured in the first seven patients studied.

Pulmonary capillary wedge pressure in Group I showed no significant change in prepacing, maximal pacing and

Table 1. Clinical Characteristics and Angiographic Data in 5 Patients Without (Group I) and 20 Patients With (Group II) Significant Coronary Artery Disease *(continued)*

| Patient | Ventriculographic Analysis | | | Vessels With CAD |
	EDVI (ml/m²)	ESVI (ml/m²)	EF (%)	
Group I				
1	70	25	64	0
2	66	24	67	0
3	74	22	70	0
4	67	25	63	0
5	41	11	73	0
Mean ± SD	64 ± 13	21 ± 5	67 ± 4	
Total				
Group II				
1	81	30	63	3 LAD, LCx, RCA
2	76	20	73	3 LAD, LCx, RCA
3	90	32	64	2 LAD, RCA
4	82	31	62	3 LAD, LCx, RCA
5	83	40	52	2 LAD, RCA
6	127	103	19	1 RCA
7	83	46	45	3 LAD, LCx, RCA
8	86	37	57	3 LAD, LCx, RCA
9	70	32	54	1 RCA
10	81	40	51	3 LAD, LCx, RCA
11	74	25	65	3 LAD, LCx, RCA
12	71	22	69	3 LAD, LCx, RCA
13	59	29	51	1 RCA
14	62	19	70	2 LAD, LCx
15	34	13	62	1 LAD
16	32	10	69	2 LCx, RCA
17	83	25	71	1 RCA
18	84	45	46	3 LAD, LCx, RCA
19	89	49	45	3 LAD, LCx, RCA
20	66	25	61	3 LAD, LCx, RCA
Mean ± SD	76 ± 20*	33 ± 19†	58 ± 12*	3VD:11 2VD:4 1VD:5

RCA = right coronary artery; SD = standard deviation; s/p = status post; 1VD = one vessel disease; 2VD = two vessel disease; 3VD = three vessel disease.

Table 2. Effects of Pacing Tachycardia on Hemodynamics and Myocardial Thallium Uptake in Group I (patients without significant coronary artery disease)

	Case 1	Case 2	Case 3	Case 4	Case 5	Mean ± SD
Heart rate (beats/min)						
Pre	60	80	75	80	76	74 ± 8
Max	150	143	146	150	174	153 ± 12
Post	60	75	78	70	102	77 ± 16
SBP (mm Hg)						
Pre	130	120	150	125	145	134 ± 13
Max	120	140	125	115	130	126 ± 10
Post	128	130	160	120	150	138 ± 17
RPP (mm Hg × beats/min)						
Pre	17,800	9,600	11,250	10,000	11,020	9,934 ± 1,377
Max	18,000	20,020	18,250	17,250	22,620	19,228 ± 1,949
CI (liters/min per m^2)						
Pre	3.0	3.1	2.8	2.8	4.5	3.2 ± 0.8
Max	3.3	3.6	2.0	2.8	4.3	3.2 ± 0.9
avO$_2$ (ml/liter)						
Pre	42	37	33	38	40	38 ± 3
Max	39	44	44	42	36	41 ± 3
SVR (dynes·s·cm^{-5})						
Pre	1,607	939	1,636	1,328	1,147	1,331 ± 299
Max	1,325	853	1,976	1,376	1,062	1,318 ± 424
LVEDP (mm Hg)						
Pre	13	12	13	14	16	14 ± 2
Max	6	8	5	10	17	9 ± 5
Post	9	14	11	15	16	13 ± 3
PCW (mm Hg)						
Pre	7	12	12	6	16	11 ± 4
Max	6	12	8	6	18	10 ± 5
Post	4	10	5	4	13	7 ± 4
PA (mm Hg)						
Pre	18	21	22	14	22	19 ± 3
Max	16	20	14	16	26	18 ± 5
Post	16	18	12	14	22	16 ± 4
Thallium score						
Maximal	0	1	0	1	0	0.4 ± 0.5
Delayed	0	1	0	0	0	0.2 ± 0.4
Redistributed	0	0	0	1	0	0.2 ± 0.4

avO$_2$ = arteriovenous oxygen difference; CI = cardiac index; LVEDP = left ventricular end-diastolic pressure; Max = maximal pacing; PA = mean pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; Post = postpacing; Pre = prepacing; RPP = rate-pressure product; SBP = systolic blood pressure; SD = standard deviation; SVR = systemic vascular resistance.

postpacing periods (Fig. 3). In contrast, patients in Group II demonstrated an increase in pulmonary capillary wedge pressure during maximal pacing (prepacing 11 ± 4 mm Hg, maximal pacing 17 ± 5 mm Hg, p < 0.01) that returned toward baseline in the postpacing period (postpacing 14 ± 8 mm Hg, p = NS).

Similarly, there was no significant change in mean pulmonary artery pressure in Group I during prepacing, maximal pacing and postpacing periods (Fig. 3). However, Group II demonstrated an increase in mean pulmonary artery pressure during maximal pacing (prepacing 18 ± 4 mm Hg, maximal pacing 22 ± 5 mm Hg, p < 0.01) that returned to normal in the postpacing period (postpacing 20 ± 6 mm Hg, p = NS).

Thallium scintigraphy with pacing tachycardia (Tables 2 and 3). *Patients with normal scans at maximal pacing.* Three patients in Group I and three patients in Group II had normal thallium scans at maximal pacing. None of these patients experienced chest pain.

Patients with abnormal scans at maximal pacing. Two patients in Group I and 17 in Group II had abnormal thallium scans at maximal pacing. Mean total thallium score at maximal pacing, reflecting the number of segments hypoperfused at maximal pacing stress, was significantly lower for Group I than Group II (0.4 ± 0.5 versus 4.9 ± 3.1 segments, p < 0.01). Quantification of redistributing defects in both groups was obtained by subtracting the thallium score during delayed scanning from the total thallium score

Figure 2. Changes in cardiac index, systemic vascular resistance (SVR) and arteriovenous oxygen (avO₂) difference with pacing tachycardia. CAD = coronary artery disease; max pace = maximal pacing; p = probability.
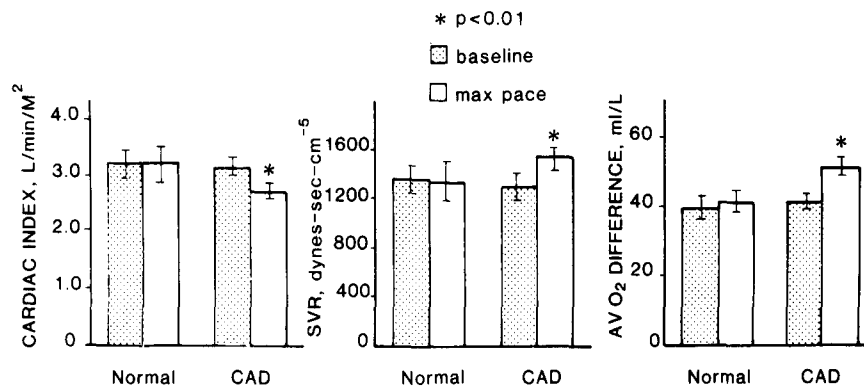
at maximal pacing to obtain a redistributed thallium score for each patient. The mean redistributed thallium score was lower for Group I than Group II (0.2 ± 0.4 versus 2.4 ± 2.7 segments, p < 0.01).

Patients with defects on delayed scans. One patient in Group I and 13 patients in Group II had persistent defects that were present on delayed scans obtained 4 hours after the cessation of pacing. Twelve of the 13 patients in Group II had clinical evidence of prior myocardial infarction and in all patients, there was a thallium defect that corresponded to the location of prior myocardial injury.

Of the two patients in Group I who had an abnormal scan at maximal pacing, one manifested a transient defect that disappeared during the delayed scans; neither patient had chest pain or a significant hemodynamic abnormality during pacing. Of the 17 patients that had an abnormal thallium scan at maximal pacing, 14 had redistributing defects with improved thallium perfusion during delayed imaging. Nine of these patients experienced chest pain during pacing that resolved promptly after the cessation of pacing; the three patients with fixed nonredistributing defects did not experience chest pain.

Correlation between hemodynamic variables and thallium score (Fig. 4 and 5). There was no significant correlation between thallium scores and pacing-induced changes in cardiac index, arteriovenous oxygen difference, systemic vascular resistance, mean arterial pressure and mean pulmonary artery pressure. There was, however, a significant correlation (Spearman rank r = 0.64, p < 0.01) between redistributed thallium score and the increase in left ventricular end-diastolic pressure in the postpacing period (Fig. 4). There was an even higher correlation (Spearman rank r = 0.90, p < 0.001) between total thallium score at maximal pacing and an increase in left ventricular end-diastolic pressure in the postpacing period (Fig. 5). Analysis of the relation between thallium score and an increase in mean pulmonary capillary wedge pressure during maximal pacing revealed a poor correlation (Spearman rank r = 0.46, p < 0.05) for redistributed thallium score and a slightly better correlation (Spearman rank r = 0.49, p < 0.02) for maximal paced thallium score.

Correlation between hemodynamic changes, thallium scores and coronary angiography. To further examine the relation between hemodynamic changes and the amount of ischemic or infarcted myocardium, or both, the relation between hemodynamic abnormalities and the number of diseased coronary vessels was investigated. There was a significant correlation (Spearman rank r = 0.82, p < 0.001) between the number of diseased vessels and the postpacing increase in left ventricular end-diastolic pressure. In addi-

Figure 3. Changes in left ventricular end-diastolic pressure (LVEDP), mean pulmonary capillary wedge pressure (PCW) and mean pulmonary artery pressure (PA) with pacing tachycardia. post pace = after pacing, other abbreviations as in Figure 2.
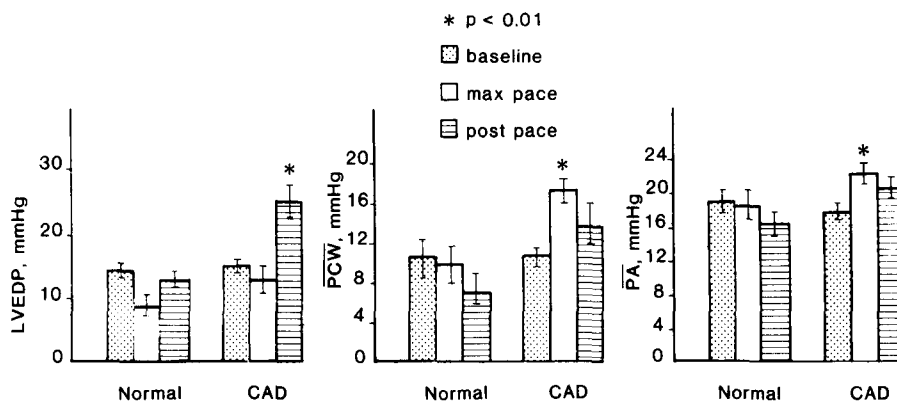
Table 3. Effects of Pacing Tachycardia on Hemodynamics and Myocardial Thallium Uptake in Group II (patients with significant coronary artery disease)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Heart rate (beats/min)										
Pre	60	70	53	60	73	77	84	60	99	112
Max	140	125	150	110	174	144	155	140	155	182
Post	65	70	56	60	75	92	110	57	82	113
SBP (mm Hg)										
Pre	124	160	180	135	110	140	160	130	15	100
Max	140	175	180	150	80	110	145	150	35	100
Post	140	175	170	120	160	120	140	130	135	100
RPP (mm Hg × beats/min)										
Pre	7,440	11,200	9,540	8,100	8,030	10,780	13,440	7,800	13,365	11,200
Max	19,600	21,875	27,000	16,500	13,920	15,840	22,475	21,000	20,925	18,200
CI (liters/min per m^2)										
Pre	2.3	n 3.5	3.1	2.8	3.2	2.6	2.8	2.5	3.5	4.6
Max	1.9	2.3	2.5	2.7	1.6	1.9	2.4	2.8	2.5	3.1
avO$_2$ (ml/liter)										
Pre	42	44	52	69	21	41	37	48	37	38
Max	55	47	59	66	76	59	53	50	56	42
SVR (dynes·s·cm^{-5})										
Pre	2,379	2,085	1,627	1,172	876	1,400	1,568	1,400	1,018	771
Max	2,475	2,189	1,838	1,651	1,600	1,733	1,709	1,712	1,423	1,202
LVEDP (mm Hg)										
Pre	10	4	18	14	7	19	16	10	18	20
Max	‡	‡	‡	‡	‡	12	12	6	14	5
Post	‡	‡	‡	‡	‡	24	‡	18	22	20
PCW (mm Hg)										
Pre	11	5	14	11	6	18	10	8	8	9
Max	17	15	13	31	24	18	16	17	18	13
Post	14	10	12	20	12	19	†	13	13	13
PA (mm Hg)										
Pre	23	10	21	14	16	20	18	14	18	15
Max	21	18	14	18	33	28	22	18	27	19
Post	24	15	22	34	30	19	20	14	22	17
Thallium score										
Maximal pacing	4	0	2	10	6	5	5	6	0	6
Delayed	0	0	1	5	5	5	1	3	0	6
Redistribution	4	0	1	5	1	0	4	3	0	0

tion, the number of diseased vessels correlated with the maximal paced thallium score (Spearman rank r = 0.59, p < 0.005) and with the redistributed thallium score (Spearman rank r = 0.61, p < 0.002).

Discussion

This study demonstrated that in a group of 25 patients stressed with pacing-induced tachycardia, the largest changes in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure occurred in the patients with both the largest maximal paced total thallium scores and the largest redistributed thallium scores. This suggests that these hemodynamic abnormalities reflect the amount of myocardial tis-

sue at ischemic jeopardy, and may be useful in estimating the total amount of nonfunctioning myocardium during maximal pacing stress.

Pacing-induced hemodynamic changes: comparisons with previous studies. Previous investigators (1–14) described the hemodynamic alterations associated with the pacing-induced ischemic state and contrasted the hemodynamic changes seen in patients with normal coronary arteries and those observed in patients with significant coronary obstructive disease. Patients without ischemic heart disease who are stressed by atrial-paced tachycardia generally demonstrate no significant change in cardiac output, mean arterial pressure, systemic vascular resistance and arteriovenous oxygen difference. In addition, they exhibit a decrease in left ventricular end-diastolic pressure during maximal

Table 3. Effects of Pacing Tachycardia on Hemodynamics and Myocardial Thallium Uptake in Group II (patients with significant coronary artery disease) *(continued)*

	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16	Case 17	Case 18	Case 19	Case 20	Mean ± SD
Heart rate (beats/min)											
Pre	56	75	88	56	95	57	77	60	52	72	72 ± 17
Max	128	140	171	133	143	150	156	110	154	156	146 ± 19
Post	60	75	78	73	109	57	75	63	52	53	74 ± 19
SBP (mm Hg)											
Pre	140	120	105	130	110	130	130	180	110	120	132 ± 23
Max	130	110	105	170	120	130	130	180	115	115	134 ± 28
Post	130	120	120	150	110	135	130	190	110	120	135 ± 23
RPP (mm Hg × beats/min)											
Pre	7,840	9,000	9,240	7,280	10,450	7,410	10,010	10,800	5,720	8,640	9,266 ± 1,974
Max	16,640	15,400	17,955	22,610	17,160	19,500	20,280	19,800	17,710	17,940	19,249 ± 3,191
CI (liters/min per m²)											
Pre	2.3	3.5	3.2	3.8	4.0	3.5	3.2	2.8	2.6	2.9	3.1 ± 0.6
Max	2.1	3.5	3.4	3.7	3.5	2.9	3.1	2.8	2.8	2.7	2.7 ± 0.6*
avO$_2$ (ml/liter)											
Pre	45	38	47	35	28	36	44	40	41	53	42 ± 10
Max	57	46	44	41	37	43	49	52	43	56	52 ± 9*
SVR (dynes·s·cm^{-5})											
Pre	1,450	1,018	1,007	833	773	1,300	1,152	1,660	1,076	1,191	1,288 ± 425
Max	1,725	909	952	1,177	1,061	1,607	1,202	1,758	1,133	1,296	1,517 ± 411*
LVEDP (mm Hg)											
Pre	21	18	16	19	10	16	16	12	23	14	15 ± 5
Max	26	15	12	29	6	4	23	†	16	7	13 ± 8
Post	40	30	26	39	20	19	23	†	34	22	25 ± 9*
PCW (mm Hg)											
Pre	20	12	10	16	7	12	5	8	14	11	11 ± 4
Max	27	16	14	18	8	12	15	14	20	18	17 ± 5*
Post	34	10	13	36	6	4	5	7	14	10	14 ± 8
PA (mm Hg)											
Pre	26	19	15	21	17	20	16	16	20	15	18 ± 4
Max	29	24	20	32	18	20	19	20	22	19	22 ± 5*
Post	29	20	14	29	14	20	16	15	17	18	20 ± 6
Thallium score											
Maximal pacing	9	8	7	7	1	0	5	3	9	4	4.9 ± 3.1†
Delayed	1	4	7	2	0	0	1	0	8	0	2.5 ± 2.7†
Redistribution	8	4	0	5	1	0	4	3	1	4	2.4 ± 2.7†

*p < 0.01 compared with prepacing value; †p < 0.01 compared with Group I; ‡ not measured. Abbreviations as in Table 2.

pacing tachycardia with no significant increase in end-diastolic pressure after pacing. Patients with coronary artery disease paced to angina may also show no significant change in cardiac output, mean arterial pressure, systemic vascular resistance and arteriovenous oxygen difference, but generally differ from nonischemic subjects in that they demonstrate either no change or a slight increase in left ventricular end-diastolic pressure during maximal pacing with a marked increase in end-diastolic pressure in the postpacing period. This study confirms previously reported pacing-induced hemodynamic changes in patients with normal coronary arteries with respect to cardiac output, systemic vascular resistance, arteriovenous oxygen difference and left ventricular end-diastolic pressure. In addition, however, our results suggest that cardiac output in patients with obstruc-

tive coronary disease may actually decrease from baseline values with a concordant increase in systemic vascular resistance and a widening of arteriovenous oxygen difference during maximal pacing tachycardia. Moreover, we have described additional pacing-induced changes in pulmonary capillary wedge and mean pulmonary artery pressures differentiating patients with normal coronary arteries from those with significant coronary obstructions.

Mechanisms underlying hemodynamic abnormalities. Although our findings differ somewhat from those of Parker et al. (2), they are similar to those of Helfant et al. (4) and Sowton et al. (1), and the differences probably reflect the wide spectrum of pacing-induced hemodynamic abnormalities in patients with coronary artery disease. With respect to cardiac output, for example, Helfant and coworkers (4)
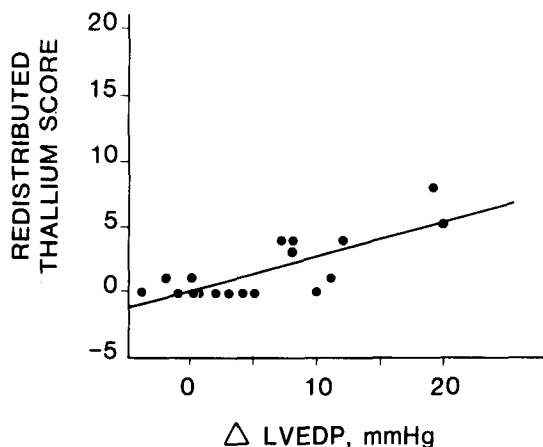
Figure 4. Correlation of redistributed thallium score with an increase in left ventricular end-diastolic pressure (LVEDP) in the post-pacing period (Spearman rank r = 0.64, p < 0.01).

observed a decrease in cardiac output in the presence of pacing-induced angina. Sowton et al. (1) found no change in cardiac output, but noted an increase in pulmonary capillary wedge pressure and mean pulmonary artery pressure in a subset of patients with pacing-induced angina. These partly conflicting results may be related to the intensity of pacing-induced ischemia, its duration before the measurement of hemodynamic variables and the amount of myocardium that has become ischemic. At the onset of angina, only a small proportion of the myocardium may be ischemic, and there may be little or no change in the hemodynamic status. However, as ischemia progresses with the continuation of pacing tachycardia, a larger proportion of jeopardized myocardium presumably develops ischemic dysfunction with characteristic hemodynamic deterioration. The hemodynamic changes in this study were measured after approximately 5 minutes of pacing-induced angina that the patient described as moderately intense (>5 on a scale of 1 to 10, where 1 = barely perceptible angina and 10 = severe angina). As a result, the decrease in cardiac output that was noted in our patients with coronary artery disease, measured both by a decrease in thermodilution flow measurements and a widening of arteriovenous oxygen difference, probably reflects more extensive myocardial ischemia. Accompanying this decrease in cardiac output, one would expect a reflex increase in systemic vascular resistance mediated by arterial baroreceptors in an attempt to maintain systemic blood pressure, and this did occur in our patients.

The mechanism of the increased left ventricular end-diastolic pressure in the setting of pacing-induced ischemia has been a subject of much interest (2,6,7,9–14). The increase in end-diastolic pressure is probably related not only to an increase in left ventricular end-diastolic volume (2,6,9–11), but also to an upward shift in the left ventricular

diastolic pressure-volume relation so that pressure is higher at any given volume or myocardial segment length throughout diastole (6,7,9,11–14). Although some patients with ischemia manifest an increase in end-diastolic pressure during the period of maximal pacing, most investigators have documented the largest increase in pressure during the immediate postpacing period. An increase in left ventricular end-diastolic pressure may not occur during maximal pacing because of the substantial decrease in end-diastolic dimension and volume that occurs with pacing-induced tachycardia (7,10).

Pulmonary capillary wedge and mean pulmonary artery pressures, unlike left ventricular end-diastolic pressure, increased most significantly during the period of maximal pacing tachycardia in patients with coronary artery disease. The increase in these pressures suggests that left ventricular filling during maximal pacing is impeded not only by a shortened diastole secondary to tachycardia, but also by a decrease in left ventricular distensibility in the setting of pacing-induced ischemia. In addition, a role for pacing-induced mitral regurgitation cannot be ruled out as a cause for increased pulmonary capillary wedge and mean pulmonary artery pressures during maximal pacing; notably, two patients in Group II developed significant V waves during pacing-induced angina that resolved soon after the cessation of pacing. Pulmonary capillary wedge and mean pulmonary artery pressures generally decreased with the cessation of pacing and resultant immediate decrease in heart rate in Group II patients, and neither variable remained significantly increased above its prepacing baseline value.

Hemodynamic correlates of myocardium at risk. Although investigators have previously noted the variable magnitude of pacing-induced hemodynamic changes, it has not been possible to determine whether the magnitude of

Figure 5. Correlation of maximal paced total thallium score with an increase in left ventricular end-diastolic pressure (LVEDP) in the postpacing period (Spearman rank r = 0.90, p < 0.001).
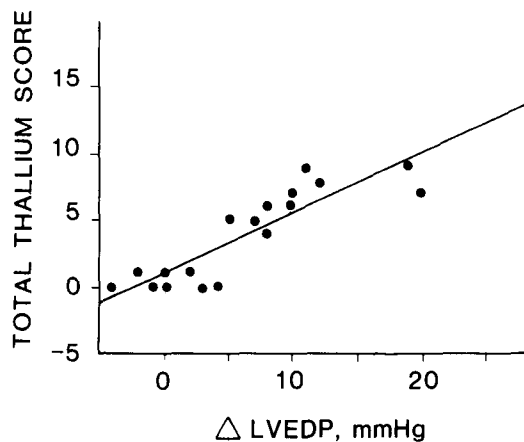
these hemodynamic abnormalities is a direct function of the mass of reversibly ischemic myocardium. The development of thallium-201 imaging in conjunction with treadmill exercise testing has not only resulted in an improved sensitivity and specificity of routine exercise electrocardiography, but has provided a means of quantifying both ischemic and infarcted myocardium (16–23). Thallium defects at maximal exercise presumably represent both ischemic and infarcted tissue, whereas persistent defects during delayed imaging after reversible ischemia has been abolished are thought to represent infarcted myocardium. By analogy with exercise thallium-201 imaging, the thallium score at maximal pacing tachycardia in this study would represent a measure of both infarcted and ischemic tissue, whereas the difference between maximal paced thallium score and thallium score at the time of delayed scanning, represented as a redistributed thallium score, should represent the amount of reversibly ischemic myocardium.

The positive correlation between redistributed thallium score and the increase in postpacing left ventricular end-diastolic pressure indicates that those patients with the greatest increase in end-diastolic pressure tended to have the largest areas of reversible ischemia, as judged from the thallium scintigrams. This further suggests that the magnitude of the increase in end-diastolic pressure after pacing tachycardia stress testing may be useful in predicting the amount of myocardium at jeopardy from ischemic events. Although the increase in pulmonary capillary wedge pressure during maximal pacing correlated positively with the amount of myocardial ischemia, this correlation was much less impressive than the correlation for end-diastolic pressure in our study. In some patients, it is possible that the presence of mitral regurgitation secondary to pacing-induced papillary muscle ischemia may have led to an increase of pulmonary capillary wedge pressure out of proportion to the mass of ischemic myocardium.

Hemodynamic correlates of the total mass of nonperfused myocardium. Although it seems clear from our study that pacing-induced hemodynamic changes correlate significantly with the amount of ischemic myocardium, the factor that showed the best correlation with postpacing end-diastolic pressure and maximal pacing pulmonary capillary wedge pressure was the total thallium score at maximal pacing tachycardia. Because the maximal pacing total thallium score is a measure of both ischemic and infarcted myocardium, this suggests that hemodynamic changes are proportional not only to the amount of reversibly ischemic tissue, but also to the total amount of nonfunctioning myocardium. Notably, three patients in Group II with a history of prior myocardial infarction showed no evidence of reversible ischemia by thallium redistribution, but demonstrated fixed thallium defects corresponding to their prior infarction. All three of these patients had a significant increase in left ventricular end-diastolic pressure in the postpacing period.

To explain the hemodynamic changes in these patients, several possible alternatives must be considered. One possibility is that the fixed thallium defects in these patients obscured the presence of a truly reversible defect. Thus, although there is generally a good correlation between postmortem myocardial infarct size and the estimated size of thallium defects at rest in scans obtained in patients with myocardial infarction (25,27), defects at rest may also include a significant proportion of ischemic myocardium in the border zone surrounding infarcts. For example, Bulkley et al. (26) found a very close correlation between defect size and the size of infarcts measured at autopsy in 24 patients undergoing scanning at the time of their infarction. In five patients, however, there was a significant discrepancy between the size of the thallium defect and the infarct size in which the thallium defect overestimated a relatively small amount of myocardial necrosis at the time of autopsy. All five patients manifested widespread electrocardiographic abnormalities and severe left ventricular dysfunction suggesting the presence of a much larger area of reversibly ischemic myocardium surrounding the infarct zone. Peri-infarct myocardium is certainly different from myocardium that has been made ischemic by pacing; however, clinically late (for example 24 hours) redistribution is occasionally seen during exercise testing when 4 hour delayed imaging appears to show only fixed defects (39). It is possible, therefore, that systolic and diastolic function changes in a borderline ischemic zone may explain pacing-induced hemodynamic changes in patients with an apparently "fixed" thallium defect.

An alternative explanation for the increase in postpacing end-diastolic pressure in patients with primarily fixed thallium defects is that these patients experienced a change in myocardial loading conditions secondary to pacing tachycardia. Patients in Group II had an overall decrease in cardiac output during maximal pacing with an associated increase in systemic vascular resistance. As a result, left ventricular end-diastolic pressure in these patients and increase transiently secondary to an increased afterload in the immediate postpacing period.

Correlations between hemodynamic changes and coronary anatomy. In addition to the positive correlations between hemodynamic changes and thallium scores, there was a significant correlation between the number of diseased vessels and the postpacing increase in left ventricular end-diastolic pressure. Because the number of diseased vessels represents, at best, only a crude measure of myocardium at risk (for example, location of stenoses, proximal or distal, is not taken into account), one would not expect this correlation to be extremely high. Nevertheless, the positive correlation between coronary anatomy and postpacing left ventricular end-diastolic pressure as well as the positive

correlations between coronary anatomy and thallium scores add further evidence that pacing-induced hemodynamic changes may reflect the mass of ischemic and infarcted myocardium.

Additional studies. To assess the overall role of the pacing stress test, and particularly the meaning of pacing-induced hemodynamic changes, it will be necessary to examine pacing-induced hemodynamic abnormalities in a larger group of patients than has been included in this study. In particular, if the pacing-induced increase in left ventricular end-diastolic and pulmonary capillary wedge pressures is indeed specific for pacing-induced myocardial ischemia due to large vessel coronary artery disease, it will be necessary to rule out pacing-induced hemodynamic abnormalities in patients with other forms of heart disease, including those with valvular, hypertensive and cardiomyopathic processes. In addition, it is notable that all patients in this study had moderately well preserved ventricular function, with all but one patient having an ejection fraction greater than 45%. It is possible that patients with more severe left ventricular dysfunction manifest different or more severe patterns of hemodynamic dysfunction.

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