Adaptation to the stress of tachycardia in patients with coronary artery disease: insight into the mechanism of the warm-up phenomenon

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ABSTRACT Adaptation to exercise or the “warm up phenomenon” has been observed in some patients with angina pectoris. To investigate adaptation, eleven patients with exertional angina pectoris and angiographic evidence of coronary artery disease underwent two identical bouts of sequential tachycardia stress separated by a brief recovery period. Manifestations of ischemia were less during the second stress, as evidenced by a reduction in the severity of angina pectoris, less ST segment depression, and improved lactate extraction. Peak coronary blood flow during the second stress (81 ± 20 ml/min) was not significantly different from that during the first (95 ± 32 ml/min). Regional myocardial oxygen consumption, however, was significantly (p = .03) lower during the second stress (8.8 ± 2.4 ml O2/min) when compared with the first (11.4 ± 3.0 ml O2/min). Thus, patients with coronary artery disease can develop anginal tolerance to the stress of tachycardia similar to that observed after repeated bouts of exercise. A relative reduction in myocardial oxygen consumption, rather than an increase in coronary blood flow, appears to account for this phenomenon.


IN 1785, William Heberdeen described a patient in whom angina pectoris initially developed during exercise but then paradoxically disappeared as exercise was continued.¹ This phenomenon has been termed “walk through” or “second wind” angina. A related form of angina has also been acknowledged wherein a patient, after terminating exercise because of the development of angina, is subsequently able to resume angina-free exercise. This latter adaptation has been termed the “warm up phenomenon” or “angina of first effort.”

Several investigators have documented reduced myocardial ischemia in patients demonstrating either walk-through angina or the warm-up phenomenon during exercise stress testing. MacAlpin and Kattus² described 12 patients who were able to adapt to treadmill exercise. Nine patients demonstrated the disappearance or lessening of anginal pain and ischemic ST segment depression with continued walking. Three patients showed increased exercise capacity after having been “warmed up” by a prior exercise period that resulted in angina. Jaffe and Quinn³ observed less electrocardiographic evidence of ischemia in 21 of 22 patients during the second of two bicycle exercise tests when the second test had been preceded by a 30 min period of walking.

Although both the warm-up phenomenon and walk-through angina are acknowledged clinical entities, their mechanisms have not been identified. MacAlpin and Kattus³ inferred a common underlying mechanism since the enhanced exercise tolerance that is fundamental to both is dependent on antecedent exercise. They further emphasized the interrelationship between the two entities by suggesting that the warm-up phenomenon may be a forme fruste of walk-through angina since they observed patients in whom the former evolved into the latter. These investigators and others³,⁴ have suggested that a decrease in myocardial oxygen consumption is not the underlying mechanism responsible for increased tolerance to exercise. Rather, they postulate that enhanced coronary blood flow during the second exercise period is the responsible mechanism.

With these considerations in mind, we designed a protocol to further investigate adaptation to stress in patients with exertional angina pectoris. Coronary blood flow and myocardial oxygen consumption were

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measured during two successive bouts of tachycardia stress in symptomatic patients with obstructive coronary artery disease. Specific objectives were to determine (1) if the second of two episodes of pacing tachycardia stress results in less myocardial ischemia and (2) if ischemia is less whether the mechanism is an increase in coronary oxygen delivery, a reduction in myocardial oxygen consumption, or both.

Methods

Patient population. Subjects were selected from a group of patients undergoing diagnostic cardiac catheterization and with a history of stable exertional angina pectoris. The following inclusion criteria had to be met: (1) coronary angiographic documentation of 70% or greater (diameter reduction) stenosis of the proximal left anterior descending coronary artery, (2) absence of 50% or greater stenosis of the left main, circumflex, or right coronary artery, (3) no nitrate administration during the diagnostic phase of cardiac catheterization, (4) ability to catheterize the great cardiac vein of the patient with a thermodilution catheter, (5) presence of sinus rhythm, and (6) willingness of the patient to participate in the investigation. Eleven patients were recruited. No attempt was made to extract a history of either walk-through angina or the warm-up phenomenon from these patients before their recruitment.

Study protocol. Patients were catheterized while in a fasting state and premedicated with either 10 mg oral diazepam or 50 mg diphenhydramine. All antianginal medications had been discontinued the day before the procedure. After the diagnostic catheterization, a No. 7F or 8F coronary sinus flow catheter (Willon-Webster Co., Altadena, CA) was advanced under fluoroscopic guidance into the great cardiac vein. The catheter tip was positioned at the junction of the anterior interventricular and the great cardiac veins. Coronary venous drainage at this site originates from myocardium in the distribution of the left anterior descending coronary artery. In seven patients an additional bipolar electrode pacing catheter was positioned in the mid right atrium. Pacing in the remaining four subjects was accomplished by means of electrodes in the thermodilution catheter. The relationship of one of the opaque electrodes of the thermodilution catheter to a bony landmark during the inspiratory phase of the respiratory cycle served as a reference for maintaining catheter position. If such a relationship was not present, then the position of the electrode was marked in ink on the video monitor screen for reference. Systemic arterial blood pressure and arterial blood samples for determination of oxygen content and lactate concentration were obtained through No. 7F NIH catheter placed in the descending aorta. Atrial or coronary sinus pacing was achieved with an external pulse generator calibrated to permit serial pacing at selected rates. Patients were instructed to report the occurrence of any symptoms resembling their anginal discomfort. Furthermore, in reporting their discomfort, patients were requested to quantify the severity of discomfort on a 1 to 10 scale with 1 being discomfort that was just perceptible and 10 being extremely severe discomfort. The study protocol was initiated at least 20 min after diagnostic angiography.

The study protocol was composed of five phases. During the first phase, control 1 (C1), the heart of each patient was paced to 20 beats/min faster than the basal sinus heart rate, or to approximately 80 beats/min. After 2 min of accommodation, systemic arterial pressure, heart rate, electrocardiographic lead V5, and great cardiac vein flow were recorded. Simultaneous paired samples of great cardiac vein and aortic blood were obtained for determination of oxygen content and lactate concentration.

During the second phase of the protocol, pacing 1 (P1), the rate of atrial pacing was incrementally increased 20 beats/min every 2 min until the development of moderate (grade 5/10) angina or a heart rate of 150 beats/min. If second-degree atrioventricular block limited achievement of the above end points, 1.0 mg atropine was administered intravenously. If moderate angina occurred, the elapsed time to the development of angina was recorded while pacing continued (2 to 4 min) without a further increase in rate. Values for the parameters listed above were again recorded and blood samples obtained, after which pacing was terminated. The degree of ST segment shift resulting from tachycardia stress was determined immediately after the cessation of pacing.

After P1, patients were allowed a brief (5 to 15 min) recovery period.

Control 2 (C2) was the next phase of the protocol. Atrial pacing was initiated at the same rate as in C1 for a similar 2 min accommodation period, after which hemodynamic parameters were again recorded and blood samples obtained.

The final phase of the protocol was pacing 2 (P2). The rate of atrial pacing was increased incrementally in the same fashion as in P1. The pacing rate was advanced to the same heart rate and elapsed time as in P1, after which all parameter values were again obtained. Hence, P2 duplicated P1.

Systemic arterial blood pressure, great cardiac vein flow, and the electrocardiogram were recorded simultaneously on a multichannel recorder (Electronics for Medicine, Model VR 12, White Plains, NY). Oxygen content, lactate concentration, rate-pressure product, regional myocardial oxygen consumption, and myocardial lactate extraction were determined as previously described.6

The presence and extent of electrocardiographic ST segment shift were determined by measuring the difference between the PQ junction and the ST segment 0.08 sec beyond the J point in precordial lead V5, for each pacing period.7 The value of ST depression was an average of the first five QRS complexes after cessation of pacing.

Serial observations were analyzed by two-way analysis of variance. Data from individual patients were considered as second factors to remove interpatient differences. Significant differences between specific means were determined by the Newman-Keuls multiple comparison test. Differences were considered to be significant if the p value was less than .05.

Results

Eleven patients underwent the investigational protocol. Complete subjective and objective data were obtained in nine patients. Coronary flow data were not attainable in two patients because of technical difficulties.

Of the 11 patients nine were men and two women. Ages ranged from 49 to 72 with a mean of 59 years.

Angina pectoris. During P1, nine of 11 patients developed angina pectoris (table 1). Among patients experiencing angina, the severity score ranged from 5 to 8 and averaged 6.6 ± 3.7 (mean ± SD). Elapsed time from onset of pacing to the development of angina ranged from 1 to 5 min and averaged 2.6 min. Cessation of rapid pacing resulted in the prompt relief of angina in each patient.

During P2 eight of 11 patients developed angina. Among these patients, the severity of angina ranged
from 1 to 7, with an average score of 3.7 ± 2.4, a value less than that for P1 (p = .002). One patient who experienced angina, grade 5/10, during P1 experienced no angina during P2. During P2, angina was less severe in six of eight patients. No patient who failed to develop angina during P1 subsequently developed angina during P2.

**Electrocardiographic changes.** Immediately after termination of rapid pacing during P1, ST segment depression greater than or equal to 0.5 mm was observed in nine of 10 patients. The extent of ST segment depression ranged from 0.5 to 2.5 mm and averaged 1.09 ± 0.70 mm (table 1). Among these nine patients, the ST segment was downsloping in one, flat in five, and upsloping in three.

After P2, ST segment depression greater than or equal to 0.5 mm was again observed in nine of 10 patients. The degree of ST segment depression ranged from 0.5 to 1.5 mm, with an average of 0.67 ± 0.35 mm, a value less than that for P1 (p = .03). No patient demonstrated downsloping ST segment depression, flat ST segments were seen in only two patients, and seven had upsloping ST segments. Compared with P1, a similar degree of ST segment depression was observed in three patients and less ST segment depression was noted in six patients. No patient demonstrated greater ST segment depression during P2 compared with P1.

**Myocardial lactate extraction.** Complete lactate data were available for nine patients (table 2, figure 1).

**TABLE 1**
Results of sequential pacing-induced tachycardia stress on the development of angina pectoris and ST segment depression

<table>
<thead>
<tr>
<th>Angina pectoris</th>
<th>Severity score</th>
<th>ST segment depression (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>9/11</td>
<td>6.6 ± 3.7, 1.09 ± 0.70</td>
</tr>
<tr>
<td>P2</td>
<td>8/11</td>
<td>3.7 ± 2.4, 0.67 ± 0.35</td>
</tr>
</tbody>
</table>

As determined on the electrocardiogram.

p < .05 P1 vs P2.

During C1 all patients extracted lactate, with a group mean value of 21 ± 15%. During P1 lactate extraction declined in each patient, with five patients demonstrating lactate production. The group mean lactate extraction during P1, −12 ± 31%, was lower (p = .01) than that during C1.

During C2 the group mean value of lactate extraction of 20 ± 17% was similar to that during C1, although one patient demonstrated lactate production. At P2, each patient again demonstrated a decline in lactate extraction. In only two patients, however, was lactate extraction changed to lactate production. The group mean lactate extraction during P2 of 7 ± 22% was lower than that during C2 (p = .04), but higher than that for P1 (p = .02). Thus, although both P1 and P2 resulted in a decrease in lactate extraction in each patient, the degree of reduction was less during P2 when compared with P1.

**FIGURE 1.** Values for lactate extraction from each patient during control (C1 and C2) and peak pacing stress (P1 and P2). Values above the dashed line indicate net lactate extraction while values below the dashed line signify lactate production. The decline in lactate extraction observed during P2 was less than that during P1.

**TABLE 2**
Coronary circulatory dynamics and myocardial metabolism during sequential tachycardia stress

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>P1</th>
<th>C2</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>81 ± 11</td>
<td>139 ± 20A</td>
<td>83 ± 10</td>
<td>138 ± 20A</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg/min \times 10^{-3})</td>
<td>12.4 ± 2.2</td>
<td>20.3 ± 5.6A</td>
<td>12.9 ± 2.4</td>
<td>20.5 ± 4.2A</td>
</tr>
<tr>
<td>GCVF (ml/min)</td>
<td>56 ± 17</td>
<td>95 ± 32A</td>
<td>58 ± 18</td>
<td>81 ± 20A</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml O2/min)</td>
<td>6.7 ± 1.8</td>
<td>11.4 ± 3.0A</td>
<td>6.3 ± 1.6</td>
<td>8.8 ± 2.4A B</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (%)</td>
<td>68 ± 6</td>
<td>68 ± 5</td>
<td>66 ± 8</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>21 ± 15</td>
<td>−12 ± 31A</td>
<td>20 ± 17</td>
<td>7 ± 22A B</td>
</tr>
</tbody>
</table>

GCVF = great cardiac vein flow.

*p < .05 C1 vs P1 or C2 vs P2; *p < .05 P1 vs P2.
Hemodynamics. Heart rate during C1 (81 ± 11 beats/min) did not differ from that during C2 (83 ± 10 beats/min: table 2). Peak pacing heart rates of 139 ± 20 and 138 ± 20 beats/min during P1 and P2, respectively, were nearly identical. Rate-pressure product rose from 12.4 ± 2.2 mm Hg/min at C1 to 20.3 ± 5.6 mm Hg/min at P1 (p = .001). A significant and very similar increase in rate-pressure product was also observed during P2 compared with C2. P1 and P2 values did not differ.

Great cardiac vein flow during C1 was 56 ± 17 ml/min and it increased to 95 ± 32 ml/min during P1 (p = .003; figure 2). Flow at C2, 58 ± 18 ml/min, was not dissimilar from that during C1. Flow increased (p = .05) to 81 ± 20 ml/min during P2, a value not significantly different from that at P1.

Regional myocardial oxygen consumption also rose (p = .001) with the initial tachycardia stress from 6.7 ± 1.8 to 11.4 ± 3.0 ml O₂/min (figure 3). Myocardial oxygen consumption at C2 was lower than at C1 in six of nine patients; the difference for the group, however, was not statistically significant. Compared with C2, P2 resulted in a significant increase in myocardial oxygen consumption to 8.8 ± 2.4 ml O₂/min. This value, however, was significantly (p = .03) lower than that during P1. Myocardial oxygen extraction did not change from control during either P1 or P2.

Discussion

The objective of this investigation was to determine whether patients with exertional angina could develop tolerance to stress and, if so, to gain insight into the mechanism(s) responsible. Pacing tachycardia was the chosen stress rather than exercise. Pacing is an easily reproduced stress in a given individual and permits stable positioning of the sampling catheter. Patients were carefully selected to ensure that coronary circulatory and myocardial metabolic data reflected the status of the zone of myocardial ischemia.

Symptomatic tolerance during the second stress test was observed in seven of the nine patients who developed angina pectoris during the initial test. A significant reduction in the angina score was noted for the group. This observation parallels the results of Jaffe and Quinn,¹ who observed less angina in their patients during the second of two sequential exercise stress tests. Our observation that patients with angina pectoris can adapt to pacing-induced tachycardia stress is also in agreement with the findings of Thadani et al.,⁸ who noted inability to reproduce angina in patients with coronary artery disease at similar heart rates during the second of two bouts of pacing tachycardia.

The decrease in frequency of angina or its severity during the second stress test was associated with a reduction in myocardial ischemia. The extent of ST depression, an electrocardiographic marker of ischemia, was less during P2 than P1, and the ST configuration also was suggestive of lessened ischemia. These observations are in accord with those of Jaffe and Quinn¹ and McAlpin and Kattus,² who observed less ST segment depression during exercise in patients demonstrating either the warm-up phenomenon or walk-through angina. Furthermore, although each patient in the present investigation demonstrated a decrease in lactate extraction during each subsequent
stress test, the extent of decline in lactate extraction was significantly less during P2 than during P1. Thus, both electrocardiographic and metabolic evidence indicate that patients were less ischemic during the second pacing stress.

It should be noted that a history of either walk-through angina or warm-up phenomenon was not a requisite for patient participation in this investigation. A history of chronic angina provoked by exercise was the only historical inclusion criterion. In such patients the prevalence of adaptation, as determined by simple clinical measures, was 78%. Hence, adaptation to sequential tachycardia stress is readily induced in patients with angina pectoris. This conclusion is further supported by the study of Jaffe and Quinn, who observed adaptation in 21 of 22 patients. Furthermore, variability in the degree of adaptation was observed in this study. One patient who noted angina during the first stress experienced no angina during the second, while others demonstrated a less dramatic degree of relief. A similar variability in the reduction of degree of ischemia was observed in individual values for lactate extraction. Thus, patients who readily acknowledge a history of walk-through angina or warm-up phenomenon may experience a very marked degree of adaptation and represent one end of the clinical spectrum of this phenomenon.

Reduced ischemia, or a more favorable balance between oxygen delivery and demand during P2, could have resulted from either a relative increase in coronary blood flow, a relative decrease in myocardial oxygen consumption, or both. A decrease in regional myocardial oxygen consumption rather than an increase in coronary blood flow was observed. This observation is in agreement with observations by Thadani et al. that angina could be provoked in patients during the second of two pacing-induced stresses if the heart rate during the second test was increased to a value higher than that during the first. Thus, in their investigation an additional increase in heart rate resulted in an additional increase in myocardial oxygen consumption during the second stress test to the point where oxygen need exceeded oxygen delivery.

By what mechanism was regional myocardial oxygen consumption reduced during the second pacing stress? This investigation was not specifically designed to address this question, and thus discussion in this regard must be speculative. There are three major determinants of myocardial oxygen consumption: (1) tension development, (2) contractile state, and (3) heart rate. Several additional factors also contribute to myocardial oxygen consumption, although to a much smaller degree. Since the paced heart rate was similar during each stress this determinant can seemingly be excluded as a responsible variable. Wall tension, a second major determinant, is directly related to left ventricular radius and intraventricular pressure and inversely related to ventricular wall thickness. In this investigation, peak systolic pressure at P2 did not differ from that at P1. Diastolic wall thickness was not measured, but would not be expected to change over the short term. A reduction in left ventricular volume as a result of decreased preload that in turn results from fluid loss and reduced peripheral vascular resistance has been postulated as a mechanism to explain the warm-up phenomenon related to exercise. Left ventricular volume was not measured in our investigation. To account for the observations of this investigation, left ventricular volume would have had to have been less during P2 than during P1. Studies in an animal preparation, however, do not support this possible explanation. In the awake, closed-chest pig with severe coronary artery stenosis, end-diastolic length within an ischemic zone decreased to a similar degree during each of two sequential episodes of tachycardia stress. Similar directional changes were observed in the non-ischemic zone. Hence, a differential decrease in left ventricular volume, more pronounced during P2 when compared with P1, would not be expected.

Finally, a reduction in regional myocardial contractility might account for the observed reduction in oxygen consumption. This concept implies that systolic contractile function of the ischemic zone during the second stress was less than that during the first. Variability in the extent of shortening of segments located at different sites within an ischemic zone has been described. While segments within the center of the ischemic zone exhibit holosystolic bulging, attenuated shortening is observed near the edge of the ischemic zone. Furthermore, the degree to which shortening is impaired within any single segment may vary according to interventions that may modify ischemia. Hence, in our investigation it is reasonable to consider that the ischemic zone was composed of segments demonstrating both severe and moderate impairment of contractile function during P1. During P2 segments that had previously demonstrated moderate impairment of systolic contractile function may have demonstrated more severe impairment. Such a cumulative, deleterious effect resulting from repetitive episodes of ischemia has been described in the anesthetized, closed-chest dog. That left ventricular contractile function during the second stress was more impaired than during the first is in agreement with the hemody-
namic observations of Thadani et al. They reported that in some of their patients cardiac output was lower during the second of two successive bouts of tachycardia stress. Furthermore, in their investigation these patients were the ones in whom enhanced tolerance to angina was most pronounced.

We conclude that patients with coronary artery disease can develop tolerance to tachycardia stress similar to the warm-up phenomenon observed in patients undergoing exercise testing. A reduction in myocardial oxygen consumption rather than an increase in coronary blood flow appears to account for this observation.

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