PATHOPHYSIOLOGY AND NATURAL HISTORY

ANGINA PECTORIS

Resting angina with fixed coronary artery stenosis: nocturnal decline in ischemic threshold

JAIME FIGUERAS, M.D., JUAN CINCA, M.D., FREDDY BALDA, M.D., ANGEL MOYA, M.D., and JORGE RIUS, M.D.

ABSTRACT Atrial pacing was performed in 16 patients with angina at rest and significant coronary artery stenosis (> 70%) over 2 consecutive days in the morning (10 A.M. to 1 P.M.), in the afternoon (4 to 7 P.M.), and at night (12 midnight to 3 A.M.) to assess possible circadian variations of their ischemic threshold. Overall, the incidence of resting angina was highest at night. All pacing results were positive (≥ 1.0 mm ST segment shift) and tended to be reproducible in nine patients, whereas some or all were negative in seven. Among all positive results, ischemic thresholds at night were significantly lower than those in the morning and in the afternoon (125 ± 3 vs 138 ± 3 and 139 ± 2 beats/min, mean ± SEM; p < .005). In nine patients, 19 pacing tests produced ST segment elevation, of which 13 were performed at night (68%). We conclude that patients with resting angina and severe coronary stenosis often exhibit a nocturnal decline in their ischemic threshold, which seems to facilitate development of transmural ischemia during atrial pacing. Circulation 74, No. 6, 1248–1254, 1986

A PRIMARY REDUCTION in coronary blood flow is currently recognized as the cause of resting angina regardless of the presence or severity of underlying coronary organic stenosis.1-4 Signs of left ventricular failure, electrocardiographic changes, or reduction in coronary flow before increases in blood pressure and heart rate often associated with the onset of pain1-4 have helped to clarify this issue. Nevertheless, it remains to be determined whether changes in blood flow in these unstable patients represent sporadic bouts of localized spasm, as it seems to occur in patients with “pure” coronary spasm (i.e., those with insignificant fixed coronary stenoses),5-7 or whether they correspond to diffuse increases in coronary vascular tone, as recently advocated.8,9 The existence of these diffuse changes in coronary tone, although largely speculative, could possibly modify the ischemic threshold and follow a circadian variation. Demonstration of these hypothetical alterations in threshold could help to explain, at least in some patients, the higher incidence of resting angina during certain intervals of the day, particularly at night.10,11 Ischemic threshold is commonly measured by exercise stress test, but in patients with unstable resting angina and significant coronary artery disease, performance of conventional stress tests has been avoided because of increased risk of complicating events.12,13 Atrial pacing, however, has been proved to be a safe procedure to test coronary reserve in patients with preinfarction angina14 or during the very first days of a myocardial infarction.15 Accordingly, pacing could also be used to assess the ischemic threshold in patients with resting angina at the bed side. Therefore, this study was undertaken to improve our knowledge of the status, reproducibility, and possible circadian variations of the myocardial ischemic threshold in patients with unstable resting angina and significant coronary artery stenosis.

Methods

Patients. Each of 16 patients with resting angina included in this study fulfilled the following criteria: (1) presence of transient ST segment changes during one or more episodes of pain; (2) absence of previous myocardial infarction; (3) absence of valvular heart disease, atrial fibrillation, or bundle branch block; and (4) age 70 years or less. All patients were admitted to the coronary care unit for continuous electrocardiographic monitoring. Myocardial enzymes were analyzed every 6 hr over the first 5 days; heart rate and arterial blood pressure, by cuff, were measured every 2 to 4 hr and during and after the episodes of chest pain; a standard 12-lead ECG was taken daily and during and after the anginal attacks; and coronary arteriography was performed between the fifth and fifteenth days. Patients with a
PATHOPHYSIOLOGY AND NATURAL HISTORY—ANGINA PECTORIS

70% or less coronary artery stenosis were subsequently excluded.

Pacing protocol. Within the first 72 hr, and once the enzyme profile had ruled out the existence of myocardial necrosis, right heart catheterization was performed, introducing a No. 7F Swan-Ganz catheter through the left subclavian vein. After measurement of right atrial, right ventricular, pulmonary arterial, and pulmonary capillary wedge pressures and cardiac output by thermodilution, the pulmonary catheter was withdrawn and, with the same vein dilator, a No. 6F or 7F electroeacatheter was advanced into the coronary sinus for atrial pacing. Pacing was started at a rate of 100 beats/min and was subsequently increased by steps of 10 beats. Each step was maintained for 2 min. Pacing was discontinued when anginal pain, similar to that experienced during the spontaneous episodes, developed or when a heart rate of 150 beats/min was reached and maintained for 5 min. After each pacing step, atrial stimulation was stopped for 10 to 15 sec to allow recognition of possible ischemic changes in the ECG. These changes were analyzed after the first 5 sec to avoid interference by nonischemic artifact changes. A positive pacing response was based on the presence of an ST segment shift of 1.0 mm or greater at 0.08 sec or longer after the J point.

In each patient a minimum of six pacing episodes was performed over 2 to 4 consecutive days. At least two pacing episodes were carried out at each of the following intervals: (1) morning, from 10 A.M. to 1 P.M.; (2) afternoon, from 4 to 7 P.M.; and (3) night, from midnight to 3 A.M. During each pacing test, all patients were in bed, lying at an angle of 10 to 20 degrees. If administered, intravenous nitroglycerin was discontinued at least 2 hr before the test and sublingual isosorbide dinitrate, topical nitroglycerin, or oral nifedipine were discontinued at least 6 hr before any pacing. No other antianginal medication was given during the study, except for sublingual nitroglycerin for chest pain. In each instance, pacing was performed at least 60 min after relief of a possible episode of resting angina. Informed consent was obtained before patients entered the study. The Student t test for paired or unpaired samples was used for statistical analysis.

Results

Clinical data. Relevant data are summarized in table 1. All patients were men and most of them (12/16, 75%) had resting angina of recent onset (≤ 1 month). Eleven patients had history of effort angina but in only six of 16 (38%) was it longer than 1 month. History of nocturnal angina was present in eight patients. During the hospital course, all patients had at least two episodes of resting angina, with an average of 8.8 ± 8 (mean ± SEM) episodes per patient. The incidence of resting angina was highest at night, particularly between 8 and 11 P.M. There were two additional peaks after lunch and after supper (12 A.M. to 1 P.M. and 7 to 8 P.M.; figure 1). A similar distribution was found when analyzing all episodes of resting angina, regardless of the patient in whom they occurred. Most patients had ST segment elevation during one or more episodes of resting angina, but four had ST segment depression in all episodes. The majority of attacks were associated with increases in blood pressure, which were of little magnitude when measured at the onset of pain. Changes in heart rate, when present, were within 10% of prepain values. Eleven patients (69%) had angina at night while sleeping, being awakened by the pain.

Pacing data. All pacing episodes were positive in

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>61</td>
</tr>
<tr>
<td>16</td>
<td>57</td>
</tr>
</tbody>
</table>

RA = resting angina; HTN = arterial hypertension; EA = effort angina; Local. = localization; Ant = anterior; Inf = inferior; Lat = lateral.
FIGUERAS et al.

FIGURE 1. Circadian distribution of episodes of resting angina over 6 to 10 days of observation. Each time interval represents 30 min before and 30 min after the hour. Note the high incidence of angina at night, between hours 20 and 23. At meal time, breakfast (8:30 to 9:00 A.M.), lunch (12:30 to 1:00 P.M.), and supper (6:30 to 7:00 P.M.), there was also an increased incidence of resting angina. Of additional interest is the reduced incidence of angina from 24 to 2 hr, during which nocturnal pacing was performed.

nine patients and ischemic threshold tended to be reproducible. In the remaining seven patients, all pacing episodes were negative in one, five of six in one, four of six in four, and two of six in one. Considering all positive pacing episodes, ischemic thresholds in the morning and in the afternoon were comparable. At night, however, they were significantly lower (table 2, figures 2 and 3). Furthermore, when all pacing episodes were considered, assigning arbitrarily a heart rate of 160 beats/min to each of the negative tests, a significantly lower ischemic threshold was observed at night than in the morning or in the afternoon (133 ± 3 vs 145 ± 2 and 145 ± 2, beats/min; p < .01 and p < .005, respectively).

In nine patients (Nos. 1, 3, 4, 5, 6, 7, 13, 14, and 15), a total of 19 pacing episodes caused ST segment elevation. Thirteen of these 19 were performed at night. In most of these patients, myocardial ischemia was anterior (figure 4). In one patient (No. 5), and in two instances, significant ST segment elevation (4 and 9 mm) occurred 2 and 6 min, respectively, after cessation of pacing. In nine patients, almost all positive pacing episodes were associated with angina, whereas in the rest, more than half of the positive pacing episodes caused no pain. In 10 patients, additional pacing episodes were carried out over a third day, and the results were comparable with those of the first 2 days. Overall, double product (heart rate × systolic blood pressure) during resting angina was consistently lower than that during pacing-induced ischemia, particularly when measurements were taken at the onset of the attacks. There were no complications during pacing, and all symptoms and electrocardiographic changes were reversed within the first 5 min after the test was discontinued.

Hemodynamic and coronary arteriographic findings. There was no relationship between the ischemic threshold and resting right atrial, pulmonary capillary wedge, and left ventricular end-diastolic pressures, cardiac index, and left ventricular ejection fraction. All patients presented a 90% or greater diameter lumen stenosis of at least one vessel (table 3). Seven patients had one-vessel disease; five had two-vessel disease, and four had three-vessel or left main disease. Eight of the nine patients (89%) in whom some pacing caused ST segment elevation had a 95% or greater stenosis of at least one vessel.

Discussion

As other studies have documented,1,16-18 we observed that most patients with resting angina and fixed coronary stenosis present with severe obstruction of at least one vessel even in the absence of a previous myocardial infarction, as in all our patients. However, our study demonstrates the existence in these patients of a reduction of the ischemic threshold at night. Such a decline in threshold was found in spite of the fact that patients were continuously at bed rest and that during nocturnal pacing they were awake and had prepacing

![Graph showing circadian distribution of episodes of resting angina over 6 to 10 days of observation.](http://circ.ahajournals.org/DownloadedFrom.png)

**TABLE 2**

Pacing ischemic thresholds in the morning (M), in the afternoon (A), and at night (N) (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>M C</th>
<th>C P</th>
<th>A C</th>
<th>P C</th>
<th>M N</th>
<th>P C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>72 ± 2</td>
<td>138 ± 3</td>
<td>72 ± 3</td>
<td>139 ± 2</td>
<td>72 ± 3</td>
<td>125 ± 3</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>127 ± 5</td>
<td>136 ± 5</td>
<td>133 ± 4</td>
<td>141 ± 5</td>
<td>127 ± 4</td>
<td>130 ± 5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>88 ± 2</td>
<td>93 ± 3</td>
<td>89 ± 2</td>
<td>99 ± 3</td>
<td>88 ± 2</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>SBP × HR</td>
<td>926 ± 36</td>
<td>1895 ± 86</td>
<td>960 ± 48</td>
<td>1947 ± 74</td>
<td>914 ± 48</td>
<td>1634 ± 82</td>
</tr>
</tbody>
</table>

C = control; P = pacing ischemic threshold; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.
heart rates and blood pressures similar to those of the morning and afternoon. Seemingly, therefore, sympathetic tone was comparable in these three circumstances. Given the growing awareness of the high incidence of acute coronary thrombosis in the early morning in transmural myocardial infarction, the increased prevalence of resting angina at night, and the angiographic demonstration of a partial or completed coronary occlusion by thrombosis in some patients with unstable angina, it may be speculated that the lowering of the ischemic threshold at night seen in our study could have resulted from further decreases in the vessel lumen by deposition of platelet aggregates.

In support of this hypothesis is the experimental evidence of cyclic decreases in coronary flow in stenosed vessels linked to transient deposition of platelet aggregates, the presence of circulating platelet aggregates in unstable angina, and the claim that similar cyclic flow changes have been prevented clinically by antiplatelet agents. However, in view of the reproducible decline in threshold at night over a span of 2 to 3 hr (midnight to 3 A.M.) reported here, one might expect a higher incidence of complete coronary occlusion than observed, if it is assumed that this apparently sustained reduction in threshold was due to the persistent presence of platelet aggregates. Thus a different interpretation for these changes seems warranted and could relate to alterations in the coronary vascular tone. Indeed, a circadian variability of the ischemic threshold during exercise stress test has been shown by in patients with resting angina, mostly without critical coronary stenosis. In these patients there was a decrease in threshold in the early morning that was angiographically correlated with increases in coronary vascular tone. Moreover, in similar patients, documented an increase in the vasoconstrictive response, also in the early morning, since at that time, lower doses of ergonovine were needed for a positive test than in the afternoon. Furthermore, in some patients with resting angina and significant coronary disease, have shown that the ischemic threshold of a stress test in the morning may vary on different days. Therefore, it

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** Double product (heart rate × systolic blood pressure) at the ischemic threshold during the three time intervals (M = morning; A = afternoon; and N = night) in all positive pacing episodes. The trend toward a reduced threshold at night can be appreciated.

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Heart rate at the ischemic threshold in all positive pacings. In nine patients the lowest threshold was found at night, and in five of the remaining seven at least one of the nocturnal thresholds was among the lowest. Pacing tests performed in the morning are represented by open blocks, those performed in the afternoon by open circles, and those performed at night by closed circles. Negative pacing episodes are grouped above the dotted line.
may be that the lowering of the ischemic threshold at night seen in our patients was also caused by temporary increases in coronary tone.

It has been recognized that in patients with significant coronary disease, episodes of resting angina, either during the day or at night, are caused by a primary reduction in myocardial blood flow in view of the absence of increased myocardial oxygen demands before the onset of ischemia. As in previous studies, we noted that the changes in heart rate during resting angina were minimal and that the frequently present increases in arterial pressure were small at the onset of pain. In our study, and as other investigators have documented, double product during resting angina was consistently lower than that during a positive pacing episode with or without angina. Thus, in contrast to a recent interpretation that nocturnal angina in patients with advanced coronary disease is caused by spontaneous increases in myocardial oxygen demands, we contend that it is the decline in ischemic threshold at night that favors the increased prevalence of nocturnal angina, since smaller increases in coronary vascular tone are required to produce ischemia. Nevertheless, as suggested by the reduced incidence of resting angina between midnight and 3 A.M. when threshold was lowest, these increases in coronary tone

FIGURE 4. Illustrative case (patient 3) of ST segment elevation during atrial pacing. It is apparent that there was no ST segment depression preceding ST segment elevation and that 3 min after cessation of pacing, the ST segment changes had virtually reverted.
may not suffice to cause ischemia in some patients without a superimposed spasm. This lack of congruence between the time at which ischemic threshold was lowest (midnight) and the time at which the incidence of resting angina was highest (evening) could also be explained by the possibility that, although not tested in our study, the ischemic threshold in the evening may be similar to or even lower than that at midnight, which because of greater patient alertness may enhance the occurrence of angina.

Elevation of the ST segment during exercise stress testing in some patients with variant angina, with or without significant coronary disease, is a well-documented observation. However, there are no reports on this phenomenon occurring during atrial pacing, except for an isolated case in which a patient with variant angina and insignificant coronary lesions developed ST segment elevation after 15 min of continuous pacing at 150 beats/min. Our findings are therefore of interest because, in contrast to ST elevation during exercise, which seems attributable to an active vasoconstriction secondary to increases in sympathetic drive and levels of circulating catecholamines, we demonstrated that increases in heart rate alone may also induce some degree of transmural ischemia, since sympathetic tone or catecholamine levels reportedly remain unchanged during pacing.

Because in many of our patients there was no ST segment depression before the ST segment elevation, the presence of a concomitant coronary spasm is suggested. In most instances, however, myocardial ischemia was reversed after cessation of pacing, which indicates that it was linked to the increases in heart rate. In this respect, there are recent clinical and experimental studies that indicate that a reduction in blood flow may occur during rapid atrial or ventricular pacing in patients with severe coronary stenosis. Turbulence of flow at the stenotic level or a passive reduction in the diameter of the stenosis due to distal vasodilatation with a fall in distal pressure are mechanisms suggested to account for the decreases in flow. Conversely, increases in distal coronary resistance caused by edema and increased wall tension secondary to ischemia have been identified as a possible explanation.

Limitations. Admittedly, the number of patients we studied is too small to firmly establish the reduction of the ischemic threshold at night. It would be important to explore the status of coronary reserve during the intervals not analyzed in our protocol, particularly when the incidence of resting angina was highest. It is possible that a number of patients in whom pacing was negative and who tended to have higher thresholds would have had a positive exercise stress test, probably at a greater workload. However, the more accurate control of the increases in myocardial oxygen demands achieved by pacing and the exclusion of other factors that may contribute to ischemia aside from the increases in oxygen consumption rendered atrial pacing a more appropriate tool to test low thresholds. Also, stress tests have rarely been performed during or soon after the unstable phase of resting angina because they carry an increased risk of ventricular arrhythmias and conduction disturbances, which were not seen in our protocol. Moreover, all pacing was performed at bed rest, which maintains a highly comparable control state before each pacing. Finally, it should be emphasized that our observations were made in hospitalized patients in whom circadian rhythm activity is altered. In this regard, our findings might not be totally applicable to an outpatient population.

Clinical implications. Our study demonstrates that atrial pacing can be performed safely in patients with unstable resting angina and severe underlying coronary disease. On the other hand, these findings suggest that even though a positive response may identify some patients with advanced disease very early, there may be others with critical stenosis who have normal coronary reserve. Furthermore, a decline of coronary reserve and a high incidence of resting angina at night underscore the need in these patients for higher nocturnal pharmacologic protection.

References


14. Linhart JW: Atrial pacing in coronary artery disease, including preinfarction angina and postoperative studies. Am J Cardiol 30: 603, 1972
Resting angina with fixed coronary artery stenosis: nocturnal decline in ischemic threshold.
J Figueras, J Cinca, F Balda, A Moya and J Rius

Circulation. 1986;74:1248-1254
doi: 10.1161/01.CIR.74.6.1248

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/74/6/1248

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

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

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