PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

α-Adrenergic receptors and coronary spasm: an elusive link

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ABSTRACT In 14 consecutive patients with variant angina we investigated the possible role of coronary α-adrenergic receptors in the genesis of coronary spasm. In eight patients, computerized, beat-by-beat analysis of the electrocardiogram recorded during continuous Holter monitoring failed to reveal any increase of heart rate and corrected QT interval (both indexes of cardiac sympathetic activation) in the period preceding the onset of ST segment changes in 197 episodes of ischemia caused by coronary spasm. In the same patients, analysis of the circadian distribution of ischemic episodes revealed a significantly higher incidence in the early morning hours, when sympathetic activity is at the lowest level. Twelve patients underwent serial provocative testing with cold pressor, phenylephrine, or norepinephrine infusion and administration of ergonovine maleate. Ergonovine consistently reproduced coronary spasm in all 12 patients, while results of cold pressor testing were positive in only one. Infusion of phenylephrine (eight patients) or norepinephrine after β-blockade (four patients) failed to precipitate myocardial ischemia. In five patients infusion of phentolamine at the highest tolerated dose did not reduce significantly the number of ischemic attacks when compared with placebo. In contrast to results of previous reports, our data seem to rule out the hypothesis that an increase of sympathetic outflow to the heart plays an important role in the genesis of coronary spasm. We cannot, however, exclude the possibility of localized α-stimulation of epicardial arteries.

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STIMULATION of coronary α-adrenergic receptors has been repeatedly implicated as a mechanism potentially responsible for coronary spasm. The evidence for this hypothesis is mainly based on anecdotal observations reporting that spasm can be precipitated by both pharmacologic1, 2 and reflex3 α-adrenergic stimulation and prevented or reversed by α-blockade.1, 4 Prolongation of the QT interval has also been observed before episodes of variant angina4 and attributed to increased sympathetic activity to the heart. However, some of these observations have not been confirmed, and the only study that evaluated sympathetic function in variant angina failed to show significant differences between patients with this syndrome and a group of normal controls.5

We report here the results of a systematic study performed in 14 consecutive patients with variant angina, with the objective of evaluating the role of α-adrenergic receptors in the genesis of coronary vaso-spasm. To detect the possible presence of electrocardiographic signs of cardiac sympathetic activation in the period preceding episodes of ischemia caused by coronary spasm, the electrocardiogram (ECG) was continuously monitored by the Holter technique. α-Adrenergic stimulation and blockade was also performed in an attempt to either induce or prevent coronary spasm.

The results of our study seem to rule out the possibility that a generalized increase of sympathetic outflow to the cardiovascular system plays an important role in the genesis of coronary spasm.

Patients and methods

We studied 14 patients in whom the clinical diagnosis of variant angina had been established on the basis of frequent, recurrent episodes of chest pain, mainly occurring at rest and associated with transient ST segment elevation (>0.2 mV). Before entering the study, all patients underwent continuous electrocardiographic monitoring in the coronary care unit for an objective assessment of the actual frequency of ischemic episodes. All patients had frequent daily episodes of transient myocardial ischemia with or without pain (three to 35 per day). All patients performed a symptom-limited exercise test (bicycle ergometer or treadmill) and five had positive results for different levels of external workload. Only one patient with a 90% lesion...
Holter monitoring of the ECG was performed in the eight patients recruited for the study. Recordings were obtained in the hospital after all antianginal treatment had been discontinued for at least 24 hr. Only sublingual or oral nitrates were given if required. After careful preparation of the skin, four self-adhesive pregelled ECG electrodes were applied to the chest to record two bipolar leads (modified leads III and V5); frequency modulated dual channel Holter recorders (Oxford Medilog 2) were used. Patients were kept under careful control by medical and nursing personnel but were allowed to leave their beds and move around the ward and the adjacent hospital facilities. Holter tapes were played back at 60 times the real time to be assessed visually on an Oxford Medilog 2 analyzer; only tapes free of artifacts were considered for further analysis. After analog-to-digital conversion at 100 samples/sec, recordings from the lead showing the most evident changes during ischemia were processed by a computer program that we had developed and validated against standard reference techniques.6-9 With use of a 1000F Hewlett Packard computer. For the whole of each 24 hr tape the following parameters were calculated on a beat-by-beat basis: (1) heart rate, (2) ST-T positive and negative areas, (3) level of J point (J), (4) ST segment level 80 msec after J point (J2), and (5) corrected QT interval (QT/RR). The beat-to-beat values of each derived parameter were averaged on 10 sec periods and plotted against time by a 2608A Hewlett Packard line printer. For a better assessment of the temporal relationships between ST-T wave changes, heart rate, and QT changes, beat-by-beat printouts of the different derived parameters were also obtained for the periods containing ischemic episodes (figure 1). For the analysis of the corrected QT interval we selected only episodes in which the end of the T wave was clearly detectable. In 88 of these episodes, selected randomly from the eight patients, manual, beat-by-beat measurements of the QT interval were also performed in the 60 sec preceding the onset of ST changes, on analog ECG recordings at 50 mm/sec paper speed.

α-Adrenergic stimulation. Twelve patients were studied; two with prolonged spontaneous episodes were excluded. In all, medical treatment had been stopped for at least 48 hr before the study. Reflex and pharmacologic α-adrenergic stimulation were achieved by the cold pressor test and by administration of phenylephrine (eight patients) or norepinephrine after β-blockade (four patients). The cold pressor test was performed by patients immersing one hand in ice for 2 min. Phenylephrine was infused intravenously at three increasing rates (50, 100, and 150 μg/min) lasting 5 min each. When norepinephrine was used (2, 4, or 8 μg/min), it was administered intravenously 10 min after propranolol (0.1 mg/kg iv). In each patient the actual coronary responsiveness to vasoconstrictor stimuli was checked by the response to ergonovine maleate. The ergonovine test was performed at the end of the session; incremental doses of ergonovine maleate (25 to 300 μg) were given intravenously at 5 min intervals until the appearance of electrocardiographic signs of ischemia or the achievement of the maximal cumulative dose (475 μg). In all patients the sequence of interventions was as follows: cold pressor, phenylephrine or norepinephrine, ergonovine. Each test was separated by an interval of at least 30 min. Throughout the study the 12-lead ECG and the arterial pressure (indwelling cannula) were monitored continuously. The occurrence of ischemia was also independently assessed by continuous monitoring of left ventricular function by a single crystal scintillation probe (Nuclear Stethoscope; BIOS, Inc.), after la-

<table>
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</table>

ST ↑ = ST-segment elevation; T ↑ = pseudonormalization or peaking of inverted or flat T wave; RBBB = right bundle branch block; LAD = left anterior descending artery; LCX = left circumflex artery; RC = right coronary artery.

*Patient did not consent to coronary arteriography.
beling of the red cells in vivo by 0.2 mg/kg of stannous pyrophosphate followed by 10 mCi of technetium-99 as pertechnetate. The technique allows for the recording of beat-by-beat time-activity curves, which are proportional to changes in left ventricular volumes.\textsuperscript{10, 11} The 12-lead ECG, blood pressure, and analog output of the Nuclear Stethoscope were recorded continuously on a multichannel tape recorder (Racal-Store 14). At the end of each study the analog waveforms were played back, converted (analog to digital), and analyzed with the 1000F Hewlett Packard computer\textsuperscript{12, 13}; the following derived parameters were calculated beat by beat: (1) heart rate, (2) ST-T positive and negative areas, (3) systolic, diastolic, and mean arterial pressures, and (4) indexes of left ventricular end-systolic and end-diastolic volumes, stroke volume, and ejection fraction (figure 2). For each study, low- and high-speed analog playbacks of all recorded signals were also obtained by a 14-channel ink recorder (Minograph 14 Elema Shoenander). A provocative test was considered to be positive when it induced anginal pain and/or ST-T changes similar to those observed during spontaneous ischemic episodes, accompanied by a transient increase in left ventricular volumes and reduction in stroke volume and ejection fraction (figure 2). In all patients but one (who refused angiography), evidence for ergonovine-induced coronary spasm was obtained at angiographic examination, performed in a separate session during the same admission. Spasm was defined as a transient total or subtotal coronary occlusion with delayed or absent distal filling, and was reversed by sublingual or intracoronary nitrates.

\textbf{\textalpha-Adrenergic blockade.} Of the 14 patients, we studied five who had a high daily frequency of ischemic episodes. The study was conducted in the coronary care unit under continuous electrocardiographic monitoring and recording on magnetic tape. The electrocardiographic lead showing the most evident changes during ischemia was selected for this purpose. Phentolamine mesylate was infused continuously for 6 hr periods, alternated with equivalent periods of placebo infusion. The number of phentolamine and placebo infusions varied in the different patients, depending on the number of ischemic episodes. Total duration of the study ranged from 24 to 96 hr. The rate of infusion of phentolamine was titrated individually according to the hemodynamic response observed; the drug was considered to be effective when a stable drop of at least 15 mm Hg in systolic arterial pressure was observed. Doses ranged from 25 to 40 mg/hr.

The heart rate was continuously monitored throughout the study, and blood pressure was measured by a cuff manometer every 10 min in the first hour of infusion and every hour afterwards.

The ECG lead recorded continuously throughout the study was played back at the end of each infusion, to be analyzed by computer as described above.

\section*{Results}

\textbf{Continuous ECG monitoring.} During 22 periods of 24 hr continuous electrocardiographic monitoring, a total of 385 ischemic episodes was recorded; only 47 (14\%) were associated with anginal pain. A total of 252 were characterized by ST segment elevation, 32 by ST segment depression, and 101 by pseudonormalization or peaking of inverted or flat T waves. In patients with variant angina, all these changes have been shown to be consequent to different degrees of severity of myocardial ischemia caused by coronary vasoconstriction.\textsuperscript{14} More than one type of change indicative of ischemia was observed in each patient’s ECG during different episodes. In all episodes the relationship between heart rate and onset of ischemia was analyzed; 197 were also suitable for the analysis of the QT inter-
val. Of these, 133 were characterized by ST segment elevation, 12 by ST segment depression, and 52 by pseudonormalization of inverted T wave.

No consistent increase in heart rate or corrected QT interval preceded any of the ischemic episodes, suggesting that no detectable increase in sympathetic outflow to the heart preceded acute myocardial ischemia in these patients. Heart rate usually increased slightly during ischemia. The average increase was 9 ± 5 beats/min (11%) and was usually more pronounced in the episodes accompanied by pain. A progressive increase in the corrected QT interval was also observed after or coincident with the onset of ST-T wave changes in 129 episodes with ST segment elevation, in four with ST segment depression, and in 28 with T wave changes. Computer and manual analysis of QT intervals gave superimposable results. The changes in QT intervals paralleled those of the ST segment, reached a maximum at peak ischemia, and disappeared altogether with ST-T changes (figure 1 and 3). Analysis of the circadian distribution of ischemic episodes revealed a significantly higher incidence during the night. Sixty-seven percent of episodes occurred between 8 p.m. and 8 a.m., with a peak at 3 a.m. (figure 4).

α-Adrenergic stimulation. In all patients ergonovine maleate produced ST segment changes similar, for location and direction, to those observed during spontaneous episodes of ischemia. ST segment changes were accompanied by increases in indexes of both systolic (89 ± 23%, mean ± SD) and end-diastolic (39 ± 14%) volumes and by a decrease in stroke volume (27 ± 9%) and ejection fraction (29 ± 11%).

Hemodynamic response to the cold pressor test was characterized by an increase in both systolic and diastolic arterial pressures and by a slight increase in heart

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

**FIGURE 2.** Example of the assessment of the response to provocative tests, showing behavior of heart rate, systolic and diastolic arterial pressures, left ventricular end-diastolic and end-systolic volumes, and ejection fraction during one episode of ST segment elevation induced by ergonovine. A progressive increase in left ventricular volumes with decrease in ejection fraction precedes and accompanies ST segment changes and is reversed by amyl nitrite. In the same patient, no ischemic changes were induced with the cold pressor test and infusion of norepinephrine (see also text).

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

**FIGURE 3.** Average behavior of the corrected QT interval observed during 133 episodes of ST segment elevation. The dashed line indicates the onset of ST changes indicative of ischemia. Points from 1 to 7 represent the QT value (mean ± SD) during control (60 sec before the onset of ST segment elevation, point 1), 5 sec before, and 5 and 20 sec after onset of ischemia (points 2, 3, and 4), at peak ischemia (point 5), and during recovery (points 6 and 7). See also figure 1.
rate (table 2). Transient myocardial ischemia was precipitated by the cold pressor test in only one patient, who had a very high daily frequency of ischemic episodes (>30/day); the reproducibility of the response to the cold pressor test was evaluated in this patient on three occasions and proved to be variable; the test was either negative or positive with ST segment elevation or with ST segment depression on the same electrocardiographic leads. All other patients had no ECG or left ventricular volume changes during the cold pressor test.

Stepwise infusion of phenylephrine and norepinephrine consistently resulted in a dose-dependent increase in mean arterial pressure, accompanied by a reflex decrease in heart rate (table 2). In none of the patients did these drugs precipitate ECG or left ventricular volume changes indicative of acute myocardial ischemia. A slight, progressive increase of both systolic and diastolic volumes with no significant changes in stroke volume occurred in three patients during infusion of phenylephrine, presumably resulting from increase of left ventricular afterload.

**α-Adrenergic blockade.** Phentolamine, alternated with placebo, was infused for a total period of 12 hr in three patients, 24 hr in one, and 48 hr in another. In four patients the drug produced a sustained decrease in arterial pressure; in one, no evident changes in arterial pressure were observed even at the highest rate of infusion (40 mg/hr), despite the presence of signs of peripheral vasodilatation (marked nasal and conjunctival congestion). In this patient a marked increase in heart rate occurred during the infusion. A total of 97 attacks were recorded during the study. Fifty-two were characterized by ST segment elevation, 26 by ST segment depression, and 19 by pseudonormalization of inverted or flat T waves. Twenty-three were accompanied by anginal pain while 74 were asymptomatic.

In four patients no significant difference was evident between the number of episodes recorded during infusion of phentolamine and that recorded with placebo.

**FIGURE 4.** Diurnal distribution of ischemic episodes in the eight patients who underwent continuous electrocardiographic Holter monitoring. The highest incidence is observed between 12 midnight and 8 a.m., with a peak at 3 a.m.

**TABLE 2**

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<tr>
<th>Patient</th>
<th>HR</th>
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<th>CP</th>
<th>Ph/Ne</th>
<th>SAP</th>
<th>C</th>
<th>CP</th>
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Mean ± SD 80 ± 9 88 ± 10 64 ± 7 135 ± 14 163 ± 16 184 ± 11 80 ± 7 93 ± 9 105 ± 9

HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; C = control; CP = cold pressor; Ph/Ne = phenylephrine or norepinephrine (levels at peak infusion rate).
PATHOPHYSIOLOGY AND NATURAL HISTORY—CORONARY ARTERY DISEASE

FIGURE 5. Results of administration of phentolamine in the five patients who underwent the trial. The columns represent, for the five individual patients, the total number of ischemic episodes observed during placebo and phentolamine.

(figure 5). Furthermore, in these patients, duration and severity of ST-T changes indicative of ischemia were similar in the two conditions as was the incidence of episodes accompanied by pain. However, in one patient the number and duration of ischemic episodes, all characterized by ST segment elevation and all associated with chest pain, increased progressively during infusion of phentolamine, requiring the interruption of the infusion. All patients responded to the intravenous administration of isosorbide dinitrate (4 to 10 mg/hr).

Discussion

Although the role of α-receptors in the autonomic regulation of the coronary circulation is now well established,15–18 our data do not support the hypothesis that their activation plays an important role in the genesis of coronary spasm in Prinzmetal’s variant angina. In the period preceding episodes of ischemia, we could not detect signs of increased sympathetic activity to the heart such as an increase in heart rate or prolongation of the QT interval, as described by Ricci et al.4 We believe that the discrepancy between our results and those reported by these authors can be largely explained by methodologic differences. The finding of prolonged QT intervals before ischemia was probably related to the inability to accurately determine the onset of the ST segment by manual measurements.

In agreement with previous studies,19,20 we observed a significantly higher incidence of ischemic episodes in the early morning hours, when sympathetic activity is at its lowest level.21,22 We can also reasonably rule out the possibility that nocturnal episodes were precipitated by paroxysmal bursts of sympathetic hyperactivity caused by rapid eye movement sleep, because no changes in heart rate and QT interval were observed before these episodes and because, with the exception of one anecdotal report,23 no consistent association between rapid eye movement and episodes of variant angina has been found.24

The observation of an increase in heart rate and corrected QT interval during, but not before, ischemia is in keeping with the results of Robertson et al.,25 who measured arterial and coronary sinus epinephrine and norepinephrine during spontaneous episodes of variant angina. Although a significant increase in catecholamine levels was measureable in the late phase of the episodes, no changes relative to control were detectable at the very onset of electrocardiographic changes. These findings suggest that in patients with coronary spasm, increase in cardiac sympathetic tone is likely to be a consequence rather than the cause of transient acute ischemia.

With only one exception, spasm in our patients was neither precipitated by reflex or pharmacologic α-adrenergic stimulation nor prevented by α-blockade with phentolamine. The first observation is consistent with the findings of a recent report, showing only a 10% incidence of positive results of the cold pressor test in a group of 34 patients with variant angina, 32 of whom (94%) responded to ergonovine.26 We certainly cannot exclude that in our patients α-stimulation could have produced minor degrees of coronary vasoconstriction, insufficient to cause ST segment changes, as described in two patients by Raizner et al.4 However, this possibility appears rather unlikely, at least in the eight patients with coronary lesions equal or greater than 90% in whom even minimal changes in coronary cross-sectional area should be critical enough to produce acute myocardial ischemia. Although coronary spasm can be undoubtedly precipitated in some patients with very active disease by various sympathetic maneuvers, the reproducibility and specificity of this response have not yet been assessed and its actual relevance to the pathophysiologic mechanism of coronary spasm has not been demonstrated.

The negative results we obtained with phentolamine are difficult to interpret, since this drug is active on both α1- and α2-receptor subtypes. Blockade of α2 presynaptic receptors could have resulted in inhibition of norepinephrine reuptake from sympathetic nerve endings and increased adrenergic activity to the heart. Similar considerations, however, also apply to phenoxycbenzamine, which has been reported by Yasue et al.1 and Ricci et al.9 to be effective in preventing vaso-
spasm. The results of these studies have to be considered with caution, since the response to treatment is extremely difficult to assess in patients with variant angina unless double crossover trials are used. Indeed, in agreement with our results, a recent placebo-controlled, double-blind, crossover study performed in six patients showed no significant difference between placebo and oral treatment with the selective α-blocker prazosin.27

The results of our study were obtained in a group of 14 consecutive patients with variant angina, all in a clinically active phase of their disease and evenly distributed throughout the anatomic spectrum of the syndrome. Our data contradict those reported by previous workers and seem to rule out the hypothesis that a generalized increase of sympathetic outflow to the cardiovascular system plays an important role in the genesis of coronary spasm. However, we cannot exclude the possibility of local sympathetic stimulation of epicardial arteries, not necessarily reflected by systemic changes and not necessarily prevented by systemic α-blockade or induced by generalized α-stimulation.

References
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