Unstable angina with tachycardia: Clinical and therapeutic implications

We prospectively evaluated 19 patients with prolonged chest pain not evolving to myocardial infarction and accompanied with reversible ST-T changes and tachycardia (heart rate >100 beats/min) in order to correlate heart rate reduction with ischemic electrocardiographic (ECG) changes. Fourteen patients (74%) received previous long-term combined treatment with nifedipine and nitrates. Continuous ECG monitoring was carried out until heart rate reduction and at least one of the following occurred: (1) relief of pain or (2) resolution of ischemic ECG changes. The study protocol consisted of carotid massage in three patients (16%), intravenous propranolol in seven patients (37%), slow intravenous amiodarone infusion in two patients (10%), and intravenous verapamil in four patients (21%) with atrial fibrillation. In three patients (16%) we observed a spontaneous heart rate reduction on admission. Patients responded with heart rate reduction from a mean of 128 ± 10.4 beats/min to 64 ± 7.5 beats/min (p < 0.005) and an ST segment shift of 4.3 ± 2.13 mm to 0.89 ± 0.74 mm (p < 0.005) within a mean interval of 13.2 ± 12.7 minutes. Fifteen (79%) had complete response and the other four (21%) had partial relief of pain. A significant direct correlation was observed for heart rate reduction and ST segment deviation (depression or elevation) (r = 0.7527 and 0.8739, respectively). These patients represent a unique subgroup of unstable angina, in which the mechanism responsible for ischemia is excessive increase in heart rate. Conventional vasodilator therapy may be deleterious, and heart rate reduction is mandatory. (Am Heart J 1988;116:1188.)

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Unstable angina is a syndrome encompassing a variety of clinical and pathophysiologic entities. Features of instability are largely determined by dynamic obstructions superimposed on a widely variable fixed obstruction. Continuous hemodynamic and electrocardiographic (ECG) monitoring indicate that most episodes of ischemia in patients with unstable angina are not triggered by increases in the major determinants of myocardial oxygen consumption. We recently discussed the prognostic implications of the various patterns of ischemic ECG changes in patients with unstable angina without evidence of increased myocardial oxygen demand.

Because heart rate is the best single index for myocardial oxygen consumption, we used this parameter to evaluate prospectively a subgroup of patients with unstable angina and tachycardia. The purpose of the present study was to characterize this group clinically and electrocardiographically and to correlate heart rate reduction with clinical presentation and ischemic ECG changes.

METHODS

Nineteen consecutive patients (14 men and 5 women) with unstable angina and tachycardia were selected for study provided they fulfilled the following criteria: (1) prolonged typical chest pain lasting longer than 15 minutes accompanied by reversible ST-T wave changes and (2) heart rate above 100 beats/min not related to effort with careful clinical evaluation to assure that it was not secondary to underlying physiologic abnormalities (dehydration, fever, anemia, overt heart failure). Patients with complete left bundle branch block or with subsequent development of a new Q wave or with diagnostic elevation in cardiac isoenzymes were excluded. ST segment deviation was defined as a shift >1 mm from the PR segment 80 msec after the J point. A 12-lead ECG was recorded on admission. All patients entered a protocol in which they underwent continuous ECG monitoring in the lead presenting the maximal ST segment deviation until heart rate reduction to 100 beats/min or less and at least one of the following: (1) relief of pain or (2) restoration of...
ECG changes. In order to assess the net effect of heart rate reduction on clinical features (pain) and ischemic ECG changes, no nitrates or analgesic treatment was given throughout the study protocol. This protocol was as follows: (1) gentle carotid massage for 3 minutes; (2) when carotid massage was ineffective or contraindicated (cervical murmurs, previous TIA), intravenous propranolol up to 0.1 mg/kg at the rate of 1 mg/min was administered; (3) when propranolol was contraindicated (bronchial asthma, heart failure), amiodarone, 300 mg, was given in 30 minutes as a slow intravenous infusion; (4) in patients with supraventricular tachycardia or atrial fibrillation, verapamil was given intravenously up to 10 mg.

Statistical analysis. All data are presented as the mean ± standard deviation. Comparisons were done by a paired t test. A p value <0.05 was considered significant.

RESULTS

The study group (Table I) consisted of 19 patients (14 or 74% were men) with a mean age of 65 ± 9.8 years. Five patients had an old myocardial infarction, four had a recent (within 2 weeks) myocardial infarction, seven had hypertension, five had diabetes, and three had both hypertension and diabetes. Fourteen patients (74%) received previous long-term treatment with nifedipine and nitrates in a dose up to 60 mg and 160 mg, respectively; only one of these patients received concomitant treatment with beta blockers. One patient (No. 17) was admitted 24 hours after abrupt withdrawal of long-term beta blocker therapy. Eight patients received sublingual nitrates for a short term (average dose 10 mg; range, 5 to 20 mg) without clinical subjective improvement.

Four patients (21%) had ST segment elevation. All had a recent myocardial infarction and the maximal ECG changes occurred in the same lead demonstrating the previous infarction: two (50%) were in lead V₃ and the other two were in lead III (Fig. 1). Fifteen patients had ST segment depression. In 13 (87%) the maximal changes were observed in leads V₄ and V₅ (Fig. 2). All patients had typical chest pain lasting at least 15 minutes and ranging from 15 to 420 minutes (mean 153 ± 130).

Three patients (16%) responded to carotid massage. Seven patients (37%) were treated with beta
Table I. Clinical data and therapeutic modalities in patients with unstable angina and tachycardia

<table>
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<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Previous medical therapy</th>
<th>Type of tachycardia</th>
<th>ST segment deviation</th>
<th>Lead with max ST changes</th>
<th>Duration of pain (min)</th>
<th>Therapy</th>
<th>Interval till effect (min)</th>
<th>Heart rate beats/min</th>
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AF, atrial fibrillation; BB, beta blockers; CM, carotid massage; IE, isoelectric; IV, intravenous; N, nifedipine; NT, nitrates; P, propranolol; SL, sublingual; ST, sinus tachycardia.

*ST wave inversion.

blockers, four (21%) were treated with verapamil, and two (10%) were treated with amiodarone. In three (16%) we observed spontaneous heart rate reduction on arrival. Patients responded with heart rate reduction from a mean of 125 ± 10.4 to 84 ± 7.5 beats/min (p < 0.005) and an ST segment shift of 4.3 ± 2.13 mm to 0.89 ± 0.74 mm (p < 0.005). Within a mean interval of 13.2 ± 12.7 minutes. 15 patients (79%) had complete relief of pain and the other four (21%) had partial relief of pain. The correlation between heart rate and ST segment deviation (depression or elevation) is shown in Figs. 3 and 4. A significant direct correlation was observed for both groups (r = 0.7527 and 0.8739, respectively).

DISCUSSION

Although it is widely recognized that unstable angina is a syndrome accompanying a variety of clinical and pathophysiologic entities, clinical trials and guidelines for management still consider patients with this syndrome as a single homogeneous group. The current most widely used clinical classifications for unstable angina are based on descriptive features of the patient's symptoms and the number of angiographically detected diseased vessels. It seems reasonable to assume that predictions of greater accuracy are achievable if patients can be classified into more homogeneous groups by the use of more precise anatomic and functional criteria. We believe that such criteria must include the different patterns of ischemic ECG changes, and we recently correlated those patterns with prognosis and coronary anatomy.

Continuous hemodynamic and ECG monitoring indicate that most episodes of ischemia in patients with unstable angina are not preceded by increased cardiac activity. Because heart rate is the best single index for myocardial oxygen consumption, we used this parameter to characterize a subgroup of patients with unstable angina and tachycardia not related to effort, according to the following clinical features.

Duration of pain. The definition of unstable angina used by the Veterans Administration cooperative Study on the protective effect of aspirin against infarction and death included duration of pain longer than 15 minutes. The Coronary Artery Surgery Study (CASS) investigators classified patients with unstable angina into four subgroups and defined coronary insufficiency as chest pain lasting longer than 30 minutes. In the present study, we evaluated patients with prolonged chest pain ranging from 15 to 420 minutes without development of a new Q wave or diagnostic elevation of cardiac isoenzymes. This is most remarkable in the face of the
known correlation between duration of pain and probability of evolution to infarction.

**Ischemic ECG changes.** ST segment depression reflects a diffuse subendocardial ischemic process and therefore does not suggest the artery causes the ischemia. The nonspecificity of the site of ST segment depression during stress testing for localizing the likely region of myocardial ischemia is well known. Irrespective of the artery involved, leads V₅ and L₉ are the leads with the higher prevalence of positivity. It is noteworthy that in the present study, in 87% of our patients the maximal magnitude of ST depression was observed in these leads. The combination of this pattern of ischemic ECG changes and tachycardia found in this study resembles the findings of a positive stress test, besides its lack of relation to effort. ST elevation, on the contrary, reflects the site of ischemia and localizes the region perfused by the vessel involved. Most studies have indicated that ST segment elevation during stress testing is uncommon. The prevalence of such a finding is up to 30%, and it is not related exclusively to the presence of prior infarction. The present study has shown ST segment elevation in 21% of patients—all with recent myocardial infarction in the same anatomic region.

**Previous medical therapy.** There are several reports that nifedipine and other vasodilators could worsen or provoke angina pectoris. Several mechanisms have been proposed to explain this paradoxic response: (1) vasodilator-induced hypotension may cause an abrupt drop in coronary perfusion pressure and may sufficiently attenuate subendocardial perfusion, producing myocardial ischemia; (2) pharmacologic agents with pronounced vasodilator properties (especially nifedipine) may induce a “coronary steal” by diverting perfusion away from an ischemic coronary vascular bed to a normal nonischemic area of the heart; (3) a reflex increase in heart rate to the extent that it shortens the duration of diastole and increases oxygen demands may worsen or provoke myocardial ischemia. In our study, 14 patients (74%) received combined treatment with nifedipine and nitrates in a dose up to 60 mg and 160 mg, respectively. Only one of these 14 received concomitant treatment with beta blockers. Eight patients received nitrates sub-
lingually before hospital admission (average dose 10 mg; range, 5 to 20 mg). One patient was admitted 24 hours after abrupt withdrawal of long-term therapy with propanolol in a dose of 120 mg. Because none of our patients were hypotensive on arrival and all had heart rates above 100 beats/min (mean 125 ± 10.4) not related to fever, anemia, or overt heart failure, we speculate that a paradoxical increase in oxygen demand due to reflex-mediated tachycardia may be the underlying mechanism for myocardial ischemia in our patients. The tachycardia observed in our patients may be related to previous medical therapy and may provoke myocardial ischemia by increasing oxygen demand. On the other hand, tachycardia may be secondary to the ischemic event and may worsen it further. Indeed, continuous ECG and hemodynamic monitoring in patients with stable and unstable angina has shown consistent increase of heart rate paralleling but not preceding the progression of ST segment changes during most ischemic episodes. However, the dramatic response to heart rate reduction without concomitant vasodilator or analgesic treatment in the present study should at least suggest causal relationships between the tachycardia and the ischemic events.

**Therapy.** Three of our patients had spontaneous reduction of heart rate with simultaneous relief of pain and restoration of ECG changes on admission. The other 16 patients all responded to therapeutic intervention to reduce heart rate within a mean interval of 13.2 ± 12.7 minutes. A significant direct correlation was achieved between heart rate reduction and ST segment deviation. Fifteen patients had complete response and the other four had partial relief of pain.

**Clinical implications.** Attenuation of the increase in major determinants of myocardial oxygen consumption is undoubtably the basis of the salutary actions of beta blockers in chronic stable angina. The issue is less clear in unstable angina, in which myocardial ischemia appears to be less frequently produced by increases in oxygen demand. In the present study, we evaluated a subgroup of patients with unstable angina with prolonged chest pain not evolving to myocardial infarction. They had received previous medical therapy with vasodilators, and their tachycardias and ischemic ECG changes were compatible with a positive stress test and a dramatic response to heart rate reduction. We believe that the mechanisms responsible for ischemia in our study patients is an excessive increase in heart rate, possibly iatrogenic, due to previous medical therapy with vasodilators. Overzealous use of vasodilators in the setting presented here may be deleterious and may worsen the ischemia further by creating a vicious circle in which more pain leads to more vasodilators, more tachycardia, and more ischemia. Therapeutic intervention aimed at heart rate reduction may abort this hazardous cycle and terminate the ischemic event.

Although our data were not obtained in a randomized comparative study, the results observed were of high statistical significance. The marked effect of heart rate reduction on ischemic ECG changes and clinical features may have very significant consequences upon our therapeutic approach to this subgroup of patients with unstable angina.

**REFERENCES**