Role of Abnormal Pain Sensitivity and Behavioral Factors in Determining Chest Pain in Syndrome X

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Objectives. We sought to investigate whether patients with syndrome X have an abnormal perception of cardiac pain.

Background. Previous studies have reported an increased sensitivity to potentially painful cardiac stimuli in patients with syndrome X. However, it is not clear whether this increase is due to an increased perception of pain or to an enhanced tendency to complain.

Methods. We assessed cardiac sensitivity to pain in 16 patients with syndrome X and 15 control subjects by performing right atrial and ventricular pacing with increasing stimulus intensity (1 to 10 mA) at a rate 5 to 10 beats higher than the patient’s heart rate. False and true pacing were performed in random sequence, with both patients and investigators having no knowledge of the type of stimulation being administered.

Results. No control subject had pacing-induced pain; conversely, 8 patients with syndrome X reported angina during atrial pacing (50%, p < 0.01) and 15 during ventricular pacing (94%, p < 0.001). During atrial stimulation, both true and false pacing caused chest pain in a similar proportion of patients (50% vs. 63%, p = 0.61), whereas during ventricular stimulation, true pacing caused chest pain in a higher proportion of patients (94% vs. 50%, p < 0.05). Pain threshold and severity of pain (1 to 10 scale) were similar during true and false atrial pacing, whereas true ventricular pacing resulted in a lower pain threshold (mean ± SD 3.7 ± 3.0 vs. 7.9 ± 2.8 mA, p < 0.001) and a higher level of pain severity (7.3 ± 2.7 vs. 3.1 ± 3.5, p < 0.001) than did false pacing.

Conclusions. Patients with syndrome X frequently reported chest pain even in the absence of cardiac stimulation. Yet, in addition to this increased tendency to complain, they also exhibited a selective enhancement of ventricular painful sensitivity to electrical stimulation.

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Up to 20% of patients with angina pectoris undergoing coronary angiography are found to have normal coronary arteries (1). The presence of ischemia-like electrocardiographic (ECG) changes during exercise testing in many of these patients, grouped under the term syndrome X, suggests a cardiac (and possibly ischemic) origin of chest pain (2). However, the mechanisms responsible for the frequent episodes of chest pain in patients with syndrome X remain unclear (3). Previous clinical studies (4–6) reported an enhanced perception of pain in response to cardiac stimuli in these patients, whereas other studies (7,8) showed a high prevalence of psychologic disorders, which can lead to an enhanced tendency to complain. Thus, it is not known whether the reported enhanced pain perception is merely a consequence of these behavioral features or is caused by a true disorder of pain sensitivity. To clarify this point, we assessed cardiac sensitivity to pain in a group of patients with syndrome X by using a randomized, double-blind, controlled protocol of electrical stimulation of the right heart chambers.

Methods

Patients. A total of 16 consecutive white patients with syndrome X (mean age ± SD 51 ± 8 years; 12 women) undergoing diagnostic cardiac catheterization were included in the study. All patients had effort angina, a positive exercise test result (rectilinear or downsloping ST segment depression >0.1 mV) and entirely normal coronary arteries. Patients with hypertension, diabetes or psychiatric disorders (history of major depression or panic attacks, as assessed by a psychiatric consultant) were excluded from the study. Results of baseline ECG and echocardiograms were normal in all patients and ergonovine testing did not provoke coronary spasm in any of them.

Control subjects. We studied as a control group 15 white patients (age 53 ± 8 years; 10 women) undergoing electrophysiologic study because of documented or suspected supraventricular tachyarrhythmias. All subjects had no symptoms of chest pain and had no history of hypertension, diabetes or valvular disease. Results of a rest ECG, echocardiogram and symptom-limited exercise testing were normal in all subjects.
Cardiac sensitivity to pain. All antianginal drugs in patients with syndrome X were withdrawn at least 72 h before the study, but use of sublingual nitrates for relief of chest pain was allowed. After written informed consent to participate in the study was obtained, the following protocol was performed in both patients and control subjects. After premedication with diazepam (10 mg orally), a 6F pacing wire was introduced through the right femoral vein and advanced into the right atrium. Two pacing protocols (true and false pacing) were then performed in a double-blind, randomized order under continuous 12-lead ECG monitoring. At the beginning of each pacing sequence, each subject was simply informed that a possibly painful stimulation would be performed and was instructed to report spontaneously chest pain, if it occurred, but he or she was never asked directly about the occurrence of chest pain thereafter. Pain similar to that experienced during daily life was defined as typical pain. True pacing was performed at a rate 5 to 10 beats/min faster than the basal stable sinus rate, starting with a stimulus of 1 mA. The stimulus intensity was increased progressively by 1 mA every 10 s either until chest pain developed or until a maximal stimulus of 10 mA was reached. True pacing was alternated, in a randomized order, with a false pacing sequence, which was performed with the pacemaker turned off but simulating the 1- to 10-mA sequence of true stimulation. The randomized pacing protocol was performed by a technician, with both patient and investigator unaware of the pacing sequence, as they could neither watch the ECG monitor nor hear the sound indicator of heart pacing, which was turned off throughout the protocol procedure. If chest pain was reported by the patient during the first pacing sequence, the next pacing sequence was performed ≥5 min after the complete relief of pain. Pain threshold was defined as the stimulus intensity (in mA) at the onset of typical chest pain; if no chest pain occurred, the pain threshold was assumed to be 10 mA in statistical analyses. The severity of chest pain was estimated according to a scale ranging from 0 (no pain) to 10 (unbearable pain). After the two atrial stimulations were completed, the pacing wire was advanced to the apex of the right ventricle, and the true/false pacing sequence was repeated with use of the same protocol.

Statistical analysis. Continuous baseline variables were compared between groups by unpaired two-tailed t test. Pain threshold and pain severity, which did not show a normal distribution, were compared by Mann-Whitney U test. Paired data within groups were analyzed by Wilcoxon signed rank test, whereas differences among multiple repeated measures were tested by Friedman analysis of variance (ANOVA). Proportions were compared by two-tailed Fisher exact test or McNe-

Results

Study group. The main features of patients and control subjects are summarized in Table 1. The two groups were similar in age, gender, menopausal status, risk factors for ischemic heart disease, basal heart rate and blood pressure (BP). No ECG changes were detected during the study, and no patient or control subject reported pain before the pacing protocol was started with simple placement of the catheter wire.

Atrial stimulation. No control subject experienced pain during either true or false atrial pacing. Conversely, eight patients with syndrome X (50%, p < 0.01 vs. control subjects) experienced typical chest pain during true pacing. However, typical chest pain was also induced by false stimulation in 10 patients (63%, p = 0.61 vs. true pacing) and both pain threshold (7.2 ± 3.5 vs. 6.6 ± 3.2 mA, p = 0.42) and pain severity (3.4 ± 3.7 vs. 3.7 ± 3.2, p = 0.87) were similar during true and false pacing (Fig. 1). BP did not change significantly

Figure 1. Pain severity (left) and pain threshold (right) during true and false stimulation in the right atrium in patients with syndrome X. Both severity and threshold of pain were similar during either true or false pacing.
sharp contrast, 15 patients with syndrome X (94%) reported chest pain during ventricular pacing (either true or false). In significantly lower (3.7 vs. 6.3 mA, p = 0.001) (Fig. 2) than during false pacing. Again, there were no significant changes in BP during the study. In particular, in patients with syndrome X, systolic BP was 129 ± 9 mm Hg before and 127 ± 8 mm Hg during true pacing.

Ventricular stimulation. No control subject experienced chest pain during ventricular pacing (either true or false). In sharp contrast, 15 patients with syndrome X (94%) reported typical pain during true ventricular pacing (p < 0.001 vs. control subjects), whereas only 8 of them (50%) reported chest pain during false pacing (p = 0.04 vs. true pacing). Furthermore, during true pacing chest pain occurred at a threshold significantly lower (3.7 ± 3.0 vs. 7.9 ± 2.8 mA, p = 0.001) (Fig. 2) and with a severity strikingly higher (7.3 ± 2.7 vs. 3.1 ± 3.5, p < 0.001) (Fig. 2) than during false pacing. Again, there were no significant changes in BP during the study. In particular, in patients with syndrome X, systolic BP was 129 ± 10 mm Hg before and 126 ± 9 mm Hg during true pacing.

Three of the 16 patients reported chest pain only during true stimulation (2 during ventricular pacing and 1 patient during both atrial and ventricular pacing), whereas 12 patients had pain during at least one false stimulation and 1 patient reported no symptoms throughout the entire study. Individual results are reported in detail in Table 2. Overall, pain threshold was significantly lower and pain severity higher during true ventricular stimulation (p < 0.01) than during the other three pacing sequences (false ventricular and true and false atrial stimulations).

### Discussion

In this study most patients with syndrome X reported typical chest pain during false stimulation (i.e., in absence of the electrical stimulus) in both the right atrium and ventricle. However, in the right ventricle, true pacing resulted in a significantly higher prevalence of pain, which occurred at a lower threshold and with a greater severity than during false pacing. Taken together, these findings suggest that pain complaint in patients with syndrome X usually has two causes: 1) an enhanced painful perception of potentially painful cardiac stimuli; and 2) subjective psychologic factors that bring them to report pain also in the absence of a true stimulus.

**Abnormal pain perception in syndrome X.** Patients with syndrome X often have recurrent and sometimes debilitating episodes of chest pain (2). The association with transient ischemia-like ST segment changes indicates a cardiac, and possibly ischemic, origin of the pain. Indeed, several studies (9–11) have reported signs of coronary microvascular dysfunction in at least a subgroup of these patients. However, other studies (12,13) failed to show detectable signs of myocardial ischemia, thus questioning the ischemic nature of the syndrome. Although the difficulty of obtaining reliable signs of myocardial ischemia does not necessarily exclude the microvascular nature of the disease (2,11), the discrepancy between the poor detection of ischemia and the severity of symptoms suggested that an abnormal perception of pain may have a relevant role in the pathogenesis of syndrome X (14).

Indeed, several studies (4–6) in patients with angina and normal coronary arteries have consistently reported an increased painful sensitivity to cardiac stimuli, including intracardiac injection of saline solution or catheter manipulation, right heart pacing and intracoronary injection of contrast medium. Furthermore, patients with syndrome X had a higher rate of angina during intravenous infusion of dipyridamole (15), adenosine (16) or epinephrine (17), even in the absence of evidence of ischemia.

Although these studies consistently suggest the presence of a lower pain threshold to cardiac stimuli, it is not clear whether this abnormality is confined to the heart or is part of a generalized nociceptive disorder. A lower pain threshold to forearm ischemia (18,19) and to electrical skin stimulation (18), as well as to esophageal stimulation (20), has been reported in patients with angina and normal coronary arteries. However, under more controlled conditions, cutaneous pain sensitivity, assessed by either multiple thermal (5) or electrical (21) stimulation, was found to be similar in patients with syndrome X and control subjects; furthermore, tolerance to esophageal stimulation was recently found (21) to be increased in patients with syndrome X. Thus, the presence of a generalized abnormality in pain perception in syndrome X is still controversial, and the results of previous studies may have been biased by the behavioral features of these patients.

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**Table 2. Individual Results of Atrial and Ventricular Stimulations in Patients With Syndrome X**

<table>
<thead>
<tr>
<th>Pain During Ventricular Pacing</th>
<th>No Pain</th>
<th>FP Only</th>
<th>TP Only</th>
<th>FP + TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at atrial pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FP only</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TP only</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>FP + TP</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are presented as number of patients. FP = false pacing; TP = true pacing.
Present study. Previous studies that assessed cardiac pain sensitivity in patients with angina and normal coronary arteries (4–6) used uncontrolled protocols. Therefore, it is not completely clear whether the increased reporting of pain by these patients depended on an abnormal response of the nociceptive system or was due to an enhanced tendency to complain. Indeed, an abnormal psychologic background, including anxiety disorders, panic attacks and depression, has been found in most patients with chest pain and normal coronary angiograms (7,8,22). All these behavioral disorders are associated with frequent somatic symptoms (including dyspnea, palpitation and chest pain) and may directly affect the perception of pain, leading to a tendency to report “typical” symptoms during stressful conditions, especially when they are expected to occur, as during an experimental study on pain perception.

By using a controlled protocol, we demonstrated that cardiac pain sensitivity is actually increased in patients with syndrome X. However, we also showed that the mere expectation of pain often brings these patients to report it in the absence of any stimulus, thus indicating that psychologic and behavioral factors are also significantly involved in their pain perception. Whether specific psychologic disorders may account for this response cannot be established from our data, as no psychometric evaluation was performed in this study. Yet, a recent study (23) did not find any significant relation between pain perception during uncontrolled right ventricular pacing and psychologic disorders in patients with angina and normal coronary arteries.

The other outstanding result of our study is the demonstration that the abnormal pain sensitivity in patients with syndrome X is selectively localized, or is much more easily appreciable, in the right ventricle than in the atrium, where the characteristics of chest pain were similar during false and true pacing. Finally, a major implication of our data is that, in these patients, pain assessment during clinical or research investigations should always be performed under careful controlled conditions.

In this study we evaluated as a control group, subjects who had never experienced chest pain. The investigation of patients with a history of anginal pain, such as those with chronic stable angina, could have provided more complete information on the specific tendency of patients with syndrome X to report chest pain. However, previous studies (5,6) showed that the prevalence of chest pain during cardiac pacing in patients with stable angina is similar to that of asymptomatic control subjects, thus suggesting that the tendency to report pain in stressful conditions may be a specific feature of patients with syndrome X.

Pathogenetic mechanisms. Although several studies (4–6) have shown an increased sensitivity to cardiac pain in patients with syndrome X, the pathophysiologic substrate of this feature is not known at present: theoretically it could involve either central or peripheral neural mechanisms.

Changes in BP have been shown (24,25) to influence pain perception. However, it is unlikely that such changes had any role in our study, because baseline BP was similar in patients and control subjects and BP did not change during the pacing study in our patients.

We (26) recently demonstrated that cardiac efferent adrenergic function is considerably altered in most patients with syndrome X. This finding may suggest that coincidental abnormalities of the afferent cardiac nerve system may be present and may contribute to the abnormal pain sensitivity of these patients, although such a relation needs to be addressed in appropriate future studies.

References


