Sequence and Magnitude of Ventricular Volume Changes in Painful and Painless Myocardial Ischemia

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Stimulation of left ventricular stretch receptors has been proposed as a possible mechanism for the occurrence of cardiac pain. Changes in left ventricular volume were continuously assessed in 12 patients during 11 spontaneous (two painful) and 12 ergometrine-induced (nine painful) ischemic attacks with a precordial scintillation probe and blood pool labeling with technetium-99m. In all ischemic episodes, spontaneous or induced, painful or painless, severe dilatation of the left ventricle was consistently observed. These changes always preceded the onset of ST segment shifts and occurred long before pain, when present. The maximum increase in end-diastolic volume was slightly greater in painful than in painless episodes, 38 ± 8.0% versus 28 ± 12.4%, but no significant difference was observed in the rate of volume change or in the maximum increase of end-systolic volume (133 ± 50% and 110 ± 27.3%), stroke volume (−28 ± 15% and −25 ± 12.4%), or ejection fraction (−32 ± 8.7% and −26 ± 6.0%). Although the maximum end-diastolic volume achieved is greater in painful episodes, this effect cannot be separated from that of duration, and, furthermore, there was no significant difference in end-diastolic volume at the moment chest pain began. Thus, in patients with angina at rest, transient asymptomatic ST segment shifts are consistently associated with large changes in left ventricular volume, similar to those observed during painful episodes. The rate and extent of acute left ventricular dilatation do not appear to be factors directly causing anginal pain. (Circulation 1988;78:310–319)

The mechanisms responsible for the appearance of cardiac pain during acute myocardial ischemia are still poorly understood.1,2 The absence of pain during episodes of acute myocardial ischemia, which has been repeatedly documented in both patients with variant3–6 and patients with stable angina,7,8 has been attributed to a defective warning system.2

Stimulation of chemoreceptors by ischemic metabolites9 was proposed about half a century ago as a stimulus that could be responsible for the appearance of anginal pain. However, the hypothesis implicating chemical mediation of pain seems questionable on the basis of animal and clinical observations. A pseudo-effective reaction can be elicited in unanesthetized animals by coronary occlusion but not by intracoronary injection of veratridine,10 a potent stimulator of chemoreceptors, or by infusion of bradykinin,11 a known somatic pain simulator. In patients with variant or unstable angina, the severity and duration of acute myocardial ischemia, presumably related to release of ischemic metabolites, were not significantly different in painful and painless episodes.3

Activation of mechanoreceptors by bulging of the ischemic area12,13 has also been proposed as a mechanism potentially responsible for cardiac pain. To check this hypothesis, we have explored the possibility that the magnitude or the rate of change of left ventricular volume during acute myocardial ischemia, or a combination of these parameters, could account for the presence or absence of anginal pain.

Patients and Methods

Patients

Twelve patients were selected for study either because they presented with spontaneous episodes of acute myocardial ischemia or because they had a
TABLE 1. Patient Characterization

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Effort angina</th>
<th>Spon-</th>
<th>Effort test</th>
<th>Ergometrine test</th>
<th>ST change</th>
<th>Left ventriculogram</th>
<th>Coronaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.B.</td>
<td>51</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>NP</td>
<td>NP</td>
<td>el</td>
<td>Normal</td>
<td>Basal</td>
</tr>
<tr>
<td>S.M.</td>
<td>54</td>
<td>F</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>el</td>
<td>Normal</td>
<td>LAD stenosis</td>
<td>During ST change</td>
</tr>
<tr>
<td>A.D.</td>
<td>68</td>
<td>M</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>dep</td>
<td>Inferior dyskinesia</td>
<td></td>
</tr>
<tr>
<td>J.J.</td>
<td>50</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>el</td>
<td>Normal</td>
<td></td>
<td>LAD stenosis</td>
<td></td>
</tr>
<tr>
<td>D.P.</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>NP</td>
<td>el</td>
<td>NP</td>
<td>Three-vessel disease</td>
<td></td>
</tr>
<tr>
<td>W.W.</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>dep</td>
<td>Anterior, lateral</td>
<td>LAD stenosis Circumflex occlusion</td>
<td></td>
</tr>
<tr>
<td>B.G.</td>
<td>68</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>dep</td>
<td>Normal</td>
<td>Diffuse vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>J.C.</td>
<td>57</td>
<td>M</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>dep</td>
<td>Normal</td>
<td>LAD stenosis</td>
<td></td>
</tr>
<tr>
<td>F.W.</td>
<td>56</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>el</td>
<td>Normal</td>
<td>LAD stenosis</td>
<td></td>
</tr>
<tr>
<td>O.S.</td>
<td>56</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>el</td>
<td>Apical dyskinesia</td>
<td>LAD stenosis</td>
<td></td>
</tr>
<tr>
<td>J.N.</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>dep</td>
<td>Apical akinesia</td>
<td>LAD stenosis</td>
<td></td>
</tr>
<tr>
<td>A.B.</td>
<td>74</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>dep</td>
<td>Anterior hypokinesia</td>
<td>LAD stenosis</td>
<td></td>
</tr>
</tbody>
</table>

NP, not performed; el, ST elevation; LAD, left anterior descending artery; +, positive; -, negative.

Davies et al Ventricular Volume in Painless Ischemia

Positive ergometrine provocation test. Their clinical, electrocardiographic, and coronary angiographic characteristics are listed in Table 1. Approval for the study was obtained from the local ethical committee, and each patient gave informed consent. One patient (E.B.) was excluded from the ergometrine test because Holter monitoring showed frequent episodes of ST segment elevation, and angiography was not performed in one patient (D.P.) because of associated cerebrovascular disease.

Nine patients investigated for atypical chest pain were considered controls and studied during the ergometrine test in the same manner as were the patients with transient ST segment changes. All patients had a negative exercise test, absence of episodes of ST segment change on 48 hours of Holter monitoring, and normal coronary arteriograms, both in the basal state and during provocative tests for ischemia.

In five patients with normal left ventriculograms and no spontaneous or inducible myocardial ischemia, an atrial pacing test was performed to validate the measurement of left ventricular volume monitoring described below.

Protocol

With the patient lying supine, the 12-lead electrocardiogram, arterial pressure (brachial arterial cannula, Statham P231D transducer Spectramed, Coventry, UK), and the analog signal from the scintillation probe (see below) were continuously recorded onto a multichannel analog tape recorder (14 DS, Racal Thermionics, Southampton, UK). Recordings were made for 30 minutes in the resting state, during incremental doses of ergometrine malate (0.025, 0.05, 0.1, and 0.2 mg at 6-minute intervals until ST segment changes or chest pain occurred), and after the administration of amyl nitrite. Amyl nitrite was given within 1 minute of the onset of angina when this occurred. The total duration of data recording used for analysis in each patient was 90 minutes. In one patient (E.B.), the oxygen saturation in the great cardiac vein was continuously monitored with a 7F fiber-optic catheter that was connected to an in vivo hemoreflectometer (Schwarzer IVH3) and introduced via the coronary sinus. In five patients, stroke volume (thermodilution method, model IL701, Instrumentation Laboratory, Warrington, Cheshire, UK) and stroke counts (scintillation probe, see below) were measured during 5-minute periods of atrial pacing at increments of 10 beats/min up to a rate of 120 beats/min. An average of five estimations of stroke volume was calculated for each heart rate and plotted against stroke counts, acquired simultaneously.

Left Ventricular Volume

The blood pool was labeled with an in vivo method with 10 mCi technetium-99m as pertechnetate, administered intravenously 30 minutes after 0.2 mg/kg sodium stannous pyrophosphate. A single scintillation probe was positioned over the left ventricle, in the modified left anterior oblique projection, by a previously described method. The projection of the collimator aperture onto the skin was marked with an ink pen to allow repositioning after background assessment and to allow for patient or probe movement. The patient’s position was fixed with respect to three dimensions and checked before and after recording. The occurrence of rotation of the patient was checked by the relative height of both sides of the chest. No movement of patient or collimator could be made that could not be detected by a combination of these methods. Background activity was recorded by moving the
TABLE 2. Variability of Left Ventricular Volumes in Basal State

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>End-diastolic volume</th>
<th>End-systolic volume</th>
<th>Stroke volume</th>
<th>Ejection fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.84 ± 0.76</td>
<td>1.68 ± 1.32</td>
<td>3.51 ± 2.89</td>
<td>1.20 ± 0.95</td>
</tr>
<tr>
<td>2</td>
<td>1.67 ± 0.59</td>
<td>2.59 ± 2.56</td>
<td>3.56 ± 2.91</td>
<td>1.24 ± 0.86</td>
</tr>
<tr>
<td>3</td>
<td>2.16 ± 1.32</td>
<td>3.47 ± 2.40</td>
<td>3.82 ± 2.81</td>
<td>1.50 ± 0.92</td>
</tr>
<tr>
<td>4</td>
<td>1.15 ± 0.53</td>
<td>1.66 ± 1.72</td>
<td>4.10 ± 3.33</td>
<td>1.16 ± 1.09</td>
</tr>
<tr>
<td>5</td>
<td>1.18 ± 1.23</td>
<td>2.32 ± 1.42</td>
<td>2.00 ± 1.55</td>
<td>0.84 ± 0.58</td>
</tr>
<tr>
<td>6</td>
<td>2.25 ± 1.44</td>
<td>4.57 ± 3.67</td>
<td>3.08 ± 1.90</td>
<td>1.60 ± 1.15</td>
</tr>
<tr>
<td>7</td>
<td>1.17 ± 0.95</td>
<td>7.43 ± 4.80</td>
<td>2.97 ± 2.52</td>
<td>2.28 ± 1.51</td>
</tr>
<tr>
<td>Total</td>
<td>1.54 ± 1.10</td>
<td>3.39 ± 3.31</td>
<td>3.29 ± 2.59</td>
<td>1.40 ± 1.08</td>
</tr>
</tbody>
</table>

Figures are mean ± SD percent change from mean value and are based on 10 observations in each patient.

probe to a position inferolateral to the left ventricular region of interest where periodicity is lost and average counts first begin to decrease. The output voltage was calibrated in terms of counts with a point source, and the probe was positioned over the left ventricle. An index of left ventricular volume could be recorded over several hours, allowing accurate detection of transient changes within that period. This technique, first described by Wagner et al., is based on the observation that changes in radioactive counts reflect proportional changes in left ventricular volume. A close correlation between this technique and that of contrast ventriculography in the assessment of ejection fraction was reported by Berger et al.

Data Analysis

The data were replayed at high speed onto paper running at 15 mm/sec with a Mingograph 16-channel ink-jet recorder (Siemens, Sunbury-on-Thames, UK). Visual inspection allowed the detection of transient changes in the ST segment, arterial pressure, and left ventricular volume and the study of their temporal relation. From this trace, periods of interest could be chosen for computer analysis after analog-to-digital conversion. Of the 12 ECG leads, the lead showing the earliest and most marked ST segment change was selected for further analysis. For the selected period of monitoring, all signals were digitized at 100 Hz with a Hewlett-Packard 21mx F series computer. The data were stored on digital tape and transferred to disk for further analysis.

![Figure 1](http://circ.ahajournals.org/) Top panel: Continuous plot of (from top to bottom) digital ECG, left ventricular volume index, and arterial pressure signals. Raw left ventricular volume signal is shown in second row from top, and the result of mobile-averaging (seven cycles) derivative is shown in third row. Bottom panel: Continuous ECG and raw left ventricular volume curve recorded for 1 hour in basal state. No decay correction or mobile-averaging of curve has been made.
Electrocardiogram. The R wave of the electrocardiogram was used both to compute the heart rate from the series of RR intervals and as a reference point for computerized, R-wave gated averaging of the left ventricular volume curve (see below). The positive and negative components of the ST segment area were computed with a previously described algorithm.\(^{18}\)

Arterial pressure. The systolic, diastolic, and mean arterial pressures were calculated.

Left ventricular volume. An index of left ventricular volume was taken as the magnitude of the above-background activity detected by the probe (corrected for the physical decay of technetium-99m). To minimize noise related to counting statistics and to improve the stability of the probe signal, computerized ECG-gated mobile averaging was performed, producing an output curve exactly synchronous with the input curve.\(^{19}\) From this continuous beat-to-beat volume curve, an index of end-diastolic and end-systolic volumes was calculated as the above-background end-diastolic and end-systolic counts, respectively. Stroke counts were taken as an index of stroke volume, and the left ventricular ejection fraction was calculated by dividing this by the end-diastolic counts. The values of heart rate ST segment area; arterial systolic, mean, and diastolic pressures; left ventricular end-diastolic, end-systolic, and stroke volume indexes; left ventricular ejection fraction; and great cardiac vein oxygen saturation were continuously plotted against time for each cycle.

The percent change from basal of each parameter was calculated at 1-minute intervals from the onset of change (defined as a deviation of the mean value of 10 cycles greater than two standard deviations of the basal mean value and persisting for more than 30 seconds) for each ischemic episode. In addition, the maximum percent change from basal was calculated for each parameter.

In seven of the nine control patients, the indexes of end-diastolic, end-systolic, and stroke volumes and the ejection fraction were calculated from the computer-averaged volume curve at 10 equally spaced points over the 30-minute basal recording period to assess the constancy of the volume signal. The values for each patient were expressed as the percent difference from the mean. The mean ± standard deviation of this percent difference was calculated for each parameter in each patient and for the entire group.

In the five patients subjected to atrial pacing, the mean value (over 10 cycles) of the stroke counts was plotted against the mean value of stroke volume, as estimated with the thermodilution technique.

Statistical analysis. The analysis of variance was used to compare the differences in the maximum percent changes from basal, the rate of change of left ventricular volume, and the interval between left ventricular volume change and the duration of the episodes between the groups. Linear regression analysis was used to compare the stroke volume and stroke counts obtained during atrial pacing.

Results

Validation of Technique

The correlation coefficient of the relation between counts and volume in the five patients studied during atrial pacing ranged from 0.781 to 0.906. The minimum detectable change in volume was 10.4 ± 5.0 ml (range, 5–18 ml; i.e., 100% detection when changes exceeded 18 ml).

The values relating to the constancy of output of the scintillation probe, assessed in seven of the control patients, are given in Table 2. The average change from the mean value for the group was 1.54 ± 1.10%, 3.39 ± 3.31%, 3.29 ± 2.59%, and 1.40 ± 0.180% for end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction, respectively. Examples of the ECG, arterial pressure, and scintillation probe signal, recorded over 1 hour in the basal state, are shown in Figure 1.
The interobserver differences (20 episodes in 12 patients for each observer) in the measurement of the indexes of basal end-diastolic volume, end-systolic volume, and stroke volume and of ejection fraction were 3.5±4.5% (mean±SD), 5.7±6.7%, 5.8±7.2%, and 5.4±6.9%, respectively. The differences during ischemia were 2.1±2.4%, 2.3±3.5%, 10.7±8.2%, and 8.8±7.3%, respectively. The intraobserver differences (20 episodes in 12 patients) in the measurement of the indexes of end-diastolic volume, end-systolic volume, and stroke volume and of ejection fraction were 3.9±5.1%, 7.0±10.1%, 5.8±9.5%, and 6.8±9.2%, respectively, during the basal state and 1.6±2.4%, 2.4±3.8%, 9.5±13.0%, and 9.2±11.6%, respectively, during ischemia.

**Control Patients**

A small increase in left ventricular volume was induced by ergometrine (Figure 2). The maximum change after administration of 0.35 mg ergometrine was 18±8% for end-diastolic volume, 38±21% for end-systolic volume, 3±7% for stroke volume, and −2±8% for ejection fraction.

**Sequence of Events**

In the 12 patients, 23 episodes (1.9 episodes/patient; range, 1–3) of ST segment shifts were analyzed, of which 11 were spontaneous (five patients) and 12 were ergometrine-induced (eight patients). ST segment elevation occurred in 13 patients, and ST segment depression occurred in 10.

Irrespective of whether the attack was spontaneous or induced, painful or painless, the sequence of changes was consistently similar. Progressive dilatation of the left ventricle with reduction of stroke volume and ejection fraction was followed by the development of ST segment changes. Pain, when present, was a late manifestation (Figure 3). During

![Figure 3. Arterial pressure, ECG, and raw and computer-averaged volume changes during the basal state and after incremental doses of ergometrine (E, mg). P, pain; A, amyl nitrite; ISDN, isosorbide dinitrate (2.5 mg i.v.). Initial, expanded portion of trace shows variation in left ventricular volume throughout the cardiac cycle. Vertical interrupted line indicates the point at which the ST segment depression becomes diagnostic of ischemia. Ergometrine induces progressive dilatation of the left ventricle, preceding the onset of pain, partially reversed by amyl nitrite and completely by isosorbide dinitrate.](image-url)
ischemia, the changes in ventricular function (reflected by ejection fraction and stroke volume changes) were dynamic with no development of a true steady state. Compared with spontaneous attacks, ergometrine-induced episodes were usually longer with slower development of ventricular dilatation (Table 3), and the increase in end-systolic and end-diastolic volumes usually preceded the reduction in stroke volume (135 ± 91 seconds [mean ± SD]; range, 67–280 seconds). The progression of ventricular dilatation was slower in attacks associated with ST segment depression than in those with ST segment elevation. Figure 3 illustrates the sequence of changes associated with an ergometrine-induced episode of ST segment depression and pain. Spontaneous attacks were usually of shorter duration (Table 3) and were characterized by the rapid evolution of volume changes with virtually simultaneous ventricular dilatation and stroke volume reduction, followed by ST segment changes. Whether the attacks terminated spontaneously or were relieved by amyl nitrite administration, the regression of volume changes and the return of basal ventricular function were rapid. Figures 4 and 5 show the typical sequence of events during spontaneous and ergometrine-induced ST segment elevation. In the patient in whom great cardiac vein oxygen saturation was continuously monitored (Figure 4), in each of the 30 episodes recorded, the first change was a progressive fall in oxygen satura-
tion, clearly preceding changes in ventricular volume and blood pressure. The dilatation and the extensive regional impairment of left ventricular function during the second episode shown in Figure 5 are shown in the ventriculograms in Figure 6.

**Anginal Pain**

Eleven episodes were associated with typical anginal pain (two spontaneous, nine induced), and 12 were completely painless (nine spontaneous, three induced). Although episodes of shorter duration were usually painless, the difference in duration of electrocardiographic changes between painful and painless episodes (Table 3) attacks did not reach statistical significance. The sequence of changes in left ventricular function and their relation to ST segment changes were similar in both painful and painless attacks, whether they occurred spontaneously or were induced by ergometrine. Pain was invariably a late manifestation of the attack, occurring 90–560 seconds after the onset of left ventricular volume change and 30–180 seconds after the onset of electrocardiographic change. The rate of volume change was slower during ergometrine-induced episodes than in spontaneous episodes (Figure 5). However, no significant difference in the rate of volume change was found between painful and painless episodes. Although the maximum change in end-diastolic volume was greater ($p<0.05$) when pain occurred (Table 4), there was no significant difference in stroke volume, end-systolic volume, or ejection fraction.

**Discussion**

Rapid changes in ventricular function occur during myocardial ischemia, and often a steady-state condition is not achieved (Figure 2). We, therefore, used a scintillation probe to continuously monitor left ventricular volume to detect these changes and to measure the rate of volume change. This would not be possible with conventional imaging techniques because they cannot follow such rapid changes. The requirements for the application of the technique described in the present study are less stringent than those for absolute measurements because the essential information that we wish to extract is 1) the presence of changes in ventricular function and their temporal relation to the onset of the electrocardiographic changes and to pain and 2) the percentage change from the basal state within each individual patient.

The absence of detectable changes over the 30-minute control period in the seven control patients and the good correlation between percent changes in stroke counts and thermodilution estimates of stroke volume during pacing are consistent with previous findings and provide validation of the technique for our purposes.

**Sequence of Left Ventricular Volume Changes During Ischemia**

The classic studies of Tennant and Wiggers demonstrated the rapid development of impaired myocardial contraction after coronary artery occlusion. Abnormalities of left ventricular function have been shown in animal experiments to precede the onset of ST segment changes induced by a graded reduction in coronary arterial flow. More recent animal studies have demonstrated early changes in left ventricular function in the absence of electrocardiographic changes during submaximal flow reduction. Regional left ventricular wall motion abnormality and reduction in wall thickness have been demonstrated by echocardiography to occur before the onset of ST

**Table 4. Maximum Percent Changes in Left Ventricular Function Parameters**

<table>
<thead>
<tr>
<th></th>
<th>End-diastolic</th>
<th>End-systolic</th>
<th>Stroke</th>
<th>Ejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>volume</td>
<td>volume</td>
<td>volume</td>
<td>fraction</td>
</tr>
<tr>
<td>Painful</td>
<td>13.9±8.0</td>
<td>133±50</td>
<td>-28±16.8</td>
<td>-32±8.7</td>
</tr>
<tr>
<td>Painless</td>
<td>26.0±12.4</td>
<td>110±27.3</td>
<td>-25±12.4</td>
<td>-26±6.0</td>
</tr>
<tr>
<td>ST elevation</td>
<td>308±18</td>
<td>132±45</td>
<td>30.2±8.3</td>
<td>31.7±14.6</td>
</tr>
<tr>
<td>ST depression</td>
<td>36.3±7.3</td>
<td>107±30.4</td>
<td>26.8±7.4</td>
<td>19.4±11.4</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>26.3±13.5</td>
<td>125±45.9</td>
<td>-28.6±13.7</td>
<td>-28.8±8.3</td>
</tr>
<tr>
<td>Ergometrine-induced</td>
<td>36.8±7.8</td>
<td>117±36.5</td>
<td>-24.3±15.3</td>
<td>-28.6±7.9</td>
</tr>
<tr>
<td>Controls</td>
<td>18.0±8.0</td>
<td>38±21</td>
<td>3±7</td>
<td>-2±8</td>
</tr>
</tbody>
</table>

Figures are mean±SD maximum percent change during attacks compared with basal. Percentages in controls are peak effect of ergometrine with respect to basal and are compared for significance with the ergometrine-induced attacks of ischemia.

NS, not significant.
FIGURE 6. Left ventriculograms obtained in the basal state (left panel) (end-diastole above; end-systole below) and during the episode of ergometrine-induced ischemia (right panel). During ST segment elevation, there is end-diastolic and end-systolic dilatation with apical dyskinesia.

segment changes during exercise-induced myocardial ischemia in humans.23

This study shows that progressive dilatation of the left ventricle with reduction in stroke volume and ejection fraction consistently accompanies all episodes of acute myocardial ischemia associated with diagnostic ST segment changes and typical anginal pain, whether spontaneous or ergometrine induced. Continuous monitoring of the changes in ventricular function over long periods of time has enabled us to establish that the onset of these changes precedes the development of diagnostic electrocardiographic changes, and their consistency is comparable with that of changes in left ventricular pressure and dP/dt observed during invasive monitoring.3 The similarity in the sequence of events in painless episodes of ST change strongly supports the notion that they do represent acute myocardial ischemia.

The rate of left ventricular dilatation was more rapid in spontaneous episodes than in those induced by ergometrine. Ergometrine causes a gradual, modest, dose-dependent increase in end-diastolic volume in normal hearts24 in the absence of significant changes in stroke volume. This increase in volume appears to be due to systemic venoconstriction.25,26 However, the onset of ischemia appears to be independent of the direct effect of ergometrine on volume24 because it is consistently associated with a fall in stroke volume, a further, rapid increase in end-diastolic and, particularly, in end-systolic volume, and a fall in ejection fraction. Thus, while in spontaneous episodes left ventricular dilatation and fall in stroke volume occurred simultaneously, in ergometrine-induced ischemia, a prolonged, parallel rise in end-diastolic and end-systolic volumes, and thus decrease in ejection fraction, preceded the decrease in stroke volume. The more gradual variation in volume observed on the whole in ergometrine-induced episodes may also be accounted for by a less abrupt onset and a lesser severity of ischemia compared with spontaneous episodes, which were almost invariably accompanied by ST segment elevation or pseudonormalization of inverted T waves, known to be associated with transmural ischemia.27,28
Relation of Pain to Severity and Duration of Ischemia and to Ventricular Dilatation

There were no significant differences in the magnitude of end-systolic and stroke volume changes, reflecting the severity of ischemia, in painful or painless attacks, whether spontaneous or induced by ergometrine. These results confirm the observation that the increase of left ventricular filling pressure does not appear to be directly related to the development of pain. Furthermore, there was no difference in the rate of change in left ventricular volume between painless and painful attacks, spontaneous or induced. The greater maximum end-diastolic volume in painful episodes could not be separated from the effect of longer duration. However, there was no statistically significant difference between the maximum end-diastolic volume during painless episodes and the end-diastolic volume at the onset of pain in the painful episodes. Short episodes of ischemia, regardless of severity and magnitude of ventricular dilatation, were invariably painless. Therefore, ventricular dilatation alone, which is likely to be associated with intense stimulation of mechanoreceptors, is not sufficient to cause pain. Moreover, severe ischemia, however brief, should be sufficient for the stimulation of specific nociceptors; therefore, their existence in the myocardium remains doubtful. The occurrence of pain seems to be at least partially related to the duration of ischemia because relatively long attacks are more likely to be associated with chest pain. However, the duration of ischemia per se is not a sufficient condition because prolonged, painless episodes are frequently observed. It, therefore, appears that neither the severity of ischemia, its duration, nor the magnitude and rate of ventricular dilatation are, in isolation, sufficient to induce angina. This suggests that pain results from the convergence of different afferent impulses arising from various receptors and modulated at higher levels within the central nervous system.

In conclusion, continuous, noninvasive assessment of left ventricular volume shows impairment of global ventricular function to be an early, consistent marker of acute myocardial ischemia regardless of whether it is accompanied by anginal pain. The rate and severity of acute dilatation do not appear per se sufficient to explain the presence of anginal pain.

References

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KEY WORDS • anginal pain • ventricular volume monitoring • painless ischemia • scintillation probe
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G J Davies, W Bencivelli, G Fragasso, S Chierchia, F Crea, J Crow, P A Crean, T Pratt, M Morgan and A Maseri

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