Original articles

Regional distribution and timing of wall motion abnormalities during echo-dipyridamole stress test in patients with stable angina: the elusive link between coronary stenoses and myocardial ischemia

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Coronary stenosis; Dipyridamole; Myocardial ischemia; Stable angina.

Background. **Classic experimental studies have shown that in the presence of a flow-limiting coronary artery stenosis, myocardial ischemia during metabolic or pharmacological arteriolar vasodilation causes wall motion abnormalities, which precede electrocardiographic (ECG) changes in the myocardial regions supplied by the stenotic branch. The aim of this study was to establish whether in patients with chronic stable angina the regional distribution of wall motion changes and sequence of ischemic events are similar to that observed in experimental models, as currently believed.**

Methods. **The study population consisted of 20 men and 4 women (mean age 59 – 10 years) who were recruited on the basis of the following criteria: 1) a history of chronic stable angina without clinical and instrumental evidence of previous myocardial infarction; 2) reproducible positive exercise tests for ECG myocardial ischemia and anginal pain; 3) angiographically normal left ventricular function; 4) isolated stenosis of the left anterior descending coronary artery (LAD). Patients underwent continuous 12-lead ECG and echocardiographic monitoring during dipyridamole infusion.**

Results. **During dipyridamole infusion 3 patients (13%) did not develop echocardiographic changes, ECG changes or angina, 14 (58%) exhibited ECG changes, 18 (75%) lamented angina and 16 (67%) developed echocardiographic changes. In 5 of these 16 patients (31.5%) echocardiographic changes occurred in LAD-dependent territories only, in 5 they occurred in non-LAD-dependent territories only (31.5%) and in 6 (37%) they occurred in both LAD- and non-LAD-dependent territories. A total of 14 patients exhibited both echocardiographic and ECG changes and/or angina. In 6 of these 14 patients (43%) echocardiographic changes were the first ischemic events; in the remaining 8 patients (57%) ECG changes and/or angina were the first ischemic events.**

Conclusions. **In the majority of patients during dipyridamole infusion regional wall motion changes occur in territories supplied by non-stenotic coronary artery branches; they are probably caused, therefore, by distal vessel dysfunction. Furthermore, the sequence of ischemic events is different in individual patients. These findings indicate that in stable angina the mechanisms of ischemia are multiple and that the link between coronary stenoses and myocardial ischemia is very elusive.**

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Classic experimental studies have shown that in the presence of a flow-limiting coronary artery stenosis, usually created using a snare positioned around a normal epicardial coronary artery, stress-induced myocardial ischemia causes wall motion abnormalities, which precede electrocardiographic (ECG) changes in the myocardial regions supplied by the stenotic branch[1]. For many years it has been assumed that, in patients with obstructive coronary atherosclerosis and stable angina, stress-induced myocardial ischemia causes a similar sequence of events in myocardial regions perfused by stenotic coronary branches[2]. Yet, patients with obstructive coronary atherosclerosis, different from experimental models, present a diffuse impairment of both proximal and distal coronary vessels[3]; the mechanisms responsible for myocardial ischemia, therefore, might be related to reduced coronary flow reserve caused by epicardial coronary obstruction, coronary microvascular dysfunction or both.

We hypothesized that in patients with chronic stable angina, stress-induced myocardial ischemia is caused not only by epicardial coronary obstruction but also by mi-

crovascular dysfunction. To test this hypothesis we assessed the regional distribution of wall motion changes and the temporal sequence of ischemic events in a well selected group of patients with chronic stable angina and a single critical stenosis in the proximal segment of the left anterior descending coronary artery (LAD) who underwent ECG and echocardiographic continuous monitoring during dipyridamole infusion.

Methods

Study population. The study was carried out in a consecutive series of patients consisting of 20 men and 4 women (mean age 59 – 10 years, range 41-76 years) who were recruited on the basis of the following criteria: 1) a history of chronic stable angina (class II-III of the Canadian Cardiovascular Society; symptom duration ranging from 6 to 24 months) without clinical history and instrumental evidence of previous myocardial infarction; 2) reproducible positive exercise tests for ECG myocardial ischemia (horizontal or downsloping ST segment depression 2.0 mm of the baseline value 0.08 s after the J point) and anginal pain; 3) angiographically normal left ventricular function (mean left ventricular ejection fraction 62 – 6%; range 50-67%); 4) isolated stenosis of the LAD (mean reduction in luminal diameter 87 – 10%, range 70-98%, measured by quantitative computerized angiography); 5) right dominant coronary circulation. ECG and echocardiogram at rest were normal in all patients. No patient had evidence of left ventricular hypertrophy, mitral valve prolapse or conduction defects that could interfere with the interpretation of ST segment changes and no patient was taking digitalis. Blood potassium levels were within the normal range in all patients. Family history of ischemic artery disease in first degree relatives before the age of 60 years was present in 13 patients; hypertension (blood pressure > 140/90 mmHg) was present in 5 patients and hypercholesterolemia (plasma cholesterol levels > 200 mg/dl) was present in 14 patients. Six patients were current smokers (> 5 cigarettes per day). No patient had a personal history nor family history of diabetes or glucose intolerance. A period of pharmacological washout of at least 72 hours was allowed before the study with the exception of sublingual nitrates if needed and all patients abstained from caffeine-containing drinks for 48 hours before the study. The study protocol was approved by the institutional ethics committee and written informed consent was obtained by all patients.

Study protocol. After patients were placed in the left lateral decubitus position, two-dimensional echocardiograms were obtained using a commercially available phased-array imaging system with 2.5-MHz transducers (Hewlett Packard, Sonos 2500, Andover, CA, USA). All studies were recorded on VHS videotape. Four views (parasternal long-axis, parasternal short-axis at the mitral, papillary muscle and apical level, apical 4-chamber and 2-chamber view) were obtained as previously described[4]. Two-dimensional echocardiographic monitoring was performed at baseline, during dipyridamole infusion (0.56 mg/kg in 4 min immediately followed by 0.28 mg/kg in 2 min) and up to 20 min after the end of dipyridamole administration. The cumulative dose of dipyridamole infused was 0.84 mg/kg over 6 min. Wall motion score index was assessed in a qualitative manner at rest and during stress. To this end the left ventricle was divided into 16 segments, which were graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic[4]. Echocardiographic myocardial segments were arbitrarily divided into LAD-dependent and non-LAD-dependent regions (Fig. 1). Regional wall motion score index was evaluated independently by two expert echocardiographers not directly involved in the study. A third investigator reviewed the echocardiograms in a blinded manner if the first two investigators were not in agreement. The time to onset of regional wall motion abnormalities (in seconds from the beginning of dipyridamole infusion) was recorded.

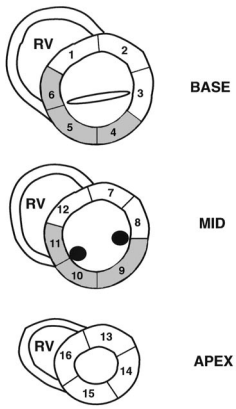

Figure 1. *Sixteen-segment model for wall motion analysis. White segments were considered left anterior descending coronary artery (LAD)-dependent myocardial segments (n = 10); shaded segments were considered non-LAD-dependent myocardial segments (n = 6). 1 = proximal anterior septum; 2 = proximal anterior wall; 3 = proximal lateral wall; 4 = proximal posterior wall; 5 = proximal inferior wall; 6 = proximal inferior septum; 7 = mid anterior wall; 8 = mid lateral wall; 9 = mid posterior wall; 10 = mid inferior wall; 11 = mid inferior septum; 12 = mid anterior septum; 13 = distal anterior wall; 14 = distal lateral wall; 15 = distal posterior wall; 16 = distal anterior septum; RV = right ventricle.*

A 12-lead ECG was continuously monitored during the procedure and recorded every minute for the total duration of the procedure. The level of ST segment, 80 ms after the J point, was calculated after signal averaging by means of a computer assisted system in all 12 leads. The time to onset of ST segment depression 0.5 mm below the baseline value (measured in seconds from the beginning of dipyridamole infusion) and the ECG lead was immediately recorded.

At the beginning of dipyridamole infusion, patients were informed that they could develop pain or other unpleasant symptoms, and this was not repeated during dipyridamole infusion in order to avoid any potential bias.

Patients were also instructed to promptly report the onset of pain and to record the maximal severity of the pain. The time to onset of typical anginal pain (in seconds from the beginning of dipyridamole infusion) was immediately recorded. Immediately after the infusion, patients were asked to report the maximal severity of pain using a visual analogue scale as previously described[5]. To this end the 100 mm scale was marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject s mark in millimeters.

During the procedure, blood pressure (by the Riva-Rocci cuff sphygmomanometer) was recorded every minute. All patients received intravenous aminophylline (240 mg) at the end of the test.

Statistical analysis. Continuous normally distributed data are expressed as mean – 1 SD and were analyzed by two-tailed unpaired Student s t-test. Non-normally distributed data are expressed as median and interquartile range and were analyzed by the Mann-Whitney rank-sum test. Factorial analysis of variance was used to compare multiple groups; for a p value of < 0.05 pairwise comparisons were performed by using the Scheffe F-test. The χ^2 test with continuity correction was applied to compare proportions. Differences between groups were considered to be statistically significant at a p value of < 0.05.

Results

ECG and two-dimensional echocardiograms were adequate for analysis in all patients. Dipyridamole infusion was well tolerated by all patients so that the test could always be completed. The intravenous infusion of aminophylline abated anginal pain and ECG and echocardiographic changes in all patients. The detailed hemodynamic findings recorded during the procedure are reported in table I.

Prevalence of ischemic events. During dipyridamole infusion, 3 patients (13%) did not develop ST segment changes, regional wall motion abnormalities or anginal pain (Fig. 2). Fourteen patients (58%) presented ST segment depression > 0.5 mm: in 13 patients the maximal

Table I. Hemodynamic data*.

Variables	Baseline	Dipyridamole
Heart rate (b/min)	80 – 12	91 – 14**
Systolic blood pressure (mmHg)	129 – 19	115 – 16**
Diastolic blood pressure (mmHg)	75 – 9	68 – 9**
Double product (mmHg × b/min) × 100	103 – 15	105 – 18

* plus-minus values are means – 1 SD; ** $p < 0.05$.

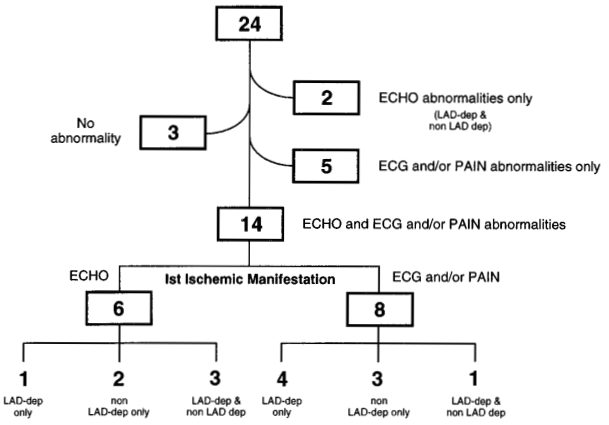

Figure 2. *Flow chart showing the different ischemic events in the study group during dipyridamole infusion. Numbers in squares indicate the number of patients. LAD = left anterior descending coronary artery.*

ST segment depression was localized in leads V_4-V_6 and in 1 patient in leads II, III, aVF. Maximal ST segment depression was 1.6 – 0.5 mm. Eighteen patients (75%) lamented angina during dipyridamole infusion (Fig. 2); the type of pain was similar to the habitual angina experienced during daily life; maximal pain severity was 55 – 19 mm. Four patients had transient facial flushing and 1 had transient headache. During dipyridamole infusion 16 patients (67%) developed regional wall motion abnormalities at echocardiography. The severity of wall motion score index was 2 (interquartile range 2-3.25).

Regional distribution of regional wall motion abnormalities. Regional wall motion changes were present in LAD-dependent territories only in 5 of the 16 patients (31.5%), in non-LAD-dependent territories only in 5 patients (31.5%), in both LAD- and non-LAD-dependent territories in 6 patients (37%) (Fig. 2). The severity of wall motion abnormalities was similar in patients with regional wall motion changes detected in LAD-dependent territories only and in those with abnormalities detected in non-LAD-dependent territories only (2, interquartile range 2-3.25 vs 2, interquartile range 2-3, $p = 0.81$). The prevalence of cardiovascular risk factors and the presence of collateral circulation were similar in these three groups of patients as well as LAD stenosis severity (93 – 6 vs 85 – 11 vs 84 – 11%, $p = 0.09$).

Temporal sequence of the ischemic events. During dipyridamole infusion, 14 patients exhibited both wall motion abnormalities and ECG changes and/or anginal pain. In 6 patients (43%) regional wall motion abnormalities represented the first ischemic event; in the remaining 8 patients (57%) the first ischemic event was represented by ECG changes in 7 patients and pain in 1 patient (Figs. 2 and 3). The time interval between the first and the second ischemic event was similar in the two groups (169 – 113 vs 178 – 129 s, $p = 0.88$). The prevalence of car-

diovascular risk factors and the presence of collateral circulation were similar in patients in whom the first ischemic event was represented by regional wall motion abnormalities or ECG changes associated or not with anginal pain (Tab. II). LAD stenosis severity was similar in the two groups (82 – 11 vs 90 – 10%, p = 0.84).

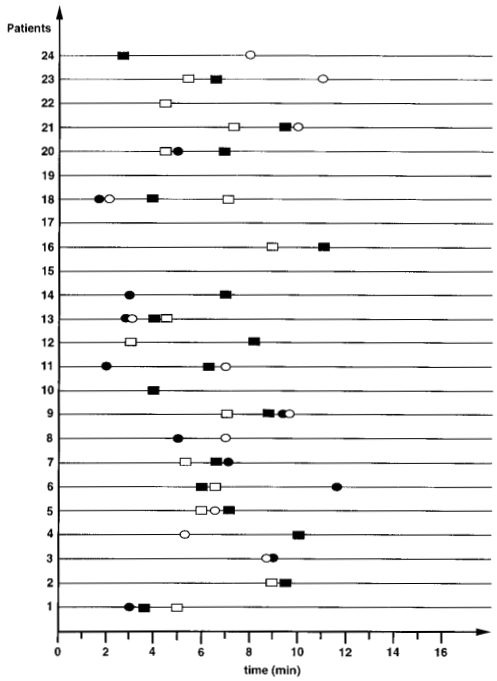

Figure 3. *Schematic representation of the temporal sequence of ischemic events during dipyridamole infusion in each patient.* Black squares: *angina pectoris;* white squares: *ECG changes;* black circles: *echocardiographic alterations in non LAD-dependent myocardial segments;* white circles: *echocardiographic alterations in LAD-dependent myocardial segments. LAD = left anterior descending coronary artery.*

Table II. Prevalence of cardiovascular risk factors and collateral circulation in patients with regional wall motion abnormalities (echo) or electrocardiographic (ECG) changes and/or pain as first manifestation of myocardial ischemia.

Variables	Echo (n=8)	ECG (n=13)
Family history of IHD	5/8 (62)	6/13 (46)
Systemic hypertension	3/8 (37)	2/13 (16)
Hypercholesterolemia	3/8 (37)	10/13 (76)
Tabagism	3/8 (37)	3/13 (23)
Collateral circulation	4/8 (50)	4/13 (31)

Number in brackets are percentage. Differences between groups are not statistically significant. IHD = ischemic heart disease.

Discussion

This study was carried out in a well selected group of consecutive patients with chronic stable angina, normal left ventricular function and isolated proximal LAD stenosis. In about two thirds of patients who developed dipyridamole-induced regional wall motion changes the latter occurred in non-LAD-dependent territories. Furthermore, among patients who exhibited both echocardiographic and ECG changes and/or angina, the sequence of events was remarkably different in individual patients; indeed, about half of these patients exhibited mechanical changes first, while the remaining half exhibited ECG changes and/or angina first. These findings indicate that in patients with chronic stable angina the mechanisms of ischemia are multiple and the link between coronary stenoses and myocardial ischemia is strikingly elusive.

An intriguing observation in our study is the high prevalence of regional wall motion abnormalities during dipyridamole infusion in myocardial regions not supplied by the culprit vessel. Indeed, in about two thirds of our patients regional wall motion abnormalities could be detected in myocardial regions perfused by angiographically normal coronary vessels. The present study is the first, to the best of our knowledge, to demonstrate stress-induced regional wall motion abnormalities in myocardial regions perfused by angiographically normal coronary vessels in patients with chronic stable angina. Our findings are in agreement with previous studies which demonstrated regional wall motion abnormalities in non-infarct-related artery-dependent myocardium immediately following thrombolysis in the setting of acute myocardial infarction[6,7]. Of note, Gregorini et al.[6] observed an improvement in wall motion abnormalities in non-infarct-related artery-dependent myocardium following alpha-blockade and suggested that regional myocardial dysfunction was caused by coronary stretch and ischemia which are known to reflexly increase the cardiac sympathetic nerve activity followed by intense alpha-mediated vasoconstriction[8,9].

The causes responsible for regional wall motion abnormalities in myocardial regions perfused by angiographically normal coronary vessels in our patients cannot be deduced from the results of this study. Theoretically, they might be caused by the spasm of large epicardial vessels, which is unlikely because these patients did not have a clinical history suggesting vasospastic angina, but showed transient ST segment depression rather than elevation (an accepted marker of coronary spasm) and, finally dipyridamole is a weak stimulus for coronary spasm[10]. Therefore, it is more likely that in our patients wall motion abnormalities in myocardial regions dependent on angiographically normal epicardial coronary arteries were caused by distal vessel dysfunction. Previous clinical investigations in patients with chronic ischemic syndromes associated with obstructive atherosclerosis, have shown stress-induced transient ECG alterations not entirely explained by epicardial coronary stenoses[11] or perfusion abnormalities in myocardial regions perfused by angiographically normal coronary vessels in the presence of endothelial dysfunction[12] and following successful coronary angioplasty[13] or stenting[14,15]. However, these studies failed to provide evidence

that distal vessel alterations were so severe as to cause transient regional wall motion dysfunction. Furthermore, following coronary angioplasty and stenting it is difficult to rule out the presence of a significant residual stenosis at angiography[14,15].

An important role of distal vessel dysfunction in the genesis of wall motion abnormalities in our patients is also suggested by the temporal sequence of ischemic events. Indeed, the classic ischemic cascade is characterized by a well defined time sequence of events in which alterations in left ventricular regional wall motion are considered to represent the first manifestation of myocardial ischemia followed, at a later stage, by ECG changes and, in a subset of patients, by angina pectoris[1,2]. In the clinical setting, this sequence of events translates into a higher sensitivity of imaging techniques, such as echocardiography and radionuclide angiography, compared to the ECG signs of ischemia[16,17]. Of note, this classic temporal sequence of ischemic events has generally been described in unselected groups of patients under different clinical conditions and with different angiographic patterns by using ischemic stimuli which increase myocardial oxygen demand, such as exercise test[18-21] and atrial pacing[22] or reduced oxygen supply, such as coronary angioplasty[23] or Prinzmetal s angina[24]. In the present study, we evaluated the sequence of ischemic events in a well selected group of patients by using a different but well accepted pharmacological stressor, i.e. the intravenous infusion of dipyridamole, a potent vasodilator of distal coronary vessels[16]. In the presence of a critical epicardial coronary artery stenosis, dipyridamole determines an inappropriate dilation of distal coronary vessels which results in subepicardial overperfusion and subendocardial underperfusion. This maldistribution of coronary blood flow results in subendocardial ischemia (vertical steal). Our findings indicate that myocardial ischemia resulting from transmural redistribution of coronary blood flow determines different temporal sequences of ischemic events in individual patients. Indeed, different from the classic ischemic cascade, in about 20% of our patients ECG changes and pain occurred even in the absence of regional wall motion changes. Furthermore, in about half of the patients who exhibited both regional wall motion changes and ST segment depression and/or angina the latter occurred first. Convincing clinical observations indicate that in some clinical conditions associated with angiographically normal epicardial coronary arteries and distal coronary vessel dysfunction such as syndrome X[25,26], hypertrophic cardiomyopathy[27], systemic hypertension[28,29] and acute rejection of transplanted heart[30], dipyridamole-induced ischemic-like ECG changes typically occur in the absence of wall motion abnormalities. Thus, ECG changes and/or pain occurring in the absence of or earlier than regional wall motion abnormalities might represent a true marker of myocardial ischemia possibly related to distal coronary vessel dysfunction; this working hypothesis, however, remains to be definitively proved[31].

The causes of distal vessel dysfunction, which are probably multiple and different in individual patients, resulting in stress-induced dysfunction of myocardial regions supplied by non-stenotic coronary artery branches, and the role played by the presence of coronary stenoses in branches supplying remote regions cannot be deduced from the results of our study.

A limitation of our study was the utilization of a pharmacological ischemic stimulus different from the ischemic stimuli operating during daily life. Yet, the utilization of this pharmacological stimulus allowed us to accurately monitor regional ventricular function which is more difficult to obtain during exercise testing. Furthermore, the sympathetic activation, which is probably more intense during exercise than during dipyridamole infusion, should, if anything, enhance distal vessel constriction. Another limitation of our study was the enrollment of a well selected population of patients without previous infarction and with isolated LAD stenosis; therefore, the results cannot be extrapolated to patients with different clinical and angiographic features. Finally, diastolic myocardial function was not monitored thus preventing us from assessing a potential early marker of myocardial ischemia.

In conclusion, our study demonstrates that the mechanisms of myocardial ischemia in patients with obstructive atherosclerosis are multiple. Furthermore, we found evidence of myocardial ischemia during dipyridamole infusion in myocardial regions perfused by angiographically normal coronary vessels in about two thirds of a consecutive series of patients, thus indicating that myocardial ischemia in regions not supplied by stenotic coronary branches is a strikingly frequent phenomenon. Our results suggest that the treatment of myocardial ischemia in chronic stable angina should be guided by the prevailing mechanisms of ischemia which may be different in individual patients. The results of recent studies showing that statins can improve myocardial ischemia in patients with chronic stable angina independently of their effect on epicardial coronary stenoses, demonstrate that already existing drugs can be effective in treating epicardial stenosis-independent myocardial ischemia[32]. Finally, an interesting clinical implication of this study is that, in agreement with previous findings[33-35], echo-dipyridamole stress test seems to have a rather low sensitivity in revealing myocardial ischemia in patients with isolated LAD stenosis. Indeed, patients included in our study were selected on the basis of significant ECG changes and symptoms during an exercise test, yet one third of them did not develop regional wall motion abnormalities during dipyridamole infusion.

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