Long-term survival of patients with chest pain syndrome
and angiographically normal or near-normal coronary
arteries: the additional prognostic value of dipyridamole
echocardiography test (DET)

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Aims Patients with normal coronary arteries have a heterogeneous prognosis. Aim of this study was to
assess whether dipyridamole stress echocardiography positivity identifies a prognostically less benign
subset.

Methods and results We selected 457 patients (245 males; 56 ± 10 years) who underwent stress high-
dose dipyridamole echocardiography and had angiographically non-significant (~50% visually assessed)
stenosis in any major vessel and preserved left ventricular function. All patients were followed up for a
median of 7.1 years (first quartile 5 and third quartile 10.5). Dipyridamole echocardiography test (DET)
positivity for regional dysfunction occurred in 43(9%) patients. Kaplan–Meier survival estimates showed
a significant better outcome for those patients with negative dipyridamole echocardiography test com-
pared with those with a positive test (90 vs. 75.7%, at 140 months of follow-up, \(P = 0.0018\)). At multi-
variable analysis, mild or moderate irregularity on coronary arteriogram (HR = 3.3, CI 95% = 1.7–6.2)
diabetes (HR = 3.5, CI 95% = 1.4–9.2), and wall motion score index at peak stress (HR = 6.7, CI
95% = 2.5–17.8) were independent predictors of all-cause death.

Conclusion DET adds incremental value to the prognostic stratification achieved with clinical and angi-
ographic data in the subset of patients with normal or near-normal coronary arteries.

KEYWORDS Dipyridamole echocardiography test (DET); Prognosis; Normal coronary artery

Introduction

The occurrence of an angina-like chest pain in patients
without evidence of obstructive epicardial coronary artery
disease is a relatively frequent observation in clinical
practice. In patients undergoing coronary angiography for
the investigation of chest pain, the incidence of normal
or near-normal coronary arteriographic findings varies
between 10 and 20%, on the characteristics of the patient group studied.1 In general, patients without sig-
ificant epicardial coronary artery disease have an excellent
prognosis2,3 but the long-term outcome for the subset of
patients with an ‘ischaemic’ imaging stress test response is
not known. Pharmacological stress echocardiography with
either dipyridamole or dobutamine has consistently shown
an excellent specificity,4 but it remains to be clarified
whether diagnostic ‘lies’ (i.e. false-positive responses
occurring in <10% of patients) may reflect prognostic ‘truths’ (i.e. they identify trouble-makers in the long run).
In order to clarify the prognostic meaning, if any, of the
heterogeneous stress echo response in patients with angiographically normal coronary arteries, we evaluated the
long-term follow-up of 457 patients enrolled in the echo labor-
atory of the Institute of Clinical Physiology in Pisa over the
last 20 years. By selection, all had a dipyridamole stress
echo and subsequent (within 15 days) coronary angiography
showing coronary arteries with normal or non-significant
coronary artery disease. All entered a clinical follow-up
program.

Methods

Study population

From the Institute of Clinical Physiology Data Bank between 1983
and 2002, 568 patients were selected according to the following
criteria: history of chest pain, pharmacological stress echocardi-
ography with either high-dose dipyridamole (0.84 mg/kg over
10 min) or high-dose dobutamine (up to 40 μg/kg/3 min (DET)
performed before (within 15 days) coronary angiography; coronary
angiography showing either absent or non-significant (~50%
visually assessed) stenosis in any major vessel or secondary
branch. Of this initial population, 27 patients were excluded
because they underwent a previous revascularization, 24 performed

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only a low-dose stress echocardiography, 16 had a reduced left ventricular function (five of these patients had a severe valvular disease), eight had a previous myocardial infarction, and six were lost to follow-up. Of this initial population, those patients who underwent dobutamine stress echocardiography were excluded from the final analysis.

Therefore, the study group consisted of 457 consecutive patients (245 men, mean age 56 ± 10 years) The pre-test likelihood of coronary artery disease was estimated from age, sex, and symptoms. The estimated likelihood of coronary artery disease was <50% in 104 patients (23%), 50 to 80% in 203 patients (44.4%), and >80% in 150 patients (33%). According to individual's needs and physician's choices, 359 patients were evaluated after antianginal drugs had been discontinued and 98 patients were evaluated during antianginal treatment (nitrates and/or calcium antagonists and/or beta-blockers).

Coronary angiography and DET were separately and independently performed and analysed by cardiologists, unaware of the results of the other tests. Data are entered in the data bank at the time of testing on the same day of test performance. Follow-up information on outcome is updated by a dedicated team of technicians supervised by physicians. The study was approved by the institution review board. All patients gave their written informed consent when they underwent stress echocardiography and coronary angiography. When patients signed the written informed consent, they also authorized physicians to use their clinical data according to the Italian law.

Stress protocol
Two-dimensional echocardiography and 12-lead electrocardiographic (ECG) monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 10 min) with coadministration of atropine up to 1 mg, in accordance to well-established protocol. During the procedure, blood pressure and ECG were recorded each minute.

Echocardiographic analysis
Two-dimensional echocardiographic monitoring was performed throughout and up to 10 min after the end of the drug infusion. Two-dimensional images were recorded at baseline and at the end of each step. Regional wall motion analysis was evaluated at baseline and at peak stress with a semiquantitative assessment of a wall motion score index (WMSI), with the 16-segment model of the left ventricle, each segment ranging from 1 = normal/hyperkinetic to 4 = dyskinetic, according to the recommendations of the American Society of Echocardiography. WMSI was derived by dividing the sum of individual segment scores by the number of interpretable segments. Test positivity was defined as the occurrence of at least one of the following conditions: (i) new dyskinesia in a region with normal rest function (i.e. normokinesia becoming hypokinesia, akinesia, or dyskinesia) in at least two adjacent segments; (ii) worsening of rest dyskinesia (i.e. hypokinesia becoming akinesia or dyskinesia). Resting akinesia becoming dyskinesia was not considered a criterion of positivity, because this can result from passive stretching phenomena rather than from active ischaemia. Non-echocardiographic test endpoints were the following: peak atropine dose; 85% of target heart rate; and achievement of conventional end-points (such as severe chest pain and/or diagnostic ST-segment changes). The test was also stopped, in the absence of diagnostic endpoints, for one of the following reasons of constituting a submaximal, non-diagnostic test: intolerable symptoms and limiting asymptomatic side effects consisting of: (i) hypertension (systolic blood pressure >220 mmHg; diastolic blood pressure >120 mmHg; (ii) hypotension (relative or absolute): >30 mmHg fall of blood pressure; (iii) supraventricular arrhythmias: supraventricular tachycardia or atrial fibrillation; (iv) ventricular arrhythmias: ventricular tachycardia; frequent, polymorphous premature ventricular beats. Intraobserver and interobserver agreement in regional wall motion analysis has already been shown to be high (>90%) in our laboratory.

Coronary angiography
Coronary angiography in multiple views was performed according to the standard Judkins or Sones technique. At least five views (including two orthogonal views) were acquired for the left and at least two orthogonal views for the right coronary arteries, respectively. Additional appropriate projections were obtained in case of superimposition of side branches or foreshortening of the segment of interest. All angiograms were visually evaluated by two independent observers who identified the stenotic segments and scored control arteries as smooth or irregular. All stenotic segments were evaluated by an automated edge detection system (Mipron, Kontron, Germany) providing the per cent stenosis diameter. The previously assessed intraobserver and interobserver variabilities of the method were 7 and 6%, respectively.

Follow-up data
Follow-up data were obtained from at least one of four sources: review of the patient's hospital record, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient conducted by trained personnel, and a staff physician visiting the patients at regular intervals in the out-patient clinic. By inclusion criteria, follow-up data were obtained from all patients. Events were defined as death for all causes, cardiac death, and non-fatal myocardial infarction. In patients who died in-hospital or at home, the cause of death was elucidated from the medical record, the family and the local physician who signed the death certificate. The definition of cardiac death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In case of deaths, out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. Myocardial infarction was defined as a cardiac event requiring admission to hospital with the development of new ECG changes and cardiac enzyme level increase. Therefore, the outcome events were all-cause death (defined as cardiac and non-cardiac death) for survival and hard events (death and non-fatal myocardial infarction) for infarction-free survival. Only the most severe outcome was considered an endpoint when follow-up was censored at the time of revascularization procedures.

There is controversy over whether or not coronary artery bypass surgery and coronary angioplasty should be considered cardiac events. They are likely to reflect the presence of severe disease. However, the decision to perform these procedures may be subjective and not by itself an adverse outcome. Therefore, the data were analysed excluding revascularization procedures.

Statistical analysis
Values are expressed as mean ± standard deviation. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox’ regression model. The individual effect of certain variable on event-free survival was evaluated with the use of the Cox’ regression model (SPSS statistical software, SPSS Inc., Chicago, IL, USA and S-plus 6.1). To adjust for several risk factors, multivariable Cox’ analysis was performed with all the variables found to be significant at the univariate analysis entering in a single step. The proportional hazards assumptions of Cox’ model were verified with the linear correlation test. A significance of 0.05 was required for a variable to be included into the multivariable model, whereas 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated.
The following covariates were analysed: age, sex, smoking habit, typical chest pain, hypertension, diabetes, hypercholesterolaemia, resting WMSI, left ventricular mass index, positive echocardiographic result, WMSI at peak stress, change in WMSI (the difference in WMSI from rest to peak stress), ECG modifications during pharmacological stress, presence of angina during pharmacological stress, presence of medical therapy at time of testing, mild or moderate vessel irregularity on coronary angiogram, ectasic coronary artery disease, calcific coronary artery disease, and the combination of these parameters. Continuous variables were compared by the unpaired two-sample t-test. Proportions were compared by the χ² statistic; a Fisher’s exact test was used when appropriate. Kaplan–Meier life table estimates of spontaneously occurring rates between groups were tested by the log-rank test. All tests were two-sided and a P-value of less than 0.05 was considered statistically significant.

Results

The main clinical and echocardiographic data are reported in Table 1.

Stress echocardiographic findings

Resting WMSI was 1.0 ± 0.2. Forty-three (9%) patients had a positive DET. The average WMSI at peak DET was 1.11 ± 0.2 and 356 patients had a normal WMSI.

Coronary angiography

All patients had “non-significant” coronary artery disease by selection. However, 359 patients had completely normal, smooth coronary arteries; 45 had ‘mild’ (0–20%, mean10 ± 8% diameter stenosis) irregularities of at least one vessel; 50 had ‘moderate’ (20–40%, mean 31 ± 8% diameter stenosis) irregularities; nine had evidence of coronary artery calcification without irregularity; six had poor run-off and/or delayed contrast washout; four had ectasic coronary artery disease; and 17 had angiographically assessed coronary artery spasm. The average per cent diameter stenosis was 21 ± 13%. Stress echo positivity occurred in 31/359 (8%) patients with totally normal and in 13/98 (13%) patients with near-normal coronary arteries (showing at least one of the previously described abnormalities). Patients with coronary irregularities were older (59±9 vs. 56 ± 10, P = 0.005) than patients with completely normal coronary arteries, had a higher incidence of family history for coronary artery disease (59 vs. 41%, P = 0.003) and smoking habit was significantly higher (53 vs. 35.4%, P = 0.002).

Follow-up data

During a median follow-up of 7.1 years (first quartile 5 and third quartile 10.5), a total of 43 (10.6%) events (38 deaths of which 14 were attributed to cardiac causes and six myocardial infarctions) occurred.

Considering total mortality, there were eight events in patients with a positive vs. 30 events in patients with a negative test (18 vs. 7.2%, P = 0.018). The distribution of events is reported in Table 2. Sensitivity of stress echocardiography for all-cause death was 30% in patients with normal coronary arteries and 11% in patients with irregularities (P = 0.23). The death rate was 7.3% in patients with WMSI = 1 and 11.8% in patients with WMSI > 1, P = 0.15; the hard events rate was 8.4% in patients with WMSI = 1 and 13.8% in patients with WMSI > 1, P = 0.12.

Univariate predictors of total mortality are reported in Table 3. Using Cox’ proportional hazards model, mild or moderate irregularity on coronary arteriogram (HR = 3.3 CI 95% = 1.7–6.2, diabetes (HR = 3.5, CI 95% = 1.4–9.2), and WMSI at peak stress (HR = 6.7 CI 95% = 2.5–17.8) were independent predictors of all-cause death. Kaplan–Meier survival estimates for total mortality showed a better outcome for those patients with negative DET compared with those with a positive test (90 vs. 76%, P = 0.0019, at 140 months of follow-up) (Figure 1). The same pattern of survival was observed when cardiac death alone or hard cardiac events were considered (Figures 2 and 3). In Table 4, the independent variables predicting all-cause death in patients with a normal WMSI are reported.

Discussion

This study indicates that a DET positivity in patients with chest pain and angiographically normal or near-normal coronary arteries is associated with a worse long-term survival. The ‘anatomic lies’ of stress echocardiography—i.e. false-positive responses occurring in patients with non-significant epicardial coronary artery disease—can be overturned into ‘prognostic truth’ when long-term outcome is considered.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Rest and stress findings in the study population</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>457</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>245/212</td>
</tr>
<tr>
<td>Family history</td>
<td>209 (46%)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>179 (39%)</td>
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<tr>
<td>Hypertension</td>
<td>172 (38%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>151 (31%)</td>
</tr>
<tr>
<td>History of angina</td>
<td>231 (50%)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>20 (4.3%)</td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>109 ± 29</td>
</tr>
<tr>
<td>Positive DET</td>
<td>43 (9.4%)</td>
</tr>
<tr>
<td>WMSI at rest</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Patients WMSI = 1</td>
<td>356</td>
</tr>
<tr>
<td>WMSI at peak stress</td>
<td>1.11 ± 0.2</td>
</tr>
<tr>
<td>ECG changes during DET</td>
<td>116 (25%)</td>
</tr>
<tr>
<td>Chest pain during DET</td>
<td>137 (30%)</td>
</tr>
<tr>
<td>Test performed on antianginal therapy</td>
<td>98 (21%)</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Event rate occurrence in relation to DET</th>
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<tr>
<td></td>
<td>Negative DET (n = 414)</td>
</tr>
<tr>
<td>Death</td>
<td>30</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>11</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>6</td>
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</table>
Qualitative, subjective reading of echo images still remains the ‘state-of-the-art’ method for wall motion analyses in stress echocardiography. Therefore, human error in interpretation because of over-reading is certainly a source of ‘false-positive’ responses. However, in our laboratory, we have adopted—since the beginning of our clinical stress echo activity—a conservative reading policy, deliberately ignoring minor or questionable forms of hypokinesis, especially when isolated in segments such as infero-basal septum or basal inferior wall, which are known sources of error in stress echo reading due to their large variability in contractile behaviour in resting conditions and during stress. In most cases, the false-positive response probably reflected true myocardial ischaemia—if we agree with John Ross that ischaemia is reduction in myocardial blood flow sufficient to cause a decrease in myocardial contraction.

First, it is known that even a ‘non-critical’ coronary stenosis may critically reduce coronary flow reserve. Results of functional testing are more tightly linked to coronary flow reserve than to anatomic appearance. In fact, stress echo positivity was more frequent in patients with ‘near-normal’ coronary arteries than in patients with totally normal, smooth coronary arteries. True ischaemia can, however, occur also in patients with normal coronary arteries, due to alterations of coronary flow reserve linked to left ventricular hypertrophy and/or cardiomyopathy.

In fact, of the 43 patients with a false-positive response, 25 had regional wall motion abnormalities and/or left ventricular hypertrophy on baseline echocardiogram. In both of these conditions, stress may induce subendocardial underperfusion and wall motion abnormalities, as shown by clinical and experimental evidences.

The heterogeneous entity of angiographically ‘normal’ coronary arteries

The angiographic label of ‘normal coronary arteries’ readily identifies a prognostically benign subset. However, there can be substantial morphological heterogeneity within this cohort, encompassing truly normal, smooth coronary arteries and non-significant stenoses—which may be mild or moderate, isolated or multiple, in one or more vessels. In addition, a coronary angiography can show an ectatic anatomic pattern—which is a sign of atherosclerosis. Another important angiographic sign can be coronary calcification.
which is known to be associated with more extensive coronary atherosclerosis and worse prognosis.29 A normal coronary artery can also show an altered delayed washout with poor run-off: this is considered a sign of increased downstream resistance, possibly indicating a functional and/or organic disease of the coronary microcirculation. Finally, a normal or near-normal epicardial coronary artery can show a focal spontaneous spasm or a diffuse constriction with abnormal vasodilatation after nitrates: these angiographic signs are indices of abnormal coronary vasoconstriction, which can be an important pathogenetic mechanism of life-threatening ischaemia in variant angina.21 In fact, one or more of these minor abnormalities were found in 101 of our patients, and tended to be associated with more hard events and more stress echo positivity, a response known to be more tightly linked to physiological rather than anatomic correlates of coronary artery disease. In the study by Zimmerman,22 no significant difference was found in survival rates among patients with normal arteries, and minimal or moderate disease, but the re-infarction rate was higher in those with minimal and moderate disease (11 and 16%, respectively, P = 0.0002) than in patients with angiographically normal arteries.

Comparison with previous studies

Several previous studies reported the generally benign prognosis of patients identified angiographically as having non-significant coronary artery disease.1,2,3,23-42 However, most of these studies have a relatively small sample size, with only four of them besides our own recruiting more than 400 patients.2,3,23,33 In addition, only nine studies (including the present one) had a mean follow-up duration >5 years.2,3,23,33,36-39 The selection criteria of these studies were heterogeneous, some recruiting patients having non-significant coronary artery disease (stenosis <50%),2,3,23,30,32,40,43 and others only considering patients with totally normal coronary arteries—without even minimal isolated lesions or wall irregularities.26,27,29,31,35,36,38,39,41,42 These variable angiographic selection criteria may substantially affect prognostic results, because coronary events are rare in patients with normal arteriograms, six-fold more frequent in patients with mild and 15-fold more frequent in patients with moderate (and still non-significant) lesions.2 Another important variable in previous studies is the resting left ventricular function, because a normal baseline function was considered as an inclusion criteria in some studies,3,29,31,35,36,39,40 but not in others.2,27,30 Finally, in most studies, the results of stress testing were not available. Few of them reported survival results in relation with exercise ECG testing1,3,18 and only one study reported results on pharmacological stress echocardiography consistent with the present results.44 Recently, it has been reported that women with chest pain, normal coronary arteries but positive nuclear magnetic resonance spectroscopy consistent with myocardial ischaemia had a higher incidence of anginal hospitalization, repeat catheterization, and greater treatment costs.39 In a recent meta-analysis,45 it has been demonstrated that many of the patients with normal or near-normal coronary artery disease frequently have persistence of symptoms, are rehospitalized, have stress-induced myocardial ischaemia and have relatively high rates of progression to obstructive coronary artery disease and adverse cardiac events.

Study limitations

Our study design was observational, not randomized, and the analysis was retrospective, although the data were acquired in a prospective fashion and entered the data bank at the time of initial assessment. The selection criteria included all patients referred for stress echo with subsequent documentation of ‘normal’ coronary arteries in the same hospital admission. This led to inclusion of patients with different clinical conditions and heterogeneous angiographic patterns.46 Patients with syndrome X, variant angina, hypertension, or occult cardiomyopathy were pooled together in this analysis which, however, reflects the wide variety of patients referred to the stress echo laboratory for suspected coronary artery disease. Physicians responsible for updating the follow-up information were unaware of stress echo and coronary angiography data.

Clinical implications

In patients with angiographically assessed normal coronary arteries and chest pain, DET can identify a subgroup of patients with a less benign prognosis. It is conceivable that these higher risk patients should be treated more aggressively in terms of lifestyle changes and risk factor modifications.47

Acknowledgement

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