The value of ECG and echocardiography during stress testing for identifying systemic endothelial dysfunction and epicardial artery stenosis

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Background In the stress imaging era, ECG positivity is regarded as a frequent source of false-positive responses. However, it is known that normal coronary arteries frequently coexist with abnormal endothelial function in patients with chest pain.

Aim To evaluate the anatomical coronary epicardial, and functional systemic endothelial determinants of wall motion and electrocardiographic responses during stress testing.

Method Sixty-eight in-hospital patients with chest pain syndrome, no previous myocardial infarction, and off- nitrate therapy at the time of testing underwent, on different days, in random order and within 1 month: (1) stress ECG echo testing (with dipyridamole in 43, dobutamine in 3, and exercise in 22 patients); (2) coronary angiography; (3) endothelium-dependent, flow-mediated dilation of the brachial artery during reactive hyperaemia using high-resolution ultrasound. Criteria of positivity were: ST segment depression >0.1 mm in the stress ECG; regional dysfunction >2 segments demonstrated by stress–echo; diameter reduction >50% on coronary angiography; and <5% flow-mediated dilation as revealed by endothelial function.

Results Significant coronary artery disease was present in 39 patients, and was predicted on multivariate analysis by stress-induced wall motion abnormalities (OR=108.8; 95% CI=8·5–1389·4, P=0·0003), but not by either ST segment depression (P=0·13; OR=0·47; 95% CI=0·7–1·3) or reduced flow-mediated dilation (P=0·81; OR=0·87; 95% CI=0·27–2·8). Abnormal flow-mediated dilation was present in 53 patients (78%), and was predicted by stress-induced ST segment depression (P=0·023; OR=6·2; 95% CI=1·3–30·5), but not by either stress echo positivity (P=0·66; OR=0·77; 95% CI=0·23 to 2·5) or angiographically assessed coronary artery disease. There was no correlation between flow-mediated dilation and extent of coronary artery disease as assessed by the angiographic Duke score (from 0=normal to 100=most severe disease): r=-0·13, P=0·91.

Conclusion Epicardial coronary artery anatomy affects wall motion abnormalities, and systemic endothelial dysfunction affects ST segment depression during stress. However, echocardiographic positivity is unrelated to endothelial dysfunction, and electrocardiographic positivity is an inaccurate predictor of coronary stenosis. An integration of ECG and functional markers is warranted in the stress testing lab.

Key Words: Stress echocardiography, electrocardiography, endothelium, ultrasound.

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Introduction

In the stress imaging era, electrocardiographic (ECG) information is usually disregarded as an obsolete diag-
function\textsuperscript{[5,6]} and can be evaluated non-invasively with brachial ultrasound\textsuperscript{[7,8]}. The microcirculatory endothelial component can profoundly affect the functional impact of a given anatomical coronary stenosis\textsuperscript{[9,10]} and may determine ischaemic-like changes on the electrocardiogram\textsuperscript{[11]} as well as perfusion defects\textsuperscript{[12]}, by preventing appropriate blood flow responses during stress. The present study’s hypothesis is that both coronary artery disease assessed angiographically and systemic endothelial function assessed ultrasonically may co-modulate the wall motion and ECG results of stress testing for myocardial ischaemia. In order to assess the relationship between systemic endothelial dysfunction, results of stress testing, and angiographically assessed coronary artery disease, we evaluated 68 in-hospital patients with chest pain syndrome by brachial artery ultrasound, stress echo testing and coronary angiography.

**Methods**

Sixty-eight hospitalized patients (age=59 $\pm$ 9 years, 17 females) were prospectively enrolled in the study. They met the following inclusion criteria: (1) chest pain syndrome; (2) reference to the echo lab for stress echocardiography; (3) coronary angiogram performed within 1 month of enrolment during patients’ hospitalization for chest pain syndrome; (4) off nitrate therapy at the time of endothelial function evaluation.

In particular, the indication for stress echocardiography met one of the following indications: (a) patients with positive exercise-ECG in concomitance with conditions lowering the positive predictive value of the ECG marker of ischaemia (for instance, female gender or arterial hypertension); (b) patients with chest pain in the absence of significant electrocardiographic changes during routine exercise-ECG; (c) patients unable to achieve the target heart rate response during routine exercise-ECG; (d) patients unable to exercise.

Patients with conditions (a) and (b) were referred to exercise stress echo or (in patients with resting echo images of only sufficient quality) to dipyridamole (which is less technically demanding than exercise). Patients with conditions (c) and (d) were referred for pharmacological echo (usually dipyridamole: dobutamine when dipyridamole was contraindicated). All patients admitted to the hospital underwent coronary angiography independent of stress echo results, since our is a tertiary care referral centre and coronary angiography was the reason for referral.

The following were exclusion criteria: (1) uninterpretable resting ECG (left bundle branch block, pre-excitation, $>$1 mm ST segment depression or elevation, or typical digitalis repolarization pattern); (2) technically poor acoustic window (good visualization of less than 13 of the 16 left ventricular segments); (3) cardiomyopathy or severe valvular disease; (4) myocardial infarction or revascularization procedure (whether percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) occurrence before completion of the three tests of the protocol; (5) incapacity or refusal to give written informed consent. All three tests (brachial artery ultrasound, stress echo, and coronary angiography) were performed on different days, in random order, by independent observers unaware of the results of the other tests. The study was approved by the institutional review board. All patients gave their written informed consent before entering the study.

**Brachial artery study**

All patients were studied at least 4 h after their last meal, according to a standard protocol previously described in detail\textsuperscript{[13]}. Briefly, the patients were instructed to lie in a supine position, quietly for 10 min before the study. All studies were performed in a temperature-controlled room (20–25 °C). The diameter of the brachial artery was measured from 2D ultrasound images. In each study, scans were taken at rest, during reactive hyperaemia, at rest again, and after sublingual nitrates. The brachial artery was scanned in longitudinal section, on the dominant arm, 2–15 cm above the elbow. The focus zone was set to optimize images of the lumen/arterial wall interface, and machine-operating parameters were not changed during the rest of the study.

The arterial diameter was measured at a fixed distance from an anatomical marker, such as a bifurcation. Measurements were taken from the anterior to the posterior ‘m’ line at end-diastole, incident with the R-wave on the ECG. Three cardiac cycles were analysed for each scan and measurements were averaged. Following the baseline measurements, a pneumatic tourniquet was inflated below the elbow to a pressure of 250 mmHg; forearm cuff occlusion was maintained for 4.5 min. Sustained maximal vessel dilatation and maximal flow change occur after 4.5 min of cuff occlusion and a higher cuff occlusion time does not provide a greater response. A shorter duration of cuff occlusion provides a less intense stimulus and fails to achieve sustained vasodilatation 1 min after cuff release. Therefore artery diameter was measured at 1 min following cuff deflation.

After 10 min of vessel recovery, resting scan and flow measurements were repeated. Sublingual nitrate (0·3 mg glyceryl trinitrate, Trinitrina (Pharmacia)) was then administered to evaluate endothelium-independent vasodilation. The last set of scans was performed 3 min after nitrate intake. Endothelial-dependent peripheral flow-mediated dilation is expressed as a percent change in brachial artery diameter 1 min after forearm occlusion release, using the baseline resting diameter as a reference; a response $<$5% represents endothelial dysfunction. Endothelium-independent peripheral vasodilation is expressed as a percent change in brachial artery diameter 3 min after sublingual nitrate administration, using the baseline resting diameter as a reference. Intra- and inter-observer variabilities in our laboratory have been evaluated at 2·5 and 2·0%, respectively\textsuperscript{[13]}. 

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Stress echocardiography

Stress echo was performed with dipyridamole (up to 0.84 mg . kg$^{-1}$ over 10 min with atropine up to 1 mg when needed), dobutamine (up to 40 μg . kg$^{-1}$. min$^{-1}$, with atropine up to 1 mg when needed) or upright bicycle exercise — according to standard protocols[14]. Commercially available imaging systems with digital acquisition were used. All standard echocardiographic views were obtained when possible. The left ventricle was divided into 16 segments, as suggested by the American Society of Echocardiography[6]. Segmental wall motion was graded as follows: normal=1; hypokinetic=2; akinetic=3; and dyskinetic=4. Inadequately visualized segments were not scored. Stress echo was considered positive when one left ventricular segment was increased by one grade or more at peak stress. The wall motion score index was derived at by dividing the sum of individual visualized segment scores by the number of visualized segments. Appearance of ST segment depression >1 mm 0:08 s after the J point, as determined by the physician, was taken as evidence of a positive stress ECG. Intra- and inter-observer agreement has already been shown to be high (>90%) in our laboratory[15].

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 view for the right coronary arteries. All angiographic studies were performed by experienced observers who ignored the results of non-invasive stress testing. The percent diameter stenosis was determined by quantitative coronary angiography using an automated edge-detection system (Mipron; Kontron, Germany). In our laboratory, intra- and inter-observer variabilities of this method are 7 and 6%, respectively[16]. A vessel was considered to have significant obstruction if its diameter was narrowed by 50% or more, with respect to the pre-stenotic tract. A Duke score was calculated in each patient according to the method described elsewhere[17]. Briefly, this prognostically validated index describes the extent and severity of CAD using a scale from 0 to 100 (from non-significant coronary artery disease to severe left main disease). It takes into account the number of major diseased vessels and location and severity of stenosis.

Statistical analysis

Values are expressed as mean ± standard deviation. Comparisons between groups were performed with Student’s t-test (two-tailed) for continuous variables and chi-square test for categorical variables. Angiographically assessed coronary artery disease and endothelial dysfunction were chosen as dependent variables. For univariate predictors associated with $P<0.01$, a forward stepwise logistic regression model was performed to determine independence. The criteria for entry into and removal from the model were 0·05 and 0·10 respectively. A two sided, 95% confidence interval was constructed around each point estimate of risk ratio. Correlation analysis was performed using Pearson’s correlation coefficient. A $P$ value <0·05 was considered statistically significant.

Results

Twenty-two (34%) of the subjects had hypertension, six (9%) diabetes, 40 (59%) hypercholesterolaemia and 27 (40%) were active smokers. Fifty-one (75%) were under antiischaemic therapy (beta-blockers and/or calcium antagonists) at the time of stress-echo testing.

Brachial artery study

Mean flow-mediated dilation was 3·55 ± 2·08%. Fifty-three patients had an abnormal (<5%), and 15 a preserved (≥5%) endothelial response. Mean endothelium-independent peripheral vasodilation (following sublingual nitrates) was 10± 5±56%. Typical examples of an abnormal endothelial function response is shown in the lower right panel of Fig. 1 (in a patient with significant coronary artery disease) and in the lower right panel of Fig. 2 (in a patient with normal coronary arteries).

Stress test response

Eighteen patients had angina (26·5%), and 50 remained asymptomatic (73·5%) during stress echo testing (dobutamine in three, exercise in 22, dipyridamole in 43). Twenty-eight patients had diagnostic ECG changes (41·2%), and 22 no diagnostic ECG changes (58·8%). Twenty-four patients had a positive (35·3%), and 44 a negative stress echo study (64·7%). The mean resting wall motion score index was 1·07 ± 0·16 and rose to 1·14 ± 0·23 at peak stress. The mean change in wall motion score index in patients with positive stress echo testing was 0·14 ± 0·17. A typical example of an abnormal stress echo study is shown in the left upper panel of Fig. 1, in a patient with significant coronary artery disease. A typical example of a normal stress echo study is shown in left upper panel of Fig. 2, in a patient with normal coronary arteries.

Coronary angiography

Twenty-nine patients had normal (41·4%) and 39 abnormal coronary arteries (55·7%): 14 patients had one-, 15 two- and 10 three-vessel disease. The average Duke
score in patients with significant coronary artery disease was 41.3 ± 17.8 (range=23 to 82).

Correlation between coronary angiography and stress test response

Stress ECG positivity showed a sensitivity and specificity of 33% and 48%, respectively, for coronary artery disease detection. Stress ECG diagnostic values were similar for pharmacological (n=46) and exercise (n=22) stress regarding sensitivity (pharmacological=37 vs exercise=27%, P=ns) and specificity (pharmacological=41 vs exercise=71%, P=ns). Stress echo positivity showed a sensitivity and a specificity of 59% and 97% for coronary artery disease detection, respectively. Stress echo diagnostic values were also similar for pharmacological (n=46) and exercise (n=22) stress regarding sensitivity (pharmacological=58 vs exercise=60%, P=ns) and specificity (pharmacological=95 vs exercise=100%, P=ns).

By univariate analysis, significant coronary artery disease was best predicted by echocardiographic positivity (Table 1). Of note, neither ECG positivity nor angina during stress could predict the presence of significant coronary artery disease. By multivariate analysis, echo positivity, cigarette smoking and high cholesterol were predictive of significant coronary artery disease (Table 1).

No significant correlation was observed between systemic flow-mediated dilation and coronary angiographic Duke score (r = −0.13; P=0.91). Patients with stress echo positivity had significantly higher Duke score values when compared to patients with stress echo negativity (45.6 ± 19.3 vs 11.8 ± 18.1, P<0.001). Duke score was also correlated with peak stress wall motion score index (r=0.51; P<0.001) (Fig. 4) and an increase in wall motion score index during stress echo testing (r=0.52; P<0.001). Inversely, no significant correlation was found between Duke score and maximal ST depression in mm during stress echo testing (r=0.16; P=0.33). Patients with echo positivity were further divided into two subgroups, with (n=13) and without (n=11) concomitant ECG positivity: the two groups had similar angiographic Duke scores (51 ± 22 vs 39 ± 13, P=0.58) while patients with concomitant ECG positivity showed a trend to lower % flow-mediated dilation values (2.5 ± 2.6 vs 4.7 ± 3.3, P=0.08).
Figure 2 Example of a typical pattern of test results in a patient with an anginal syndrome and normal coronary angiogram (right upper panel). Dipyridamole stress echo testing (with representative end-systolic frames) reveals hyperkinetic wall motion response at peak stress (left upper panel), but significant ST segment depression at peak stress (left lower panel); brachial artery flow-mediated dilation confirmed systemic endothelial dysfunction (right lower panel).

Table 1 Prediction of epicardial coronary artery stenosis by univariate and multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>$P$ value</th>
<th>Chi-square</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>0.96</td>
<td>0.002</td>
<td>1.02 (0.4–2.8)</td>
</tr>
<tr>
<td>FMD &lt;5%</td>
<td>0.81</td>
<td>0.06</td>
<td>0.9 (0.27–2.8)</td>
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<tr>
<td>Nitrate-mediated brachial artery dilation &lt;10%</td>
<td>0.75</td>
<td>0.10</td>
<td>1.2 (0.4–3.1)</td>
</tr>
<tr>
<td>Angina during stress echo</td>
<td>0.66</td>
<td>0.19</td>
<td>1.3 (0.42–3.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.46</td>
<td>0.52</td>
<td>1.5 (0.52–4.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.20</td>
<td>1.58</td>
<td>4.1 (0.45–37.3)</td>
</tr>
<tr>
<td>ECG positivity during stress echo</td>
<td>0.13</td>
<td>2.30</td>
<td>0.47 (0.17–1.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia*</td>
<td>&lt;0.05</td>
<td>6.10</td>
<td>3.6 (1.3–9.9)</td>
</tr>
<tr>
<td>Smoking*</td>
<td>&lt;0.01</td>
<td>7.20</td>
<td>4.5 (1.5–13.4)</td>
</tr>
<tr>
<td>Male gender*</td>
<td>&lt;0.01</td>
<td>9.20</td>
<td>7.1 (2.0–25.2)</td>
</tr>
<tr>
<td>Stress echo positivity*</td>
<td>&lt;0.001</td>
<td>11.90</td>
<td>40.2 (4.9–326.8)</td>
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<tr>
<td>Predictors in multivariate analysis</td>
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</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.013</td>
<td>6.2</td>
<td>8.7 (1.6–48.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.0046</td>
<td>8.0</td>
<td>11.7 (2.1–64.6)</td>
</tr>
<tr>
<td>Stress echo positivity</td>
<td>0.0003</td>
<td>13.0</td>
<td>108.8 (8.5–1389.4)</td>
</tr>
</tbody>
</table>

FMD=brachial artery flow-mediated vasodilation.

*Significant univariate predictor of coronary artery stenosis.
Angiographic and stress test correlates of systemic endothelial function

By univariate analysis, systemic endothelial dysfunction was predicted by stress-induced ST segment ischaemic changes during stress (Table 2), but not by stress-induced wall motion abnormalities or any other clinical or angiographic parameter. Systemic flow-mediated dilation was not correlated with peak stress wall motion score index ($r=0.05; P=0.67$): Fig. 5. In the 29 patients with non-significant coronary artery disease, there was no difference in flow-mediated dilation values between the 15 patients with and the 14 without stress-induced ST segment depression (3.03% vs 4.23%, $P=\text{ns}$).

**Discussion**

In patients with chest pain syndrome, angiographically assessed coronary artery disease is poorly correlated to systemic endothelial dysfunction. During stress, wall motion abnormalities are linked to underlying coronary anatomical macrovascular disease, whereas electrocardiographic changes are more often associated to impaired systemic endothelial function.

**Comparison with previous studies**

The data of the present study are consistent with an extensive literature showing that stress echocardiography positivity provides a highly specific marker of the presence and extent of angiographically assessed coronary artery disease\[18\]. We used one of three main types of stressors — dipyridamole, dobutamine or exercise — which give similar diagnostic and prognostic results and are all accepted options in stress echocardiography\[14,19\]. The present data also confirm the limited diagnostic accuracy of stress-induced ST segment depression for the identification of angiographically assessed coronary artery disease. This is especially true in patients with a class I indication to imaging stress testing referred to the stress echo lab, i.e. patients with a non-diagnostic ECG or with a positive stress ECG with conditions lowering the positive predictive value of the electrocardiographic signal, such as hypertension or female gender\[1\]. The present study confirms that endothelial dysfunction is a poor non-invasive marker of the presence and severity of angiographically assessed coronary artery disease\[20\], and that ‘ischaemic-like’ ST segment depression during stress can occur in the presence of angiographically normal coronary arteries, when there is a systemic endothelial dysfunction\[4,21,22\], in the absence of any wall motion abnormality as demonstrated by echocardiography\[21–23\]. This also emphasizes an important difference between functional (wall motion) and perfusion (radionuclide) imaging, since the latter may have a higher sensitivity for mild coronary artery disease detection, but is frequently positive also in the presence of isolated microvascular disease\[24\].

**The pathophysiological basis of observed findings**

During stress, wall motion abnormalities are tightly linked to coronary stenosis. This is consistent with experimental data showing that a regional dysfunction must be associated with a flow reduction greater than 50% in comparison with resting values and involving at least 20% of transmural wall thickness and about 5% of
the total myocardial mass\cite{18,25}. This critical ischaemic mass cannot be achieved by isolated microcirculatory impairment, which can however, prevent appropriate blood flow responses during stress. Thus, relatively milder and more localized forms of myocardial flow maldistribution or under-perfusion do not leave echocardiographic fingerprints and represent the physiological scotoma of the echocardiographic eye when confronted with ischaemia. It is important to note that normal left ventricular function consistently recorded during stress echocardiography in patients with normal coronary arteries and abnormal endothelial function is not incompatible with true myocardial ischaemia, since the presence or absence of abnormal wall motion appears to be related to the amount of subendocardial tissue reduced ischaemic and even subendocardial infarction can occur without wall motion abnormalities\cite{26}.

**Table 2** Prediction of endothelial dysfunction by univariate logistic regression analysis

<table>
<thead>
<tr>
<th>Univariate predictors</th>
<th>P value</th>
<th>Chi-square</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.93</td>
<td>0.01</td>
<td>0.94 (0.28–3.2)</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>0.87</td>
<td>0.03</td>
<td>0.9 (0.3–2.9)</td>
</tr>
<tr>
<td>Significant epicardial coronary artery stenosis</td>
<td>0.81</td>
<td>0.05</td>
<td>0.9 (0.3–2.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.74</td>
<td>0.11</td>
<td>1.4 (0.16–13.5)</td>
</tr>
<tr>
<td>Stress echo positivity</td>
<td>0.66</td>
<td>0.19</td>
<td>0.77 (0.23–2.5)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.61</td>
<td>0.25</td>
<td>0.69 (0.2–2.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.53</td>
<td>0.39</td>
<td>0.69 (0.2–2.2)</td>
</tr>
<tr>
<td>Angina during stress echo</td>
<td>0.5</td>
<td>0.46</td>
<td>1.6 (0.39–6.6)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.20</td>
<td>1.60</td>
<td>0.44 (0.12–1.6)</td>
</tr>
<tr>
<td>ECG positivity during stress echo*</td>
<td>&lt;0.05</td>
<td>5.20</td>
<td>6.2 (1.3–30.5)</td>
</tr>
</tbody>
</table>

*Significant predictor of endothelial dysfunction.

**Clinical implications**

Since there is doubt about the reliability of ST segment depression in predicting coronary anatomy, echocardiographic information is warranted during stress testing for identifying significant coronary artery disease\cite{18}. However, when a standard, different from coronary anatomy is used, ST segment depression can be useful, since it identifies an abnormal endothelial function — which does not affect wall motion abnormalities. Endothelial dysfunction is not an innocent finding of pure pathophysiological interest, since it has been implicated in the pathogenesis of different cardiovascular events, many of which involve rupture of a previously non-critical (and, thereby, ‘stress-lucent’) plaque\cite{27}. In addition, preliminary evidence suggests that flow-mediated dilation might have prognostic value in patients with chest pain\cite{28}.

This may account for the previously described finding that wall motion abnormalities and ECG positivity may have additive, incremental prognostic value in risk stratification, possibly indicating that the two markers observe two different physiological variables. In patients with stress echo positivity, which defines a high risk subset, concomitance of ST segment depression identifies an even higher risk subgroup\cite{29}. In patients with hypertrophic cardiomyopathy, the finding of normal coronary arteries and negative stress echo identifies a prognostically benign subset; however, within this low risk population, stress-induced ST segment depression identifies patients at higher risk for subsequent events\cite{30}. Therefore, ECG ischaemic changes during stress echo testing has shown its independent and incremental value in several different clinical settings. The present study clarifies the possible pathophysiological substrate of this prognostic finding, documenting that ‘ischaemic-like’ ST segment depression is a poor marker of angiographically assessed coronary artery disease but a reliable sign of systemic endothelial dysfunction. It integrates and complements stress-induced wall motion abnormalities, which are accurate markers...
of coronary artery disease but are unrelated to systemic endothelial dysfunction.

**Study limitations**

Our results apply to the selected population meeting the study entry criteria. In particular, our patients were referred to the echo lab for stress echocardiography and had no previous myocardial infarction or revascularization procedure. These two criteria may account for some peculiarities of the study population and explain the observed results. In our series, 29 patients (41%) had normal coronary angiograms, and the diagnostic accuracy — and especially specificity — of stress ECG for diagnosis of coronary artery disease was very low. These data may seem to conflict with earlier studies showing substantially better accuracy of ECG stress testing (during dipyridamole or dobutamine), similar to that of the exercise test\(^{31,32}\). However, initial efficacy studies necessarily evaluate different patients from effectiveness studies, when the technique is deployed in the field and applied to patients in whom its incremental value is highest\(^ {33,34}\). Over the years the indications for stress echo testing have evolved and been refined, and the currently accepted recommendations include patients with an intermediate-to-high pre-test probability of coronary artery disease, with inconclusive routine exercise test results, representing true diagnostic challenges.

Our findings cannot be extrapolated to the variety of consecutive patients evaluated for a chest pain syndrome, but are more likely to mirror the reality of the selected population referred for stress echo imaging. Finally, 75% of patients were under antiischaemic therapy at the time of testing, and it is known that this may affect stress test sensitivity\(^ {35}\) and — at least for some calcium-antagonists — also endothelial function. This may explain the absence of an association between coronary risk factors and systemic endothelial dysfunction. Nevertheless, withdrawal of therapy in all patients would have been impractical and/or unethical.

**Conclusions**

The electrocardiographic signal is often disregarded as pure diagnostic ‘noise’ in the cardiac imaging era. However, the present study shows that although the ECG signal is of little value in identifying coronary artery disease in the selected population referred for stress echo testing, it may offer insight into systemic endothelial dysfunction, which is an important physiological parameter of established pathophysiological and emerging prognostic interest. Old techniques — such as the simple electrocardiogram — can still offer surprising dividends when they are combined with newer imaging tools.

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