Myocardial ischaemia in patients with coronary endothelial dysfunction: insights from body surface ECG mapping and implications for invasive evaluation of chronic chest pain

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Aims
Coronary endothelial dysfunction (ED), by predisposing to abnormal vasomotion, may cause chest pain in individuals with non-obstructed coronary arteries. The aim of this study was to correlate the magnitude of coronary ED with the presence and extent of inducible myocardial ischaemia using body surface electrocardiogram (ECG) mapping in symptomatic patients.

Methods and results
In 30 patients with chest pain and angiographically normal coronary arteries or mild atherosclerosis, we studied endothelium-dependent responses with acetylcholine (ACH) and endothelium-independent function with nitroglycerin and adenosine in the left anterior descending artery. Eighty-lead body surface ECG maps were collected at baseline and after each dose of ACH. There was a significant correlation between the maximal change in epicardial diameter with ACH and the magnitude of ST-segment shift $[r = -0.44 \ (95\% \ CI: -0.097 \ to \ -0.69), \ P = 0.015]$. Patients with $\geq 0.05 \ mV$ ST-segment shift/lead had greater epicardial vasoconstriction (31.6 vs. 15.6%, $P = 0.019$), and lower coronary flow reserve (2.9 vs. 3.6, $P = 0.047$) compared with those with ST-segment shift $< 0.05 \ mV$. Four patients had inducible ischaemia with ACH in the absence of abnormal epicardial or global microvascular vasomotion ($>20\%$ decrease in diameter or $>50\%$ increase in blood flow).

Conclusions
This study demonstrates that abnormal vasomotion due to coronary ED is associated with myocardial ischaemia in patients with chest pain. The magnitude of ischaemia correlates with the extent of ED. A small subset of patients develop myocardial ischaemia during ACH infusion without significant abnormalities in epicardial or global microvascular endothelium-dependent blood flow responses.

Keywords
Endothelial dysfunction • Vasospasm • Acetylcholine • Ischaemia • Electrocardiography

Introduction
Endothelial dysfunction (ED) is believed to play a key role in the pathophysiology of myocardial ischaemia and precipitating cardiovascular events.¹ In normal individuals, endothelial cells regulate coronary blood flow by responding to changes in shear stress, myogenic constriction, and vasoconstrictors such as acetylcholine (ACH) and endothelin, by releasing vasodilators such as nitric oxide.² – ⁴ Endothelial dysfunction develops in patients with cardiovascular risk factors and in turn predisposes to vasoconstriction and impaired homeostasis.⁵ – ⁷ The presence and severity of ED can be measured invasively in the cardiac catheterization laboratory by evaluating coronary epicardial and microvascular blood flow responses to ACH.⁸ – ¹⁰ The clinical utility of identifying coronary ED remains uncertain, in part, because it has been difficult to demonstrate that coronary ED is associated with...
myocardial ischemia. This is particularly challenging because the three-lead electrocardiogram (ECG) monitoring that is used in most cardiac catheterization laboratories does not have the sensitivity to detect mild ischemia. In a recent study, we observed that even with the use of 12-lead ECG, ischemia was only detected in <10% of patients with ED. We hypothesized that body surface ECG mapping, by sampling the entire circumference of the chest, will improve the detection of transient myocardial ischemia in patients with non-obstructed coronary arteries undergoing invasive evaluation for coronary vasomotor function. Thus, the aim of our study was to correlate the magnitude of coronary ED, as assessed by ACH provocation, with the presence and extent of myocardial ischemia.

Methods

Study population

We performed a retrospective analysis of 48 consecutive patients referred for cardiac catheterization for evaluation of chest pain between April 2008 and July 2009. The decision to refer patients for an ACH provocation study was made by referring cardiologists. Inclusion criteria for the study were: (i) angiographically smooth arteries or mild irregularities (≤30% lumen diameter stenosis by visual assessment in all major epicardial arteries) and (ii) the proximal coronary arteries were >2.0 mm in diameter. Criteria for exclusion were coronary atherosclerosis with >30% epicardial diameter stenosis, intolerance to ACH, age <18 years, poor-quality ECG data (13 patients), inability to interpret ECG tracing due to left bundle branch block or early repolarization (three patients), suboptimal angiographic images for quantitative coronary angiography (one patient), and the presence of catheter-induced spasm (one patient). Long-acting nitrates and calcium-channel blocking agents were withheld for 36–48 h before the study to allow for the assessment of coronary physiology in the baseline state. The study was approved by the Mayo Clinic Institutional Review Board. Patients who refused consent for their medical records to be used for research were excluded.

Study protocol

Coronary angiography was performed using a standard femoral percutaneous approach with a 7 Fr Judkins guide. Intravenous heparin was administered at the beginning of the procedure to maintain a therapeutic activated clotting time. Non-ionic contrast was used for all patients. Following baseline coronary angiogram acquisition, a 0.014-inch Doppler guidewire (Volcano Corp., Rancho Cordova, CA, USA) was introduced within a 2.2 Fr coronary infusion catheter into the left anterior descending coronary artery. Coronary vascular responses were studied according to a previously reported protocol that is performed as an integral part of our clinical practice. Endothelium-independent coronary flow reserve was measured using a bolus of intracoronary adenosine (36–60 μg) via the guide catheter. Following recovery to baseline, endothelium-dependent responses were assessed using selective intracoronary infusions of ACH at 1 mL/min at concentrations of 10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L for 3 min durations each. Finally, 200–300 μg of intracoronary nitroglycerin bolus was given to assess endothelium-independent epicardial dilation.

As previously described, we defined coronary epicardial ED as a decrease in diameter >20% in response to ACH. Microvascular ED was defined as <50% increase in coronary blood flow in response to the maximal dose of ACH. Patients who did not receive the peak dose of ACH, the highest dose tolerated was used for calculation of change in blood flow and epicardial diameter. At baseline and after each infusion, the following data were obtained: the heart rate and blood pressure, coronary angiogram, Doppler coronary blood flow velocities, and body surface ECG map.

Quantitative coronary angiography

Epicardial artery diameter was analysed from digitized images with a modification of the technique previously described. An end-diastolic still frame at each infusion (baseline, ACH, and nitroglycerin) was selected from the angiographic sequence. Epicardial diameter was measured 5 mm distal to the tip of the Doppler wire to calculate flow and in the distal artery. The measurements were made by a trained technician who was blinded to the ECG data.

Assessment of coronary blood flow

Doppler flow velocity spectra were analysed on-line to determine time-averaged peak velocity. Volumetric coronary blood flow was determined as follows: cross-sectional area × average peak velocity × 0.5. Coronary flow reserve was calculated as the ratio of hyperaemic to basal average peak velocity following adenosine administration.

Electrocardiogram data

The methodology and application of body surface ECG mapping using the 80-lead PRIME ECG® (Verathon, Inc., Bothell, WA, USA) has been described previously. PRIME ECG consists of a flexible plastic anterior and a posterior integrated electrode ‘vest’. The front of the chest and axilla are covered by 64 electrodes, including 3 proximal bipolar limb leads and the posterior chest is covered with 16 electrodes (Figure 1). As described previously, each electrode is assigned to one of four distinct territories (anterior, posterior, and inferior/right ventricle) that approximately correspond with areas of the chest wall overlying the myocardium perfused by left anterior descending, left circumflex, and right coronary arteries, respectively. The information is recorded and displayed on a screen using the proprietary PRIME analysis software. QRS onset and offset and T-wave offset are automatically marked, and manually edited if required, to facilitate the measurement of the ST0 isopotential which measures the ST-segment potential relative to the TP segment in each electrode, at the J-point. The data from each electrode may be viewed as a traditional ECG signal as well as a colour map to facilitate interpretation. ST-segment elevation is highlighted in red and areas of ST-depression in blue (Figure 2). Signal quality from each electrode is monitored throughout the procedure in a live acquisition mode. Signal from poor-quality leads is automatically, and if needed manually excluded during the off-line analysis. Patients were excluded from the study if any one of the PRIME ECG acquisitions, <70% of anterior or <50% of inferior, posterior, and right ventricular leads had a good signal quality.

The average ST0 potential (mV/lead) in each of the four PRIME ECG territories was calculated by adding the absolute ST0 potentials in each lead in a given territory and dividing by the number of leads. The change in ST0 potential (ST-segment shift) during ACH infusion was calculated by subtracting the post-ACH average ST0 potential from that measured at baseline.

Statistical analysis

Continuous variables are summarized as median and inter-quartile range. A two-tailed P-value <0.05 was considered statistically significant. The Wilcoxon rank-sum test was used to compare coronary vasomotor response according the presence or absence of ECG-detected ischemia. Spearman’s rank correlation coefficients were estimated for the association between the change in coronary
artery diameter to ACH and the amount of ST-shift. Confidence intervals for the correlation coefficient were based on Fisher's $z$-transformation. The Kruskal–Wallis test was used to test for the difference in median ST-shift between the four ECG territories. Multivariate analysis of variance (MANOVA) was used to test for the difference in ST-shift across ECG territories between patients with and without ED. Confidence intervals for sensitivity and specificity were based on exact binomial methods. All statistical analyses

**Figure 1** Distribution of the electrocardiogram electrodes for body surface map.

**Figure 2** Example of serial body surface electrocardiogram maps in a patient with significant ST segment elevation in anterior territory, during acetylcholine infusion, illustrated by the red zone on the acquisition at the peak dose (bottom right panel). ST0 represents the “J” point. The adjacent number is the magnitude of ST-segment elevation in millimeters in precordial lead V4.
were performed using JMP (Version 7, SAS Institute, Inc., Cary, NC, USA).

Results

Clinical, angiographic, and haemodynamic characteristics

The baseline clinical characteristics of the patients are summarized in Table 1. Twenty patients had angiographically normal coronary arteries and the remaining had mild luminal irregularity (<30% diameter stenosis). All patients had epicardial constriction with ACH administration with a median change in diameter of −20.0% (−11.9; −32.7). Fifteen (50%) patients had >20% epicardial constriction with ACH indicating the presence of ED. The median increase in coronary blood flow was 113% (72.0; 156). Seven (23%) patients had <50% increase in coronary blood flow indicating the presence of microvascular ED. Two of these seven patients had <20% epicardial constriction (i.e. absence of epicardial ED). Thus, there were a total of 17 (57%) patients with ED (epicardial and/or microvascular). The median increase in epicardial diameter with intracoronary nitroglycerin in those with and without ED was 22.7% (11.8; 40.8) and 21.1% (15.4; 35.9) \( (P = 0.81) \). Median coronary flow reserve in those with and without ED was 22.7% (11.8; 40.8) and 21.1% (15.4; 35.9) \( (P = 0.81) \).

Table 1 Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.5 (39–55)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.7 (24.7–35.5)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Family history of coronary disease (%)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>History of chest pain (%)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Non-invasive stress test (%)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Positive stress test (%)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>61 (59–65)</td>
</tr>
<tr>
<td>Baseline haemodynamic parameters</td>
<td></td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>75.5 (67–83)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>133 (109–143)</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>76.5 (70–81)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>102 (90–108)</td>
</tr>
<tr>
<td>Proximal epicardial diameter, mm</td>
<td>3.12 (2.53–3.70)</td>
</tr>
<tr>
<td>Distal epicardial diameter, mm</td>
<td>1.48 (1.35–1.75)</td>
</tr>
</tbody>
</table>

Coronary vasomotion and ischaemia

The median ST-segment shift during the ACH infusion in the anterior, inferior, right ventricle, and posterior leads were 0.026 (0.026; 0.078), 0.060 (0.030; 0.083), 0.021 (0.013; 0.047), and 0.037 (0.025; 0.654) mV/lead \( (P = 0.0003) \), respectively. Figure 3 illustrates the relationship between endothelium-dependent change in epicardial diameter with ACH and the maximum magnitude of ST-segment shift in each of the four ECG territories. There was a statistically significant correlation \( [r = −0.44 (95% CI: −0.097 to −0.69), P = 0.015] \) in the anterior territory, but no correlation was observed in the other three ECG territories. There was not a significant correlation between the maximal change in coronary blood flow and the magnitude of ST-segment shift in the anterior territory \( [r = −0.22 (95% CI: −0.54–0.16), P = 0.25] \). The data were also analysed in a dichotomous fashion by comparing the coronary vasomotor responses in patients with less than or greater than a ST-segment shift of 0.05 mV/lead in the anterior territory, the cut-off value representing an approximation to the median. (Table 2). Patients with >0.05 mV shift had significantly greater epicardial vasoconstriction, and a lower coronary flow reserve, but similar nitroglycerin and coronary blood flow responses. Patients with ED had greater myocardial ischaemia (ST-segment shift) compared with those without ED (Figure 4). Figure 5 categorizes the study population into distinct groups based on their epicardial and microvascular vasomotion, and extent of ST-segment shift in order to provide a clinical perspective on our findings. We used the median value of >0.05 mV/lead of ST-segment shift to define significant ischaemia during ACH infusion. Nine of 15 (60%) patients with epicardial ED had inducible ischaemia, but neither of the two patients with isolated microvascular ED, measured as the blood flow response to ACH, had inducible ischaemia. The sensitivity and specificity of the body surface ECG mapping to detect the presence of ED were 53% (95% CI: 27.8–77.0) and 69% (95% CI: 38.6–90.0), respectively. Four patients had inducible ischaemia in the absence of epicardial ED or impaired global blood response to ACH. Two of these patients developed chest pain during the ACH infusion.

Discussion

We studied patients with a chronic history of chest pain and non-obstructed coronary arteries undergoing invasive evaluation of coronary vasomotion simultaneously with body surface ECG mapping. The novel findings of the present study are that: (i) myocardial ischaemia can be detected frequently in association with ED; (ii) the magnitude of ischaemia correlates with the extent of abnormal vasomotion; and (iii) myocardial ischaemia may be induced in a minority of patients in the absence of significant epicardial or global microvascular ED.

Impaired coronary vasomotion and myocardial ischaemia

There has been considerable debate over the implications of demonstrating the presence of coronary ED among patients with chest pain and angiographically normal coronary arteries.19 This is,
in part, due to uncertainty regarding the functional significance of abnormal vasomotion during invasive provocation testing. Our study is the first to report that there is a relationship between the extent of ED and the severity of inducible myocardial ischaemia (ST-segment shift) (Figure 3). The validity of this finding is supported by the fact that the significant ECG changes were selectively observed in the anterior territory of the body surface map which corresponded with the distribution of the left anterior descending artery into which the drugs were infused. A cut-off value of 0.05 mV/lead of ST-segment shift during the ACH infusion correlated with significantly greater ED and lower endothelium-independent coronary flow reserve. There was greater ischaemia detected among the 57% of patients with ED when compared with those without (Figure 4). Since these findings are from an exploratory study, they require prospective validation in a larger patient population. Further, these findings differ considerably from a previous analysis from our laboratory in which 12-lead ECG monitoring was utilized.13 In that study, ST-segment shift during ACH infusion was detected in only 1 of 69 patients. The poor sensitivity for detecting ischaemia was most likely due to the limited spatial resolution of 12-lead monitoring compared with body surface ECG mapping. The fact that ischaemia was induced even when there was a net increase in blood flow in the epicardial artery is likely a manifestation of the heterogeneity of vasomotion in the microcirculation in the presence of ED.20 Finally, our findings, by quantifying the extent of ischaemia, extend the observations from a prior study in which we demonstrated the presence of abnormal myocardial perfusion, as detected by sestamibi SPECT imaging, in association with impaired coronary vasomotion due to ED.15

Although demonstrating the relationship between impaired coronary vasomotion and ischaemia is of pathophysiological interest, the clinically important question is how do we identify patients with chronic intermittent chest pain in whom the coronary ED may be contributing to their symptoms? While our study was not designed to address this question directly, we believe, based on our clinical experience of conducting invasive testing in over

![Figure 3](image-url) Correlation between the maximum change in epicardial diameter in response to acetylcholine (endothelium-dependent vasomotion) and maximal mean ST-segment shift/lead in each of the four electrocardiogram territories.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt;0.05 mV/lead (n = 17)</th>
<th>≥0.05 mV/lead (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter change</td>
<td>15.6% (7.4; 23.7)</td>
<td>31.6% (14.2; 50.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>Maximum coronary flow change</td>
<td>135.6% (102.9; 235.6)</td>
<td>96.3% (6.6; 142.2)</td>
<td>0.060</td>
</tr>
<tr>
<td>Diameter change after NTG</td>
<td>21.1% (11.9; 37.4)</td>
<td>25.3% (13.8; 55.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>3.6 (3.1; 4.2)</td>
<td>2.9 (2.6; 3.8)</td>
<td>0.047</td>
</tr>
</tbody>
</table>
**Figure 4** Maximum ST-segment shift/lead (median and inter-quartile range) according to electrocardiogram territory between those with and without epicardial endothelial dysfunction.

**Figure 5** Grouping of patients based on the presence or absence of endothelial dysfunction and ischaemia (defined as ST-segment shift $\geq 0.05$ mV/lead). We speculate that the two groups of patients with inducible ischaemia represent those in whom endothelial dysfunction is a potential cause for chest pain.
a thousand such patients,¹⁰ that the ability to demonstrate inducible ischaemia using body surface mapping in patients with ED is likely to be highly relevant in this regard. This is especially so in light of the fact that non-invasive stress tests have limited diagnostic accuracy for identifying coronary vasomotor dysfunction in this patient population.²¹ In accordance, only 3 of the 12 patients with coronary ED who underwent non-invasive stress tests had a positive result.

**Ischaemia in the patients without significant impairment of coronary vasomotion**

Four patients (13%) had ACH-induced ischaemia in the absence of epicardial or microvascular ED. The mean ST-segment shift in these patients was significant at 0.09 mV/lead and two of these patients developed typical chest pain during the study suggesting that the ECG changes represented ischaemia. A potential explanation for the fact that ischaemia was induced despite normal epicardial vasomotion and global microvascular responses to ACH is that there was regional microvascular dysfunction. This was first proposed by Maseri et al.,²² as a potential mechanism for microvascular angina. To the best of our knowledge, this is the first demonstration of this phenomenon in humans during invasive testing. Moreover, heterogeneous microvascular function may result in a blood steal phenomenon within the myocardium.²⁰ Previous studies from Japan have reported a high frequency of myocardial ischaemia in the absence of significant epicardial artery constriction during ACH infusion and have referred to the phenomenon as microvascular spasm.²³,²⁴ However unlike our investigation, these studies lacked data on coronary blood flow, as they predated the use Doppler wires, and hence do not provide a direct measure of microvascular function. Our findings lend support to the concept that microvascular angina may indeed be a cause of chest pain in a minority of patients without fixed or inducible coronary epicardial stenosis.

**Limitations**

This is an exploratory, retrospective single-centre analysis and is subject to the limitations of such analyses. However, the body surface maps and the coronary flow data were recorded prospectively, which reduces some of the limitations of the retrospective study design. The inclusion of patients into our study population is subject to referral bias due to the fact numerous patient and physician-related factors would have determined the selection of subjects for cardiac catheterization, and hence our findings may not be applicable to all patients with chest pain without obstructive coronary atherosclerosis. Owing to the fact that invasive evaluation for coronary endothelial function is performed infrequently, the sample size of the study is small and hence the findings should be interpreted accordingly. Intravascular ultrasound was not performed and hence we cannot confirm the presence or absence of atherosclerotic plaque in those with angiographically normal coronary arteries. Finally from the statistical aspect, multiple hypothesis tests were evaluated and thus the overall type 1 error rate of the data may be >0.05.

**Conclusions and implications**

Using a combination of invasive coronary vasomotion testing and non-invasive body surface ECG mapping, we demonstrate that inducible myocardial ischaemia can be detected frequently in association with ED, and that there is a modest correlation between the magnitude of ischaemia and the extent of abnormal vasomotion. Moreover, we observed that myocardial ischaemia may occur in the absence of significant epicardial or global microvascular ED in a subset of patients.

We believe that the ability to document ischaemia in association with ED will assist in evaluating patients suspected of coronary artery spasm and microvascular ischaemia.¹⁹,²⁵–²⁷ Our study highlights a potential clinical role for body surface ECG mapping. Future studies that investigate the ability of this technique to detect myocardial ischaemia during non-invasive testing for ED (e.g. exercise or mental stress); and treatment strategies based on the severity of ischaemia would be extremely helpful.

**Conflict of interest:** none declared.

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