Progressive epicardial coronary blood flow reduction fails to produce ST-segment depression at normal heart rates

Marilyn de Chantal,1,4 Jean G. Diodati,1,2,4 James B. Nasmith,1,2,4 Robert Amyot,1,2,4 A. Robert LeBlanc,1,4 Erick Schampaert,1,2,4 and Chantal Pharand1,3,5

1Research Center, 2Division of Cardiology and 3Pharmacy Department, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada; and Faculty of 4Medicine and 5Pharmacy, Université de Montréal, Montréal, Québec, Canada

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De Chantal, Marilyn, Jean G. Diodati, James B. Nasmith, Robert Amyot, A. Robert LeBlanc, Erick Schampaert, and Chantal Pharand. Progressive epicardial coronary blood flow reduction fails to produce ST-segment depression at normal heart rates. Am J Physiol Heart Circ Physiol 291: H2889–H2896, 2006. First published August 11, 2006; doi:10.1152/ajpheart.00400.2006.—ST-segment depression is commonly seen in patients with acute coronary syndromes. Most authors have attributed it to transient reductions in coronary blood flow due to nonocclusive thrombus formation on a disrupted atherosclerotic plaque and dynamic focal vasospasm at the site of coronary artery stenosis. However, ST-segment depression was never reproduced in classic animal models of coronary stenosis without the presence of tachycardia. We hypothesized that ST-segment depression occurring during acute coronary syndromes is not entirely explained by changes in epicardial coronary artery resistance and thus evaluated the effect of a slow, progressive epicardial coronary artery occlusion on the ECG and regional myocardial blood flow in anesthetized pigs. Slow, progressive occlusion over 72 min (SD 27) of the left anterior descending coronary artery in 20 anesthetized pigs led to a 90% decrease in coronary blood flow and the development of ST-segment elevation associated with homogeneous and transmural myocardial blood flow reductions, confirmed by microspheres and myocardial contrast echocardiography. ST-segment depression was not observed in any ECG lead before the development of ST-segment elevation. At normal heart rates, progressive epicardial stenosis of a coronary artery results in myocardial ischemia associated with homogeneous, transmural reduction in regional myocardial blood flow and ST-segment elevation, without preceding ST-segment depression. Thus, in coronary syndromes with ST-segment depression and predominant subendocardial ischemia, factors other than mere increases in epicardial coronary resistance must be invoked to explain the heterogeneous parietal distribution of flow and associated ECG changes.

ST-segment elevation; epicardial resistance; myocardial perfusion

ACUTE CORONARY SYNDROMES (ACS) are broadly divided into two clinical entities based on the ECG: I) ST-segment elevation myocardial infarction (STEMI) and 2) unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI). This classification defines two ACS subgroups with different epidemiological profiles, pathophysiological characteristics, and probability of future ischemic events. This ECG-based dichotomy also carries significant therapeutic implications (1, 8, 9, 32, 42). The presence of persistent ST-segment elevation, as observed in STEMI, is an indication for immediate reperfusion by mechanical or pharmacological means (1, 15, 20, 31, 47). In contrast, patients with UA/NSTEMI, who commonly present ST-segment depression episodes, will benefit most from antithrombotic treatments, followed by early revascularization in higher risk suitable patients (3, 10, 16).

These ECG changes have commonly been attributed to the extent of coronary blood flow (CBF) reduction with, on one hand, a narrowed yet patent vessel (ST-segment depression) and, on the other hand, an occluded artery (ST-segment elevation) (14, 30, 45). Although a well-known continuous relation is hypothesized between progressive proximal stenosis and falling perfusion pressure, to implicate the severity of epicardial coronary obstruction as the only determinant of ST-segment expression may be simplistic and unsupported by clinical observations (19, 22). In stable angina patients and in classic animal models, moderately severe coronary lesions produce ST-segment depression only in the presence of tachycardia, which shortens the diastolic filling time and reduces perfusion more severely in the subendocardium than in the subepicardium (22, 35, 36). On the contrary, in UA/NSTEMI patients, plaque rupture and activation of the coagulation and inflammatory cascades commonly generate ST-segment depression at normal heart rate in the presence of coronary stenoses of severity comparable to that of stable angina patients (2, 13, 29, 38). Finally, a smooth spectrum of ST-segment behavior typical of a single mechanism operating along a spectrum of values cannot be found when the evolution of ST-segment changes during ACS is carefully examined. For example, progressive fibrinolysis and recanalization of a coronary occlusion in STEMI does not register as ST-segment depression on the way to complete resolution after ST-segment elevation.

Whereas theoretical studies predict that ST-segment depression might occur in precordial leads during subendocardial ischemia (26), to our knowledge, clinical and experimental studies have never demonstrated the transition from ST-segment depression to ST-segment elevation with progressive CBF reduction. Moreover, coronary lesions manifest themselves distinctly on the ECG under different conditions. Hence, there is a need to revisit the paradigm that assumes all ST-segment shifts can be accounted for by epicardial coronary resistance alone. We postulated that ST-segment depression occurring at normal heart rates, as in UA/NSTEMI, might not be entirely explained by increases in epicardial coronary artery resistance alone (14, 22, 30, 35, 45).

Hence, the purpose of this study was to evaluate the contribution of epicardial coronary vascular resistance to ST-seg-
ment depression observed in patients with UA/NSTEMI, by confirming the absence of any ST-segment depression before the appearance of ST-segment elevation during acute epicardial occlusion without tachycardia. To achieve this goal, we sought to determine the effect of slow, progressive coronary flow reduction on the development, distribution, and ECG expression of myocardial ischemia in healthy pigs with normal heart rates. A porcine model was chosen to explore this hypothesis because it has numerous and well-documented similarities to humans, at both anatomic and physiological levels (5, 43, 46). The epicardial coronary constriction was designed to mimic the presence of thrombus partially but dynamically occluding the artery, as thought to occur in UA/NSTEMI patients.

METHODS

Animal preparation. Experiments were conducted on 25 male domestic Landrace swine 34.9 kg (SD 1.8) in compliance with the Canadian Council for Animal Care guidelines. Experiments were approved by the Institutional Animal Care Committee. Five animals were excluded from analysis: three for tachycardia, one for hypotension (fall in systolic blood pressure > 25 mmHg), and one for faulty CBF signal acquisition. We therefore report results on 20 animals.

All animals received 325 mg daily of acetylsalicylic acid (Apotex, Toronto, Canada) for 3 days before the experimentation to prevent increased platelet aggregation during surgical preparation of the animals. Animals were anesthetized with intramuscular ketamine-xylazine (20 mg/kg and 2 mg/kg; Wyeth Pharmaceuticals, Montreal, Canada), intubated, and ventilated with a positive pressure ventilator (Ohmeda 7800 anesthesia ventilator; DRE Medical, Louisville, KY) with fraction of inspired oxygen maintained constant at 20–30%.

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Hemodynamic and ECG monitoring. ECG and hemodynamic signals (systemic arterial pressures and CBF) were amplified, digitally converted at 500 samples/s, and continuously recorded on a personal computer (Z Pro Pentium IV; IBM, New York, NY). To obtain a better time resolution of QRS and ST-segment dynamics, an averaged QRS-T complex was calculated off-line for each 10-s interval (VCGMI version 3.0, Centre de Recherche, Hôpital du Sacré-Cœur de Montréal, et Institut de Génie Biomédical, Montréal, Canada, 2000). ST-segment amplitude was measured at J + 60 ms. The software also calculated systolic and diastolic pressures as well as averaged CBF.

Assessment of regional MBF by nonradioactive colored microspheres. To assess regional MBF, colored microspheres were injected at three time points: baseline, partial occlusion, and critical occlusion. Different colors were used at each of these time points. For each microsphere injection, a total of 1 × 10^6 15-μm nonradioactive colored microspheres was dispersed by vortex agitation in 0.01% Tween 80 (E-Z Trac Colored Ultraspheres; Interactive Medical Technologies, Irvine, CA) and added to 9 ml of normal saline. Microspheres were injected in the left atrium over 15 s. To calculate regional MBF appropriately, a reference blood sample was withdrawn at each microsphere injection from the femoral artery over 2 min, starting 15 s before microsphere administration (23).

At the end of the experiment, while the heart was still beating, methylene blue was selectively injected into the LAD via a Berman catheter to define the area at risk. The animals were then killed, and the hearts were removed. The right heart and left atrium were dissected to keep only the left ventricle (LV), which was sliced into four layers. From top to bottom, they were 1) base, 2) perivascular constrictor layer, 3) layer below the balloon constrictor, and 4) apex (23, 33). For the purpose of the present experiments, only layer 3 was analyzed. This layer was dissected at the blue demarcations to obtain two pieces: blue (LAD region) and nonblue (control region). Finally, each piece was further cut up to separate subepicardial from subendocardial tissue.

All pieces were weighed and processed according to the manufacturer’s instructions. The microspheres from the reference blood sam-
s and from the myocardial tissue of each region were recovered by
digestion and directly counted with the Improved Neubauer Hemol
cytometer (Thomas Scientific, Swedesboro, NJ). CBF was calculated
by the following equation: \( Q_m = \frac{C_m \times Q_q}{C_r} \), where \( Q_m \) is the MBF
per gram of tissue (ml·min\(^{-1}\)·g\(^{-1}\)), \( C_m \) is the microsphere count per
gram of tissue, \( Q_q \) is the withdrawal rate of the reference blood sample
(ml/min), and \( C_r \) is the microsphere count in the reference blood
sample.

Assessment of MBF by MCE. Animals received a single intrave
nous perflutren (Definity; BMS Medical Imaging, North Billerica,
MA) infusion at a rate of 0.0364 ml/min (administered as a diluted
solution of 1.3 ml in 125 ml of normal saline at 3.5 ml/min) over ~5
min. The contrast agent was prepared with an activation device
(Vialmix; BMS Medical Imaging) within minutes of its administration
at baseline and critical occlusion. This dose provided optimal, sus-
tained myocardial opacification in our open-chest model, as deter-
mimed by previous experiments using the same protocol, where it
was found that higher infusion rates of perflutren produced a shadowing of the
LV posterior wall. A latex bag filled with normal saline was
positioned intra-abdominally between the diaphragm and the trans-
ducer to serve as an acoustic interface. A waiting period of at least 2
min from the start of infusion to image acquisition was allowed to
obtain steady-state concentrations of the contrast agent and also
allowed a sufficiently long time period to gather ECG data that would
not be affected by the operator’s manipulations.

Echocardiographic images were acquired with a broadband 4–2
MHz transducer via a commercially available ultrasound system (HDI
5000; Advanced Technology Laboratories, Seattle, WA). The LV was
scanned in short axis at the papillary muscle level. Color-coded
harmonic power-pulse inversion imaging was performed with ultra-
sonound transmitted at 2 MHz and received at 4 MHz by low-output
power (mechanical index = 0.12) real-time imaging at 11–13
frames/s. A low dynamic range was used, and the pulse repetition
frequency was fixed at 2,500 Hz. Instrument settings were held
constant for each experiment. A burst of high output “flash” frames
(mechanical index = 0.8) resulted in periodic microbubble disruption
yielding unopacified myocardium. Resuming low-energy real-time
imaging between flashes allowed microbubble replenishment of the
myocardial microvasculature.

Digitally captured images were analyzed off-line. Myocardial
videointensity was quantified using QLAB 3.0 software (Philips
Medical Systems, Markham, Canada) in four regions of interest,
namely, in the subepicardium and subendocardium of both the LAD
and control territories. Care was taken to avoid visually attenuated
segments or high-intensity echoes from epicardial and endocardial
structures. Myocardial videointensities in selected regions of interest
were plotted as a function of time after flash (for every end-systolic frame), and an exponential function was derived:
\( y = A(1 - e^{-\beta t}) + C \), where \( y \) is videointensity at time \( t \), \( A \) is the peak videointensity
value during a low mechanical index imaging sequence that reflects
microvascular cross-sectional area, \( \beta \) is the rate constant of the
exponential recovery of videointensity after bubble destruction
(reflecting myocardial microbubble velocity), \( t \) is time after flash, and \( C \) is offset of intensity. The product of \( A \) and \( \beta \) provides a measure (in
dB·s\(^{-1}\)) that is proportional to the value of MBF (48).

Assessment of coronary artery diameter. The LAD diameter was
assessed by quantitative coronary angiography (Integris Allura 9;
Philips Medical Systems), using iopamidol (Isovue; Bracco Diagnos-
tics, Mississauga, Canada) as the contrast agent. Measurements (In-
turis Suite Viewer 2.2 software; Philips Medical Systems) were
performed at baseline and at partial and critical occlusions. We
reported the luminal diameter and area (by densitometry). All mea-
sures were taken at two different sites: within the segment of the
perivascular balloon constrictor and in a segment 1 cm distal to the
constriction.

Statistical analysis. Results are reported as means (SD). ANOVA
for repeated measures with appropriate contrast (partial occlusion vs.
baseline and critical occlusion vs. baseline) was performed for hemo-
dynamic, ECG, angiographic, and MBF data. A paired t-test was used
to analyze the MCE data (critical occlusion vs. baseline). A \( P < 0.05 \)
was considered statistically significant. All statistics was performed
with SPSS 13.0 (SPSS, Chicago, IL).

RESULTS

Hemodynamic and ECG data. Slow, progressive inflation of the
perivascular balloon constrictor led to partial LAD occlu-
sion [CBF reduction of 49.3%, 11.1 ml/min (SD 6.3), 95%
confidence interval (CI) 8.1–14.0 ml/min; \( P < 0.0001 \)] in
51.0 min (SD 30.3) and critical occlusion [CBF reduction of
89.9%, 19.7 ml/min (SD 12.1), 95% CI 14.1–25.3 ml/min;
\( P < 0.0001 \)] in 72.0 min (SD 27.4) from start of balloon
inflation (Fig. 1). At partial occlusion, arterial pressure de-
creased by 5.9% systolic \([-4.6 \text{ mmHg (SD 5.3), 95% CI} 1.8–7.5 \text{ mmHg;} \ P = 0.003 \] and by 5.6% diastolic \([-2.7
\text{ mmHg (SD 4.2), 95% CI} 0.5–5.0 \text{ mmHg;} \ P = 0.02 \] pressures compared with baseline values. Further decreases in
arterial pressures were observed at critical occlusion, with a
17.2% decline in systolic \([-11.9 \text{ mmHg (SD 11.4), 95%\]
CI = -17.9 to -5.8 mmHg; P = 0.001] and a 17.5% decline in diastolic [-8.5 mmHg (SD 7.1), 95% CI = -12.3 to -4.7 mmHg; P < 0.0001] pressures compared with baseline values. The heart rate slightly increased at partial coronary occlusion [2.7%, 2.1 beats/min (SD 7.9), 95% CI = 1.6–5.8 beats/min; P = 0.2] and at critical occlusion [12.2%, 9.5 beats/min (SD 13.2), 95% CI = 3.3–15.7 beats/min; P = 0.004). However, it remained below tachycardic levels at all times for all swines (24).

ST-segment changes were not observed in any lead from baseline to partial occlusion (Figs. 2 and 3). From partial to critical occlusion, only minor (<100 μV) and concomitant ST-segment elevations in the PA lead and depressions in lead III were observed in all but one animal, which presented ST-segment depression of 114 μV in the PA lead at partial occlusion. By the time critical occlusion was reached, ST-segment elevation appeared in the PA lead of all the animals.

Regional MBF. Microspheres demonstrated similar reductions in regional MBF in the subendocardium and subepicardium of the LAD territory, both at partial and critical occlusions. In the latter case, the reductions were of greater magnitude (Fig. 4). Decreases in regional MBF were also noted in the control territory at critical occlusion, but these were of much lesser magnitude than what was observed in the LAD territory. As a result, flow distribution in the LAD territory, expressed as the ratio of subendocardium to subepicardium regional MBF, did not display any significant heterogeneity at partial and critical occlusion (Fig. 5).

These results were corroborated by MCE, which showed significant decreases in MBF in the LAD territory at critical occlusion, in both the subendocardium and subepicardium (Fig. 6). As with microspheres, the control subendocardium and subepicardium also demonstrated a significant, but milder decrease in signal intensity.

Angiographic data. As expected, the LAD luminal area progressively decreased at partial [-85.1%, -3.67 mm² (SD 3.07) 95% CI = -8.55 to 1.22 mm²; P = 0.1] and critical [-99.3%, -4.28 mm² (SD 3.39), 95% CI = -9.68 to 1.13 mm²; P = 0.09] occlusion at the constriction site compared with baseline values (Fig. 7). Congruent changes were seen in the luminal diameter as well. One centimeter distal to the constrictor, luminal area and diameter were only slightly decreased, at both partial and critical occlusions. This confirms that vasospasm was not a major confounding variable.

DISCUSSION

This study demonstrates in a model of healthy pigs without tachycardia, monitored to detect ST-segment depression and elevation, that slow, progressive obstruction of an epicardial...
coronary artery such as the LAD does not induce ischemic, nonreciprocals ST-segment depression. Rather, it leads to the development of myocardial ischemia in the affected territory, which is solely expressed as ST-segment elevation on the ECG, a key finding never reported previously. We recognize that, during subendocardial ischemia, depression of the ST-segment potential is recorded from precordial leads in humans as well as in pigs (and other species), in agreement with theoretical predictions from healthy heart models (26). The point of this paper is to question the occurrence of such electrocardiographic signs of purely subendocardial ischemia with gradual reduction of proximal coronary artery patency in an otherwise healthy heart, in the absence of tachycardia.

Several authors have postulated that plaque rupture leading to ST-segment depression in the setting of UA/NSTEMI, normally not associated with any tachycardia, resulted from supply ischemia generated by transient reductions in CBF caused by intermittent thrombus occlusion and dynamic vasocostriction occurring at the site of a disrupted atherosclerotic plaque (6, 7, 44, 49). However, supply ischemia is classically induced by severe epicardial coronary stenosis or thrombosis, which increases proximal resistance, causes transmural ischemia, and registers on the ECG as ST-segment elevation (e.g., patients presenting with STEMI and total coronary occlusion) (14, 18, 30, 36, 45).

We found only one article in which experimental data were reported in support of the concept that ST-segment depression could be induced by increased epicardial coronary resistance. Kato et al. (30) observed that partial constriction (15% stenosis) of a coronary artery in dogs induced ST-segment depression on epicardial electrogram, whereas slightly more severe constriction (25% stenosis) displayed ST-segment elevation. As previously discussed, such a dual ECG manifestation elicited by modulation of the epicardial coronary resistance was not observed in our experimental model and was not corroborated by other groups. The discordance between the results of Kato et al. and ours may be related to the experimental protocol used, but several methodological issues need to be underlined as well. First, Kato et al. used dogs, which are somewhat protected against transmural ischemia by good collateral flow (12). Second, neither the method used to assess coronary artery diameter nor the heart rate achieved during the experiment (a major determinant of myocardial oxygen consumption) was described. Finally, the observed ECG changes occurred at levels of stenosis severity not believed to be flow limiting, thus leaving doubts on the comparability and/or validity of the results.

Previous reports of stepwise flow reduction models demonstrated that ST-segment depression was never generated over the ischemic zone, whatever the degree of epicardial stenosis, unless tachycardia was simultaneously present (22, 35, 36). In the absence of tachycardia, initial ECG manifestations during total or near-total coronary constriction are ST-segment elevations over the affected territory; ST-segment depression occurs solely over other parts of the heart (14, 30, 36, 45). One major limitation of these studies was the rapidity with which total occlusion was achieved.

From computer simulations, Hopenfeld et al. and Li et al. (27, 28, 35) demonstrated that, when ST-segment depression occurs, it does so over a boundary between ischemic and healthy tissue and never over the affected territory. This occurs with or without ST-segment elevation directly over the ischemic zone.

Thus our findings are consistent with classic articles and expand our understanding of the mechanism of typical supply ischemia, which does not produce ST-segment depression, even when generated from slow, progressive, and continuous, as opposed to rapid, stepwise CBF reductions (22, 35). Hence, the common belief that ST-segment depression occurs secondarily to moderately increased epicardial resistance is, in fact, an unsubstantiated extrapolation from a demand ischemia model, in which exercise- or pacing-induced tachycardia is required to produce ischemia, in the presence of a moderate, fixed proximal stenosis that does not cause any CBF reduction at rest.

Our model was chosen to study the sole influence of epicardial coronary artery resistance in the development of myocardial ischemia and to minimize the contribution of endothelial dysfunction, microcirculation pathology, or activation of the coagulation and inflammatory cascades. In this model, ST-

![Figure 6](image1.png)

**Fig. 6.** MBF quantification (product of maximum videointensity \( A \) and rate constant of rise of videointensity \( \beta \)) calculated after curve fitting of myocardial signal intensity data over time, determined by myocardial contrast echocardiography at baseline and critical LAD occlusion. Values are means (SD); \( n = 7 \) pigs. *\( P < 0.01 \) vs. baseline. †\( P < 0.001 \) vs. baseline.

![Figure 7](image2.png)

**Fig. 7.** Luminal diameter (left) and area of LAD (right) at the constriction site and 1 cm distally at baseline, partial, and critical occlusions, determined by quantitative coronary angiography. Values are means (SD); \( n = 4 \) pigs. *\( P < 0.05 \) vs. baseline.
segment elevations occurred late, when critical (90%) reductions in CBF were achieved. ST-segment depression was not observed in any ECG lead before the development of ST-segment elevation. Minor ST-segment depression occurring simultaneously with ST-segment elevation was observed in the nonischemic territory. As would be expected during transmural, ST-segment elevation ischemia, MBF, at both partial and critical occlusions, was homogeneously decreased in the LAD territory, demonstrated by preserved subendocardial to subepicardial ratios (34). The lack of a preferential reduction in subendocardial blood flow suggests that selective subendocardial ischemia was not produced in the LAD territory and that the minor ST-segment depression observed in lead III possibly represents reciprocal ST-segment changes in the remote lead over nonischemic territory (22, 35, 37). We postulate that the lesser reduction in MBF observed in the control region during critical occlusion was secondary to ischemia in the LAD territory, causing a fall in blood pressure.

Many factors may contribute to ST-segment depression. The relative contribution of each of these needs to be addressed separately. We targeted coronary epicardial vascular resistance in isolation because it is often assumed to be the principal culprit. The advancement of this article over previous studies is that we ruled out proximal stenosis as a contributor to ST-culprit. The advancement of this article over previous studies is that we ruled out proximal stenosis as a contributor to ST-segment depression in the absence of tachycardia.

Hence, our results give mechanistic insights to everyday clinical observations. UA/NSTEMI patients commonly present with normal or even slow heart rates due to beta-blocker administration (2, 13, 29, 38). Furthermore, a significant proportion of these patients (23–42%) demonstrate <70% coronary diameter stenosis in the culprit vessel (50). Therefore, increased epicardial coronary resistance or increased myocardial oxygen consumption cannot entirely explain the ECG manifestation observed in these patients. A third mechanism must be involved. One hypothesis that could integrate all of this information is that, in UA/NSTEMI patients, ST-segment depression results from an increase in microvascular resistance that is more prominent in the subendocardium. The presence of endothelial dysfunction and/or unstable coronary lesions with release of vasoactive substances from ruptured plaques could preferentially reduce microvascular blood flow at the subendocardial level, which would translate into subendocardial ischemia manifested as ST-segment depression.

The present study has some limitations. Although a pig model was chosen for its numerous similarities to humans, it also does present differences (such as autonomic innervation) that may render our results more difficult to extrapolate to humans (11). Our data were intentionally derived from observations in healthy animals that presumably presented a normal distal vascular response to increasing proximal obstruction and, as such, should not possess defective, endothelium-dependent vasomotion as is known to exist in atherosclerotic patients. The reason for this choice was to isolate the role of epicardial resistance alone from the contribution of underlying coronary artery disease in modulating the ECG response. In addition, because of the time required to collect data with the techniques used, assessment of MBF was performed only at three time points: baseline, partial (50% reduction in baseline CBF) occlusion, and critical occlusion (emergence of persistent ST-segment changes). It would have been informative to collect MBF data between partial and critical occlusions. Moreover, our model may have introduced discrepancies in our results in two ways. First, isoflurane was used to anesthetize the animals; it is known to alter autonomic regulation and to affect cardiac ion channels, as well as to mimic ischemic preconditioning and attenuate the degree of ST-segment changes during ischemia (17, 40). Myocardial ischemia and ST-segment changes of greater amplitude may have occurred if a nonvolatile anesthetic agent had been administered, but many disadvantages restrain its use (4, 25, 41). In addition, the use of an open-chest model, which increases the insulation of the heart, results in higher-amplitude epicardial electrograms, without affecting the distribution patterns. The effect of such an open-chest model on the surface electrocardiograms is not as clearly defined (21, 22). Finally, even though we did demonstrate that a slow, progressive coronary occlusion did not result in ST-segment depression, our study did not allow us to determine whether vasoconstriction of the microcirculation was a determinant factor for the development of ST-segment depression ischemia.

In conclusion, we confirmed that progressive epicardial stenosis of a coronary artery induces, at normal heart rate, homogeneous, transmural reduction in regional MBF and ST-segment elevation without an intervening ST-segment depression phase. The clinical implications of these results may be of importance because current treatment strategies used for the management of UA/NSTEMI mostly target the epicardial stenosis, therapies that are most likely suboptimal if one considers that increased epicardial resistance may not be the sole factor responsible for the development of ST-segment depression observed in this disease. Alternatively, heterogeneous vasoconstriction of the microcirculation might be playing a significant role. Further experiments are needed to confirm this hypothesis.

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Present address for J. B. Nasmith: Toronto Western Hospital, Toronto, ON, Canada MST 2S8.

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