Measurement of coronary collateral flow and resistance in the presence of an open critical stenosis, and the response to intra-arterial thrombosis

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Abstract

\textbf{Objective:} (1) Can one measure coronary collateral flow around an open critical stenosis? (2) Does intracoronary platelet thrombosis affect native coronary collateral vessels? \textbf{Methods:} We measured regional myocardial blood flow by the radioactive microsphere technique in seven anaesthetised dogs with an ultrasonic flowmeter on the circumflex branch of the left coronary artery (LCx). Measurements were made (a) in a control period, (b) after induction of a tight stenosis on the LCx, and (c) after additional arterial damage at the stenosis to induce intraluminal thrombosis. Collateral flow was calculated from LCx tissue flow (in ml/min/g tissue) minus LCx flowmeter flow which is in ml/min. Therefore, it was necessary to use scaling by reference back to the control measurements and conversion to ml/min/g tissue equivalent. \textbf{Results:} LCx stenosis induced collateral flow from the other coronary arteries into the LCx area of supply, which decreased (mean±S.E.) from 0.23±0.03 to 0.15±0.05 ml/min/g tissue with thrombosis. Collateral resistance correspondingly increased with thrombosis from 187.6±18.2 to 1069±544 mmHg/ml/min/g (P<0.02). \textbf{Conclusion:} Coronary collateral flow around an open stenosis can be measured by reference back to control conditions. The coronary collaterals vasoconstrict in the presence of thrombosis even though they are in the stream of blood coming from normal coronary arteries. © 2000 Elsevier Science BV. All rights reserved.

\textbf{Keywords:} Blood flow; Collateral circulation; Coronary circulation; Ischemia; Platelets; Thrombosis/embolism; Vasoconstriction/dilation

This article is referred to in the Editorial by L.C. Becker (pages 217–218) in this issue.

1. Introduction

Previous observations during circumflex coronary arterial occlusion in a stenosed segment of the left circumflex coronary artery, failed to show any effect of intraluminal thrombosis on collateral flow and resistance [1]. However, the maximal ischemic vasodilatation of occlusion may have masked possible effects on collateral vessels to the circumflex arterial territory, which, in the dog heart, originate from the left anterior descending and/or right coronary artery [2,3]. Classical techniques for measuring collateral flow, of which the microsphere method [4,5] is usually preferred, require measurements during arterial occlusion. This allows flow from a collateral source to be distinguished from direct flow, since at occlusion, there is zero antegrade flow. In order to study a situation analogous to unstable angina, we needed to estimate collateral flow in the presence of some direct flow through the stenosed artery (Fig. 1) with and without the presence of thrombus.

The theoretical basis of this approach can be explained by considering a model of the coronary circulation (Fig. 1). In the absence of a stenosis on the left circumflex coronary artery (LCx), there is no collateral flow (no pressure gradient exists across the collateral bed). The LCx

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2. Methods

2.1. Experimental model

We used our modification of the Folts model [6] as described previously with an additional ultrasonic flowmeter on the LAD as well as the LCx [1]. The investigation was in accordance with UK Home Office regulations and with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No.85-23, revised 1996). Seven beagle dogs (weight range 12–17 kg) of either sex, were premedicated with acepromazine (0.2 mg/kg i.v.) followed by sodium pentobarbitone (20 mg/kg i.v.). Supplementary barbiturate anaesthesia (3 mg/kg i.v.) was administered at 30-min intervals. Positive pressure ventilation was via a Manley volume cycled ventilator with a 1:2 N₂O/O₂ mixture.

A left thoracotomy was performed and the heart suspended in a pericardial cradle. A silastic catheter was inserted and secured in the left atrial appendage for later injection of radioactive microspheres. An ultrasonic transit time flowmeter (Transonic) flow transducer was placed around the left anterior descending branch of the left coronary artery to act as a normal reference. The circumflex branch of the left coronary artery was dissected along a length in the atrioventricular groove. Around this artery were placed, in series going from proximal to distal: (1) another Transonic flow transducer; (2) a tight artificial stenosis as previously described [1], which was deemed sufficiently tight if a pressure gradient was established across the collateral bed; this stenosis was not sufficiently tight to cause occlusion of the artery during any part of the experiment; (3) a fine Teflon catheter (Abbocath, Abbott Ireland Ltd.) to measure the pressure distal to the stenosis and to allow calculation of pressure gradient (arterial pressure minus distal coronary pressure); (4) a ligature to allow occlusion of the artery in order to establish zero flow values.

Crushing the LCx with a haemostat, with the stenosis still in place induced platelet thrombus formation.

- Fig. 1. Relationship between proximal and distal circumflex (LCx) and left anterior descending (LAD) coronary artery and collateral flows (left) with no stenosis and (right) tight stenosis on the LCx. Collateral flow with the stenosis is assumed to be supplied entirely from all parallel arteries represented by a single conduit, labelled b. Flows measured by flowmeter on epicardial arteries: $a_1$ = LCx without stenosis, $a_2$ = LCx flow with stenosis; $b_1$ = parallel coronary flow (LAD + right coronary artery (RCA)) without stenosis, $b_2$ = LAD + RCA flow with stenosis. Flows measured with the microsphere technique: $c_1$ = tissue flow to LCx area with no stenosis; $d_1$ = tissue flow to LAD and RCA areas with no stenosis; $q$ = collateral flow with stenosis; tissue flow to LCx area with stenosis = $a_2 + q$. Pressures: $P_a$ = arterial pressure transmitted to epicardial coronary arteries with no stenosis. $P_c$ = LCx coronary pressure distal to stenosis. Collateral resistance with no stenosis is unknown. Collateral resistance with stenosis = $(P_a - P_c)/q$. A second situation similar to the right-hand panel, stenosis + thrombosis yields third values $a'_1$, $b'_1$, $c'_1$, $d'_1$, and a second value for $q$. Flowmeter value equals regional circumflex coronary blood flow using microspheres ($a_1 = c_1$), and likewise left anterior descending artery (LAD) flowmeter flow should be equal to microsphere flow ($b_1 = d_1$). The application of a tight artificial stenosis on the LCx establishes a sufficient pressure gradient (arterial pressure minus peripheral coronary pressure) across the collateral bed to produce flow through native collateral vessels. The peripheral coronary pressure needs to be clearly below the arterial level for such a pressure drop from arterial pressure to occur. The change in microsphere flow is less than the decrease in LCx flowmeter flow by the amount of the collateral flow contribution ($q$) to the LCx from the parallel coronary arteries. Thus, the measured LCx microsphere flow value will be equivalent to $c_1 = a_2 + q$ (Fig. 1, right). Unfortunately, it is not possible, for reasons given below, to compute the total tissue flow of each arterial bed from microspheres. The microspheres flows are therefore, large samples of this flow normalised to mass of tissue. $c_2$ has units of ml/min/g tissue and $a_2$ is in ml/min. However, reference back to the values in the unrestricted artery (Fig. 1, left) allows collateral flow to be computed from:

$$q = c_2 - a_2 \cdot c_1 / a_1$$

A second value during thrombosis could be obtained from $c_2 - a_2 \cdot c_1 / a_1$, enabling us to achieve our objective of measuring the response of the collateral vessels to the presence of thrombosis.
2.1. Measurement of haemodynamic variables

LCx and LAD flows were measured with a Transonic transit time ultrasonic flowmeter (Transonic Systems Inc., USA). The purpose of the LAD flowmeter was to observe to what extent collateral flow from LAD to LCx registers as an LAD flow increase. A standard three-limb ECG, arterial pressure (Statham P23Db pressure transducer) and coronary venous pressure (from the coronary sinus) were measured continuously on a computer via a MacLab/8s analogue to digital converter with built in filters for signal conditioning.

2.1.1. Measurement of haemodynamic variables

LAD blood flow was measured with an LAD flowmeter connected to its output. The purpose of the LAD flowmeter was to observe to what extent collateral flow from LAD to LCx registers as an LAD flow increase. A standard three-limb ECG, arterial pressure (Statham P23Db pressure transducer) and coronary venous pressure (from the coronary sinus) were measured continuously on a computer via a MacLab/8s analogue to digital converter with built in filters for signal conditioning.

2.1.2. Measurement of regional blood flow (radioactive microsphere technique) [4]

Regional blood flow measurements were achieved with the use of 15.5±0.1 μm NEN-TRAC radioactive microspheres (NEN™ Life Science Products, Boston, MA), suspended in 10% dextran and made up to volume (10 ml) with 0.9% saline solution. About 3×10⁶ microspheres labelled with any one of ¹¹¹Ce, ¹⁰³Ru, or ¹¹¹Sn (chosen at random and variable order) were administered into the left atrium [1]. Reference sample collection from a femoral (iv) 100 µl sample of blood was measured simultaneously in a min / g. The radioactivity of the heart and reference and myocardial sample counts after corrections to the flowmeter reading. Collateral flow due to constriction by the stenosis and from the LCx and LAD coronary arteries, respectively [1].

The ventricle was sliced post-mortem perpendicular to the long axis of the left ventricle (The atria and right ventricles were removed and discarded. The left ventricle was fixed in 10% formaldehyde solution prior to analysis). The regions of left ventricle supplied by the LAD or LCx were separated post mortem. UV light was applied to each cross-sectional myocardial slice-LCx artery (yellow), LAD (blue), mixed tissue (green); other perfusion territories (colourless). Maps were made to permit regional flow of each weighed piece to be ascertained after radioactive counting. Each counting tube contained at least 0.5 g of tissue, ensuring that no counted piece contained less than 400 spheres [7].

The post-mortem injection of fluorescent spheres into the respective arterial beds allowed delineation of the perfusion area only of that portion of the vessel distal to the fluorescent sphere injection sites.

2.2. Experimental protocol

Flow through the stenosis section continued throughout the experiment as recorded by the circumflex artery ultrasonic flowmeter. Three radioactive microsphere measurements were made during the first three phases of the experiment (example in Fig. 2):

(i) No stenosis (control phase). Microspheres injected in steady state
(ii) Tight stenosis-basal circumflex flow decreased by 10–60%. Microspheres injected in steady state less than 30 min after (i)
(iii) Tight stenosis plus thrombosis characterised by cyclical reductions (CFRs) in coronary blood flow [8]. We injected microspheres at a time of full steady flow before stenosis resistance rose with thrombus growth [9], less than 30 min after (ii)
(iv) 100 µg/kg of 170809 was injected to make sure that cyclic flow reductions were abolished by platelet inhibition [10]

2.3. Fluorescent and radioactive microsphere analysis

Any areas of myocardium with no stain (fluorescence) were discarded. Where such areas occurred, they accounted for less than 5% of total left ventricular mass. In areas of myocardium where vessels from LCx and LAD beds interdigitate, it is impossible to completely separate prospective regions of interest. In our tissue samples, these areas of mixed tissue, appearing green under UV light (yellow plus blue fluorescence), were discarded (about 5–10% of total tissue). Thus the counted tissue represents only a large sample (normalised for tissue mass) of the total flow measured by the flowmeter. It was therefore necessary to assign an equivalent flow value in ml/min/g to the flowmeter reading. Collateral flow due to constriction by the stenosis and on subsequent thrombosis was obtained from c₂ − a₂ · c₁/a₁ for the stenosis and from c₄ − a₄ · c₃/a₃ for stenosis plus thrombosis, both in ml/min/g.

Vascular resistances to perfusion territories of interest were based on radioactive measurements normalised for tissue mass and computed as follows: Collateral resistance = pressure gradient across the collateral vessels, corresponding to mean arterial pressure (P_A) minus distal coronary pressure (P_C) divided by the calculated collateral flow, q (Fig. 1). Distal circumflex resistance = distal coronary pressure (P_C) minus coronary venous pressure (P_v) divided by the circumflex regional blood flows (microspheres, c₁, c₂, c₃). Stenosis resistance (R_g) = mean arterial...
Fig. 2. Chart recording of one experiment, showing the changes in haemodynamics in the four phases indicated. $P_a =$ mean arterial blood pressure, $P_c =$ pressure recorded from a cannula in the LCx, distal to the stenosis, $P_v =$ venous pressure in the coronary sinus. LCx and LAD flows were recorded in the proximal epicardial arteries (proximal to the stenosis for the LCx) with ultrasonic transit time transducers.

3. Results

3.1. Effects of a tight circumflex artery stenosis on systemic and coronary haemodynamics

These are presented in Table 1 (mean±S.E.M.) and a sample tracing in Fig. 2. The tight stenosis on the LCx resulted in a 36±6% decrease in basal epicardial arterial circumflex flow from 25.5±3.4 to 15.8±3.2 ml/min ($n = 7$; $P<0.01$). This significant decrease in flow was associated with a similar fall in distal coronary pressure, 105.9±6.1 to 62.1±9.4 mmHg ($n = 7$; $P<0.02$). The stenosis was not associated with any consistent changes in blood flow through the LAD, recorded by flowmeter (Fig. 2, panel 2 shows an example of an increase). This flow value increased in five but decreased in two experiments (14.7±1.4 to 18.8±2.6 ml/min; NS). The stenosis did not cause any discernible general systemic effects as evidenced from the mean arterial pressure and heart rate (Table 1).
3.2. Effects of platelet thrombosis on components of circumflex arterial flow and resistance

3.2.1. Stenosis flow and resistance

CFRs are shown in Fig. 2, 3rd panel. With residual thrombus after embolisation, the stenosis+thrombus resistance (Fig. 3) was higher (4.7±1.1 mmHg/ml/min) compared to stenosis alone (3.6±0.9 mmHg/ml/min) (n = 7; P < 0.03).

3.2.2. Tissue LCx flow and vascular resistance

Regional blood flow to myocardium perfused by the LCx (microspheres) was little changed after establishment of the stenosis around the circumflex coronary artery, despite the decrease in proximal LCx flow (Table 1). This indicates a flow contribution from a collateral source (i.e. recruitment of native collaterals) due to tight stenosis. After induction of thrombosis in the constricted LCx artery, flow significantly decreased in all seven experiments (P = < 0.05; Table 1). These flow changes were associated with a significant decrease in distal LCx vascular resistance, from 162.2±22.0 (control) to 94.41±23.41 with stenosis, as expected from autoregulation in response to reduced perfusion pressure. The subsequent increase to 117.0±28.6 with stenosis+thrombus (mmHg/ml/min/g), is consistent with previous observations [1] but did not reach statistical significance in this series using Dunn’s test.

3.3. Effects of stenosis and thrombosis on collateral flow and resistance

Positive values for collateral flow (ml/min/g) to the LCx region of supply, were obtained following application of the stenosis and then stenosis+thrombus (Fig. 4), from 0.23±0.03 to 0.15±0.05 ml/min/g (NS). Thrombosis caused a fall in collateral flow in five experiments with little change in the other two. However, the calculated resistance of the collateral vessels (Fig. 5), increased significantly with stenosis plus thrombosis from 187.6±18.2 with stenosis to 1069±544 for stenosis+thrombus (mmHg/ml/min/g; P < 0.02). The observed increase in collateral resistance with thrombosis was partly

Table 1
Mean results (±S.E.M.)

<table>
<thead>
<tr>
<th>Phase of experiment</th>
<th>Units</th>
<th>Control</th>
<th>Stenosis</th>
<th>P (control vs. stenosis)</th>
<th>Stenosis + thrombosis</th>
<th>P (stenosis vs. + thrombosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (P_a)</td>
<td>mmHg</td>
<td>106.0±5.6</td>
<td>107.2±4.9</td>
<td>NS</td>
<td>105.8±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Distal coronary pressure (P_d)</td>
<td>mmHg</td>
<td>105.9±6.0</td>
<td>62.1±9.3</td>
<td>&lt;0.05</td>
<td>56.4±5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary venous pressure (P_v)</td>
<td>mmHg</td>
<td>12.2±1.0</td>
<td>11.8±1.3</td>
<td>NS</td>
<td>11.3±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>beats/min</td>
<td>150.4±7.6</td>
<td>153.7±8.5</td>
<td>NS</td>
<td>155.6±8.2</td>
<td>NS</td>
</tr>
<tr>
<td>P_a–P_v</td>
<td>mmHg</td>
<td>−</td>
<td>47.8±7.5</td>
<td>−</td>
<td>49.6±5.8</td>
<td>NS</td>
</tr>
<tr>
<td>P_a–P_c</td>
<td>mmHg</td>
<td>94.7±5.8</td>
<td>95.3±5.0</td>
<td>&lt;0.02</td>
<td>94.6±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>LCx flow (microspheres) (c_1,c_2,c_3)</td>
<td>ml/min/g</td>
<td>62.6±0.07</td>
<td>60.1±0.08</td>
<td>NS</td>
<td>0.47±0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LCx flow (flowmeter) (d_1,d_2,d_3)</td>
<td>ml/min</td>
<td>25.5±3.4</td>
<td>15.8±3.2</td>
<td>&lt;0.01</td>
<td>12.7±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>LAD flow (microspheres) (a_1,a_2,a_3)</td>
<td>ml/min/g</td>
<td>0.59±0.05</td>
<td>0.67±0.07</td>
<td>NS</td>
<td>0.54±0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LAD flow (flowmeter) (b_1,b_2,b_3)</td>
<td>ml/min/g</td>
<td>14.7±1.4</td>
<td>18.8±2.6</td>
<td>NS</td>
<td>19.7±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Collateral flow</td>
<td>ml/min/g</td>
<td>−</td>
<td>0.23±0.03</td>
<td>−</td>
<td>0.15±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis resistance</td>
<td>mmHg/ml/min</td>
<td>−</td>
<td>3.56±0.87</td>
<td>−</td>
<td>4.66±1.11</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>LCx flow resistance</td>
<td>mmHg/ml/min/g</td>
<td>162.2±22.0</td>
<td>94.4±25.4</td>
<td>&lt;0.001</td>
<td>117.0±28.6</td>
<td>NS</td>
</tr>
<tr>
<td>Collateral resistance</td>
<td>mmHg/ml/min/g</td>
<td>−</td>
<td>187.6±18.2</td>
<td>−</td>
<td>1069±544</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LAD resistance</td>
<td>−</td>
<td>168±16.9</td>
<td>155±19.7</td>
<td>NS</td>
<td>188±23.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*No gradients detected. P calculated from Wilcoxon signed-rank test. Other P values calculated from Dunn’s multiple comparison test if Friedman statistic < 0.05.

Fig. 3. Resistance (mmHg/ml/min) across the stenosed epicardial segment of the LCx. Left, stenosis only; right, stenosis + platelet thrombus. The open squares represent means±S.E.M. The lines connect pairs of measurements for each individual experiment.
method for measuring collateral flow in the presence of a stenosis only (open) as opposed to in the presence of an occlusion. It is necessary to calculate collateral flow indirectly by using the difference between tissue and proximal flowmeter flow values, comparing control and stenotic conditions. Unfortunately there is no absolute method for comparison.

It has been suggested [11] that native collaterals in the dog heart are not maximally dilated immediately after an acute coronary occlusion, but that there is a progressive dilation of these vessels for at least 15 min. Their study did not make any measurements in the presence of a prior (acute) critical stenosis on the coronary artery supplying the collateral dependent bed. If, as our data suggests, there is already recruitment of pre-existing native collaterals with such a stenosis, this may have some bearing on the failure to discern a vasoconstrictive effect of thrombus during maximal ischemic vasodilation. The time-scale during which pre-existing native collaterals become maximally dilated, after abrupt occlusion following acute critical constriction of the epicardial artery supplying the collateral dependent zone, has not been determined to our knowledge. Previous studies have documented increasing collateral flow to the ischemic zone at variable time intervals after abrupt occlusion [12,13]. Whilst there is controversy surrounding the exact time profile of post-occlusive variations in collateral flow [12±17], there is a general consensus that collateral flow increases in the first few minutes post-occlusion [18]. Invariably these studies fail to provide a measure of collateral resistance.

Our observations do not apply to the more mature collaterals that develop in response to prolonged ischemic stimuli and involve a process of vessel remodelling [19]. Not only are these vessels different structurally, but there is evidence that they are subject to different regulatory mechanisms [11,20]. The native collateral network in the dog heart is predominantly epicardial in origin although endocardial connections are known to exist [21,22]. Schaper [23] described these native vessels as small arterioles, averaging 40 \( \mu \)m in diameter, thin-walled, with only one or two smooth muscle layers.

The response of the collateral network to purely mechanical factors irrespective of the status of the myocardium was demonstrated by Kemp et al. [24] who showed that a segment of a coronary artery distal to an induced obstruction could be filled by a pressure gradient after the obstruction was removed. Evidence of collateral flow during partial circumflex occlusion has also been found [25]; this was detected by an electromagnetic flow probe sited on a distal branch with progressive acute constriction of the central circumflex artery over a period of 6 h. This retrograde flow was apparent only after peripheral coronary pressure had decreased to the levels reported in the present study.

Unfortunately in the present study, the ‘thrombosis’ and ‘no-thrombosis’ periods cannot be randomised; thrombosis
always followed no thrombosis. In a previous series of experiments, time controls showed that our observations during thrombosis were not due to deterioration of the experimental preparation [1]. We also tried to minimise the time between the no thrombus and thrombus measurements to an absolute minimum, just 30 min or less. This was desirable for two reasons, (1) to minimise any possibility of a deteriorating preparation affecting our results and, (2) to show that the observed effects during thrombosis are apparent a short time after damage of the artery is induced.

In previous experiments using complete occlusion instead of stenosis [1], there was no difference in flow and resistance of the collateral vessels supplying the maximal ischæmically diluted circumflex bed, before and after induction of platelet-rich thrombosis. It is possible that the vasoconstrictive effect of platelet thrombus on these ‘native’ collateral vessels was masked in those experiments by the vasodilatory response to arterial occlusion. In the present study, autoregulation is preserved in the LCx microcirculation as evidenced from the maintenance of tissue (microsphere) flow when perfusion pressure ($P_c$) decreased on application of the stenosis (Table 1).

The observation that the effects of thrombus may extend to the collateral vessels is unexpected because these collaterals originate from vessels remote to the site of the main thrombus. The observed increase in collateral resistance cannot be attributed to any consistent change in the pressure and flow components of this resistance calculation. One is then left with no option but to attribute the resistance increase to a reduction in lumen diameter, i.e. vasoconstriction. Native collaterals although thin-walled with apparently very little smooth muscle [23] are capable of vasomotion in response to neurohumoral [26] and pharmacological stimuli [20]. Previous studies have demonstrated that native [11,20] and mature [27,28] collaterals retain a vasodilatory capability. However, several studies have failed to show a vasoconstrictive response in native collaterals, after sympathetic stimulation [29] or with α-adrenoreceptor agonists [20]. This has been attributed to an absence of functioning α-adrenergic receptors [30], and/or differences in morphology of collaterals compared to that of ‘normal’ arterioles.

Mature collaterals have been shown to constrict in response to physiological concentrations of platelet derived mediators including serotonin (5HT), catecholamines, thromboxane and platelet-activating factor [31,32]. However, the response of native collaterals to these agents is not so clear cut. It has been suggested that the response of these vessels to 5HT is dependent on several factors including the size of the collateral vessels and the receptor sub-population [33]. In the dog, collateral vessels <100 μm dilate in response to 5HT. Larger vessels constrict or show no dilatory response to 5HT [33]. It has also been suggested that ultimately the response of microcirculatory vessels to 5HT may depend to some extent on a balance between responses mediated via various receptor subtypes, vasoconstriction mediated via $\text{5HT}_2$ receptors on vascular smooth muscle and vasodilation via $\text{5HT}_1$ receptors in the endothelium, involving nitric oxide release. No inference can be drawn about the predominant size of the collateral vessels, or on receptor sub-populations in the studies reported herein. This is relevant to the variability in response of coronary vessels to catecholamines due to their size [26]. This heterogeneity of response of the native collaterals is perhaps borne out by the observations of an almost complete ‘shut-down’ (large increase in resistance) of the collaterals in four of the experiments (Fig. 5). In two experiments on the other hand, the collateral resistance increases were much smaller. The mechanisms by which these differences may occur, and the phenomenon of ‘remote’ coronary vasoconstriction during thrombosis, require further investigation.

Acknowledgements

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References