Effect of Proximal and Distal Coronary Pressure Change on the Resistance of Stenotic Coronary Segment

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SUMMARY

While dynamic changes in the resistance of stenotic coronary segments were recently proposed by several investigators, the mechanisms of these changes are obscure. This study was conducted to correlate changes in coronary pressure distal to the stenosis to dynamic changes in the stenosis resistance in the canine heart. Coronary pressure distal to the stenosis was raised by either proximal aortic pressure elevation or intracoronary blood infusion distal to the stenosis. The pressure rise resulted in a significant fall in the stenosis resistance. Distal coronary pressure drop induced by phlebotomy or removal of blood from the distal coronary bed caused the reverse effects on resistance. Linear regression analysis revealed a close relationship between changes in distal coronary pressure (ΔDCP) and those in resistance of the stenotic coronary segment (ΔRL) represented by the following equation; ΔRL (dyne·cm⁻⁴·sec×10⁻³)=0.50×[ΔDCP (mmHg)]−6.0×10⁻², r=0.86, p<0.01. The results suggest that dynamic changes in stenosis resistance appear largely to be a function of the pressure changes distal to the stenosis.

Additional Indexing Words:
Distal coronary pressure  Stenosis resistance  Coronary blood flow

Traditionally, it has been generally considered that coronary stenoses are fixed, and that passive lesions do not respond to hemodynamic changes. With constant flow, coronary perfusion pressure distal to the stenotic segment...
depends solely on the pressure proximal to the stenosis. However, several recent reports raised the possibility that dynamic changes in stenosis resistance could be induced by various vasodilatory and constrictory stimuli. The presence of severe coronary stenosis caused stenosis resistance to increase in response to isoproterenol infusion, exercise and brief myocardial ischemias. Of the many possible explanations of the dynamic resistance changes, distal coronary pressure seems to play a role in the phenomenon. However, there have been no reports of detailed investigations of the relationship between distal coronary pressure and stenosis resistance. The purpose of the present study was to estimate the quantitative relationship of stenosis resistance to coronary pressure distal to the stenosis using varying distal coronary pressures in the presence or absence of changes in coronary pressure proximal to the stenosis.

**Methods**

Healthy mongrel dogs of either sex weighing 15–20 Kg were anesthetized with sodium pentobarbital (25–30 mg/Kg, i.v.). Respiration was controlled to maintain blood gases within normal ranges by volume adjustment and supplemental oxygen. Small polyethylene catheters were inserted and positioned in the inferior vena cava and the ascending thoracic aorta for blood withdrawal and systemic pressure monitoring, respectively. Left thoracotomy was performed and the heart was suspended within a pericardial cradle. Approximately 2.5 cm of the left circumflex artery (LCx), from its origin to the first major branch, was dissected free from surrounding tissues and an electromagnetic flow probe and a pneumatic occluder cuff were placed around the vessel. A thick cotton string (diameter 1.0 mm, length 5 cm) for producing coronary stenosis was loosely positioned around the vessel between the flow transducer and the cuff. A small, polyethylene end-hole catheter was inserted into a small branch of the LCx distal to the occluder cuff for coronary pressure monitoring. An umbilical tape was placed around the descending thoracic aorta to raise proximal aortic pressure by 20–50 mmHg. The dog received a dose of 5,000–7,000 units of heparin intravenously just before coronary catheterization and 1,000 units every 30 min thereafter. In order to verify that the coronary catheter did not impair the flow response, the LCx was occluded for 15 sec before and after inserting the coronary catheter and the hyperemic response observed.

*Changes in proximal coronary pressure:*

Ten dogs were used for this experiment. After baseline flow and pressures were recorded, the LCx was constricted with a cotton string at a degree which nearly eliminated reactive hyperemia: peak reactive hyperemia flow
rate after 15 sec of coronary occlusion was less than 120% of the preocclusion flow rate. After 5 min to establish a new steady state, the hemodynamic parameters were recorded, following which the descending thoracic aorta was constricted by the umbilical tape to elevate blood pressure. After recording of coronary flow and distal coronary and proximal aortic pressures were performed, the umbilical tape was completely released to allow aortic pressure to return to the control level. After 30 min, blood pressure was lowered by 15-50 mmHg by removal of blood from the inferior vena cava via the catheter.

Changes in distal coronary pressure:
This experiment was conducted in 7 dogs using surgical preparations similar to those described above except that the LCx of the dog received one more coronary catheter, 1.0 mm in outer diameter, distal to the first catheter as illustrated in Fig. 1. In order to verify that the second coronary catheter did not affect the distal coronary resistance, coronary flow response to a 15 sec occlusion of the LCx was observed before and after inserting the coronary catheter. When the difference between peak flow rate during reactive hyperemia before and after insertion of the coronary catheter was greater than 15%, the results were not included in the data. The proximal end of the second coronary catheter was connected to a Harvard constant infusion pump. Coronary pressure distal to the stenosis was varied by blood infusion into or blood withdrawal from the LCx with the pump. In order to elevate distal coronary pressure, approximately 25 ml of arterial blood were removed anerobically from the aorta just before use and infused into the LCx via the second coro-

Fig. 1. Schematic illustration of the instrumentation. Coronary stenosis was produced using a thick cotton string.
nary catheter using the pump at a rate of 4.1 ml/min. The lowering of distal coronary pressure was achieved by removing blood from the LCx via the coronary catheter at a rate of 4.1 ml/min with the pump. Hemodynamic data were obtained during steady state before and 3 min after the beginning of blood infusion or withdrawal.

When the experiments were completed, an intracoronary injection of Evans blue marked the myocardium under study and the dog was killed with an intracardiac injection of a saturated KCl solution. The weight of the dye-stained myocardium served as the basis for expressing coronary flow rates. The resistance of coronary segments was calculated as follows:

i) Resistance of small coronary vessels \( (RS, \text{ dyn cm}^{-5} \cdot \text{sec} \times 10^{-3}) = \frac{\text{distal coronary pressure (mmHg)} \cdot \text{coronary blood flow to the distal vascular bed of the LCx (ml/min per 100 Gm)}}{80} \)

ii) Resistance of large coronary segment \( (RL, \text{ dyn cm}^{-5} \cdot \text{sec} \times 10^{-3}) = \frac{\text{pressure gradient across the stenosis (mmHg)} \cdot \text{blood flow at the site of flow probe (ml/min per 100 Gm)}}{80} \)

iii) Total coronary resistance \( (RT, \text{ dyn cm}^{-5} \cdot \text{sec} \times 10^{-3}) = RS + RL \)

Statistical assessment of the results employed a repeated-measurements analysis of variance. Group data are expressed as mean±SD.

**Results**

Changes in proximal coronary pressure:

Coronary constriction did not affect heart rate and aortic pressure, but decreased coronary blood flow and distal coronary pressure from 88±11.9 to 50±9.1 ml/min per 100 Gm and from 86±13.2 to 46±14.9 mmHg, respectively. For coronary resistance, RT increased from 85.6±10.4 to 145.6±37.6 dyn cm⁻⁵·sec·x·10⁻³ and RS decreased from 81.6±10.4 to 75.2±25.6 dyn cm⁻⁵·sec·x·10⁻³, resulting in a significant rise in RL from 4.0±0.8 to 74.4±22.4 dyn cm⁻⁵·sec·x·10⁻³. The effects of aortic constriction on coronary hemodynamics in the dog with coronary stenosis are summarized in Table I. Fig. 2 illustrates actual records of proximal coronary pressure changes. The left panel shows the effects of aortic constriction and the right shows those of aortic pressure fall caused by rapid removal of blood. Aortic constriction raised the proximal aortic pressure by approximately 40%, coronary blood flow by 60%, coronary pressure distal to the stenosis by 50% and decreased heart rate by 9%. The pressure gradient across the coronary stenosis increased from 46±11 to 58±16 mmHg. However, a greater increase in coronary flow than in pressure gradient produced a significant fall in RL. Conversely, phlebotomy decreased aortic pressure by 28%, coronary blood flow by 14% and distal coro-
Table I. Effect of Proximal Coronary Pressure Changes on Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>HR (beat/min)</th>
<th>AoP (mmHg)</th>
<th>DCP (mmHg)</th>
<th>CBF (ml/min/100 Gm)</th>
<th>Coronary vascular resistance (dyne·cm⁻²·sec×10⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RT</td>
</tr>
<tr>
<td>Before aortic constriction</td>
<td>159±21</td>
<td>91±17</td>
<td>47±14</td>
<td>50±9.1</td>
<td>146±37.3</td>
</tr>
<tr>
<td>During aortic constriction</td>
<td>148±20**</td>
<td>127±25**</td>
<td>69±22**</td>
<td>80±14.3**</td>
<td>130±31.4**</td>
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<tr>
<td>Before phlebotomy</td>
<td>156±18</td>
<td>113±23</td>
<td>68±14</td>
<td>67±12.9</td>
<td>138±33.0</td>
</tr>
<tr>
<td>During phlebotomy</td>
<td>153±16</td>
<td>81±13**</td>
<td>39±7*</td>
<td>58±10.1</td>
<td>114±25.6*</td>
</tr>
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</table>

Data are expressed as mean±SD.

HR=heart rate; AoP=aortic pressure; DCP=distal coronary pressure; CBF=coronary blood flow at the site of flow probe; RT=resistance of total circumflex artery bed; RS=resistance of small coronary artery; RL=resistance of large coronary segment with stenosis.

Significantly different from values before each intervention at levels of **p<0.01 and *p<0.05.

Fig. 2. Original records of effects of aortic constriction (left panel) and blood withdrawal from the aorta (right panel). RL before and during aortic constriction were 65.8 and 50.7 dyne·cm⁻²·sec×10⁻³, respectively. Phlebotomy increased RL from 54.3 to 72.2 dyne·cm⁻²·sec×10⁻³.

Coronary pressure by 43%, but did not affect heart rate significantly. Systemic pressure reduction caused a fall in RT and RS and a 12% increase in RL.

Changes in distal coronary pressure:

RL increased to 76.8±39.2 dyne·cm⁻⁵·sec×10⁻³ with coronary constriction in association with decreases in coronary blood flow and distal coronary pressure by 64 and 53%, respectively. Heart rate and aortic pressure did
Table II. Effect of Distal Coronary Pressure Changes on Hemodynamics

<table>
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<tr>
<th></th>
<th>HR (beat/min)</th>
<th>AoP (mmHg)</th>
<th>DCP (mmHg)</th>
<th>CBF (ml/min/100 Gm)</th>
<th>Coronary vascular resistance (dyne·cm⁻²·sec×10⁻³)</th>
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<td></td>
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<td></td>
<td>RT</td>
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<tr>
<td>Before blood infusion</td>
<td>141 ± 16</td>
<td>93 ± 8</td>
<td>48 ± 12</td>
<td>50 ± 8.9</td>
<td>153 ± 40.0</td>
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<tr>
<td>During blood infusion</td>
<td>141 ± 16</td>
<td>92 ± 9</td>
<td>57 ± 12**</td>
<td>46 ± 6.8</td>
<td>115 ± 25.6**</td>
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<tr>
<td>Before blood withdrawal</td>
<td>139 ± 19</td>
<td>91 ± 7</td>
<td>52 ± 9</td>
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<td>129 ± 21.6</td>
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<tr>
<td>During blood withdrawal</td>
<td>139 ± 19</td>
<td>90 ± 10</td>
<td>41 ± 10**</td>
<td>65 ± 15.8</td>
<td>138 ± 22.4</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.
HR = heart rate; AoP = aortic pressure; DCP = distal coronary pressure; CBF = coronary blood flow at the site of flow probe; RT = resistance of total circumflex coronary artery bed; RS = resistance of small coronary artery; RL = resistance of large coronary segment with stenosis.
Significantly different from values before each intervention at levels of ** p<0.01 and * p<0.05.

Fig. 3. Original records of effects of blood infusion into and withdrawal from the LCx distal to the stenosis. Blood infusion decreased RL from 64.8 to 51.2 dyne·cm⁻²·sec×10⁻³, and withdrawal increased RL from 70.4 to 80.0 dyne·cm⁻²·sec×10⁻³.

not change. Results of blood infusion or withdrawal are summarized in Table II. Fig. 3 shows original records of distal coronary pressure changes. The left panel indicates the effects of blood infusion and the right shows those of blood withdrawal from the distal coronary artery. Blood infusion into the LCx caused distal coronary pressure to increase in the absence of significant changes in heart rate, aortic pressure and coronary blood flow at the site of the flow probe. Coronary blood flow distal to the infusion catheter, which was the sum of proximal coronary blood flow and infused blood, increased to 65±9.0 ml/
Fig. 4. Relationship between changes in distal coronary pressure (ΔDCP) and those in resistance of stenotic coronary segment (ΔRL). In the figure the interventions are represented by the symbols: ●, aortic constriction; ○, phlebotomy; △, blood infusion into the LCx; ×, blood withdrawal from the LCx.

min per 100 Gm. RL decreased by approximately 20% with blood infusion in association with almost constant RS, resulting in a marked reduction in RT. Withdrawing blood from the LCx decreased distal coronary pressure by approximately 20%. Coronary blood flow at the probe site increased by 12% but blood flow to the peripheral circumflex coronary bed was not affected since the rate of blood withdrawal from the vessel was the same as the increased flow rate at the probe site. This resulted in a 16% increase in RL in the presence of an insignificant decrease in RS. Heart rate and aortic pressure did not change significantly.

Fig. 4 represents the relationship between changes in distal coronary pressure (ΔDCP) and changes in resistance of the large coronary segment with stenosis (ΔRL). As a result of the superimposing interventions having directionally opposite effects on DCP compared to control values, which themselves varied, it was possible to examine these relationships over a wide range. Linear regression analysis revealed a close relationship represented by the following equation: ΔRL (dyne·cm⁻²·sec⁻¹·10⁻³) = 0.50·ΔDCP (mmHg)⁻⁶.0·10⁻², r=0.86, p<0.01.

DISCUSSION

The present study demonstrated that in the presence of a significant coronary stenosis, coronary pressure distal to the stenosis is of critical importance in determining the coronary resistance at the site of the stenosis. Raising blood
pressure proximal to, or blood infusion distal to the stenosis elevated the distal coronary pressure, resulting in a decrease in stenosis resistance. Lowering proximal coronary pressure, or withdrawing blood from the distal coronary bed caused the reverse effects on the resistance of the stenosis. Changes in distal coronary pressure by the above interventions closely correlated with alterations of stenosis resistance as represented in Fig. 4. It has been previously shown that resistance is related to the flow velocity through a stenosis, with resistance increasing directly with a rise in flow velocity. However, in the present study involving modification of proximal aortic pressure, since stenosis resistance decreased in association with a rise and increased with a fall in coronary flow, flow velocity change did not account for the change in stenosis resistance. Gould and Kelley observed with intracoronary injection of papaverine that the cross-sectional areas of the normal artery proximal and distal to the stenosis increased significantly during high flow, thereby causing the diameter of the stenosis to increase in association with an increase in the pressure gradient across the stenosis solely due to changes in stenosis geometry. While the dimensions of the normal coronary arteries were not measured, it is highly unlikely that an increased cross-sectional area of the normal artery adjacent to the stenosis was related to the phenomenon observed in the present study. Aortic constriction decreased heart rate by approximately 10 beats/min or 7%, which could cause a fall in stenosis resistance. However, our previous study revealed that changes in heart rate of 30 beats/min or 20% caused only a 4.2% change in RL (1.9 dyne cm$^{-5}$ sec$^{-1}$ x 10$^{-3}$). The magnitude of the resistance change was not large enough to explain the change caused by aortic constriction. Thus, it is unlikely that the change in heart rate was responsible for the increase in RL observed during aortic constriction. Raising proximal aortic pressure possibly increased the cross-sectional area of the coronary artery not only proximal to, but also distal to the stenosis. The elevation of pressure also lowered stenosis resistance in association with a significant increase in coronary blood flow. Reduction in aortic pressure caused the opposite effects on stenosis resistance, coronary blood flow and possibly the cross-sectional area of the adjacent normal coronaries.

Recent studies of the sympathetic regulation of coronary vascular tone have demonstrated that alpha adrenergic control plays a major role in large coronary arteries. Alpha adrenergic stimulation is powerful enough to reduce the cross-sectional area of large coronary arteries. An increase in pressure in the proximal aorta will suppress sympathetic tone through a baroreflex mechanism resulting in coronary dilation while a fall in pressure will have the opposite effect. However, it is also unlikely that alpha adrenergic control contributed to the stenosis resistance changes. The coronary artery site utilized
for measuring resistance of a large coronary segment (RL) was dissected free from the surrounding tissue, including the autonomic nerves. Furthermore, alpha adrenergic tone could not be affected in those experiments where distal blood flow was modified directly by blood infusion into or withdrawal from the distal coronary bed. Our previous studies revealed that a brief period of coronary occlusion\textsuperscript{15} and isoproterenol infusion\textsuperscript{5} caused stenosis resistance to increase and distal coronary pressure to decrease. We utilized a stenosis with a sharp orifice which caused resting coronary blood flow to decrease by approximately 40\%, whereas clinically observed coronary stenoses are of variable length. While a long stenosis produced a larger pressure drop through the stenosis than does a sharp orifice, the difference is most pronounced for a moderate stenosis and disappears when the stenosis becomes more severe.\textsuperscript{16} When an approximately 90\% stenosis is required to produce any reduction in coronary blood flow,\textsuperscript{8} the orifice and the long stenosis behave essentially identically.\textsuperscript{16} It was suggested that the wall elasticity of the artery contributed to changes in resistance.\textsuperscript{17} For an isolated carotid artery segment or flexible rubber tubing with an anatomically fixed stenosis, the calculated stenosis resistance was increased in association with a reduction of the distal pressure, while solid polyethylene tubing showed no significant changes in stenosis resistance due to alterations in distal pressure. Santomore and Walinsky\textsuperscript{18} have proposed that the reduction in distal coronary pressure causes a mechanical collapse of the wall at the stenotic segment of the coronary artery resulting in a passive narrowing of the segmental stenosis. Our results are very consistent with their assumption: an elevation of distal coronary pressure lowered the stenosis resistance and a fall in pressure raised the resistance. Thus, the present study confirmed their hypothesis and expanded it to include a quantitative estimation of changes in stenosis resistance as a result of changes in distal coronary pressure.

References


