Effects of Major Coronary Artery Stenosis on the Pressure-Flow Relationship of an Adjacent Intact Coronary Artery Branch in Isolated Supported Canine Left Ventricle

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SUMMARY

We investigated whether the relationship between the mean left anterior descending and septal coronary blood flow and the mean perfusion pressure varies with left circumflex coronary stenosis. We used excised, perfused canine heart preparations (n=10), in which variables to influence the myocardial oxygen demand and supply relation can be fairly well controlled. The results showed that coronary blood flow in the adjacent, non-stenosed coronary artery increased significantly following LCX stenosis; this increased flow was found at the same values of heart rate, left ventricular end-diastolic pressure and perfusion pressure, as those in the pre-ischemic state. Moreover, this increased flow was also observed when the values of peak left ventricular pressure and pressure-length loop area were similar between the pre-ischemic and ischemic states. Thus, contributions of neurohumoral factors or alterations in mechanical factors determining the myocardial oxygen demand and supply relation are negligible. This increased flow may be important in maintaining overall cardiac function in cases of acute coronary stenosis or coronary occlusion.

Additional Indexing Words:
Coronary resistance  Intercoronary reflex  Perfusion pressure-coronary flow relationship  Left ventricular pressure-length loop

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THE coronary flow of an intact major coronary artery has been reported to increase significantly following occlusion of an adjacent coronary artery.\textsuperscript{1,2,3,4,5,6} It should be noted, however, that many contributory factors are involved in this phenomenon and that variables such as heart rate, preload and afterload, which are known to influence coronary blood flow, have not been controlled in the previous intervention studies. Therefore, it is not yet clear whether the relationship between coronary pressure and coronary flow itself changes. In addition, this phenomenon has not yet been fully investigated in the presence of coronary artery stenosis alone.\textsuperscript{5,6} This problem seems to be quite important, because ischemia in man has been reported to be rarely initiated by total occlusion.\textsuperscript{7} The purpose of this study, therefore, was to investigate the coronary perfusion pressure-coronary flow relationship in non-stenosed left anterior descending and septal (LAD+S) coronary branches with and without stenosis of the left circumflex coronary (LCX) artery, with maintenance of a constant heart rate and preload throughout the experiment.

**METHODS**

1. **Preparation**

Mongrel dogs of both sexes, weighing between 15.2 Kg and 19.0 Kg, were used for the isolated heart preparations. Dogs were anesthetized with pentobarbital (30 mg/Kg, i.v.). The trachea was intubated and ventilation was maintained with a Harvard respiratory pump. After a bilateral thoracotomy in the third intercostal space, the heart was excised using the Langendorff perfusion method.\textsuperscript{8,9} Briefly, a Gregg-type cannula was inserted into the ascending aorta through the brachiocephalic artery and the distal part of the aorta was ligated. Coronary perfusion was maintained with blood from the femoral artery of a support dog through this cannula. The heart was then fibrillated with AC current and excised. The tip of the cannula was advanced into the ostium of the left main coronary artery, where it was tied securely in place with a silk thread. During surgical preparation, perfusion pressure was maintained between 70 and 100 mmHg. After the right coronary artery was ligated at its origin, the right ventricular free wall was removed, and the edge of the muscle was then ligated to prevent bleeding (Fig. 1).

A wide cannula was connected to a large, height-variable reservoir filled with saline and its temperature was kept constant at 37±0.5°C. By changing the height of this preload reservoir, we were able to adjust the left ventricular end-diastolic pressure to any desired level.
Fig. 1. Experimental schema. (a) shows coronary perfusion system of an excised heart, in which the preload reservoir and hydraulic afterload model were connected to the left atrium (LA) and the aorta, respectively.

(b) shows an excised heart preparation, in which left main coronary artery flow (LMCorF), left circumflex coronary (LCX) flow, segmental lengths in the LCX perfused area and left anterior descending perfused area (i.e., control area), and left ventricular pressure (LVP) were measured in the pre-ischemic and ischemic states. Myocardial ischemia was induced by coronary stenosis of the LCX artery ( ). EMF=electromagnetic flow probe; LCA=left coronary artery; AoP=aortic pressure; Rc=characteristic resistance component; L=inertial component; C=total arterial compliance component; Rp=total peripheral resistance component; PP=perfusion pressure. See text for details.

About 1.5 cm from the aortic valve, the aorta was cut and the hydraulic loading model was connected to the proximal portion of the aorta. This loading system consists of four components8,9): an inertial component (L), a total arterial compliance component (C), a characteristic resistance component (Rc) and a total peripheral resistance component (Rp). In the present study, we set the values of L, C and Rc constant at their physiologic values, i.e., L: 10 dyne sec² cm⁻⁵, C: 2×10⁻⁴ dyne⁻¹ cm⁵ and Rc: 0.2×10³ dyne sec cm⁻⁵. On the other hand, the values of Rp were varied throughout the experiment. We used five Rp values (i.e., Rp I: 16.1×10³, Rp II (control Rp): 10.5×10³, Rp III: 6.2×10³, Rp IV: 4.7×10³ and Rp V: 3.3×10³ dyne sec cm⁻⁵). After completion of these surgical preparations, the heart was defibrillated with DC current. The heart rate was held constant at 100–140 beats/min by bipolar electrical stimulation (Nihon Kohden, model SEN-7103 M) of the right atrium throughout each experiment. To measure regional dimensions, two pairs of miniature (2.0 to 2.5 mm in diameter) ultrasonic crystals were implanted roughly parallel to the minor axis and subendocardially (one pair at the center perfused by the LAD branch, and the other pair at the center perfused by the LCX branch).
Arterial pressure and arterial blood gas of the support dog were monitored and adjusted to within their physiologic ranges by means of blood transfusions, sodium bicarbonate or lactated Ringer's solution and by controlling ventilation and $O_2$ inhalation. We maintained the arterial $PO_2$ at 75–95 mmHg, $PCO_2$ at 34–46 mmHg, pH at 7.33–7.45 and hemoglobin concentration at 11–15 g/dl. Coagulation was prevented with heparin calcium (Eisai Co Ltd); 10,000 U i.v. initially and 5,000 U i.v. every hour thereafter.

A servo-controlled coronary perfusing system was used following defibrillation of the excised hearts. In this perfusion system, the difference between mean aortic pressure and mean perfusion pressure was within 2 mmHg in a steady state of hemodynamics.8) It should be noted, however, that the pressure drop due to the Gregg-type cannula was 2.0, 3.0 and 3.8 mmHg at flow rates of 60, 88 and 98 ml/min, respectively.

2. Measurements

Left coronary perfusion pressure (PP) was measured from the side arm of the perfusion line just before the Gregg-type cannula, using a strain gauge pressure transducer (Tokyo Sokki, MPU 0.5). The pressure drop through the cannula was disregarded in the present analysis of the coronary perfusion pressure-flow relationship. The zero-pressure reference was taken to be the middle level of the heart. Mean left coronary blood flow was measured with an extracorporeal type probe (3 mm ID, Nihon Kohden, type FF-030T) positioned on the perfusion line. Furthermore, a corporeal type probe (2 mm ID, Nihon Kohden, type FS-020T) was positioned near the origin of the LCX branch. The flow transducers were connected to an electromagnetic flowmeter (Nihon Kohden). The values of mean LAD+S blood flow (LADF) were calculated by subtracting the mean LCXF from the mean left coronary blood flow. The baseline coronary flow was measured by momentary occlusion of the distal part of each flow probe. Cardiac output was measured by collecting the amount of saline ejected during a 20 sec period. The left ventricular pressure and aortic pressure were also measured, as described above.

Pressures, flows and regional dimensions were recorded on a direct pen recorder (Sanei Sokki, 8 channel Rectigraph) and on magnetic tape (Sony Magnescale Inc, model UFR 71460 S).

3. Experimental conditions and protocol

Following implantation of the ultrasonic crystals, we set the mean aortic pressure at 100 mmHg at the Rp II value (pre-ischemic control condition) by adjusting the height of the preload reservoir containing saline. Thus, although left ventricular end-diastolic pressure was different from heart to heart
(3–12 mmHg, 6.9±1.3 mmHg), its value was kept constant throughout the experimental session. After observing 20–30 min of steady-state hemodynamics, we measured cardiac output, and recorded all the other variables. We then changed Rp in a stepwise fashion at approximately 3 min intervals in the order, Rp I, III, IV, V and II, and recorded all variables, as was done with the control Rp.

We then induced LCX stenosis by constricting the LCX branch with a screw driven metal clamp just distal to the flow probe at the LCX branch. Stenosis was adjusted so that LCXF was reduced to approximately 45% (33–58%) of the pre-ischemic value (at Rp II). About 5 min after LCX stenosis, a hemodynamic steady state was usually obtained. It is clear from previous experiments that this steady-state condition continues for at least 20 min, during which time our experimental protocol was completed. We sequentially changed the Rp value in the same way as had been done without LCX stenosis. Thus, we were able to obtain the coronary perfusion pressure-coronary flow relationships of LAD+S and LCX arteries in both pre-ischemic and ischemic states (n=6) within a relatively wider range of PPs.

Moreover, in additional experiments (n=4), we compared the mean LADF following LCX stenosis with that in the pre-ischemic state under the same hemodynamic conditions; the left ventricular end-diastolic pressure (7.5±1.5 mmHg), heart rate (120±4 beats/min) and mean aortic pressure (90.0±0.5 mmHg) were held constant throughout the pre-ischemic and ischemic states. Aortic pressure was adjusted by changing the value of Rp.

4. Data analysis

We used the following criteria to ensure that the preparation was stable during the experimental run. First, during the pre-ischemic and the ischemic states, the difference in cardiac output and peak left ventricular pressure, compared at the same control (Rp II), was within 5% in each run; however, we show only the first value obtained at Rp II. Second, after a 15-sec complete occlusion of the LCX artery, peak LCXF during reactive hyperemia was not less than 200% of that measured in the pre-ischemic control state.

We investigated the perfusion pressure (PP)-coronary flow relationships in each coronary artery, the mean PP/mean LADF and mean PP/mean LCXF at different values of Rp in the pre-ischemic and ischemic states, and the relationships between mean PP/mean LADF vs. mean PP, and mean PP/mean LCXF vs. mean PP. Since we did not measure PP distal to the stenosed LCX branch, the relationship between LCXF vs. PP does not indicate the characteristics of the stenosed LCX artery alone.

In this experimental series, we paid attention to the behavior of the
pressure-length loop in the non-ischemic LAD perfused area alone, because the behavior of the non-ischemic LAD area at different aortic pressures might be important in determining whether dysfunction of the ischemic area elicits increased function of the non-ischemic area, leading to changes in coronary resistance in the non-ischemic area. The pressure-length loop in the ischemic area following afterload change, was similar to results of previous studies.9) We expressed P-L loop areas at various values of Rp in the pre-ischemic and ischemic states as a percentage of the value obtained at Rp II without LCX stenosis in each experiment.

The statistical significance in cardiac output and peak left ventricular pressure between the pre-ischemic and ischemic states was determined by using a paired t-test at each Rp value. The significant difference in the perfusion pressure-coronary flow relationships, and the relationships between mean PP vs. mean PP/coronary flow in the pre-ischemic and ischemic states were analyzed as follows. Since the relationships between coronary blood flows and PPs at the LCX and (LAD+S) branches seemed to be linear under these experimental conditions, we used multiple linear regression methods to examine the relationships between the three independent variables, PP, coronary blood flow and LCX stenosis. Furthermore, by introducing indicator (dummy) variables,10) we eliminated the effects of individual differences between animals from the intervention study, which is valid because we changed values of Rp in all experiments in the same way under both non-ischemic and ischemic conditions. One example among the 6 experimental animals was arbitrarily taken as control, and therefore five dummy variables were necessary to avoid animal variations. Thus, coronary blood flows could be indicated by using PP and LCX stenosis as independent variables according to the model:

\[ y = b_0 + \sum_{i=1}^{5} b_i X_i + b_6 X_6 + b_7 X_7 + e \]  

where \( y \) is the mean coronary blood flow (ml/min) at each Rp value and \( b_0, b_1, b_2 \ldots b_7 \) are constants. In this expression, 
\[ \sum_{i=1}^{5} b_i X_i: \] sum of the dummy variables. This indicates the weighting due to animal variations in this experimental series.

\( X_6: \) independent variable taking the value of 0 in the absence of LCX stenosis, and 1 with LCX stenosis.

\( X_7: \) values of PP corresponding to each coronary flow.

\( e: \) random error.

The above equations can be rearranged as follows,

\[ y - \sum_{i=1}^{5} b_i X_i = b_0 + b_6 X_6 + b_7 X_7 + e \]
where \( y - \sum_{i=1}^{n} b_i X_i \) is the value of mean coronary blood flow or mean PP/mean coronary flow adjusted by animal variations. By using this equation, we can express the relationships between coronary flow vs. PP, taking into account the animal variations. This equation was also adopted for determining the relationship between calculated mean coronary vascular resistance (mean PP/mean LADF or LCXF) vs. mean PP. All data were expressed as mean±SEM, and significance was tested by t-statistics, taking as significant a p value less than 0.05.

**RESULTS**

1. The relationship between coronary blood flow and perfusion pressure in pre-ischemic and ischemic states

The LCXF was reduced by constricting the LCX artery from the pre-ischemic value of 64.0±10.3 ml/min to 29.6±2.6 ml/min (46.2%) at the same Rp II value. As a result, the values of the pressure-length loop in this perfused area decreased to 59.6±7.1% (p<0.001) of the pre-ischemic state values. Also, the cardiac output and peak left ventricular pressure values, decreased from 765±12 ml/min and 124.7±3.7 mmHg to 617±21 ml/min (p<0.001) and 106.0±4.3 mmHg (p<0.01) respectively, as shown in Table I.

Fig. 2 shows LADF in the ischemic state following LCX stenosis, during which mean aortic pressure, heart rate and left ventricular end-diastolic pressure were adjusted to almost the same value as the pre-ischemic state in order to examine whether coronary flow in the non-stenosed LAD+S arteries increases. As is clearly shown in Fig. 2, LADF increased following LCX stenosis, whereas LCXF decreased as a result of LCX stenosis. This trend was also found in the other 3 experiments [i.e., LADF, 116±7% (p<0.02), LCXF, 29±8% (p<0.01) (n=4) of values in the pre-ischemic state].

Fig. 3a shows the LCX perfusion pressure-coronary flow relationship

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Significant difference: * p<0.05, ** p<0.02, *** p<0.01, **** p<0.001.
Simultaneous tracings of pressures and flows without (left panel) and with LCX stenosis (right panel). Following LCX stenosis, LAD flow increased significantly from the pre-ischemic state value. Throughout the intervention, heart rate, perfusion pressure and left ventricular end-diastolic pressure were held constant. LVP = left ventricular pressure; AoP = aortic pressure; AoF = aortic flow; AoF = mean aortic flow; AoP = mean aortic pressure; Perf. P = mean perfusion pressure; LADF = mean LAD flow; LCXF = mean LCX flow.

Fig. 2. Simultaneous tracings of pressures and flows without (left panel) and with LCX stenosis (right panel). Following LCX stenosis, LAD flow increased significantly from the pre-ischemic state value. Throughout the intervention, heart rate, perfusion pressure and left ventricular end-diastolic pressure were held constant. LVP = left ventricular pressure; AoP = aortic pressure; AoF = aortic flow; AoF = mean aortic flow; AoP = mean aortic pressure; Perf. P = mean perfusion pressure; LADF = mean LAD flow; LCXF = mean LCX flow.

derived from overall experimental data (n=6) in pre-ischemic and ischemic states. Fig. 3b, though, shows the perfusion pressure-coronary flow relationship in the LAD+S branches. As shown in Fig. 3b, the relationship in the LAD+S branches shifted to the left following LCX stenosis. The following four equations were obtained (Table II):

1. \[ \text{LADF} = -40.60 + 17.63S + 0.85 \text{PP} \]
2. \[ \text{LCXF} = -0.54 - 21.87S + 0.49 \text{PP} \]
3. \[ \frac{\text{PP}}{\text{LADF}} = 2.714 - 0.439S - 0.003 \text{PP} \]
4. \[ \frac{\text{PP}}{\text{LCXF}} = 5.392 + 1.884S - 0.038 \text{PP} \]

where S = 1 for the data taken with LCX stenosis and S = 0 for the data taken without LCX stenosis (Units: LADF and LCXF, ml/min; PP, mmHg; PP/LADF and PP/LCXF; mmHg/ml/min, for significances of the parameters, see Table II. Abbreviations: LADF = mean LADF; LCXF = mean LCXF;
Fig. 3.  

a (upper): This figure shows the relationship between mean left circumflex artery flow (LCXF) and mean perfusion pressure (PP) before and after left circumflex artery stenosis. Following the stenosis of the left circumflex artery, the relationship shifted to the left, showing an increase in calculated mean coronary resistance. The perfusion pressure was measured proximal to the site of LCX stenosis. Corrected LCXF was derived from equation 2 in the text.

b (lower): This figure shows the relationship between mean left anterior descending and septal arterial blood flow (LADF) and mean perfusion pressure (PP) before and after left circumflex artery stenosis. Following stenosis of the left circumflex artery, the relationship shifted to the right, showing a decrease in calculated mean vascular resistance. Corrected LADF was also derived from equation 2 in the text.
Table II: Coronary Blood Flows (LADF and LCXF) and Calculated Mean Coronary Vascular Resistances (PP/LADF and PP/LCXF) Expressed by the Independent Variables, PP and LCX Stenosis (i.e., $y = b_0 + \sum_{i=1}^{6} b_i X_i + b_6 X_6 + b_7 X_7 + e$)

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As described in “Results”, for example, $\bar{\text{LADF}}$ is expressed as follows, i.e., $\bar{\text{LADF}} = -40.60 + 17.63** S + 0.85** PP$ where $S = 0$ for the data taken without LCX stenosis and $S = 1$ for the data taken with LCX stenosis.

Units: LADF, LCXF, ml/min; PP/LADF, PP/LCXF, mmHg/ml/min. Abbreviations: N=total experimental number used for the analysis; SE and R=standard error and correlation coefficient of multiple linear regression, respectively. * $p<0.05$, ** $p<0.01$, see text for details.
$PP =$ mean coronary perfusion pressure).

2. Pressure-length loop areas in the LAD region due to alteration of Rp values with and without LCX stenosis

As shown in Fig. 4, pressure-length loop areas in the LAD region following LCX stenosis appeared to be the same as in each corresponding pre-ischemic state at relatively lower ranges of Rp. Also, there was no significant difference between pre-ischemic and ischemic values for identical Rp values, although pressure-length loop areas in the LAD region following LCX stenosis were likely to be larger at equivalent mean aortic pressure values (Fig. 5).

**Discussion**

According to previous studies\(^{1,2,5,6}\) small but consistent increases in coronary blood flow are observed in one major branch of the left coronary

![Fig. 4. Pressure-length loop areas of the non-ischemic LAD area at different levels of peripheral resistance (i.e., 10.5, 6.2 and $4.7 \times 10^3$ dyne sec cm$^{-5}$) are presented before (left panel) and after LCX stenosis (right panel). LAD pressure-length loop areas without and with LCX stenosis changed together in a similar fashion depending on the reduction of peripheral resistance.](image-url)
artery within 1–2 min after occlusion of another major branch, although the opposite result has been reported with coronary embolization. However, there are relatively few studies which deal with the perfusion pressure-coronary flow relationship in the presence of coronary artery stenosis. Furthermore, the perfusion pressure-coronary flow relationships of the non-stenosed coronary artery have not been investigated in controlled conditions or under a relatively wider range of coronary perfusion pressures or coronary blood flows. Accordingly, it is uncertain whether blood flow changes in the non-stenosed coronary artery are due to changes in the myocardial oxygen demand-supply relation or whether changes in pressure-flow relations are always present at any perfusion pressure or coronary blood flow level.

The present study showed that, following stenosis of the adjacent LCX artery, the perfusion pressure-coronary flow relationship of a non-stenosed coronary artery significantly shifted to the left, indicating a decrease in coronary resistance at all perfusion pressures tested. This decrease in coronary resistance did not seem to relate to a greatly augmented mechanical function in the perfused area.

Although our experimental model has several useful features, we must consider the following methodological limitations. First, we used excised per-
fused canine heart preparations. Thus, coronary autoregulation may not be intact. However, we found a similar or slightly smaller grade of reactive hyperemic response than that found in anesthetized, open chest dogs. In addition, the effects of neuro-humoral control have been removed in our preparations. If they are present, they might modify our results. Second, the relationship between mean coronary blood flow vs. mean perfusion pressure were likely to be linear in our experimental setting—that is, no evidence of autoregulation was found over a range of perfusion pressures classically well within the autoregulatory range. However, the coronary bed is not considered to be fully vasodilated in the presence of a relatively sufficient reactive hyperemic response. Instead, we speculate as follows: when perfusion pressure is increased, Rp is increased and myocardial oxygen consumption increases. As a result, coronary flow increases. On the other hand, to lower perfusion pressures, Rp is reduced and myocardial oxygen consumption can fall so that the resulting coronary flow falls. Thus, it is reasonable that the coronary perfusion pressure-flow points in Fig. 3b are highly linear. Our objective was to compare the perfusion pressure-coronary flow relationships between pre-ischemic and ischemic states under similar experimental conditions. Therefore, adoption of linear regression analysis was sufficient in the present study. Third, since myocardial blood flow was not determined in our experiment, it is unclear how the increased LADF which followed LCX stenosis was distributed.

Although the precise mechanism(s) responsible for the shift of the perfusion pressure-coronary flow relationship in a non-stenosed coronary artery in the ischemic state is unclear, there are several possible explanations. Since we investigated the mean perfusion pressure-mean coronary flow relationship through one cardiac cycle, many factors which affect the perfusion pressure-coronary flow relationship in diastole, and systole (such as extravascular compression and/or regional myocardial work) are available. In addition, increased collateral flow due to a pressure gradient between partially occluded and unoccluded arteries, and the intercoronary reflex may also be considered as a possible mechanism responsible for this finding. However, the role of the intercoronary reflex seems to be negligible because we used excised heart preparations, in which neural reflexes are not considered to be intact. Also, the extravascular compression factor may not play an important role in this phenomenon, because a definite increase in LADF (19.5±5.6 ml/min, p<0.02) appeared without a change in mean perfusion pressure (2.5±2.4 mmHg, n.s.) when peak LVPS (99.0±3.5, 97.0±4.7 mmHg, Table 1) at Rp IV and Rp III were similar between the pre-ischemic and ischemic states. Moreover, as suggested by Lew et al, since left ventricular end-diastolic...
pressure was kept constant throughout the intervention, the pressure-length loop in the non-ischemic LAD area did not significantly increase following LCX stenosis. Thus, although pressure-length loop area is only an approximate index of the regional work, it seems unlikely that a greatly augmented myocardial function in the non-ischemic LAD area is the main factor responsible for increased blood supply to that region. A contribution of collateral flow has been discounted in the coronary occlusion model.\textsuperscript{11,18} On the contrary, Messina et al\textsuperscript{19} recently reported that collateral flow may have an important effect on the assessment of pressure-flow relations in an adjacent coronary artery, when pressure gradients between branches of the left coronary artery are present. Finally, independent of the mechanism(s) of increased coronary flow of an adjacent non-stenosed coronary artery, there is the possibility that this phenomenon may be important in salvaging the ischemic border zone through an increase of "the perfusion mass" of the non-ischemic area in at least the acute phase following ischemia, irrespective of complete or partial coronary occlusion.

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\textbf{References}