Effects of the pericardium on the diastolic left coronary pressure-flow relationship in the isolated dog heart

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ABSTRACT We studied the effects of the pericardium on diastolic left coronary pressure-flow relationships in heart-blocked and isolated canine preparations. In these preparations, the left and right coronary arteries were dilated with adenosine and perfused by means of a pressurized arterial reservoir. The diastolic left heart pressure (LHP) was controlled by the height of a reservoir connected to the left atrium and left ventricle. The right atrial and ventricular pressure i.e., coronary outflow pressure, was kept constant at 0 mm Hg. Before and after pericardiectomy, diastolic coronary pressure-flow relationships were obtained at three values of LHP (0, 15, and 30 mm Hg) with driving pressure decreasing (2 mm Hg/sec or less) from approximately 60 mm Hg to the actual zero-flow pressure (Pf = 0) during a single long diastole induced by cessation of ventricular pacing. The slopes of the coronary pressure-flow relationships were approximated by a linear regression analysis in which the correlation coefficients were greater than 0.98 in all cases. Before pericardiectomy, with LHP increasing from 0 to 15 and 30 mm Hg, the value of Pf = 0 significantly increased from 7 ± 1 to 16 ± 1 (p < .01) and 28 ± 2 mm Hg (p < .01), respectively. After pericardiectomy, it increased from 7 ± 1 to 14 ± 1 (p < .01) and 17 ± 2 mm Hg (p < .01), respectively. When LHP was at 0 and 15 mm Hg, the pericardiectomy had no effect on the value of Pf = 0. However, pericardiectomy lowered the value of Pf = 0 (p < .01) when LHP was at 30 mm Hg. On the other hand, the slopes of the regression lines were not significantly changed by either an increase in LHP or by pericardiectomy. From these results, we conclude that the pericardium plays an important role in regulating the coronary circulation by changing the effective back pressure, i.e., Pf = 0, when the intracardiac pressure increases beyond a certain degree.


AFTER Bellamy’s report,1 many investigators have examined the diastolic coronary pressure-flow relationship in which the zero-flow pressure (Pf = 0) is significantly higher than the coronary outflow pressure. Consequently, the Pf = 0 value and the shape of the coronary pressure-flow relationships have been shown to be affected by several factors, including coronary autoregulation,2,3 coronary venous pressure,4 coronary capacitance,2,5 diastolic intracardiac pressure,5 and coronary arterial collateral flow.6

We hypothesized that the pericardium was one of several important factors affecting the diastolic coronary pressure-flow relationship for the following reasons. First, after pericardiectomy, the intramyocardial pressure or stress distribution seems to vary with changes in the transmural pressure and/or heart chamber size,7,8 even if the intracardiac pressure remains constant. Alteration of the intramyocardial pressure or stress should influence the perivascular tissue pressure and might affect the coronary pressure-flow relationship.1,9-11 Second, it is possible that the intrapericardial pressure directly affects the coronary pressure-flow relationship, since Uhlig et al.12 have reported that the vascular waterfall mechanism acts in the epicardial coronary veins.

This study was designed to test the hypothesis that the pericardium affects the diastolic coronary pressure-flow relationship, using isolated perfused dog hearts to eliminate effects of the various factors mentioned above. Coronary pressure-flow relationships were determined at three different values of the diastolic intracardiac pressures before and after pericardiectomy.

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Methods

Nine mongrel dogs weighing 11 to 19 kg (average 13.8) were anesthetized with α-chloralose (50 mg/kg iv) and urethane (500 mg/kg iv). After bilateral thoracotomy under positive-pressure respiration, the heart was isolated with an intact pericardium. Details of the heart isolation are described elsewhere. 13 Figure 1 shows the experimental layout. A large cannula with multiple holes that open in both the left atrium and the left ventricle was inserted from a pulmonary vein, and another cannula of the same type was inserted into the right atrium and the right ventricle from the superior vena cava. Each cannula was connected to a variable-height reservoir. With this system, the left and the right heart pressures (LHP and RHP) were controlled independently. Complete atrioventricular block was produced by injection of 10% formalin into the atrioventricular node. 14 A pair of pacing electrodes were sewn to the right ventricle and the heart was paced at 100 to 120 beats/min. Fluid-filled systems were attached to the side arms of the left and the right heart cannulas for measurement of LHP and RHP by pressure transducers (Toyo Sokki, MPU 0.5). The zero-pressure level was adjusted to the middle point of the left ventricle.

Coronary circulation circuit. A Gregg type cannula was inserted into the left main coronary artery via the right subclavian artery and secured with a silk ligature. The left coronary artery was perfused by means of a pressurized arterial reservoir in which the pressure was controlled by a compressed air source. The right coronary artery was cannulated at its proximal portion and also perfused by the common arterial pressurized reservoir. The pressure drop between the site of measurement of coronary perfusion pressure and the left coronary cannula tip was nearly equal to that of the right coronary cannula. Arterial blood from the support dog was pumped into the common arterial reservoir with a Harvard pump (Model 1215). The arterial blood was heated by a water jacket system and the blood volume level in the arterial reservoir was kept constant by a servo-control system. The coronary venous blood was returned to the support dog through the overflow system of the reservoir connected to the right heart cavity. After surgical preparation, the two sites of small pericardiostomies made for coronary cannulation were loosely sutured. In-line electromagnetic flow probes were inserted into the circuit to measure left and right coronary blood flow with a gated sine wave flowmeter (Nihonkoden Model MFV 1200).

Blood coagulation was prevented by administration of heparin calcium (Eisai Co. LTD.) to the support dog (initially 5000 U, then 2500 U every hour). Coronary autoregulation was abolished by continuous infusion of adenosine (500 μg/min) into the coronary circuit. Maximum vasodilation was confirmed by the absence of reactive hyperemia after 15 sec of coronary occlusion. After infusion of adenosine, coronary perfusion pressure was adjusted to approximately 60 mm Hg and remained constant for 20 min, indicating that the experimental preparation was in a steady-state condition during this time period.

Experimental protocols. Extremely long diastoles (over 30 sec) were induced by cessation of right ventricular pacing. To suppress the escape beats, if required, 1 mg of lidocaine was injected into the coronary circuit before induction of the long diastole. The coronary pressure-flow relationship was obtained while decreasing perfusion pressure from approximately 60 mm Hg to Pf = 0 during a single long diastole. To avoid the effects of coronary capacitance, perfusion pressure was reduced very slowly. In one case, the absence of capacitive effects on the diastolic coronary pressure-flow relationship was confirmed at the slow perfusion pressure decrease rate of 2 mm Hg/sec.

The diastolic capacitance-free coronary pressure-flow relationships were determined at three different values of LHP (0, 15, and 30 mm Hg). The diastolic RHP was kept constant at 0 mm Hg throughout the study. After pericardectomy, the same protocol was repeated.

Data analysis. Pressure and flow data and the electrocardiogram were recorded with an eight-channel thermal pen recorder (Nihonkoden, WS681G). Also, coronary flow data and perfusion pressure were simultaneously digitized by a microcomputer (Fujitsu, MB2520; sampling interval 100 msec). In the pressure-flow plane, the diastolic coronary pressure-flow relationships were drawn on a digital XY-plotter (Graphtec, DA6000). Pf = 0 was determined by the value of the pressure axis intercept in these graphs. Since the diastolic coronary pressure-flow relationship seemed to be nearly linear, linear regression analysis was performed to approximate the slope. Data are presented as mean ± SEM. Statistical difference was evaluated by an analysis of variance with differences considered significant at the p < .05 level.

Results

Figure 2 shows typical tracings of left and right coronary flow tracings with coronary perfusion pressure decreasing (top panel) and coronary pressure-flow relationships (bottom panel) in the long diastole, when both LHP and RHP were constant at 0 mm Hg. The perfusion pressure decreased slowly in a nearly linear fashion. Note that the pressure-flow relationships were nearly linear and that the left and right coronary Pf = 0 values were nearly equal at 11 mm Hg. In this study we analyzed the left coronary pressure-flow relationship.

Figure 3 shows that the capacitive effects of the coronary vessel on the pressure-flow relationship are dependent on the rate of decrease in perfusion pressure. Namely, when the rate was slower, for example 2 or 4 mm Hg/sec, the coronary pressure-flow relationship shifted to the left of that observed at the higher rate.
of decrease of 11 mm Hg/sec. The pressure-flow relationships were nearly coincident when the rate of decrease in perfusion pressure was 2 and 4 mm Hg/sec. These results agree with the report of Aversano et al., which indicated that coronary capacitive effects were negligible when the rate of decrease in perfusion pressure was 3 mm Hg/sec. Therefore the rate of decrease of approximately 2 mm Hg/sec was adopted to obtain a capacitance-free diastolic coronary pressure-flow relationship.

Effects of pericardiectomy on the left coronary pressure-flow relationship at three different levels of LHP. Figure 4 shows a typical left coronary pressure-flow relationship at three different levels of LHP (0, 15, and 30 mm Hg) before and after pericardiectomy. When LHP was 0 mm Hg, pericardiectomy did not affect the pressure-flow relationship. However, pericardiectomy shifted the pressure-flow relationship to the left after an increase in LHP. This tendency was observed in the low perfusion pressure range when LHP was 15 mm Hg, and it became apparent throughout the pressure range examined when LHP was 30 mm Hg. In this case, with elevation of LHP from 0 to 15 and 30 mm Hg, Pf = 0 increased from 11 to 21 and 31 mm Hg before the pericardiectomy, whereas after pericardiectomy it increased from 11 to 17 and 19 mm Hg. The diastolic pressure-flow relationships were slightly curvilinear when the perfusion pressure was low, and the curvature seemed to be accentuated by an increase in LHP and pericardiectomy (middle and right panels of figure 4).

Figure 5 shows the mean values of Pf = 0 in nine dogs. Before pericardiectomy, with an increase in LHP from 0 to 15 and 30 mm Hg, Pf = 0 significantly increased from 7 ± 1 to 16 ± 1 (p < .01) and 28 ± 2 mm Hg (p < .01), respectively. After pericardiectomy it increased from 7 ± 1 to 14 ± 1 (p < .01) and 17 ± 2 mm Hg (p < .01), respectively. When LHP was either 0 or 15 mm Hg, there was no difference between the values of Pf = 0 before and after pericardiectomy. However, pericardiectomy lowered Pf = 0 (p < .01) when LHP was 30 mm Hg.

Table 1 shows the regression slopes of the pressure-flow relationship in nine hearts. The correlation coefficients were greater than .98 in all cases (mean .99). With an increase in LHP from 0 to 30 mm Hg, the slopes decreased slightly from 3.2 ± 0.4 to 2.7 ± 0.3 (NS) before pericardiectomy and from 3.3 ± 0.4 to 2.9 ± 0.4 ml/min/100 g/mm Hg (NS) after pericardiectomy. There was no significant difference between the values before and after pericardiectomy at each LHP level.

![FIGURE 2](image-url)  
**FIGURE 2.** Top, Typical tracings of left and right coronary (LC and RC) blood flow with decreasing coronary perfusion pressure (CPP) during long diastolic arrest. CPP decreased in a nearly linear fashion. CBF = coronary blood flow. Bottom, LC and RC pressure-flow relationships were nearly linear and had the same Pf = 0. The value of Pf = 0 was determined in the pressure-flow plane as the actual pressure axis intercept. LHP and RHP remained constant at 0 mm Hg.

![FIGURE 3](image-url)  
**FIGURE 3.** Effects of the rate of decrease in coronary perfusion pressure (CPP) on the pressure-flow relationships. When the rate of decrease was below 4 mm Hg/sec, the coronary pressure-flow relationships showed little change compared with that at a rate of 11 mm Hg/sec.
Discussion

These results show that pericardiectomy does not change the slope of the left coronary pressure-flow relationship approximated by the linear regression but does lower the value of Pf = 0 when LHP is high, although the downward concave curvilinearity of the relationship seems to increase at perfusion pressures close to Pf = 0. Interestingly, when LHP is 30 mm Hg before pericardiectomy, the value of Pf = 0 is nearly equal to LHP, suggesting a cause-and-effect relationship. After pericardiectomy, the close coupling disappears and the LHP-induced increase in the value of Pf = 0 is much less.

In this experiment, by using an isolated heart preparation in which an extremely long diastole allowed a slow rate of decrease in coronary perfusion pressure to obtain the coronary pressure-flow relationship, effects of capacitive flow on the diastolic coronary pressure-flow relationship\(^2\) were eliminated. Furthermore, with this preparation we were able to easily and precisely maintain the coronary outflow pressure (i.e., the right atrial and ventricular diastolic pressure) at 0 mm Hg. Effects of coronary autoregulation on the diastolic coronary pressure-flow relationship\(^3\) were abolished by inducing maximum vasodilatation with adenosine. Effects of coronary collateral flow on the coronary pressure-flow relationship\(^6\) might also be negligible because both the left main coronary artery and right coronary artery were perfused by a common arterial reservoir and no pressure gradient could occur between the left and right coronary branches. Although the presence of a non–coronary sinus pathway to the left ventricle such as the Thebesian vein may possibly affect the coronary pressure-flow relationship, especially the value of Pf = 0, these pathways are not likely to explain the differences in Pf = 0 before and after pericardiectomy in the absence of changes in LHP.

Effects of pericardiectomy on Pf = 0. The middle and right panels of figure 4 indicate that after pericardiectomy, the value of Pf = 0 decreases with an accentuation of the curvilinearity at the lower level of perfusion.

![FIGURE 4. Coronary pressure-flow relationship at three different values of the diastolic LHP before and after pericardiectomy [PERI(+) and PERI(-)]. When LHP was 0 mm Hg (left), pericardiectomy did not affect the coronary pressure-flow relationship. However, when LHP was 30 mm Hg (right), the pressure-flow relationship was clearly shifted to the left after pericardiectomy. In the middle panel, a small shift was observed in the low perfusion pressure range.](image)

![FIGURE 5. Summary of Pf = 0 data in nine dogs. Values increased significantly with increase in LHP. Pericardiectomy lowered Pf = 0 when the diastolic LHP was 30 mm Hg but had little effect on the value of Pf = 0 when LHPs were 0 and 15 mm Hg. PERI(+) = before pericardiectomy; PERI(-) = after pericardiectomy.](image)

**TABLE 1**

Regression slopes of the diastolic coronary pressure-flow relationship at three values of LHP (n = 9).

<table>
<thead>
<tr>
<th>LHP (mm Hg)</th>
<th>0</th>
<th>15</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Pf = 0</td>
<td>3.2±0.4</td>
<td>3.3±0.3</td>
<td>2.7±0.3</td>
</tr>
<tr>
<td>After Pf = 0</td>
<td>3.3±0.4</td>
<td>3.1±0.4</td>
<td>2.9±0.4</td>
</tr>
</tbody>
</table>

LHP is diastolic left ventricular pressure, which was controlled by the variable-height reservoir. Slopes are expressed as mean ± SEM (ml/min/100 g/mm Hg).
pressure. In a report by Aversano et al.,\textsuperscript{5} measured values of Pf = 0 were slightly higher than those in the present study after pericardiectomy when the LHP was at nearly the same level. These differences in the values of Pf = 0 may be partly explained by the different levels of coronary outflow pressure, which has been reported to affect the diastolic coronary pressure-flow relationship.\textsuperscript{4} As previously described, we maintained coronary outflow pressure at 0 mm Hg in the present study, whereas the outflow pressure in the study of Aversano et al.\textsuperscript{5} was 8 ± 2 mm Hg.

It is unclear why pericardiectomy lowered the value of Pf = 0, when the value of LHP was high. It should be noted that the size of the heart chambers increases after pericardiectomy under constant intracardiac pressures.\textsuperscript{15} This enlargement of the heart chamber may be expected to affect the coronary pressure-flow relationship by increasing the intramyocardial stress, if we simply apply the “law of Laplace.” In spite of this expectation, the value of Pf = 0 decreased after pericardiectomy when LHP was high. Therefore the other mechanisms are required to explain the effects of pericardiectomy on the value of Pf = 0.

Pf = 0 is the pressure of the last part of the myocardium to be perfused, and most studies, such as that of Ellis and Klocke,\textsuperscript{10} indicate that the subepicardial muscle layer has the lowest Pf = 0. Accordingly, pericardiectomy might result in a decrease in the intramyocardial tissue pressure of this layer. The presence of the pericardium allows the myocardium to be more effectively compressed by stresses arising in the left heart cavity. That is, before pericardiectomy LHP is more effectively transmitted across the full thickness of the myocardium, causing a more uniform distribution of transmural intramyocardial tissue pressure. Therefore it is probable that effects of the pericardiotomy are great when the intracardiac pressure is high because it is known that the intrapericardial pressure is elevated with an increase in the intracardiac pressure when the cardiac volume exceeds the elastic limits of the pericardium.\textsuperscript{16} As a result, it is reasonable that a close coupling between the value of Pf = 0 and LHP was found when LHP was high and the pericardium was intact, and the close coupling disappeared after pericardiectomy. This mechanism of the pericardial contribution to the value of Pf = 0 seems to be important, if the value of Pf = 0 is determined by the mechanism of the “modified” waterfall that exists in the resistant vessels and is influenced by the perivascular tissue pressure.\textsuperscript{1, 4}

Another possible mechanism is a direct action of the intrapericardial pressure and/or the pericardial surface pressure\textsuperscript{17, 18} to the epicardial coronary vessels. If we adopt the conclusion of Uhlig et al.\textsuperscript{12} that a vascular waterfall mechanism is present in the epicardial coronary veins, it is likely that the intrapericardial and/or pericardial surface pressures directly affect these veins and change Pf = 0. That is, one might expect that pericardiectomy lowered the value of Pf = 0 by removing the compressive effects on these veins.

If the vascular waterfall mechanism acts in the epicardial coronary veins and plays some role in changing Pf = 0, the compressive effects on the epicardial veins may alter coronary blood flow in all myocardial layers. On the other hand, if the mechanism of the pericardial contribution to the value of Pf = 0 acts by changing transmural intramyocardial pressures as mentioned above, there might be a differential effect across the myocardial wall. To clarify which mechanism operates in determining Pf = 0, further experiments including measurement of intramyocardial pressure, intrapericardial pressure, and transmural coronary blood flow are needed.

**Effects of the pericardium on the slope of the coronary pressure-flow relationship.** The slopes of the regression lines decreased slightly but not significantly with increase in LHP (table 1). This may be partially explained by the accentuation of the concavity of the diastolic coronary pressure-flow relationship in the lower range of perfusion pressure. This accentuation with an increase in the diastolic LHP has also been pointed out in the study of Aversano et al.\textsuperscript{5} in the absence of the pericardium. The middle and right panels of figure 4 show that pericardiectomy accentuates the curvilinearity. Dole and Bishop\textsuperscript{3} reported a nearly linear coronary pressure-flow relationship in closed-chest dog preparations with intact pericardia under maximum coronary vasodilatation, suggesting that the presence of the pericardium may make the coronary pressure-flow relationship more linear. In this study we calculated the slopes of the regression lines as an indicator of how the intervention influenced the coronary pressure-flow relationship. Thus even if the coronary pressure-flow relationship with decreasing perfusion pressure shows strong linearity, it is questionable whether the slopes of the regression lines express a unique coronary conductance. This is because the instantaneous perfusion pressure may change the coronary vascular conductance\textsuperscript{19} and the diastolic coronary pressure-flow relationship may be linear when the coronary conductance is changing.\textsuperscript{20}

Finally, our results indicate that increased intracardiac pressure depressed coronary circulation with increasing Pf = 0, which might reflect the effective
coronary back pressure, 1, 21, 22 but without changing the slope of the coronary pressure-flow relationship. These changes in Pf = 0 and the slope have been experimentally demonstrated in hydraulic systems when the surrounding pressure is increased around a long collapsible tube. 23 This intracardiac pressure-induced depression in coronary circulation with increasing Pf = 0 is augmented by the presence of the pericardium. In the past, the pericardium has received little attention as a regulatory factor in coronary circulation. The importance of this study is that it characterizes the effects of the pericardium on the coronary pressure-flow relationship. Although our results may be related to changes in the intrapericardial pressure and/or intramyocardial stress distribution, we did not measure these pressures or stresses because of methodologic problems. Therefore further experiments will be needed to analyze the pericardial contribution to the diastolic coronary pressure-flow relationships.

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