Influences of Pressure Surrounding the Heart and Intracardiac Pressure on the Diastolic Coronary Pressure-Flow Relation in Excised Canine Heart

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We investigated the change in the instantaneous diastolic left coronary pressure-flow relation (DPFR) when the pressure surrounding the heart (SHP), right heart pressure (RHP), and left heart pressure (LHP) were systematically varied. Eight excised and maximally vasodilated canine hearts placed in an air-tight chamber were used. To obtain a capacitance-free DPFR, coronary perfusion pressure was slowly decreased (about 2 mm Hg/sec) during a prolonged diastole. The zero-flow pressure (Pf=0) and the slope of the DPFR were analyzed. The mean values of the slope did not change significantly throughout the interventions. The mean value of Pf=0 in the control state (SHP = RHP = LHP = 0 mm Hg) was 6.0±2.0 mm Hg (mean±SD, n=8), significantly higher than the venous outflow pressure, RHP (p<0.001), and the other two pressures (p<0.001). When SHP was raised to 15 and 30 mm Hg, while the other pressures remained at 0 mm Hg, the mean values of Pf=0 increased to 20.9±2.4 and 35.6±3.1 mm Hg (p<0.001 and p<0.0005, respectively, vs. control). The mean values of Pf=0 when only RHP was elevated to 15 and 30 mm Hg were 16.0±1.5 and 29.3±1.5 mm Hg (p<0.001 and p<0.0005 vs. control). On elevation of LHP to 15 and 30 mm Hg, the mean values of Pf=0 were 12.0±2.8 and 17.3±3.6 mm Hg (p<0.01 and p<0.01 vs. control). When both SHP and LHP were almost evenly elevated to about 15 and 30 mm Hg, the mean values of Pf=0 were raised to 22.0±2.9 and 35.3±3.2 mm Hg, respectively. These mean values were not significantly different from those when only SHP was elevated to the comparable levels. The observation that Pf=0 exceeded RHP in the control state and that RHP, which was elevated above the preceding Pf=0, was identical with the present Pf=0 supports the vascular waterfall mechanism when RHP is low. Furthermore, the evidence that the degree of DPFR shift was almost linearly dependent on the SHP level rather than on the LHP level indicates that the pressure on the epicardial side is one of the factors that determines the pressure at the top of the vascular waterfall. (Circulation Research 1988;63:788-797)

The instantaneous diastolic coronary pressure-flow relation (DPFR) has been investigated by many researchers, beginning with the report of Bellamy. However, the problem of how extravascular components influence the DPFR has not been studied systematically.

Bellamy et al investigated the effects of the elevation of coronary sinus pressure. They reported that zero-flow pressure (Pf=0) was raised by occlusion of the coronary sinus and always exceeded the coronary sinus pressure. They assumed that downstream pressure affects the tissue pressure surrounding the collapsible vessels in which the vascular waterfall mechanism operates.

On the other hand, it has been known that elevation of diastolic left ventricular pressure also shifts the coronary pressure-flow relation to the right and raises Pf=0. Aversano and colleagues reported that Pf=0 exceeded left ventricular diastolic pressure when the diastolic pressure was 17 mm Hg or less, but at higher diastolic pressures, Pf=0 was lower than ventricular diastolic pressure. They also discussed the transmural variations in Pf=0, which

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may be highest in the subendocardium because of the higher local stress caused by the elevated intracavitary pressure.

We reported similar effects of the intracavitary pressure and, in addition, emphasized the importance of the pericardium. When diastolic left heart pressure was elevated, the coronary pressure-flow relation was influenced remarkably by the pericardium. That is, in the presence of the pericardium, $P_f=0$ was significantly higher than after pericardiectomy even though intracavitary pressure was maintained at the same level. Uhlig et al. asserted that the vascular waterfall is present in epicardial veins. In their study, there were the apparent pressure differences through the epicardial veins in the high-flow condition.

The results of these latter two reports imply a very important role for the pressure on the epicardial side, or the pressure surrounding the heart, in the coronary circulation system as well as the intracavitary and venous outflow pressures. However, there has been no study that describes the effects of the pressure surrounding the heart on DPFR change, nor a systematic study regarding the effects of intracavitary and venous outflow pressures.

In the present study, we compared the effects of the pressure surrounding the heart on the DPFR with that of the intracavitary pressure and venous outflow pressure, and tried to clarify the role of each pressure in determining the DPFR.

**Materials and Methods**

**Surgical Preparation**

Surgical methods used in the isolated supported canine heart preparation have been reported previously. Eight mongrel dogs (body weight 12.2–16.5 (mean ± SD, 14.2 ± 1.4 kg)) for use as heart donors, were anesthetized with intravenously administered α-chloralose (50 mg/kg) and urethane (500 mg/kg). Another eight mongrel dogs (24.3 ± 5.2 kg) were used as support dogs under the same anesthesia. Bilateral thoracotomy was performed in the two chambers.

A glass cannula for coronary perfusion was advanced into the left main coronary artery and cannulated via the epicardial side. Afterward, the glass cannula just above the aortic valve was advanced into the left main coronary artery and fixed tightly there. The coronary perfusion pressure of both branches was evenly controlled by a common compressed air chamber. Pressure losses through both cannulas were 4 mm Hg at a blood flow rate of 100 ml/min. The two cannulas were carefully selected to have equal resistances; i.e., the left cannula was longer and of larger diameter than the right cannula (the length and external and internal diameters were 50.2 × 1.4 × 2 mm and 12.5 × 1.4 × 2 mm, respectively).

Right atrial and right ventricular pressure (right heart pressure, RHP) were varied with a variable height reservoir with an overflow system. The reservoir was connected to a multi-holed wide cannula inserted from the superior vena cava to the right ventricle. This cannula allowed us to measure the pressure in the right side chambers as a single chamber. Left atrial and left ventricular pressure (left heart pressure, LHP) were also controlled by a similar system. The pulmonary artery, azygos vein, and vena cavae were ligated. Overflowed venous blood was gathered and returned by gravity to the femoral vein of the support dog. Finally, the excised heart was put into an air-tight transparent chamber. Pressure surrounding the heart (SHP) could be controlled by pumping air into the chamber. It is obvious that each pressure change in RHP, LHP, and SHP was accompanied by volume changes in the two chambers.

After defibrillation, complete atrioventricular block was accomplished by injection of 10% formalin into the atrioventricular junction. The heart was then paced constantly (120–150/min) at the right ventricular free wall.

**Measurements**

SHP, RHP, and LHP were measured with short fluid-filled tubes connected to strain gauge pressure transducers (Toyo Sokki, MPU 0.5). Coronary perfusion pressure was also measured from a side arm of the perfusion cannula. In four additional cases, coronary venous pressure was measured in a posterior vein of the left ventricle that flowed into the great cardiac vein. The posterior vein was dissected free and cannulated with a 16G Teflon tube (2 cm long) and a microtip transducer (SPR-249, Millar, Houston, Texas) was attached to the end of the tube. A common zero reference pressure was taken to be the pressure at the middle point of the heart, namely, at almost the same level as the coronary sinus outlet. Instantaneous left and right coronary flows were measured with cannulating type electromagnetic flowmeters (Nihon Kohden MFV 1200).
Calibration was performed by timed blood volume collection after the experiment. The zero-flow point was frequently confirmed by brief occlusion of the perfusion line.

A two-dimensional echocardiogram was obtained in three cases. The probe was attached at the middle level of the left ventricle through a small slit of the chamber. The slit was covered with a latex membrane. We obtained only short axis images when SHP was elevated and did not evaluate the image quantitatively. The aim of this measurement was to confirm the patency of the left ventricular cavity in SHP elevation.

Experimental Procedures and Protocols

To dilate the coronary vessels maximally and to avoid coronary vasoconstriction in long diastole, adenosine was infused continuously (500 µg/min) into the perfusion line. We confirmed the abolition of reactive hyperemia following 15 seconds perfusion line occlusion.

Thereafter, coronary perfusion pressure was set at 60 mm Hg. This level of pressure was determined empirically for two reasons. Higher pressure induces the larger blood flow from the support dog and sometimes leads to deterioration of the support dog’s condition. Another reason is that higher pressure requires a longer arrested time because the decreasing rate of perfusion pressure was constant. We were concerned about escaped beats that might occur in the later diastolic phase. Long diastole was induced by stopping the ventricular pacing and by intracoronary infusion of lidocaine, if necessary. Lidocaine somewhat depressed the contractile state of the heart but did not affect the present results with respect to the coronary circulation system because we obtained identical lines before and after the injection of lidocaine. Coronary perfusion pressure was slowly and quasi-linearly decreased (about 2 mm Hg/sec) by letting air out of the compression chamber until left coronary flow reached zero. Instantaneous coronary perfusion pressure and coronary flow were measured throughout the long diastole.

The measurement was repeated under various levels of SHP, RHP, and LHP; that is, after the control measurement (all of the pressures were set at 0 mm Hg), each pressure was elevated to 15 mm Hg and then to 30 mm Hg, while the other two pressures were maintained at 0 mm Hg. Thereafter, both SHP and LHP were set at 15 and 30 mm Hg while RHP was kept at 0 mm Hg. At the end of the experiment, the reproducibility of the DPFR was established under the same pressure condition as in the control state (all pressures were 0 mm Hg).

We performed additional protocols. In four cases, we measured venous pressure at the posterior vein of the left ventricle and observed the effect of SHP or RHP elevation (0, 15, and 30 mm Hg) on DPFR and venous pressure. In three cases, only RHP was elevated to more than 30 mm Hg. In one case, three or four values of RHP (0, 15, 30, and 45 mm Hg) were applied at three different values of SHP (0, 15, and 30 mm Hg). Finally, in one case, LHP was set at 15 mm Hg and RHP was scanned from 0 to 37 mm Hg in steps of 7 or 8 mm Hg.

Data Analysis

SHP, RHP, LHP, and ECG, as well as the instantaneous coronary perfusion pressure and left coronary blood flow, were recorded on an eight-channel thermal pen recorder (Nihon Kohden WS681G). Coronary perfusion pressure and coronary blood flow were digitized every 100 msec by a microcomputer (Fujitsu MB 25020) and recorded on a X-Y plotter (Graphtec DA 6000). Pf=0 was read directly as the pressure axis intercept of the coronary pressure-flow relation.

All data were expressed as mean±SD and the statistical significance of mean values of Pf=0 was determined by one-way analysis of variance. We employed one-way analysis of covariance for determining the statistical significance of the slopes of pressure-flow relations among the interventions using a computer system (IBM 4381) with a Statistical Analysis System (SAS*, version 5). The significance level of the p value was taken to be less than 0.05.

Results

Figure 1 shows a representative recording taken during a long diastole. In the left panel, SHP, RHP, and LHP were maintained at 0 mm Hg. Following the cessation of pacing, coronary perfusion pressure (CPP) was slowly decreased from 60 mm Hg until the left coronary flow (LCF) reached zero. Right coronary flow (RCF) ceased at almost the same level of coronary perfusion pressure at which the left coronary flow ceased. The left coronary flow remained zero for several seconds while coronary perfusion pressure was maintained at zero-flow pressure. In the right panel, SHP was elevated to 30 mm Hg while RHP and LHP were maintained at 0 mm Hg. Left coronary artery flow was decreased at any pressure perfusion tested and the zero-flow pressure was raised remarkably.

DPFRs in the left coronary circulation from the case of Figure 1 are presented in Figure 2. SHP elevation (Panel A) caused a shift in the pressure-flow relation to the right without apparent change in slope or curvature. RHP elevation (Panel B) or LHP elevation (Panel C) also shifted the pressure-flow relation toward the right. In RHP elevation, the degree of the shift was about half-way between SHP and LHP elevation. The pressure axis intercept of the highest RHP level was nearly coincident directly as the pressure axis intercept of the coronary pressure-flow relation.

Slopes of the left coronary pressure-flow relations obtained by the least-squares method, supposing that the relations were linear, are presented in Table 1. The mean values of slope decreased with the
FIGURE 1. A representative recording during a long diastole. RHP, right heart pressure; LHP, left heart pressure; SHP, pressure surrounding the heart; CPP, coronary perfusion pressure; LCF, left coronary artery blood flow; RCF, right coronary artery blood flow. RHP and LHP were maintained at 0 mm Hg. Only SHP was varied from 0 (left panel) to 30 mm Hg (right panel). CPP was slowly decreased from 60 mm Hg until LCF reached zero level. The right panel indicates that elevation of SHP decreased LCF and raised the zero-flow pressure (Pf=0). When LCF reached zero level (in both panels), CPP was retained at this level of pressure for an additional several seconds. The LCF remained at zero level during this period.

elevation of each pressure. However, in all interventions, the degree of change in slope was small and there were no significant differences among them.

The mean values of Pf=0 are presented in Table 1. When SHP was elevated from 0.1 ± 4.0 (control) to 14.6 ± 0.8 and 29.4 ± 0.8 mm Hg, Pf = 0 increased significantly from 6.0 ± 2.0 to 20.9 ± 2.4 (p < 0.001 vs. control; all p values below are compared with control) and 35.6 ± 3.1 mm Hg (p < 0.0005), respectively. Note that the mean difference between SHP and Pf = 0 was almost constant. Pf = 0 also increased significantly on elevation of RHP. Values of mean Pf = 0 at RHP values of 0.1 ± 0.3, 13.8 ± 1.2, and 28.4 ± 1.2 mm Hg were 6.0 ± 2.0, 16.0 ± 1.5 (p < 0.001), and 29.3 ± 1.5 mm Hg (p < 0.0005), respectively. There was a significant difference between Pf = 0 and the lowest RHP (i.e., 0.1 ± 0.3 mm Hg) (p < 0.001), but these did not significantly differ at the other two elevated RHP levels. The mean Pf = 0 values at the intermediate and highest RHP levels were significantly lower than those at the corresponding SHP levels (16.0 ± 1.5 vs. 20.9 ± 2.4 mm Hg, p < 0.01, 29.3 ± 1.5 vs. 35.6 ± 3.1 mm Hg, p < 0.001). In three cases, RHP was raised to more than 30 mm Hg and each value of Pf = 0 is presented as a function of RHP in Figure 3. Pf = 0 in all three cases was nearly identical with RHP in the RHP range over 30 mm Hg. When LHP was elevated from 0.5 ± 0.9 to 13.6 ± 1.5 and 28.8 ± 1.3 mm Hg, Pf = 0 increased to 12.0 ± 2.8 (p < 0.01) and 17.3 ± 3.6 mm Hg, respectively (p < 0.01). At the highest LHP level, Pf = 0 was significantly lower than LHP (p < 0.01). When both SHP and LHP were evenly elevated to 15.0 ± 0.6 and 14.2 ± 0.8 mm Hg, respectively, while RHP remained at 0 mm Hg, the mean Pf = 0 value was 22.0 ± 2.9 mm Hg. In the next stage, both pressures were elevated to 28.1 ± 4.2 and 29.8 ± 1.1 mm Hg, respectively, and Pf = 0 increased to 35.3 ± 3.2 mm Hg. These mean Pf = 0 values were not different from those when only SHP was elevated to the same level.

The differences between Pf = 0 and SHP at the three different SHP levels are presented in Figure 4 together with the differences between Pf = 0 and RHP or LHP following each pressure increase. These results denote that Pf = 0 was about 6 mm Hg.
higher than SHP at any SHP level (5.9 ± 2.2, 6.3 ± 2.6, and 6.3 ± 3.2 mm Hg, p < 0.001), in contrast to RHP or LHP elevation. The differences between Pf=0 and RHP disappeared at elevated RHPs; that is, the differences were 5.9 ± 2.1 (p < 0.001), 2.2 ± 1.7 (NS) and 0.8 ± 0.8 mm Hg (NS) at corresponding RHP levels of 0.1 ± 0.3, 13.8 ± 1.2, and 28.4 ± 1.2 mm Hg. On the other hand, the differences between Pf=0 and LHP disappeared at an LHP of 13.6 ± 1.5 mm Hg (−1.6 ± 2.6 mm Hg, NS) and became negative at 28.8 ± 1.3 mm Hg (−14.0 ± 6.3 mm Hg, p < 0.001).

Figure 5 illustrates the changes in coronary venous pressure and Pf=0 in four additional cases when SHP and RHP were elevated as in the preceding protocol. On SHP elevation (the left panel), venous pressure elevated equally with SHP; i.e., venous pressure attained values of 1.0 ± 1.1, 15.3 ± 3.3, and 29.3 ± 5.0 mm Hg corresponding to SHP values of 0, 15, and 30 mm Hg, respectively. All of the mean values of Pf=0 (9.5 ± 2.5, 25.0 ± 4.1, and 41.5 ± 4.4 mm Hg) were significantly higher than the corresponding mean values of venous pressure (p < 0.01, p < 0.01, and p < 0.001, respectively) and the differ-

Table 1. Controlled Pressures, Slopes, and Zero-Flow Pressures

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<tr>
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<th>1 (control)</th>
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<tr>
<td>SHP (mm Hg)</td>
<td>0.1 ± 0.4</td>
<td>14.6 ± 0.8†</td>
<td>29.4 ± 0.8†</td>
<td>0.2 ± 0.4</td>
<td>0.8 ± 0.6</td>
<td>0.8 ± 0.6</td>
<td>15.6 ± 0.6†</td>
<td>28.1 ± 4.2†</td>
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<tr>
<td>RHP (mm Hg)</td>
<td>0.1 ± 0.3</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>13.8 ± 1.2†</td>
<td>28.4 ± 1.2†</td>
<td>0.0 ± 0.0</td>
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<tr>
<td>LHP (mm Hg)</td>
<td>0.5 ± 0.9</td>
<td>1.0 ± 2.1</td>
<td>0.4 ± 0.7</td>
<td>0.5 ± 0.8</td>
<td>0.7 ± 1.0</td>
<td>13.6 ± 1.5†</td>
<td>28.8 ± 1.3†</td>
<td>14.2 ± 0.8†</td>
<td>29.8 ± 1.1†</td>
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<tr>
<td>Slope (ml/min/mm Hg)</td>
<td>3.0 ± 0.9</td>
<td>2.7 ± 0.8</td>
<td>2.5 ± 0.6</td>
<td>2.7 ± 1.0</td>
<td>2.5 ± 0.8</td>
<td>2.8 ± 0.7</td>
<td>2.4 ± 0.6</td>
<td>2.6 ± 0.9</td>
<td>2.5 ± 0.8</td>
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<tr>
<td>Pf=0 (mm Hg)</td>
<td>6.0 ± 2.0</td>
<td>20.9 ± 2.4†</td>
<td>35.6 ± 3.1†</td>
<td>16.0 ± 1.5†</td>
<td>29.3 ± 1.5†</td>
<td>12.0 ± 2.8*</td>
<td>17.3 ± 3.6*</td>
<td>22.0 ± 2.9†</td>
<td>35.3 ± 3.2†</td>
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SHP, pressure surrounding the heart; RHP, right heart pressure; LHP, left heart pressure; Slope, slope of the diastolic coronary pressure-flow relation calculated by least-squares method supposing that the relations are linear. r, correlation of coefficients; Pf=0, zero-flow pressure. Statistical significance marked at the right shoulder was examined by comparing with control values. Mean ± SD, n = 8, †p < 0.01, ‡p < 0.001, §p < 0.0005.
FIGURE 3. The zero-flow pressure (Pf=0) change when right heart pressure was elevated by more than 30 mm Hg in three cases. Thick oblique line indicates the value identical with the abscissa. There was no substantial difference between Pf=0 and right heart pressure when right heart pressure was elevated more than 30 mm Hg.

ences between them were almost constant. When RHP was elevated from 0 to 15 and 30 mm Hg, venous pressure rose significantly, to 1.0±1.1, 14.0±0.8, and 28.3±1.0 mm Hg, respectively. There were significant differences between Pf=0 and venous pressure only in the control state (Pf=0, 9.5±2.9 mm Hg). At the two elevated RHP levels, there was no significant difference between RHP, venous pressure, and Pf=0 (15.0±1.8 and 28.8±2.6 mm Hg).

In one case, RHP was scanned from 0 to 37 mm Hg in 7 or 8 mm Hg steps while LHP was maintained at 15 mm Hg (Figure 6A). At the lower RHP levels, Pf=0 showed little increase but at the higher levels, Pf=0 increased proportionately and remained close to the identity line. In this case, coronary venous pressure varied with RHP level and these two pressures were almost identical (RHP vs. coronary venous pressure: 0 vs. 1, 9 vs. 10, 17 vs. 17, 25 vs. 24, 31 vs. 30, and 37 vs. 35 mm Hg, respectively).

In another case, RHP was elevated to three or four levels while SHP was maintained at 0, 15, or 30 mm Hg (Figure 6B). At the RHP of 30 mm Hg, Pf=0 was identical with the outflow pressure (=RHP) when SHP was 0 and 15 mm Hg. When SHP was elevated to 30 mm Hg, the Pf=0 value was higher than the RHP, in the RHP range from 0 to 30 mm Hg. At an RHP of 45 mm Hg, Pf=0 was again identical with RHP. This result indicates that RHP could reach the same level as Pf=0, if RHP were elevated sufficiently. The right panel of Figure 6 shows the identical data as a function of SHP. Pf=0 tended to converge to a level several millimeters of mercury higher than the SHP.

The two-dimensional echocardiogram in three cases revealed that the left ventricular cavity became smaller but was always apparently patent when SHP was elevated to 15 and 30 mm Hg.

FIGURE 4. The mean differences between zero-flow pressure (Pf=0) and controlled pressures (SHP, pressure surrounding the heart; RHP, right heart pressure; LHP, left heart pressure) at three levels (0, 15, and 30 mm Hg). Differences between Pf=0 and SHP are almost constant, but differences between Pf=0 and RHP decreased progressively and disappeared. In LHP elevation, Pf=0 is significantly lower than LHP at 30 mm Hg.

At the end of the experiment, Pf=0 and the slope obtained under the same conditions as the control were 6.3±1.9 mm Hg and 2.7±0.7 ml/min/mm Hg, respectively. These mean values were not different from those obtained at the beginning of the experiment (6.0±2.0 mm Hg and 3.0±0.9 ml/min/mm Hg).

Discussion

Methodological Consideration

In the present study, right atrial and right ventricular pressures were evenly varied to a given level that was taken to be the coronary outflow pressure. There are numerous outflow pathways from the coronary venous into the right side chambers in addition to the coronary sinus.9,10 Hence, elevation of coronary sinus pressure cannot be equated with elevation of total coronary outflow pressure. This may be the main reason that our results are not completely in accordance with those of Bellamy et al.9 In their study, Pf=0 increased by only two thirds of the increase in coronary sinus pressure,
and coronary sinus pressure could not attain the same level as the Pf=0.

Atrioventricular blocked and isolated heart yielded a very long diastole (more than 30 seconds). This long asystole allowed a slowly decreasing perfusion pressure. In comparison with intramyocardial coronary vessel capacitance values which have been reported by several investigators11-16 (i.e., the reported values ranged from 0.07 to 0.25 ml/mm Hg/100 g LV), the rate of decrease in the perfusion pressure (about 2 mm Hg/sec) may be slow enough that the capacitance effect can be disregarded.4 The study of Chilian and Marcus15 showed that venous outflow persisted for only several seconds after cessation of arterial inflow following a rapid decrease in perfusion pressure. The time constant of coronary vessels reported by Kajiya et al16 is less than 3 seconds. These studies also support our view that coronary venous flow and/or intramyocardial microvessel flow may be minimal or negligible at the end of the long diastole, in the present study.

The right and left coronary arteries were perfused with a common compressed air chamber. Therefore, the effects of the interaction between branches through collateral channels may have been minimal.17 Uhlig et al6 indicated that coronary sinus pressure increased when left ventricular end-diastolic pressure was elevated even at low right atrial pressure. Therefore, we must consider the possibility that the effects of LHP elevation are not only exerted via the endocardium but also via the epicardial vein. Elevation of RHP caused an identical increase in coronary venous pressure (Figure 5). However, Pf=0 did not change until RHP exceeded LHP (Figure 6, Panel A). Thus, we believe that the effects of LHP on Pf=0 via the coronary venous pressure can be regarded as minimal, at least for LHP less than RHP.

We did not measure the drainage venous flow into the left side chambers. Scharf et al,10 using isolated nonworking dog hearts, reported that the fraction of venous flow into the left ventricle is about 10% over a wide range of coronary sinus pressure. Hammond and Austen9 also estimated the fraction to be about 5%. The differences in pressure conditions between their study and ours must be noted, but it is possible to speculate that the fraction into the left ventricle may not markedly exceed 10% when LHP or RHP is elevated. The effects of simultaneous

**Figure 5.** Zero-flow pressure (Pf=0, ○) and coronary venous pressure (CVP, ×) changes when pressure surrounding the heart (SHP) and right heart pressure (RHP) were elevated to 30 mm Hg. Mean values of CVP changed almost identically with SHP (left panel) and RHP (right panel). However, the differences between Pf=0 and CVP were almost constant and always significant in SHP elevation. However, there was no difference between Pf=0 and CVP in elevated RHP levels.

**Figure 6.** Change of zero-flow pressure (Pf=0) when right heart pressure (RHP) and pressure surrounding the heart (SHP) were varied in various combinations. Panel A: Change in Pf=0 when RHP varied from 0 to 37 mm Hg while LHP was maintained at 15 mm Hg. In lower RHP levels, the changes in Pf=0 were minimal; then, Pf=0 increased following an increase in RHP. Panels B and C: Same data presented on the abscissa of RHP or SHP. Thick lines indicate the identical value with the abscissa. In Panel B, RHP caught up the Pf=0 at higher pressure levels independent of SHP. On the other hand, Pf=0 tended to converge to a certain level which was several millimeters of mercury higher than SHP independent of RHP level.
elevation of SHP and LHP on the DPFR were not additive. In fact, the change in Pf=0 equaled the increase in SHP over the range of LHP that was studied. Therefore, we can presume that the influence of the venous return to the left ventricle on the DPFR in SHP elevation is not pronounced.

Mechanisms Determining DPFR

The results of this study indicate that SHP, RHP, and LHP are all very important factors for determination of Pf=0 in the DPFR. However, none of the three pressures significantly affected the slope of the DPFR, although the concavity was somewhat exaggerated by LHP elevation. Therefore, the main effect of the elevation of these pressures is a parallel shift of the DPFR to the right side. In other words, these pressures act on the DPFR through varying the effective back pressure, Pf=0. However, the modes of participation differ in each case.

One might speculate that the effects of SHP elevation are mediated by a rise in the coronary venous pressure; therefore, the effect of SHP elevation does not differ essentially from that of RHP elevation. Figure 5 indicates that SHP elevation raises coronary venous pressure to almost the same level as SHP itself. However, Pf=0 with both elevated SHP and coronary venous pressure was quite different from that when venous pressure was raised to the same level by RHP elevation. The mean values of Pf=0 with SHP elevation were significantly larger than those with RHP elevation (Table 1). These results indicate that SHP acts on the coronary circulation system not only through the coronary venous system but also through some other route. The results shown in Figure 6 also support this viewpoint.

These different responses of the Pf=0 to the three kinds of pressures give rise to some interpretations and/or speculations.

First, it seems almost certain that the capacitance of coronary vessels plays a very important role in the coronary circulation system, and the DPFR is apparently sensitive to the effects of capacitance. However, other factors may play a role in determining the DPFR, because the DPFR at 0 mm Hg of RHP, without being influenced by coronary vessel capacitance, exhibits a Pf=0 that is small, but significantly higher than the outflow pressure. Furthermore, coronary blood flow remained zero when the perfusion pressure was kept at the zero-flow pressure for several seconds. This finding has also been reported by Dole et al (Figure 4 in his paper).

Second, the findings that Pf=0 virtually coincided with the elevated outflow pressure (RHP) of 30 mm Hg or more, is reported here for the first time, as far as we know. At least in coronary circulation, this result would deny the hypothesis, based on rheological considerations, in which interactions between microvessels and blood maintain Pf=0 at a level higher than the outflow pressure. Third, the responses of Pf=0 to the changes in RHP shown in Table 1 and Figures 3, 5, and 6 may support the vascular waterfall theory. According to this theory, outflow pressure should not affect the effective back pressure until outflow pressure exceeds the back pressure. Following this argument, the present results are compatible with the vascular waterfall theory. When RHP was scanned from low to high level with LHP maintained at 15 mm Hg (Figure 6A), Pf=0 was relatively independent of RHP, then closed on the identity line. Similar evidence was observed when SHP was maintained at a given level (Figure 6B), or when the other pressures were kept at 0 mm Hg (Figure 3 and Table 1).

Fourth, critical closure theory is another cogent theory. According to these arguments, when perfusion pressure is below a critical level, all vascular channels regulating vasomotor tone should collapse and stop coronary blood flow. It is advantageous for critical closure theory that Pf=0 is influenced by vasomotor tone. But the possibility of complete closure in microvessels has been in doubt or contradicted. Furthermore, there has been no direct observation supporting the closure of resistance vessels. However, the present study, performed only in the maximally dilated coronary vessels, cannot exclude the possibility of critical closure, especially when the vasomotor tone is intact.

Fifth, our results regarding the behavior of the DPFR in LHP elevation are similar to the previous data and essentially agree with other reports, although the mean values of Pf=0 in their study were a little higher than those in the present study. We assumed that this small discrepancy can be attributed to the differences in the methods used. In their study, Pf=0 was the mean value obtained with two different DPFRs in which perfusion pressure was varied in an up-and-down fashion.

The effects of extracoronal vascular pressure on the perfusion pressure–blood flow relations in other organs have also been investigated. Graham et al reported the effects of alveolar pressure on the pulmonary vascular pressure-flow relation. Elevation of alveolar pressure shifted the pressure-flow relation to the right, but the shift was small in the lower perfusion pressure range. The similarity of behavior of the relation suggests that the same mechanism is also operating in the coronary circulation system.

The present study is the first to show that the degree of the shift in LHP elevation is smaller than that observed with SHP elevation. The differences between Pf=0 and LHP decreased and became negative with elevation of LHP (Figure 4). On the other hand, SHP elevation always raised the Pf=0 to a level almost 6 mm Hg higher than the SHP itself. Furthermore, when LHP was elevated equally and simultaneously with SHP, the mean values of Pf=0 nearly coincided with those of SHP elevation alone (Table 1). These results indicate that the effects of the two pressures on DPFR or Pf=0 are not additive, and Pf=0 is predominantly ruled by...
The SHP and partially affected by the LHP in the ranges examined.

Compression of the heart by SHP may cause deformation of the heart. It is then probable that the deformation yields a kinking or distortion of the intramyocardial vessels and might result in an increase in Pf=0 or vessel resistance. This is a possible mechanism governing DPFR in addition to the mediation of intramyocardial pressure. When both SHP and LHP are elevated even the cardiac geometry may be almost constant and the deformation may be minimal. In this case, mean Pf=0 values do not differ from those of SHP elevation alone, in which the cardiac size decreased and the deformation was large. Therefore, deformation of the intramyocardial vessels induced by the SHP elevation does not seem to play a leading role in determining Pf=0 or DPFR. In a similar manner, mean myocardial stress may not have a determinative influence on Pf=0. It was determined with two-dimensional echocardiography that the cardiac size is smaller in SHP elevation than in LHP elevation. In addition, it was also observed that the left ventricular cavity is still considerably patent at maximally elevated SHP. Therefore, the mean stress on the myocardium can be assumed to be higher with LHP elevation compared with SHP elevation. On the other hand, the increase in Pf=0 was apparently lower on LHP elevation than on SHP elevation. Thus, the mean stress is not likely to be a major factor for determination of Pf=0.

The present study does not clarify why Pf=0 exceeds the extramyocardial pressure; even in the case of simultaneous elevation of LHP and SHP, Pf=0 was significantly higher than these extramyocardial pressures (Table 1). It is certain that the intramyocardial pressure plays a key role, although we cannot state the relation between intramyocardial and extramyocardial pressures exactly. If intramyocardial and extramyocardial pressures were identical, the higher Pf=0 should be explained by the intrinsic characteristics of the coronary vessels even under the sufficient infusion of adenosine. Another possible explanation is that intramyocardial pressure is intrinsically higher than extramyocardial pressure. This kind of tissue pressure then determines the height of the vascular waterfall. In the current study, we were unable to determine which is the predominant mechanism. However, it is not plausible that the maximally dilated vessels have the ability to close themselves. Further investigation employing an adequate method for tissue pressure measurement is needed.

It is notable that Pf=0 indicates the zero-flow pressure in the last region in which flow stops. Therefore, it is not necessarily true that flow stops at Pf=0 in all myocardial layers. Coronary blood flow might have stopped at higher pressures in other regions of the heart. We speculate that the coronary vessels most closely related to determining Pf=0 are not homogeneously distributed from the subendocardium to the subepicardium, but that this specific vasculature may exist in the outer layer of the myocardium. In other words, we speculate that the outer layer has the lowest Pf=0, especially when only LHP is elevated.

In the present study, SHP elevation generated a pressure difference between the branch of the coronary vein and the right chamber. Coronary venous pressure increased with SHP while RHP remained at 0 mm Hg. This result indicates that there is a collapsible part between the coronary vein and the right atrium, and is not incompatible with the results of Uhlig et al. They concluded that epicardial veins are the collapsible part following the vascular waterfall mechanism. However, it is also probable that the actual operating part in which the coronary back pressure is determined exists upstream from that suggested by Uhlig et al. because Pf=0 was always significantly higher than venous pressure, except on RHP elevation.

Clinical Implication

In clinical situations, SHP is substituted for intrapericardial pressure or intrathoracic pressure. Thus we comment on the possibility that a large amount of pericardial effusion or positive pressure ventilation interferes with the coronary blood flow by reduction of actual perfusion pressure, especially in the presence of coronary artery stenosis.

In summary, the vascular waterfall mechanism may be operating in the outer layer of the myocardium in maximally vasodilated and excised canine heart. SHP is one of the factors that determines DPFR by varying Pf=0, which may correspond to the pressure at the top of the vascular waterfall.

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References


32. Stein PD, Sabbah HN, Marzilli M, Blick EF: Comparison of the distribution of intramyocardial pressure across the canine left ventricular wall in the beating heart during diastole and in the arrested heart. Evidence of epicardial muscle tone during diastole. *Circ Res* 1980;47:258-267

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