Effects of Preload on the Transmural Distribution of Perfusion and Pressure-Flow Relationships in the Canine Coronary Vascular Bed

AVERY K. ELLIS AND FRANCIS J. KLOCKE

SUMMARY We studied the effects of preload on transmural myocardial perfusion and coronary pressure-flow relationships in mongrel dogs. The left circumflex (LC) artery was cannulated and perfused through an external circuit of rigid tubing originating in the left subclavian artery and containing an electromagnetic flowmeter (EMF), a solenoid, and a short segment of soft tubing which could be occluded. The solenoid, triggered by the R-wave of the ECG, was adjusted so that perfusion occurred only during diastole. Autoregulation was abolished by maximal vasodilation with carbocromen. In 16 dogs, overall radioactive microsphere flow in the perfused LC segment was 1.67 ± 0.17 (SEM) ml/min per g at normal preload and 1.54 ± 0.19 ml/min per g at elevated preload. The endocardial:epicardial flow ratio decreased from 0.76 ± 0.03 at normal preload to 0.55 ± 0.04 at elevated preload (P < 0.01). EMF pressure-flow curves, determined by stepwise constriction of the perfusion circuit in the same dogs, showed a rightward shift with increased preload and an increase in PZF, the pressure at which inflow became zero (12 ± 0.9 mm Hg at normal preload vs. 19 ± 1.0 mm Hg at elevated preload, P < 0.01). Microsphere pressure-flow curves in eight additional dogs suggested that a small endocardial:epicardial difference in diastolic PZF at normal preload is accentuated at elevated preload. We conclude that effects of increased preload produced by volume expansion are 2-fold: (1) a selective reduction of flow in the inner layers of the heart, and (2) a shift to the right of the diastolic pressure-flow relationship. The former seems reasonably related to direct effects of preload on intramyocardial tissue pressure, whereas the latter suggests additional effects of local reflex, myogenic or mechanical phenomena.


EFFECTS of ventricular diastolic pressure on the transmural distribution of coronary blood flow are controversial. The primary difficulty in previous studies has been the separation of effects of preload from effects of autoregulatory resistance and/or mechanical consequences of systolic contraction. One approach (Kjekshus, 1973) has been to study changes in endocardial:epicardial flow ratio as a function of preload in a segment of myocardium in which autoregulation presumably was abolished by ischemia. Another (Archie and Brown, 1974; Archie, 1978) has been to minimize systolic forces by hypocalcemic diastolic arrest and then to quantify the transmural distribution of flow and resistance after maximal pharmacological vasodilation of the coronary bed. Even in these studies, however, effects of ischemia and hypocalcemic arrest remain potentially complicating factors which could account for the divergent results reported.

The present study was undertaken to quantify effects of preload on the transmural distribution of myocardial blood flow in a canine preparation in which the heart was supporting the circulation in the usual fashion and the complicating factors just mentioned were not present. Coronary flow was limited to diastole to avoid effects of systolic contraction. In addition, the coronary bed was maximally dilated pharmacologically so that changes in the distribution of coronary flow could be interpreted independently of effects of autoregulation. Pharmacological vasodilation also assured that local myocardial perfusion rates remained well above the levels normally associated with ischemia. Diastolic pressure-flow curves were obtained simultaneously in the maximally dilated bed to allow observed changes in flow to be evaluated in terms of newer concepts of coronary pressure-flow relationships (Bellamy, 1978).

Methods

Mongrel dogs weighing 20-30 kg were anesthetized with sodium pentobarbital (25 mg/kg, iv) and ventilated through a cuffed endotracheal tube with a Harvard positive pressure respirator. The chest and pericardium were opened and several catheters introduced into the left atrial appendage: one for the measurement of pressure and one for the injec-
Transmural Distribution of Perfusion at Normal and Elevated Preload

Radioactively labeled microspheres, 8–10μm in diameter (3-M Company), suspended in 10% dextran, were used to determine coronary blood flow (Rudolph and Heymann, 1967) in 16 dogs following precautions recently reviewed (Heymann et al., 1977). Specific tracers varied among experiments but included \(^{125}\)I, \(^{141}\)Ce, \(^{51}\)Cr, \(^{85}\)Sr, \(^{95}\)Nb, and \(^{46}\)Sc. Approximately \(3 \times 10^7\) microspheres were present in each injection, which was flushed into the left atrium over 15 seconds without detectable hemodynamic effects. Collection of three timed 30-second reference femoral arterial samples was begun a few seconds prior to each microsphere injection. Flow through the arterial-sampling catheter was adjusted to a rate of \(\sim 15\) ml/min and blood allowed to drip into weighed collection vials to which 1 ml of heparin had been added. Volumes of the three successive samples differed by less than 15% in all cases; only \(0.81 \pm 0.19\%\) (SEM) of the total activity was contained in the third sample. In five experiments, an additional sampling catheter was placed in the left carotid artery to verify the absence of any systematic error in reference sampling related to poor mixing of microspheres; the mean difference in carotid and femoral activity per unit flow (counts/min per ml per min) was only \(3.7 \pm 0.8\%\). Coronary venous samples were collected in five experiments coincident with microsphere injections to estimate the proportion of untrapped spheres. Venous blood from the coronary sinus was allowed to drip into a weighed collection vial containing 1 ml of heparin, beginning with the first arterial reference sample and continuing for 4–5 minutes thereafter. The percent shunting was calculated (Archie et al., 1973) and averaged only \(1.7 \pm 0.2\%\).

In each experiment, microspheres were injected under three conditions: control, vasodilation with diastolic perfusion in the LC distribution at normal preload, and vasodilation with diastolic LC perfusion at elevated preload. Vasodilation was accomplished with carbocromen (5 mg/kg, iv). Its completeness was verified by the continuing absence of reactive hyperemia after a 30-second occlusion of the inflow line; in several dogs, reactive hyperemia also was noted to be absent after a 60-second inflow occlusion. Preload was elevated by the infusion of homologous blood into a femoral vein until mean left atrial pressure reached a stable level of \(\sim 20\) mm Hg.

At the end of each experiment, the dog was killed and the heart removed and placed in 10% formalin for 3–5 days. After discarding the atria and right ventricle, the left ventricle (including the free wall and septum) was divided into five rings parallel to the mitral valve ring. The apex was discarded. The four remaining rings were cut into eight wedges, and each wedge was further subdivided into four transmural layers: subepicardium, subendocardium, and two midmyocardial layers. Each individual sample was weighed and placed in vials for \(\gamma\) counting along with the reference arterial samples. A 512-channel multiple region-of-interest \(\gamma\) counter (model 25601, Nuclear-Chicago) was employed using standard region-of-interest analysis (Heymann

![Figure 1](image-url)
operational and one with the vent closed as in the normal and elevated preload: one with the vent leave the system through this low-resistance path subsequently will be referred to as EMF pressure-sion circuit over a 1 to 2-minute period. These data variations in individual dogs was randomized, and a period of 3–5 minutes of unrestricted inflow was allowed between measurements. Tissue and reference arterial samples were analyzed in the same manner as described above, and pressure-flow curves were calculated for the epicardial and endocardial layers and the full-thickness myocardial segment. These data will be referred to as microsphere pressure-flow data.

Because untrapped microspheres in large arteries may discharge into the epicardium during systole when the solenoid is closed (Hess and Bache, 1976), five of the 16 dogs also were studied with the external perfusion circuit vented to the atmosphere during systole. This modification of the perfusion circuit is shown in the inset of Figure 1. A second solenoid, also triggered by the R-wave of the electrocardiogram, was attached to a vent tube placed between the in-line solenoid and EMF. During diastole, the in-line solenoid was open and the vent closed, so that only forward flow occurred. During systole, when the in-line solenoid was closed, the vent was open so that any microspheres that squeezed out of the larger intramural arteries would leave the system through this low-resistance path rather than being redistributed into the epicardium. Two sets of microspheres were injected at both normal and elevated preload: one with the vent operational and one with the vent closed as in the previous experiments.

Pressure-Flow Studies at Normal and Elevated Preload

In the same 16 dogs, pressure-flow studies of the perfused LC segment were performed in conjunction with microsphere measurements at both normal and elevated preload. Instantaneous end-diasstolic LC pressure and EMF flow were measured at various levels of occlusion of the inflow line, after the usual vasodilation and activation of the in-line solenoid. In four dogs, these injections were performed at normal preload in four other dogs, an initial injection was made at normal preload and subsequent injections at elevated preload. The magnitude of sequential occlusions in individual dogs was randomized, and a period of 3–5 minutes of unrestricted inflow was allowed between measurements. Tissue and reference arterial samples were analyzed in the same manner as described above, and pressure-flow curves were calculated for the epicardial and endocardial layers and the full-thickness myocardial segment. These data will be referred to as microsphere pressure-flow data.

Summary data are expressed as the mean value ± SEM. Statistical differences between findings at normal and elevated preload were evaluated by Student’s paired t-test (Snedecor and Cochran, 1967).

Results

Transmural Distribution of Perfusion at Normal and Elevated Preload

In the 16 dogs* studied at both normal and elevated preload, no systematic differences were noted between the normal area (LAD) and perfused segment (LC) during the control microsphere injection. Regional flow averaged 0.97 ± 0.09 (SEM) ml/min per g in the LAD distribution and 1.07 ± 0.11 ml/min per g in the LC (0.05 < P < 0.10, paired t test). Mean endocardial/epicardial (endo:epi) flow ratio was 0.91 ± 0.05 in the LAD distribution and 1.01 ± 0.03 in the LC (0.40 < P < 0.50).

Figure 2 shows hemodynamic tracings from a representative experiment. Panel A represents full-cycle perfusion at normal preload following vasodilation. Central aortic and LC pressure tracings show that a significant pressure gradient has developed across the perfusion circuit secondary to the increased flow velocities associated with vasodilation. Panel B shows diastolic perfusion at normal preload after activation of the solenoid; the phasic flowmeter tracing verifies that no LC inflow occurred from the beginning of isovolumic contraction to the completion of isovolumic relaxation. Panel C shows similar features at elevated preload.

Table 1 lists hemodynamic and microsphere flow data for the perfused LC segment. Mean left atrial pressure rose from an initial level of 6 ± 0.5 to 20 ± 0.9 mm Hg at elevated preload (P < 0.01). The increase in left atrial pressure was associated with an increase in mean central aortic and LC pressures of ~10 mm Hg and a decrease in heart rate of ~12 beats/min. Mean right atrial pressure, measured in five dogs, increased from 3 ± 0.5 mm Hg at normal preload to 8 ± 1.6 mm Hg at elevated preload (P < 0.05). LC microsphere flow for the full-thickness left ventricular wall averaged 1.67 ± 0.17 ml/min per g at normal preload and 1.54 ± 0.19 ml/min per g at elevated preload (P > 0.50). Epicardial flow remained unchanged when preload was elevated, whereas endocardial flow decreased from 1.40 ± 0.15 to 1.10 ± 0.15 ml/min per g (P < 0.05). The endo:epi flow ratio decreased from 0.76 ± 0.03 at normal preload to 0.55 ± 0.04 at elevated preload (P < 0.01). Figure 3 illustrates the transmural gradient of flow at normal and elevated preload across the entire myocardial wall. To reduce variation among experiments, flow in each transmural slice has been normalized by dividing it by the corresponding epicardial flow. At both normal and ele-

---

* Studies in three additional dogs in which either heart rate or central aortic pressure changed by >35% were arbitrarily discarded, although results were directionally similar to those in the 16 dogs reported here.
EFFECTS OF PRELOAD ON CORONARY PERFUSION/ Ellis and Klocke

FIGURE 2  Hemodynamic records from a representative experiment. Panel A shows tracings taken after vasodilation but prior to activation of the solenoid. Perfusion is full cycle and the mean EMF flow of 88 ml/min is 3 times greater than the prevasodilation level. Although not shown, reactive hyperemia was absent. In panel B preload is still normal, and the solenoid has been activated. An upward deflection corresponds to the open position and a downward deflection to the closed position. Panel C shows the hemodynamics at elevated preload. Abbreviations as in Figure 1.

vated preload, relative flow decreases monotonically across the myocardial wall from epicardium to endocardium. At elevated preload, the transmural gradient is appreciably greater because of the selective reduction of flow in the inner layers of the myocardium.

Hemodynamic effects of systolic venting are illustrated in Figure 4, taken from a representative experiment at normal preload. In panel A, the systolic vent has not been activated, and there is no flow, either forward or backward, during systole. In panel B, the systolic vent is operational, and the

TABLE 1  Hemodynamic and Left Circumflex Microsphere Flow Data

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean LAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>P_a (mm Hg)</th>
<th>P_i (mm Hg)</th>
<th>LC microsphere flow (ml/min per g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Normal preload</td>
<td>Mean</td>
<td>±SEM</td>
<td>±SEM</td>
<td>±SEM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>±0.5</td>
<td>±4</td>
<td>±4</td>
<td>1.67</td>
</tr>
<tr>
<td>Elevate preload</td>
<td>Mean</td>
<td>±0.9</td>
<td>±5</td>
<td>±5</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td>*/NS</td>
<td>*</td>
<td>NS</td>
</tr>
</tbody>
</table>

LAP = left atrial pressure; HR = heart rate; P_a = aortic pressure; P_i = left circumflex inflow pressure; epi = epicardial flow; endo = endocardial flow; NS = not significant (P > 0.05).

*P < 0.01, paired t-test; †P < 0.05, paired t-test.
Pressure-Flow Studies at Normal and Elevated Preload

Results from two representative EMF pressure-flow studies in the perfused LC segment are illustrated in Figure 5. Instantaneous end-diastolic flow has been plotted against end-diastolic pressure to minimize any capacitive effects occurring immediately after the solenoid is opened. A least squares linear regression line has been fitted to each set of data. The solid line was obtained at normal preload and the dashed line at elevated preload. Slopes and intercepts from all experiments are shown in Table 3. The pressure at which EMF flow became zero (PZF), taken as the intersection of each regression line with the x-axis, averaged 12 ± 0.9 mm Hg at normal preload. When preload was elevated, each regression line shifted to the right and the x-intercepts increased to 19 ± 1.0 mm Hg (P < 0.01). The mean value of the slopes, however, was unchanged (3.3 ± 0.4 vs. 3.2 ± 0.4 ml/min per mm Hg, 0.20 < P < 0.40). Correlation coefficients for individual linear regression lines varied from 0.98 to 1.00 and averaged 0.995 ± 0.007.

Representative microsphere pressure-flow studies for two of the eight additional dogs studied are shown in Figure 6. One study is at normal preload (panel A) and the other at elevated preload (panel B). In each case, three linear regression lines have been calculated: one for the pressure-flow relationship in the full-thickness LC segment, one for the epicardium, and one for the endocardium. Panel B also shows the single point obtained prior to elevation of preload. The pressure at which each microsphere flow became zero (PZF) again has been taken as the x-intercept of the regression line. Microsphere data and data from simultaneous EMF pressure-flow regression lines are summarized in Table 4. At both normal and elevated preload, PZF’s for EMF regression lines did not differ significantly from PZF’s for full-thickness, epicardial and endocardial microsphere regression lines. On the other hand, epicardial and endocardial microsphere PZF’s varied slightly but significantly at normal preload (15 ± 1.3 vs. 17 ± 1.4 mm Hg, P < 0.01) and to a greater degree at elevated preload (20 ± 2.3 vs. 26 ± 2.8 mm Hg, P < 0.05). In the dogs studied at increased preload, endocardial, epicardial, and overall microsphere flows for the preliminary injection at normal preload always fell to the left of the elevated preload regression lines (panel B, Fig. 6).

Discussion

This study indicates that, in the absence of autoregulation, increases in preload produce (1) a selective reduction in diastolic endocardial flow with an accentuated transmural gradient of flow and (2) a rightward shift of the EMF pressure-flow curve. The findings need to be considered in light of previous related work. Kjekshus (1973) reported effects of preload on both normal myocardium with
TABLE 2  Endo:Epi Ratios at Normal and Elevated Preload with and without Systolic Venting

<table>
<thead>
<tr>
<th>Dog</th>
<th>Normal preload</th>
<th>Elevated preload</th>
<th>Difference</th>
<th>Normal preload</th>
<th>Elevated preload</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.94</td>
<td>0.75</td>
<td>0.19</td>
<td>0.73</td>
<td>0.48</td>
<td>0.25</td>
</tr>
<tr>
<td>11</td>
<td>1.05</td>
<td>0.85</td>
<td>0.20</td>
<td>0.78</td>
<td>0.56</td>
<td>0.22</td>
</tr>
<tr>
<td>13</td>
<td>0.88</td>
<td>0.64</td>
<td>0.24</td>
<td>0.66</td>
<td>0.55</td>
<td>0.11</td>
</tr>
<tr>
<td>14</td>
<td>1.26</td>
<td>1.14</td>
<td>0.12</td>
<td>1.01</td>
<td>0.96</td>
<td>0.05</td>
</tr>
<tr>
<td>16</td>
<td>0.80</td>
<td>0.48</td>
<td>0.32</td>
<td>0.80</td>
<td>0.46</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Mean $\pm$ SEM 0.99 $\pm$ 0.08 0.77 $\pm$ 0.11 0.21 $\pm$ 0.03

Table 3 Slopess and X-Intercepts for EMF Pressure-Flow Studies

<table>
<thead>
<tr>
<th>Dog</th>
<th>Normal preload</th>
<th>Elevated preload</th>
<th>Normal preload</th>
<th>Elevated preload</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>24</td>
<td>5.1</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>19</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>24</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>16</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>15</td>
<td>2.5</td>
<td>1.8</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>21</td>
<td>4.1</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>20</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>18</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>18</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>18</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>22</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>22</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>22</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>13</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>18</td>
<td>1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>25</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Mean $\pm$ SEM 12 $\pm$ 0.9 19 $\pm$ 1.0 3.3 $\pm$ 0.4 3.2 $\pm$ 0.4

$P_{cz} = \text{zero-flow pressure (x-intercept of linear regression line).}$
FIGURE 6 Microsphere pressure-flow data from two different dogs, one at normal preload (panel A) and one at elevated preload (panel B). $P_{LC}$ in this case is the mean value for the entire period in which the solenoid is open. Three linear regression lines have been plotted in each case: one for the full-thickness LC segment (unfilled circles), one for the epicardium (filled squares), and one for the endocardium (filled triangles). Panel B also shows the single point obtained prior to elevation of preload.

contant infusion of adenosine. Endo:epi ratio decreased in four of five dogs when left ventricular pressure was elevated. The influence of the continuous mechanical activity associated with ventricular fibrillation is difficult to assess. In contrast to the findings of Kjekshus and Downey, Archie and Brown (1974) reported no statistically significant effects of preload on overall or regional flow or resistance in five normal dog hearts maximally vasodilated with adenosine and subjected to hypocalcemic diastolic arrest. EMF pressure-flow curves were performed only at normal preload, and the derived values for $P_{2F}$ were used for calculations of resistance at elevated as well as normal preload. Since coronary artery inflow pressures were relatively high (73-103 mm Hg), it is possible that modest effects of preload were not appreciated. A similar larger study with lower perfusion pressures (Archie, 1978) reported a decrease in endo:epi ratio with increases in preload to 20 mm Hg. Finally, the recent study of Baird and Adisesiah (1976) reporting an increase in endo:epi ratio with elevation of preload were performed with full-cycle perfusion and intact autoregulation. With coronary reserve available and no change in heart rate, the observed increase in endo:epi ratio could have reflected an increase in demand in the endocardium relative to the epicardium at elevated preload.

The present findings also need to be considered in light of several features of the experimental preparation. Elimination of autoregulation with carbocromen was deemed preferable to ischemia because the higher absolute flows could be quantified more reliably with the microsphere technique (Buckberg et al., 1971) and because potential changes in local tissue compliance resulting from ischemia were avoided. Even in the endocardium at elevated preload, flows equaled or exceeded pre-carbocromen flows in 11 of 16 dogs. Ischemia was further excluded in seven dogs by measuring percent lactate extraction simultaneously in the midcoronary sinus and at the junction of the anterior interventricular and great cardiac veins. Mean differences between these two sites were 0.3 ± 0.6% at normal preload and −1 ± 1.3% at elevated preload. These differences are well below the threshold values for detection of regional ischemia recently suggested by Roberts et al. (1979).

The most important limitation of our preparation is the likelihood that microspheres contained in intramural arteries were discharged preferentially to the epicardium during systole when the solenoid was closed (Hess and Bache, 1976). The consistent early peak in phasic LC diastolic flow in the absence of autoregulation (panels B and C, Fig. 2) suggests a refilling of prearteriolar vessels which have partially discharged their contents during systole. In view of this consideration, the endo:epi ratio of less than 1.0 at normal preload must be interpreted with caution; i.e., the observed average value of 0.76 probably represents an underestimation of the true value because of systolic redistribution of blood in intramural arteries favoring the epicardium. This interpretation is supported by the five experiments performed with and without systolic venting to the atmosphere. In these latter studies, the endo:epi flow ratio at normal preload was 0.80 ± 0.06 without venting but did not differ statistically from 1.0 with...
vent (0.99 ± 0.8). The difference in endo:epi ratio between normal and elevated preload was the same irrespective of venting (0.21 ± 0.03 vs. 0.19 ± 0.05, \( P > 0.50 \)). This difference remained constant despite potentially greater wall stresses at elevated preload, perhaps reflecting only modest increases in wall stress during volume overload (Wong and Rautaharju, 1968). Because of the small but significant increase in mean diastolic PLC and decrease in heart rate when preload was elevated, an analysis of covariance (Snedecor and Cochran, 1967) was performed to determine effects of changes in these parameters on the change in endo:epi ratio. The observed decrease in endo:epi ratio was unrelated statistically to changes in these parameters (\( P > 0.50 \) for heart rate and 0.40 < \( P < 0.50 \) for mean diastolic PLC). Additionally, endo:epi ratio decreased in all dogs regardless of whether PLC and/or heart rate changed. Thus, we conclude that increases in preload have an effect on transmural flow distribution which is independent of microsphere redistribution during systole and the modest observed changes in perfusion pressure and heart rate. This conclusion remains subject to the limitations of the experimental preparation outlined. Because of the reduced coronary perfusion pressure related to the perfusion circuit during maximal vasodilation, the observed change in flow distribution may be larger than would occur in the normally perfused heart. The systolic redistribution of flow is presumably also accentuated by the aortic-LC pressure gradient, as reflected in the endo:epi ratios in the experiments without venting. Since the experimental design was intended to avoid ischemia, the present findings could be modified during ischemia by additional complexities, e.g., altered myocardial compliance.

The approaches used to analyze EMF pressure-flow curves deserve additional comment. The curves illustrated in Figure 5 and summarized in Table 3 have been fitted by a least squares linear regression line, although individual data points in five of the total of 26 curves did suggest a slight curvilinear relationship at low pressure (e.g., Fig. 5, panel B). When a least squares second-order regression line was determined for each of the sets of data, x-intercepts (PZF) differed by only 1 ± 0.06 mm Hg. Accordingly, the first-order equation was deemed adequate. The linearity of our EMF pressure-flow relation is similar to that found by Kjekshus (1973) and Archie and Brown (1974). In contrast, Downey and Kirk (1975) predicted a vascular waterfall model for a maximally dilated coronary bed which is linear at high perfusion pressures but becomes nonlinear at the point at which perfusion pressure equals the highest tissue pressure in the system. Since these authors employed full-cycle perfusion, their EMF pressure-flow curves became curvilinear at the point at which inflow pressure equaled peak systolic pressure. In the present experiments, inflow was limited to diastole and any such "break point" might have been difficult to appreciate, since it would have occurred at very low pressures.

Of particular interest is the consistent shift to the right of the EMF pressure-flow curves when preload is elevated (Fig. 5, Table 3). The fact that these curves remain linear with the same slope at high preload implies that whatever mechanism has caused the shift affects all layers of myocardium equally. For this reason, direct effects of elevated preload on intramyocardial pressure are probably not the only mechanism involved; such effects should be greater in the endocardium than the epicardium, causing the data point actually observed at zero flow and high preload to be consistently less than the x-intercept of the regression line. The rightward shift of the pressure-flow curve also indicates that driving pressure changed less during elevated preload than suggested by the increase in LC pressure. The difference between PLC and PZF averaged 39 ± 3.6 mm Hg at normal preload and 43 ± 5.3 mm Hg at elevated preload (0.20 < \( P < 0.30 \), paired t test). Bellamy (personal communication) has suggested that coronary venous pressure is a major determinant of PZF on the basis of observations that increases in coronary sinus pressure cause an increase of similar magnitude in PZF for EMF.
pressure-flow curves derived from single heart beats. Thus, our observed increase in $P_{ZF}$ from 12 to 19 mm Hg with increased preload may relate to the increase of similar magnitude observed in right atrial pressure (3 to 8 mm Hg). The mechanism of such an effect of outflow pressure remains speculative but could involve mechanical effects of venodilation on adjacent resistance vessels as well as local reflex changes (Haddy and Gilbert, 1966; Johnson, 1959; Baez et al., 1974) unaffected by carbocromen. Myogenic or mechanical effects unrelated to venodilation are other possibilities.

The present study emphasizes the advantages of pressure-flow curves, as contrasted with single-point calculations of resistance, in characterizing impedance within the coronary bed. Limitations of single-point calculations are 3-fold: (1) because a linear relationship between driving pressure and flow is assumed, potential changes in cross-sectional area of the vascular bed as driving pressure is altered can not be appreciated; (2) since values of $P_{ZF}$ often exceed the values of right atrial or left ventricular diastolic pressure used to calculated driving pressure, absolute values for resistance are overestimated (Hoffman, 1978); (3) changes in flow relating to shifts of the pressure-flow curve are attributed incorrectly to changes in vascular cross-sectional area, rather than to changes in $P_{ZF}$. The latter changes have been inadequately considered in most previous studies of the coronary bed and may involve quantitatively important physiological mechanisms as yet undefined. The general shape of a pressure-flow curve provides information about changes in resistance as inflow pressure is altered. A linear curve implies a constant resistance (and thus a constant cross-sectional area) as inflow pressure is lowered. The reciprocal of the slope of the regression line gives a direct measure of resistance. In the present studies, since zero-flow pressure was higher than right atrial pressure at all levels of preload, calculated resistance would have been overestimated by 15-25% had driving pressure been taken as the difference between inflow pressure and right atrial pressure. Since zero-flow pressure also exceeded left ventricular diastolic pressure (at least at normal preload), resistance also would have been overestimated if driving pressure were taken as the difference between inflow and LV pressures.

Our microsphere pressure-flow data provide potential additional information about variation in diastolic $P_{ZF}$ across the myocardial wall. The endocardial-epicardial difference in $P_{ZF}$ of 2 mm Hg at normal preload increased to 6 mm Hg at elevated preload, with both differences being statistically significant. The increased difference at elevated preload presumably reflects the direct mechanical effects of preload on intramyocardial tissue pressure. These effects are manifest in our primary series of experiments as an increased transmural gradient of flow at elevated preload (Fig. 3). The failure of all microsphere $P_{ZF}$'s to differ from EMF $P_{ZF}$'s may be a result of the relatively small number of dogs studied, since one would intuitively expect EMF $P_{ZF}$ to correspond more closely to epicardial $P_{ZF}$ than to overall or endocardial $P_{ZF}$. These microsphere pressure-flow data are also subject to important limitations in interpretation, however. Microsphere flow measurements are necessarily mean values for the entire cardiac cycle; in this preparation, they include effects of systolic redistribution of blood in intramural arteries to a greater degree than end-diastolic EMF pressure-flow curves. The magnitude of this redistribution probably increases as $P_{LC}$ is reduced in the face of a constant left ventricular cavity pressure. An additional point relates to the small positive microsphere flows measured when the perfusion circuit was occluded totally, viz., the single lowest points in panels A and B, Figure 6 (EMF inflow = 0). These microsphere flows presumably originated through collateral channels as a result of the pressure gradient between the LAD and LC beds. As outlined previously, we have chosen to fit linear regression lines using all data points and to conclude that a small endocardial-epicardial difference in microsphere $P_{ZF}$ at normal preload is accentuated at elevated preload.

In summary, we conclude that effects of increased preload produced by volume expansion are 2-fold: (1) a selective reduction in flow in the inner layers of the heart and (2) a shift to the right of the diastolic pressure-flow relationship. The former seems reasonably related to direct effects of preload on intramyocardial tissue pressure, whereas the latter suggests additional effects of local reflex, myogenic, or mechanical phenomena.

Acknowledgments

We would like to acknowledge the excellent technical assistance of Charles Solos and John Curran. Dr. Rolf-Eberhard Nitz kindly provided the carbocromen for use in these studies.

References


Baird RJ, Adiseshiah M (1976) The response of diastolic myocardial tissue pressure and regional coronary blood flow to increased preload from blood, colloid, and crystalloid. Surgery 79: 644-651

† This conclusion would not be changed if the lowermost data points in each curve were excluded from the linear regression calculation.
Responses of the Heart to Stimulation of Aortic Body Chemoreceptors in Dogs

F. Karim, R. Hainsworth, O.A. Sofola, and L.M. Wood

SUMMARY We stimulated the aortic chemoreceptors in dogs that were anesthetized with chloralose and artificially ventilated by perfusing the isolated aortic arch with venous blood. Inotropic responses were determined by measuring the maximum rate of change of left ventricular pressure (dP/dt max) with aortic pressure and heart rate held constant. Stimulation of the aortic chemoreceptors resulted in an average increase in heart rate of 14 ± 2.0 beats/min (mean ± SE) from 166 ± 7.7 beats/min and an increase in dP/dt max of 501 ± 85 mm Hg/sec from 3508 ± 154 mm Hg/sec. These changes were statistically significant (P < 0.001). The afferent pathway of the reflex was shown to be in the vagus nerves and the efferent pathway in the cardiac sympathetic nerves. In some of the dogs, the carotid chemoreceptors were also stimulated. This resulted in decreases in heart rate and dP/dt max of 24 ± 24 beats/min and 758 ± 142 mm Hg/sec. Thus we have shown that stimulation of aortic chemoreceptors evokes chronotropic and inotropic responses opposite to those evoked from stimulation of carotid chemoreceptors. Circ Res 46: 77-83, 1980

STIMULATION of the carotid body chemoreceptors, with ventilation held constant, results in reflex bradycardia (Daly and Scott, 1958) and negative inotropic responses (Hainsworth et al., 1979). However, there has been no adequate study of the effect of physiological stimulation of the aortic body chemoreceptors on the inotropic and chronotropic state of the heart. Several groups of investigators have attempted to stimulate these receptors by injection of drugs such as nicotine into the open aortic arch, but the results are inconclusive largely because of inadequate localization of the stimulus to the chemoreceptors and control of pressure to the baroreceptors (Comroe and Mortimer, 1964; Stern and Rapaport, 1967; Biro et al., 1973; Stern et al., 1964).

In the present study, by vascularly isolating the aortic arch, we were able to stimulate the chemoreceptors with venous blood. The inotropic responses were assessed by measuring the maximum rate of change of left ventricular pressure (dP/dt max) with heart rate and aortic pressure held constant (Furnival et al., 1970). In four of the experiments, we also examined the cardiac responses to stimulation of the carotid body chemoreceptors.

Methods

Dogs weighing 20–29 kg were anesthetized with chloralose (0.1 g/kg body weight, Cambrian Chemicals Ltd.) infused through a catheter inserted into
Effects of preload on the transmural distribution of perfusion and pressure-flow relationships in the canine coronary vascular bed.

A K Ellis and F J Klocke

doi: 10.1161/01.RES.46.1.68

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/46/1/68.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/