Elevated right atrial pressure does not reduce collateral blood flow to ischemic myocardium

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Yu, Ying, Johnathan D. Tune, and H. Fred Downey. Elevated right atrial pressure does not reduce collateral blood flow to ischemic myocardium. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2296–H2303, 1997.—Right atrial pressure (RAP) may become substantially elevated during heart failure and has been reported to reduce collateral flow to the ischemic myocardium of isolated hearts. The effect of elevated RAP on blood flow to collateral-dependent and normal myocardium of in situ hearts was studied in 20 open-chest anesthetized dogs with acute occlusion of the left anterior descending coronary artery. Regional myocardial blood flow was measured with radioactive microspheres while RAP was elevated by restricting right ventricular (RV) outflow with constant aortic pressure. Increasing RAP from 3.8 ± 0.5 to 21.5 ± 0.8 and then to 34.3 ± 0.9 mm Hg did not reduce blood flow to any transmural region of LV normal or collateral-dependent myocardium. Further elevation of RAP to 49.3 ± 1.1 mm Hg reduced subepicardial but not subendocardial collateral flow. Blood flow to normal RV increased. Retrograde flow and peripheral coronary pressure increased as RAP was elevated. Previously injected 11-µm microspheres were present in the retrograde flow when RAP was elevated; thus retrograde capillary flow contributed to the retrograde flow. The results explain discrepancies among previous reports, and they are consistent with a waterfall phenomenon in the coronary collateral circulation.


coronary venous pressure; coronary waterfalls; microspheres; retrograde flow; regional myocardial blood flow

RIGHT ATRIAL PRESSURE (RAP) may become substantially elevated during heart failure, especially right ventricular (RV) failure. The venous drainage of the coronary circulation is predominantly to the right atrium via the coronary sinus and the anterior cardiac veins (9). Thus elevated RAP might impair coronary blood flow, particularly to ischemic myocardium.

The effect of elevated RAP on coronary and coronary collateral flow is controversial. Several investigators (3, 4, 20) have presented evidence of vascular waterfalls operating on the coronary circulation. In the presence of these waterfalls, changes in RAP and coronary venous pressure (CVP) would not affect coronary blood flow at values less than myocardial tissue pressure. Eng and Kirk (6) described waterfalls in the coronary collateral circulation that would obviate increases in RAP up to 20 mm Hg. They used the retrograde flow technique to indirectly assess coronary collateral flow. In contrast, Manor et al. (13) reported linear reductions in coronary collateral flow as RAP was increased to 23 mm Hg. They also used the retrograde flow technique to assess indirectly the effect of elevated RAP on collateral flow. Ignoring the concept of vascular waterfalls, Manor et al. (13) argued that the pressure gradient for collateral flow would fall in proportion to the rise in RAP.

In contrast to the negative implications of the report by Manor et al. (13), other investigators have demonstrated that acute, ischemia-induced myocardial damage may be alleviated by coronary sinus perturbations, i.e., intermittent coronary sinus occlusion and coronary venous retroperfusion (5, 14, 15, 17). Most recently, Sato et al. (17) measured collateral flow to the acutely ischemic myocardium of isolated nonworking hearts with partial coronary sinus obstruction. When CVP was elevated to 30 mm Hg, they detected a slight increase in collateral flow. They did not address the waterfall concept or the apparently conflicting observations of Manor et al. (13).

Whereas much of the left coronary circulation drains into the right atrium through the coronary sinus, a significant portion drains directly to the right atrium and RV (9, 18). A smaller portion drains into the left ventricle (LV) (9, 18). To what extent acute coronary artery occlusion alters the venous drainage pattern of ischemic myocardium is unknown, but drainage through pathways parallel to the coronary sinus would likely be enhanced by coronary sinus obstruction. Thus recruitment of venous pathways alternative to the coronary sinus in the presence of selective coronary sinus hypertension might explain the disparate results of Sato et al. (17) and Manor et al. (13). To date, the effect of elevated RAP on coronary collateral flow has not been measured directly.

Thus the primary aim of this study was to directly quantify the effect of elevated RAP on directly measured blood flow to acutely ischemic and normal canine myocardium. Secondary aims were to determine the effect of elevated RAP on peripheral coronary pressure (PCP; the pressure distal to a coronary obstruction) and to reexamine its effect on retrograde flow and to determine the influence of elevated RAP on the distribution of coronary venous outflow. A third aim was to determine if the increase in retrograde coronary flow produced by elevated RAP was due, at least in part, to retrograde capillary flow in the ischemic region. When RAP was elevated, we found the following. 1) Blood flow did not decrease in normal myocardium. In acutely ischemic myocardium, elevation of RAP to 30–39 mm Hg had no effect on collateral flow; further elevation to 45–53 mm Hg depressed collateral flow but only in subepicardial tissue. 2) Retrograde flow and PCP increased. 3) Coronary venous outflow drainage into the LV tended to increase. 4) Previously injected 11-µm microspheres were dislodged from the microcirculation and appeared in the retrograde flow.
METHODS

Experimental Preparation

The present study was performed in accordance with the guidelines established for animal experimentation by the Institutional Animal Care and Use Committee. Successful experiments were performed on 20 adult mongrel dogs of either sex weighing 17–31 kg. General anesthesia was induced with pentobarbital sodium (30 mg/kg iv). Supplemental pentobarbital sodium (3–4 mg/kg iv) was administered as needed to maintain a stable level of anesthesia. The dogs were ventilated with room air supplemented with oxygen.

Model 1. In model 1 (n = 16 dogs), the effects of elevated RAP were investigated in a working in situ heart. A catheter was inserted through the right femoral artery and advanced to the thoracic aorta for measuring aortic pressure (AoP). A second catheter was inserted into a femoral vein for administering supplemental pentobarbital sodium, heparin, and sodium bicarbonate. Two smaller catheters were inserted into the left femoral artery and advanced to the abdominal aorta to collect reference arterial blood samples required for measuring regional myocardial blood flow (MBF) with microspheres.

The heart was exposed through a left thoracotomy, and the fifth and sixth ribs were removed. Before the pericardium was incised, the main trunk of the azygos vein was ligated. The main trunk of the pulmonary artery and the inferior and superior venae cavae were isolated. The left anterior descending coronary artery (LAD) was isolated below its first major diagonal branch. A catheter was inserted through the left external jugular vein and advanced into the right atrium to measure RAP. After the left atrial appendage was incised, a Millar catheter-tip transducer was inserted and placed in the LV to measure LV pressure (LVP) and the changing rate of LVP (LV dP/dt). Two catheters were placed in the left atrium for measuring left atrial pressure (LAP) and for injecting radioactive microspheres.

After heparinization (500 U/kg), the right atrium was cannulated with a large cannula (ID 8 mm) that was used to supply venous return to the right heart. The right atrial cannula was connected to a 2-liter blood reservoir through a roller pump. The blood reservoir and the right atrial perfusion line were primed with blood from a donor dog. The inferior vena cava was centrally ligated and then cannulated and allowed to drain freely into the blood reservoir. During this cannulation, AoP was maintained at 50 mmHg by adjusting the right atrial perfusion. After the inferior vena cava was cannulated, the pump-controlled venous return to the right heart was adjusted to keep AoP at 85–90 mmHg. Blood reservoir temperature was kept at 37–38°C by a circulating water jacket. A filter and air trap in the perfusion system prevented air bubbles from entering the aorta. The perfusion temperature was kept at 37–38°C by a heat exchanger in the perfusion line. The pulmonary artery was ligated, and a cannula was inserted into the pulmonary artery and advanced into the LV to collect coronary venous outflow entering the right heart. A catheter was placed in the lumen of the LV through the LV apex to collect coronary venous outflow entering the left atrium. Blood from the pulmonary arterial cannula and from the LV cannula was collected in a reservoir and returned to the support dog through the femoral veins.

In experimental dogs, a catheter was inserted through the left carotid artery and advanced to the root of the aorta for measuring AoP. Another catheter was placed in the right atrium through the left jugular vein for monitoring RAP. A catheter was inserted into the right jugular vein and secured for administering supplemental pentobarbital sodium, heparin, and sodium bicarbonate before establishing the isolated heart model. The azygos vein was ligated, and the pulmonary artery, inferior and superior venae cavae, brachiocephalic trunk, and left subclavian artery were isolated. A Millar catheter-tip transducer was inserted through the left atrial appendage and placed in the LV for measuring LVP.

After the support and experimental dogs were heparinized, the left subclavian artery of the experimental dogs was cannulated centrally with a cannula connected to a pump-controlled perfusion system, which was filled with arterial blood from the support dog. The purpose of this infusion line was to maintain aortic root pressure for coronary perfusion. The brachiocephalic trunk, descending aorta, and inferior and superior venae cavae were ligated to isolate the heart from the systemic circulation. The infusion rate of arterial blood to the aorta of the experimental dog was adjusted to keep AoP and coronary perfusion pressure constant at 100 mmHg. A filter and air trap in the perfusion system prevented air bubbles from entering the aorta. The perfusion temperature was kept at 37–38°C by a heat exchanger in the perfusion line. The pulmonary artery was ligated, and a cannula was inserted into the pulmonary artery and advanced into the RV to collect coronary venous outflow entering the right heart. A catheter was placed in the lumen of the LV through the LV apex to collect coronary venous outflow entering the LV. Blood from the pulmonary arterial cannula and from the LV cannula was collected in a reservoir and returned to the support dog through the femoral venous cannula by a roller pump. The LAD was occluded and cannulated distal to its first diagonal branch to measure retrograde flow and PCP.

Experimental Protocol

Model 1. After surgical preparation, arterial blood gases were frequently monitored and kept normal by adjusting respiratory rate, tidal volume, and fractional inspired O₂ concentration. AoP was kept constant by adjusting the rate at which blood was pumped into the right atrium. Before LAD occlusion, lidocaine was given intravenously (1–1.5 mg/kg) to suppress cardiac arrhythmias. After LAD ligation, baseline regional flow was measured by injecting the first dose of differently labeled microspheres into the left atrium with normal RAP.

The superior vena cava was obstructed with a snare, and RAP was increased by gradually constricting the main trunk of the pulmonary artery with a snare. A second dose of differently labeled microspheres was injected into the left atrium when the RAP was moderately elevated to 21.9 ± 1.1 mmHg. In five dogs, RAP was then further elevated to 34.3 ± 1.3 mmHg and a third dose of differently labeled microspheres was injected into the left atrium. In four additional dogs, after regional MBF was labeled under control conditions, RAP was elevated to 49.3 ± 1.1 mmHg. AoP was held at the same normal level for all measurements of regional flow.

In six dogs, retrograde flow was measured before microsphere injection by timed collection (30–60 s) during normal
and elevated RAP with constant AoP. In three dogs, retrograde flow was also collected following microsphere injection during normal RAP. A series of retrograde flow samples was collected at normal and elevated RAP, starting 3 min after the microspheres were injected. The samples were analyzed for radioactivity. These experiments were conducted to determine whether retrograde capillary flow during elevated RAP contributed to the observed increase in retrograde flow from the vented LAD. Regional flow was not measured in these hearts. PCP was measured in one heart of this model.

Model 2. The arterial blood gases of the support dog were monitored and kept normal. The AoP of the experimental dog was kept at 100 mmHg by adjusting the flow of blood into the aortic root. RAP was elevated by restricting the RV drainage following pulmonary artery ligation. Before the LAD occlusion, the amount of coronary venous outflow that drained into the LV was assessed by timed collection during normal and increased RAP. The LAD was occluded and cannulated distal to its first diagonal branch to measure retrograde flow and PCP. Coronary drainage into the LV was again measured at normal RAP, moderately elevated RAP, and further elevation of RAP. Retrograde flow was measured by timed collection (30–60 s) during normal and increased RAP. PCP was measured in two hearts of this model. After these determinations, differently labeled doses of microspheres were injected into the aortic perfusion line to measure regional MBF during normal and increased RAP.

Measurement of Collateral Blood Flow

Collateral flow was assessed by myocardial trapping of radioactive microspheres [114 ± 0.1 µm (SD)] labeled with 141Ce, 113Sn, or 46Sc (DuPont NEN, Boston, MA). Before injection, the microspheres were dispersed in a solution of 10% dextran and agitated in an ultrasonicator and in a vortex mixer.

In model 1, ~5 × 10^6 microspheres were injected into the left atrium for each flow measurement. Duplicate reference arterial blood samples were withdrawn from the left femoral artery, starting 15 s before microsphere injection. In model 2, ~3.5 × 10^6 microspheres were injected into the perfusion line near the aortic root for each flow measurement. Duplicate reference arterial blood samples were withdrawn from the perfusion line below the site of microsphere injection. These samples were collected at a constant rate (3.5–4.3 ml/min) for 3 min, starting 15 s before microsphere injection.

At the end of the experiment, India ink was injected into the LAD cannula to identify the perfusion territory of the occluded LAD. The heart was removed and frozen. The dried tissue was defined as the collateral-dependent region. Myocardial tissue samples were taken from the normally perfused and collateral-dependent free wall of the LV and divided into epicardial, middle, and endocardial layers; from the RV and divided into epicardial and endocardial layers; and from the interventricular septum and divided into LV, middle, and RV layers. Reference arterial blood samples and tissue samples were weighed and analyzed for radioactivity in a gamma spectrometer (model 1185, Canberra Industries, Meriden, CT). MBF (ml/min) was calculated as (F_t × R_t)/R, (10), where F_t is the sampling rate of reference arterial blood and R_t and R are the radioactivities of the tissue and reference samples, respectively. MBF was divided by the tissue sample weight (g) and reported as milliliters per minute per gram. Data from duplicate sets of blood reference samples were used to compute a mean flow factor (F_t/R_t) for each microsphere injection. The difference between this mean factor and those from the individual sets averaged 1.8 ± 2.0% (SD).

Statistical Analysis

All values are presented as means ± SE unless otherwise noted. A one-way analysis of variance (ANOVA) for repeated measures was used to analyze hemodynamic variables and regional MBF. To meet the assumptions of the parametric ANOVA, subjects were randomly assigned, a Kolmogorov-Smirnov test was used to verify normality, and variability about the group mean was utilized to verify homogeneity of variances. When significance (P < 0.05) was found with ANOVA, a Student-Newman-Keuls test was then used to identify significant differences among experimental groups. In the four hearts exposed to the highest RAP, data were not collected at intermediate RAP. For these hearts, statistical comparisons were made only between control and elevated RAP. Significance was indicated by P < 0.05. Linear regression was used to analyze relationships between 1) RAP and blood flow to collateral-dependent myocardium, 2) RAP and blood flow to normal myocardium, 3) RAP and retrograde flow, 4) RAP and PCP, and 5) RAP and coronary drainage into the LV.

RESULTS

Hemodynamic Variables

Table 1 presents hemodynamic data from models 1 and 2. Mean RAP was elevated similarly in both models by restricting RV outflow. In addition, RAP was further elevated in four model 1 dogs. Systemic arterial pressure did not vary as RAP was elevated in model 1. Aortic root pressure was controlled in model 2. There were no significant changes (P > 0.05) in systemic hemodynamic variables other than RAP in either model.

Regional MBF

Preliminary analyses detected no differences between models 1 and 2 in the effect of elevated RAP on regional MBF. Therefore, observations from both models were combined and are presented in Table 2. Moderate (21.5 ± 0.8 mmHg) or further elevation of RAP (34.3 ± 0.9 mmHg) had no significant effect on transmural MBF in collateral-dependent LV myocardium (P > 0.05). Severe elevation of RAP (49.3 ± 1.1 mmHg) reduced coronary collateral flow only in subepicardium (P < 0.05). Transmural flow was not affected within the normally perfused LV myocardium or in the middle and LV layers of the interventricular septum (P > 0.05). Transmural blood flow in normally perfused RV myocardium and in the RV layer of the interventricular septum increased with moderately elevated RAP but did not increase further when RAP was elevated severely. Figure 1 shows individual values for coronary collateral flow as a function of RAP. The previously recognized variation in baseline collateral flow of the canine heart (2) is evident in Fig. 1. Most important is the absence of any tendency for elevated RAP to decrease mean collateral flow. Figure 2 shows similar data for the normally perfused region of the LV. Again, the absence of any effect of elevated RAP on normal blood flow is evident. Figure 3 presents individual measurements of blood flow in the normally perfused RV. A significant, positive effect of RAP on RV blood flow is evident (P < 0.05).
apparent aortic valvular insufficiency. LAD occlusion in dogs. Data from one dog were excluded because of severe aortic regurgitation.

Coronary Drainage Into LV

PCP also increased with RAP (Fig. 5). Retrograde flow (\( Q_{\text{ret}} \)) increased with increasing RAP (Fig. 6). The positive effect of RAP on retrograde flow is evident. Individual values are plotted in Fig. 4, where the positive effect of RAP on retrograde flow is evident.

Retrograde Flow and PCP

Retrograde flow (\( Q_{\text{ret}} \)) averaged 5.9 ± 1.3 ml/min under baseline conditions, 6.5 ± 0.8 ml/min when RAP was elevated moderately (21.5 ± 0.8 mmHg), 7.4 ± 1.2 ml/min when RAP was elevated further (34.3 ± 0.9 mmHg), and 13.5 ± 2.5 ml/min when RAP was elevated severely. Individual values are plotted in Fig. 4, where the positive effect of RAP on retrograde flow is evident.

PCP also increased with RAP (Fig. 5).

Coronary Drainage Into LV

Coronary drainage into the LV was measured in four dogs. Data from one dog were excluded because of apparent aortic valve insufficiency. LAD occlusion had no significant effect on coronary drainage into the LV (\( P > 0.05 \)). However, ventricular drainage tended to increase (\( P < 0.1 \)) as RAP was elevated (Fig. 6). Pressure in the vented LV averaged 2.3 ± 2.3 mmHg at control RAP and did not change significantly when RAP was elevated.

Radioactivity From Previously Injected Microspheres in Retrograde Flow

Figure 7 shows the fraction of the injected dose present in the retrograde flow as a function of RAP for coronary stump perfusion. A significant increase was observed with increasing RAP. The fraction of the injected dose present in the retrograde flow increased from 4.8% ± 2.7% at control RAP to 34.3% ± 14.4% when RAP was further elevated (30–39 mmHg). The increase was statistically significant (\( P < 0.05 \)).

Table 1. Hemodynamic data

<table>
<thead>
<tr>
<th>Model</th>
<th>Control</th>
<th>19–27</th>
<th>30–39</th>
<th>45–53</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>6</td>
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<tr>
<td>RAP, mmHg</td>
<td>4.1 ± 0.6</td>
<td>21.9 ± 1.1*</td>
<td>34.3 ± 1.3†</td>
<td>49.3 ± 1.1‡</td>
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<td>AoP, mmHg</td>
<td>88.4 ± 6.9</td>
<td>86.5 ± 8.2</td>
<td>90.0 ± 2.9</td>
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<tr>
<td>LAP, mmHg</td>
<td>9.2 ± 1.1</td>
<td>9.9 ± 1.1</td>
<td>11.2 ± 1.7</td>
<td>11.1 ± 1.7</td>
</tr>
<tr>
<td>LVE, mmHg</td>
<td>96.5 ± 3.8</td>
<td>95.0 ± 5.2</td>
<td>100.0 ± 4.5</td>
<td>95.0 ± 7.9</td>
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<tr>
<td>LV dP/dt, mmHg</td>
<td>6.4 ± 0.8</td>
<td>7.4 ± 1.5</td>
<td>5.4 ± 1.3</td>
<td>7.1 ± 2.6</td>
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<td>LV dP/dt, mmHg/s</td>
<td>1,286 ± 88</td>
<td>1,350 ± 182</td>
<td>1,500 ± 207</td>
<td>1,138 ± 191</td>
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<tr>
<td>LV dP/dt, mmHg/s</td>
<td>-1,427 ± 156</td>
<td>-1,500 ± 197</td>
<td>-1,580 ± 225</td>
<td>-1,063 ± 146</td>
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<td>HR, beats/min</td>
<td>160 ± 5.6</td>
<td>164 ± 6.8</td>
<td>171 ± 9.4</td>
<td>168 ± 4.8</td>
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</tbody>
</table>

Values are means ± SE; n, no. of dogs. RAP, right atrial pressure; AoP, mean aortic pressure; LAP, left atrial pressure; LVE, left ventricular end-diastolic pressure; LV dP/dt, maximum rate of left ventricular pressure development; LV dP/dt, minimum rate of left ventricular pressure development; HR, heart rate; NM, not measured. * \( P < 0.05 \) vs. control; † \( P < 0.05 \) vs. moderately elevated RAP (19–27 mmHg); ‡ \( P < 0.05 \) vs. further elevated RAP (30–39 mmHg).

Table 2. Regional myocardial blood flow

<table>
<thead>
<tr>
<th>RAP, mmHg</th>
<th>Control</th>
<th>19–27</th>
<th>30–39</th>
<th>45–53</th>
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<tr>
<td>n</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>2.3 ± 0.5</td>
<td>20.4 ± 0.4*</td>
<td>34.3 ± 1.4†</td>
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<tr>
<td>AoP, mmHg</td>
<td>100.0 ± 0.0</td>
<td>100.0 ± 0.0</td>
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</tr>
<tr>
<td>HR, beats/min</td>
<td>120 ± 8.7</td>
<td>120 ± 8.7</td>
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</table>

Values are means ± SE; n, no. of dogs. LV, left ventricle; RV, right ventricle; epi, mid, and endo, epicardial, middle, and endocardial layers of ventricular free wall, respectively. * \( P < 0.05 \) vs. control group.

Fig. 1. Relationship between right atrial pressure (X) and blood flow to collateral-dependent myocardium (Y; n = 17). Line illustrates linear regression equation: \( Y = 0.221 + 0.000136X; R^2 = 0.0003; P > 0.05 \).
one experiment. Radioactivity from previously injected microspheres in the retrograde flow collection was very low at normal RAP (2–6 mmHg) but gradually increased as RAP was elevated further (23–35 mmHg). This radioactivity increased strikingly when RAP was elevated severely (45–50 mmHg). Similar results were found in two additional experiments. Figure 8 shows the peak fraction of the injected dose of microspheres detected in the retrograde flow as a function of RAP for the three experiments. These data indicate that flow through vessels <12 µm contributed to the retrograde flow.

**DISCUSSION**

The most important finding of this investigation was that the elevation of mean RAP to values as high as
34 mmHg had no significant effect on blood flow to any transmural region of canine LV. RAP of 50 mmHg decreased collateral flow in subepicardial but not subendocardial ischemic tissue. Other important new findings were 1) elevated RAP did not affect flow to normally perfused LV myocardium but did increase flow to normally perfused RV myocardium; 2) elevated RAP increased retrograde coronary flow and PCP; and 3) elevated RAP tended to increase coronary venous drainage to the LV. These findings bear directly on the question of whether patients with RV failure would be particularly vulnerable to LV ischemia secondary to coronary artery obstruction. Previous investigations have approached this question indirectly and have produced conflicting conclusions. This is the first report of directly measured collateral flow in the presence of elevated RAP.

Recently, Manor et al. (13) investigated the effect of elevated RAP on coronary collateral flow in an isolated, nonworking canine heart model. Their approach was to measure retrograde coronary flow as RAP was increased. Manor and co-workers found, as we did, that retrograde flow increased as RAP was elevated. Although their laboratory has previously argued that retrograde flow directly reflects collateral flow (19), they reasoned that the increase in retrograde flow produced by elevated RAP was due to a redistribution of collateral flow, such that the flow through microvascular precapillary collaterals was diverted retrogradely away from the collateral-dependent region. Thus Manor et al. (13) concluded that collateral blood flow falls linearly as RAP is elevated, although they made no measurements of regional MBF. Ignoring the concept of vascular waterfalls in the coronary circulation (3, 4, 20), they argued that any increase in CVP would directly reduce the perfusion pressure gradient for coronary flow, especially to the collateral-dependent region.

Although our conclusions are different from those of Manor et al. (13), our observation of increased retrograde flow with elevated RAP is consistent with their primary data. Clearly, a different interpretation of this increase in retrograde flow is required to account for...
our observed constancy of collateral flow in the presence of elevated RAP. To resolve this dilemma, we offer evidence of two mechanisms capable of increasing retrograde flow in addition to redistribution of microvascular collateral flow. First, as shown in Fig. 5, elevation of RAP produced an increase in PCP. This would follow from a rise in collateral source pressure secondary to elevated RAP and would increase retrograde flow independently of any redistribution of microvascular collateral flow. Because PCP is a measure of the perfusion pressure gradient for antegrade collateral flow, the RAP-related rise in PCP prevented this pressure gradient from falling linearly with increased RAP as postulated by Manor et al. (13). Second, reducing the PCP to atmospheric pressure for measuring retrograde flow resulted in retrograde capillary flow when RAP was elevated. Although the phenomenon of venous coronary perfusion has been investigated by Manor and Scheel (12), they did not take into account this contribution to retrograde flow. As evidence of retrograde capillary flow, we observed that previously administered 11-µm radioactive microspheres were dislodged from the microcirculation and were detected in the retrograde flow when RAP was elevated (Figs. 7 and 8). Thus the primary observation of Manor et al. (13), that elevated RAP increases retrograde flow, can be well explained without inferring that elevated RAP decreases blood flow to collateral-dependent myocardium.

Eng and Kirk (6) did not measure blood flow to collateral-dependent myocardium as a function of RAP, but their observations on retrograde flow are relevant to this question. Eng and Kirk measured retrograde flow following acute coronary obstruction in the canine heart and found that elevation of the retrograde outflow pressure up to 23 mmHg had no effect on the retrograde flow rate. They concluded that the perfusion pressure gradient for retrograde flow was independent of this outflow pressure due to vascular waterfalls in the collateral circulation. It would follow from this argument that collateral flow would be independent of CVP or RAP as long as the waterfall pressure was not exceeded. This interpretation is consistent with the direct evidence of the present investigation that substantial elevation of RAP has no effect on directly measured blood flow to ischemic myocardium.

The presence of waterfalls in the coronary collateral circulation (6) would make collateral flow insensitive to changes in venous pressure as long as venous pressure does not exceed the waterfall pressure, which is generally considered to be a function of myocardial tissue pressure. Estimates of tissue pressure vary (11) but have ranged as high as 50 mmHg (1). To confirm the presence of waterfalls, we raised RAP to ~50 mmHg and found that collateral flow was reduced, but only in ischemic subepicardium. We hypothesize that venous drainage of ischemic midmyocardium and subendocardium has access to alternative pathways not directly affected by RAP, such as those to the LV lumen. This notion is consistent with our observation that RAP tended to increase coronary venous drainage to the LV. However, heterogeneity of venous drainage patterns within the ventricular wall has not been delineated. In addition, higher subendocardial tissue pressures might have minimized the effect of the elevated CVP on collateral flow. Rouleau and White (16) offered this explanation for the absence of a subendocardial flow deficit in normal myocardium when coronary sinus pressure was elevated to 28 mmHg following maximal vasodilation.

Most recently, Sato et al. (17) directly measured collateral flow to acutely ischemic myocardium of isolated, nonworking, canine hearts with partial coronary sinus obstruction. When CVP was elevated to 30 mmHg, they detected a slight increase in collateral flow. This increase was explained by ill-defined “sink and squeezing effects,” because collateral flow did not increase with elevated CVP in the nonbeating heart. They did not address the waterfall concept or the conflicting observations of Manor et al. (13). They did, however, offer their findings as support for coronary sinus perturbations, i.e., intermittent coronary sinus occlusion and retroperfusion (5, 14, 15, 17), which other investigators have found to alleviate damage to acutely ischemic myocardium.

Our finding that elevating RAP as high as ~34 mmHg did not reduce collateral flow to ischemic myocardium may have significant clinical implications. Patients with elevated RAP due to chronic RV failure may also experience regional LV ischemia. Whereas reperfusion of the ischemic region is clearly the highest priority, our findings indicate that steps to reduce RAP would do little to alleviate the ischemia.

Raising RAP by restricting RV output increased RV pressure and volume. The resulting increase in wall tension would have elevated RV oxygen demand and produced the metabolic hyperemia we observed. This agrees with the report of Fixler et al. (8) that increased RV pressure increased RV coronary blood flow. At the highest elevation of RAP, we did not observe a further increase in RV blood flow. We speculate that distension of the right coronary vasculature may have prevented a further increase in flow when RAP was elevated to ~30 mmHg.

In summary, raising RAP to ~34 mmHg did not affect blood flow to collateral-dependent and normal LV canine myocardium; RV blood flow increased. These findings are consistent with a waterfall phenomenon in the coronary collateral circulation, such that myocardial tissue pressure rather than RAP limits collateral flow to acutely ischemic myocardium. This waterfall protects collateral flow to ischemic LV myocardium from detrimental effects of elevated RAP. In addition, the vasculature of the ischemic inner LV wall may drain collateral flow to the LV lumen, further lessening the potentially detrimental effects of elevated RAP.

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