Transmural Right Ventricular Blood Flow During Acute Pulmonary Artery Hypertension in the Sedated Dog

Evidence for Subendocardial Ischemia Despite Residual Vasodilator Reserve

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SUMMARY. Right ventricular failure during acute pressure overload has been attributed to ischemia which occurs when maximal coronary vasodilation is achieved so that further increases in myocardial blood flow cannot occur. To test the hypothesis that coronary vasodilator reserve is exhausted during acute right ventricular pressure overload, right and left ventricular myocardial blood flow was measured in 14 awake dogs during progressive pulmonary artery occlusion; coronary vasodilator reserve was tested by infusion of adenosine (4 μM/kg per min) before and during pulmonary artery occlusion. Right ventricular myocardial blood flow rose from 0.77 ± 0.09 ml/min per g (mean ± SEM) during control conditions to 1.69 ± 0.26 ml/min per g during moderate pulmonary artery occlusion (P < 0.01). With further pulmonary artery occlusion to cause increased right ventricular end-diastolic pressure and decreased aortic pressure, a selective decrease in myocardial blood flow to the right ventricular subendocardium was observed, and the right ventricular subendocardial-to-subepicardial blood flow ratio fell from 1.36 ± 0.14 to 0.77 ± 0.06 (P < 0.05). With restoration of mean aortic pressure to control levels, right ventricular systolic pressure increased, right ventricular end-diastolic pressure decreased, and the right ventricular subendocardial-to-subepicardial ratio increased to 1.36 ± 0.18 (P < 0.01). Adenosine infusion during pulmonary artery occlusion in five dogs caused an increase in mean right ventricular blood flow (1.11 ± 0.10 to 2.25 ± 0.30; P < 0.05). This increase was most marked in the outer layers but, nevertheless, was also significant in the subendocardium. These data indicate that acute severe right ventricular pressure overload may be associated with right ventricular subendocardial hypoperfusion, even when coronary vasodilator reserve is not exhausted. (Circ Res 51: 196–204, 1982)
right ventricular pressure overload with flow during pharmacological coronary vasodilation produced by infusion of adenosine.

Methods

Eighteen adult mongrel dogs weighing 14–27 kg were anesthetized with sodium thiopental (25 mg/kg) and ventilated with a Harvard model 607 ventilator. Under sterile conditions, a left thoracotomy was performed via the 4th intercostal space. Polyvinyl catheters, 3 mm o.d., were inserted into the left atrial cavity via the left atrial appendage, the left ventricle via the apical dimple, and the right ventricular cavity via a stab wound in the right ventricular outflow tract, and secured with purse string sutures. In addition, a similar catheter was placed in the root of the aorta via the left internal thoracic artery. Hydraulic vascular occluders 16–22 mm i.d. (Hazen-Evenett Co., Inc.) were secured around the main pulmonary artery and the descending aorta just beyond the left subclavian artery. A bipolar epicardial pacing electrode was sutured to the right ventricular outflow tract. The catheters were filled with heparin solution and, together with the pacemaker wire and vascular occluder connector tubing, were tunneled to the base of the neck and placed in a subcutaneous pouch. The pericardium was loosely closed, the thoracotomy repaired, and the chest evacuated of air.

Studies were performed 7–10 days after the surgical procedure; at the time of study, each animal appeared fully recovered and was free of signs of infection. On the day of the study, the animal was sedated with a combination of fentanyl 0.01–0.02 mg/kg and droperidol 0.4–0.6 mg/kg (Innovar-Vet) to achieve a level of sedation so that the animal was sleeping when undisturbed but would respond to noises in the laboratory. The catheters, pacemaker wire, and occluder tubing were exteriorized from the subcutaneous pouch using 2% lidocaine infiltration anesthesia. The right and left ventricular catheters and the aortic catheter were connected to Statham P23Db electromanometers. The pacemaker was connected to a Grass model 588 physiological stimulator through a stimulus isolation unit. Pacing was accomplished with 3-msec square pulses at 25% above threshold voltage. Lead III of a standard electrocardiogram was obtained. Hemodynamic data were recorded on a direct-writing oscillograph system (Hewlett-Packard Co., model 8800). Studies were performed with the animals on their right sides, loosely restrained. Four of the 18 dogs were found to have right ventricular systolic pressures greater than 50 mm Hg due to premature compression of the pulmonary artery by the occluder, and were excluded from the experiment.

In the remaining 14 dogs, measurements of myocardial blood flow were made with serial injection of microspheres 15μm in diameter labeled with γ-emitting radionuclides 121I, 141Ce, 51Cr, 85Sr, 90Nb, 46Sc (3M Company) and 113Sn (New England Nuclear). The microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran so that 1.0 ml, the volume injected, contained approximately 2 × 10^6 microspheres. Before each injection, the microspheres were thoroughly mixed by alternate agitation for at least 10 minutes in an ultrasonic bath and vortex agitator. One milliliter of the microsphere suspension then was injected into the left atrium over a 3-second interval via the previously implanted catheter and flushed with 6 ml of warm saline. During each injection, a reference sample of arterial blood was withdrawn from the ascending aorta via the previously implanted catheter. Collection of the reference sample was begun 5 seconds prior to the microsphere injection and continued for 90 seconds. Reference blood samples were collected at a rate of 14 ml/min with a model 1210 Harvard withdrawal pump.

Each animal underwent several trial occlusions of the main pulmonary artery to establish the degree of pulmonary stenosis to be used during the study. The pulmonary artery occluder was gradually inflated by hand injection of saline until a point was reached at which right ventricular systolic pressure would rise no further and any further occlusion resulted in a rise in the right ventricular end-diastolic pressure, while the right ventricular systolic pressure and mean arterial pressure were observed to decrease. When a steady state had been achieved for at least 3 minutes, the volume injected into the occluder was noted; the occluder was deflated and the animal allowed to recover. This degree of pulmonary artery occlusion was designated moderate pulmonary artery constriction (MPAC).

A second more severe level of occlusion was performed by injection of additional saline sufficient to produce a rise in the right ventricular end-diastolic pressure to >10 mm Hg and a fall in mean arterial pressure of >25 mm Hg. During this intervention, severe pulmonary artery constriction (SPAC), the right ventricular systolic pressure was usually noted to decrease. Except for the intervention MPAC, all subsequent interventions with pulmonary artery occlusion were performed with this same volume of injection required to produce SPAC.

While pacing at the heart rate noted during SPAC, a third pulmonary artery occlusion was performed with the previously determined volume of injection to again produce SPAC. After a steady state was achieved for 3 minutes, the previously implanted occluder on the descending aorta was gradually inflated to restore mean arterial pressure to the previous control level; with this maneuver, right ventricular systolic pressure usually increased (Fig. 1). This intervention was designated severe pulmonary artery constriction with restoration of aortic pressure (SPAC+AP). Both occluders were then released and the animals were allowed 30 minutes to return to a hemodynamic steady state.

Measurements of regional myocardial blood flow were made during control resting conditions in 14 dogs, during MPAC (nine dogs), SPAC (14 dogs), and SPAC+AP (nine dogs). In addition, while pacing at the heart rate observed during SPAC, coronary vasodilation was produced by an infusion of adenosine (4μM/kg per min, iv), using a Harvard model 901 syringe pump. This dosage of adenosine was presumed to cause maximal coronary vasodilation because (1) no further increase in coronary blood flow is observed when larger doses are used and (2) this dosage has been observed to abolish reactive hyperemia following brief periods of coronary occlusion (Cobb et al., 1974). In addition, the dosage of adenosine of 4 μM/kg per min is equal to 1.08 mg/kg per min. This is greater than the dosage used by Rembert and associates (1980), who found that at least 1 mg/kg per min is required to produce maximal coronary vasodilation, whereas smaller dosages were found to produce non-uniform vasodilation across the wall of the left ventricle. Adenosine was dissolved in warm saline so that the desired dosage would be delivered by an infusion rate of 0.76 ml/min. The infusion was begun 10 minutes before the injection of microspheres. During the adenosine infusion, myocardial blood flow was measured during control resting right ventricular pressure in 12 dogs. In five dogs, myocardial blood flow was measured during adenosine
infusion with SPAC, and in seven dogs, blood flow was measured during adenosine infusion and pulmonary artery plus aortic occlusion identical to the intervention SPAC+TAP.

After completion of the study, the dogs were killed with a lethal dose of pentobarbital, and the hearts were removed and fixed in 10% buffered formalin. The atria, aorta, and large epicardial vessels were dissected from the heart and discarded. The area of right ventricular outflow tract, where the catheter had been implanted and the epicardial pacemaker attached, was removed and discarded. The right ventricular free wall was divided into four sections of approximately equal weight. Each section then was divided into four equal transmural layers from endocardial to epicardial surface, weighed, and placed in vials for counting.

The mean weight for the transmural right ventricular sections was 1.67 ± 0.35 g (z = 0). The left ventricle then was sectioned into four transverse sections of approximately equal thickness parallel to the mitral valve ring. The two central sections were divided into six regions: anterior free wall, septum, posterior free wall, posterior papillary muscle region, lateral wall, and anterior papillary muscle region, as previously described (Cobb et al., 1974). Each region was sectioned into four equal transmural layers from epicardium to endocardium, weighed, and placed in vials for counting. For the remainder of this paper, these layers will be referred to as “layers 1 through 4,” with layer 1 being the layer closest to the epicardium, and layer 4, the layer closest to the endocardium. Radioactivity was determined with a Packard model 5912-9771 counter, at window settings corresponding to the peak energies emitted by each radionuclide. The activities recorded in each window and the corresponding sample weights were entered into a digital computer programmed to correct for contaminant activity contributed by the associated nuclides and for background activity, and to compute the corrected counts/min per g of myocardium (Domenech et al., 1969; Heymann et al., 1977). Since the rate of withdrawal of the reference sample (Qr) and the radioactivity of the reference sample (Cr) were known, the myocardial radioactivity was used to compute myocardial blood flow (Qm): Qm = Qr × Cm/Cr.

Flow during each of the interventions was compared by three-way analysis of variance (Sokal and Rohlf, 1969). When the analysis of variance showed a significant result with P < 0.05, the Student-Newman-Keuls procedure for multiple comparisons was used (Snedecor and Cochran, 1967).

Validation of the Seven-Microsphere Method

Although Domenech et al. (1969) and Heymann et al. (1977) described stripping methods applicable to as many as six microspheres, seven microspheres were used in seven of the dogs in this study. Validation of the program for processing seven radionuclides was accomplished by counting 10 aliquots of each of the seven isotopes, then combining them and counting each of the tubes containing all seven isotopes. One group of seven isotopes was used to construct the transmural right ventricular computed components in the nine remaining groups. The mean differences, in percent, between actual and computed activity ranged from −1.25 ± 0.99% (±SEM for 51Cr to 1.03 ± 0.61% for 113Sn.

Several considerations are important for obtaining satisfactory data when using six or seven isotopes simultaneously. First, it is critical that the activity in the lower energy windows (51Cr and 141Ce) be maintained at a relatively high level, since the activity recorded in these low energy windows is subjected to multiple corrections for overlapping activity from higher energy isotopes. Conversely, the activities of the higher energy isotopes (65Sc and 85Sr) may be kept at a relatively lower level of activity, since these isotopes are subject to little overlap from higher energy compounds. Accordingly, when six or seven isotopes are used simultaneously, the relative specific activities of the isotopes must be carefully controlled. We used a specific activity for 65Sc from 2 to 5, a specific activity for 85Sr from 4 to 8, specific activity for 113Sn and 85Sr 5 to 10, and specific activity for 125I and 141Ce from 8 to 14. Because of its considerably lower counting efficiency, we used a specific activity 30 to 40 for 51Cr. Adequate separation of six or seven isotopes analyzed simultaneously requires narrow window settings to include the energy peaks for each isotope but to minimize contaminant activity from the accompanying radionuclides. This was facilitated in our laboratory by means of a Packard model 9012 multi-channel analyzer which has 1,024 channels. The count data derived from these channels is displayed continuously in histogram form on a television monitor. With this display system, the limits for each window are set at the point where the activity for that isotope exceeds 20% of the ambient activity, which includes background activity as well as activity contributed by the associated isotopes. Because the energy windows used are relatively narrow, it is critically important that the calibration of the γ-counter remain constant throughout the counting period, since even slight draft will be of significance when narrow window settings are used. Monitoring of the window settings is facilitated by the continuous visual display of all 1,024 channels, so that the windows set for each isotope may be monitored visually at any time. The windows that we have customarily used when seven isotopes are counted simultaneously are as follows: 125I from 32 to 72 keV, 141Ce from 136 to 166 keV, 51Cr from 304 to 348 keV, 113Sn from 368 to 430 keV, 85Sr from 488 to 548 keV, 85Sr from 726 to 804, and 65Sc from 834 to 1160 keV.

Results

Figure 1 shows a representative recording from a single dog. At the beginning of the tracing, the pulmonary artery occluder has been inflated (SPAC). Right ventricular systolic pressure is approximately 90 mm Hg and mean aortic pressure is 50 mm Hg. There is horizontal S-T segment depression in the coronary artery occluder has been inflated (SPAC+fAP), right ventricular systolic pressure increased with SPAC, and in seven dogs, blood flow was maintained at a relatively lower level of activity, since these isotopes are subject to little overlap from higher energy compounds. Accordingly, when six or seven isotopes are used simultaneously, the relative specific activities of the isotopes must be carefully controlled. We used a specific activity for 65Sc from 2 to 5, a specific activity for 85Sr from 4 to 8, specific activity for 113Sn and 85Sr 5 to 10, and specific activity for 125I and 141Ce from 8 to 14. Because of its considerably lower counting efficiency, we used a specific activity 30 to 40 for 51Cr. Adequate separation of six or seven isotopes analyzed simultaneously requires narrow window settings to include the energy peaks for each isotope but to minimize contaminant activity from the accompanying radionuclides. This was facilitated in our laboratory by means of a Packard model 9012 multi-channel analyzer which has 1,024 channels. The count data derived from these channels is displayed continuously in histogram form on a television monitor. With this display system, the limits for each window are set at the point where the activity for that isotope exceeds 20% of the ambient activity, which includes background activity as well as activity contributed by the associated isotopes. Because the energy windows used are relatively narrow, it is critically important that the calibration of the γ-counter remain constant throughout the counting period, since even slight draft will be of significance when narrow window settings are used. Monitoring of the window settings is facilitated by the continuous visual display of all 1,024 channels, so that the windows set for each isotope may be monitored visually at any time. The windows that we have customarily used when seven isotopes are counted simultaneously are as follows: 125I from 32 to 72 keV, 141Ce from 136 to 166 keV, 51Cr from 304 to 348 keV, 113Sn from 368 to 430 keV, 85Sr from 488 to 548 keV, 85Sr from 726 to 804, and 65Sc from 834 to 1160 keV.

Table 1 shows hemodynamic measurements during each intervention. Spontaneous heart rate increased (P < 0.01) over control during MPAC, and although heart rate increased further during SPAC, the change was not significant. Right ventricular systolic pressure increased in all dogs during SPAC, and then increased with restoration of aortic pressure by aortic constriction in the nine dogs in which aortic constriction was performed. Mean aortic pressure fell and right ventricular end-diastolic pressure increased with SPAC.

Table 2 shows mean myocardial blood flow for the right ventricle, left ventricle (excluding the interventricular septum), and the interventricular septum for
the nine dogs on which all four interventions were performed prior to adenosine infusion. Right ventricular myocardial blood flow increased significantly over control during MPAC. A significant decrease in mean right ventricular myocardial blood flow occurred from MPAC to SPAC (1.69 ± 0.26 to 0.81 ± 0.18 ml/min per g; \( P < 0.01 \)). The transmural distribution of right ventricular myocardial blood flow during SPAC was significantly altered from MPAC with a decrease in the right ventricular END/EP ratio from 1.36 ± 0.14 to 0.77 ± 0.06 (\( P < 0.05 \)). Following restoration of aortic pressure, a significant increase in mean right ventricular myocardial blood flow occurred (0.81 ± 0.18 to 1.72 ± 0.29; \( P < 0.01 \));

**Table 1**

<table>
<thead>
<tr>
<th>Hemodynamics during Acute Pulmonary Artery Occlusion (n = 9 dogs)</th>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>RV pressure (mm Hg)</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
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</tbody>
</table>

Values are mean ± se. Abbreviations: RV = right ventricle; MPAC = moderate pulmonary artery constriction; SPAC = severe pulmonary artery constriction; SPAC + TAP = SPAC after restoration of aortic pressure.

* \( P < 0.01 \), compared with control.
† \( P < 0.05 \), compared with SPAC.
simultaneously, blood flow to the subendocardium increased from 0.66 ± 0.15 to 1.79 ± 0.34 ml/min per g (P < 0.01) (Fig. 2), and the ENDO/EPI ratio was restored to 1.36 ± 0.18 (P < 0.01). These alterations in the distribution of right ventricular myocardial blood flow suggest right ventricular subendocardial hypoperfusion during SPAC.

Mean myocardial blood flow to the intraventricular septum was altered during the interventions in a manner similar to the right ventricle (Table 2). Examination of the distribution of blood flow across the interventricular septum also demonstrated a close parallel with the changes in right ventricular myocardial blood flow (Fig. 3). Myocardial blood flow to the right side of the interventricular septum rose with MPAC, fell with SPAC, and rose once again with SPAC + AP, whereas the left-sided layer had no significant change in myocardial blood flow. Thus, the ratio of myocardial blood flow to the rightmost layer of the interventricular septum and the leftmost layer (RV/LV) rose from 0.81 ± 0.03 during control to 1.61 ± 0.16 during MPAC (P < 0.01). RV/LV then fell to 0.78 ± 0.16 during SPAC (P < 0.01) and increased to 1.56 ± 0.15 following restoration of aortic pressure (P < 0.01) (Table 2). The changes in myocardial blood flow suggested that the interventricular septum was involved in the cardiac response to pulmonary artery occlusion and that underperfusion of the right side of the interventricular septum may occur during severe pressure overload.

Left ventricular myocardial blood flow was not significantly changed from control during any of the interventions (Table 2). The decrease in left ventricular ENDO/EPI ratio from 1.25 ± 0.04 to unity during pulmonary artery occlusion (P < 0.05) was probably due to changes in heart rate and aortic pulse pressure.

Myocardial blood flow was measured during adenosine induced vasodilation during control resting right ventricular pressure in all dogs. In five dogs (Table 3) adenosine was infused during SPAC with hypotension, and in seven dogs (Table 4) during SPAC after restoration of aortic pressure. Right coronary vasodilator reserve did not appear to be exhausted in either group, as adenosine increased right ventricular myocardial blood flow over that observed during both SPAC and SPAC + AP. The increase in blood flow by adenosine during SPAC occurred in the absence of any change in perfusion pressure (Table 3).

Figure 4 demonstrates that although adenosine improved blood flow to all transmural layers of the right ventricle, the increase was most marked in the outer layers. Although the increase to layer 4 was significant (0.88 ± 0.10 to 1.36 ± 0.20; P < 0.05), the ENDO/EPI actually fell slightly from 0.76 ± 0.05 to 0.61 ± 0.02 (not significant 0.10 > P > 0.05), suggesting that there

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**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Right ventricle</th>
<th>Left ventricle</th>
<th>Interventricular septum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flow (ml/min per g) ENDO/EPI</td>
<td>Flow (ml/min per g) ENDO/EPI</td>
<td>Flow (ml/min per g) RV/LV</td>
</tr>
<tr>
<td>Control</td>
<td>0.77 ± 0.07</td>
<td>1.23 ± 0.09</td>
<td>0.96 ± 0.11</td>
</tr>
<tr>
<td>MPAC</td>
<td>1.69 ± 0.26†‡</td>
<td>1.36 ± 0.14‡</td>
<td>1.18 ± 0.13</td>
</tr>
<tr>
<td>SPAC</td>
<td>0.81 ± 0.18†</td>
<td>0.77 ± 0.06†</td>
<td>0.81 ± 0.09</td>
</tr>
<tr>
<td>SPAC+AP</td>
<td>1.72 ± 0.29†‡</td>
<td>1.36 ± 0.18‡</td>
<td>1.14 ± 0.11</td>
</tr>
</tbody>
</table>

Abbreviations: ENDO/EPI = ratio of endocardial to epicardial blood flow; RV/LV = ratio of rightmost layer to leftmost layer blood flow.

* P < 0.05, compared with control.
† P < 0.05, compared with MPAC.
‡ P < 0.05, compared with SPAC.
was appreciably less vasodilator reserve in the sub-
endocardium than in the outer layers.

During the adenosine infusion, the left ventricular tran-
smural blood flow was uniformly distributed, supporting that an adequate dose of adenosine was used for vasodilation, as lower doses have been shown to increase endocardial blood flow selectively and result in ENDO/EPI ratios that are much greater than unity (Rembert et al., 1980).

**Discussion**

In an early study, Guyton et al. (1954) demonstrated a close correlation between the maximal increase in right ventricular systolic pressure during pulmonary artery occlusion and the preclosure systemic arterial pressure in dogs in which circulatory reflexes had been abolished, thus signaling the importance of right coronary perfusion pressure during increased right ventricular pressure. Salisbury (1955) and more recent investigators demonstrated a reversal of acute right ventricular failure by augmentation of aortic pressure (Cooper et al., 1975; Spotnitz et al., 1971; Vlahakes et al., 1979) or by mechanically increasing right coronary artery blood flow (Brooks et al., 1971).

Fixler and coworkers (1973) demonstrated an initial increase followed by a decline in right ventricular myocardial blood flow during progressive pulmonary artery occlusion. These investigators postulated that during acute right ventricular pressure overload, maximal coronary vasodilation occurs in the right coronary bed so that myocardial blood flow becomes dependent upon the pressure gradient between the aorta and right ventricle. Thus, right ventricular myocardial blood flow, and, therefore, right ventricular performance, would be altered by changes in mean arterial pressure during acute right ventricular hypertrophy. The present study extends these findings by demonstrating in the awake dog the ability to reverse right ventricular failure during acute pulmonary artery occlusion by increasing aortic pressure. However, these data indicate that although coronary vasodilator reserve did not appear to be exhausted, severe pulmonary artery occlusion was associated with a significant reduction in the right ventricular ENDO/EPI ratio. Restoration of aortic blood pressure selectively increased myocardial blood flow to the inner layer of the right ventricular free wall and improved right ventricular performance without altering the degree of pulmonary artery occlusion. The relatively modest increase in right ventricular myocardial blood flow following augmentation of aortic pressure in this study differs from previous reports. Cooper et al.

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>RV pressure (mm Hg)</th>
<th>Aortic pressure (mm Hg)</th>
<th>Aortic pressure (mean mm Hg)</th>
<th>RV MBF (ENDO/EPI)</th>
<th>LV MBF (ENDO/EPI)</th>
<th>IVS MBF (ENDO/EPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAC</td>
<td>190 ± 4 (paced)</td>
<td>80 ± 4*</td>
<td>67 ± 3*</td>
<td>50 ± 3*</td>
<td>1.11 ± 0.10†</td>
<td>0.65 ± 0.07†</td>
<td>0.77 ± 0.06‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 ± 1*</td>
<td>43 ± 2*</td>
<td></td>
<td>(0.76 ± 0.08)</td>
<td>(1.40 ± 0.10)</td>
<td>(0.85 ± 0.11)</td>
</tr>
<tr>
<td>Adenosine†</td>
<td>197 ± 9 (paced)</td>
<td>77 ± 4*</td>
<td>75 ± 5*</td>
<td>52 ± 2*</td>
<td>2.25 ± 0.30†</td>
<td>2.30 ± 0.52†</td>
<td>1.86 ± 0.48†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 ± 3*</td>
<td>42 ± 1*</td>
<td></td>
<td>(0.61 ± 0.02)</td>
<td>(1.35 ± 0.25)</td>
<td>(0.90 ± 0.30)</td>
</tr>
<tr>
<td>Adenosine‡</td>
<td>197 ± 9 (paced)</td>
<td>42 ± 1‡</td>
<td>105 ± 8‡</td>
<td>68 ± 3‡</td>
<td>3.92 ± 1.06‡</td>
<td>4.33 ± 1.07‡</td>
<td>4.07 ± 1.02‡</td>
</tr>
<tr>
<td>No PAC</td>
<td>197 ± 9 (paced)</td>
<td>2 ± 1†</td>
<td>52 ± 2†</td>
<td></td>
<td>(1.24 ± 0.02)</td>
<td>(0.76 ± 0.03)</td>
<td>(1.12 ± 0.09)</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR = heart rate (beats/min); MBF = myocardial blood flow (ml/min per g); LV = left ventricle (septum not included); IVS = interventricular septum; PAC = pulmonary artery constriction. Remainder the same as Table 1.

* P < 0.05 vs. adenosine, no PAC.
† P < 0.05 vs. SPAC.
‡ P < 0.05 vs. SPAC + adenosine.
Hemodynamics and Regional Myocardial Blood Flow in Dogs with Adenosine Infusion during SPAC+|AP (n = 7)

<table>
<thead>
<tr>
<th>HR (mm Hg)</th>
<th>RV pressure (mm Hg)</th>
<th>Aortic pressure (mean mm Hg)</th>
<th>Aortic pressure (mean mm Hg)</th>
<th>RV MBF (ENDO/EPI)</th>
<th>LV MBF (ENDO/EPI)</th>
<th>IVS MBF (ENDO/EPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAC+</td>
<td>AP 173 ± 8</td>
<td>87 ± 7*</td>
<td>115 ± 8</td>
<td>88 ± 6</td>
<td>1.40 ± 0.18</td>
<td>1.17 ± 0.17</td>
</tr>
<tr>
<td>Adenosine 173 ± 8</td>
<td>87 ± 6*</td>
<td>106 ± 8</td>
<td>77 ± 4</td>
<td>2.08 ± 0.35†</td>
<td>1.96 ± 0.32†</td>
<td>1.61 ± 0.29†</td>
</tr>
<tr>
<td>SPAC+</td>
<td>AP (paced) 8 ± 2*</td>
<td>65 ± 5</td>
<td>(1.35 ± 0.27)</td>
<td>(0.98 ± 0.06)</td>
<td>(1.38 ± 0.26)</td>
<td></td>
</tr>
<tr>
<td>Adenosine 173 ± 8</td>
<td>34 ± 3†§</td>
<td>118 ± 7</td>
<td>89 ± 6</td>
<td>4.57 ± 0.76†§</td>
<td>4.70 ± 0.63†§</td>
<td>4.95 ± 0.90†§</td>
</tr>
<tr>
<td>No PAC (paced) 2 ± 1†§</td>
<td>67 ± 7</td>
<td>(1.63 ± 0.29)</td>
<td>(0.99 ± 0.18)</td>
<td>(1.28 ± 0.07)</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: Same as Table 3.
* P < 0.05, compared with adenosine and no PAC.
† P < 0.05, compared with SPAC+|AP.
§ P < 0.05, compared with adenosine + SPAC+|AP.

(1975) and Vlahakes et al. (1979) reported substantial increases in right ventricular myocardial blood flow after increasing aortic pressure during acute right ventricular pressure overload. Both of these studies, however, utilized open-chest anesthetized animals, so that coronary vascular reflexes may have been altered. Also, in this study, mean aortic pressure was restored only to control levels, whereas both previous studies raised aortic pressure to approximately 140% of control. In this study, heart rate was controlled by pacing to prevent the reflex decrease in heart rate following aortic constriction. Neither previous study reported the effects of aortic constriction on heart rate, nor was pacing used to control this variable.

Previous reports which examined the transmural distribution of right ventricular myocardial blood flow did not detect significant changes in the ENDO/EPI ratio during right ventricular pressure overload (Fixler et al., 1973; Manohar et al., 1978). Fixler et al. (1973) utilized open-chest dogs and achieved a mean right ventricular systolic pressure of 53.1 ± 15.4 mm Hg, considerably less than in this study. Also, the right ventricular free wall was sectioned into three layers, versus four in this study. This difference in sampling technique may have obscured subtle differences in transmural blood flow distribution. There are several methodological differences between the study by Manohar et al. (1978) and this study. Closed-chest ponies were studied under ketamine hydrochloride and sodium thiouamil anesthesia, paralyzed with d-tubocurarine, and ventilated with positive pressure respiration. In addition, the right ventricular free wall was sectioned into only two layers.

The significant decline in the right ventricular ENDO/EPI ratio observed in this study during severe pulmonary artery occlusion suggests subendocardial ischemia (Buckberg et al., 1972). This finding is in agreement with the report by Vlahakes et al. (1979), who demonstrated a decrease in ATP and creatine phosphate, as well as an increase in the ratio of lactate to pyruvate content in right ventricular myocardial biopsies obtained during acute right ventricular failure. The marked horizontal ST segment depression in lead III of the electrocardiogram, although not specific for the right ventricle, also suggests myocardial ischemia (Fig. 1).

The alteration in transmural right ventricular myocardial blood flow in this study is similar to alterations observed in the left ventricle during an abrupt increase in aortic systolic pressure (Anrep effect). Walton et al. (1978) reported significant subendocardial underperfusion early (5 seconds) after abrupt aortic

![Figure 4. Transmural distribution of right ventricular myocardial blood flow during SPAC and SPAC plus adenosine infusion. Despite no change in arterial perfusion pressure, MBF (ml/min per g) increased in all layers, the increase was most marked in the outer layers, although flow to layers 3 and 4 also increased significantly. Abbreviations: Same as Table 1. * P < 0.05, compared with SPAC.](http://circres.ahajournals.org/)

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occlusion to produce acute left ventricular systolic overload, followed by restoration of uniform transmural blood flow at 30 seconds, as the left ventricle recovered from initial decompensation. In the present study, pulmonary artery occlusion was performed more gradually, and measurements of myocardial blood flow were made 3 minutes after the dogs had achieved a hemodynamic steady state. Nevertheless, it is likely that increased impedance to subendocardial blood flow during systole contributed to the decrease in ENDO/EPI ratio during severe pulmonary artery occlusion (Walston et al., 1978; Monroe et al., 1972). Myocardial blood flow during systole is principally determined by the dynamic interaction of perfusion pressure, vasomotor tone, and intramyocardial pressure (Downey and Kirk, 1974; Hess and Bache, 1976; Hess and Bache, 1979; Bellamy and Lowensohn, 1980). Unlike the left ventricle, during normal intraventricular pressures, right coronary artery blood flow occurs equally throughout the cardiac cycle (Lowensohn et al., 1976). However, when right ventricular systolic pressure is equal to or greater than aortic pressure, right coronary artery blood flow decreases during systole so that flow occurs mainly in diastole (Fixler et al., 1973). In this situation, vasomotor tone in the right coronary bed would have to be altered so that diastolic blood flow could be preferentially distributed to the right ventricular subendocardium. Despite residual coronary vasodilator reserve, the capacity to direct flow to the subendocardium appeared to be exhausted during severe pulmonary artery constriction in this study. It is likely that the increased right ventricular diastolic pressure further impaired right ventricular subendocardial perfusion in a manner similar to that which occurred in the left ventricle, as demonstrated by Kjekshus (1973).

The present data support the concept that right ventricular ischemia contributes to the development of failure during acute systolic overload, since increases in right ventricular blood flow produced by increasing aortic perfusion pressure improved right ventricular performance. Despite evidence for right ventricular ischemia during acute systolic overload (Vlahakes et al., 1979), it is clear that the coronary vasculature was not maximally vasodilated, since infusion of adenosine significantly increased right ventricular blood flow during right ventricular pressure overload. This paradox of residual coronary vasodilator capacity at a time when failure is occurring suggests the possibility that reflexly mediated coronary vasoconstriction may have limited myocardial blood flow during acute right ventricular systolic overload. In support of this, Domenec and Ayuy (1974) demonstrated that left ventricular blood flow decreased 18.9% during moderate pulmonary artery constriction in open chest dogs, whereas, after α-adrenergic blockade with phenoxybenzamine, left ventricular blood flow increased 14% during a similar degree of pulmonary artery constriction. This finding suggested that right ventricular overload elicited α-adrenergic coronary vasoconstriction which caused a reduction of left ventricular myocardial blood flow. Competition between metabolic vasodilator influences and α-adrenergic vasoconstrictor influences has previously been demonstrated (Schwartz and Stone, 1977). Murray and Vatner (1979) found that coronary blood flow increased to higher levels during exercise in dogs after α-adrenergic blockade, again supporting the concept of competition between metabolic vasodilator influences and sympathetic vasoconstrictor tone. The finding in the present study that coronary vasodilator reserve capacity had not been exhausted during severe pulmonary artery occlusion similarly suggests that reflexive vasoconstrictor activity may have limited right ventricular myocardial blood flow.

It is of interest that during right ventricular pressure overload, adenosine infusion caused increases in mean right ventricular blood flow which were similar to or greater than those produced by aortic constriction, but these adenosine-induced increases in myocardial blood flow were not associated with enhanced ability of the right ventricle to generate pressure and did not significantly decrease right ventricular end-diastolic pressure. This difference may have resulted from the difference in the distribution of the increased blood flow during adenosine infusion as compared with aortic constriction. Thus, in nine dogs with severe pulmonary artery constriction, increasing the aortic pressure increased the right ventricular ENDO/EPI blood flow ratio from 0.77 ± 0.06 to 1.36 ± 0.18 (P < 0.01) (Table 2), while increasing right ventricular blood flow with adenosine in five dogs resulted in a further decrease in the ENDO/EPI ratio from 0.76 ± 0.05 to 0.61 ± 0.02 (Table 3). If severe right ventricular pressure overload causes ischemia primarily in the subendocardium, recovery from failure may require substantially increased blood flow to the subendocardium, a change which was especially prominent during increased aortic pressure but significantly less during adenosine infusion.

Manohar et al. (1978) suggested that additional coronary vasodilator capacity existed during acute right ventricular hypertension by demonstrating higher right ventricular myocardial blood flow during the combination of pulmonary occlusion and hypoxia than during pulmonary artery occlusion alone. Moreover, previous studies of right ventricular myocardial blood flow (Love and O’Meallie, 1963; Aukland et al., 1967; Fixler et al., 1973; Domenec and Ayuy, 1974; Manohar et al., 1978; Vlahakes et al., 1979) during acutely increased right ventricular pressure reported levels of right ventricular myocardial blood flow less than those observed in the right ventricle during maximum vasodilation with adenosine or during heavy exercise (Ball et al., 1975).

Similar to previous reports (Fixler et al., 1973; Manohar et al., 1978) blood flow to the right side of the septum during increased right ventricular pressure was altered in a manner similar to the changes observed in the right ventricular free wall. Blood flow to the rightmost layer of the septum decreased markedly during severe pulmonary artery constriction and rose
with restoration of aortic pressure, paralleling changes in the right ventricular subendocardium. This observation provides support for the hypothesis that ischemia of the interventricular septum may contribute to the development of right ventricular failure (Kajan, 1952; Fixler et al., 1977; Brooks et al., 1977).

In summary, there is substantial evidence that myocardial ischemia may occur during acute right ventricular hypertrophy. In this study severe systolic overload resulted in right ventricular subendocardial hypoperfusion, and restoration of uniform transmural right ventricular myocardial blood flow was associated with enhanced right ventricular mechanical performance. Despite right ventricular subendocardial hypoperfusion during acute right ventricular hypertrophy, vasodilator reserve was not exhausted, since adenosine infusion further increased right ventricular myocardial blood flow.

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