Regional Myocardial Blood Flow and Myocardial Function during Acute Right Ventricular Pressure Overload in Calves

MURLI MANOHAR, GERALD E. BISGARD, VICTORIA BULLARD, JAMES A. WILL, DEBRA ANDERSON, AND JOHN H. G. RANKIN

SUMMARY  Hemodynamics, myocardial function, and regional myocardial blood flow (MBF) were measured during acute right ventricular (RV) pressure overload created by inflation of a previously implanted cuff to constrict the pulmonary artery trunk (PAC) in seven closed-chest, anesthetized calves during normoxia (PaO₂: 90-110 mm Hg) and hypoxia (PaO₂ ~ 40 mm Hg). MBF was determined by the microsphere method. With PAC, mean RV systolic pressure approached 90 mm Hg or higher and tricuspid regurgitation occurred frequently. There was no indication of increased RV contractility when alterations in preload and afterload were taken into account, nor was there evidence to suggest deterioration of left ventricular contractility during PAC with normoxia or hypoxia. During normoxia + PAC, there was an insignificant increase in blood flow to the RV free wall and right side of the interventricular septum over their respective control values. However, with hypoxia + PAC, myocardial perfusion to these regions registered a significant increase over the control hypoxic values despite similar coronary driving pressure and RV tension time index. This suggests that coronary vascular reserve had not been exhausted during normoxia + PAC in these areas of the ventricular myocardium. Selective underperfusion of RV endocardium did not occur during either PAC period. The tendency of blood flow to increase in the right side of the septum with PAC during normoxia and hypoxia supports the view that the right side of the septum aids the RV contraction.

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A SIGNIFICANT number of cattle exposed to chronic hypoxia of high altitude develop right ventricular (RV) failure (Hecht et al., 1962; Jensen et al., 1976), classically referred to as brisket disease or high mountain disease. Hemodynamic measurements on normal calves exposed to acute as well as chronic hypoxia have revealed that, besides a significantly increased pulmonary vascular resistance, there is a pronounced decline in stroke volume, although the cardiac output remains virtually unchanged (Ruiz et al., 1973). A similar decline in stroke volume has been reported in man (Klausen, 1966) on chronic exposure to high altitude hypoxia. Although the mechanism responsible for such a significant decrease in stroke volume is still a matter of speculation (Will and Bisgard, 1975), it has been observed that administration of 100% oxygen to calves after 4 weeks of exposure to high altitude reverses this decline in stroke volume, a finding which has prompted the suggestion that there is a reversible depression of myocardial contractility during hypoxic exposure in the calf (Ruiz et al., 1973). Grover et al. (1976) have observed a significant decrease in left ventricular (LV) blood flow in human volunteers exposed to high altitude hypoxia. Although the right ventricle is the chamber under immediate stress from hypoxic pulmonary hypertension, data on blood flow to the RV myocardium of the calf during the stress of acute or chronic RV pressure overload are not available.

The existing literature on myocardial blood flow (MBF) during acute RV pressure overload is often contradictory. Fixler et al. (1973) did not find a significant increase in blood flow to RV myocardium at moderate RV pressure overload in open-chest anesthetized dogs (mean RV systolic pressure = 53.1 mm Hg), whereas blood flow to the LV wall and the septum decreased significantly. In another report (Domenech and Ayuy, 1974), the acute RV pressure overload in dogs resulted in a marked decline in total cardiac flow, although the fraction going to RV myocardium increased by 16.3% above the control values. Some authors (Aukland et al., 1967) have reported increases in blood flow to the RV myocardium with little or no change in coronary vascular resistance (CVR) in the LV wall during RV pressure overload in canines. Others (Gregg et al., 1943; Love and O'Meallie, 1963) have observed a decrease in CVR in LV myocardium and thus an increase in left coronary flow.

The purpose of the present experiments was to study the regional MBF and myocardial function during acute RV pressure overload during normoxia
(defined as the period when the calves breathed a mixture of $O_2$ and $N_2$ sufficient to maintain their arterial $O_2$ tension between 90 and 110 mm Hg) and acute isocapnic hypoxia in closed-chest anesthetized calves.

**Methods**

Seven male calves belonging to the Holstein (three calves), Brown Swiss (two), Jersey (one), and Ayreshire (one) breeds were used. Their mean weight was 90.8 kg ($\pm 7.5$ SEM). All the animals were judged, based on physical examination including auscultation, to be in good physical condition and free of detectable cardiovascular disease. Each calf was studied during two different periods normoxia and isocapnic hypoxia, before (control) and during RV pressure overload induced by partial constriction of the pulmonary artery (PAC) trunk. PAC was accomplished by inflation of a previously implanted cuff around the main pulmonary artery. Between 15 and 45 days prior to the study, each calf underwent left lateral thoracotomy for implantation of an inflatable cuff around the pulmonary arterial trunk. Also, two catheters were implanted in the pulmonary artery, one proximal (towards the right ventricle) and one distal to the cuff. Another catheter was advanced into the left atrium via the pulmonary vein draining the apical lobe of the left lung.

**Preparations and Procedures**

On the day of study, the calves were anesthetized with thiamylal sodium administered intravenously (25 mg/kg body weight). After intubation, the left jugular vein and left carotid artery were exteriorized to advance a 7F catheter tip manometer (Millar Instruments, Inc.) in each ventricular chamber. PE 190 catheters were advanced via the same jugular vein into the right atrial and RV chambers. Also, we catheterized the right saphenous artery (five calves) or the middle coccygeal artery (two calves) for withdrawal of reference arterial blood.

After the catheters were positioned in the proper cardiac chambers and blood vessels, anesthesia was maintained by intravenous administration of ketamine hydrochloride (Vetalar, Parke-Davis), 1–2 mg/kg body weight, at intervals of 25–35 minutes. After the change to ketamine, $d$-tubocurarine chloride (Eli Lilly & Co.) was administered by a slow intravenous injection (0.1 mg/kg body weight), and artificial ventilation was begun with a Bird Mark 9 respirator and a flow-regulated system to deliver the desired mixture of $O_2$ and $N_2$. The ventilation was adjusted to maintain arterial pH and $P_{aco_2}$ within normal limits.

An interval of at least 30–60 minutes elapsed between the start of artificial ventilation and the first set of control normoxic measurements. Curare was administered whenever the calf attempted to breathe spontaneously. The aortic, proximal pulmonary arterial (close to the pulmonic valve), distal pulmonary arterial (near bifurcation of the artery), RV, right atrial, and left atrial pressures were recorded by fluid-filled systems free of bubbles and Statham P23Db (Statham Medical Instruments, Inc.) strain gauges on a physiograph (Gilson Medical Electronics). Indocyanine green (Cardiogreen; Hynson, Westcott & Dunning) was injected into the right ventricle and blood was withdrawn from the aorta at a known constant rate through a linear densitometer. The area of the resultant curve was measured by semilogarithmic plotting of the downslope by computer program. Simultaneous with aortic blood withdrawal, blood also was withdrawn from the right atrium at a constant rate through another densitometer, to detect the presence of tricuspid insufficiency. In two calves, cardiac output also was determined by injection of indocyanine green into the pulmonary artery and aortic blood withdrawal as described above.

After the above measurements had been completed, the RV pressure was recorded at a paper speed of 200 mm/sec from the catheter tip micromanometer, and the signal was differentiated using the R-C differentiating circuit to record its dP/dt. Also, the proximal pulmonary arterial pressure was recorded simultaneously from the Statham P23Db transducer, as was the base-apex lead electrocardiogram. The LV pressure from the catheter tip manometer and its dP/dt, the aortic pressure from the Statham P23ID transducer, the base-apex lead electrocardiogram, and the external phonocardiogram then were recorded simultaneously at a paper speed of 200 mm/sec (DR-8, Electronics for Medicine).

Regional myocardial blood flow was determined in each calf by four different nuclides. Only microspheres (3M Company, Nuclear Products) 15 ± 3 $\mu$m in diameter (labeled with $^{111}$Ce, $^{46}$Sc, $^{125}$I, $^{113}$Sn) were used. The microspheres were injected into the left atrium, and a reference arterial sample was drawn at a constant rate of 13.8 ml/min from a peripheral (saphenous or middle coccygeal) artery, beginning just before the microsphere injection and continuing for 90 seconds after the injection. Each injection of microsphere suspension had approximately 3,000,000 spheres. The order of isotopes was randomized between the four steps (normoxia, normoxia + PAC, hypoxia, and hypoxia + PAC) of the study. Since the microspheres are distributed in proportion to flow, the regional myocardial flow was determined from the equation: myocardial flow/myocardial nuclide activity = reference sample flow/reference sample activity. Hemoglobin concentration of the blood was determined with each blood flow measurement by the cyanmethemoglobin technique.

At the end of each experiment, calves were killed and their hearts were removed. The epicardial fat, large coronary vessels, great arteries, valves, chordae tendineae, and atria were separated from the ventricles. The free wall of the RV was cut from
the interventricular septum and was divided into two layers of about equal thickness. The free wall of the LV was separated from the septum and divided into three layers (endocardial, middle, and epicardial) of about equal thickness. Similarly, the interventricular septum was divided into right, middle, and left layers of about equal thickness. The tissue from each region was cut into tiny pieces, put into several preweighed vials which were weighed again, and the tissue was counted in a gamma scintillation counter (1185 series, Nuclear-Chicago).

Before starting any set of measurements for this study, we collected anaerobically one or more arterial blood samples for determination of pH, PaO2, and PaCO2, using appropriate electrodes at 38°C (Radiometer, The London Company). The blood variables were corrected to the calf's rectal temperature according to temperature coefficients published for humans (Severinghaus, 1966).

**Measurements and Calculations**

The cardiac output and stroke volume were corrected for body surface area (BSA) to calculate cardiac index (CI) and stroke index (SI) by the formula (Brody, 1945): BSA (in m²) = 0.15 × (body weight in kg) 0.42. LV and RV work were calculated as follows: LV work (kg·m/min/m²) = CI × AOM × 13.6/1000, and RV work (kg·m/min/m²) = CI × PPA × 13.6/1000, where AOM and PPA stand respectively, for mean aortic pressure and mean pulmonary arterial pressure proximal to the cuff.

The LV oxygen consumption was estimated from the rate pressure product (RPP = aortic peak systolic pressure × heart rate/100), and the LV tension time index (LVTTI) was measured by planimetry of the area under the systolic portion of the LV pressure curve (Sarnoff et al., 1958). The right ventricular tension time index (RVTTI) was measured by planimetry of the area beneath the systolic portion of the RV pressure curve. Several investigators (Fixler et al., 1973; Buss and Bisgard, 1976) have suggested the use of RVTTI as a hemodynamic variable. For the contractility data, the analysis of variance was carried out in the same manner, with individual beats serving as a third factor. A value of P < 0.05 was considered statistically significant.

The hemodynamic data (Table 2) reveal that the CI was significantly increased from the control values during hypoxia alone, but this increase in CI was not due to an increase in SI, which remained almost unchanged. Each PAC was associated with an insignificant decline in CI and SI from the cor-

The pressure-velocity indices VPM and Vmax (Mason, 1969) based on total ventricular pressure for the LV also were calculated, as follows. Total LV pressure (PT) and simultaneous dP/dt were digitized manually at 5-msec intervals throughout the period of isovolumic contraction. A graph plotting PT on the abscissa and the quantity dP/dt/PT on the ordinate was constructed. A constant K, representing the stiffness factor of the series elastic component, was omitted from these calculations, because an appropriate value for this constant has not been established for the calf heart (Buss and Bisgard, 1976). The maximal calculated value of (dP/dt)/PT was recorded as peak measured velocity or VPM. The points from each beat that fell on the linear downslope of the pressure-velocity curve were extrapolated to zero PT by linear regression (Steel and Torrie, 1960). This was called Vmax.

CVR was calculated by the formula: CVR = mean aortic pressure/regional myocardial flow.

**Analysis of Data**

The hemodynamic data were analyzed by a two-way analysis of variance followed by Duncan’s multiple range test (Steel and Torrie, 1960) for testing significance among treatment means for a given variable. For the contractility data, the analysis of variance was carried out in the same manner, with individual beats serving as a third factor. A value of P < 0.01 was considered statistically significant.

The data on MBF and CVR were subjected to a two-way analysis of variance, following which appropriate comparisons were tested by orthogonal partitioning (Steel and Torrie, 1960) of the sum of squares of the treatments. A value of P < 0.01 was considered statistically significant. Duncan’s multiple range test also was employed.

**Results**

Arterial blood gas tensions, pH, and hemoglobin values are presented in Table 1. The pH and PaCO2 were maintained close to control values throughout the study.

**Hemodynamics**

The hemodynamic data (Table 2) reveal that the CI was significantly increased from the control values during hypoxia alone, but this increase in CI was not due to an increase in SI, which remained almost unchanged. Each PAC was associated with an insignificant decline in CI and SI from the cor-
TABLE 1  **Summary of Acid-Base Data and Arterial Blood Gas Tensions**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normoxia</th>
<th>Normoxia + PAC</th>
<th>Hypoxia</th>
<th>Hypoxia + PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.385 ±0.010</td>
<td>7.345 ±0.030</td>
<td>7.375 ±0.018</td>
<td>7.365 ±0.016</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>40.0 ±0.8</td>
<td>41.6 ±0.8</td>
<td>40.0 ±1.0</td>
<td>40.5 ±1.0</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>108.0 ±7.5</td>
<td>107.8 ±9.4</td>
<td>43.2* ±1.6</td>
<td>40.7* ±2.0</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>10.2 ±0.4</td>
<td>9.9 ±0.4</td>
<td>10.1 ±0.4</td>
<td>10.6 ±0.7</td>
</tr>
</tbody>
</table>

All values are means ± SEM. The number in parentheses represents the number of experimental observations; PAC = main pulmonary artery constriction.

* — Significantly different from normoxia at p < 0.01.

**TABLE 2  Hemodynamic Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normoxia</th>
<th>Normoxia + PAC</th>
<th>Hypoxia</th>
<th>Hypoxia + PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 ±10</td>
<td>111 ±12</td>
<td>141 ±14</td>
<td>146 ±14</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>3.987 ±0.474</td>
<td>3.006 ±0.575</td>
<td>5.164±0.457</td>
<td>4.922±0.711</td>
</tr>
<tr>
<td>SL (ml/beat per m²)</td>
<td>37.7 ±6.52</td>
<td>31.6 ±6.86</td>
<td>39.2 ±5.37</td>
<td>35.1 ±5.68</td>
</tr>
<tr>
<td>RV peak systolic pressure (mm Hg)</td>
<td>45 ±4</td>
<td>94 ±4</td>
<td>63 ±4</td>
<td>98 ±5</td>
</tr>
<tr>
<td>RV maximal dP/dt (mm Hg-sec⁻¹)</td>
<td>698 ±78</td>
<td>978 ±153</td>
<td>1119 ±149</td>
<td>1430±121</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>7 ±2</td>
<td>8 ±1</td>
<td>11±2</td>
<td>14±2</td>
</tr>
<tr>
<td>Proximal P₉₅A (mm Hg)</td>
<td>35 ±35</td>
<td>43±3</td>
<td>64*±4</td>
<td>63*±3</td>
</tr>
<tr>
<td>Distal P₉₅A (mm Hg)</td>
<td>34 ±3</td>
<td>33 ±4</td>
<td>38*±3</td>
<td>37*±2</td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure (mm Hg)</td>
<td>23 ±2</td>
<td>34 ±3</td>
<td>43*±4</td>
<td>43*±3</td>
</tr>
<tr>
<td>RV work (kg m/min per m²)</td>
<td>1.86 ±0.34</td>
<td>2.48 ±0.47</td>
<td>2.82 ±0.41</td>
<td>4.09*±0.57</td>
</tr>
<tr>
<td>RVTII (mm Hg-sec/min)</td>
<td>998 ±155</td>
<td>2137±1334</td>
<td>1334±214</td>
<td>2166±121</td>
</tr>
<tr>
<td>Aortic peak systolic pressure (mm Hg)</td>
<td>153 ±8</td>
<td>137 ±7</td>
<td>144 ±7</td>
<td>138 ±9</td>
</tr>
<tr>
<td>AOM (mm Hg)</td>
<td>135 ±2</td>
<td>121 ±2</td>
<td>126 ±2</td>
<td>120 ±2</td>
</tr>
<tr>
<td>LV maximal dP/dt (mm Hg-sec⁻¹)</td>
<td>1755 ±109 (6)</td>
<td>1562 ±201 (6)</td>
<td>2249 ±252 (6)</td>
<td>2204 ±350 (6)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>18 ±3</td>
<td>13 ±1</td>
<td>13 ±2</td>
<td>12 ±2</td>
</tr>
<tr>
<td>LVTII (mm Hg-sec/min)</td>
<td>3129 ±224 (6)</td>
<td>2529 ±389 (6)</td>
<td>2246 ±367 (6)</td>
<td>2294 ±403 (6)</td>
</tr>
<tr>
<td>LV work (kg m/min per m²)</td>
<td>7.3 ±1.0</td>
<td>5.1 ±1.2</td>
<td>8.3* ±1.02</td>
<td>8.08±1.9</td>
</tr>
<tr>
<td>RPP (mm Hg x beats/min x 10⁻⁶)</td>
<td>173 ±20</td>
<td>153 ±22</td>
<td>202 ±24</td>
<td>202 ±25</td>
</tr>
</tbody>
</table>

All values are mean ± SEM. The number in parentheses represents the number of experimental observations for that parameter.

Proximal P₉₅A = mean pulmonary artery pressure proximal to the cuff; distal P₉₅A = mean pulmonary artery pressure distal to the cuff. Level of significance = P < 0.05.

* — Significantly different from the preceding treatment.
† — Significantly different from the preceding treatment at P < 0.01.
§ — Significantly different from normoxia.
‡ — Significantly different from normoxia + PAC.

responding control values. The heart rates did not change appreciably between the controls and their PAC treatment periods. All the calves at one stage or another during PAC did have tricuspid insufficiency. During each period, PAC resulted in significant elevation of RV peak systolic pressure over the control values, and the peak RV systolic pressures achieved by PAC during both periods were comparable. As expected, the proximal as well as distal pulmonary arterial mean pressures increased from the normoxic control values during isocapnic hypoxia, but the AOM did not change appreciably (Table 2). Aortic systolic pressure, LVTII, LVW, and RPP did not vary significantly between the controls and the RV pressure overload situations.

The RVEDP and RVTII rose significantly with each RV pressure overload over the control value (Table 2). RV work increased from its control value during each PAC, but the increment achieved statistical significance only during hypoxia.

Only during hypoxia + PAC was the RV maximal
dP/dt found to be significantly elevated from the normoxic control value. The following indices: time to maximal RV dP/dt, RV maximal dP/dt/EDP, and dp/dt/DP, calculated to correct for the effects of changing RV preload, were not found to be significantly different from controls during either PAC. No significant changes occurred in the isovolumic LV contractility indices measured, including maximal LV dP/dt, t-max LV dP/dt, dp/dt/LVEDP, dp/dt/DP, VPM, and Vmax, thereby suggesting that LV function remained relatively stable throughout the study.

**MBF and CVR**

The mean values of the total RV, interventricular septal, and LV MBF are presented in Table 3. The RV endocardial as well as epicardial perfusion increased with each PAC over the corresponding control values. However, the increment was statistically significant only during hypoxia (Fig. 1). The mean values for RV endocardial blood flow were 83, 101, 161, and 258 ml/min per 100 g during normoxia, normoxia + PAC, hypoxia, and hypoxia + PAC, respectively. The corresponding mean values for the RV epicardial perfusion were 63, 90, 151, and 240 ml/min per 100 g. The calculated CVR (Table 3) across the RV free wall declined significantly with RV pressure overload from the corresponding controls during both normoxia and hypoxia. Although the RV endocardial-epicardial blood flow ratio had significantly decreased from the control normoxic value during normoxia + PAC, acute isocapnic hypoxia, and hypoxia + PAC (Table 3), the ratio was always greater than unity, and therefore underperfusion of the RV subendocardium did not occur during any step of the study.

At normoxia, the ratio of RV to LV MBF was 0.74 ± 0.08 (mean ± SEM), and the corresponding perfusion values were 73 ± 13 and 97 ± 12 ml/min per 100 g. The RV/LV blood flow ratio increased significantly above the control normoxic value with each PAC (Table 3). There was an insignificant decline in the blood flow to all three layers of the LV myocardium during normoxia + PAC, and the CVR across the LV free wall remained unchanged. The mean LV endocardial perfusion values in the present study were 108, 94, 178, and 255 ml/min per 100 g. The mean LV endocardial-epicardial blood flow ratio had significantly decreased from the control normoxic value during normoxia + PAC, acute isocapnic hypoxia, and hypoxia + PAC (Table 3), the ratio was always greater than unity, and therefore underperfusion of the RV subendocardium did not occur during any step of the study.

**Table 3** MBF, Ventricular Blood Flow Ratios, and CVR Data

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Normoxia + PAC</th>
<th>Hypoxia</th>
<th>Hypoxia + PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>RV MBF (ml/min per 100 g)</td>
<td>73 ±13</td>
<td>96 ±19</td>
<td>156*11 ±22</td>
<td>250*11±34</td>
</tr>
<tr>
<td>RV endocardial-epicardial perfusion ratio</td>
<td>1.38 ±0.08</td>
<td>1.12* ±0.04</td>
<td>1.10* ±0.08</td>
<td>1.11* ±0.05</td>
</tr>
<tr>
<td>LV MBF (ml/min per 100 g)</td>
<td>97 ±12</td>
<td>90 ±11</td>
<td>167*11 ±21</td>
<td>240*11±36</td>
</tr>
<tr>
<td>LV endocardial-epicardial perfusion ratio</td>
<td>1.35 ±0.06</td>
<td>1.29 ±0.07</td>
<td>1.18 ±0.09</td>
<td>1.17 ±0.03</td>
</tr>
<tr>
<td>RV/LV (not including the septum) perfusion ratio</td>
<td>0.74 ±0.08</td>
<td>1.11* ±0.09</td>
<td>0.92 ±0.07</td>
<td>1.08* ±0.09</td>
</tr>
<tr>
<td>Septal MBF (ml/min per 100 g)</td>
<td>95 ±10</td>
<td>91 ±6</td>
<td>1.75* ±31</td>
<td>2.20* ±48</td>
</tr>
<tr>
<td>CVR across RV free wall</td>
<td>2.16 ±0.32</td>
<td>1.31* ±0.10</td>
<td>0.94* ±0.18</td>
<td>0.51* ±0.05</td>
</tr>
<tr>
<td>CVR across LV free wall</td>
<td>1.52 ±0.19</td>
<td>1.44 ±0.13</td>
<td>0.88 ±0.08</td>
<td>0.54* ±0.15</td>
</tr>
<tr>
<td>CVR across right side of the interventricular septum</td>
<td>1.62 ±0.14</td>
<td>1.25* ±0.08</td>
<td>0.74* ±0.09</td>
<td>0.48* ±0.07</td>
</tr>
</tbody>
</table>

All values are mean ± SEM. CVR values are in mm Hg/ml per minute per 100 g.

* = Significantly different from the preceding treatment at P < 0.01.
† = Significantly different from normoxic control at P < 0.01.
‡ = Significantly different from normoxia + PAC at P < 0.01.
§ = Significantly different from hypoxic control at P < 0.05.
100 g (Fig. 2) during normoxia, normoxia + PAC, acute isocapnic hypoxia, and hypoxia + PAC, respectively. The corresponding mean values for the LV subepicardial perfusion were 85, 74, 165, and 230 ml/min per 100 g. The LV endocardial-epicardial perfusion ratio was well maintained during the four steps of the study (Table 3). The values for the LV midwall blood flow were intermediate between the endocardial and the epicardial blood flow values (Fig. 2).

Hypoxia by itself augmented blood flow to all the regions of the ventricular myocardium (Figs. 1–3), compared to control normoxic values, but the increase was greater to the epicardium than to the endocardium, thus reducing the endocardial-epicardial blood flow ratio in both ventricles (Table 3). The values for the LV free wall-LV free wall blood flow ratio approached 0.92 ± 0.07 (mean ± SEM) with hypoxia.

The changes in blood flow to the various subregions of the interventricular septum during normoxia + PAC were of interest. The total septal perfusion (Table 3) and the MBF to the middle and left layers (Fig. 3) of the interventricular septum registered an insignificant decline, whereas the perfusion rose from 97 ± 13 ml/min per 100 g during normoxia (control) to 104 ± 6 ml/min per 100 g during hypoxia + PAC in the right side of the septum. The blood flow to all three layers of the interventricular septum was very similar during hypoxia. With PAC during hypoxia, the blood flow increased to all the regions of the septal myocardium, but only the increment for the right side of the septum (from 190 ± 28 ml/min per 100 g during hypoxia to 292 ± 47 ml/min per 100 g during hypoxia + PAC) achieved statistical significance (Fig. 3).

The percent distribution of MBF between the various regions of the ventricular myocardium changed significantly with each PAC in favor of the RV myocardium (Fig. 4). The percent of the total ventricular MBF received by the RV free wall increased from 22 ± 2% during normoxia to 29 ± 2% with PAC, whereas that for the left ventricle decreased from 51.5 ± 1.8% to 45.8 ± 1.7%; these changes were statistically significant. The percent distributions of the total ventricular MBF during the two PAC situations were very similar.
Discussion

Critique of the Methods

Ketamine anesthesia supplemented with muscle relaxant (d-tubocurarine chloride) was used in this study. Ketamine is known to increase heart rate, systemic and pulmonary arterial blood pressures, cardiac output, and LV work in dogs. It is also believed to increase MBF in dogs, but that increment is not sufficient to meet the increased myocardial oxygen requirement (Folts et al., 1975). Whether the same was true for the calves in this study cannot be determined; however, the normoxic control MBF values were within the normal range. By itself, ketamine is believed to have a negative inotropic effect, but its myocardial depressant action in vivo is largely overcome by sympathetic stimulation (Horwitz, 1977). It was to this end, namely, to avoid the myocardial depressant action of barbiturates, that ketamine was employed as the anesthetic for the study. The pH, Paco₂ were maintained within normal limits throughout the study, because acidosis (Beierholm et al., 1975) and high Paco₂ (Drake et al., 1976) may have deleterious effects on myocardial contractility.

Because the maximal RV dP/dt usually occurs after the pulmonic valve opens, this measure has been regarded as invalid as an inotropic index for the RV (Niehus et al., 1972). In the isolated heart-lung preparation it was observed that auxotonic RV maximal dP/dt tended to overestimate slightly the isovolumic dP/dt (Hoppe et al., 1976), but that the difference between the two was within the error range of the method employed. Thus these authors recommended the use of auxotonic RV maximal dP/dt for evaluating the relative change in RV inotropic status. Buss and Bisgard (1976) also have used this index to the same end in awake calves. Although we have calculated the isovolumic indices of RV contractility, it must be recognized that, during PAC, tricuspid regurgitation had occurred, and the right ventricle was not having a truly isovolumetric contraction.

Because in the present experiments the number of microspheres contained in each reference arterial sample as well as each subregion of the ventricular wall exceeded 3000, the criteria described by Buckberg et al. (1971) for measurement of MBF using labeled microspheres were satisfied.

The frequent occurrence of tricuspid insufficiency in calves during PAC despite an intact pericardium is suggestive of a weak anatomic support structure of the tricuspid valve in bovines, as is the case in other species including man. Tricuspid insufficiency is known to occur in calves suffering from brisket disease (Hecht et al., 1962).

Contractility Indices

The t-max RV dP/dt as suggested by Hoppe et al. (1976) proved to be a poor index. This index, as well as the indices maximal RV dP/dt/RVEDP and maximal RV dP/dt/DP, used to correct max RV dP/dt for alterations in RV preload, failed to distinguish between the treatment and the control. The LV contractility indices employed in this study indicate no significant variation in LV contractility when acute RV pressure load was produced under normoxia and hypoxia. Thus there is no evidence to suggest from these indices that LV contractility was jeopardized during RV pressure overload under any of the conditions studied.

Coronary Driving Pressure (CDP), Regional MBF, and Myocardial O₂ Demand

Total RV free wall blood flow increased slightly with normoxia + PAC despite a decrease in CDP. This result is suggestive of a compensatory coronary vasodilation, which also is indicated by significantly decreased CVR across the RV wall. Although the aortic-RV pressure gradient and the RVTTI were similar between the two PAC situations, the increase in RV coronary blood flow over the control normoxic value was meager during normoxia + PAC, whereas the RV myocardial perfusion had increased significantly above the control hypoxic value during hypoxia + PAC. Because of the higher cardiac output, RV work during hypoxia + PAC significantly exceeded that during normoxia + PAC (Table 2). However, it has been established for the LV that “volume” work is only a minor component contributing to the total LV oxygen utilization (Sarnoff et al., 1958; Braunwald, 1971; Rowe, 1974). Because MBF to the RV myocardium could rise significantly during hypoxia + PAC over the normoxia + PAC value, and because the aortic-RV pressure gradient was similar between the two conditions, it is concluded that maximal RV coronary vasodilation had not been achieved during normoxia + PAC. The insignificant change in RV myocardial perfusion during normoxia + PAC is suggestive of an increased arterial-RV coronary venous O₂ difference so as to meet the increased RV myocardial oxygen demand. Because we did not determine the O₂ content of the RV coronary venous drainage, this must remain a matter for speculation.

It has been shown that blood flow to the RV myocardium increases with mild to moderate acute RV systolic hypertension, but further increases in RV systolic pressure fail to increase blood flow to RV myocardium when cardiac failure might ensue (Aukland et al., 1967; Fichter et al., 1973). These studies have suggested that during mild to moderate RV systolic hypertension, maximal vasodilation of the RV coronary bed occurs, and further increases in RV systolic pressure decrease RV MBF, because, with maximal vasodilation, the pressure-time dependency of the MBF is established. In the present study, RV systolic pressure was much higher than in either of the above reports, and MBF...
to the RV free wall during hypoxia + PAC significantly exceeded that observed during normoxia + PAC despite similar CDP, and RV subendocardial underperfusion did not occur. Because the RV endocardial-epicardial flow ratio was maintained at its control level even with PAC during hypoxia, we believe that maximal vasodilation had not been achieved in the RV subendocardium during hypoxia + PAC. It is logical, however, to believe that, during RV systolic hypertension, one of the limiting factors (besides tachycardia) to increases in MBF to the RV free wall is the CDP. High intracavity pressure together with prolongation of the RV systole (Fixler et al., 1973) and high RV diastolic pressure would oppose RV myocardial perfusion during systole and diastole, respectively.

The blood flow to the LV myocardium has been shown to increase significantly during hypoxia (Hellem et al., 1975), as was observed in the present study. During hypoxia + PAC, the heart rate, maximal LV dP/dt, and maximal LV dP/dt/DP had not changed significantly from the control hypoxic values, but the LVTTI and LV work were slightly decreased. Yet an increase in blood flow to the LV myocardium (Fig. 2) occurred. This is difficult to explain, but it has been shown in dogs that hypoxemia alone can result in an increase in myocardial oxygen consumption despite the absence of change or a decrease in the magnitude of hemodynamic correlates of myocardial oxygen consumption (Powers and Powell, 1973). This would suggest that during hypoxia + PAC, the left ventricle was operating at a decreased mechanical efficiency. The finding that blood flow to the right side of the septum rose with the stress of RV systolic hypertension during normoxia, whereas the flow to the middle and the left side of the septum registered a decline, is in keeping with the proposition that RV contraction is aided by contraction of the right side of the septum (Brooks et al., 1971; Fixler et al., 1977). Further evidence to support this view comes from our observations during hypoxia. Hypoxia by itself stressed the right heart, as evidenced by the significantly increased RV systolic pressure, which resulted in equal blood flows to the right and left sides of the septum (Fig. 3). When the stress of hypoxia was superimposed with RV pressure overload, the flow to the right side of the septum underwent a significant further increase, but the rise in blood flow to other regions was not statistically significant.

The flow to the RV free wall and right side of septum during PAC under normoxia did not increase to the extent (Figs. 1 and 3) one would have expected from the change in RVTTI. This renders questionable the use of RVTTI as a reliable index for RV oxygen requirements. Elevated RVEDP during PAC would suggest increased RV diameter consequent to increased filling of the chamber. RVTTI may therefore underestimate the total tension developed by the right ventricle. However, we believe that it is reasonable to assume that RV myocardial oxygen needs move in the same direction as the RVTTI, as has been suggested by others (Fixler et al., 1973; Buss and Bisgard, 1976). Several investigators have shown experimentally that neither extensive ischemia (Brooks et al., 1971) nor damage (Guiha et al., 1974), e.g., by thermodiery of the RV free wall (Kagan, 1952), results in significant deterioration of pulmonary and systemic hemodynamics under normal circumstances. However, the importance of properly functioning RV myocardium during the stress of RV systolic hypertension has also been recognized (Fixler et al., 1973). This should hold especially true for a chronic situation, e.g., hypoxic pulmonary hypertension of high altitude, in which overall cardiac performance may depend on proper RV functioning. To apply inferences drawn from these acute experiments to the chronic RV pressure overload situation would be misleading, since the latter is associated with RV hypertrophy and dilation, and the compliance characteristics of both ventricles would be significantly altered.

From the present experiments, it can be concluded that acute RV systolic hypertension does not result in significant augmentation of RV contractility when the alterations in preload and afterload are taken into consideration. Increments in blood flow to the stressed areas of the myocardium occur during normoxic RV pressure overload; these increases become statistically significant with hypoxia. It is not possible to determine from this study how long these high increments in blood flow to the RV free wall and the right side of the septum can be sustained with low coronary driving pressure in the presence of chronic arterial hypoxemia of high altitude. This may be important in answering the basic question: why do appreciable numbers of cattle develop RV failure at high altitude? It is likely that the augmented RV myocardial oxygen demand (due to the marked rise in RV systolic pressure) superimposed upon arterial hypoxemia of high altitude may result in maximal coronary vasodilation in the hypertrophied RV subendocardium of these cattle. The RV diastolic shortening as a consequence of prolonged RV systole, along with a significant reduction in diastolic RV coronary driving pressure predominantly due to a significant rise in RV diastolic intramyocardial pressure, may therefore cause RV subendocardial ischemia and right heart failure in these calves.

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