Regional Myocardial Blood Flow and Coronary Vascular Reserve in Unanesthetized Young Calves Exposed to a Simulated Altitude of 3500 m for 8–10 Weeks

Murli Manohar, Christine M. Parks, Michael A. Busch, William J. Tranquilli, Gerald E. Bisgard, Thomas A. McPherron, and Michael C. Theodorakis

With the technical assistance of S. Chasnov

From the Departments of Veterinary Biosciences and Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, Illinois, and the Department of Veterinary Science, University of Wisconsin, Madison, Wisconsin

SUMMARY. We determined regional myocardial blood flow (15-μm tracer microspheres) and hemodynamics in nine normal calves, seven calves with right ventricular (RV) hypertrophy induced by pulmonary artery banding (PAB) at sea level, and five calves exposed to simulated high altitude (HA) of 3,500 m (P0 = 500 mm Hg) for 8–10 weeks. Progression of RV hypertrophy was very rapid in HA calves. RV weight:body weight ratio of 2.74 ± 0.20 g/kg at 8–10 weeks of sojourn at HA significantly exceeded that in PAB calves (1.98 ± 0.11 g/kg) 20 weeks post-banding. All calves were studied unanesthetized at sea level before (control) and during maximal coronary vasodilatation (iv adenosine; 4 μM/kg per min). Normal and HA calves were also studied during acute hypoxemia (Pao2: 42 ± 1 mm Hg) induced by administration of 12–13% O2 + N2 in the inhaled gas. RV myocardial blood flow was significantly increased only in PAB calves, whereas in HA calves it was similar to that in normal calves. Left ventricular (LV) mass and blood flow were identical in three groups of calves. Polycythemia did not occur in HA calves. Minimal coronary vascular resistance per unit weight of the hypertrophied RV was identical to that in the normal RV myocardium. This suggested that, despite very fast progression of RV hypertrophy in HA calves, functional cross-sectional area of the RV coronary vascular bed kept pace with the increase in cardiac mass. Minimal coronary vascular resistance per unit weight of the left ventricular myocardium was also identical in three groups of calves. This suggested that chronic hypoxemia by itself did not cause an increase in the functional cross-sectional area of the LV coronary vascular bed. Acute hypoxemia resulted in a significant increase in myocardial blood flow in all calves, but in HA calves, RV endo:epi perfusion ratio decreased below 1.00. Transmural RV myocardial blood flow and RV systolic pressure in HA calves during acute hypoxemia significantly exceeded that in normal calves. (Circ Res 50: 714–726, 1982)

A SIGNIFICANT number of cattle exposed to high altitude develop right heart failure, commonly referred to as “brisket disease” or “high mountain disease.” Because cattle have hyperactive pulmonary vasoconstrictor response to alveolar hypoxia, resulting in severe pulmonary hypertension upon hypoxic exposure (Bisgard, 1977; Will et al., 1977); marked right ventricular hypertrophy develops rapidly in calves exposed to chronic hypoxia. It is likely that the eventual decapsulation of the hypertrophied right ventricle in these animals may be due to inadequate compensatory adjustments of coronary circulation perfusing the increased cardiac mass.

The following lines of evidence may be considered: It has been shown in calves (Manohar et al., 1981a), dogs (Murray et al., 1979; Murray and Vatner, 1981) and ponies (Manohar et al., 1981b) that pressure overload-induced right ventricular hypertrophy is characterized by a progressive, selective increase in right ventricular myocardial perfusion during basal conditions and that this elevated right ventricular myocardial blood flow occurred at the expense of decreased available coronary vascular reserve. In canine hypertrophied right ventricular myocardium, no change in the ratio of capillary number to muscle fiber number was observed (Murray and Vatner, 1979), and the minimal coronary vascular resistance was significantly increased (Murray and Vatner, 1981). However, in unanesthetized calves in which right ventricular hypertrophy was produced by banding the main pulmonary artery within 24–48 hours after birth, minimal coronary vascular resistance per unit weight of the right ventricular myocardium was identical to that in the normal calves (Manohar et al., 1981a). This was interpreted to suggest that functional cross-sectional area of the vascular bed supplying the hypertrophied bovine right ventricular myocardium kept pace with increasing cardiac mass. Because bovine right ventricular hypertrophy progresses at a much faster rate in response to hypoxic pulmonary hypertension of high altitude [compared to right ventricular hypertrophy induced by pulmonary artery banding in calves at sea level (Manohar et al., 1981a)], it was speculated that a discrepancy may
develop and that the functional cross-sectional area of the right ventricular coronary vascular bed may not be able to keep pace with the rapidly increasing cardiac mass. This, along with the observation that baseline myocardial blood flow is significantly increased in the hypertrophied bovine right ventricular myocardium and the fact that, at high altitude, there is a constant background of hypoxia, may severely limit the net available coronary vascular reserve in the hypertrophied right ventricular myocardium of calves exposed to chronic hypoxemia. At the same time, however, we were cognizant of the suggestion that chronic hypoxic exposure may, by itself, lead to proliferation of capillaries in the myocardium (Miller and Hale, 1970), although Clark and Smith (1978) were unable to document this in the left ventricular myocardium of young rats exposed to high altitude hypoxia (Pb = 380 mm Hg).

The primary goals of the present study, therefore, were: (1) To examine transmural maximal coronary vasodilator capacity in the bovine right ventricular myocardium, hypertrophied at a much faster rate in response to severe pulmonary hypertension induced by chronic exposure to simulated altitude of 3500 m. Comparisons were made with normal calves born and raised at sea level and with calves in which marked right ventricular hypertrophy was produced by pulmonary artery banding at sea level. It should be noted that in none of the previous studies have the effects of rate of development of hypertrophy on maximal coronary vasodilator capacity been examined, although it was suggested as an important factor which might have modulating influence on the adaptive response of coronary circulation to hypotrophy (Manohar et al., 1981a, 1981b; Murray and Vatner, 1981). In both models of right ventricular hypertrophy (hypoxic pulmonary hypertension-induced, and pulmonary artery banding-induced), coronary arterial hypertension is not present. Thus morphological changes of the coronary vasculature induced by prolonged exposure to elevated perfusion pressure, as are usually seen in frequently employed models of left ventricular hypertrophy (O'Keefe et al., 1978), are avoided. (2) To determine whether functional cross-sectional area of the coronary vascular bed is increased by chronic hypoxemia. This was accomplished by comparing the minimal coronary vascular resistance (at maximal coronary vasodilation induced by iv infusion of adenosine) in the left ventricular myocardium of calves exposed to high altitude for 8–10 weeks with that in the normal calves born and raised at sea level, as well as with that in pulmonary artery-banded calves raised at sea level. The left ventricle is not subjected to increased mechanical load which affects the right ventricle under hypobaric conditions. However, both ventricles are subjected to the same degree of hypoxemia. Changes in maximal coronary vasodilatory capacity of the left ventricle will, therefore, reflect the effects of chronic arterial hypoxemia alone on the myocardium, independent of the effects of work hypertrophy. No such data are available at the present time. It should be noted that in calves exposed to high altitude and in calves with pulmonary artery banding (Manohar et al., 1981a), left ventricular weight:body weight ratio remains normal. Another feature in calves is that, unlike other species, they do not develop polycythemia upon chronic exposure to hypoxia (Bisgard, 1977), and thus hemodynamic alterations related to polycythemia-induced hyperviscosity are obviated. This is especially important when changes in minimal coronary vascular resistance are to be examined.

Methods

Animals Used

Twenty-three healthy male calves, born and raised at sea level, belonging to Holstein-Friesian (20 calves), Brown Swiss (one calf), and Ayreshire (2 calves) breeds were used for the present study. All animals were maintained on ration comprised of alfalfa hay and grain provided ad libitum. These calves were divided into three groups of nine (control group), seven (pulmonary artery-banded calves), and seven (high altitude group) calves. All animals were raised in similar surroundings and their growth rates were identical. At the time of surgical preparation, these animals were 8–9 weeks old.

Surgical Preparation of Animals

All surgical procedures were accomplished using general anesthesia induced and maintained with halothane administered in a mixture of 50% nitrous oxide and 50% oxygen via a circle absorber system and a ventilator (Ohio Medical Products).

Control Group

Ten to 12 weeks prior to the study, a left lateral thoracotomy was performed by resecting the 4th rib. Fluid-filled Tygon catheters were implanted in the left atrium and the main pulmonary artery via 1 cm in diameter apertures that were made in the pericardium. Connecting ends of these catheters were exteriorized on the upper lateral chest wall and housed subcutaneously, from which location they were exposed on the day of study via a small incision using local anesthesia. At the time of the study, these calves weighed between 150 and 173 kg. These calves were kept at sea level (Urbana, Illinois) and, hereafter, are referred to as “normal” calves.

Pulmonary Artery-Banded (PAB) Calves

Twenty weeks prior to the study, PAB calves were subjected to a left lateral thoracotomy at the 4th intercostal space. An umbilical tape, encircled by a pliable medical grade rubber tubing, was passed around the main pulmonary artery midway between the pulmonic valve and its bifurcation. The main pulmonary artery was constricted by tightening the tape. External circumference of the main pulmonary artery was reduced by 20% of its original measurement.

At this surgery, a fluid-filled catheter also was implanted in the left atrium. The pericardium around the ventricles remained intact. At the time of the study these calves weighed between 196 and 230 kg. These animals were also kept at sea level.

High Altitude (HA) Group

Four weeks prior to exposure to high altitude, these Holstein-Friesian calves were surgically prepared as de-
scribed for “normal” calves. Catheters were implanted in the left atrium and the pulmonary artery.

These calves, completely recovered from surgery, were transported by truck to Madison, WI, and exposed to a simulated altitude of 3500 m (Pb = 500 mm Hg) for 8-10 weeks in a hypobaric chamber (Biotron, University of Wisconsin, Madison, Wisconsin). The hypobaric chamber was returned to sea level everyday for 35-40 minutes for cleaning and to replenish feed bins. One calf died on the 28th day of exposure to high altitude. In this calf, severe right ventricular hypertrophy was present (right ventricular weight: left ventricular weight = 0.69). An earlier study from our laboratory (Ruiz et al., 1973) reported that, after 4 weeks of exposure to 3400 m, systolic pressure in bovine pulmonary artery approached 100 mm Hg. Another calf developed right ventricular failure (Brisket disease) on the 35th day of exposure to high altitude. This calf was removed from the chamber and killed 48 hours later. In this calf too, marked right ventricular hypertrophy was present (right ventricular weight: left ventricular weight = 0.71; right ventricular weight: left ventricular weight = 1.07).

All of the remaining five calves remained healthy and did not show any evidence of right heart failure. Hemodynamics and myocardial blood flow values obtained from these calves are presented in this report. At the time of the study, these calves weighed between 145 and 165 kg.

For these experiments, the HA calves were removed from the chamber on 56th (two calves), 63rd (one calf), and 70th (two calves) day and transported for 250 miles by truck to our laboratory located at sea level in Urbana, Illinois. Studies were carried out 24-48 hours later. In order to minimize our concern that these data may be affected by transportation stress, we studied three normal (control) calves 24 hours after they were transported the same distance in the same truck at the same highway speed. We compared their blood gas tensions, hemodynamic and myocardial blood flow data obtained during control/baseline conditions, adenosine infusion, and acute hypoxemia (see protocol) with that of six normal calves that were not transportation stressed. No differences in any of these variables were encountered, thus data from these three normal calves were pooled with data from the other six calves.

Preparations and Procedures

Twenty-four hours before the study, the abdominal aorta was catheterized percutaneously at the level of first lumbar vertebra (Manohar et al., 1973) and a 100-cm-long Teflon catheter was advanced toward the heart. The tip of this catheter was located in the ascending aorta, as confirmed on autopsy. This catheter was used for monitoring phasic and mean aortic pressure as well as for anaerobically withdrawing blood samples for determining gas tensions (Pao2, Paco2), pH, hemoglobin concentration, and total oxygen content.

On the day of the study, the middle coccgeal artery was catheterized with low epidural anesthesia (1.5 ml of 2% lidocaine HCl solution deposited in the epidural space via a hypodermic needle inserted at the sacrococcygeal joint). This catheter was used for withdrawing reference arterial blood during myocardial blood flow and cardiac output determination by the microsphere method (Manohar et al., 1979, 1981a).

The saphenous vein on the left hind leg was also percutaneously catheterized. This catheter was used for adenosine infusion. Another fluid-filled catheter was advanced into the right ventricle via the left jugular vein.

Connecting ends of previously implanted left atrial and pulmonary artery catheters were exposed, using local anesthesia (2% lidocaine HCl infiltration).

All calves were trained to stand in a stanchion and were accustomed to being handled by people. For the study, all animals stood in the stanchion. No tranquilization or sedation was employed. A plastic mask was placed over the calf’s muzzle and taped in place. An oxygen line was attached to the mask so that the calf breathed oxygen-enriched air at sea level. The flow of oxygen was adjusted to ensure maintenance of arterial Pao2 above 100 mm Hg. A wide opening in the mask prevented rebreathing of the exhaled gas. This arrangement of mask and oxygen line was employed to help maintain arterial hemoglobin saturation at 100% while arterial Paco2 varied between 41 and 44 mm Hg during the first two steps of the study.

An interval of 15-30 minutes elapsed after the mask had been positioned, before control (baseline) measurements were made.

At each step of the study, myocardial blood flow was determined, using radionuclide-labeled 15 µm in diameter microspheres (3M Company) injected into the left atrium. Our techniques for calibration of microsphere suspension and nuclide counting are the same as described by Heymann et al. (1977). Reference arterial blood was withdrawn from the aorta (close to iliac bifurcation) at a constant rate of 14.5 ml/min beginning just prior to the injection of microspheres and continuing up to 90 seconds post-injection. A well-agitated ultrasonicated microsphere suspension containing 6 to 7 million microspheres was injected for each blood flow determination. Five different isotopes (141Ce, 51Cr, 85Sr, 95 Nb, 46Sc) were used, and their order was randomized among the steps of the study (see protocol). Our procedure for determining regional myocardial blood flow and cardiac output in calves has been described previously (Manohar et al., 1979, 1981a, 1981c). The entire procedure was carried out with careful hemodynamic monitoring.

Simultaneous with every myocardial blood flow determination, we recorded electrocardiogram and pressures in aorta, right ventricle, pulmonary artery (except in PAB calves), and the left atrium on a multichannel physiograph (Gould-Brush Medical Instruments, Inc.). We regarded the scapulohumeral joint as the level of right atrium. Pressure transducers (P23ID, Statham Medical Instruments, Gould Inc.) were zeroed at this level. Immediately before and after each myocardial blood flow determination, we also determined arterial blood gas tensions, pH (Radiometer, The London Co.), total arterial oxygen content (Lex-O-Con, Lexington Instruments), hematocrit and hemoglobin concentration (cyanmethemoglobin technique, Sigma Technical Bulletin 525A).

At the end of each experiment, the calves were killed and their hearts were removed. Epicardial fat, large coronary vessels, atria, great arteries, valves and chordae tendineae were separated from the cardiac ventricles. Right ventricular freewall was separated and divided into four regions as described below. At first, right ventricular freewall as divided into two segments along a vertical line starting at the anterior margin of the atrioventricular (tricuspid) valve. This line passed just anterior to the base of the right ventricular papillary muscle. The anterior segment was subdivided into two portions along a line commencing at the posterior margin of the pulmonic valve and running parallel to the anterior margin of the right ventricular freewall. The anterior of these two portions was called the outflow tract and the other the intermediate region of right ventricular freewall. The posterior segment was divided into two portions: region of the papillary muscle and
Coronary Blood Flow in High Altitude-Exposed Calves

Manohar et al.

Experimental Protocol

All experiments were conducted at sea level (Urbana, Illinois) on unanesthetized healthy calves. None of the calves had ascites, hepatomegaly, pleural effusion, or other signs (distended peripheral veins, dyspnea at rest or exertion, and anorexia) of congestive heart failure. Measurements were made at the following steps during steady state conditions as judged by stability of heart rate, various continuously monitored hemodynamic parameters, and arterial blood gas tensions.

1. Control (baseline) measurements: (Pao₂ > 100 mm Hg; Paco₂ = 41–44 mm Hg).

2. Maximal coronary vasodilation: This was achieved by intravenous administration of adenosine (4.0 μM/kg per min). Measurements were made 4–5 minutes after instituting the adenosine infusion when a steady state existed. Following completion of measurements, adenosine infusion was discontinued and 15–20 minutes were allowed for complete recovery of hemodynamic variables to baseline values.

In two separate experiments on normal conscious calves, this dose of adenosine was observed to have abolished the reactive hyperemic response to 15-second occlusion of the right coronary artery as well as the left anterior descending coronary artery. These occlusions were carried out in duplicate at 5-minute intervals.

In order to demonstrate that this dose of adenosine would have also caused maximal coronary vasodilation in the hypertrophied right ventricles, we implanted an electromagnetic flow probe and an occluder onto the right coronary artery of a calf in which pulmonary artery banding had been done 22 weeks ago. This procedure was done using halothane-nitrous oxide anesthesia. Marked right ventricular hypertrophy was present in this calf (right to left ventricular weight ratio = 0.953). Twenty-four hours later, we tested reactive coronary hyperemic response (in duplicate, 5 minutes apart) before and during adenosine infusion in the unanesthetized state. It was observed that adenosine infused at 3.75 μM/kg per min abolished reactive hyperemia in response to a 20-sec occlusion of the right coronary artery. This was also true for adenosine infused at 4.0 μM/kg per min.

3. Arterial hypoxemia (Pao₂ = 42 ± 1 mm Hg): This was produced by making calves breathe a gas mixture containing 12–13% oxygen in nitrogen (P0₂ of the inspired gas = 83–90 mm Hg). With inhalation of hypoxic gas mixture, calves hyperventilated and the arterial CO₂ tension varied between 33 and 36 mm Hg. This step of the study was carried out on normal calves and calves exposed to high altitude.

All Pao₂, Paco₂, and pH values were corrected to the animal’s rectal temperature, which was monitored continuously, using coefficients published for human blood (Severinghaus, 1966).

Measurements and Calculations

Myocardial blood flow was computed from the equation:

\[ MBF = Qr \times \frac{Cm}{Cr} \]

where \( MBF \) is the myocardial blood flow (ml/min/g), \( Qr \) is the cardiac output (ml/min), \( Cm \) is the radioactivity in the reference blood, and \( Cr \) is the radioactivity in the reference arterial sample (ml/min). Cardiac output was determined from the equation: cardiac output (ml/min) = CPM / Ci / Cr; where Ci stands for total radioactivity injected into the left atrium. All criteria for regional blood flow and cardiac output determination by the microsphere method (Archie et al., 1973; Buckberg et al., 1971; Heymann et al., 1977) were completely satisfied.

To determine Ci, the following procedure was employed: Once the lack of aggregation/clumping of microspheres had been confirmed under the microscope, the vigorously agitated, ultrasonicated microsphere suspension was drawn into a plastic disposable syringe. A small drop (8–15 mg) of microsphere suspension from this syringe was placed in a preweighed γ-counting vial. The syringe as well as the vial were then quickly weighed individually. Contents of the syringe were emptied into a 90-cm-long line attached to the left atrial catheter and quickly flushed with 20 ml of warm saline. The syringe was weighed again and the weight of microsphere suspension injected determined by difference. The vial containing the drop of microsphere suspension was counted in a γ scintillation counter (Nuclear-Chicago) connected to a multichannel analyzer (Canberra Industries). Tissue height from bottom of the vials did not exceed 1 cm.

\[ Cm = \frac{CPM \times Ci}{Cr} \]

Because CPM per microsphere are known, CPM injected can be converted into the number of microspheres injected. In our hands, cardiac output values thus obtained are within 5% of those determined by dye-dilution technique.

Hemodynamic variables were measured over several (50–80) consecutive beats recorded simultaneously with myocardial blood flow determination at each step. Total peripheral resistance and total pulmonary resistance were calculated by dividing mean aortic pressure and mean pulmonary artery pressure (in mm Hg), respectively, with cardiac output (ml/min per kg). Rate-pressure product was calculated as the product of peak aortic systolic pressure (mm Hg) and heart rate (beats/min) divided by 100.

Coronary vascular resistance (mmHg/ml/min per g) for both ventricles was calculated as the quotient of mean aortic...
pressure minus right ventricular end-diastolic pressure and the transmural myocardial blood flow (Manohar et al., 1981a, 1981b; Murray and Vatner, 1981). Because right ventricular end-diastolic pressure may not represent the true back pressure opposing myocardial perfusion, these values of coronary vascular resistance are subject to error. We also calculated mean coronary vascular resistance for the entire right and left ventricles and normalized it for body weight (O'Keefe et al., 1978). This calculation was done according to the following equation:

\[
\text{Normalized coronary vascular resistance (mm Hg/ml per min per kg)} = \frac{1}{\text{Body weight (kg)}} \left( \frac{\text{Mean aortic pressure} - \text{Right ventricular end-diastolic pressure}}{\text{Coronary blood flow for the entire ventricle (ml/min)}} \right)
\]

This calculation was done to facilitate examination of changes in coronary vascular bed independent of differences in heart weight and total body mass (O'Keefe et al., 1978).

Statistical Analysis

The data were analyzed by analysis of variance using a split-plot design (Steel and Torrie, 1960). In this design, group and treatment effects were considered as "fixed" and the animals were nested within groups. For each group of calves, the data were also analyzed by two way analysis of variance. For those variables where significant F values were encountered, Scheffe's multiple range test was employed to test for significant differences among treatment means as well as group means. A probability level of \( P < 0.05 \) was considered statistically significant. The data are presented as mean ± 1 SEM.

Results

Morphological Characteristics of Right Ventricular Hypertrophy (Table 1)

Right ventricular weight:body weight, right ventricular weight:left ventricular weight, right ventricular weight:left ventricular + septal weight ratios were significantly increased for PAB and HA calves. These ratios in HA calves were also significantly higher compared to PAB calves. Left ventricular weight:body weight ratio was unchanged from that in the normal calves. In PAB calves and HA calves, ratio of the septal weight:left ventricular weight was increased, but the ratio of septal weight:body weight was not significantly changed in comparison to normal calves.

Control Measurements

Right ventricular systolic and end-diastolic pressures were significantly increased \((P < 0.001)\) in PAB and HA calves compared to normal values, whereas the heart rate, aortic pressure, and cardiac output were unaltered (Table 2). However, the right ventricular systolic pressure of HA calves was significantly lower than that in PAB calves. Arterial oxygen content, hemoglobin concentration, and total peripheral resistance were not different among the three groups of calves (Table 2). Although mean pulmonary artery pressure of HA calves was significantly increased compared to normal calves, the calculated value of total pulmonary resistance was not different.

Blood flow per unit weight of the normal bovine right ventricular myocardium (Fig. 1; Table 3) was significantly lower \((P < 0.001)\) than that in the left ventricular myocardium (Fig. 2; Table 4), and no differences in blood flow were observed among the various regions of the right ventricular outflow tract. Blood flow in the hypertrophied right ventricular myocardium of PAB calves was significantly increased in comparison to both the normal calves \((146\%) \) and the HA calves \((61\%); \) Fig. 1; Table 3), the increment being largest in the region of outflow tract. Blood flow in the outflow tract of HA calves also exceeded that in the other regions of the right ventricular freewall. Although blood flow per unit weight of the hypertrophied right ventricular myocardium in HA calves was elevated \((by 53\%)\) compared to that in the normal calves, the difference was not statistically significant (Fig. 1; Table 3). However, because of the increased right ventricular mass (Table 1) in HA calves, blood flow for the entire right ventricular freewall was sig-

### Table 1

Morphological Characteristics of Right Ventricular Hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>Normal calves</th>
<th>Pulmonary artery-banded calves</th>
<th>Calves exposed to high altitude (3500 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 9 )</td>
<td>( n = 7 )</td>
<td>( n = 5 )</td>
</tr>
<tr>
<td>RV wt:body wt (g/kg)</td>
<td>1.21 ± 0.04</td>
<td>1.98 ± 0.11*</td>
<td>2.74 ± 0.20†</td>
</tr>
<tr>
<td>LV wt:body wt (g/kg)</td>
<td>2.42 ± 0.08</td>
<td>2.29 ± 0.07</td>
<td>2.47 ± 0.09</td>
</tr>
<tr>
<td>RV wt:LV wt</td>
<td>0.50 ± 0.01</td>
<td>0.90 ± 0.03*</td>
<td>1.12 ± 0.09†</td>
</tr>
<tr>
<td>RV wt:LV + S wt</td>
<td>0.36 ± 0.01</td>
<td>0.60 ± 0.03*</td>
<td>0.76 ± 0.06†</td>
</tr>
<tr>
<td>S wt:body wt (g/kg)</td>
<td>0.96 ± 0.04</td>
<td>0.99 ± 0.03</td>
<td>1.13 ± 0.06</td>
</tr>
<tr>
<td>S wt:LV wt</td>
<td>0.38 ± 0.01</td>
<td>0.45 ± 0.01*</td>
<td>0.46 ± 0.02*</td>
</tr>
</tbody>
</table>

Body weight has been corrected for weight of rumen contents. RV, LV, and S, respectively, stand for right ventricular myocardium, left ventricular myocardium, and the interventricular septum.

* Significantly different from normal calves at \( P < 0.001 \).
† Significantly different from pulmonary artery banded calves at \( P < 0.01 \).
significantly increased ($P < 0.001$) in comparison to normal calves, but it remained substantially lower (0.05 < $P < 0.10$) than that in PAB calves. The left ventricular coronary blood flow (Table 4; Fig. 2) and coronary vascular resistance (Table 5) were similar for the three groups of calves. The subendocardial: subepicardial perfusion ratio (endo:epi) exceeded 1.00 in various regions of both ventricles in all calves (Tables 3 and 4).

Blood flow in the right side of the interventricular septum of PAB calves was significantly increased (Fig. 2), although total septal blood flow per unit weight was not different among the three groups of calves (Table 4). The left:right side perfusion ratio (endo:epi) for the septum was also similar.

Coronary vascular resistance per unit weight of the hypertrophied right ventricular myocardium was significantly decreased (Table 5), its value being 39% (PAB calves) and 72% (HA calves) of that for normal calves. Because coronary blood flow for the entire right ventricular freewall of PAB and HA calves was significantly increased, coronary vascular resistance for the entire right ventricular myocardium of PAB and HA calves was significantly reduced (Table 5, cf: Normalized CVR). Coronary vascular resistance (per gram basis) for the right ventricular myocardium of HA calves was, however, significantly higher than that for PAB calves (Table 5).

**Maximal Coronary Vasodilatation**

Hemodynamic effects of intravenous adenosine infusion included marked rise in heart rate and cardiac output, whereas mean aortic pressure as well as diastolic aortic pressure registered precipitous decline from control values (Table 2) in all calves. Heart rate, aortic diastolic pressure, and the cardiac output were not different among the three groups of calves. In HA calves, peak aortic pressure and mean aortic pressure

---

**TABLE 2**

Hemodynamic Data from Nine Normal (N) Calves, Seven Pulmonary Artery-Banded (PAB) Calves, and Five Calves Exposed to High Altitude (HA; 3500 m)

<table>
<thead>
<tr>
<th></th>
<th>Control (baseline)</th>
<th>Adenosine</th>
<th>Acute hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>PAB</td>
<td>HA</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>HA</td>
<td>N</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90 ± 5</td>
<td>85 ± 3</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>Cardiac output (ml/min per kg)</td>
<td>113 ± 14</td>
<td>111 ± 6</td>
<td>133 ± 15</td>
</tr>
<tr>
<td>Arterial oxygen content (ml/dl)</td>
<td>14.9 ± 0.3</td>
<td>15.1 ± 0.4</td>
<td>15.5 ± 0.4</td>
</tr>
<tr>
<td>Hemoglobin concentration (g/dl)</td>
<td>11.00 ± 0.05</td>
<td>11.10 ± 0.03</td>
<td>11.21 ± 0.05</td>
</tr>
<tr>
<td>Hematocrit (volume percent)</td>
<td>34 ± 2</td>
<td>33 ± 1</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Right ventricular peak systolic pressure (mm Hg)</td>
<td>46 ± 2*</td>
<td>130 ± 2*</td>
<td>69 ± 2</td>
</tr>
<tr>
<td>Right ventricular end diastolic pressure (mm Hg)</td>
<td>7 ± 1</td>
<td>15 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>34 ± 2*</td>
<td>47 ± 2</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>Total pulmonary resistance (mm Hg/ml per min per kg)</td>
<td>0.30 ± 0.02</td>
<td>0.35 ± 0.02</td>
<td>0.20 ± 0.02‡</td>
</tr>
<tr>
<td>Aortic peak systolic pressure (mm Hg)</td>
<td>137 ± 2</td>
<td>145 ± 2</td>
<td>135 ± 5</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>117 ± 6</td>
<td>115 ± 6</td>
<td>117 ± 6</td>
</tr>
<tr>
<td>Aortic diastolic pressure (mm Hg)</td>
<td>108 ± 2*</td>
<td>99 ± 2</td>
<td>106 ± 2</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml per min per kg)</td>
<td>1.04 ± 0.03</td>
<td>1.00 ± 0.07</td>
<td>0.88 ± 0.07</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg X beats/min X 10^-5)</td>
<td>123 ± 2</td>
<td>123 ± 2</td>
<td>134 ± 2</td>
</tr>
</tbody>
</table>

* Significantly different from normal calves for the same treatment.
† Significantly different from pulmonary artery-banded (PAB) calves for the same treatment.
‡ Significantly different from control values for the same group of animals.
§ Significantly different from adenosine values for the same group of animals.
were markedly reduced compared to normal as well as PAB calves (Table 2). Total peripheral resistance of HA calves was also significantly decreased. Right ventricular peak systolic and end-diastolic pressures were not significantly altered during adenosine infusion in PAB and HA calves. In normal calves, however, a pronounced reduction in right ventricular end-diastolic pressure was observed (Table 2).

With maximal coronary vasodilation, transmural left ventricular myocardial blood flow increased \((P < 0.001; \text{Fig. 2})\) and the endo:epi perfusion ratio decreased \((P < 0.001; \text{Table 4})\) in all groups to a similar level. Minimal coronary vascular resistance in the left ventricular myocardium was also similar among the three groups of calves (Table 5).

Although transmural right ventricular myocardial blood flow had increased significantly \((P < 0.001; \text{Fig. 1})\) during adenosine infusion, interesting differences were observed among the three groups of calves. Whereas in normal calves, the endo:epi perfusion ratio was well maintained, this ratio was significantly decreased in PAB calves throughout all regions of right ventricular myocardium (Table 3). In PAB calves as well as HA calves, blood flow to the right ventricular papillary muscle and the associated subendocardium increased to a significantly lower level \((P < 0.025)\) than in normal calves (Fig. 1, bottom right panel). Also during adenosine infusion, subendocardial blood flow in the intermediate region of the right ventricular myocardium in HA calves remained significantly below that observed in normal calves (Fig. 1, top right panel). In HA calves, therefore, endo:epi perfusion ratio for these two regions of the right ventricular freewall had decreased significantly (Table 3).

The minimal level of right ventricular coronary vascular resistance achieved during maximal coronary vasodilation (expressed on per unit weight basis) was not different in the three groups of calves (Table 5). However, the normalized total right ventricular coronary vascular resistance (expressed on per kg body weight basis) was significantly decreased \((P < 0.01)\) in the PAB calves compared to normal calves (Table 5). In HA-exposed calves, this value of normalized coronary vascular resistance was significantly decreased from that for the normal calves \((P < 0.0001)\) as well as from that for the PAB calves \((P < 0.001)\).

During adenosine infusion, blood flow in the right side of the interventricular septum increased to a significantly lower level in PAB and HA calves (Fig. 2, bottom right panel). Thus in these two groups of calves, left:right (endo:epi) perfusion ratio for the
interventricular septum decreased less dramatically compared to that for normal calves (Table 4).

**Acute Hypoxemia**

Breathing of hypoxic gas resulted in a significant similar reduction in arterial oxygen content of both groups (Table 2). Concomitantly, there was a marked increase in heart rate, right ventricular systolic pressure, mean pulmonary artery pressure, and total pulmonary resistance, while cardiac output remained unaltered from respective control values. These changes were much more prominent in HA-exposed calves, in which right ventricular systolic pressure was 138 ± 9 mm Hg at Pao2 = 42 ± 1 mm Hg (Table 2). Rate-pressure product for both groups of calves was similarly increased.

Right ventricular transmural myocardial blood flow increased significantly in both groups of calves during acute hypoxemia (Table 3); the level of blood flow was markedly higher in the HA calves. However, the increment in right ventricular myocardial blood flow above respective control values was similar between the two groups (232% in normal calves vs. 254% in HA calves), despite the fact that right ventricular systolic pressure of HA calves during acute hypoxemia was 112% higher. In HA calves, mean endo:epi perfusion ratio in each of the four regions of the right ventricle had decreased below 1.00, whereas it did not decrease below 1.00 in the normal calves (Table 3). Coronary vascular resistance in the right ventricular myocardium had decreased significantly. Right ventricular coronary vascular resistance in HA calves was only 54% of that in the normal calves (Table 5).

Left ventricular coronary blood flow of HA calves was only insignificantly different from that in the normal calves (Table 4), but the coronary vascular resistance of HA calves was significantly lower (Table 5). Endo:epi perfusion ratio for the left ventricular myocardium remained above 1.00 in both groups. Although total septal blood flow was not different (Table 4), blood flow in the right side of the interventricular septum of HA calves (2.42 ± 0.30 ml/min per g) significantly exceeded that for the normal calves (1.67 ± 0.21 ml/min per g).

**Discussion**

The major findings of this study can be summarized as follows: (1) Maximal coronary vasodilator capacity in the hypertrophied right ventricular myocardium of
unanesthetized young calves was not diminished. Whether the rate of increase in right ventricular mass was rapid (HA calves) or slow (PAB calves), the increase in cardiac mass was accompanied by a proportionate increase in the functional cross-sectional area of the coronary vascular bed supplying the enlarged ventricle. (2) Chronic hypoxemia did not result in increased functional cross-sectional area of the coronary vascular bed supplying the left ventricular myocardium. (3) Increased baseline perfusion in the hypertrophied right ventricular myocardium is most likely due to augmented metabolic requirements.

Rate of Development of Right Ventricular Hypertrophy (Table 1)

In calves exposed to a simulated altitude of 3500 m (Pa = 500 mm Hg) for 8–10 weeks, right ventricular weight:body weight as well as right ventricular weight:left ventricular weight ratios were significantly increased compared to PAB calves which were studied 20 weeks postbanding. Because the rate of growth was identical for both groups of calves, we believe rapid development of very severe right ventricular hypertrophy in HA calves was due to the rapid rate at which stimulus (pressure-overload) was applied. We did not measure right ventricular pressure in these calves during exposure to high altitude. However, a previous study from our laboratory (Ruiz et al., 1973) has demonstrated that in Holstein-Friesian calves exposed to high altitude (3400 m), systolic pressure in the pulmonary artery was 82 ± 5 mm Hg at 2 weeks and 98 ± 10 mm Hg in the unanesthetized state at 4 weeks of sojourn. By comparison, in unanesthetized PAB calves, right ventricular systolic pressure approached 100 mm Hg at 91 ± 3 days postbanding. In PAB calves, right ventricular pressure was 60 ± 2 mm Hg at 4 weeks post-banding and 78 ± 3 mm Hg at 8 weeks post-banding.

In two calves of the HA group, in which ventricular hypertrophy was rapid (HA calves) or slow (PAB calves), the extent of right ventricular hypertrophy was not different from that in the other five HA calves. Whether the rate of increase in right ventricular mass was rapid (HA calves) or slow (PAB calves), the increase in functional cross-sectional area of the coronary vascular bed supplying the left ventricular myocardium, (3) Increased baseline perfusion in the hypertrophied right ventricular myocardium is most likely due to augmented metabolic requirements.

Blood Flow in the Hypertrophied Right Ventricular Myocardium during Baseline Conditions

In newborn calves (Manohar et al., 1981a), dogs (Murray et al., 1979; Murray and Vatner, 1981), and adult ponies (Manohar et al., 1981b), development of pressure overload-induced right ventricular hypertrophy is characterized by a significant increase in right ventricular myocardial blood flow and a marked decrease in right ventricular coronary vascular resistance. The reasons for higher perfusion in the hyper-
Figure 2. Transmural distribution of blood flow in the bovine left ventricular and septal myocardium before and during maximal coronary vasodilation. *Significantly different from normal calves for the same treatment. †Significantly different from high-altitude (HA) calves for the same treatment. All blood flow values for maximal coronary vasodilation are significantly (P < 0.001) higher than control values.

Table 5
Coronary Vascular Resistance (CVR) in Right and Left Ventricles of Nine Normal (N) Calves, Seven Pulmonary Artery-Banded (PAB) Calves, and Five Calves Exposed to High Altitude (HA; 3500 m)

<table>
<thead>
<tr>
<th></th>
<th>Right ventricle</th>
<th>Left ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVR/g (mm Hg/ml/min per g)</td>
<td>Normalized CVR (mm Hg/ml/min per kg)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>234 ± 9</td>
<td>194 ± 8</td>
</tr>
<tr>
<td>PAB</td>
<td>91 ± 7*</td>
<td>48 ± 5*</td>
</tr>
<tr>
<td>HA</td>
<td>169 ± 12†</td>
<td>61 ± 12*</td>
</tr>
<tr>
<td>Adenosine (maximal coronary vasodilation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>18 ± 1‡</td>
<td>15 ± 1‡</td>
</tr>
<tr>
<td>PAB</td>
<td>21 ± 3‡</td>
<td>11 ± 1*‡</td>
</tr>
<tr>
<td>HA</td>
<td>16 ± 1‡</td>
<td>6 ± 1*‡</td>
</tr>
<tr>
<td>Acute hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>69 ± 5§</td>
<td>57 ± 5§</td>
</tr>
<tr>
<td>HA</td>
<td>37 ± 10*§</td>
<td>14 ± 2*§</td>
</tr>
</tbody>
</table>

* Significantly different from normal (N) calves for the same treatment.
† Significantly different from pulmonary artery-banded (PAB) calves for the same treatment.
‡ Significantly different from control value for the same group of animals at P < 0.001.
§ Significantly different from control value as well as adenosine value for the same group of animals at P < 0.001.
trophied right ventricular myocardium remain unclear but may be related to inefficient oxygen utilization and low oxygen extraction (Archie et al., 1974) or to augmented right ventricular metabolic requirements. Based on the results of the present study, the latter possibility is more likely. Reasoning for this is as follows.

Blood flow (per unit weight) in the hypertrophied right ventricular myocardium of unanesthetized HA calves was only insignificantly increased (53%), whereas, in PAB calves, it was significantly increased (147%; Fig. 1). In HA calves, due to alleviation of hypoxic stimulus for pulmonary vasoconstriction, right ventricular systolic pressure during control conditions was significantly decreased (Table 2). It is likely that at this reduced level of right ventricular systolic pressure, wall stress in the hypertrophied right ventricle of HA calves would have been lower than that in the PAB calves. Because wall stress/tension is a major determinant of myocardial oxygen consumption (Braunwald, 1971; Rowe, 1974), other factors being equal, lower wall stress in the right ventricle of HA calves may have been responsible for the lower value of transmural myocardial blood flow (Fig. 1).

Because for technical reasons, RV wall stress is difficult to measure directly, Archie et al. (1974) designed an index of RV wall stress making numerous assumptions: P<sub>RV</sub> × W<sub>R</sub>/W<sub>RV</sub>, where P<sub>RV</sub>, W<sub>R</sub>, and W<sub>RV</sub> respectively, stand for right ventricular systolic pressure, right ventricular weight, and body weight. Using this index with all its assumptions (Archie et al., 1974), we found RV wall stress to be significantly higher (74%; P < 0.01) in PAB calves, whereas, in the hypertrophied right ventricle of HA calves, it was 34% lower than that in the normal bovine right ventricle. Thus, we believe that higher baseline right ventricular perfusion of PAB calves is most likely related to augmented metabolic requirements.

Maximal Coronary Vasodilator Capacity in the Hypertrophied Right Ventricular Myocardium (Table 5)

Minimal coronary vascular resistance per unit weight of the hypertrophied right ventricular myocardium in PAB as well as HA calves was similar to that in the normal bovine right ventricular myocardium. Total right ventricular coronary vascular resistance normalized for body weight (O'Keefe et al., 1978) was significantly decreased in the PAB calves. This decrease was much more pronounced in HA calves. These data indicate that a 64% increase in right ventricular weight/body weight ratio in PAB calves was accompanied by 27% (±2% sem) increase in functional cross-sectional area. The respective values for high altitude-exposed calves were 126% (±4.5% sem) and 60% (±2% sem). It is interesting to note that the increase in right ventricular weight/body weight ratio in HA calves was almost twice that for PAB calves, while the decline in normalized right ventricular coronary vascular resistance of HA calves was also twice that for PAB calves. These findings strongly suggest that in PAB as well as HA calves, the increase in cardiac mass was accompanied by a proportionate increase in the functional cross-sectional area of the right ventricular coronary vascular bed. The rapid progression of right ventricular hypertrophy in HA calves, therefore, did not appear to have limited the maximal coronary vasodilator capacity in the hypertrophied myocardium.

This finding that functional cross-sectional area of the coronary vascular bed supplying the right ventricular myocardium kept pace with the increase in cardiac mass in both PAB and HA calves, is in conflict with the observation in dogs (Murray and Vatner, 1981) that the increase in right ventricular mass was not accompanied by proportionate increase in the functional cross-sectional area of its coronary vascular bed. In contrast with the findings of Lowensohn et al. (1976) on conscious dogs with congenital pulmonic stenosis, Murray and Vatner (1981) also reported attenuated right coronary reactive hyperemic response in dogs with marked right ventricular hypertrophy following brief acute myocardial ischemia. These divergent findings may be attributable to species differences and/or to differences in age at which stimulus for development of hypertrophy was applied. The latter is likely because Archie et al. (1974) also observed that isoproterenol-induced coronary vasodilation was enhanced in tranquilized lambs with right ventricular hypertrophy produced in response to pulmonary artery banding at 2 days of age. This suggested an increase in vascularity of the hypertrophied right ventricle.

We have previously observed that functional cross-sectional area of the right ventricular coronary vascular bed kept pace with increasing cardiac mass of calves in which PAB was carried out within 24-48 hours after birth (Manohar et al., 1981a). The present study extends this finding to calves in which stimulus for development of hypertrophy was applied at 2 (PAB calves) to 3 (HA calves) months of age. It is likely that, in young animals, the increase in cardiac mass may be achieved by hypertrophy as well as hyperplasia.

Although we do not believe that the major conduit arteries were limiting the increase in myocardial blood flow during high flow states, we do not have data to prove that conduit arteries increased in size commensurate with the degree of right ventricular hypertrophy.

Effect of Chronic Hypoxemia on Maximal Coronary Vasodilator Capacity in the Left Ventricular Myocardium (Table 5)

Minimal coronary vascular resistance in the left ventricular myocardium of HA calves was identical to that in other calves born and raised at sea level. This suggests that functional cross-sectional area of the left ventricular coronary vascular bed did not increase in response to chronic hypoxemia. It should be noted that at any given altitude, cattle are more hypoxemic...
than other species. This is at least partially due to the fact that cattle, unlike other species, fail to sustain hyperventilation at high altitude and, also, they do not develop polycythemia (Bisgard, 1978).

This conclusion for unanesthetized cattle is supported by the observation that muscle fiber number:capillary number remained unchanged in the left ventricular myocardium of rats exposed to simulated high altitude (Pₐ = 380 mm Hg) for 34 days (Clark and Smith, 1978). Also, in these rats, reduction in myofiber size did not occur in response to chronic hypoxia of 34 days’ duration. This is in contrast to observations made on skeletal muscle fibers (Banchero, 1975; Eby and Banchero, 1976).

Miller and Hale (1970) reported that capillary density in the myocardium had increased upon exposure to chronic hypoxia. It is likely that the divergent observations of Clark and Smith (1978), and Miller and Hale (1970) may be due to the different perfusion techniques employed. Clark and Smith perfused the heart at 120 mm Hg, whereas Miller and Hale perfused the myocardium at 74 mm Hg. Despite these different morphological findings, we believe our data during adenosine infusion-induced maximal coronary vasodilation provide an accurate evaluation of the functional cross-sectional area of the left ventricular coronary vascular bed independent of the effects of work hypertrophy.

**Regional Differences in Transmural Myocardial Blood Flow during Adenosine-Induced Maximal Coronary Vasodilation**

During maximal coronary vasodilation, total right ventricular myocardial blood flow (per unit weight) was similar among the three groups of calves, but the endo:epi ratio for both PAB and HA calves had decreased significantly from control values (Table 3). In PAB calves, this ratio was also significantly lower than that in normal calves during adenosine infusion. As shown in Figure 1, in the papillary muscle region of the right ventricular freewall of PAB and HA calves, the blood flow rose to a significantly lower level in the subendocardium as well as the papillary muscle. This underperfusion during adenosine infusion in PAB calves may have been due to enhanced systolic compression on the right ventricular coronary vasculature as well as markedly elevated diastolic right ventricular pressure. In the HA calves, however, the right ventricular systolic pressure was significantly lower than that in PAB calves, and subendocardial underperfusion was also observed in the intermediate region of the right ventricular freewall. It would thus appear that, in the hypertrophied right ventricular myocardium of PAB and HA calves, the net available coronary vascular reserve in deeper layers of the intermediate and papillary muscle regions may be lower than that in the outflow tract and the posterior freewall regions. These areas may thus be the first to develop ischemia when augmented myocardial oxygen requirements require marked utilization of coronary vascular reserve.

In PAB and HA calves, blood flow in the right side of the septum also increased to a significantly lower level (Fig. 2; Table 4). We believe that in PAB calves this may have been the consequence of high right ventricular systolic and diastolic pressures, but the reasons for this occurrence in HA calves are not clear.

We have previously reported that in both normal and PAB calves, endo:epi perfusion ratio during adenosine infusion was maintained at approximately 1.00 in both ventricles (Manohar et al., 1981a). The differences in the endo:epi ratios then reported and those in the present study are due to the fact that in the present study right ventricular myocardium was divided into three transmural layers rather than two (Manohar et al., 1981a), and the left ventricular myocardium as well as septum were divided into four transmural layers instead of three.

**Myocardial Blood Flow during Acute Hypoxemia**

Systemic and pulmonary hemodynamic responses to acute hypoxia in the present study (Table 2) were similar to those previously reported for sea level calves and calves exposed to an altitude of 3400 m for 4 weeks (Ruiz et al., 1973). Right ventricular systolic and end-diastolic pressures of HA calves were significantly higher, mainly because of a very significant increase in pulmonary vascular resistance, while cardiac output, heart rate, and aortic pressure were similar to those of normal calves (Table 2). During acute hypoxemia, blood flow in the hypertrophied right ventricular myocardium of HA calves increased to a significantly higher level in comparison to normal calves (Table 3) for the same degree of reduction in arterial oxygen content (Table 2). This may be related to higher metabolic needs of right ventricular myocardium in HA calves. Although it may be surmised that pressure-overload (a 100% increase in right ventricular systolic pressure in response to hypoxia-induced pulmonary vasoconstriction) imposed onto the hypertrophied right ventricle of HA calves resulted in higher wall stress, causing an increase in right ventricular myocardial oxygen utilization, the calculated values of right ventricular wall stress index (Archie et al., 1974) were not different for the two groups of calves during acute hypoxemia (54 ± 2 for normal calves vs. 50 ± 4 for the HA calves).

Although right ventricular myocardial blood flow was increased significantly during acute hypoxemia in all calves, the endo:epi perfusion ratio in all regions of the hypertrophied right ventricular myocardium of HA calves had decreased significantly (P < 0.001; Table 3). Because right ventricular peak systolic pressure of HA calves (138 ± 9 mm Hg) was approaching that in the aorta (133 ± 8 mm Hg), right ventricular subendocardial perfusion most likely occurred predominantly during diastole (Hoffman and Buckberg, 1976; Lowensohn et al., 1976). This is in contrast to normal calves in which right ventricular perfusion could occur during systole as well as diastole (Hess and Bache, 1979). It is thus conceivable that the available right ventricular subendocardial coronary
vascular reserve in HA calves during acute hypoxemia may have been smaller than that in the subepicar-
dium, for the latter could be perfused in both systole
diastole. It should also be noted that, although
right ventricular coronary vascular resistance (per
unit weight) of HA calves during acute hypoxemia
was only 54% of that for normal calves, the mean drop in
coronary vascular resistance of normal calves (167
mm Hg/ml per min per g) was greater than that in
HA calves (132 mm Hg/ml per min per g).

Left ventricular coronary blood flow of HA calves
had a tendency to be somewhat higher than that in
normal calves during acute hypoxemia (Table 4), but
endoepi perfusion ratio remained above 1.00 in all
calves. The observation that blood flow in the right
side of the interventricular septum of HA calves
significantly exceeded that for the normal calves
during acute hypoxemia, is supportive of the hypothesis
that the right side of the septum supports RV con-

We gratefully acknowledge the excellent technical assistance of
David Dilley, Julia Dawson, Joan Otto, Walter Coeckel, and
Gordon Johnson. Thanks are due to Ms. Carol Prussa for preparing
the graphs. Thanks are also due to the staff of the Word Processing
Center, College of Veterinary Medicine, for meticulous typing of
the manuscript. Cooperation of the staff at the Biotron, University
of Wisconsin-Madison, is also highly appreciated. Thanks are due
to Dr. John C. Thurmon for making available some of the facilities
used in carrying out these experiments.

This work was supported by the American Heart Association
(with funds contributed in part by the Illinois Affiliate) and the
College of Veterinary Medicine, University of Illinois at Urbana-
Champaign.

Drs. Manohar, Parks, and Theodorakis are affiliated with the
Department of Veterinary Biosciences, and Drs. Tranquilli and
McPherren with the Department of Clinical Medicine, at the
College of Veterinary Medicine, University of Illinois. Drs. Busch
and Bigard are affiliated with the University of Wisconsin,
Madison, Wisconsin.

Address for reprints: Murli Manohar, BVSc, Ph.D., 222 Large
Animal Clinic, Department of Veterinary Biosciences, College of
Veterinary Medicine, University of Illinois, Urbana-Champaign,
1101 West Peabody Drive, Urbana, Illinois 61801.

Received August 13, 1981; accepted for publication February 2,
1982.

References

Archie JP, Fixler DE, Ulliyot DJ, Hoffman JIE, Uitley J, Carlson E
(1973) Measurement of cardiac output with and organ trapping
Regional myocardial blood flow in lambs with concentric right
ventricular hypertrophy. Circ Res 34: 143-154
Banchero N (1975) Capillary density of skeletal muscle in dogs
439

Comp Med 21: 151-172
Braunwald E (1971) Control of myocardial oxygen consumption:
Physiologic and clinical considerations. Am J Cardiol 27: 416-
432
Burke GD, Luck KC, Payne DB, Hoffman JIE, Archie JP, Fixler
DE (1971) Some sources of error in measuring regional blood
Clark DR, Smith P (1978) Capillary density and muscle fiber size
in the hearts of rats subjected to simulated high altitude. Cardio-
vasc Res 12: 578-584
Eby SH, Banchero N (1976) Capillary density of skeletal muscle in
Hess DS, Bache RJ (1979) Transmural right ventricular myocardial
flow measurements with radionuclide labelled particles. Prog
Cardiovasc Dis 20: 55-79
Hoffman JIE, Buckberg GD (1976) Transmural variations in myo-
cardial perfusion. Prog Cardiol 5: 37-89
Lowensohn HS, Khouri EV, Gregg DE, Pyle RL, Patterson RE
(1976) Phasic right coronary artery blood flow in conscious dogs
with normal and elevated right ventricular pressures. Circ Res
39: 760-765
Manohar M, Kumar R, Bhargava AK, Nigam JM, Tyagi RPS (1973)
Cardiac catheterization in unanesthetized cattle. J Am Vet Med
Assoc 163: 351-354
Manohar M, Bisgard GE, Bullard V, Will IA, Anderson D, Rankin
JHG (1979) Regional myocardial blood flow and myocardial
function during acute right ventricular pressure overload in
calves. Circ Res 44: 531-539
Manohar M, Thurmon JC, Tranquilli W, Devous MD, Theodorakis
MC, Shawley RV, Feller DL, Benson GJ (1981a) Regional myo-
cardial blood flow and coronary vascular reserve in unanesthe-
ized young calves with severe concentric right ventricular hyper-
Manohar M, Bisgard GE, Bullard V, Rankin JHG (1981b) Blood
flow in the hypertrophied right ventricular myocardium of
Manohar M, Thurmon JC, Devous MD, Tranquilli WJ, Shawley
RV, Benson GJ (1981c) Regional coronary blood flow and coro-
nary vascular reserve in unanesthetized calves at rest and during
Miller A, Hale D (1970) Increased vascularity of brain, heart, and
Murray PA, Vatner SF (1981) Reduction of maximal coronary
vasodilator capacity in conscious dogs with severe right ventric-
Murray PA, Baig H, Fishbein MC, Vatner SF (1979) Effects of
experimental right ventricular hypertrophy on myocardial blood
O'Keefe DD, Hoffman JIE, Chetlin R, O'Neill MJ, Allard JR,
left ventricular hypertrophy. Circ Res 43: 43-51
Rowe GG (1974) Responses of coronary circulation to physiologic
changes and pharmacologic agents. Anesthesiology 41: 182-196
Ruiz AV, Bisgard GE, Will JA (1973) Hemodynamic responses to
hypoxia and hyperoxia in calves at sea level and altitude. Pfue-
gers Arch 344: 275-286
1108-1116
New York, McGraw-Hill
and cardiac hemodynamics on the removal of norepinephrine
(NE) by the lung in animal subjects. Chest 71S: 287-289
Regiona myocardial blood flow and coronary vascular reserve in unanesthetized young calves exposed to a simulated altitude of 3500 m for 8-10 weeks.
M Manohar, C M Parks, M A Busch, W J Tranquilli, G E Bisgard, T A McPherron and M C Theodorakis

Circ Res. 1982;50:714-726
doi: 10.1161/01.RES.50.5.714

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/50/5/714

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

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

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