Regional Myocardial Blood Flow in Lambs with Concentric Right Ventricular Hypertrophy

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ABSTRACT

Chronically hypertrophied right ventricles function normally under high systolic pressures, whereas normal right ventricles fail when they are acutely subjected to similar pressures. This phenomenon may be partly due to adaptation of the coronary circulation as well as to hypertrophy. Knowledge of the magnitude and distribution of coronary blood flow and the degree of coronary vascular reserve are important in understanding the function of hypertrophied myocardium. We studied these variables in 16 awake, 5-12-week-old, tranquilized lambs; 9 of the lambs had had their main pulmonary artery banded at 2 days of age. Pressures, cardiac output, and coronary blood flow (radioactive microsphere method) were measured at rest and during two stress states—isooproterenol and dextran infusion. Ventricular function was similar in control and banded lambs. We found significant right ventricular hypertension and both right ventricular and septal hypertrophy in the banded lambs. Total coronary blood flow per gram was slightly higher in banded lambs in all states, and right ventricular flow per gram was significantly elevated at rest and during isoproterenol infusion. Right ventricular coronary resistance per gram was significantly lower in banded lambs in all states. These changes demonstrate that hypertrophied right ventricular tissue is not ischemic at rest, since there is vascular reserve. The changes also raise the question of increased vascularity in hypertrophied myocardium. Right ventricular oxygen supply per unit oxygen demand was increased in banded lambs at rest and during isoproterenol infusion. This finding suggests that hypertrophied myocardium has inefficient oxygen utilization, slow oxygen extraction, or both.

KEY WORDS
radioactive microspheres  pulmonary stenosis  coronary blood flow
coronary vascular resistance  subendocardial flow  Dextran 70  isoproterenol

Coronary blood flow to the right ventricular myocardium depends on right ventricular coronary driving pressure (1)—aortic pressure minus right ventricular pressure—and coronary vascular resistance. During acute, moderate right ventricular hypertension, decreased driving pressure is compensated for by coronary vasodilatation so that the increased oxygen needs of the right ventricular muscle can be met. Once maximum vasodilatation has occurred, further acute increases in right ventricular systolic pressure decrease both right ventricular coronary driving pressure and coronary blood flow (2-4); the resultant discrepancy between oxygen supply and oxygen demand causes failure of the right ventricle as evidenced by a rise in end-diastolic pressure and a fall in cardiac output and aortic blood pressure. For this reason, experimental acute narrowing of the pulmonary artery seldom produces right ventricular systolic pressures which equal or exceed left ventricular systolic pressures. By contrast, patients with congenital pulmonic stenosis and dogs subjected to chronic pulmonary artery banding can have peak right ventricular systolic pressures that exceed systemic pressures without there being any apparent evidence of myocardial ischemia or failure. Furthermore, they can lead normally active lives; evidently, the increased oxygen needs of their hypertrophied right ventricles can be met at rest and on exercise for many months or years.

The factors responsible for the differences in oxygen supply in acute and chronic right ventricular hypertension have not been studied, in part because of the technical difficulties of measuring right ventricular coronary blood flow. Therefore we studied awake, tranquilized lambs, some of which had right ventricular hypertrophy second-
ary to chronic banding of the pulmonary artery, at rest, during isoproterenol infusion, and after dextran infusion. We used the radioactive microsphere method (5-7) to measure regional and subregional blood flows to the septum and the free walls of each ventricle. In each of the three states, we compared these flows, coronary vascular resistance, and regional myocardial oxygen delivery in the control and the banded lambs. We also compared right ventricular flows and oxygen delivery per unit myocardial oxygen demand as estimated by heart rate and an index of peak ventricular wall stress.

Methods

Preparation.—Within 24-28 hours after birth, 19 lambs were medicated with diazepam (Valium) (5 mg, iv), given methohexibarbital (Brevital) (5 mg, iv), intubated with an endotracheal tube, and ventilated with a volume-controlled respirator using a mixture of 50% nitrous oxide and 50% oxygen containing 1% halothane. Under sterile conditions, a left thoracotomy was performed at the fourth intercostal space, and the ductus arteriosus was ligated. Polyethylene catheters (no. 5F) were placed in the internal mammary artery and vein and in the left atrium via a pulmonary vein branch. A catheter (no. 5F end hole) was placed in the right ventricle through a hole in the outflow tract surrounded by a purse-string suture. In 12 lambs, umbilical tape was passed around the main pulmonary artery, and a stenosis was created by tightening the tape. We used the occurrence of either a peak systolic right ventricular pressure of approximately two-thirds peak aortic pressure, an arrhythmia, or a significant decrease in aortic pressure—whichever occurred first—as the end point in the narrowing of the pulmonary artery. The tape was then tied and the chest closed. Seven control lambs were subjected to the same surgical procedure except that the tape was not placed. The pericardium was left open in all of the lambs, and a chest tube was used for several hours to ensure full lung expansion. Catheters were brought out through percutaneous stab wounds in the back and flushed daily or every other day with dilute heparinized saline. Approximately half of the lambs were rejected by their mothers and were bottle fed for 5-6 weeks.

Study.—All lambs were studied at 5-12 weeks of age when they weighed 6.8-26.4 kg. They were given only liquids overnight prior to study. They were tranquillized with diazepam (1 mg/kg, iv), weighed, and restrained. At the time of study, all of the arterial catheters were found to be occluded; so polyethylene catheters (no. 5F) were placed in fore- and hind-limb arteries under 1% xylocaine local analgesia and advanced into the aorta for pressure measurements and reference sample collection. If the left atrial catheter was occluded, a catheter (no. 5F) was passed via the carotid artery into the left ventricle. The right external jugular vein was used to pass a polyethylene catheter (no. 8F) into the right ventricle when its chronically implanted catheter was occluded or the pressure recording from it damped. A right atrial catheter was placed via a femoral vein. The cut-down wounds were then closed, and 2,000 units of heparin were given intravenously. Electrocardiogram limb leads were placed. We calibrated four Statham P23Dc pressure transducers and set zero pressure at midchest level with the lamb's left side dependent. Pressures, electrocardiograms, and dye-dilution curves were recorded on an eight-channel Beckman ink oscillograph. Cardiac output was measured either by the microsphere method (8) or from indocyanine green dye-dilution curves. The latter were determined by injecting indocyanine green dye into the right atrium and drawing blood from a peripheral artery through a Waters X-302 densitometer at 28 ml/min. Three-point calibration curves were established using lamb's blood for the studies with the lambs at rest and during isoproterenol infusion and repeated at the level of dextran infusion at which myocardial blood flow was measured. Dye-dilution outputs were measured immediately before or immediately after microsphere injection.

Microspheres 4–12μ (mean 7μ) in diameter labeled with 144Ce, 153Sm, and 46Sc and spheres 15μ in diameter labeled with 125I were used. For each measurement approximately 150,000–500,000 microspheres suspended in 2 ml of 0.5% Tween were injected over 45 seconds with 10–15 ml of saline at body temperature. The method of preparation and injection of microspheres and the method of collection of arterial reference samples have been reported (6, 7). Over 98% of the microspheres are trapped in the first circulation through the heart (8). When the radioactivity of reference samples from upper and lower extremities varied more than 35% or the withdrawal rate of one reference sample was not constant, the injection was discarded if it had been made into the left ventricle. A single reference sample was accepted if the injection was in the left atrium (7).

Protocol.—Cardiac output, pressures, and myocardial blood flow were measured in each lamb at rest. Then isoproterenol infusion at 0.1 μg/kg min⁻¹ was begun; measurements were usually made after 10 minutes when pressures and heart rate had been stable for approximately 5 minutes. The isoproterenol infusion was stopped, the lamb was allowed to rest for several minutes, and a slow infusion of Dextran 70 was then begun and continued until the left atrial pressure increased 15–20 mm Hg. The final isotope was given at this stage of the infusion. Because 15μ spheres may not measure transmural flow distribution as accurately as do 4–12μ spheres and because not as many large spheres can be trapped in the first circulation through the heart (8), when the radioactivity of reference samples from upper and lower extremities varied more than 35% or the withdrawal rate of one reference sample was not constant, the injection was discarded if it had been made into the left ventricle. A single reference sample was accepted if the injection was in the left atrium (7).

We killed the lambs by injecting barbiturates intravenously and removed the heart and great vessels; the surface vessels, fat, and epicardial scars were removed from the heart. The pulmonary veins and vena
cava were cut close to the atria, and the right and left atria were dissected from the ventricles and from each other by dividing the atrial septum. The free wall of the right ventricle was cut away from the septum and dissected into three layers: right ventricular endomyocardium, midmyocardium, and epicardium. The septum was divided from the free wall of the left ventricle, and both were dissected into four layers. Papillary muscles were included in the endomyocardial layers from each ventricle and the right layer of the septum. All specimens were weighed and placed in vials; then their gamma radioactivity was counted. Following counting, the right ventricles of all of the lambs were dried at 110°C for 48 hours and reweighed. All of the lambs were examined for pleural effusion, ascites, and hepatomegaly. The pulmonary band was observed in all of the banded lambs.

Calculations.—Stroke work, minute work, and tension–time index were computed (9). Total and regional coronary vascular resistance per unit weight were computed by dividing mean aortic pressure minus mean right atrial pressure by flow per unit weight. However, we also calculated the resistance per unit weight to right ventricular flow by using the pressure index (1, 2) as the driving pressure; the pressure index is the integrated difference per minute between aortic and right ventricular pressures.

Left ventricular wall stress has been estimated using both spherical and elliptical Laplace formulas (10, 11). Right ventricular stress (τrv) can be similarly calculated if right ventricular geometry and transmural pressure are known. For a spherical right ventricle the Laplace equation is

\[ \tau_{rv} = \frac{P_{tr}}{2h} \]

where \( P \) is right ventricular transmural pressure, \( h \) is mean wall thickness, and \( r \) is radius. We did not measure right ventricular radius or geometry. We estimated peak right ventricular wall stress by assuming that right ventricular end-diastolic volume was similar in control and banded lambs of equal body weight (\( W_b \)) at a given end-diastolic pressure. Based on this assumption, the ratio \( r/W_b = k_2 \), a constant. Furthermore, this assumption implies that for lambs of equal body weight right ventricular weight (\( W_{rv} \)) is proportional to wall thickness (\( h \)); \( W_{rv}/2h = k_2 \), another constant. If these two relationships are substituted into the spherical Laplace equation, we have

\[ \tau_{rv} = k_1 k_3 P_{tr} W_{rv}/W_{rv} \]

Since \( k_1 \) and \( k_2 \) are constants, this equation can also be written as

\[ \tau_{rv} = k_1 k_3 P_{tr} W_{rv}/W_{rv} \]

where \( k_1 k_3 \) is the product of \( k_1 \) and \( k_3 \) as unity and estimated an index of right ventricular wall stress from the equation \( \tau_{rv} = P_{tr} W_{rv}/W_{rv} \), recognizing that all values were in error by the unknown constant multiple \( k_1 k_3 \). The study of Laks et al. (12) in adult dogs showed that right ventricular volume increased after the pulmonary artery was banded and then declined toward normal. From these data and on the assumption that the right ventricles of our lambs behaved in a similar fashion to those of their dogs, we calculated that we underestimated wall stress in the lambs with right ventricular hypertrophy by as much as 17% compared with controls. We calculated an index of left ventricular wall stress in a similar way from \( \tau_{lv} = P_{lv} W_{lv}/W_{lv} \).

A normalized distribution of flow within the subregions of the right and left ventricles and septum was computed by dividing the flow per unit mass of each subregion by the flow per unit mass of each region. This procedure gives a measure of deviation from uniform flow for each region at each state studied. The mean of all subregion values is not necessarily unity because of the variation in weights for each subregion. Coronary oxygen delivery was calculated as arterial oxygen content times coronary flow; content was determined by multiplying hemoglobin by 1.33, since all of the lambs had arterial blood saturated at more than 98%.

Results

All 7 control lambs (no pulmonary artery band) and 9 of the 11 banded lambs were studied. None of the lambs studied had pleural effusion, ascites, or hepatomegaly, and they were all normally active. No lamb had a patent foramen ovale or any congenital heart defect. One banded lamb had severe tricuspid insufficiency believed to be secondary to ventricular catheter trauma and fibrous tissue growth; we included only the subregional flow distribution data from it. We were unable to obtain adequate reference samples necessary for flow calculation for each lamb at every state in the protocol. Since subregional distribution of flow is computed as a ratio of subregional to regional flow per unit weight, reference samples are not needed for this ratio; hence, these results are relatively complete. We rejected 8 of 26 (31%) of the left ventricular and 2 of 26 (8%) of the left atrial injections because of variability between upper and lower limb arterial reference sample concentrations. One injection was disregarded because of blood pressure and heart rate changes during injection.

Hypertrophy.—Various combinations of weights of right and left ventricles, right and left atria, septum and total body are given in Table 1. There was hypertrophy of the right atria and ventricles, and the ratios of ventricular dry weight to ventricular wet weight demonstrated the absence of edema as a component of right ventricular weight in banded lambs.

We calculated regression lines by the method of least squares to relate right ventricular weight or the ratio of right ventricular weight to total body weight to either resting right ventricular peak systolic pressure, minute work, stroke work, or ten-
TABLE 1
Regional Heart and Body Weight Ratios

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Control (7)</th>
<th>Banded (9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>( W_{RV} / W_T )</td>
<td>0.247 ± 0.0068</td>
<td>0.395 ± 0.0156</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( W_{RV} / W_{LV} )</td>
<td>0.463 ± 0.0204</td>
<td>0.954 ± 0.0916</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( W_s / W_T )</td>
<td>0.218 ± 0.0465</td>
<td>0.215 ± 0.0100</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_s / W_{LV} )</td>
<td>0.400 ± 0.0102</td>
<td>0.492 ± 0.0263</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{RV} / W_s )</td>
<td>0.000933 ± 0.0000632</td>
<td>0.00177 ± 0.000153</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_s / W_{RA} )</td>
<td>0.000806 ± 0.0000518</td>
<td>0.000923 ± 0.0000356</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{LV} / W_s )</td>
<td>0.00202 ± 0.000091</td>
<td>0.00197 ± 0.000166</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{RA} / W_s )</td>
<td>0.000374 ± 0.000193</td>
<td>0.000454 ± 0.0000260</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{RV} / W_B )</td>
<td>0.08 ± 0.106</td>
<td>1.45 ± 0.115</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{RA} / W_{LA} )</td>
<td>0.150 ± 0.0064</td>
<td>0.156 ± 0.0040</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>( W_{RV} / W_B )</td>
<td>0.98 ± 0.106</td>
<td>1.45 ± 0.115</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

All values are means ± se; \( P \) values were determined using an unpaired \( t \)-test. \( W_{RV} \), \( W_s \), \( W_{LV} \), \( W_T \), \( W_{RA} \), \( W_{LA} \), and \( W_B \) are wet weights of right ventricle, septum, left ventricle, total ventricle (RV + S + LV), right atrium, left atrium, and total body, respectively. Number of lambs in each group is in parentheses.

Ventricular Function.—The measured and calculated variables other than coronary blood flow are shown in Table 2. Different numbers of lambs appear in each group because of inadequate reference samples in some studies. As expected, right ventricular peak systolic pressure, stroke work, and tension-time index were elevated, tension-time index. All correlations with the weight ratio were higher than those for the absolute right ventricular weight; the highest correlations and the smallest deviations from regression occurred with peak right ventricular systolic pressure and tension-time index: the correlation coefficients were 0.952 and 0.935, respectively, and the coefficients of variation were 13.75% and 15.97%, respectively. The regression line relating the weight ratio to pressure had an intercept that was not significantly different from the origin.

Ventricular Function.—The measured and calculated variables other than coronary blood flow are shown in Table 2. Different numbers of lambs appear in each group because of inadequate reference samples in some studies. As expected, right ventricular peak systolic pressure, stroke work, and tension-time index were elevated.

TABLE 2
Pressures and Flows for Control and Banded Lambs in Three States

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Isoproterenol infusion</th>
<th>Dextran infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (6)</td>
<td>Banded (6)</td>
<td>Control (5)</td>
</tr>
<tr>
<td>Age (days)</td>
<td>60 ± 11.0</td>
<td>60 ± 11.0</td>
<td>61 ± 10.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>17.4 ± 2.0</td>
<td>15.3 ± 3.1</td>
<td>17.7 ± 2.4</td>
</tr>
<tr>
<td>HR (beats / min)</td>
<td>167 ± 17</td>
<td>196 ± 15</td>
<td>289 ± 11</td>
</tr>
<tr>
<td>( P_{Ao} ) (mm Hg)</td>
<td>98 ± 2.0</td>
<td>101 ± 3.3</td>
<td>89 ± 2.2</td>
</tr>
<tr>
<td>( P_{LV} ) (mm Hg)</td>
<td>112 ± 2.0</td>
<td>120 ± 4.5†</td>
<td>110 ± 6.7</td>
</tr>
<tr>
<td>( P_{LA} ) (mm Hg)</td>
<td>4.5 ± 1.8</td>
<td>6.8 ± 3.05</td>
<td>4.8 ± 2.00</td>
</tr>
<tr>
<td>( P_{RV} ) (mm Hg)</td>
<td>34 ± 5.7</td>
<td>78 ± 9.04</td>
<td>47 ± 10.0</td>
</tr>
<tr>
<td>( P_{RA} ) (mm Hg)</td>
<td>1.5 ± 0.41</td>
<td>4.2 ± 1.92</td>
<td>2.0 ± 1.55</td>
</tr>
<tr>
<td>CI (liters/min/kg⁻¹)</td>
<td>0.165 ± 0.025</td>
<td>0.166 ± 0.024</td>
<td>0.200 ± 0.020</td>
</tr>
<tr>
<td>( T_{RV} ) = ( P_{RV} W_s / W_{RV} ) (mm Hg × 10³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW (mg/m²)</td>
<td>40.0 ± 3.69</td>
<td>39.5 ± 3.21</td>
<td>53.3 ± 7.02</td>
</tr>
<tr>
<td>TTI (min Hg)</td>
<td>14.2 ± 2.29</td>
<td>32.2 ± 3.92†</td>
<td>21.6 ± 2.68</td>
</tr>
<tr>
<td>Hb (g/100 ml blood)</td>
<td>9.3 ± 0.65</td>
<td>10.6 ± 0.90</td>
<td>11.3 ± 1.15</td>
</tr>
</tbody>
</table>

All values are means ± se; probability was determined using an unpaired \( t \)-test between control and banded lambs at each state. \( P \) = mean pressure; \( P \) = peak systolic pressure; CI = cardiac output index; \( T_{RV} \) = peak systolic wall stress; TTI = tension-time index; SW = stroke work; Hb = hemoglobin concentration; HR = heart rate; \( A_o \) = aorta; other abbreviations are the same as they are in Table 1. Number of lambs tested is given in parentheses.

\*0.01 < \( P \) < 0.05.
\( \dagger \)0.05 < \( P \) < 0.10.
\( \ddagger \)\( P \) < 0.01.

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usually significantly, in the banded lambs in all three states. The index of peak systolic wall stress in the right ventricle was not different in the lambs with hypertrophy. The expected physiological effects of isoproterenol and dextran infusions were seen in control and banded lambs. The percent changes from the resting state were similar for control and banded lambs in almost all respects.

**Regional Distribution of Flows.**—The percent of flow to right ventricle, septum, and left ventricle in both groups of lambs at rest and with isoproterenol and dextran infusions is given in Figure 1. As expected, the left ventricle dominated the percent of total flow in control lambs, whereas relatively equal proportions of flow went to right and left ventricles in the banded lambs. The changes in the proportions were significant. The distributions were not altered by the infusions.

Figure 2 shows the flow per unit weight for each ventricular region in all three states. Hypertrophied right ventricle had significantly greater flow per gram than did normal right ventricle during isoproterenol and dextran infusion; the difference was nearly significant at rest \(0.10 > P > 0.05\). Although total coronary flow per gram was not significantly different, the ratio of right to left ventricular flow per gram was significantly higher in banded lambs than it was in control lambs during isoproterenol and dextran infusions and tended to be so at rest \(0.10 > P > 0.05\). Both the infusions significantly increased all regional flows over resting values in both groups of lambs. Septal flow per gram was intermediate in amount between the two ventricular flows but was usually closer to left ventricular flow per gram. There was a strong trend for the right and left sides of the septum to behave like the right and left ventricular free walls, respectively.

The regional resistance to flow per unit weight of myocardium is given in Figure 3. Right ventricular resistance by both methods of calculation was significantly lower in banded lambs in all three states, but the resistances of the septum and the left ventricle were similar for control and banded
lambs in all states. All regions of the myocardium in control and banded lambs had significantly decreased resistance during isoproterenol infusion compared with that during rest.

Subregional Distribution of Flows.—The subregional distribution of flows in the right and left ventricles and the septum are given in Figure 4. There was no significant difference between the fractional weights of each subregion in control and banded lambs (unpaired t-test). The flows were normalized for average flow per unit weight for that region. Only flows measured with 4–12μm microspheres appear in these figures, and each subregion contained at least 400 microspheres.

There was unequal distribution of transmural flow in both normal and hypertrophied right ventricles: the midmyocardial layer had significantly more flow per unit weight. The relative flow to right ventricular subendocardium in banded lambs was slightly but not significantly less than it was in control lambs in all three states (analysis of variance).

The left ventricular midinner layer always had the highest relative flow of any of the left ventricular layers in control and banded lambs, and the outer layer always had the lowest flow. The right side of the septum had the lowest septal flow at rest and during dextran infusion, but the left side of the septum had the lowest flow during isoproterenol infusion.

Right Ventricular Oxygen Supply and Demand.—Stroke flow per gram, coronary oxygen delivery per gram, and stroke coronary oxygen delivery per gram are given in Table 3 for the right and left ventricular free walls. At rest and during isoproterenol infusion all values were higher in banded lambs than they were in control lambs; the significance of the differences is indicated in Table 3. The ratio of these variables to the determinants of oxygen demand (heart rate and peak systolic wall stress) for the right ventricle are also given in Table 3. Right ventricular flow per gram per unit of peak systolic wall stress (Q_RV/τ_RV) was higher in banded lambs in all states, but the differences were

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*Flow per gram for each region and state (mean ± se). Groups, symbols, and numbers of lambs per group are the same as they are in Figure 1. The column for the septum is divided into three parts. The solid bars next to the right and left ventricular bar are the values for the right and left layers of the septum, respectively. The line is the mean value for the whole septum. Comparison of control and banded lambs by unpaired t-tests: * 0.01 < P < 0.05, † 0.05 < P < 0.10.*
neither great nor significant. However, at rest, coronary oxygen delivery per gram per minute per unit peak systolic wall stress \( (Q_{RV}Hb \times 1.33 / TRV) \) was significantly elevated in banded lambs, and the increased stroke coronary oxygen delivery per unit of peak systolic wall stress \( (Q_{RV}Hb \times 1.33 / HRTRV) \) in banded lambs approached statistical significance. The ratio of right to left ventricular oxygen delivery per gram per unit wall stress was significantly higher in banded lambs at rest and during isoproterenol infusion.

**Discussion**

We chose the experimental model of pulmonary artery banding because the procedure produces hypertrophy and simulates a common congenital heart defect. In the newborn animal, main pulmonary arterial stenosis is easy to produce and, if done early, can cause changes like those of congenital pulmonic stenosis. We chose lambs because of their docility and size. An animal weighing 10-20 kg is ideal for regional myocardial flow studies with radioactive microspheres, since any subregion in which flow is to be measured must be large enough to contain at least 400 microspheres for each flow measurement (7) and yet not have a significant number of blocked capillaries. Roberts and Wearn (13) measured about 4,000 capillaries/mm\(^3\) in the young human myocardium. Therefore, a subregion of myocardium weighing 1 gram would have approximately \( 4 \times 10^6 \) capillaries; even 4,000 microspheres/g tissue would occlude only about 0.1% of the capillary bed. This calculation assumes that 4–12µ microspheres embolize mainly to the capillaries. Larger spheres would occlude a much larger fraction of the microcirculation and hence could cause decreased local flows.

We studied the lambs while they were awake and tranquilized with diazepam, which is reported to have minimum hemodynamic effects in dogs (14) and cats (15). The effects of diazepam on coronary flow are unknown. We placed electromagnetic flowmeters on the anterior descending branch of the left coronary artery in two anesthetized lambs and administered diazepam (1 mg/kg, iv). There was an initial 20-40% increase in flow with return...
REST

ISOPROTERENOL INFUSION

DEXTRAN INFUSION

FIGURE 4

Variation from uniform flow. Flow per unit weight of subregion divided by flow per unit weight of region for control and banded lambs at rest (top), during isoproterenol infusion (middle), and during dextran infusion (bottom). Columns give means and vertical bars indicate ± SE. q = flow per gram, I = subendocardial layer, M = middle layer, O = subepicardial layer, R = right layer of septum, MR = middle right: second layer of septum next to right-sided layer, ML = middle left: third layer of septum next to left-sided layer, L = left layer of septum, MI = middle inner: second layer of left ventricular free wall next to subendocardial layer, MO = middle outer: third layer of left ventricular free wall next to subepicardial layer.

to prediazepam levels within 2 minutes. In addition, 2–3 mg diazepam/kg given intravenously did not change aortic pressure or heart rate.

Hypertrophy.——Right ventricular and atrial hypertrophy were produced in lambs by banding their main pulmonary artery in the first 48 hours after birth. In the adult sheep this procedure is believed to produce hypertrophy in which myocardial cells increase in size but not number (16, 17). In the newborn, hyperplasia may account for part of the increased right ventricular weight. The biochemical changes associated with the onset of hypertrophy suggest an “injury phase” (18), but this phase has been studied only in adult dogs. However, it is probable that hypertrophy of the right ventricle in this study was in a state of relatively stable hyperfunction as described by Meerson et al. (18). The lambs were 4–12 weeks old at the time of study; they were growing normally, showed normal activity levels, and had no evidence of fluid retention. The band around the pulmonary artery provided a fixed obstruction so that with growth and increased cardiac output there was an increase in right ventricular pressure, as also noted by Overy et al. (19) in similar preparations.

In banded lambs the weights of the right ventricle and the septum were increased relative to body weight, but the left ventricle was not hypertrophied. This finding confirms similar results obtained by banding the pulmonary artery in swine (20), lambs and ewes (19), and dogs (21). Laks et al. (12) did find left ventricular hypertrophy in adult dogs after the main pulmonary artery had been banded but this change was not detected until 4 months after banding.

Our excellent correlation of right ventricular weight as a fraction of total body weight with resting peak right ventricular systolic pressure confirms other work in lambs (19), cats (22), and cattle (23). This correlation suggests that the degree of right ventricular hypertrophy might be determined by right ventricular pressure. Recently Ingwall et al. (24) have demonstrated in embryonic chick skeletal muscle grown in tissue culture that an increase in creatine concentration on the order of that expected when muscle work is increased will specifically stimulate the synthesis of myosin, actin, and relaxing protein. It is possible that any increase in wall stress liberates more creatine locally, thus stimulating the process of hypertrophy. The hypertrophy would continue until wall stress returns to normal and restores physical and chemical
stroke oxygen delivery per unit wall stress (ml/min g⁻¹ mm Hg⁻¹ × 10⁻²)

RV stroke oxygen delivery per unit wall stress (ml/stroke g⁻¹ mm Hg⁻¹ × 10⁻²)

Ratio of RV to LV oxygen delivery per unit wall stress

All values are means ± SE; probability was determined using an unpaired t-test between control and banded lambs at each state.

Number of lambs tested is given in parentheses. Q = flow per gram; other abbreviations are the same as in Tables 1 and 2.

*0.05 < P < 0.10.
1P < 0.01.
2P < 0.05.

Equilibrium. Interestingly, our calculated index of right ventricular stress did not differ in control and banded lambs. Similar equivalence of wall stress in normal and hypertrophied left ventricles was observed in man by Sandler and Dodge (10) and by Hood (25).

Ventricular Function.—At rest, control and banded lambs had similar systemic pressures, flows, resistances, and minute work; the lower left ventricular stroke work in banded lambs was largely related to their higher heart rates. These systemic measurements usually changed similarly with isoproterenol and dextran infusions. Right ventricular pressures and work were elevated in the banded lambs and, in both control and banded lambs, changed similarly during the infusions. Thus, the normality of most measurements and their normal response to stress fit well with the clinical normality of patients with moderate congenital pulmonary stenosis.

Subregional Flows.—The similarity of distribution of subregional flow per gram in control and banded lambs in all three states suggests that right ventricular subendocardial ischemia did not occur when the lambs were stressed. Buckberg et al. (26) have shown that left ventricular subendocardial ischemia can occur with normal coronary arteries in stress states in which the diastolic pressure–time index (the area per minute between aortic and left ventricular pressures) is reduced well below the tension-time index. In the banded lambs, the right ventricular diastolic pressure–time index exceeded the tension-time index in all three states so that right ventricular subendocardial ischemia would not have been expected.

Sarcomere length is maximum in the midinner
layer of normal canine left ventricles (27). If this finding holds for lambs, it might explain why we found the highest relative flows in this layer: the greater sarcomere lengths could indicate greater local developed stress and hence greater local oxygen demand (28, 29). Also, if this explanation accounts for the greater relative flow in the mid-myocardial right ventricular layer, then perhaps the right ventricular sarcomeres are longest in this layer. We are not aware of studies that have investigated this possibility.

Regional Coronary Flow.—The ability of all heart regions in both control and banded lambs to increase total coronary flow and decrease total coronary vascular resistance with isoproterenol and dextran infusions indicates well-marked vasodilator reserve. Furthermore, right ventricular resistance per gram as calculated by both methods is significantly lower in banded lambs than it is in control lambs in all states, suggesting that these hypertrophied right ventricles have either more vessels, greater vasodilatation, or both. There were no significant differences between banded and control lambs in resistance for the septum and left ventricle, suggesting that these regions are not involved in the vascular effects of hypertrophy. Since right ventricular resistance in hypertrophied hearts could decrease markedly with the infusions, the likelihood of right ventricular ischemia at rest is very low.

In open-chest dogs with normal right ventricles, acute pulmonary banding first causes an increase in right ventricular coronary flow per gram; then, as right ventricular pressure rises further, the driving pressure is diminished and right ventricular coronary flow becomes inadequate to meet the needs of the muscle (2-4). Acute cardiovascular collapse eventually occurs. With similar or greater reduction of right ventricular coronary driving pressure in our banded lambs, right ventricular coronary flow could increase normally (Fig. 3, Table 3). This finding suggests that the vascular reserve per gram of right ventricular muscle is greater in the hypertrophied ventricle than it is in the normal right ventricle for equivalent increases in right ventricular systolic pressure.

Right Ventricular Oxygen Supply and Demand.—In attempting to assess whether a given flow is adequate for the needs of the myocardium, we were not able to measure right ventricular venous blood to determine if there was excessive oxygen extraction or lactate production. Therefore, we depended on inferences based on known determinants of myocardial oxygen needs. Heart rate was similar in the two groups in all states and so should not account for any of the observed differences in oxygen delivery (30). A change in inotropic state influences myocardial oxygen use (31-33), but the response to isoproterenol was similar in the two groups. However, the contractile state is decreased in right ventricular papillary muscle from cats with right ventricular hypertrophy (22) so that, all other determinants being equal, we should expect less oxygen demand from hypertrophied myocardium. The principal determinant of myocardial oxygen need is wall tension or stress (28, 29). Both peak pressure (34) and tension-time index (9) correlate well with oxygen demand in normal myocardium, but the use of tension-time index to predict oxygen needs is valid only when the ratio of wall thickness to radius of curvature is constant, as already discussed. Therefore, relating right ventricular coronary blood flow to its tension-time index gives a lower value for banded lambs than it does for control lambs, but this difference is an artifact due to an inadequate correlation between tension-time index and wall stress in hypertrophied ventricles.

Studies by other investigators of coronary flow with left ventricular hypertrophy in man (35-40) or dogs (41) have shown that coronary blood flow and myocardial oxygen uptake per gram of left ventricle are either normal or slightly raised. There is some doubt about the accuracy of the methods used to measure coronary flow especially when marked regional variations in flow would have occurred (42). Only one of these studies related coronary flow to wall tension, and that study made no allowance for wall thickness.

In our banded lambs, the stroke oxygen delivery to hypertrophied right ventricular muscle was significantly higher than that to normal muscle at rest and during isoproterenol infusion. Even when an allowance was made for wall stress the oxygen delivery to hypertrophied right ventricular muscle was significantly higher than that to normal muscle. The ratio of right to left ventricular oxygen delivery per unit peak systolic wall stress removes variables common to both ventricles such as heart rate, arterial blood oxygen content, and the variability of the microsphere arterial reference sample (7). The significantly higher value of this ratio in banded lambs at rest and during isoproterenol infusion further supports the conclusion that right ventricular oxygen supply exceeds predicted oxygen demand in the banded lambs. Before accepting this
conclusion, however, we ought to consider if the increase is due to an underestimate of wall stress caused by not correctly allowing for changes in right ventricular mean radius of curvature. For oxygen delivery per unit of wall stress to have been equal in control and banded lambs, the mean right ventricular radius of curvature at rest would have had to increase by a ratio of 42.0 to 23.4 or 80%. This increase would have been associated with a 58.4% increase in right ventricular volume, a very unlikely change. Lesser increases in ventricular volume, which are more likely, would still lead to the conclusion that oxygen delivery per unit of wall stress was in fact increased with right ventricular hypertrophy.

There was either an inefficient utilization of oxygen or a lower oxygen extraction in the hypotrophied myocardium. Evidence for the former possibility has recently been provided by Gunning and Coleman (43). The latter possibility could have resulted from a defect in the autoregulatory mechanism of coronary vascular resistance, although we have shown right ventricular coronary vascular reserve in the banded lambs, or from an increase in diffusion distance.

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References


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