Coronary Flow Reserve and Oxygen Metabolism of the Right Ventricle

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The flow reserve of the right coronary artery (RCA) and myocardial oxygen extraction are important tractors in any investigation of the mechanisms of impaired right ventricular function. The present study induced brief coronary occlusions and examined the effect on right coronary blood flow in normal dogs, and the effect on myocardial oxygen metabolism in dogs with right ventricular hypertrophy (RVH). Right coronary flow reserve, represented by occlusion duration causing a half maximum dilatation (T1/2), was greater in the RCA than in the left anterior descending coronary artery of normal dogs: 11.4 ± 2.3 sec vs 5.9 ± 1.4 sec.

Myocardial oxygen extraction ratio (EO2) of the right ventricle (RV), 51.3 ± 1.6%, was significantly (p < 0.05) lower than the index of the left ventricle (LV), 60.6 ± 1.0%, and the extraction of the RV increased significantly in association with an increase of myocardial oxygen demand. In dogs with RVH caused by chronic banding of the pulmonary artery, this dominant oxygen reserve was lost: the EO2 of the hypertrophied RV was high compared with the EO2 of the normal RV (57.3 ± 3.4% vs 51.3 ± 1.6%, p < 0.05), and no further increase in EO2 was observed in the hypertrophied RV in response to the elevation of the myocardial oxygen requirement. Oxygen usage per 100g of the RV for a certain level of overall RV work, rate-pressure product, was significantly (p < 0.02) lower in the hypertrophied RV (0.00054 mI/O2/beat-mmHg) than in the normal RV (0.0012 mI/O2/beat-mmHg). These findings suggest that the normal RV had the dominant reserve of oxygen supply through both the greater capacity of flow increment and ability to increase oxygen uptake from blood. This advantage was lost in the hypertrophied RV, but improved oxygen efficacy to overall RV mechanical work would contribute to maintain the normal function in the hypertrophied RV.

Changes in oxygen requirement of the myocardium are met by altering coronary blood flow and myocardial oxygen extraction ratio. The right coronary artery is perfused with the same perfusion pressure as the left coronary artery, while developed tension of the right ventricular (RV) pressure is less than a half of the left ventricular developed tension. This suggests different vasodilatory responses of the right coronary artery (RCA) and/or myocardial oxygen extraction between the right and the left ventricles.
TABLE 1 MORPHOLOGIC AND HEMODYNAMIC MEASUREMENTS IN NORMAL AND BANDED DOGS WITH RIGHT VENTRICULAR HYPERTROPHY

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 21)</th>
<th>RVH (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV wall thickness (mm)</td>
<td>5.41 ± 1.28</td>
<td>9.50 ± 2.15**</td>
</tr>
<tr>
<td>RV/body weight ratio (&lt; 1,000)</td>
<td>1.72 ± 0.41</td>
<td>2.80 ± 0.73**</td>
</tr>
<tr>
<td>RV/LV weight ratio</td>
<td>0.43 ± 0.13</td>
<td>0.85 ± 0.13**</td>
</tr>
<tr>
<td>CBF of RCA (ml/min/100g)</td>
<td>46 ± 13.7</td>
<td>49 ± 19.7</td>
</tr>
<tr>
<td>RV-MVO₂ (ml/min/100g)</td>
<td>4.0 ± 0.13</td>
<td>4.2 ± 1.3</td>
</tr>
<tr>
<td>RV-EO₂ (%)</td>
<td>51.3 ± 7.3</td>
<td>57.3 ± 8.6**</td>
</tr>
<tr>
<td>LV-EO₂ (%)</td>
<td>60.6 ± 4.6</td>
<td>57.6 ± 8.1</td>
</tr>
</tbody>
</table>

RVH, right ventricular hypertrophy; RV, right ventricle; LV, left ventricle; CBF, coronary blood flow; RCA, right coronary artery; MVO₂, myocardial oxygen consumption; EO₂, oxygen extraction ratio.

The data are expressed as mean ± SD. Significantly different from the normal at the levels of **p < 0.01 and *p < 0.05.

in response to the changes in myocardial oxygen requirement. In the left ventricle, it is widely accepted that the myocardium extracts oxygen almost maximally even in the physiological conditions, so that the ratio of myocardial oxygen extraction maintains constant levels despite wide variation in myocardial oxygen requirement. However, observations on myocardial oxygen extraction of the RV are controversial. Kusachi et al. reported that the RV showed lower oxygen extraction and had a significant reserve to increase oxygen uptake from blood, while Weiss and Sinha observed homogenous oxyhemoglobin saturation in the right and left ventricles. It is important to clarify the modes of oxygen supply to the RV myocardium in response to changes in oxygen demand in order to investigate the mechanisms of RV dysfunction caused by cor pulmonale. The goals of the present study were to characterize, in comparison with the left ventricle, responses of the right coronary artery flow and myocardial oxygen uptake of the RV to brief myocardial ischemias and to increases in ventricular effort.

METHODS

Experiment 1

Adult mongrel dogs of either sex were anesthetized with sodium pentobarbital, 25–30 mg/kg, and ventilated with O₂-enriched room air. The chest was opened aseptically in the left forth intercostal space, and the PA was constricted with surgical tape to raise the right ventricular pressure by approximately 40 mmHg above the baseline pressure. Then, the chest was closed, and the dog was allowed to recover. More than 6 months later, when the right ventricular hypertrophy would be established, the dog was anesthetized, and the chest was opened with midternal incision. The heart was supported in a pericardial cradle. Two or three anterior cardiac veins drained from the midportion of the right ventricle and the coronary sinus were can-

Japanese Circulation Journal Vol. 53, October 1989
nulated for measuring right and left ventricular oxygen consumption (MVO$_2$), respectively. Blood flow of the RCA, and aortic and right ventricular pressures were recorded continuously on a jet recorder. After control data were obtained, right ventricular oxygen requirement was increased with further rise in right ventricular pressure by approximately 20 mmHg or intravenous isoproterenol infusion at a rate of 0.1 $\mu$g/kg/min. Twenty five normal dogs served as control.

Data Analysis

Group data were expressed as mean ± SEM. The paired Student’s t-test was applied for comparison of the data within the group, and the unpaired Student’s t-test for comparison between groups. P < 0.05 was considered significant.

RESULTS

Experiment 1

T1/2 represented the coronary flow reserve for myocardial ischemia, because the larger T1/2 indicated the longer occlusion time required for myocardial ischemia which caused a certain level of reactive coronary vasodilation. T1/2 during the control was significantly shorter in the LAD than the time of the RCA (5.9 ± 1.4 sec, vs. 11.4 ± 2.3 sec): the value was approximately double that of the LAD. PA bandage elevated the right ventricular (RV) pressure from 28 ± 6 mmHg to 47 ± 8 mmHg without significant changes in heart rate and systemic blood pressure. This intervention shortened T1/2 of the RCA to 6.2 ± 3.2 sec, resulting in no significant difference of the index between two coronary arteries. Isoproterenol infusion increased heart rate from 142 ± 16 to 168 ± 21 beats/min, and lowered systemic blood pressure from 106 ± 14 to 98 ± 16 mmHg. T1/2 of the RCA during isoproterenol infusion decreased to 7.6 ± 0.9 sec, and reached a similar level to that of the LAD.

Experiment 2

Postmortem examination revealed that the chronic pressure overloading by the PA bandage produced right ventricular hypertrophy (RVH) as determined by RV wall thickness, weight ratio of the RV to the left, and ratio of RV weight to body weight (Table 1). RV systolic pressure at 48 ± 13 mmHg was significantly higher than

*Fig. 1. Effect of intravenous infusion of isoproterenol on normal and hypertrophied right ventricle. ● = normal, ○ = hypertrophied right ventricle, RCA = right coronary artery, EO$_2$ = oxygen extraction ratio of the right ventricle, MVO$_2$ = myocardial oxygen consumption of the right ventricle. Data are expressed as mean ± SEM. * = Significant difference from control at the level of p < 0.05.
normal (28 ± 5 mmHg). Coronary blood flow per unit myocardium in the RVH was similar to the blood flow of the RCA in the normal control dogs, and approximately 55–60% of the blood flow in the left circumflex coronary artery. The myocardial oxygen extraction ratio (EO\textsubscript{2}) of normal dogs was significantly lower in the RV than the left. Comparatively, EO\textsubscript{2} of the hypertrophied RV was elevated by 5–10% and reached values similar to those of the left ventricle (Table 1).

Intravenous infusion of isoproterenol in-
increased heart rate by about 20% and decreased blood pressure by about 15% in both normal and RVH groups. Blood flow in the right coronary artery increased from 50.9 ± 7.7 to 115.9 ± 20.2 ml/min/100 g in normal dogs and from 51.5 ± 1.6 to 81.0 ± 22.3 ml/min/100 g in dogs with RVH. The increase in coronary blood flow was substantially greater in control dogs than in RVH dogs (p < 0.02). In normal dogs, right ventricular myocardial oxygen extraction (RV-EO₂) increased without significant changes in the left ventricular EO₂, resulting in no significant difference of EO₂ between the two ventricles. On the other hand, the hypertrophied right ventricle did not cause a further increase in EO₂. These changes in coronary blood flow and EO₂ produced an increase in MVO₂ of 153% in the normal RV and 40% in the hypertrophied RV (Fig. 1).

PA constriction raised the RV systolic pressure by approximately 20 mmHg. This intervention did not affect heart rate and systemic blood pressure in normal and hypertrophied dogs. The responses of coronary blood flow, EO₂ and MVO₂ to the PA constriction were quantitatively similar to the changes caused by isoproterenol infusion. Lesser increases in right coronary blood flow and MVO₂ and no changes in EO₂ were observed in the hypertrophied RV (Fig. 2).

To compare the cardiac efficacy of normal and hypertrophied RV, MVO₂ was plotted against a rate-pressure product (RPP), i.e. the product of right ventricular systolic pressure and heart rate (Fig. 3). Linear regression analysis revealed a significant relationship between the two parameters both in normal (MVO₂ = 0.0012RPP − 0.11, p < 0.01) and hypertrophied RV (MVO₂ = 0.0005RPP + 1.43, p < 0.01).

However, the slope of the regression line was significantly less steep in hypertrophied RV than in normal dogs (p < 0.02): the slope of hypertrophied RV was approximately half that of the normal RV.

**DISCUSSION**

This study indicated that in normal dogs, the right coronary artery has a greater reserve of vasodilation than the LAD in response to brief myocardial ischemia. Furthermore, the capacity to increase myocardial oxygen extraction was also greater in the RV compared to the left. However, this advantage of the RV was lost when RV oxygen demand was increased. These data indicated that in normal dogs, there is a much greater capacity for oxygen supply to the RV than to the left mainly through a lower cardiac work of the RV.

Kusachi et al.² observed that occluding the left anterior descending coronary artery for 25 sec or more elicited maximum peak hyperemic flow responses. However, in the right coronary artery peak hyperemic flow rate continued to increase as the duration of coronary occlusion was lengthened to 60 sec. Their observations were consistent with the present results. Because of substantially lower oxygen requirement of the RV, a longer occlusion would be needed to generate a metabolic stimulus sufficient to cause maximum vasodilatation, and increases in RV-MVO₂ shortened the occlusion duration for the metabolic vasodilation. Gregg¹ reported oxyhemoglobin saturation in anterior cardiac veins ranging between 31 to 77% of the arterial levels. Marchetti et al.⁵ added to the observations, in right heart bypass preparations, that the oxyhemoglobin saturation in blood from an anterior cardiac vein was invariably higher than the saturation of coronary sinus blood. Marchetti et al.⁵ and Kusachi et al.² also observed that increases in right ventricular oxygen requirement caused by constriction of RV drainage or isoproterenol infusion reduced anterior cardiac vein saturations to levels approaching those in the coronary sinus. The observations reported here confirm that oxygen extraction is lower in the RV than the left, and suggest that augmented EO₂ can be an important reserve of oxygen supply to the RV in response to increases in MVO₂.

Our estimates of right coronary blood flow of the basal condition in hypertrophied RV made a sharp contrast with observations of Murray et al.⁶ They reported that the presence of moderate and severe hypertrophy was associated with marked increase in transmural blood flow per gram to the RV proportional to the observed increases in mass. Archie and his associates⁷ demonstrated that total coronary blood flow per gram was slightly higher in hypertrophied RV, but Wyse and his associates⁸ found unaltered myocardial blood flow per gram of muscle in hypertrophied RV compared to normal RV. RV systolic pressure of Murray's experiments was much higher than ours, 102 ± 9 (SEM) mmHg vs 47.9 ± 13.2 mmHg, while wall thickness of the RV was similar in the two experiments. Though no exact data on the right ventricular dimensions
are available in their report, one can predict that RV wall stress in our dogs would be smaller than Murray's. Sasayama and his coworkers demonstrated initial dilatation with increased wall stress followed by gradual wall thickening and consequent reduction of wall stress to near normal in response to chronic elevation of left ventricular pressure. Thus, it seems that our dogs had an adequate wall thickness to normalize wall stress for elevated right ventricular pressure, but right ventricular hypertrophy of the dogs in Murray's experiment did not develop to the level enough to normalize wall tension for the relatively high ventricular pressure. Observations in the left ventricle that myocardial blood flow was similar between normal and a stable hypertrophied left ventricle would be compatible with our observations in the hypertrophied RV.

Coronary capacity to reduce vascular tone in response to vasodilatory stimuli was limited in hypertrophied RV compared to the normal. Botham et al reported on the coronary flow reserve of the heart with moderate RVH, and found that the extent of vasodilatory reserve was similar with or without moderate RVH using the peak reactive hyperemic flow rates after brief coronary occlusions. Murray et al observed reduced maximum coronary vasodilatory capacity to brief myocardial ischemia and intravenous injection of adenosine. Wangler et al and Peters et al observed that coronary reserve was decreased when left ventricular hypertrophy in spontaneously hypertensive rats was at its peak value, while after a period of stable left ventricular hypertrophy, coronary reserve returned to normal. Thus, the discrepancy between the present data and these of Botham et al might depend on the period of time following establishment of stable ventricular hypertrophy.

In order to estimate the relationship of RV-MVO₂ to RV mechanical work, RV contractile function in term of rate-pressure product was compared with the level of RV-MVO₂. Increases in RV rate-pressure product correlated with increases in RV-MVO₂ in normal dogs and dogs with hypertrophied RV. It is widely accepted that the relationship of left ventricular minute MVO₂ to the product of mean systolic pressure and systolic ejection period per minute, or heart rate, was constant over an extreme range in various hemodynamic alterations. Thus, although the complex shape of the RV limits the likelihood, of predicting RV-MVO₂ from hemodynamic measurements, the present data suggest that rate-pressure product of the RV is of use for predicting RV-MVO₂. Slopes were significantly different for RVH dogs and normals (although both groups exhibited significant relationships between RV-MVO₂ and rate-pressure product). The results indicate that hypertrophied RV can achieve a certain level of overall cardiac work with less oxygen requirement than normal per unit weight of muscle. Wyse et al observed no significant difference in the slope of regression lines between myocardial blood flow of the RV and RV rate pressure product. We could not explain the different results in these two experiments but Wyse et al also found a significantly different level of the intercept of the slope, suggesting that the greater overall RV performance was achieved by greater unit MVO₂ in the animals with RVH than in the normal animals. The later results are consistent with ours.

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