The Pathophysiology of Failure in Acute Right Ventricular Hypertension: Hemodynamic and Biochemical Correlations

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SUMMARY Acute right ventricular (RV) hypertension and failure occur clinically. In this study we examined the mechanism of RV failure. Adult dogs were studied acutely under anesthesia; dogs were instrumented for measurement of pressures and right coronary artery blood flow. Myocardial blood flow and cardiac output were determined with radionuclide-labeled microspheres, and the presence of ischemia was determined by biochemical analysis of ventricular biopsies. RV hypertension was produced by constricting the pulmonary artery and was increased until RV failure occurred, as evidenced by decreased aortic pressure and cardiac output and increased RV end-diastolic pressure. With increasing RV systolic pressure, RV myocardial blood flow failed to increase in proportion to demand. At the onset of RV failure, there was no reactive hyperemia of right coronary flow compared with control, indicating the absence of further coronary vascular reserve; biochemical analysis demonstrated that the RV free wall was ischemic; the LV free wall was not. Infusion of phenylephrine raised aortic pressure and hence, myocardial perfusion pressure; RV failure reversed as shown by decreased RV end-diastolic pressure and increased cardiac output and RV systolic pressure; reactive hyperemia of right coronary flow was restored and the biochemical indexes of ischemia were reversed, demonstrating that ischemia is the cause of failure in acute RV hypertension.

RIGHT VENTRICULAR (RV) HYPERTENSION and consequent RV failure occur acutely in diseases such as pulmonary embolism. In 1936, Fineberg and Wiggers suggested that the right ventricle could not generate adequate pressure to overcome the resistance of the obstructed pulmonary vasculature, but they did not define the mechanisms. Salisbury demonstrated that RV failure could be improved by aortic constriction; his work suggests that myocardial perfusion may influence the ability of the right ventricle to pump against increased afterload, but he did not measure coronary blood flow. Aukland et al. and Fixler et al. went one step further and demonstrated that with increasing RV pressure, RV myocardial perfusion failed to increase as RV pressure was raised to high levels, and soon thereafter, failure occurred.

Other investigators examined the relationship between RV failure and coronary perfusion pressure. Brooks et al., who produced RV failure by pulmonary artery obstruction, demonstrated that failure improved when right coronary perfusion pressure was increased. However, they did not study regional myocardial blood flow, did not consider tricuspid insufficiency as a contributing factor to failure and did not determine the presence of ischemia. Spotnitz et al. created a model of RV hypertension and failure with pulmonary emboli of homologous blood. They demonstrated that failure produced by massive experimental pulmonary embolism could be improved by balloon counterpulsation in the right main pulmonary artery or by occluding the descending aorta; they also did not measure regional myocardial blood flow.

These studies suggest that limited blood flow and consequent ischemia may cause right ventricular failure in acute RV hypertension. In the present study we examine this question further, using an acute preparation in which failure is produced by pulmonary artery constriction. Regional myocardial blood flow and coronary vascular reserve are examined, and the presence of ischemia is determined by tissue biochemical markers of ischemia.

Methods

Experimental Preparation

Adult mongrel dogs of either sex, weighing 26.8–40.8 kg (mean ± sd 31 ± 4.4 kg), were studied acutely under anesthesia. Neuroleptic anesthesia was produced with i.v. fentanyl, 0.02 mg/kg and droperidol, 1 mg/kg (Innovar-Vet, Pitman-Moore, Inc.). After intubation, ventilation was maintained with a pump (Harvard Apparatus Co.) and a gas mixture of nitrous oxide (65%) and oxygen (35%). Paralysis was produced with pancuronium bromide, 0.25 mg/kg (Pavulon, Organon, Inc.). The chest was entered through bilateral fourth interspace thoracotomies and transverse sternotomy. Extrapericar-
dial access was used for pressure measurement. Fluid-filled catheters were placed in the aortic arch via an internal mammary artery, the right atrium via theazygos vein, the right ventricle via an internal mammary vein, and the left atrium via a tributary of the left superior pulmonary vein. Pressure measurements were made with strain gauges (Model P23Db, Statham Medical Instruments) and were recorded on a Beckman Dynograph (Beckman Instruments, Inc.). The main pulmonary artery and right coronary artery were exposed through small pericardiotomies. A pneumatic constrictor (R. E. Jones) was placed around the main pulmonary artery; a 2-mm-diameter electromagnetic flow transducer (Narco Bio-Systems, Inc.) and a hydraulic occluder were placed around the right coronary artery just distal to the sinoatrial node branch; the flow transducer and occluder were used to determine reactive hyperemia of right coronary artery flow after a 10-second occlusion.9

Cardiac output and regional myocardial blood flow were determined with radiolabeled microspheres.10 A suspension of 9-μm diameter spheres, labeled with one of six different gamma-emitting nuclides (141Ce, 89Sr, 95Nb, and 48Sc), was injected into the left atrium over 30 seconds and, starting just before the injection, a reference sample was withdrawn continuously from the aorta for 2 minutes. The order of nuclide administration was randomized in each preparation. At the end of each study, the heart was excised, weighed, fixed in 10% formalin for 7 days, and then reweighed. The atria, great vessels, valves and chordae, and epicardial fat and vessels were removed. The right and left ventricular free walls and septum were separated and each was divided into six regions; each region, in turn, was divided into three transmural layers, and their radioactivity was determined with a NaI crystal and a multichannel pulse-height analyzer (Ino-Tech, Inc.). The activity of each nuclide was determined by a modification of the method of Heymann et al.10 After correction for decay of each nuclide, regional myocardial blood flow was determined; at least 400 microspheres were present in each sample.11 The weight of each tissue sample was corrected for weight change due to fixation, and myocardial blood flow was expressed as flow per gram of fresh weight (ml/min/g). The transmural distribution of RV myocardial blood flow was determined by dividing blood flow to the endocardial layer of the RV free wall by flow to the epicardial layer to give the RV endo-epi flow ratio.

Experimental Protocol — Closed Pericardium

In nine experimental preparations, experiments were carried out with a closed pericardium. After pressures, coronary flow, and heart rate had stabilized for 20 minutes, control data were obtained. The pulmonary arterial constrictor was inflated until RV systolic pressure was approximately twice that in the control state. The pulmonary artery was then constricted further in small increments until the onset of RV failure, as defined by failure of RV systolic pressure to increase with further constriction, by rising RV end-diastolic pressure, and by decreasing aortic pressure. Phenylephrine, 1–3 μg/kg/min (Neo-Synephrine, Winthrop Laboratories), was then infused to raise aortic pressure and hence, myocardial perfusion pressure. Data were obtained in the control state, during RV hypertension, at the onset of RV failure, and during phenylephrine administration. In each instance, after reactive hyperemia was determined, microsphere administration was begun; hemodynamic data were recorded 30 seconds after the start of microsphere administration at a paper speed of 100 mm/sec. RV coronary driving pressure was calculated as the difference between mean aortic and mean RV pressures, as described by Cross.12 The right atrial pressure tracing was analyzed for evidence of tricuspid insufficiency; the depth of the “a”-to-“x” descent of the systolic portion of the wave form was compared to the “v”-to-“y” descent to determine if regurgitation was contributing to atrial filling.13

Experimental Protocol — Open Pericardium

In nine additional preparations, the pericardium was opened and fashioned into a cradle to support the heart. The previously described protocol was carried out. Four-millimeter-diameter transmural biopsies were obtained from the right and left ventricular free walls with the Allard rapid-freezing biopsy apparatus.14 Sequential biopsies were obtained in the control state, during RV hypertension, 15–30 seconds after the onset of RV failure, and during phenylephrine administration. Tissues were stored overnight under liquid nitrogen and analyzed for pyruvate, lactate, creatine phosphate and adenosine triphosphate (ATP) the next day.

Biochemical Analysis

Tissue extraction and biochemical analyses were carried out in triplicate with the methods of Lowry and Passoneau.15 Tissue processing through deproteinization was done in a cryostat at −30°C. Tissue samples were powdered with a steel percussion mortar that had been deep-cooled in liquid nitrogen. A weighed quantity of frozen, powdered tissue was mixed with three volumes of frozen, powdered 3N perchloric acid; the mixture was then allowed to thaw in an ice-alcohol bath. After homogenization, six volumes of 1 mM EDTA were added, and the resulting suspension was centrifuged at 15,000 x g for 15 minutes. The supernatant was neutralized with potassium hydroxide, and after removal of the potassium perchlorate precipitate, the supernatant was assayed immediately for pyruvate, lactate, creatine phosphate and ATP.

Pyruvate analysis was done by an indirect microfluorometric assay with lactic dehydrogenase in an NADH-to-NAD−-linked reaction; lactate analysis was done by a direct microfluorometric assay with lactic dehydrogenase in an NAD-to-NADH-linked reaction. ATP was determined by a direct microfluoro-
metric assay with glucose-6-phosphate dehydrogenase and hexokinase in a NAD-to-NADH-linked reaction; creatine phosphate was subsequently determined in the same reaction by adding ADP and creatine kinase and determining the ATP formed. ATP and creatine phosphate data were expressed as concentration in micromoles per gram of fresh tissue weight. The lactate concentration was divided by the pyruvate concentration to give the [lactate]:[pyruvate] ratio.

Statistical Analysis
Results are expressed as the mean ± SD. Statistical analyses were performed by analysis of variance. Hemodynamic and myocardial blood flow data in the two groups of preparations were first analyzed with a two-way analysis of variance with replication to determine if the pericardium influenced the variable in question. If there was no difference in the two groups for a given variable, data were pooled. Subsequently, results obtained during RV hypertension and at the onset of RV failure were compared with control, and results obtained during pheneylephrine administration were compared to RV failure by one-way analysis of variance with repeated measurements; nonparametric multiple comparisons of pooled myocardial blood flows by microspheres were made by a Kruskal-Wallis single factor analysis of variance by ranks and the Neuman-Keuls test using rank sums. Biochemical data were analyzed by one-way analysis of variance with replication. A p value < 0.05 was considered significant.

Results
All dogs were studied acutely and had arterial Po2 158 ± 36 torr (SD), PCO2 34 ± 6 torr, and pH 7.40 ± 0.05; the mean hematocrit was 36.5 ± 6.6%. There were no significant differences in these variables between preparations with an open vs a closed pericardium.

Hemodynamic Data
The hemodynamic effects of pulmonary artery constriction and subsequent elevation of aortic pressure with phenylephrine are illustrated in figure 1, which shows representative recordings from a dog with a closed pericardium. With incremental pulmonary artery constriction, RV systolic pressure failed to increase above 65 mm Hg, and as failure ensued, RV and aortic systolic pressures decreased and RV end-diastolic pressure increased. With phenylephrine infusion, aortic pressure increased, to be followed by an increase in RV systolic pressure above its previous levels; RV end-diastolic pressure decreased as RV function recovered.

Hemodynamic data for the two groups of preparations are summarized in table 1. Analysis of the effect of the pericardium demonstrated that among the variables shown, only the RV end-diastolic pressure was significantly influenced by a closed pericardium (p < 0.001), being higher with a closed pericardium during RV failure; data for the remaining variables were pooled for the two groups studied, and these pooled values are also shown in tables 1 and 2.

Pulmonary artery constriction was initially adjusted to produce approximately a twofold increase in peak RV pressure. Mean aortic pressure, left atrial pressure, and cardiac output decreased slightly, but these decreases were not statistically significant. With RV hypertension, RV end-diastolic pressure did not change significantly in preparations with an open pericardium, but increased significantly (75%) when the pericardium was left closed. RV hypertension also resulted in a significant (17%) increase in heart rate.

Pulmonary artery constriction was then increased further in small increments until RV failure occurred; this was characterized by the onset of decreasing aortic and RV pressures. The rate at which these changes occurred depended on the size of the increment in pulmonary artery constriction that produced the onset of failure. RV failure was not a steady state: if there was no intervention, failure would continue until cardiac activity finally ceased. The increment in pulmonary artery constriction that produced the onset of failure was selected so that a gradual decline in RV function occurred over 5–8 minutes, permitting adequate time for microsphere injection and reference sample collection. With RV failure, cardiac output and aortic pressure decreased significantly compared with control (49% and 37%, respectively) (table 1); ac-

**Figure 1.** Hemodynamic example of the effects of phenylephrine in acute right ventricular (RV) failure in a preparation with a closed pericardium. All three recordings were taken at a slow paper speed.
Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Control Pericardium</th>
<th>RV Hypertension Pericardium</th>
<th>Failure Pericardium</th>
<th>Phenylephrine Pericardium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Open</td>
<td>Closed</td>
<td>Open</td>
<td>Closed</td>
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<tr>
<td>Systolic RV pressure (mm Hg)</td>
<td>27 ± 5</td>
<td>30 ± 9</td>
<td>28 ± 7</td>
<td>55 ± 8</td>
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<td>Mean aortic pressure (mm Hg)</td>
<td>78 ± 15</td>
<td>78 ± 6</td>
<td>76 ± 12</td>
<td>71 ± 14</td>
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<tr>
<td>Cardiac output (ml/min)</td>
<td>2940 ± 630</td>
<td>2740 ± 1070</td>
<td>2850 ± 850</td>
<td>2510 ± 710</td>
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<tr>
<td>RV end-diastolic pressure (mm Hg)*</td>
<td>4 ± 2</td>
<td>4 ± 3</td>
<td>5 ± 3</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>129 ± 39</td>
<td>144 ± 44</td>
<td>136 ± 41</td>
<td>156 ± 30</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>5 ± 1</td>
<td>4 ± 2</td>
<td>4 ± 2</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>RV coronary driving pressure (mm Hg)</td>
<td>68 ± 14</td>
<td>62 ± 8</td>
<td>65 ± 12</td>
<td>46 ± 14</td>
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</table>

Data shown are mean ± sd; open pericardium, n = 9; closed pericardium, n = 9; pooled data, n = 18.

*RV end-diastolic pressure in open pericardium preparations was compared to that in closed pericardium preparations using two-way analysis of variance with replication and differed significantly in the two groups (p < 0.001).

Abbreviations: RV = right ventricular.

comparing the decrease in aortic pressure was a significant increase in heart rate (24%) above control. RV end-diastolic pressure increased significantly above control in both groups, 100% in preparations with an open pericardium and 225% in preparations with a closed pericardium; it also increased significantly above levels during RV hypertension, but the increase was significant only in the group with a closed pericardium (86%, p < 0.025).

The presence of tricuspid insufficiency, a potential accompaniment of RV failure and additional contribution to decreased cardiac output, was assessed by analysis of the right atrial pressure wave form. In all preparations in this study, there was no evidence of tricuspid insufficiency during the period of RV failure when data were recorded, when microspheres were being administered, and when reference samples were being withdrawn. If RV failure was allowed to progress without intervention, tricuspid insufficiency appeared as failure worsened, and its appearance was marked by a precipitous change in the right atrial pressure wave form and a precipitous decrease in aortic pressure.

Phenylephrine administration raised aortic pressure to a level significantly greater than that obtained during RV failure (160%); cardiac output and peak RV pressure also increased significantly (64% and 44%, respectively) compared with levels obtained during RV failure. RV end-diastolic pressure decreased significantly (39%) in the group with a closed pericardium; heart rate decreased significantly (18%) with phenylephrine infusion, probably by reflex mechanism.** RV coronary driving pressure was calculated and is shown in table 1; with increasing RV pressure and failure, it decreased significantly (65%) from control level. Phenylephrine administration, by increasing aortic pressure, restored RV coronary driving pressure.

If phenylephrine administration was then discontinued, aortic pressure slowly decreased and RV failure once again occurred, confirming that pulmonary artery constriction was maintained during the period of each study.

Myocardial Blood Flow

The regional distribution of myocardial blood flow was assessed with radioactive microspheres (table 2). RV hypertension produced a significant increase (51%) in RV free wall myocardial blood flow. Further increases in pulmonary artery constriction produced failure but did not result in increases in myocardial blood flow. Blood flow, in fact, was decreased in failure as compared to RV hypertension in 17 of the 18 preparations; in one preparation, blood flow increased to a value nearly 3 standard deviations greater than the mean blood flow in failure. This value was included, and therefore, myocardial blood flow was analyzed with nonparametric statistics. Mean RV myocardial blood flow at the onset of failure
Table 2. Myocardial Blood Flow Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>RV hypertension</th>
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<td>Pericardium</td>
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<td>Pooled data</td>
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<td>RV myocardial</td>
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<tr>
<td>blood flow (ml/min/g)</td>
<td>0.72 ± 0.27</td>
<td>0.61 ± 0.22</td>
<td>0.67 ± 0.25</td>
<td>1.01 ± 0.29</td>
<td>1.01* ± 0.29</td>
<td>0.68 ± 0.29</td>
<td>0.71† ± 0.33</td>
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<td>2.03 ± 0.36</td>
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<td>Open</td>
<td>Closed</td>
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<td>RV endocardial</td>
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<tr>
<td>blood flow (ml/min/g)</td>
<td>0.78 ± 0.38</td>
<td>0.62 ± 0.25</td>
<td>0.70 ± 0.33</td>
<td>1.03 ± 0.37</td>
<td>1.02* ± 0.37</td>
<td>0.64 ± 0.42</td>
<td>0.70† ± 0.41</td>
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<td>blood flow (ml/min/g)</td>
<td>0.82 ± 0.28</td>
<td>0.61 ± 0.24</td>
<td>0.71 ± 0.30</td>
<td>1.17 ± 0.28</td>
<td>1.08* ± 0.30</td>
<td>0.89 ± 0.43</td>
<td>0.88† ± 0.37</td>
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<td>2.40 ± 2.00</td>
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<td>RV endo:epi flow</td>
<td>0.94 ± 0.21</td>
<td>1.01 ± 0.35</td>
<td>0.97 ± 0.22</td>
<td>0.86 ± 0.15</td>
<td>0.96 ± 0.28</td>
<td>0.91 ± 0.16</td>
<td>0.75§ ± 0.22</td>
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<td>0.99 ± 0.91</td>
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<td>hyperemia (%) payback</td>
<td>166 ± 154</td>
<td>160 ± 169</td>
<td>174 ± 171</td>
<td>171 ± 40</td>
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Data shown are mean ± sd; open pericardium, n = 9; closed pericardium, n = 9; pooled data, n = 18.

Kruskal-Wallis single factor analysis of variance by ranks and the Neuman-Keuls test using rank sums:

- vs control: *p < 0.001.
- vs RV hypertension: †p < 0.001.
- vs failure: ‡p < 0.001.

One-way analysis of variance with repeated measures:

- vs control: §p < 0.001; ¶p < 0.01.
- vs failure: **p < 0.001; ‡‡p < 0.025.

Decreased significantly (30%) compared with RV hypertension; raising aortic pressure with phenylephrine significantly increased RV myocardial blood flow above the level found during the RV failure (161%), RV hypertension (82%), or control states (175%). When RV myocardial blood flow was examined separately in the endocardial and epicardial thirds of the RV free wall, parallel changes were noted in regional blood flows.

The transmural distribution of myocardial blood flow was assessed by determining the ratio of flow per gram of tissue in the endocardial and epicardial thirds of the RV free wall (RV endo:epi). In the control state, this ratio was found to be approximately 1; with increasing RV pressure, this ratio decreased slightly, but the decrease was not significant. With degrees of pulmonary artery constriction that produced RV failure, the RV endo:epi flow ratio decreased significantly (22%) compared with control. The higher RV coronary driving pressure produced with phenylephrine significantly increased the RV endo:epi flow ratio toward the control level (27%) compared with RV failure.

Coronary vascular reserve in right coronary artery flow was determined after a 10-second occlusion of the right coronary artery. In the control state and during RV hypertension, reactive hyperemia was present, as evidenced by substantial payback of the flow debt incurred during temporary occlusion. If reactive hyperemia was tested as the pulmonary artery constriction was gradually tightened to produce failure, the amount of payback diminished as the constriction approached that necessary to produce the onset of RV failure. At the onset of failure, there was no reactive hyperemia in right coronary flow, i.e., payback was zero, and this was significantly different from the control state. With phenylephrine infusion, reactive hyperemia returned to right coronary artery flow, to levels near those obtained in the control state, and this differed significantly from the absence of reactive hyperemia at the onset of RV failure.

Ischemia was assessed directly by determining the concentrations of metabolic markers associated with ischemia: creatine phosphate, ATP, lactate and pyruvate. Biopsies obtained from the RV free wall had a mean weight of 113 ± 42 mg and from the left ventricular free wall, 180 ± 71 mg (table 3). During RV hypertension, the concentrations of creatine phosphate and ATP and the ratio of tissue lactate to pyruvate concentrations did not change significantly from control. In biopsies obtained 15–30 seconds after the onset of failure, however, there were significant decreases in creatine phosphate (55%) and ATP (24%) concentrations. The ratio of lactate to pyruvate concentrations increased significantly (223%) at the onset of failure. With phenylephrine infusion and after hemodynamic stabilization, the creatine phosphate concentration returned toward control levels, and the 123% increase from the failure state, was statistically significant. There was a small, statistically nonsignificant increase of 20% in ATP concentration with phenylephrine infusion (0.05 < p < 0.10). The ratio of lactate-to-pyruvate concentrations returned to levels very close to those in the control state.

In contrast to the results obtained with biopsies from the right ventricle, biopsies from the left ventri-
icle did not show any significant changes in metabolic variables in any of the four states examined. There was a small, statistically nonsignificant decrease (14%) in creatine phosphate concentration (0.05 < p < 0.10) at the onset of RV failure, and the concentration increased toward control level with phenylephrine infusion. Thus, as determined by metabolic markers of ischemia, the RV free wall was ischemic at the onset of RV failure, and ischemia was ameliorated by providing a higher RV coronary driving pressure with phenylephrine. In contrast to the right ventricle, there was no evidence of ischemia of the left ventricle at the onset of RV failure.

Discussion

This study demonstrates that acute RV hypertension and hence, increased RV afterload produced by pulmonary artery constriction, results in RV failure; RV hypertension decreases coronary driving pressure in the face of increased demand, and RV failure occurs as a result of RV myocardial ischemia and consequent pump failure. In this model, RV failure could be improved without decreasing RV afterload by providing additional RV coronary driving pressure with phenylephrine and reversing RV myocardial ischemia.

An acute animal model with fixed pulmonary artery obstruction was selected for this study to determine the mechanism of failure. The anesthetic regimen of nitrous oxide with a narcotic and a tranquilizer at the doses used in this study produces minimal myocardial depression and maintains reflex changes in heart rate. This model employs a water-filled pulmonary artery occluder; in such a study of mechanism, the constancy of pulmonary artery obstruction is important. If an intervention improves RV function, it is important that spontaneous changes in the pulmonary artery obstruction do not occur, as this could artificially improve RV function; this is a potential criticism of studies that increase RV afterload with experimental pulmonary emboli. In this study, a water-filled constrictor was used, and at the conclusion of each experiment, phenylephrine infusion was discontinued. As aortic pressure decreased, RV failure once again occurred, confirming that a change in pulmonary artery constriction was not responsible for the improvement of function.

An important consideration in this study is the definition of RV failure. Other investigators have examined right coronary artery vascular reserve in RV pressure overload; they defined RV failure as a decrease in aortic pressure and an increase in RV end-diastolic pressure and found that under these circumstances, coronary vascular reserve was still present in the RV free wall, suggesting that at least part of the RV free wall was not ischemic. RV failure as defined in this manner is a steady state; cardiac output was not measured, and thus cardiac function might not have been depressed under the conditions of their study. We defined failure at the time each experiment was performed by changes in systemic and RV pressures that continued to progress without further increments in pulmonary artery constriction; depression of cardiac output was subsequently confirmed by microsphere analysis. The use of aortic systolic and RV end-diastolic pressure criteria alone is inadequate, as changes in these variables can occur with progressive pulmonary artery constriction before cardiac output decreases significantly. This difference in the definition of RV failure probably accounts for the findings of Gold and Bache, who demonstrated right coronary vascular reserve with RV pressure overload.

The lack of a steady state in RV failure presents a special problem in gathering data at the onset of failure. Pulmonary artery constriction was advanced in very small increments until failure occurred. Failure, once present as defined in this study, would progress over several minutes. Microsphere administration was begun at the onset of failure, and hemodynamic data recordings were made 20–30 seconds after each injection was begun. Thus, the time

<table>
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<tr>
<th>Table 3. Biochemical Data</th>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Creatine phosphate (μmol/g)</td>
</tr>
<tr>
<td>ATP (μmol/g)</td>
</tr>
<tr>
<td>[lactate] : [pyruvate]</td>
</tr>
</tbody>
</table>

Data shown are mean ± sd; n = 9.
One-way analysis of variance with replication:
vs control: *p < 0.001; †p < 0.025.
vs failure: ‡p < 0.001.
pressure data were recorded would correspond approximately to the time when microspheres were lodging in myocardial tissue and were being withdrawn in the arterial reference sample. Similarly, biopsies were obtained 15–30 seconds after the onset of RV failure so that biochemical data would correlate in time to hemodynamic and myocardial blood flow data. If failure was permitted to progress without intervention, profound failure with aortic pressure less than 40 mm Hg would occur 6–10 minutes after the final increment was made in pulmonary artery constriction. Thus, the slow deterioration of function at the onset of failure permitted ample time to administer microspheres, to collect data and reference samples, and to biopsy the right and left ventricles.

This study was performed in preparations with an open and a closed pericardium. Previous studies have shown that the pericardium significantly influences left ventricular pressure-volume relationships; thus, particularly in the thin-walled right ventricle, it was important to use a model with a closed pericardium, as this membrane might influence RV function, particularly with increased pressure loads. However, serial myocardial biopsies could not be obtained with an intact pericardium, so both types of preparations were examined.

Hemodynamic and myocardial blood flow data in these two groups were compared by two-way analysis of variance, and of the variables examined, only the RV end-diastolic pressure was significantly different in these two groups of preparations. Mean RV end-diastolic pressure at the onset of failure was significantly higher in preparations with a closed pericardium than in preparations with an open pericardium (p < 0.001) (table 1). Furthermore, in preparations with a closed pericardium, phenylephrine infusion produced a significant decrease in RV end-diastolic pressure as RV function recovered. Glantz et al. have suggested that the pericardium steepens the RV diastolic pressure-volume relationship; they demonstrated that with the pericardium open, the thin-walled right ventricle can undergo substantial dilatation with only small increases in RV diastolic pressure. With the pericardium closed, any increases in RV diastolic volume result in higher RV diastolic pressure due to the additional stiffness imposed by the pericardium, accounting for the differences in RV end-diastolic pressures seen with the two groups of preparations in this study.

Interaction between left and right ventricles can occur, and this interaction is markedly enhanced by the pericardium; RV distention during failure could possibly interfere with left ventricular filling and consequently could contribute to decreased cardiac output. In the present study, left atrial pressure was monitored in both groups of preparations and was significantly decreased at the onset of failure. If failure was allowed to progress without phenylephrine infusion, left atrial pressure increased in the advanced stages of RV failure when RV end-diastolic pressure was very high. Left ventricular function may also be adversely influenced by septal bulging during RV overload, but this occurs at RV end-diastolic pressures higher than those encountered in the present study.

Phenylephrine was selected as an agent to increase aortic pressure by increasing peripheral resistance. In addition to its well-recognized α-adrenergic effects on the peripheral circulation, phenylephrine also has a minor positive inotropic effect. The dose-response relationship in the intact heart for this latter effect, however, occurs only at doses 10² to 10³ times those used in the present study, so that probably no significant inotropic effect contributed to the improvement in RV function with phenylephrine infusion.

This study considers the hypothesis that ischemia of the RV free wall is the mechanism by which failure occurs in RV pressure overload. Ischemia was assessed in two ways: indirectly, by measuring myocardial blood flow and by estimating the coronary vascular reserve of right coronary artery flow; and directly, by measuring tissue biochemical indexes associated with ischemia. Reactive hyperemia, as described by Coffman and Gregg, assesses coronary vascular reserve following temporary occlusion and subsequent accumulation of flow debt; vasodilation during reactive hyperemia is a result of the accumulation of metabolic vasodilator substances such as adenosine.

In this study, reactive hyperemia was present during the control and RV hypertension states, indicating the presence of coronary vascular reserve. With RV hypertension, RV myocardial blood flow increased significantly in response to the demand of increased afterload; the transmural distribution of RV myocardial blood flow remained close to its control value of unity. With RV failure, myocardial blood flow did not increase further; in fact, because of decreased RV coronary driving pressure, myocardial blood flow was decreased to a value not significantly different from control. At the onset of failure, there was no reactive hyperemia in every experimental preparation studied, indicating that there was no further vascular reserve, and that the vascular bed in the right coronary artery distribution was maximally vasodilated. When reactive hyperemia was repeatedly examined as pulmonary artery constriction was incrementally tightened to produce RV failure, it was noted that, as the onset of failure was approached, the amount of reactive hyperemia, i.e., the percent payback of flow debt, decreased to zero. The absence of coronary vascular reserve, as indicated by the absence of reactive hyperemia, strongly suggests that the myocardium in the distribution of the right coronary artery was ischemic at the onset of RV failure. The absence of reactive hyperemia, in combination with a significant decrease in the RV endo-epi flow ratio from a control value of nearly unity, further suggests the possibility that the flow deficit was greatest in the subendocardial portion of the RV free wall.

By increasing aortic pressure and hence, RV coronary driving pressure, RV myocardial blood flow increased substantially, and the RV endo-epi flow ratio increased toward unity; reactive hyperemia returned, indicating restoration of coronary vascular reserve.

The presence of reactive hyperemia alone, however,
is not adequate to rule out the possibility of tissue ischemia. Rouleau et al.24 demonstrated in the left ventricle that with decreasing myocardial perfusion pressure, coronary vascular reserve was exhausted first in the subendocardial muscle layer. Thus, under these circumstances, reactive hyperemia of coronary artery flow could still be present due to the remaining vascular reserve of the subepicardial muscle, while the subendocardial muscle was ischemic. Therefore, tissue biochemical indexes were selected as the most reliable and sensitive means of assessing tissue ischemia.

In the present study, ischemia was examined by determining the concentrations of high-energy phosphates (creatine phosphate and ATP) and by determining the ratio of lactate to pyruvate concentrations ([lactate]:[pyruvate]), a reflection of the redox state of nicotinamide-adenine dinucleotide (NAD), and hence a sensitive indicator of the state of cellular oxidation.29,30 In particular, creatine phosphate concentration and [lactate]:[pyruvate] are two variables that have been shown to change early in ischemia.31 In this study, the Allard biopsy apparatus was used to ensure rapid harvesting and freezing of tissue samples; at least four sequential biopsies can be taken from the right and left ventricular free walls without a significant change in ventricular function.14 The assays of all four biochemical constituents could be carried out in triplicate on a single biopsy with the fluorometric techniques used in this study. Furthermore, for lactate and pyruvate, by examining the ratio of two constituents assayed in the same tissue extract, any systematic errors in tissue sampling, weighing, extracting, or diluting will cancel.

During RV hypertension, there was no biochemical evidence that the RV free wall was ischemic. At the onset of RV failure, however, there was a marked decrease in creatine phosphate concentration and a decrease in ATP concentration, suggesting that because of inadequate oxygen supply, creatine phosphate was being converted to ATP to maintain contractile function. The ratio of lactate to pyruvate concentrations increased 223%, indicating a change in the oxidation state of NAD. Thus, the RV free wall was ischemic at the time biopsies were obtained. In contrast, biopsies taken from the left ventricular free wall at the onset of RV failure demonstrate creatine phosphate and ATP concentrations and [lactate]:[pyruvate] not significantly different from control. Hence, the ischemia demonstrated in the right ventricle is specific to the right ventricle and is not a global phenomenon resulting from decreased aortic pressure.

With increased perfusion pressure and myocardial blood flow and consequent functional recovery, the biochemical indexes of ischemia reversed; creatine phosphate concentration and the ratio of lactate to pyruvate concentrations returned toward control values. The ATP concentration in RV biopsies taken during phenylephrine infusion increased toward control values, but the increase was not significant (0.05 < p < 0.10). Failure of the ATP concentration to return to the control level may be a result of decrease of the adenine nucleotide pool during ischemia at the onset of RV failure. Ischemia results in the conversion of adenine nucleotides to their deaminated derivative, inosine, which subsequently may be lost from the RV myocardium.32 Over the time course studied, complete resynthesis of the adenine nucleotide pool may not have occurred, and thus, at the time RV biopsies were taken during phenylephrine infusion, the RV tissue ATP concentration was decreased slightly as compared to control. This observation, which suggests the possibility that the total adenine nucleotide pool was decreased, would further support the fact that the RV free wall was ischemic at the onset of RV failure.

In summary, these results demonstrate that in this experimental model, with increasing RV afterload, RV myocardial blood flow fails to increase in proportion to demand; RV failure consequently occurs as a result of ischemia of the RV free wall and resulting mechanical dysfunction. Without decreasing RV afterload, increasing aortic pressure and hence myocardial perfusion pressure with phenylephrine increases myocardial blood flow, reverses ischemia, and consequently improves RV function. Furthermore, these findings suggest that maintaining systemic pressure may be an important factor in the clinical management of RV pressure overload and failure.

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