Cardiac Function in Experimental Mitral Stenosis


The results of 85 combined right and left heart catheterizations in normal dogs and dogs with experimental mitral stenosis are presented. Animals lived as long as 10 months with elevated pulmonary vein pressures. Pulmonary vein pressures in excess of 15 mm. Hg were associated with mitral orifice areas which were smaller than those found in normal animals. Elevation of pulmonary vein pressure was associated with a decrease in the pulmonary vascular pressure gradient, with no change in cardiac index as measured and with a decrease in calculated pulmonary vascular resistance.

CONDITIONS characterized by the presence of pulmonary vein hypertension have gained added prominence with the advent of cardiac catheterization and cardiac surgery. The impracticality of left heart catheterization in the human has limited our knowledge of pulmonary vascular pressure gradients, pulmonary resistance and pulmonary edema in conditions such as left heart failure and mitral stenosis. Our studies on acute elevation of pressure in the pulmonary vein of the dog have shown that pulmonary edema does not occur unless pulmonary vein pressure rises, and further that the pulmonary vascular pressure gradient decreases as the pressure is elevated in the pulmonary vein. The present communication deals with the measurement of pulmonary vascular pressures and flow in relation to chronic elevation of pulmonary vein pressure. The measurements were made possible through combined right and left heart catheterization in dogs prepared with mitral stenosis by the method of Ferrin, Adams, and Baroноfsky. Their method consists essentially of narrowing the mitral ring with silk sutures tied over buttons.

From the Department of Surgery and Physiology University of Minnesota Medical School, Minneapolis, and Ancker Hospital, St. Paul, Minn.

This work was supported by grants from the National Heart Institute of the National Institutes of Health, Public Health Service, The Louis W. and Maude Hill Family Foundation, and the Minnesota Heart Association.

Dr. Haddy is a Research Fellow of the American Heart Association.

Received for publication Dec. 22, 1952.

Methods

Mongrel dogs were anesthetized with intravenous pentobarbital sodium 33 mg. per kilogram approximately two weeks before and two weeks to 10 months after production of experimental mitral stenosis. With the animal supine, cardiac catheters were introduced into the pulmonary artery and a pulmonary vein. Employing an endotracheal tube, the animal was connected to a closed system spirometer containing 100 per cent oxygen. Pressures in the pulmonary artery, pulmonary vein, intrathoracic and femoral artery were recorded simultaneously with standard resistance wire pressure transducers (Statham strain gages). Zeros were arrived at by visualizing the tips of the catheters fluoroscopically and exposing the strain gages to atmospheric pressure at that level. The catheter in the pulmonary vein was immediately withdrawn into the left ventricle and blood samples were obtained from the two catheters for determination of the cardiac output by the direct Fick method. Into the pulmonary artery, 7.5 mg. of T-1824 dye was injected and blood samples were collected from the catheter in the left ventricle for determination of the cardiac output by the dye method. The catheter in the pulmonary artery was withdrawn into the right atrium and the pressure recorded. The above measurements and collections consumed an eight-minute period during which oxygen consumption was measured.

Integrated mean pulmonary vascular, right atrial, intrathoracic and femoral artery pressures were measured with a compensating polar planimeter, and all intrathoracic vascular pressures were expressed as zero in relation to the general intrathoracic pressure. Oxygen content of the blood samples for estimation of the “cardiac output” by the direct Fick method was determined by the Van Slyke manometric method. “Cardiac output” by the dye injection technic was calculated according to the method of Hamilton and colleagues except that collection of the blood samples from the left
EXPERIMENTAL MITRAL STENOSIS

ventricle obviated the necessity of extrapolating the curves to zero. Using Rubner’s constant in Meeh’s formula, 

\[ 11.2 \sqrt{(Wt. in \text{ Gm.})^2} \]

where \( Wt \) is the weight in grams, to calculate surface area, “cardiac output” was expressed as “cardiac index.” In the dogs that died, the mitral orifice was opened, laid flat and the circumference measured. From the circumference, the area was calculated. The area was then expressed per square meter of body surface area.

RESULTS

Table 1 presents the summarized data from 85 separate catheterizations in 73 dogs before and after the production of experimental mitral stenosis, showing the difference in frequency of distribution of pressures between normal and mitral stenosis animals. The average integrated mean pulmonary vein pressure in 44 normal animals was found to be 8.3 ± 2.6 mm. Hg. The highest normal pulmonary vein pressure was 14.8 mm. Hg. Twenty-nine catheterizations in animals with experimental

### Table 1.—Difference in Frequency of Distribution of Pulmonary Vascular Pressures in Normal Animals and Animals with Mitral Stenosis

<table>
<thead>
<tr>
<th>Integrated Mean Pulmonary Vein Pressure mm. Hg</th>
<th>Number of Catheterizations</th>
<th>Integrated Mean Pulmonary Artery Pressure mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Mitral Stenosis</td>
</tr>
<tr>
<td>0-5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5-10</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>10-15</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>15-20</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>20-25</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>25-30</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>30-35</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>41</td>
</tr>
</tbody>
</table>

Mitral stenosis revealed pulmonary vein pressures in excess of 15 mm. Hg. In 16 of the 29 instances, the pulmonary vein pressure was in excess of 20 mm. Hg. One animal with a large element of mitral regurgitation due to a torn leaflet had a pulmonary vein pressure of 33.5 mm. Hg. The animal expired several days following catheterization with severe pulmonary edema. It is to be noted that a number of animals (not presented) developed pulmonary edema following operation, and death occurred before catheterization was possible.

As would be predicted, an inverse relationship was found between mitral orifice area and pulmonary vein pressure. Figure 1 demonstrates that whenever the pulmonary vein pressure exceeded 15 mm. Hg the mitral orifice area was smaller than that found in normal animals. Animals with mitral orifice areas below 1 sq. cm. per square meter rarely survived for an extended period of time because of the occurrence of pulmonary edema. A less constant but yet significant relationship between pulmonary artery pressure and mitral orifice area was also demonstrated. Thus 13 animals with mitral orifice areas below 3 sq. cm. per square meter had pulmonary artery pressure of 24.5 ± 6.6
mm. Hg, whereas 13 animals with orifice areas above 3 sq. cm. per square meter had pulmonary artery pressure of 18.4 ± 2.8 mm. Hg. That this is a statistically significant difference is demonstrated by the Fisher $t$ test for comparison of means, $t = 3.09$, $P < 0.01$. However, because of the decreased pulmonary artery–pulmonary vein pressure gradient observed in certain animals with small orifice areas and high pulmonary vein pressures, it was hazardous in the individual case to predict either pulmonary vein pressure or mitral orifice area from the observed pulmonary artery pressure.

Upon elevation of the pulmonary vein pressure, the pulmonary vascular pressure gradient, that is, pulmonary arterial pressure minus the pulmonary vein pressure ($\Delta Pp$), decreased (fig. 2). Table 2 shows that this inverse relationship is significant when subjected to Fisher's $t$ test for comparison of means. Thus elevation of pulmonary vein pressure to 20 mm. Hg or above caused approximately a 50 per cent decrease in $\Delta Pp$.

Figure 3 shows the relationship of "cardiac index," as determined by the direct Fick method, to left ventricular filling pressure in normal and mitral stenosis dogs. It will be noted that in the normal group, an increase in left atrial pressure of approximately 2 mm. Hg was associated with an increase in "cardiac output" of about 0.8 liters per square meter per minute. Table 3 shows that the regular relationship between left atrial pressure and cardiac index is statistically reliable.

Since the operated group consisted of animals with varying degrees of stenosis, it would be predicted that this relationship between flow and left atrial pressure would no longer obtain. By segregating the operated animals into two equal groups, a low and a high, according to the left atrial pressure, it was found that the mean "cardiac index" for the low group was 4.4 ± 1.1 liters per square meter per minute, whereas for the high group it was 4.8 ± 1.3 liters per square meter per minute. Calculating the significance of the difference between the two means by application of Fisher's $t$ test, it is found that $t = 0.97$, $p = 0.3-0.4$, indicating that the values are not significantly different.

The mean "cardiac index" by the Fick
method was 4.2 ± 1.5 liters per square meter per minute in the entire group of normal animals and 4.6 ± 1.2 liters per square meter per minute in the animals with mitral stenosis. Applying Fisher's t test, it was found that the means were not significantly different, \( t = 1.19 \) and \( p = 0.3-0.2 \). The "cardiac index"

was measured by the dye injection technic in 26 normal animals and in seven animals with mitral stenosis (pulmonary vein pressure above 15 mm. Hg). The flow values by this method were 4.4 ± 1.5 and 4.3 ± 0.4 liters per square meter per minute respectively. Therefore, though the procedure raised left atrial pressure to very high values, the cardiac output as measured remained essentially unchanged in the period studied. There is evidence, therefore, that the pressure rise compensated for the imposed increase in resistance to flow through the mitral orifice.

Thus it has been shown that \( \Delta Pp \) became progressively smaller whereas "cardiac output" remained essentially unchanged as pulmonary vein pressure was progressively elevated. Calculating pulmonary vascular resistance from the formula 

\[
R_p = \frac{\Delta Pp}{C.I.}
\]

a significant inverse relationship between resistance and pulmonary vein pressure was found as indicated in table 4. Figure 4 presents the relationship of pulmonary vascular resistance to pulmonary vein pressure in six dogs studied both before and after operation in whom pulmonary vein pressure was successfully raised above 20 mm. Hg by mitral obstruction. A postoperative decrease in calculated resistance was found in each case. The pulmonary artery pressure in these six animals averaged 20.2 mm. Hg in the normal state and 29.0 mm. Hg after production of mitral stenosis.

Several of the animals lived as long as 10 months with high pulmonary vein pressures. Microscopic sections of the lungs failed to show significant narrowing of the pulmonary muscular arteries by medial hypertrophy and fibrous intimal proliferation* as observed in humans with long standing mitral stenosis. In keeping with this, subsequent catheterization in these dogs failed to reveal an increasing pulmonary pressure gradient or pulmonary vascular resistance in the period studied.

Though the femoral artery pressure was found to be 146 ± 16 mm. Hg in 31 normal dogs as compared with 137 ± 17 mm. Hg in

* The authors are indebted to Dr. J. E. Edwards for his kindness in examining the microscopic sections of the lung.
16 dogs with mitral stenosis (pulmonary vein pressure above 15 mm. Hg), the difference was found not to be statistically reliable \( t = 1.79,\) \( p = 0.1-0.05.\)

The usual physical signs of right heart failure, such as ascites and peripheral edema, failed to appear in the animals with mitral stenosis during the period studied. It was anticipated therefore that the central venous pressure would not be found to be greatly elevated by the procedure. This was found to be the case. Thus the average integrated mean right atrial pressure was 5.0 ± 1.3 mm. Hg in 43 dogs with pulmonary vein pressure below 15 mm. Hg, as compared to 6.1 ± 2.0 mm. Hg in 13 dogs with pulmonary vein pressure above 15 mm. Hg (\( t = 2.43,\) \( p = 0.01-0.02\)). Neither were there increases in the thickness of the right ventricular wall or total heart weight during the period studied.

The lung/heart weight ratio was used in an attempt to assess pulmonary edema in the animals that died from causes other than pneumonia. The lung/heart ratio was found to be 1.3 ± 0.3 in 13 animals with pulmonary vein pressures below 15 mm. Hg, whereas the value was 2.4 ± 0.9 in 17 animals with pulmonary vein pressures above 15 mm. Hg (\( t = 4.0,\) \( p < 0.01\)). This highly significant difference occurred even though there often was a long period of time between catheterization and death in animals with pulmonary vein pressures below 20 mm. Hg. Only occasionally did an animal with a pulmonary vein pressure above 25 mm. Hg live more than a few days. In reference to these unusual animals, it should be pointed out that the pressures were measured in the Nembutal-anesthetized supine state and may therefore have been lower in the unanesthetized prone state.

**DISCUSSION**

The data presented demonstrate that acute narrowing of the mitral valve to about 1 sq. cm. per square meter was associated with pulmonary vein pressures near the expected colloid osmotic pressure of plasma. Further narrowing resulted in pulmonary edema. This relationship between pulmonary vein pressure and the occurrence of pulmonary edema is in agreement with results reported earlier.\(^1\) Also in agreement with an earlier report\(^1\) is the finding that elevation of pulmonary vein pressure acutely was associated with a decrease in \( \Delta Pp.\) This relationship did not change over the 10-month period studied. Thus in certain instances very narrow mitral valves and very high pulmonary vein pressures were associated with a relatively small rise in pulmonary artery pressure. It was found to be impossible to predict either pulmonary vein pressure or mitral valve area from the pulmonary artery pressure.

Johnson and Visscher\(^10\) have recently pointed out some possible sources of error in measuring flow by the application of the Fick principle. Their calculations indicate that under certain conditions large systematic errors are possible due to the fact that the Fick principle presupposes a constancy of blood flow or A-V difference during the time of sampling, neither of which postulates is strictly valid. They point out that these errors are probably most likely to occur when breathing low oxygen mixtures\(^11\) or in the presence of A-V shunts. It is probable that the measurement of flow by the dye method is subject to similar sources of error. Cognizant of these possible sources of error, blood flow was estimated by the two methods mentioned for lack of a better method in the intact animal. Measurements were made with the animals breathing 100 per cent oxygen in an attempt to keep variations in A-V difference at a minimum during the time of sampling.

It seems proper to conclude from the data reported that in the normal dog the "cardiac output" is positively correlated with left atrial pressure. The low, left atrial pressures associated with the low outputs indicate that an inadequate filling pressure was probably the cause of the low output. As the left ventricular filling pressure was elevated, "cardiac output" increased as would be predicted from Starling's Law of the Heart. Thus a rise in left atrial pressure of 2 mm. Hg was associated with an increase in output of about 0.8 liters per square meter per minute. These findings again emphasize the importance to cardiodynamics of small pressure changes in the lesser circulation. It should be emphasized that the observations
referred to were made while the animals were in good clinical condition and before they had been exposed to any experimental procedures other than those involved in placing catheters and cannulas. The absence of correlation between flow and left atrial pressure in animals with mitral stenosis is probably related to the various degrees of stenosis in this group. The left atrial pressure was, as noted above, inversely correlated with the effective mitral valve aperture. Since “cardiac index” was not altered, one may properly infer that the extra pressure was necessary to fill the ventricle. It seems likely that, were one dealing with intra-individual variations with changes in conditions in the absence of heart failure, a positive correlation between flow and left atrial pressure would be found, but at a higher left atrial pressure level.

The observation that pulmonary resistance is inversely related to the pulmonary vein pressure is in agreement with earlier observations on acute elevation of pulmonary vein pressure. The data reported emphasize the importance of the role of the absolute intraluminal pressure in total resistance in vascular beds. Since blood vessels are distensible elastic structures, the intraluminal pressure must be an important determinant of vessel diameter. Since the volume flow for a given pressure gradient varies with the fourth power of the radius of a tube, it is obvious that this factor can be of great importance. Thus it seems proper to suggest from the data reported that as pulmonary vein pressure is elevated the cross sectional area of the pulmonary vascular bed is probably increased and that, therefore, movement of a given volume of blood is accomplished with a smaller pressure drop.

In mitral stenosis in man one ordinarily finds elevations in pulmonary artery pressure when the disease is advanced and of long duration. Since changes of comparable magnitude were not observed in dogs over the periods of study employed it is suggested that the pulmonary artery pressure rise is not a passive hydrodynamic phenomenon but rather results from slow chronic changes in the blood vessels altering their elastic and/or viscous properties. It is felt that insufficient time has passed for these changes to have taken place in the animals reported. Further, the characteristic terminal right heart failure in mitral stenosis in man and the failure to find it in dogs is possibly related to an increase in right heart work subsequent to elevation of pulmonary artery pressure in man and not in the dogs reported over the period studied.

Conclusions

The results of 85 catheterizations in normal dogs and in dogs with experimental mitral stenosis are presented. Whenever the pulmonary vein pressure exceeded 15 mm. Hg, the mitral orifice area was smaller than that found in normal dogs. A less significant inverse correlation between pulmonary artery pressure and mitral orifice area was demonstrated. Left atrial pressure was positively correlated with cardiac output in normal animals. Elevation of pulmonary vein pressure by mitral stenosis was associated with a decrease in $\Delta Pp$, with no change in cardiac index as measured and with a decrease in calculated pulmonary vascular resistance. Pulmonary edema was positively correlated with pulmonary vein pressure. Morphologic or physiologic evidence of an increasing pulmonary resistance failed to appear in the 10-month period studied. Evidence of right heart failure also failed to appear.

Acknowledgment

The generous aid provided by Dr. M. B. Vischer during the conduct of this study is gratefully acknowledged.

References


Cardiac Function in Experimental Mitral Stenosis


Circ Res. 1953;1:219-225
doi: 10.1161/01.RES.1.3.219

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1953 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/1/3/219

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

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

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