Pulmonary Vascular Resistance after Repair of Atrial Septal Defects in Patients with Pulmonary Hypertension

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The behavior of the pulmonary vascular bed in congenital heart disease is a topic of major current interest. The control of normal pulmonary vessels remains a matter for debate, in part because of difficulty in measurements and in the interpretation of the small differences in pressure across the normal pulmonary vascular bed. In the presence of pulmonary hypertension, however, the responses of the pulmonary vessels may be assessed with greater certainty, since sizable pressure gradients frequently exist.

Although a pulmonary arterial systolic pressure in excess of 30 mm. Hg is outside the normal range in this laboratory, the categorization of all patients with septal defects and pressures above this level as having pulmonary hypertension is of questionable value. Accordingly, we have adopted a pulmonary arterial systolic pressure of 60 mm. Hg as the most suitable compromise above which patients may be said to have significant pulmonary hypertension. Such a division serves to separate most patients with congenital heart disease in whom increased pulmonary arterial pressure contributes significantly to the total problem from those in whom it does not. Classification on the basis of pulmonary vascular resistance remains the most important conceptual differentiation but suffers from the use of values that are indirect and open to far greater error than is the simple measurement of pulmonary arterial pressure.

In atrial septal defects associated with pulmonary hypertension as just defined, the pulmonary vascular resistance usually is increased. That this results in part from vasoconstriction may be concluded from the response to the inhalation of 100 per cent oxygen and the infusion of acetycholine when both pressure and flow are measured. The stimulus for this vasoconstriction is not known, but the level of pressure within the pulmonary artery may be a factor in determining the level of vascular tone, as it is for the systemic circulation.

A group of 11 patients with atrial septal defects and pulmonary arterial systolic pressure in excess of 60 mm. Hg was studied hemodynamically before and after closure of the defects. The data were reviewed with the primary purpose of determining whether the changes in pulmonary arterial pressure could be related to changes in pulmonary vascular resistance.

This study also afforded an appraisal of the physiologic response to surgical closure of intra-atrial defects in patients with complicating pulmonary hypertension. Such patients present a special problem in selection for surgical treatment. The assessment of their operability based on criteria previously described for ventricular septal defect can be difficult at times. In some of these patients, a return to normality after repair of the defect is prevented by the persistence of pulmonary hypertension caused by pulmonary vascular disease. The response of increased pulmonary vascular resistance to repair of the defect then becomes of great practical as well as theoretic importance. Furthermore, the general conclusions drawn from a study of patients following repair of atrial septal defects may possibly be transferred to patients with pulmonary hypertension complicating other defects.

Our studies indicate that pulmonary vascular resistance may be reduced markedly in

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PULMONARY VASCULAR RESISTANCE

some patients with atrial septal defects. We are aware of the difficulties in the interpretation of calculated vascular resistance; nevertheless, the data support the concept that pulmonary arterial pressure may indeed play a part in the regulation of tone in the pulmonary vascular bed in some patients.

Material and Methods

Eleven patients with atrial septal defects, including 3 men and 8 women ranging in age from 25 to 51 years, all of whom had pulmonary arterial systolic pressures in excess of 60 mm. Hg, were studied at intervals of 3 to 34 months after closure of the defects. All defects were repaired by the atrial-well technic of Gross, as modified by Kirklin and associates. All patients were studied preoperatively in this laboratory by the cardiac-angiocardiography technic previously described. At this time, pulmonary and systemic blood flows were determined by the Fick method. Pulmonary pressures were measured and resistances were calculated according to standard formulas. In 9 instances, the observations were repeated while the patients breathed oxygen.

At the postoperative study, all 11 patients were found to have had complete repair of the defect. Pulmonary arterial pressures and pulmonary arterial “wedge” pressures (9 patients) were obtained, and the pulmonary blood flow was measured by the Fick method and in 1 case also by the indicator-dilution technic, with indocyanine green as the indicator. The dilution curves were recorded by means of a cuvette oximeter that was calibrated in terms of response to the concentration of dye after the study. The response to exercise in the supine position with an “exercyce” was determined as previously described. Attempts were made to obtain more than one level of pulmonary arterial pressure in 2 patients by changing the speed at which the exercyce was rotated, thus varying the level of work.

Results

Preoperative Hemodynamic Status

The ratio of pulmonary to systemic blood flow was less than 1.75 in 7 of the 11 patients (table 1). The pulmonary vascular resistance exceeded 600 dynes seconds cm.−5 in 5 patients.

Change in Basic Dynamics after Closure of Defect

Mean systolic and diastolic pulmonary arterial pressure decreased significantly in all instances except in case 2 (table 1). The average mean pulmonary arterial pressure was 49 mm. Hg before closure of the defect and 29 mm. after closure. Likewise, the pulmonary blood flow declined in every instance from an average of 7.9 to 4.9 liters per minute (fig. 1). Direct measurements of left atrial pressure were not obtained uniformly before operation. The relationship of mean pulmonary arterial wedge pressure (postoperative) to mean right atrial pressure (preoperative) suggests an increase in mean left atrial pressure after operation (fig. 2). In 3 patients, wedge pressure was obtained at the preoperative study, and it exceeded the right atrial pressure by 2 to 4 mm. Hg.

Among the patients with increased resistance, excepting case 2, the total pulmonary resistance declined from an average of 620 dynes seconds cm.−5 before repair to 440 dynes seconds cm.−5 after operation, while the pulmonary vascular resistance declined to a greater extent, the average values for the latter being 510 before operation and 230 after repair (fig. 3).

Response to Breathing 100 Per Cent Oxygen

In the preoperative study, the effect of breathing 100 per cent oxygen was determined in 9 of the 11 patients, as already noted. Seven of these 9 patients showed a significant decrease in pulmonary vascular re-
resistance while breathing oxygen; this decrease averaged 40 percent of the control level. One patient showed no change and another exhibited possibly a slight increase in resistance. The relationship of the change in resistance after closure of the defect to the change caused by breathing oxygen is shown in figure 4. With one exception, patients who had the greatest reduction in vascular resistance while breathing oxygen preoperatively tended to have the largest decrease after closure of the defect.

Response to Exercise after Closure of Defects

The changes in mean pulmonary arterial pressure, pulmonary arterial wedge pressure and pulmonary blood flow induced by exercise are shown in table 2. Patients 7 and 8 were studied under 2 and 3 different levels of exercise, respectively. The level of exercise used in every patient caused nearly a 3-fold increase in the consumption of oxygen. During exercise, both pulmonary arterial pressure and pulmonary blood flow increased (fig. 5). That the increase in pressure is much greater than the increase in flow is shown by comparing the change in flow with the change in mean pulmonary arterial pressure and with the difference in pressure between the pulmonary artery and the left atrium (fig. 6). For patients who increase their pulmonary flow by a factor greater than 50 percent, there appears to be a considerable increase in both the mean pulmonary arterial pressure and the difference in pressure between the pulmonary artery and the pulmonary arterial wedge. The values translated into total pul-
PULMONARY VASCULAR RESISTANCE

Figure 2
Change in "left atrial" pressure after closure of atrial septal defects. In all cases, the mean postoperative pulmonary arterial wedge pressure exceeded the preoperative mean right atrial pressure, the average difference being 6 mm. Hg.

Discussion
The patients in this study had atrial septal defects with a significant increase in pulmonary arterial pressure and with pulmonary blood flows that were in excess of systemic blood flows. After accepting the hazard of operation and surviving it, with complete closure of the defects, they returned for re-evaluation by cardiac catheterization not less than 3 months after closure.

As anticipated, the physiologic responses of the pulmonary vasculature differed widely among these patients, since the factors initiating and accelerating pulmonary vascular changes probably are varied. In 1 patient (case 2), a 27-year-old woman who was studied 3 months after operation, the pulmonary arterial pressure remained virtually unchanged. At a similar pressure, a lesser quantity of blood was being driven through the pulmonary vessels. This patient showed perhaps a slight increase in pulmonary vascular resistance. In the remaining patients, however, the decrease in pulmonary blood flow was proportionately less than the decrease in both mean pulmonary arterial pressure and the difference between pulmonary arterial and left atrial pressures.

Conclusions regarding the behavior of the pulmonary vascular bed in these patients depend largely on the interpretation of changes in the so-called pulmonary vascular resistance. Knowledge of calculated vascular resistance is one of the few variables for deciding on the status of the pulmonary vascular bed. For an individual patient, on the assumption that the viscosity of the blood and characteristics of the flow are not significantly different, an increase in pressure required to drive a given quantity of blood through the pulmonary vascular bed suggests that the geometric structure of the bed in some way has been narrowed. If a lesser head of pressure is required to deliver the same quantity of blood through a bed, it appears that the caliber of the bed has widened. The difficulties and dangers of such assumptions have been discussed extensively.15, 16

In 10 of our 11 patients, the mean pulmonary arterial pressure decreased significantly, and this measurement is not subject to any

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have pointed out, the pressure that determines the size of the resistance vessels of a certain distensibility and vasomotor tone is the transmural pressure. In these patients, it can be assumed that the transmural pressure varied directly with the intravascular pressure, since there is no reason to suspect the presence of a significant postoperative change in extravascular pressure.

The intravascular pressure in the resistance vessel is affected by both the perfusion pressure (mean pulmonary arterial pressure) and the outflow pressure (mean left atrial pressure). Our data indicate a considerable decline in the perfusion pressure but possibly an increase in outflow pressure. A definite increase in left atrial pressure was demonstrated clearly in cases 1 and 4. In the remainder, the apparent increase in the postoperative wedge pressure over the preoperative right atrial pressure by an average of 5 mm. Hg might suggest a true increase in pulmonary venous pressure. However, a difference of similar magnitude was noted preoperatively in cases 6, 7, and 10 and in a bigger group of patients in whom large atrial defects were found. 18 A decrease in arterial pressure tends to diminish transmural pressure in the precapillary segment, and an in-

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**Table 2**

*Effect of Exercise on Pulmonary Hemodynamics in Six Patients after Closure of Atrial Septal Defects*

<table>
<thead>
<tr>
<th>Case</th>
<th>Status</th>
<th>O₂ consumption, ml/min./M.²</th>
<th>Pressure, min. Hg</th>
<th>Pulmonary blood flow, L./min.</th>
<th>Resistance, dynes sec. cm⁻²</th>
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<tr>
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<td>20</td>
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<tr>
<td></td>
<td>Rest</td>
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<td>28</td>
<td>28</td>
<td>9.7</td>
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<tr>
<td>4</td>
<td>Rest</td>
<td>134</td>
<td>18</td>
<td>18</td>
<td>7.2*</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>56</td>
<td>22</td>
<td>32</td>
<td>9.6*</td>
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<tr>
<td>5</td>
<td>Rest</td>
<td>118</td>
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<td>52</td>
<td>52</td>
<td>7.1</td>
</tr>
<tr>
<td>7</td>
<td>Rest</td>
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<td>30</td>
<td>9</td>
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<td>39</td>
<td>8</td>
<td>6.9</td>
</tr>
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<td></td>
<td>Rest</td>
<td>—</td>
<td>33</td>
<td>—</td>
<td>—</td>
</tr>
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<td>Rest</td>
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<td>19</td>
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<tr>
<td></td>
<td>Exercise</td>
<td>560</td>
<td>37</td>
<td>17</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Cardiac output determined by indicator-dilution technic.

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**Figure 4**

*Relationship of the percentage change in pulmonary resistance associated with the breathing of oxygen before operation to the change after surgical closure of atrial septal defects in 8 patients. With the exception of case 4, a rough correlation was present between the decrease in resistance while oxygen was breathed preoperatively and the postoperative decrease in resistance.*

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important error. The magnitude of the pulmonary blood flow in all instances also declined. On some occasions, this decrease was equal in magnitude to the change of pressure, but more frequently it was much less than the change in pressure. Therefore, resistance either has not changed or has decreased (fig. 3). It follows that the vessels producing the resistance either have not changed in caliber or have dilated. As Burton and Yamada ᵃ
crease in left atrial pressure would tend to increase it in the postcapillary segment. In the normal pulmonary vascular bed, in which the capillaries, venules and veins may be of an importance that is equal to or greater than that of the arterioles in determining resistance to flow and probably have widely differing distensibilities, one would have difficulty in determining whether a change in resistance could be caused by a change in pulmonary venous transmural pressure.

In these patients, however, as in the great majority of those with congenital heart disease and pulmonary hypertension, much evidence of both hemodynamic and histologic nature indicates that most of the resistance to flow resides in a particular set of vessels, namely the arterioles and small muscular arteries. The average pressure in these vessels will be approximately midway between pulmonary arterial and pulmonary venous pressures, and by far the greater part of the total decrease in pressure to left ventricular diastolic levels takes place across them. From the data, it is seen that the average intravascular pressure at the level of the arterioles decreased in all our cases, and the change in left atrial pressure makes no difference in this conclusion. The values for resistance, however, indicate that the caliber of the vessels is unchanged or perhaps increased. The only explanation that appears possible is that the tone in the walls of the pulmonary vessels declined or that organic changes in these vessels resolved.

Figure 5
Changes in mean pulmonary arterial pressure and blood flow during exercise after closure of atrial septal defects. Note the significant increases in both pressure and flow.

Figure 6
Relationship of the change in pulmonary blood flow to the change in pulmonary pressure during exercise after closure of atrial septal defects. The line of identity for proportionate changes in pressure and flow is indicated. When the ratio of the increase in flow exceeded 1.5, the increase in both the mean pulmonary arterial pressure and the difference in the pulmonary arterial and left atrial pressures was much greater than the increase in flow.

Figure 7
Change in ratio of mean pulmonary arterial pressure to pulmonary blood flow ("resistance") during exercise after closure of atrial septal defects. Note the tendency for resistance to increase or remain unchanged.

That vasomotor tone may play a part in this process can be concluded from the comparison of pulmonary vascular resistance at rest and during exercise in the postoperative studies. Exercise produced a considerable increase in mean pulmonary arterial pressure and a slight to considerable increase in left atrial pressure. Both precapillary and postcapillary transmural pressure increased. It appears that the resistance during exercise either remains unchanged or, more frequently, increases slightly. The vessels, therefore, are not dilating and may even be constricting despite an increased transmural pressure. This could be caused by structural changes in
the vessel walls that prevent their distention or by an increased vasomotor tone that would tend to balance the increased transmural pressure without permitting vascular distention.

The facts that the pulmonary vascular resistance in cases 1 and 4 increased by 130 and 65 per cent, respectively, during exercise and that this increase in resistance in case 1 was reduced by breathing 100 per cent oxygen, which apparently is a dilator of pulmonary vessels (fig. 8), suggest that an increased vascular tone is present during exercise. All these observations are in keeping with the hypothesis that the level of vasomotor tone in patients who have pulmonary hypertension associated with atrial septal defects varies inversely with the intrapulmonary pressure.¹

The problem of the resolution of pulmonary vascular changes is uncertain. Three patients (cases 1, 4, and 5) showed extreme reduction in pulmonary vascular resistance. One of these (case 4) showed no significant reduction in vascular resistance preoperatively when breathing oxygen or when acetylcholine was used as a vasodilator; however, a dramatic decrease in resistance was noted 10 months after operation. This suggests that organic vascular disease may have resolved to some extent at least. In the other cases, the changes could be explained entirely on the basis of a reduction in vasomotor tone.

Summary and Conclusions

Eleven patients with pulmonary arterial systolic pressures in excess of 60 mm. Hg were studied before and 3 to 34 months after closure of atrial septal defects. Significant postoperative reduction in mean pulmonary arterial pressure and pulmonary blood flow occurred, averaging 21 mm. Hg and 3 liters per minute, respectively. In the 9 patients in whom it was measured, the pulmonary arterial wedge pressure exceeded the preoperative right atrial pressure by an average of 6 mm. Hg, with a range of 2 to 12.

The pulmonary vascular resistance increased after operation in 1 patient from 760 to 850 dynes seconds cm.⁻² In the 3 patients who had preoperative pulmonary vascular resistances of more than 600 dynes seconds cm.⁻², together with postoperative studies, it decreased by an average of 72 per cent; in 5 patients, who had preoperative values ranging from 190 to 460 dynes seconds cm.⁻², the average decrease was 26 per cent. Postoperative
measurements of wedge pressure were not obtained in the remaining 2 patients. The reduction in vascular resistance apparently is caused by reduction in vasomotor tone or regression of organic obstructive changes or both.

During moderate exercise, which caused a 3-fold increase in the consumption of oxygen, the average increase in pulmonary blood flow was 54 per cent and that in pressure was 99 per cent.

With the patients at rest, therefore, the hemodynamic findings are often within normal limits, but exercise produces an abnormal increase in pressure, so that the calculated resistance is increased or remains unchanged. This may be the result of increased vasomotor tone.

The findings in this study are consistent with the view that the level of pressure within the pulmonary artery is a factor regulating the degree of vasomotor tone in these abnormal vessels.

**Summario in Interlingua**

Dee-adun patientien con systolici tensiones pulmonaro-arteriali de plus que 60 mm de Hg esseva studiate ante e 3 e 34 menses post le clausio de defectos atrio-septali. Esseva constatale le occurrentia post-operatori de significative reductiones del tension pulmo-arteriali media e del fluxo de sanguine pulmonar media. Le valores medie de iste reductiones esseva 21 mm de Hg e 3 litros per minuta, respectivemente. In le 9 patientes in qui le cuneate pression pulmonaro-arteriali esseva mesurata, illo excedeva le tension dextra-atrial-pre-operatori per un valor medie de 6 mm de Hg, con extremos de 2 e 2.

Le resistencia pulmono-vascular montava in 1 patient ab 760 a 850 dynas-secundas-em.-² In le 3 patientes in qui le resistencia pulmono-vascular pre-operatori esseva plus que 600 dynas-secundas-em.-² e in qui studios post-operatori esseva effectuate, ille resistencia deesceva al media per 72 pro cento. In 5 patientes con valores pre-operatori de inter 190 e 460 dynas-secundas-em.-², le reduction media amontava a 26 pro cento. In le remanente 2 patientes, nulle studios post-operatori esseva effectuate. Le reduction del resistencia vascular es causate apparentemente per le reduction del tono vasomotori o per un regression de organic alterationes obstructive o per ambe iste factores.

In exercitio de grados moderate, causante un triplici augmento in le consumo de oxygeno, le augmento medie del fluxo de sanguine pulmonar esseva 54 pro cento e illo del tension 99 pro cento.

Con le patiente in stato de reposo, per consequente, le constataiones hemodynamie es frequentemente intra le limites del norma; sed exercitio produce alora un augmento anormal del tension, de maniera que le calculate resistencia es augmentate o remane inalterate. Isto es possibilmente le resultato de un augmento del tono vasomotori.

Le constataiones in iste studio se trova in congruenzia con le conception que le nivello de tension intra le arteria pulmonar es un del factores que entra in le regulation del grado de tono vasomotori in iste vasos anormal.

**References**

BECK, SWAN, BURCHELL, KIRKLIN


Faraday testified, 'It is quite comfortable to me to find that experiment need not quail before mathematics, but is quite competent to rival it in discovery.' The biologist should not be looked upon with disdain because his studies are sometimes not quantitative in method. Such intellectual snobishness is not warranted so long as there are highly important fields of investigation to which mathematics, as a mode of expression, is not applicable. It is a satisfaction to know that the eminent physical chemist, G. N. Lewis, has declared, 'I have no patience with attempts to identify science with measurement, which is but one of its tools, or with any definition of the scientist that would exclude a Darwin, a Pasteur, or a Kekule.' To those three may be added Harvey, Virchow, Pavlov, Sherrington and many others.—WALTER B. CANNON, M.D. The Way of an Investigator. New York, W. W. Norton & Co., Inc., 1945, p. 35.
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