The Role of Vessel Tone in Maintaining Pulmonary Vascular Resistance in Patients with Mitral Stenosis

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Changes in pulmonary vascular (arteriolar) resistance were estimated in 58 patients with mitral stenosis following mitral valvotomy and during exercise. Evidence is presented that changes in "resistance" reflect active changes in the caliber of the vessels due to alteration in their smooth muscle tone, valvotomy being followed by a decrease in tone and exercise by an increase.

It is well known that patients with mitral stenosis have medial hypertrophy of the pulmonary arteries, that a muscular media develops in the arterioles, and that these histologic changes often are accompanied by an increased resistance to blood flow through the vessels of the lungs. Many attempts have been made to define the mechanism of this increased resistance with the use of adrenergic and ganglionic blocking agents. The conflicting nature of the conclusions emphasizes the difficulty in interpreting the results. This is mainly due to the fact that the potent action of these drugs on the systemic circulation makes it difficult to decide whether the changes in the pulmonary circulation are actively or passively induced. The recent use of acetylcholine injected into the pulmonary artery in such a concentration that it is inactivated before reaching the left side of the heart has demonstrated that the high pulmonary vascular resistance in mitral stenosis is at least partly functional; that is, tone is present in the smooth muscle of the pulmonary vessels and this contributes to the pulmonary hypertension.

In the present paper, some of the factors are examined that may be concerned in the maintenance of this tone.

Methods

The hemodynamic data on 58 adult patients were analyzed. All patients had mitral stenosis as the predominant valvular lesion, as judged by clinical and laboratory findings, and this was confirmed in the majority of cases at the time of mitral valvotomy. There were 42 women and 16 men, aged 18 to 53 years, with an average age of 34 years for the women and 38 years for the men. Any patient having a systemic blood pressure higher than 140 mm. Hg systolic and 90 mm. diastolic was not included in this report.

Intravascular pressures were recorded by strain-gage manometers, the zero reference point being midchest at the level of the third interspace on the sternum with the patient supine. The cardiac output was determined by the Fick principle. The rate of consumption of oxygen was measured by collecting expired air for 5 minutes and analyzing it immediately by the Haldane method; blood samples from the pulmonary and radial arteries withdrawn midway during the collection of expired air were analyzed for their oxygen content in duplicate by the method of Van Slyke and Neill. The oxygen capacity of hemoglobin was measured by the method of Sendroy, with the modification of Roughton, Darling, and Root. Midway during the collection of the blood samples, a record of pulmonary and radial artery pressures was obtained that was considered to represent the resting state. The catheter tip was then advanced into the "wedge" position of either peripheral lung field and the pressure was measured.

For the exercise studies the catheter tip was left in the pulmonary arterial wedge position. The patient exercised in the supine position on a bicycle ergometer, which was positioned at the end of the fluoroscopy table. The revolutions of the ergometer caused the deflection of a galvanometer needle, which was visible to the patient; the deflection was recorded photographically by means of a second galvanometer. By the patient's maintaining the needle at a predetermined position, a constant speed of rotation of the exercycle was achieved. After an average of 3½ minutes from the start of exercise, a record of pulmonary arterial wedge and radial artery pressures was obtained.
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Fig. 1. Changes in pulmonary vascular resistance in 25 patients with mitral stenosis at 2 to 5 weeks (left) and 8 to 30 months (right) following mitral valvotomy. Each dot represents an individual patient; dots with numbers represent the patients studied on both occasions after operation.

Fig. 2. Relation between change in mean pulmonary artery and change in mean pulmonary arterial wedge pressures 2 to 5 weeks (left) and 8 to 30 months (right) following mitral valvotomy. Dots and accompanying numbers as described for figure 1.
The catheter tip was then withdrawn to the main pulmonary artery; after recording of the pressure, blood samples were taken simultaneously from the pulmonary and radial arteries. During this sampling period expired air was collected; its volume was measured, and the gases were analyzed by the Haldane method.

The following formulas were used in calculations:

\[
\begin{align*}
\text{total pulmonary resistance} &= \frac{P_{\text{PA}} \times 1.332}{Q} \\
\text{pulmonary vascular resistance} &= (P_{\text{PA}} - P_{\text{LA}}) \times \frac{1.332}{Q} \\
\text{total systemic resistance} &= \frac{P_{\text{LA}} \times 1.332}{Q}
\end{align*}
\]

In these formulas:
- \(P\) = mean pressure in mm. Hg
- \(Q\) = the blood flow, i.e., cardiac output in milliliters per second
- \(PA\) = pulmonary artery
- \(LA\) = left atrium
- \(SA\) = systemic artery

Mean pressures were obtained by planimetry. The mean pulmonary arterial wedge pressure was assumed to equal the left atrial pressure.\(^{15-18}\) Data obtained from this laboratory\(^{10}\) on a group of 22 normal persons studied under similar conditions were included for purposes of comparison.

**RESULTS**

**Effect of Mitral Valvotomy on Pulmonary Vascular Resistance.** Figure 1 shows the changes that had taken place in pulmonary vascular resistance 2 to 5 weeks and 8 to 30 months after mitral valvotomy. Those patients with the highest pulmonary vascular resistance before operation had the greatest decrease after operation. This decrease occurred within 2 to 5 weeks and no further important change had taken place many months later.

There can be little doubt that valvotomy resulted in decreased resistance to blood flow across the pulmonary vascular bed consequent to dilatation of pulmonary vessels. First, the pulmonary artery pressure decreased more than the pulmonary arterial wedge pressure; hence the pulmonary blood flow was maintained by a smaller perfusion pressure (fig. 2). Second, if the pulmonary vessels had behaved as a passive system, lowering of the left atrial pressure by valvotomy would tend to increase the pulmonary vascular resistance by reducing the transmural pressure of the pulmonary vessels and hence the distention of the pulmonary vascular bed.\(^{20, 21}\) On the contrary, lowering the left atrial pressure caused a reduction in resistance (fig. 3).

This dilatation of the pulmonary vessels was most likely the result of a decrease in vessel tone and not a passive phenomenon due to a decrease in extravascular compression of pulmonary vessels by edema consequent on the lowering of the capillary pressure by valvotomy. Haddy and Campbell\(^{22}\) have shown in dogs that the calculated pulmonary resistance remains low when pulmonary edema is present, and they suggested that acute
edema of the lungs per se may not be an important factor in determining the caliber of the vessel. Again, if this had been the explanation of the decreased resistance, a more definite relationship might have been expected between the changes in pulmonary vascular resistance and the changes in wedge (left atrial) pressure than that which is apparent in figure 3.

The Effect of Exercise on Pulmonary Vascular Resistance. The pulmonary vascular resistance with the patient at rest and during exercise plotted against the mean pulmonary artery pressure at rest in 34 patients with mitral stenosis is shown in figure 4. Many of the patients, and especially those with a pulmonary artery mean pressure in excess of 30 mm. Hg, showed an increase in resistance during exercise. Similar findings have been reported by Eliasch,23 Tompkins,24 and Holling and Venner.25 In suggesting that the increase in resistance was a consequence of a vasoconstriction, the previous arguments apply. The pulmonary artery pressure increased more than the pulmonary arterial wedge pressure (fig. 5), so that there was an increase in the pressure gradient across the vascular bed of the lung. The increase in pulmonary arterial wedge (left atrial) pressure would tend to distend the vessels with a consequent fall in resistance. In spite of this the pulmonary vascular resistance was increased (fig. 6). If we assume that this increased resistance was unlikely to be due entirely to pulmonary edema, then these results are compatible with the thesis that an active vasoconstriction had occurred.

Discussion

Deduction of changes in vessel caliber from values obtained from vascular resistance equations must be made with caution. The pulmonary vascular bed, subject as it is to pulsatile changes in blood flow,26 alterations in heart rate and stroke volume, is a complex system in which pressure fluctuations occur at variable frequencies and amplitudes. The equation used to determine resistance, however, applies strictly to a system in which there is laminar flow and a steady pressure. Resistance to flow through the pulmonary vascular bed is a function of the ratio of the pressure gradient between the pulmonary artery and the left atrium (perfusion pressure) to the volume of flow through the system. Despite the complexity of this system, under conditions where volume of flow and frequency change little and intrathoracic pressure is unchanged, an increase in perfusion pressure is a good indication that the caliber of the "resistance" vessels has decreased, particularly if pressure in the pulmonary vein remains the same or is increased. Under the opposite conditions it can be assumed that the caliber of the "resistance" vessels has increased, particularly if pressure in the pulmonary vein is the same or is decreased.

Considering first the results of valvotomy in cases in which the described conditions are fulfilled, there can be little doubt that the drop in resistance indicates an increase in vessel caliber, and that this increase in caliber is consequent on lowered pressure somewhere in the pulmonary system, including the left atrium. If the reduction in pulmonary vascular resistance present 2 to 5 weeks after mitral valvotomy occurred tooearly to be
FIG. 5 Left. Change in pulmonary artery and pulmonary arterial wedge pressure during exercise in mitral stenosis.

FIG. 6 Right. Comparison of changes in pulmonary vascular resistance and pulmonary arterial wedge pressure during exercise in patients with mitral stenosis.

explained by the regression of histopathologic changes in the vessel walls, then it was most likely due to vasodilatation of the pulmonary resistance vessels consequent on reduced tone of the smooth muscle. Consistent with this are the results of experiments by Ferguson and Varco,27 who found that such a pathologic regression is a comparatively slow process; unfortunately, however, complete observations of pulmonary artery pressure, left atrial pressure, and flow just before and after mitral valvotomy are not available.

The finding of increased vascular resistance with exercise is harder to evaluate. It is difficult to deduce changes in caliber by means of the simple resistance formula when definite changes occur in frequency and pressure fluctuations in the system coincident with the changes in heart rate and respiration. There is, however, some support to the thesis that the vessel caliber is decreased. The increase in left atrial pressure during exercise would tend to cause a passive increase in vessel caliber. This occurs in dogs when mitral stenosis is created,28 so that the pulmonary vascular pressure gradient decreases as the pressure is elevated in the pulmonary veins. In human beings, the situation is different. The pressure gradient between the pulmonary artery and the left atrium increases with exercise. Thus the resistance changes are contrary to those expected on mechanical grounds, which is a good indication that they are due to alterations in vessel tone opposing the distending force.

Blood vessels are distensible structures and their caliber depends on their pressure-volume characteristics. The effective distending pressure is the transmural pressure, which is the intravascular minus the extravascular pressure. If blood vessels behaved as a viscoelastic system, increases in this pressure would cause an increase in vessel caliber until the limits of elasticity were reached. This would be modified, however, by the degree of tone in the smooth muscle of the vessel wall. The normal pulmonary vessels in the adult dog have sufficient smooth muscle to be capable of strong constriction,29 and Cournand30 and Fritts and his associates31 have shown that tone is present in normal pulmonary vessels. The evidence already presented demonstrates that the increase in pulmonary vascular resistance associated with mitral stenosis can-
not result solely from organic changes in the blood vessels altering their viscoelastic properties, but that it must be due in part to increased tone in the smooth muscle. This emphasizes again Wood's concept of the important role played by vessel tone in mitral stenosis.10

In a consideration of mechanisms that might alter the tone of the pulmonary vessels in mitral stenosis one might first see whether or not the stimulus could originate outside the thorax. For example, a relationship was noted between the systemic resistance and the cardiac index during rest (fig. 7). As the index decreased, the systemic resistance increased. There was also a relation between the systemic resistance and the total pulmonary and pulmonary vascular resistances (fig. 7). It was likely that the increased systemic resistance with decreasing output was brought about through the baroreceptors in the carotid and aortic sinuses so that the systemic blood pressure was maintained. If this were so, reflex effects from the baroreceptors to the pulmonary vessels were also possible. However, Daly and Daly32 in a recent paper suggested that the changes in the pulmonary circulation with baroreceptor activity were most likely passive and not active. Furthermore, Lee and associates33 used the Valsalva maneuver and did not find evidence for reflex pulmonary vasoconstriction.

Changes in pulmonary vessel caliber can result from changes in alveolar oxygen tension.34, 35 When the pulmonary vascular resistance during rest and during exercise was plotted against the oxygen saturation of mixed venous blood, there was a suggestion that the less the oxygen saturation of blood in the pulmonary artery the greater the resistance (fig. 8). A similar correlation has also been shown by Holling and Venner.25 This would be compatible with the evidence that breathing low-oxygen mixtures can cause constriction of pulmonary vessels in mitral stenosis.36 While the relationship between the changes in pulmonary vascular resistance following valvotomy and the changes in oxygen saturation of mixed venous blood was not consistent (fig. 8), the possibility still exists that lowered oxygen saturation of mixed venous blood may be a factor in the increased pulmonary vascular resistance in mitral stenosis.

Recent studies on the human systemic circulation have shown the importance of changes in transmural pressure in modifying vessel tone.37-40 The present observations suggest that changes in pressure somewhere in the pulmonary vascular bed or the left atrium may be a stimulus capable of regulating tone.

**Fig. 7.** Relation of systemic resistance to cardiac index and pulmonary resistance during rest in patients with mitral stenosis and in healthy persons.
in the pulmonary vessels. These alterations in tone could be effected either through a local non-nervous response of the smooth muscle to the changes in pressure such as has been described for the systemic vessels, or to local nervous reflexes from the increase in pulmonary venous or left atrial pressure. Ferencz and Dammann, from their microscopic study of the lungs of patients with congenital heart disease in whom there was an obstruction of pulmonary venous drainage, suggested that the latter may be an important factor in the development of pulmonary arterial narrowing.

**SUMMARY**

The pulmonary vascular (arteriolar) resistance was measured in 58 patients with predominant mitral stenosis during exercise and 2 to 5 weeks and 8 to 30 months after mitral valvotomy.

Mitral valvotomy was followed by a decrease in resistance that was directly proportional to the magnitude of resistance before operation. Many patients showed an increase in resistance during exercise and especially those with a mean pulmonary artery pressure while resting in excess of 30 mm. Hg.

Evidence is presented that these changes in "resistance" represent active changes in the caliber of the pulmonary vessels due to alteration in their smooth muscle tone, with valvotomy causing a decrease in tone and exercise causing an increase in tone.

The thesis is advanced that changes in pressure somewhere in the pulmonary vascular bed, including the left atrium, may be a stimulus capable of regulating tone in the pulmonary vessels of patients with mitral stenosis.

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**SUMMARIO IN INTERLINGUA**

Le resistentia pulmono-vascular (i.e. arteriolar) eseva mesurate in 58 patientes con predominante stenosis mitral, durante exercitio e 2 a 5 septimanas e 8 a 30 menses post valvotomia mitral.

Valvotomia eseva sequite per un reduction de resistentia, directemente proportional al
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magnitude del resistentia ante le operation. Multe patientes manifestava un augmento de resistentia durante exercitio. Isto esseva specialmente ver in le caso del patientes qui havava un pression pulmono-arterial medie in stato de reposo de plus que 30 mm de Hg.

Es presentate datos que indicava que iste alterationes del "resistentia" representa alterationes active in le calibre del vasos pulmonar in consequentiam de un alteration in le tono de lor musculos lisie. In iste situation, valvotomia causa a reduction de tono, e exercitio causa un augmento de tono.

Es formulate le theses que alterationes de pression in le un o le altere loco del vasculatura pulmonar—incluse le atrio sinistre—es un stimulo capace a regular le tono in le vasos pulmonar de patientes con stenosis mitral.

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