THE RELATION OF MEDIAL THICKNESS OF SMALL MUSCULAR PULMONARY ARTERIES TO IMMEDIATE POSTNATAL SURVIVAL IN PATIENTS WITH VENTRICULAR SEPTAL DEFECT OR PATENT DUCTUS ARTERIOSUS

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The observation at necropsy of a patent ductus arteriosus in patients dying in the neonatal period is virtually universal. As a rule this observation is of no practical significance since death is caused by one of a large group of conditions not necessarily related to the cardiovascular system. Occasionally the finding is of importance, as in two male infants, with widely patent ducti, whom we studied recently. Both had died on the second day of life from pulmonary oedema. The onset of oedema in both patients appears to have been related to the state of the muscular pulmonary arteries, which had undergone an unusually rapid transition from the foetal to the adult form so that they appeared much thinner than comparable vessels seen in the normal infant of this age or in one with a defect allowing communication between the systemic and pulmonary circulations. This impression was confirmed by the measurement and comparison of the lumen-to-wall ratios of the small muscular pulmonary arteries in the two infants with patent ductus arteriosus, in 26 controls, and in 22 patients with congenital heart disease who survived the immediate postnatal period. Each of the 22 patients had an aorto-pulmonary or ventricular septal defect of sufficient size to equalize systolic pressures between the pulmonary and systemic circulations. We consider that this histological observation has a physiological basis of clinical importance which determines whether infants with patent ductus arteriosus survive or die in the neonatal period.

METHOD AND MATERIAL

Portions from the upper or lower lobes of the lungs in each case studied were embedded in paraffin. Sections were stained by Verhoeff's method to demonstrate elastic tissue and counterstained with van Gieson's stain to show collagen and muscle. The thickness of the media of small muscular arteries, less than 100 μ in external diameter, was measured after the method of Damman and Ferencz (1956) with the modification that intimal tissue was not included in the measurements of the media. The diameter of the lumen of the vessel was measured and divided by twice the thickness of the media, thus giving an index which expresses a ratio of size of lumen to thickness of wall. These measurements were restricted to arteries of this diameter as the ratio tends to diminish in larger vessels; hence, ratios calculated from arteries of various sizes are not comparable. In each instance 10 to 20 vessels were measured and importance was attached to the necessity of systematic examination of the section. Selective examination and mensuration of arteries leads to an erroneous ratio which usually tends to be too low, as the observer has a natural tendency to select vessels with a thick, well-formed media. With these reservations, the lumen-to-wall ratio was found to be fairly constant for any particular case.

Only early cases of hypertensive pulmonary vascular disease without severe intimal fibrosis were included in the study, for, when occlusive changes of this type develop, the vessels undergo progressive dilatation with progressive thinning of the media. In most of the cases studied there was only an increase in the medial thickness of the muscular pulmonary arteries without intimal fibrosis, and in the few cases in which intimal fibrosis was present it was minimal. In the later fibrotic stage of pulmonary vascular disease there is no fixed relation between the thickness of the media of single vessels and the level of the total pulmonary vascular resistance, since

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LUMEN-TO-WALL RATIOS IN AGE GROUPS

Three groups of patients were studied. The first (Group 1) consisted of 26 controls (Table I) who ranged in age from two newborn premature babies, each of whose foetal age was $\frac{1}{2}$ months, to an infant of 23 months. Cardiac catheterization had not been carried out in any of these, but none had diseases which predispose to pulmonary hypertension.

The second group (Group 2) consisted of 22 patients (Cases 1 to 22 inclusive) who had congenital heart disease characterized by ventricular septal defect without pulmonary stenosis or a large patent ductus arteriosus which allowed the left ventricular systolic pressure to be directly transmitted to the pulmonary circulation from birth (Table II). The age range in this group was 11 days to 13 years. In 13 instances cardiac catheterization had been performed, at which time the pulmonary artery mean blood pressures had been measured, and data had been collected which allowed a calculation of the total pulmonary vascular resistance. With one exception (Case 10) the radial artery mean blood pressure and the systemic vascular resistance had been measured so that the ratio of the total pulmonary resistance to the systemic resistance was also known. In two additional cases only the mean blood pressures in the pulmonary artery and radial artery (Case 19) or in the radial artery alone (Case 22) were known.

The third group (Group 3) consisted of two infants (Cases 23 and 24) each of whom was born with a wide patent ductus arteriosus and died from pulmonary oedema on the second day of life (Table II). In neither infant was the blood pressure in the pulmonary artery measured. A large atrial septal defect was also present in Case 23. These two patients are considered as a separate group because, although the underlying haemodynamic abnormalities in them are similar to those in Group 2, the state of the pulmonary blood vessels was different, as will be seen in the next section.

RESULTS

The lumen-to-wall ratios of the control group are shown in Table I where they are subdivided into five age groups. The ratio was 1.0 : 1 in the premature babies but had risen to a mean value...
the first month of life the ratio was 1.7: 1, indicating abnormally thick medial coats. It remained at this abnormally thick level throughout the first three years of life. The highest ratio recorded in the first year of life was in a patient in whom the ratio was 2.4: 1. Among patients between 1 and 3.5 years of age the highest ratio was 2.8: 1 (Fig. 1b and c).

Four of the seven patients more than 5 years of age had abnormally thick small muscular pulmonary arteries, the lumen-to-wall ratio ranging from 1.2 : 1 (Cases 17 and 18) to 2.3 : 1 (Case 21). However, the remainder in this age group had a ratio which was greater, ranging from 3.8 : 1 in Case 20 to 4.8 : 1 in Case 16 (Fig. 1d), but which still was far below the ratio of 8.4 : 1 noted at the end of the first year of life in the control group.

The lumen-to-wall ratios of the two patients with patent ductus arteriosus who died from pulmonary oedema on the second day of life were higher, at 3.6 : 1 and 4.5 : 1, than one would expect in a child of this age with congenital heart disease and a common ejective force (Fig. 2a, b, c, and d). Moreover these ratios were even higher than one would expect in a normal child in the first month of life.

**Comment**

The thick muscular pulmonary arteries of the normal foetus (Table I and Fig. 1a) are an anatomical expression of the underlying haemodynamic conditions. Since the foetal pulmonary arterial bed is in free communication with the descending aorta through the patent ductus arteriosus, the blood pressure in the pulmonary arteries, the aorta, and the two ventricles is of the same magnitude. In order to allow most of the blood from the right ventricle to be propelled through the ductus and hence on to the aorta and placenta, there must be high resistance to flow in the lungs. This high resistance, which underlies the pulmonary hypertension, is probably mainly a result of constriction of the thick-walled small muscular pulmonary arteries in which the lumen-to-wall ratio has been shown to be as low as 1.0: 1, although the collapsed nature of the lung also may play a part in causing a high resistance to flow (Edwards, 1957). As a
a high resistance to pulmonary flow, which ranges in our series from 510 to 5,100 dynes/second/cm.\(^2\) and is associated with pulmonary hypertension as shown in Table II. According to Barratt-Boyes and Wood (1958) the normal total pulmonary resistance in adults is 90 to 290 dynes/second/cm.\(^2\). The high pulmonary resistance often present in cases with a common ejection force prevents an excessive pulmonary blood flow which would lead to cardiac failure and pulmonary oedema associated with a high pulmonary flow.

When the duration of the pulmonary hypertension is prolonged, the walls of the small pulmonary arteries may become distended by the excessive blood pressure and then the lumen-to-wall ratio increases, as seen in Cases 16, 20, and 22 (Table II and Fig. 1d). Hence, thinning of the media can occur in association either with a diminution or exaggeration of resistance in the pulmonary circulation.

With this background we may now discuss the finding of thin-walled small muscular pulmonary arteries in the two newborn patients with widely patent ductus arteriosus (Fig. 2a, b, c, and d). Even if a communication between the two systems did not exist, this finding would indicate an unduly rapid transition to the thin-walled adult type of pulmonary vessel. However, when this transition occurs in association with a widely patent ductus arteriosus as in the present cases, the haemodynamic situation is apparently incompatible with survival. The thin-walled arteries are unable to maintain a high vascular resistance to the left-to-right shunt and this quickly results in excess pulmonary blood flow leading to cardiac failure and fatal pulmonary oedema. Probably only a small proportion of infants who die in the first few days of life do so as a result of the complications of a patent ductus arteriosus which is common at this age. We consider, however, that this small proportion could be detected by an examination of the small muscular pulmonary arteries to ascertain the thickness of the medial coats.

**Summary and Conclusions**

The lumen-to-wall ratios of muscular pulmonary arteries, less than 100 \(\mu\) in diameter, were measured in 26 infants less than 2 years of age who did not have congenital heart disease, in 22 patients having
congenital ventricular or aorto-pulmonary defects of sufficient size to equalize systolic pressures between the systemic and pulmonary circulations, and in two infants with widely patent ductus arteriosus who died from pulmonary oedema on the second day of life. Data concerning the total pulmonary vascular resistance and mean blood pressure in the pulmonary artery were known in 13 cases. The ratio of the total pulmonary to the systemic resistance was known in 12 of these cases. In two additional cases only the mean blood pressures in the pulmonary artery and radial artery or in the radial artery alone were known.

The results suggest that, in the newborn patient in whom patent ductus arteriosus is the rule, unduly rapid transition from the foetal thick-walled pulmonary artery to the thin-walled adult type of vessel may result in fatal pulmonary oedema as a complication of left ventricular failure resulting from a large left-to-right shunt.

REFERENCES