Perinatal Vascular Changes in Coarctation of the Aorta with Distal Patent Ductus Arteriosus

By Richard L. Naeve, M.D.

PULMONARY vascular changes often help to explain the circulatory abnormalities that develop in certain persons with congenital cardiac anomalies. Although such vascular changes have been described in some persons with coarctation of the aorta and distal patent ductus arteriosus,1-5 the cause of the pulmonary hypertension in other cases has remained obscure.1, 6 None of the reported studies of this type of coarctation has included quantitative comparisons of the two major circulatory beds. Such a study should provide useful information about the genesis of the high pulmonary vascular resistance in these cases.

Circulatory abnormalities in this disorder may alter the development of the vascular beds both before and after birth. Before birth, pressures in both sides of the heart may be elevated, as evidenced by the biventricular cardiac hypertrophy found in newborn infants with these anomalies.1, 7, 8 After birth, since the ductus arteriosus remains patent, the lesser circulation and most of the greater circulation are subjected to a common pressure through a common ejection force.3 Under these circumstances, at least part of the pulmonary vascular resistance and pulmonary arterial muscle mass developed during fetal life may be retained.1, 3, 4 The current report offers information regarding an abnormal development of the pulmonary vascular bed before birth in such cases. In addition, neonatal changes in both the greater and lesser circulatory beds are quantitated.

Subjects and Methods

Eighteen infants were examined who had coarctation of the aorta proximal to a widely patent ductus arteriosus. Two were stillborn, one at 28 weeks of gestation and the other at term. The remainder varied in postnatal age from several hours to 16 weeks. In all cases, the descending aorta was supplied almost entirely with pulmonary arterial blood, the coarctation being severe. In none of the cases were enlarged collateral vessels described that might have bypassed the coarctation.

The heart was enlarged in all instances, usually being two to three times the normal weight. This hypertrophy usually involved the two ventricles about equally. Dilatation was commonly noted in both chambers of the right heart. No cases were included that had anomalies in addition to the coarctation and patent ductus.

Survival was so short in most of the group that clinical observations were scanty. Most were cyanotic at or soon after birth. In some of the infants this was continuous and in others episodic. In all but two of the cases, this cyanosis was thought to be generalized and not confined to the lower portion of the body. Cardiac systolic murmurs were detected in 11 of the infants. Feeding difficulties were common and those who survived for a time usually had a poor gain in weight. Most had evidence of congestive cardiac failure at autopsy with edema of the dependent soft tissues and enlarged, congested livers.

A special study was made of small arteries and arterioles because they presumably make a major contribution to vascular resistance. Previously described methods were used to measure arterial changes in both circulations.9 In each case, multiple blocks of pulmonary tissue, selected at random, were sectioned at 6 μ and stained with Verhoeff's and Van Gieson's stains. Similar sections were prepared from one or more blocks of pancreas in 10 of the cases. With the aid of a camera lucida and a planimeter, the relative cross-sectional areas of lumen, intima, and media of muscular arteries and arterioles were determined. In each vessel, the internal elastic membrane was arbitrarily included as part of the intima. Sections from cases under study and sections from controls were thoroughly mixed and examined in a random manner to avoid bias.

Results

Initially, the mean area of intima combined with internal elastic membrane for small ar-
VASCULAR CHANGES IN COARCTATION OF AORTA

Figure 1

The mean areas of intima combined with internal elastic membrane for small arteries from patients with severe coarctation of the aorta and a distal patent ductus arteriosus. The areas in which normal values are found are lightly shaded.

arteries in each case was charted against stage of development (fig. 1). The values proved to be relatively similar and constant throughout the period of study for the two circulatory beds. Values for patients with coarctation and patent ductus arteriosus were also similar to those for normal controls. Comparable but larger values were recorded for medium-sized arteries. Therefore, the relative area of intima combined with internal elastic membrane was selected as a convenient reference baseline to which the arterial medial mass could be compared. As in the previous study, a numerical expression:

\[
\frac{\text{area arterial or arteriolar media}}{\text{area intima + internal elastic membrane}}
\]

was adopted as a relative measure of arterial muscle mass. In each case, this value was determined for 15 to 30 arterioles and small arteries between 5 and 30 μm luminal diameter in each of the two circulatory beds. Similar determinations were made on arteries with luminal diameters between 30 and 50 μm.

In patients with coarctation of the aorta and distal patent ductus, systemic arteries and arterioles were found to be normal. Examination of the ratio

\[
\frac{\text{area media}}{\text{area intima + internal elastic membrane}}
\]

defined that the medial muscle of these vessels was normal in area (figs. 2 and 3). In contrast, the ratio for pulmonary arteries and arterioles was increased, both before and after birth (figs. 2 and 3). In the two stillborn infants, the relative pulmonary arterial muscle
mass was about 30 per cent greater than that found in control cases. There was greater variation in those who survived birth by less than a week, but the mean increase for all was approximately 25 per cent. In all instances, pulmonary arterial muscle mass was relatively greater than systemic arterial muscle mass during this period. Pulmonary arterial muscle mass remained far above normal levels in those who survived for a longer period (figs. 4 and 5). In at least two cases, however, it was below that found in the systemic arterial bed. In all cases, these changes were found in all of the arteries and arterioles studied, irrespective of size (figs. 2 and 3). Intimal or elastic membrane abnormalities were absent and the pulmonary veins and bronchial vessels were structurally normal.

Discussion

The study suggests that hemodynamic abnormalities exist in the right ventricle and pulmonary circulation during fetal life in infants having severe coarctation of the aorta with distal patent ductus arteriosus. Such infants have an increased pulmonary arterial muscle mass and hypertrophy of the right ventricular wall. These are probably related to right ventricular and pulmonary arterial hypertension. An enlarged right ventricular cavity in many of these infants suggests an increased capacity of that chamber and possibly an increased right ventricular output. It is possible that these changes arise independent of the coarctation but it is more likely that they are related. They are probably the consequence of functional and structural al-

Figure 2

A ratio reflecting arterial muscle for small arteries from patients with coarctation of the aorta and distal patent ductus arteriosus. The areas in which normal values are found are lightly shaded.
terations in the left ventricle. It is also possible that the pulmonary arterial changes influence postnatal survival of these infants.

Left ventricular hypertrophy was noted in our stillborn infants and has been reported by others. The coarctation, developing during fetal life, presumably leads to rises in left ventricular pressure and an abnormal work hypertrophy of this chamber's wall. It is postulated that this hypertrophy reduces the distensibility of the left ventricle, leading to a rise in the diastolic filling pressure of that chamber. A portion of the blood in the common atrial pool that normally passes to the left ventricle during fetal life is presumably diverted to the right ventricle. The consequent increase in right ventricular output might well require an increased capacity and pressure in that chamber. This could lead to the observed changes in the right ventricle and to the increased pulmonary arterial muscle mass. Similar reasoning can be applied to cases in which the fetal output of the right ventricle is increased as a result of premature closure of the foramen ovale. The right ventricle is hypertrophied and dilated in such infants at birth and they have an increase in pulmonary arterial muscle mass.

The validity of this hypothesis depends on a demonstration that the prenatal left ventricular hypertrophy may lead to a reduction in the normally large right-to-left shunt through the foramen ovale. Edwards has illustrated a related mechanism in certain adults with interatrial septal defect. When the right ventricular wall becomes thicker...
than the left in such individuals, diastolic filling pressures on the right presumably exceed those on the left, and a part of the blood in the right atrial portion of the common atrial pool is diverted to the left ventricle. Thus, it is possible that ventricular wall thickness and distensibility are sometimes related. From another viewpoint, the increased ventricular diastolic filling pressures that alter the interatrial shunts may be related to early ventricular failure in both Edwards' cases and our own.

In our infants with coarctation of the aorta proximal to a patent ductus, the prenatal pulmonary vascular changes were continued after birth. Smooth muscle about the pulmonary arterial bed did not rapidly decrease as it does in normal infants. During the early weeks it was maintained at the birth level in some cases and at levels intermediate between the birth and normal levels in other cases. This continued abnormal development can be attributed to at least two factors. First, the pulmonary and lower systemic circulations were subjected to a common systolic pressure through the patent ductus arteriosus. Persistence of the fetal pulmonary arterial muscle mass has been attributed to this common pressure.\textsuperscript{1-5} Secondly, hypoxemia may have played a role. Cyanosis was prominent in most of our cases. Although the full mechanism is unknown, hypoxemia can induce an increase in pulmonary vascular resistance in normal newborn infants\textsuperscript{13} and might also do so in infants with preductal coarctation of the aorta. It is known that hypoxemia can induce directly or indirectly the development of an increased muscle mass about the pulmonary arterial bed.\textsuperscript{12}

What relationship does the hypertrophied pulmonary arterial muscle mass have to pulmonary vascular resistance in these cases? Direct prenatal data are not available but may be at least partially inferred from information available during the early postnatal period. Neonatal cardiac catheterization in several cases has shown a right-to-left shunt across the ductus arteriosus with high pulmonary arterial pressures.\textsuperscript{13, 14} Such findings suggest a greatly elevated pulmonary vascular resistance. Additional evidence for a high pulmonary vascular resistance was the generalized cyanosis noted in most of our cases. Cyanosis in the lower part of the body in such infants is easily explained by the fact that it was directly perfused by unsaturated blood from the right heart. Cyanosis in the upper part of the body, however, was most likely related to a high extraction of oxygen at the tissue level. Such stagnation cyanosis would imply an in-

\begin{figure}[h]
\centering
\includegraphics[width=0.4\textwidth]{figure4.png}
\caption{Pulmonary muscular artery from a 10-week-old infant. The medial muscle mass is conspicuous. The vessel is more contracted than are most pulmonary arteries in infants with preductal coarctation of the aorta. Verhoeff's and Van Gieson's stains.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.4\textwidth]{figure5.png}
\caption{Pancreatic muscular artery from the case shown in figure 4. The arterial muscle mass is somewhat less than that seen in a comparable pulmonary artery (fig. 4). Verhoeff's and Van Gieson's stains.}
\end{figure}
adequate left ventricular output, possibly due to an abnormally elevated pulmonary vascular resistance, which reduced pulmonary venous return. The very maintenance of an appreciable lower systemic flow in such cases is evidence that pulmonary vascular resistance is abnormally high. If the pulmonary resistance were to fall to normal levels, the consequent runoff into the lesser circulation would reduce systemic flow below the coarctation to a point incompatible with life.9

The evidence that the hypertrophied arterial muscle mass is responsible for the elevated pulmonary vascular resistance is indirect. The appearance of the small arteries and arterioles with their thick muscular layers suggests that they are capable of significant degrees of vascular constriction. Most important is the fact that the hypertrophied muscle is the only anatomic change in the lesser circulation that might easily explain the abnormal resistance. No microscopic abnormalities were noted in the pulmonary capillaries and veins of our infants and the submicroscopic structures of the pulmonary capillary bed in such cases is also presumably normal.15

An increased tone in such hypertrophied muscle can be demonstrated by two different methods. The change from breathing air to 99 per cent oxygen in such infants is accompanied by a fall in pulmonary arterial pressures.13 In addition, acetylcholine injected into the pulmonary artery causes a fall in pressure and an increase in pulmonary flow in patients with related anomalies.16 A reduced pulmonary vascular resistance after operative correction of the anomalies17, 18 could again be most easily explained by a decrease in pulmonary arterial tone and muscle mass.

The short postnatal survival of infants with these anomalies requires further comment. About 90 per cent die within a year of birth, most within the first weeks or months.19, 20 In addition to the elevated pulmonary vascular resistance several other factors may contribute to the progressive cardiac failure that commonly develops. With the presumed rise in pulmonary blood flow after birth, the work of the right heart is probably greatly increased in maintaining flow through the lower systemic bed. The poor oxygen supply at the tissue level could be expected to increase the demand for cardiac output with a consequent relative reduction in myocardial reserve. The work of the left heart may well be increased by the increased pulmonary venous return. In addition, left heart reserve is undoubtedly also reduced by continued outflow obstruction at the point of coarctation. The failure after birth to develop collateral vessels that might bypass the coarctation is presumably an important factor in the short survival of these infants.21 Despite these problems, all the hemodynamic abnormalities are apparently reversible following surgical correction.20

Summary

Infants with severe coarctation of the aorta and patent ductus arteriosus develop an increased pulmonary arterial muscle mass and hypertrophy of the right ventricle during fetal life. Much of this arterial muscle mass is retained after birth. The development of the systemic arterial bed is normal during both periods.

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There are, in truth, no specialties in medicine, since to know fully many of the most important diseases a man must be familiar with their manifestations in many organs.—Sir William Osler. Aphorisms From His Bedside Teachings and Writings. Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 54.
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