Prenatal Narrowing or Closure of the Foramen Ovale

By Richard L. Naeye, M.D., and William A. Blanc, M.D.

Prenatal closure or narrowing of the foramen ovale is an uncommon cardiac anomaly usually associated with neonatal death. Such cases afford a unique opportunity to study the effects of reducing a major intracardiac shunt normally present in fetal life. The current study demonstrates new consequences of reducing this shunt.

In late gestation, about one half of the blood reaching the right atrium normally passes to the left atrium through the foramen ovale. When this flow is reduced by premature narrowing of the foramen ovale, the diverted blood presumably passes into the right ventricle, increasing the output of that chamber. From this point, blood must pass through the pulmonary circuit or through the still patent ductus arteriosus. Normally, flow through the ductus is more than twice that through the lesser circulation. Unless fetal narrowing of the foramen ovale greatly increases pulmonary flow, blood flow into the left atrium and ventricle would be expected to be decreased. Most cases of narrowed or closed foramen ovale reported to date have had features suggesting this hemodynamic pattern. All but three of the published cases have had a hypoplastic left atrium and ventricle, the low capacity of these chambers suggesting a reduced volume of prenatal blood flow. Most of the clinical features of these cases have resembled the "hypoplastic left heart syndrome."

The current study suggests that the left heart may not be hypoplastic as often as previously assumed in infants with the anomaly. Twelve cases are presented in which a narrowed or closed foramen ovale was associated with left heart chambers of normal or near-normal size. Abnormalities in the lesser circulation rather than left heart changes help to explain why these infants died in the neonatal period. There is a possibility that appropriate therapy in such cases might lead to prolonged survival.

Clinical Data

Historical data on the 12 cases are detailed in table 1. A similar clinical course was observed in nine of the 10 who were liveborn. Respiratory distress was recorded almost from birth in two cases and within 12 hours of birth in six others. Cyanosis was observed soon after birth in all but cases 4 and 9 in which it was observed at 48 and at 16 hours, respectively. In case 5 it was confined to the lower two thirds of the body. Both stillborn infants were edematous as were four of the liveborn infants. In two of these latter cases, edema was noted at birth. Hepatic enlargement was detected in eight of the cases including one stillborn infant.

Of the five who were premature, four had a birth weight of less than 2,000 Gm. Immaturity probably contributed to their deaths. The only case living longer than 4 days, infant no. 7, died at age 21 days after complications developing from surgery for a tracheo-esophageal fistula. This infant apparently did not have neonatal respiratory distress, cyanosis, or edema.

Methods

To reconstruct the perinatal cardiovascular events, detailed anatomic studies were undertaken in each case on the heart and blood vessels. To permit comparison with established normal values, the methods of Schulz and Giorlando were used to measure thickness of ventricular walls and circumference of cardiac valves. The internal circumferences of the aorta and the pulmonary artery were measured at a point approximately 1 cm. above the aortic and pul-

From the Department of Pathology, The University of Vermont, College of Medicine, Burlington, Vermont, and the Department of Pathology, College of Physicians & Surgeons, Columbia University, New York, New York.

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# Table 1

**Clinical and Necropsy Data in Twelve Cases**

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<th>Case no.</th>
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<th>11†</th>
<th>12†</th>
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<td>48 hr.</td>
<td>30 hr.</td>
<td>4 days</td>
<td>4 hr.</td>
<td>36 hr.</td>
<td>3 wks.</td>
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<td>22(21)</td>
<td>23(22)</td>
<td>20(22)</td>
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<td>Congestion of spleen and liver</td>
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<td>+</td>
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<td>-</td>
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</tbody>
</table>

* Either patency in normal area or fenestration of septum primum.
† Cases 11 and 12 are from Benner's series.4

Plus sign, present; minus sign, unknown; zero, absent. Normal values are in parentheses.
monic valves. The internal circumference of the patent ductus arteriosus was measured at its mid-point and the circumference of the left common carotid or left subclavian artery at a point just distal to its origin from the aorta.

Previously described methods were used to measure arterial changes of both pulmonary and systemic circulations. In each case, multiple blocks of pulmonary tissue, selected at random, were sectioned at 6μ and stained with Verhoeff and Van Gieson stains. Similar sections were prepared from one or more blocks of pancreas for study of the systemic circulation. With the aid of camera lucida and planimeter, the relative cross-sectional areas of lumen, intima, and media of small muscular arteries and arterioles were determined. Sections from cases under study and controls were thoroughly intermixed and examined in a random manner to avoid bias. For vessels of comparable size, intimal areas were almost identical for arteries of both circulations in both study and control cases. Therefore, the area of this structure was used as an internal standard to which the area of medial muscle could be referred. The following ratio was adopted as a measure of the relative area of medial smooth muscle present in individual arteries: area of arterial or arteriolar media/area of intima + internal elastic membrane. In each case all arteries or arterioles encountered in each section that were cut in cross-section and that had a total diameter of less than 30μ were measured. A mean ratio was determined for the pulmonary and systemic circulations in each case. The mean size of renal glomeruli was also determined in eight of the cases by a previously reported method.

**Figure 1**

Drawing of heart of case 12 showing the foramen ovale with overlapping membrane. A, arrow traversing the foramen ovale; B and C, left atrium and left ventricle of normal or near normal capacity; D, hypertrophied and dilated right ventricle. From Benner, 1939; by permission of the Am. Heart J. and the C. V. Mosby Company.

**Figure 2**

Heart of case 8 demonstrates dilated right atrium and ventricle with hypertrophied wall of the right ventricle. An aneurysm of the fossa ovalis bulges into the left atrium.

**Results**

The foramen ovale was completely closed in three of the cases, whereas a tiny aperture was present in the other nine (table 1). In both groups an aneurysm of the fossa ovalis

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was usually present, which bulged into the left atrium. In patient 7, who survived for 3 weeks, it bulged into the right atrium. The three smallest infants had hearts whose weights were below those expected for their body weight. Of the others, four had enlarged and four had normal-sized hearts. No measurement is available in one case. All but the infant who survived for 3 weeks had dilated chambers of the right heart and all but patient 4 had right ventricular hypertrophy (figs. 1 and 2). Table 1 shows that the right ventricle had a thickness greater than or equal to that of the left ventricle in most instances. In normal hearts, the left ventricle is usually 1 to 2 mm. thicker than the right ventricle at birth and during the first few days of life. In most of the study cases the right ventricular hypertrophy was somewhat obscured by dilatation of that chamber (fig. 2). This dilatation had only a minor effect on valvular dimensions. The circumferences of the tricuspid and pulmonic valves were larger than expected by mean values of 5 per cent and 14 per cent, respectively. The one infant with left ventricular hypertrophy (no. 4) had a 3-mm. defect in the membranous portion of the interventricular septum. In all cases, the internal dimensions of the left ventricle were near the values published for normal hearts (figs. 1 and 3). One possible exception is case 10, in which the dimensions of the left ventricle may have been somewhat reduced. The normal or near-normal capacity of the left ventricle in these cases is most clearly evident in valvular dimensions. It was found that the circumference of the mitral valve for our infants was on the average 3 per cent greater than predicted by comparison with values published for normal hearts, whereas the circumference of the aortic valve was 5 per cent less than expected. Considering the difficulties in making precise measurements, these are probably insignificant deviations from normal values.

The dimensions of the great vessels are also of interest. The ductus arteriosus was patent and dilated in all but the infant who lived for 3 weeks. Whereas in the neonatal period the ductus normally has an internal diameter about 1.25 times that of the left common carotid or left subclavian artery, this value was exceeded in at least five of the current cases. The pulmonary artery was also dilated in those cases in which it was measured, its internal diameter being greater than that of the aorta.

Microscopic abnormalities were noted in both major circulatory beds and in spleen, liver, and kidney. In figure 4, the ratio area media/area intima + internal elastic membrane, representing arterial muscle mass for pulmonary arteries, is plotted against age. In all but one of the eight premature or stillborn infants, the pulmonary arterial muscle mass was greater than that found in any of the controls. The same was true for three of the four full-term infants who died in the neonatal period. In contrast, systemic arterial muscle mass was subnormal in six of the 10 infants in whom it was measured (fig. 5). Thrombotic or sclerotic lesions were absent in both circulatory beds. No abnormalities were detected in capillaries or veins. An increased number of erythrocytes was noted in livers and spleens. In four of the cases hemo-

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Figure 3
Heart of case 8 shows left atrium and ventricle of normal capacity. At the tip of the arrow a 3-mm. orifice is seen in the fossa ovale.
siderin deposits in the liver and spleen suggested that the congestion had been of some duration (table 1). Lastly, renal glomeruli were found to be enlarged in four of the eight cases in which measurements were made (table 1).

**Discussion**

The current study presents 11 cases in which a narrowed or closed foramen ovale was associated with left heart chambers of normal or near-normal size. Nine of these cases were collected by a single observer.

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**Figure 4**

A ratio reflecting arterial muscle mass for small pulmonary arteries plotted against age. Muscle mass for cases with narrowed or closed foramen ovales was greater than control values in all but two cases.

**Figure 5**

A ratio reflecting arterial muscle mass for small systemic arteries plotted against age. This muscle mass is subnormal in six of the cases with narrowed or closed foramen ovales.
(Dr. Blanc) through routine inspection of the foramen in a sequence of about 1,500 pediatric autopsies. Left heart chambers of normal size have been noted in only three of the 35 previously described cases.\(^2\) The paucity of reported cases with normal left hearts might be attributed to inadequate examination of the foramen or to the absence of established values for normal dimensions of the foramen. Some of the previous studies probably have required too severe a stenosis for recognition of the anomaly. Six of the current cases, each having characteristic vascular and clinical features of the disorder, had a patency greater than the 2-mm. limit set by Lev for recognition of the anomaly.\(^2\)

The capacity of the left heart in such cases probably relates to the time of closure of the foramen. Normal fetal development of the left heart chambers is presumably dependent upon a normal volume of blood flow, a flow which would be reduced if the normal interatrial shunt were reduced. A late closure of the foramen ovale best explains the normal development of left atrium and ventricle in the current cases. A large fossa ovalis in most of the current cases also suggests late closure of the foramen.

If the chambers of the left heart were normal in the current cases, why did the infants die? Abnormalities in the pulmonary arteries and in chambers of the right heart offer a partial explanation. Right atrial and ventricular enlargement suggests an increased capacity for these chambers before birth. Increased capacity is presumably related to an increased output as blood normally passing through the foramen ovale is diverted into the right ventricle. The observed right ventricular hypertrophy and the increased muscle mass about the pulmonary arteries suggest that the increased output of the right heart was associated with antenatal hypertension in the lesser circulation. These same right heart and pulmonary vascular changes are seen in infants with primary hypoplasia of the left heart in whom right heart output is also presumably increased before birth.\(^11,\)\(^12\) In both groups, it is postulated that the hypertrophied pulmonary arterial muscle is responsible for an increased pulmonary vascular resistance after birth, with consequent low pulmonary blood flow and generalized cyanosis.

The right-sided cardiac failure so evident in these cases after birth may also have existed in late fetal life. Soft tissue edema was noted at birth in several of the cases. Deposits of hemosiderin in spleen and liver of four of the cases are an additional indication that the visceral congestion recorded at necropsy may have developed before birth. Prenatal visceral congestion was also suggested by the renal glomerular enlargement found in four of the infants.\(^8\)

The clinical course of case 7 poses questions about the natural history of the anomaly. The infant lived for 3 weeks and might well have survived indefinitely if complications of a tracheo-esophageal fistula had not supervened. It is unclear how many such asymptomatic cases escape clinical attention or how such cases differ from those dying in the neonatal period. In the symptomatic group, therapy logically might be directed toward a reduction of pulmonary vascular resistance. Since the means for reducing this resistance are currently not available, an attempt might be made to reduce pressures in the right heart chambers during the critical period of neonatal right ventricular failure. A procedure such as that devised by Blalock and Hanlon to create a sizable interatrial shunt might permit survival through the period when pulmonary vascular resistance should be decreasing.\(^13\)

**Summary**

In the current study cases are presented in which a prenatally narrowed or closed foramen ovale was associated with left heart chambers of normal or near-normal size. Such infants develop an increased pulmonary arterial muscle mass with hypertrophy and dilatation of the right cardiac chambers during fetal life. Much of the arterial muscle mass persists after birth and may well be responsi-
possible for the early neonatal death of the infants. The longer asymptomatic survival of one infant suggests that therapy may be possible.

Acknowledgment

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References


Principles of Medical Sciences and Clinical Observation

Clinical observation has given to medicine very long and very honourable service. There is a certain melancholy in recognizing, as we must, that it has never been, except in the hands of an occasional genius, a very effective instrument for penetrating the fundamental secrets of health and disease, and in recognizing that we now possess far more effective instruments for this purpose. To recognize these facts is, however, by no means to acquiesce in the view that clinical observation has no longer important functions to fulfill in progressive medicine. In the first place it is still a valuable method of scientific research. At the same time it must be admitted that the method is, in some respects, far less general and far less simple than that of experiment; that it lends itself to the solution of only a limited class of problems, and that it demands, at any rate for its great strokes, a somewhat special aptitude of mind. Moreover, if it is to make itself less dependent on special aptitude, a wider interest in the need for and the means of proving its propositions will be necessary. It is possible that the increasing knowledge of experimental methods may bring this about and stimulate a renewed vigour in purely clinical work. In the second place, as successful clinical observation demands a certain special aptitude, and the unresting contemplation of a very large and rich material such as we find at its highest in, for example, a Hughlings Jackson, it should be the source and reservoir of that flow of ideas which alone can maintain the fertility of the whole field of medical science.—The Collected Papers of Wilfred Trotter, F.R.S. London, Oxford University Press, 1946, p. 126.
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