CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus
II. Coronary Embolism in the Fetus

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SUMMARY
The unexpected finding of a right coronary artery embolism in a human fetus of five months gestational age led to an examination of the hearts of 15 other fetuses lost at approximately the same period of pregnancy. No other examples of coronary embolism were found, indicating that this is not a frequent cause of fetal death. Possible mechanisms of death in the index case are discussed on the basis of the anatomic distribution of the coronary arteries, the blood supply to the sinus node and atrioventricular junction, and the configuration of the interatrial septum.

Additional Indexing Words:
Spontaneous abortion Sudden death Human fetal heart

In one of his last papers Robert P. Grant suggested that an undetermined but possibly large number of spontaneous abortions might be unrecognized fetal cardiac deaths.1 There is published evidence that coronary embolism is more frequent in infancy and childhood than is generally thought.2 This report will deal with the question of coronary embolism as a possible cause of sudden fetal death and "spontaneous" abortion.

Materials and Methods
As part of a continuing study of sudden death in babies ("crib death"), it was necessary to make comparative observations on the hearts of human fetuses to assess the normal ontogenetic development of the conduction system.3,4 In the heart of one fetus (spontaneous abortion at about 20 weeks gestational age) there was an unexpected finding of an embolus occluding the main right coronary artery. The present investigation was then undertaken to determine whether such an event was frequent or rare, as a possible cause of otherwise unexplained fetal death and abortion.

Since the index case was from the second trimester of pregnancy, it was arbitrarily elected to study 15 hearts from that period of fetal development. Gestational age of these fetuses was 12 to 25 weeks, based on crown-heel measurement and maternal history. After careful routine necropsy, all had been classified as unexpected and unexplained fetal death.

Because these hearts are so small that separate dissection is exceptionally difficult, which in any event may have served to dislodge emboli if present, each heart was kept intact and fixed in 10% neutral formalin. After embedding in paraffin, the entire heart was cut with serial sections 7 μ thick. Every tenth section was mounted and saved, and every third of these (i.e., every thirtieth section cut) was stained and examined. All were prepared with the Goldner trichrome stain. For each heart about 70 slides were studied.

Findings
The index case proved to be the only example of coronary embolism in this group, the coronary arteries of the other fifteen hearts being entirely free of lesions. This suggests that coronary embolism is infrequent in the human fetus and unlikely to be a cause of many spontaneous abortions. However, this example has a number of instructive features worth description.

The main right coronary artery was occluded by an embolus which extended from a point 1.7 mm beyond the origin from the aorta to the acute margin of the heart (figs. 1 and 2). Histologic

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This work was supported in part by the National Heart and Lung Institute (Program Project Grant HL 11,310 and MIRU Contract 4367-1441) and by the Buchholz Arrhythmia Fund.

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These three low power photomicrographs show the obstructed right coronary artery (black arrows) in three different sections, the most anterior of which is A. B is 840 microns distal to A, and C is 630 microns beyond B. The section in C is near the distal tip of the embolus. Cavities of the right atrium (RA), right ventricle (RV), left atrium (LA) and aorta (Ao) are labeled. The open arrow in A points to the left bundle branch, in B to His bundle, and in C to the A-V node. Magnification for all three pictures is indicated in A.
Figure 3

Two sections of sinus node (outlined by black arrows) are shown at the same magnification. In each the epicardium is above, the superior vena cava to the left and right atrium (RA) to the right. A is cut 840 microns from B. There is congestion with a few extravasated erythrocytes at the atrionodal junction in B.

Figure 2 (opposite)

Three sections of the main right coronary artery are shown here in more detail (all the same magnification). A and B correspond to the same sections in figure 1, while C is 430 microns distal to the section in C of figure 1. C here is just beyond the embolus. There is a crease or fold in the embolic material.
composition of the embolus, which appeared to be folded, was rather nondescript. It contained many vacuolated cells as well as an amorphous granular debris. The lumen of the main right coronary artery was distended by the embolus, which measured about 2 mm in length. There was no adherence between the embolus and the arterial wall. The internal elastic lamina was flattened in the distended portion of the artery (figs. 1, 2A, and 2B) but had the normal post mortem wrinkling in the undistended distal portion of the right coronary artery beyond the embolus (fig. 2C).

The sinus node artery originated directly at the proximal margin of the embolus and its ostium was partially obstructed. The right coronary terminated just beyond the acute margin of the right ventricle. The main left coronary artery and its two major branches were normal, with the left circumflex crossing the crux of the heart to supply the A-V (atrioventricular) node. With this pattern of distribution, most of the blood supply to the left ventricle was provided by branches of the unoccluded left coronary artery. All of the ventricular myocardium, the A-V node, and His bundle were histologically normal for this age. The sinus node exhibited congestion and a small amount of hemorrhage, particularly at some points of the atrioventricular margin (fig. 3), a histopathological feature characteristic of acute coronary occlusions which occur proximal to the origin of the sinus node artery.\(^5\)

The interventricular foramen was closed and the interventricular septum normally developed, as were all four cardiac valves. The foramen ovale in the fixed state was closed by a portion of the developing interatrial septum (fig. 4). While the right atrial and ventricular chambers were empty, those on the left side were filled with material similar to that in the right coronary artery. No other apparent source of the embolus was found, but extracardiac sources were not especially examined for that purpose.

**Discussion**

Coronary embolism is not an easy diagnosis either clinically or from necropsy. In the adult it is usually suspected with the abrupt unexpected onset of symptoms and findings of acute coronary occlusion, particularly when some source of possible embolism is known (e.g., a left atrial thrombus or myxoma). At necropsy an important difficulty is the differentiation of embolism from either ante mortem or post mortem thrombosis. Such differentiation can be made with confidence in typical cases, but there are many examples with atypical features. If the lesion includes obviously foreign fragments (tumor particles, pieces of surgical fabric, calcific, or atheromatous debris), if the arterial lumen is distended and the subjacent arterial wall is essentially normal, and if there is no adherence of the intraluminal material to the wall, the usual criteria are fulfilled. With all these caveats, we believe that the present example does represent a coronary embolism.

If the left heart chambers were the source of the embolus, then it is unclear why both coronary arteries were not occluded. Although gravity may have played a role in the unilateral location in the right coronary artery, meaningful speculation about this is limited by the impossibility of knowing the body position of the fetus when the event occurred. Likewise, the unexpected obstruction of the foramen ovale may either have preceded the coronary embolism or it may have been the consequence of abnormal hemodynamic events within the heart after the embolism. To attempt to relate the location of the coronary embolism and acute failure of the right ventricle to closure of the foramen ovale would require careful simultaneous consideration of reflex events, flow through the ductus arteriosus, competence of the A-V valves, and other factors concerning which no information is available.

One may then consider what the actual functional significance of the coronary embolism was, and this too can only be speculated upon. Even though the A-V node and His bundle were not supplied by the occluded artery, and most of the left ventricle had its coronary supply intact, it should be kept in mind that the right ventricle of the fetus has a more important hemodynamic burden than the right ventricle of the adult. Both the right and left ventricles of the fetal heart fill at approximately equal pressure and eject against approximately equal levels of resistance pressure (because of the normally large shunt flows through the foramen ovale and ductus arteriosus) and the outputs of the two sides of the heart are of similar volume.\(^6\) But the important point relative to the case being discussed is that the myocardial mass of the right ventricle is nearly the same as that of the left ventricle. Therefore, an acute right coronary occlusion in this fetal heart would cause a relatively greater volume of myocardium to become ischemic than would a similar occlusion in an adult heart with the same coronary distribution pattern, unless the adult heart had right ventricular hypertrophy.
These two sections illustrate the form of the interatrial septum, with A being 180 microns anterior to B, both photographed at the same magnification. Beginning fusion of the upper and lower portions of the septum secundum is seen in A, while the septum primum in B appears to occlude the foramen ovale, which would be an abnormal development in the second trimester of gestation. The left atrium is filled with amorphous material generally similar to that in the coronary embolus, while the right atrium appears virtually empty. SNA identifies the sinus node artery, seen in cross-section within the crista terminalis of the right atrium.

Since there was no histological evidence of myocardial infarction, any functional significance of the coronary embolism would need to be interpreted as having rapidly caused death. Electrical instability of the heart can be responsible for such deaths. Since the A-V node and His bundle were supplied by the left coronary artery, the only portion of the conduction system which could be directly affected by the embolism was the sinus node, and there was suggestive evidence that this was the case (fig. 3). Why ischemia of the sinus node may have been lethal is uncertain, although there have been other examples of sudden death in which the major histopathology of the conduction system was in the sinus node.\textsuperscript{7-10} The fact that the subsidiary sites of automaticity in the heart are strongly dependent on normal adrenergic neural input,\textsuperscript{11, 12} and the fetus has a conspicuously meager adrenergic innervation of the heart,\textsuperscript{13} would suggest that loss of the normal pacemaker function in the fetal heart may be of more grave consequence than in the adult.

Another chain of events in which impaired function of the fetal sinus node may have dangerous consequences concerns factors regulating blood flow through the fetal heart. There is an
intricate interplay of physiological forces responsible for this regulation but one of these is the maintenance of a normally rapid fetal heart rate.14 Bradycardia during hypoxic fetal distress is well known, and marked slowing of the fetal heart quickly leads to abnormal redistribution of blood flow. However, acute ischemic injury to the normal pacemaker of the heart and either total failure or very slow emergence of a subsidiary pacemaker may cause the same level of bradycardia even without generalized hypoxia. This could have been the circumstance in the present case.

Other fetal organs can also be the site of significant lesions occluding major nutrient arteries. Although there are several hypotheses as to the etiology of congenital intestinal atresia, there is experimental evidence suggesting that mesenteric arterial occlusion during fetal development may be one responsible factor.15, 16 One may equally logically suspect such lesions as possible causes of any atresia or failure to develop within almost any organ system. Even within the heart certain unexplained deformities such as Uhl’s anomaly (virtual absence of the right ventricular myocardium)17 could have been the long-term consequence of an earlier coronary occlusion, especially of the type found in the present case. Congenital heart block, subendocardial fibroelastosis and absence or anomalous distribution of the coronary arteries are additional possible examples of long-term consequences of fetal coronary embolism.

From the relatively small number of hearts which we examined one must conclude that coronary embolism is an infrequent cause of fetal death. However, many of the most important developmental anomalies found at birth are also statistically infrequent, and in them an arterial embolus or other occlusion during fetal development may be etiologically important and deserves further investigation.

References

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Circulation. 1973;48:890-896
doi: 10.1161/01.CIR.48.4.890
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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