EDITORIAL COMMENT

Congenital Ductus Arteriosus Aneurysm*

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Congenital ductus arteriosus aneurysm (DAA) is a saccular or fusiform dilation and elongation of the ductus arteriosus. By chest X-ray, it is recognized as a ductal bump (1). More recently, echocardiography has been the primary modality used to demonstrate the pathology (2,3). Although most commonly diagnosed within the first two months after birth (2), the pathology may also be diagnosed prenatally (2–5). Previously, DAA was considered a rare cardiovascular lesion, described predominantly in isolated case reports, and typically detected in association with significant complications, including thromboembolism, compression of surrounding thoracic structures and spontaneous rupture (3,6–10). It has also been observed in patients with connective tissue disorders (3,6,11–13).

Incidence of congenital DAA. Recent reports, including the current study by Jan et al. (14) in this issue of the Journal, suggest DAA may be much more common among fetuses and neonates than previously suspected. An early study of neonatal autopsies revealed a 0.8% incidence of DAA (15). In a retrospective review of neonatal X-rays, Heikkinen et al. (16) determined the incidence of a ductal bump to be 1%. We found that among 200 consecutively assessed third-trimester fetuses, 1.5% had DAA, but used a ductus arteriosus diameter of >2 SD above the mean for gestational age as an arbitrary cutoff (3). In their current, prospective, echocardiographic investigation of 548 full-term neonates, Jan et al. (14) have demonstrated an even higher incidence of congenital DAA, providing evidence that this may, in fact, represent a variant of normal anatomy. As observed most frequently among our prenatally diagnosed cases (3), the majority of affected neonates in their study were clinically asymptomatic. As such, without echocardiographic assessment, the DAA would have gone undetected.

It is of note that in the current study the measured DAs were smaller than many described in our study (3) and in some of the previously published case reports. The mean DAA diameter measured in our cohort of patients was 12.6 ± 4.1 mm, with a range of 8 to 24 mm. In fact, nearly half of the cases from our previous report had DAA diameter measurements that were >11.2 mm. Given the unbiased prospective investigation of Jan et al. (14), most affected neonates may have smaller DAA with the more symptomatic patient having the larger DAA diameter. From the data presented, the true incidence of larger DAs among newborns remains unclear.

As observed in our retrospective study (3) and in other isolated case reports (2,5), Jan et al. (14) further demonstrate the natural history of the smaller DAA to be benign in the majority of affected neonates, with 70% demonstrating progressive diminution in size of the DAA following spontaneous closure. Even in subjects with evidence of thrombus formation (30%), they found both the DAA and thrombus to have “resolved” by one month.

Management of the patient with congenital DAA. Although congenital DAA may be a variant of normal anatomy given its frequent occurrence, the potential complications of DAA cannot be completely ignored. Several reports have documented spontaneous rupture of DAA, often with dismal outcome (3,7,16–18). Patients with connective tissue disease may be at highest risk of spontaneous rupture. Extension of the DAA thrombus into the pulmonary arteries or aorta and thromboembolic events have been described in DAA (3,8,9). Also, DAA has been associated with infection (9). Finally, a larger DAA may compress surrounding vascular and nonvascular structures, including airways and the recurrent laryngeal nerve (3,7,16,17,19). The true incidence of these complications is not clear. In our retrospective review, we found 3 of 24 patients to have complications related to the DAA. However, in six patients early surgical resection was performed for larger DAA to thwart such complications (3). In contrast, Jan et al. (14) found no complications among 48 neonates with smaller DAA. It is likely that, if the incidence of DAA is as much as 8% to 9%, then the incidence of complications associated with DAA may be much less than we had observed.

When caring for an infant with DAA, the presence or potential risk of complications must guide one’s decision regarding need for surgical intervention. Larger DAA may be more commonly associated with complications. However, even smaller DAA might be associated with spontaneous rupture in the patient with connective tissue disease (3). Having reviewed the literature and our own experience (as referenced in the study by Jan et al. (14)), we had proposed that surgical resection of DAA be considered if: 1) the ductus arteriosus with DAA remains patent beyond the neonatal period; 2) the DAA is associated with connective tissue disease; 3) there is evidence of thrombus extension into other vessels or thromboembolism; or 4) there is significant compression of adjacent structures. Given the observations of Jan et al. (14) these recommendations might be modified at least for the otherwise healthy, asymptomatic

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neonate in whom it may be prudent to wait at least four to six weeks before considering surgical resection. When there are symptoms of compression that are only mild, it may also be reasonable to wait for such a period of time to see whether the DAA will spontaneously close, resulting in less severe compression. It is unclear whether the larger DAA, however, would undergo spontaneous closure. Furthermore, waiting in this situation may risk thrombus extension into the pulmonary artery or aorta, thromboembolic events and even rupture.

In addition to surgical considerations, close follow-up of the symptomatic infant or infant with the larger DAA is important; however, the necessity of follow-up of the asymptomatic neonate with the smaller DAA and spontaneous ductus arteriosus closure requires reconsideration. Because we had observed late development of cardiac manifestations of connective tissue disease in two cases of our series, we had suggested that serial assessment of all affected patients should be considered (3). Given the high incidence of DAA in neonates documented by Jan et al. (14), however, this may not be feasible or practical. In the infants with smaller DAA and spontaneous ductus arteriosus closure, assuming there is no family history or clinical evidence of connective tissue disease, it may be more appropriate to mention the possible association with the primary health care provider. Referral to a cardiologist, however, should be encouraged should the child develop other manifestations of connective tissue disease.

Pathogenesis of congenital DAA. Despite the numerous reports documenting the diagnosis of DAA, the pathogenesis of DAA remains unclear; DAA has been uniformly identified in utero in the third trimester and has not been observed earlier in gestation, despite widespread use of obstetrical ultrasound screening in midtrimester pregnancies. This suggests a late onset of prenatal development, perhaps due to an altered circulation, weakening of the wall of the ductus arteriosus or a combination of both. It is during the third trimester that the arterial blood pressure and cardiac output are greatest (19). It is also in this period that intimal cushions begin to form within the ductus arteriosus in preparation for postnatal closure (20,21).

Based on histological assessment of cases in our series, we suggested that, at least in some cases, DAA may result from lack of normal intimal cushion formation (3). We hypothesized that an inadequate amount of fibronectin, which is produced by the vascular smooth muscle cells and is required for their proliferation (22,23), may inhibit formation of the cushions. Although intimal cushions may not be present in DAA, constriction of the ductus arteriosus and even DAA might still take place after birth, providing an explanation for observations related to closure of DAA in the absence of thrombosis. Abnormal elastin deposition has also been observed in some cases of DAA, which may result in weakening of the wall of the ductus arteriosus (3). Finally, abnormal extracellular matrix deposition within the wall of the ductus arteriosus may occur in the setting of connective tissue disorders.

Jan et al. (14) had found an increased incidence of neonatal DAA in infants of diabetic mothers and in large for their gestational age infants. This could perhaps be due to the presence of circulating factors that alter the fetal or placental circulation. Fetal echocardiography studies in pregnancies complicated by diabetes have shown hyperdynamic right ventricular systolic function in the fetus (24) and altered umbilical arterial flow patterns, suggesting increased placental vascular resistance in some affected pregnancies (25,26). Circulating factors may also have a more direct influence on development of intimal cushions or extracellular matrix deposition in the ductus arteriosus. For instance, it has been shown that hyperglycemia in diabetes enhances vascular endothelial cell production of matrix metalloproteinases, enzymes responsible for the breakdown of extracellular matrix components (27,28).

The mechanism by which maternal blood group A, as shown by Jan et al. (14) to be a more common finding among neonates with DAA, could influence development of DAA is less clear. It is not likely a simple process related to B antibodies, given that infants of mothers with blood group O are not similarly affected. The link between maternal blood group and DAA development in the fetus is likely much more complicated. Differences in blood group antigen secretion have been shown to drastically alter carbohydrates present in body fluids, including serum (29), which could suggest the potential for circulating maternal factors that might induce fetal DAA development. The diverse biologic role of blood group antigens (e.g., transporters and channels, receptors, adhesion molecules, enzymes and structural proteins) and their potential genetic links to disease states are only beginning to be recognized (29,30). At this stage, animal models of abnormal intimal cushion formation or extracellular matrix formation and deposition may provide further insight into the factors that influence DAA development.

Conclusions. In summary, congenital DAA is more common than previously suspected, as demonstrated by the work of Jan et al. (14). The incidence of larger DAA, which may be more frequently associated with complications, however, remains uncertain. Given the benign course of small DAA, surgical intervention for DAA should be reserved when there is patency of the ductus arteriosus beyond four to six weeks. It may still be appropriate to consider early intervention for the larger DAA, DAA in patients with connective tissue disease and in the setting of significant symptoms or complications associated with the DAA. Further prospective population-based and multicenter studies could result in a better sense of the true incidence of complications associated with this pathology, particularly with larger DAAs, and may lead to the development of more appropriate, evidence-based guidelines in the management of affected patients.
REFERENCES


