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Fetal hemodymanic effects on ductus arteriosus development and influences on postnatal management in infants with ductal-dependent pulmonary blood flow

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Abstract

The ductus arteriosus (DA) has been studied since Galen. Initially after birth in neonates with obstruction to pulmonary blood flow, DA patency is integral to ensure output and oxygenation. While DA stenting dates back 25 years, there is emerging interest in better understanding how and when to utilize this strategy as an alternative to surgical shunt placement or ongoing prostaglandin administration. Understanding the normal fetal circulation and the perturbations that affect flow and oxygenation is integral to comprehending how normal DA anatomy and morphology may change and how this may influence technical and clinical considerations. In the normal human fetus the great majority of descending aorta circulation comes from the DA, whereas this is a small minority in pulmonary outflow lesions, resulting in size and angle abnormalities. Study of the DA morphology has previously sought to identify patients requiring early intervention and more novel classifications are contributing to knowledge of complications and increasing the likelihood of success. As well, optimal patient selection for aorto-pulmonary shunt vs DA stent remains unclear. This review seeks to convey how fetal circulation can affect the DA, how other clinical considerations such as neurocognitive development support these finding and influence management, and emphasize that the variability in the DA will affect suitability for stenting, which requires further study as guidelines and standards are developed.

KEYWORDS

Blalock-Taussig shunt, ductal stenting, ductus arteriosus, fetal circulation, ductal-dependent pulmonary blood flow

1 | INTRODUCTION

> "The physician is Nature's assistant"—Galen, A.D. 129-200

The importance of the ductus arteriosus (DA) has been known for millennia. Galen described both the foramen ovale and the DA, being the first not only to identify them but as well to describe their closure after birth, noting "And nature's destruction of fetal structures that are superfluous in the adult seems to me something much greater even than her original creation of those structures."[1,2] In normal anatomy and physiology, nature's regulation of DA closure, begins in the hours after birth with postnatal changes in oxygen tension, prostaglandin exposure, and pulmonary vascular resistance. In neonates with congenital heart disease with obstruction to pulmonary blood flow, however, nature delays DA closure. It is thought that due to limitation of the increase in arterial PO_2, the stimulus for the DA to constrict is greatly diminished, decreasing, but not eliminating, the restriction to pulmonary blood flow related to ductal constriction.[3]

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Ensuring adequate pulmonary blood flow is fundamental to postnatal care and while surgical aorto-pulmonary anastomosis has remained a mainstay for many years, DA stenting is emerging as a viable alternative. Fetal circulation and variable physiology affects the DA size, morphology, and orientation, however, which may influence which patients are suitable for this intervention. This review will discuss these influences and what factors may affect the guidelines and standards that are developed.

2 | THE NORMAL FETAL CIRCULATION AND FETAL DUCTUS ARTERIOSUS

Circulation in the fetus commences in the fourth week of gestation. From day 22 to day 28 the cardiovascular septation occurs and looping of the ventricles completes. The aortic arches then begin to evolve and at this stage bilateral DA and bilateral dorsal aorta are present. In the normal fetus, over the next week the left sixth aortic arch forms the DA and the right sixth aortic arch involutes. As the circulation develops, the DA carries lower oxygenated blood ejected from the right ventricle to be returned to the placenta via the umbilical arteries rather than circulate to the fetal head. As Rudolph points out, initial studies of cardiac output in fetal lambs agree well with studies in previable human fetuses,[3,4] which demonstrated that as a proportion of the combined ventricular output (CVO), 38% traverses the DA. Valuably, these findings have been since correlated with cardiac magnetic resonance-derived flow data performed on term fetuses, demonstrating 41% of the CVO traverses the DA.[5] It is thus estimated that only 8% of CVO actually traverses the aortic isthmus. Consequently in the normal human fetus, 84% of all circulation to the descending aorta comes from the DA, which influences both its size and course in the absence of factors that may alter these proportions. Generally these factors relate to how blood exits the ventricles and where it courses. When right ventricular outflow is obstructed postnatally end-systolic volume increases and ventricular enlargement results, however in the fetus, when the stroke volume is restricted the atrial pressure is affected only minimally due to shunting through the foramen ovale and thus venous return enters the unobstructed ventricle.[3] While total CVO can be maintained, the distribution through the ventricular outflows will vary greatly, and experimentally this has been shown to occur very quickly after induced fetal pulmonary stenosis in lambs so that obstruction may occur at various points in gestation and still result in these effects.[6]

The influence on the DA size and morphology likely is not stagnant given that the proportion of CVO circulated to the lungs changes through gestation, increasing from 13% to 25% between the second and third trimester.[7] Normally, the large fetal pulmonary artery and DA with right to left flow results in an inferior oblique angle where the DA meets the descending aorta, which becomes more acute when the pulmonary artery and DA are smaller.

3 | ALTERATIONS IN FLOW AND OXYGENATION BEYOND THE DUCTUS ARTERIOSUS

Even in the presence of significant outflow obstruction there may be no intrauterine hemodynamic issues during fetal life and the neonate is generally without distress until delivery. Understanding the abnormalities in intrauterine oxygen saturation and end organ development in pulmonary obstructive lesions helps to demonstrate the degree of aberration in hemodynamics and flow that relates to the changes in the DA. Fetal brain abnormalities have been documented for some time and in a large prospective study were present in 23% of the congenital heart disease group compared with 1.5% in controls.[8] As Rudolph discusses, at baseline in the normal fetus, the great majority of flow through the foramen ovale comes from the ductus venosus, indeed with only approximately 5% of superior vena cava flow traversing the foramen ovale.[3] A consequence of this distribution is that when flow through the right heart is perturbed, any *additional* flow through the foramen ovale must be derived from the superior or inferior vena cava with its less oxygenated blood compared with the oxygen rich blood arriving from the placenta through the ductus venosus. Thus, left atrial blood oxygen saturation, soon to be delivered to the head and neck vessels, should be lower. While it has been postulated that decreased delivery of low-oxygen pulmonary blood to the left atrium may balance these effects, Sun et al has demonstrated lower ascending aorta oxygenation. Comparing controls to congenital heart disease patients, this group showed that in controls the ascending aorta oxygenation is 7% higher than the main pulmonary artery but is only 2% higher in congenital heart disease patients and decreased ascending aorta saturation correlates with decreased fetal brain size.[9]

Importantly, cerebral oxygen delivery but not cerebral blood flow, has been shown to be lower in neonates with congenital heart disease with white matter injury sometimes noted.[10] Executive functioning, motor functioning, social aptitude, and learning proficiency are significantly affected in surviving neonates with congenital heart disease and while discerning the effects of the primary lesion from comorbidities related to cardiac surgery and anesthesia have been difficult,[11] recent studies have shown that functional brain connectivity is altered after birth but before surgery.[12]

4 | PULMONARY OUTFLOW OBSTRUCTION AND THE PULMONARY VASCULATURE

While not an exhaustive list, recognizing sequential locations of right sided obstruction provides a useful spectrum of the changes in DA anatomy. Tricuspid atresia with pulmonary stenosis or atresia, pulmonary atresia with intact ventricular septum (PAIVS), tetralogy of Fallot (TOF) including pulmonary atresia with ventricular

septal defect (PAVSD), and critical pulmonary stenosis represent the majority of right-sided obstructive lesions with which we may be concerned.

As related above, the cerebral blood oxygenation in congenital heart disease patients is of course decreased due to flow alterations across the foramen ovale, however, cerebral blood *flow* is unchanged.[10] Thus, the increased flow through the foramen ovale is ultimately conducted across the isthmus and in this case, delivers blood of a *higher* oxygenation to the descending aorta *and the DA* than would have been delivered in a normal fetus. In the case of pulmonary atresia, the DA carries less than 10% of CVO and the balance of the effects of decreased CVO of higher oxygenation is not known but is thought to result in abnormalities of the pulmonary vascular bed.[3] As increased pulmonary blood flow results in early smooth muscle hyperproliferation,[13] other abnormalities of smooth muscle development are likely in such aberrations as noted above with decreased flow or increased oxygenation. Pulmonary blood flow with higher oxygenation than usual may decrease pulmonary vascular resistance during vascular development, which has been posited as decreasing the stimulus for growth of medial smooth muscle with subsequent attenuated reaction to vasostimulation.

5 | MAINTENANCE OF PULMONARY BLOOD FLOW POSTNATALLY

Functional closure of the DA has been demonstrated to occur by 8 hours of life in 44% of normal healthy infants, and by 48 hours of life this increases to 88%, with nearly 100% closed by 72 hours.[14,15] With certain forms of congenital heart disease survival is dependent on the DA remaining patent as it may be the primary source (and sometimes the sole source) of blood flow to the lungs. Nature sometimes will delay the closure of such a connection, however ultimately, as Galen noted so long ago, it is the physician who must assist nature and ensure patency of the DA. Emerging interest in stenting of the DA as an alternative to surgical shunt placement or ongoing prostaglandin administration has led to understanding that each ductus requires individual detailed assessment. Several groups have reviewed the considerations in decision making for which strategy of stable pulmonary blood flow is optimal in different patients.[16-18] In children for whom ductal stenting is considered optimal, accomplishing this task effectively is served well by understanding the spectrum of ductal morphology in utero in various disease states. Thus an understanding of normal in utero and postnatal ductal anatomy and physiology is integral.

The changes that occur to the DA in pulmonary outflow obstructive lesions have been studied for some time, with early descriptions of the angle variation related to timing of obstruction in utero and direction of DA flow dating to 1980.[19] Not every obstruction will result in reversal of the ductal angle, defined as an inferior angle at the aortic junction of less than ninety degrees. Pulmonary atresia is thought to be most strongly associated with the reversed angle of the DA, and even in nonatretic pulmonary outflow obstruction, approximately 50% of patients will have DA angle reversal.[20] The reversed ductal angle has been shown to be predictive of requirement for balloon valvuloplasty, aorto-pulmonary shunt placement, or surgical repair within the first 28 days of life in both atretic and nonatretic pulmonary outflow lesions, and indeed a threshold of less than 65 degrees in patients with both pulmonary valve or conotruncal defects is a specific indicator for the need for early intervention.[20]

When an intervention is required, debate remains regarding the optimal approach when considering all factors. The surgical option of creating an aorto-pulmonary shunt, of course, dates to 1944 when Drs. Blalock, Taussig, and surgical technician Vivien Thomas created the first subclavian to pulmonary artery anastomosis.[21] It was 48 years before an alternative approach would be tested. First attempted in 1991 by Coe and Olley in newborn lambs,[22] followed the next year by successful deployment in humans by Gibbs et al,[23] ductal stenting has emerged as an effective alternative to surgery in some cases, though with its own comorbidities. Several groups have recently compared these two strategies with Bentham et al reporting an early survival advantage for DA stenting, with less post-procedural extracorporeal support and a reduced risk of death before repair but with an increased risk of reintervention.[16] Subsequently Glatz et al reported outcomes from four centers with no difference in death or unplanned reintervention to treat cyanosis comparing DA stenting to modified Blalock-Taussig-Thomas shunt (mBTTS) and while other reinterventions were more common after DA stenting, intensive care stay, diuretic use, and procedural complications were less frequent and larger and more symmetric pulmonary arteries were reported.[17] A helpful review of these article has been provided earlier this year by Drs. Benson and Van Arsdell, who point out that while DA stenting may be noninferior and reintervention may be the cost, it remains to be answered if the mBTTS should be replaced by DA stenting, especially given the questions that remain regarding anticoagulant regimens, the utility of drug-eluting stents, vascular access, and influences of the variability in ductal anatomy and morphology.[18]

Ductal morphology remains an important component of this equation. In an effort to better develop approaches to DA closure by catheterization, Krichenko et al formed an initial angiographic classification of isolated, patent DA with five types of varying morphology, length, stenosis location, and profile.[24] Certainly this provides a useful rubric on which to base DA stenting approaches, as demonstrated by Alwi in 2008 with description of DA morphology common for tricuspid atresia, PAIVS, and critical pulmonary stenosis compared to TOF and transposition of the great arteries with ventricular septal defect and pulmonary atresia (TGA/VSD/PA).[25] In the former group, a conical ductus with prominent aortic ampulla and constriction near the pulmonary artery end, or Krichenko type A, is more common but with

less branch pulmonary artery stenosis subsequently, whereas the latter group of TOF and TGA/VSD/PA more commonly has more vertically oriented DA from the proximal or middle aortic arch that tapers down and forms a kink at the left pulmonary artery, resulting in stenosis. While this is helpful for description of possible challenges, novel classification schemes are being developed with tortuosity of the DA a primary component and with pulmonary artery jailing, unplanned reintervention, subsequent pulmonary arterioplasty correlating with DA types (personal communication, Athar M. Qureshi, MD). With greater precision of understanding the differences in the DA in different anatomic, physiologic, and comorbid substrates, patient selection for DA stenting will become more refined.

6 | CONCLUSION

We now have much greater understanding of the congenital heart disease lesions that affect ductal development in utero and in what ways it may influence comorbid conditions, brain development, pulmonary vascular reactivity, DA size, and DA orientation. Selection of optimal intervention will depend on how narrow, oblique, mal-oriented, or tortuous any given DA may be, as well as its predicted mal-response to stimuli, which bears further study. As this approach is developed, it bears continued emphasis that with the vast variability in each congenital heart disease lesion, so will exist variability in the DA. Seventy-nine years ago, after Dr. Robert Gross closed the first patent DA surgically, in the case discussion of the first four cases, Dr. Reid wrote, "That others have thought of and tried unsuccessfully to do what you have reported here today, in no way detracts from the careful and painstaking studies you have just recited. That is the common experience of all of us and it is rather to your credit that you were not deterred by the failures of others. Permit me also to admire the words of caution with which you have surrounded this obvious advance in surgery…you have laid down certain rules or standards of procedure which should be our guiding principles until further experience or study warrants a change in them. That changes will come is inevitable, but to have this work discredited by hasty or unwise use would be deplorable."[26] Let us remember these words as we attempt to assist nature in providing adequate pulmonary blood flow to neonates with obstructive lesions and as we develop our own rules and standards of procedure for selecting neonates for each strategy.

CONFLICT OF INTEREST

None.

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