Congenital Heart Disease

Pulmonary Arteriovenous Shunting in the Normal Fetal Lung

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OBJECTIVES
We hypothesized that pulmonary arteriovenous shunting (PAVS) is normally present in fetal lungs and that cavopulmonary anastomosis-induced PAVS may represent a return to an earlier morphologic stage of development.

BACKGROUND
The surgical superior cavopulmonary anastomosis is performed as part of the staged Fontan pathway to treat univentricular forms of congenital heart disease; PAVS is a known sequela after superior cavopulmonary anastomosis and may have important clinical consequences. Although the etiology and true morphology of the structures responsible for PAVS are unknown, a leading theory is that PAVS is caused by absence of normal hepatic venous drainage to the pulmonary circulation.

METHODS
To determine whether normal fetal lungs demonstrate PAVS, we performed contrast echocardiograms on 13 fetal lambs, 8 neonatal lambs, 4 juvenile lambs, and 4 adult sheep using a blended mixture of saline and blood injected directly into the proximal pulmonary artery.

RESULTS
Pulmonary arteriovenous shunting was detected by direct epicardial echocardiography in all fetal lambs (n = 13) and neonatal animals studied at one and three days of life (n = 4) and in two of four animals studied at six to nine days of life. Pulmonary arteriovenous shunting was not present in animals studied at four weeks of life (n = 2) and in adult sheep (n = 5).

CONCLUSIONS
These studies demonstrate that PAVS is normally present in late gestation fetal and early neonatal lambs but then disappears during the later neonatal period. Furthermore, these findings suggest that PAVS associated with cavopulmonary anastomosis or other processes affecting the developing pulmonary circulation may represent a return to an earlier morphologic stage of development. (J Am Coll Cardiol 2004;44:1497–500) © 2004 by the American College of Cardiology Foundation

The surgical superior cavopulmonary anastomosis is performed as part of the staged Fontan pathway to treat univentricular forms of congenital heart disease. Pulmonary arteriovenous shunting (PAVS) is a known complication following superior cavopulmonary anastomosis and may have important clinical consequences (1–3). Several possible causes have been proposed, including direct pulmonary artery (PA)–pulmonary venous fistulas, increased pulmonary capillary angiogenesis, and pulmonary capillary dilation (4); however, the etiology and true morphologic basis of cavopulmonary anastomosis-induced PAVS remains unknown. A leading theory is that pulmonary arteriovenous communications develop in response to interruption of normal hepatic venous drainage to the pulmonary circulation. The resultant absence of an uncharacterized hepatic factor is believed to contribute to the development of PAVS. Resolution of PAVS occurs after the Fontan procedure or inclusion of hepatic veins in the pulmonary circulation (5,6).

The presence of occasional pulmonary arteriovenous communications in the human fetus has been previously described (7,8). Anabtawi et al. (9) proposed that pulmonary arteriovenous fistulas may represent the persistence of minute arteriovenous communications present in the normal fetal and neonatal lung that enlarge to become fistulous and cause precapillary shunting and arterial desaturation later in life. Although there is indirect anatomic evidence linking neonatal PAVS to the presence of abnormal pulmonary vascular structures (10), a relationship between these structures and direct pulmonary arteriovenous communications in the fetus has not been established. The development of pulmonary arteriovenous malformations after surgical cavopulmonary anastomosis may be the result of altered normal postnatal development of the infant lung, leading to phenotypic regression to more primitive (fetal) pulmonary circulation. The purpose of this study was to establish whether pulmonary arteriovenous malformations are present in the normal fetus and to elucidate the natural history of these structures.

METHODS
These studies were performed in compliance with animal welfare regulations of the University of California–San Francisco and Food and Drug Administration guidelines. Furthermore, these studies conformed to the “Position of the American Heart Association on Research Animal Use,” adopted by the American Heart Association on November
11, 1984, and were approved by the University of California-San Francisco Animal Research Institutional Review Committee.

**Fetal studies.** Thirteen mixed-breed Western ewes (125 to 145 days gestation; term 145 days) were operated on under sterile conditions. They were preanesthetized with ketamine hydrochloride (10 mg/kg intramuscularly), intubated, then anesthetized with continuous 1% to 2% isoflurane anesthesia. An 18-gauge catheter was inserted into a maternal pedal vein. A midline incision was made in the ventral abdomen, and the pregnant horn of the uterus was exposed. Through a small uterine incision, the left fetal forelimb and chest were exposed, and a left lateral thoracotomy was performed in the third intercostal space. Fetal anesthesia consisted of local anesthesia with 1% lidocaine hydrochloride and ketamine hydrochloride (20 mg intramuscularly). Succinylcholine hydrochloride (3 to 5 mg intramuscularly) was administered to prevent fetal breathing movements. The pericardium was incised along the main pulmonary trunk, and suspended with tacking sutures. A flexible 18-gauge catheter was introduced into the ascending aorta and secured with a 5.0 prolene (Ethicon Inc., Somerville, New Jersey) purse-string suture. An additional flexible catheter was introduced into the proximal main PA and secured with a 5.0 prolene (Ethicon Inc., Somerville, New Jersey) purse-string suture. A flexible 18-gauge catheter was introduced into the ascending aorta in eight of the animals. Two-dimensional cross-sectional epicardial contrast echocardiography was performed using a diagnostic ultrasound system (Aloka Co. Ltd., Tokyo, Japan) and recorded on videotape. A vigorously agitated mixture of saline and blood was used as echogenic contrast solution (11). With all four cardiac chambers visualized, 3 mm of contrast solution was rapidly injected into the main PA of each animal. Eight animals received an additional injection of contrast (3 ml) into the ascending aorta to rule out possible bronchopulmonary shunting. At the conclusion of the study, the fetuses were euthanized with a lethal dose of pentobarbital.

**RESULTS**

Contrast bubbles are normally lost in the pulmonary capillary bed. The presence of bubbles in the left atrium (LA) within three cardiac cycles of injection into the PA indicates PAVS (11) (Fig. 1). Contrast material circumventing the lungs through incompetent pulmonary and tricuspid valves and foramen ovale would appear in the right atrium before the LA. Similarly, contrast returning to the left side of the heart via the ductus arteriosus and an incompetent aortic valve would appear in the left ventricle before the LA. Contrast material returning to the LA after ascending aorta injection indicates the presence of systemic-to-LA shunting through the bronchopulmonary circulation.

We demonstrated PAVS in all prenatal and some early postnatal lambs; PAVS was detected by epicardial contrast echocardiography in all fetal sheep (n = 13) and neonatal lambs examined at one (n = 2) and three (n = 2) days of life. Pulmonary arteriovenous shunting was detected in two of four animals studied between six to nine days of life. Pulmonary arteriovenous shunting was not observed in animals examined at four weeks of age (n = 2) or adult animals (n = 5). Direct right-to-left intracardiac or systemic arteriovenous shunting was not observed in any animal. Systemic-to-LA shunting through the bronchopulmonary circulation (bronchopulmonary arterial shunting) was not observed in fetal animals (n = 8) after injection of contrast mixture into the ascending aorta.

**DISCUSSION**

The mechanism by which PAVS develops following superior cavopulmonary anastomosis is not well-understood. A leading theory is that pulmonary arteriovenous communications develop in response to the absence of an uncharacterized hepatic factor in blood that is returned to the pulmonary circulation. Pulmonary arteriovenous shunting has been shown to develop when hepatic venous drainage bypasses the pulmonary circulation and resolves once hepatic effluent is redirected to the lungs (5,12,13). Furthermore, unilateral cavopulmonary anastomosis generally results in ipsilateral PAVS (14). Although the mechanism by which hepatic venous drainage modulates pulmonary vascular modeling is unknown, it is intriguing that hepatopulmonary blood flow patterns observed after cavopulmonary anastomosis mimic those in the fetal circulation. Normally the lungs receive approximately 8% of the combined fetal cardiac output (15). Due to physiologic streaming of vena cava blood flow though the heart, fetal lungs receive blood that is relatively deficient in hepatic effluent (16). The disappearance of fetal PAVS shortly after birth may be related to normal redirection of hepatopulmonary blood flow as a consequence of foramen ovale closure. Cavopulmonary anastomosis-induced changes in hepatopulmonary blood flow, therefore, mimic those of the fetal circulation. Hence, PAVS observed in this setting may represent regres-
tion of pulmonary vascular remodeling to an earlier (fetal) developmental state.

In this study, we observed that PAVS was present in all fetal animals. Occasional direct bronchopulmonary arterial (17), bronchial arteriovenous (17), and pulmonary arteriovenous (8) communications in fetal lung have been previously characterized using sectional microscopy and corrosion casting techniques. The functional importance of these structures is unknown, and most are believed to disappear after birth (18). Using gelatin and microsphere injection techniques, Wilkinson and Fagan (10) demonstrated the presence of direct pulmonary arteriovenous communications measuring up to 55 μm in diameter (normal capillary diameter <7 μm) in postmortem infants. Because these observations were made in the postmortem setting, it is unclear whether these structures represent pathologically altered lung development or abnormal postnatal persistence of normal fetal vascular structures. Furthermore, the highly complex nature of the developing pulmonary circulation precludes systematic and comprehensive evaluation using microscopic techniques.

Contrast echocardiography is a highly sensitive method of detecting left-to-right and PAVS (1,19). Using this technique, we were able to accurately detect PAVS and differentiate it from bronchopulmonary shunting. Our finding that PAVS is present in all fetal animals suggests that direct arteriovenous communications are normally present in the fetal pulmonary circulation and may play a role in normal lung development.

We established that fetal PAVS disappears during early neonatal life and is not present in adolescent or adult sheep. The observed time course of PAVS resolution parallels that of other dynamic changes occurring in the pulmonary circulation such as closure of the ductus arteriosus and falling pulmonary vascular resistance. It is possible that these processes are mediated by similar mechanical and pharmacologic factors. Small, poorly perfused “supernumerary” arteries are present in the normal pulmonary circulation.

Figure 1. Contrast echocardiogram with injection into the main pulmonary artery demonstrating fetal pulmonary arteriovenous shunting. (A and B) Four chamber view showing the main pulmonary artery (PA), left atrium (LA), and right atrium (RA) before (A) and during (B) contrast injection. (C and D) Magnified view in a different orientation of the LA and left ventricle (LV) before (C) and during (D) contrast injection in another fetus.
(20,21). Utilizing a unique muscular sphincter, these structures are believed to function as recruitable sources of pulmonary blood flow when oxygenation demands are high (20). Additional studies are needed to further characterize these structures and determine if they play a role in fetal PAVS.

Findings from this study support the concept that cavo-pulmonary anastomosis-induced PAVS results from alterations in normal lung development due to altered hepato-pulmonary blood flow. Because PAVS progresses over time and may be more fulminate in younger patients (3), prolonging normal postnatal hepato-pulmonary circulation may confer some protection from subsequent cavo-pulmonary anastomosis-induced PAVS. Future studies involving the creation of cavo-pulmonary anastomoses in adult animals are designed to further evaluate the effect of age on the development of cavo-pulmonary anastomosis-induced PAVS.

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