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Perinatal Circulatory Physiology: Its Influence on Clinical Manifestations of Neonatal Heart Disease: Part I

By P. Syamasundar Rao, MD

INTRODUCTION

The fetal circulation is designed to utilize the placenta for gas exchange whereas the postnatal circulation uses lungs for gas exchange. Therefore, the circulatory systems must adapt to these changing requirements. An understanding of the fetal circulation and the changes that it undergoes at birth are essential for a better comprehension of the postnatal adaptation of the circulation in different types of congenital cardiac defects. The adult (Figure 1) and fetal (Figures 2-4) circulations are shown Figures 1 to 4. The objectives of this review are to:

1. present an outline of the fetal circulation;
2. discuss mechanisms that maintain fetal circulation
3. describe postnatal changes; and
4. discuss the influence of postnatal circulatory changes on the presentation of certain important congenital cardiac defects.

The first three objectives will be addressed in this (Part I) section.

FETAL CIRCULATION

Some data from human fetuses are available, but most of the information with regard to the fetal circulation is derived from the experimental observations of the animal models, particularly the lamb.[1-3] The lamb model appears to best reflect human physiology [4]. Quantitative estimates of blood flow have been derived by use of Fick

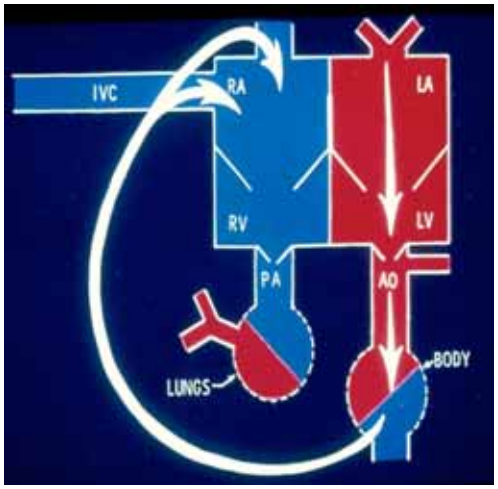

Figure 1. Diagrammatic depiction of adult circulation. The systemic venous return comes back to the right atrium (RA) via the inferior vena cava (IVC), superior vena cava (not labelled 0 and coronary sinus (not shown). The blood is pumped into the right ventricle (RV) and pulmonary artery (PA) and into the lungs for oxygenation. The pulmonary venous blood is returned into the left atrium (LA) and passed on to the left ventricle (LV) for pumping into the aorta (Ao) and the body.

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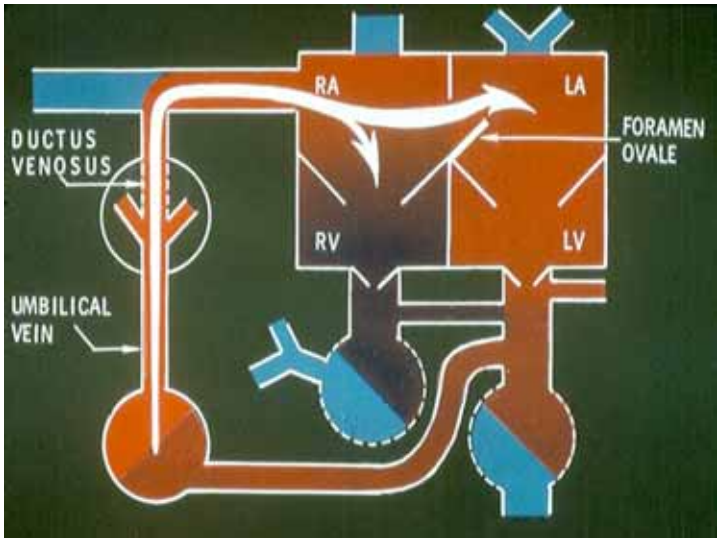

Figure 2. Diagrammatic depiction of fetal circulatory pathways. The placental venous return is carried by the umbilical vein, passes through the ductus venosus and reaches the inferior vena cava (not labeled) and right atrium (RA). From there a substantial proportion is shunted into the left atrium (LA) via the foramen ovale. The remaining portion goes into the right ventricle (RV). LV, left ventricle.

principle, electromagnetic flow transducers and by radionuclide-labeled microspheres. In the fetal circulatory states the cardiac output is expressed as the combined output of both ventricles in contradistinction to the postnatal circulatory states where the cardiac output is measured as the volume ejected by each ventricle.

Course of the Fetal Circulation

The oxygenated blood from the placenta is returned via the umbilical vein; the later enters the inferior vena cava via the ductus venosus (Figure 2). Nearly one-half of the umbilical venous blood goes through the liver and reaches the inferior vena cava via the hepatic veins. A substantial amount of the inferior vena caval blood is preferentially shunted into the left atrium (Figure 2). This appears to be related to the fact that the crista dividens, forming the upper margin of the foramen ovale (free margin of the septum secundum)

"Fetal circulation is intended to utilize placenta for gas exchange while postnatal circulation uses lungs for gas exchange."

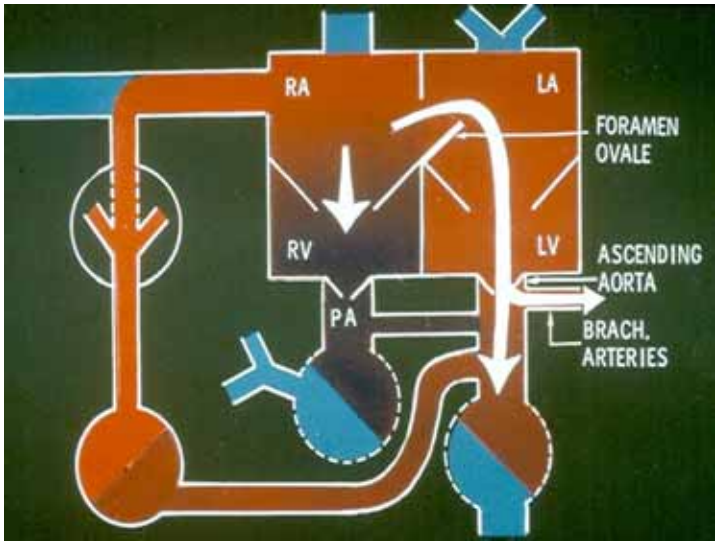

Figure 3. Diagrammatic depiction of fetal circulatory pathways. The blood reaching the left atrium (LA) via the foramen ovale is passed on to the left ventricle (LV) and from there into the aorta. The oxygenated blood reaches the coronary arteries (not shown) and central nervous system via the brachio-cephalic (BRACH.) vessels. PA, pulmonary artery; RA, right atrium, RV, right ventricle.

overrides the inferior vena cava (Figure 5).[5] The free edge of the lower margin of the foramen ovale, formed by the septum primum, is on the left side of atrial septum and the foramen ovale is kept open by the inferior vena caval stream (Figures 2 and 5). In addition, the inferior vena caval valve (Eustachian valve) diverts the inferior vena caval blood stream towards the atrial septum.[6] Consequently, the oxygenated blood enters the left ventricle and then the ascending aorta (Figure 3). Therefore, the brain (via the brachio-cephalic vessels) and the heart (via the coronary arteries) are perfused with oxygenated blood (Figure 3). The pulmonary venous return does mix with the left atrial blood but, because of small amount of return (7% of combined ventricular output), it does not significantly desaturate the highly saturated umbilical venous return. The coronary venous and superior vena caval blood along with the portion of the inferior vena caval blood that did not stream into the left atrium, enter the right ventricle via the tricuspid valve (Figure 3). This desaturated blood is pumped by the right ventricle into the main pulmonary artery (Figure 4). From the main pulmonary artery, a small amount of right ventricular ejectate enters the lungs and the majority is pumped into the descending aorta via the ductus arteriosus. Thus, the desaturated blood makes its way into the placenta for oxygenation via the umbilical arteries (Figure 4).

Mechanisms Maintaining Fetal Circulatory Pathways

The **ductus venosus** and **umbilical vessels** are kept open by the mechanical effect of flow through them.

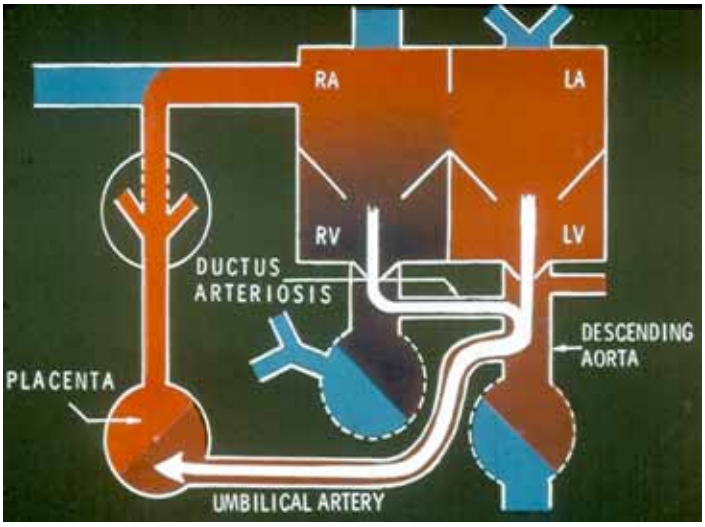

Figure 4. Diagrammatic depiction of fetal circulatory pathways. The right ventricular (RV) blood is pumped into the pulmonary artery (not labeled) and because of high resistance pulmonary circuit the majority of the blood is shunted via the ductus arteriosus into the descending aorta. From there the desaturated blood is returned to placenta via the umbilical arteries. LA, left atrium; LV, left ventricle; RA, right atrium.

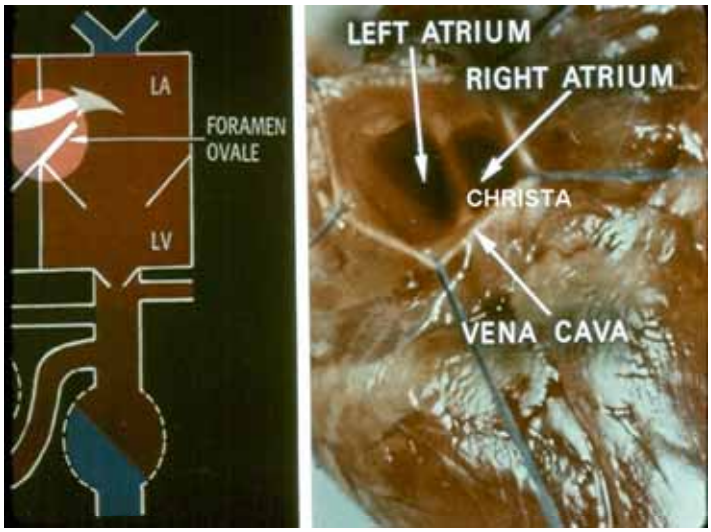

Figure 5. Diagrammatic depiction of fetal circulatory pathways (left) showing the passage of inferior vena caval blood into the left atrium (LA) via the foramen ovale. When examining the inferior portion of the heart from the inferior vena cava (right), note that a greater portion of the left atrium is seen, explaining in part the reason for shunting the inferior vena caval blood into the LA. CHRISTA, Christa dividens; LV, left ventricle.

The **foramen ovale** is kept patent in the fetus because of the mechanical effect of streaming of the inferior vena caval blood into the left atrium (Figures 2 and 5) and the physical relationship of the inferior vena cava to the left atrium (Figures 5).

Because of the muscular nature of the **ductus arteriosus**, it may have to be kept open by active dilatation. Studies examining this issue suggest that both the locally produced and circulating prostaglandins (E_2 and possibly I_2) may be responsible for this. Prostaglandins are rapidly cleared by passage through the lungs. Since the pulmonary blood flow is very low in the fetus (7% of combined ventricular output) circulating prostaglandins are high in the fetus in contradistinction to postnatal life when the prostaglandins are rapidly cleared by passage through the lungs. In addition, the placenta produces large quantities of prostaglandins. The patency of the ductal may also be related to circulating adenosine [7].

Since the ductus arteriosus is large, the pressures in the main pulmonary artery and descending aorta are equal. Consequently, the quantity of blood flow going into the placenta vs. lungs depends upon their relative resistances. Since the placental circulation is a low resistance circuit, a larger proportion of the blood goes into the placenta. Because the **pulmonary circulation** is a high resistance circuit, a smaller proportion of the combined ventricular output makes its way into the lungs. The causes of this high pulmonary vascular resistance are not clearly understood. Kinking and high degree of tortuosity of the small pulmonary vessels have been suggested as causes,[8] but there is no general agreement of this causative relationship. Some studies [9,10] demonstrated that the pulmonary arterioles have a thick smooth muscle layer which may be responsible for the high resistance. Low partial pressure of oxygen (to which the pulmonary arterioles are subjected to) keeps them thick and constricted. The pulmonary vascular resistance may also be influenced by changes in the pH and PCO_2 as well as autonomic nervous system.[9,10] Many endogenous and exogenous vaso-active materials also stimulate the fetal pulmonary vasculature. Several studies demonstrate that pharmacologic doses of prostaglandins have dramatic effect on the fetal pulmonary circulation.[9,11] Prostaglandin $F_2\alpha$ and leukotrienes (LTD_4) produce pulmonary vasoconstriction whereas prostaglandins E_1, E_2 and I_2 produce pulmonary vasodilatation.[12] The role of prostaglandins in maintaining a normally high pulmonary vascular resistance however, is not clearly defined. It is possible that prostaglandins mediate the hypoxic stimulus.

Distribution of the Cardiac Output and Oxygen Saturations in the Fetus

As mentioned in the preceding section, cardiac output is expressed as combined output (CVO) of both ventricles. The CVO in the lamb

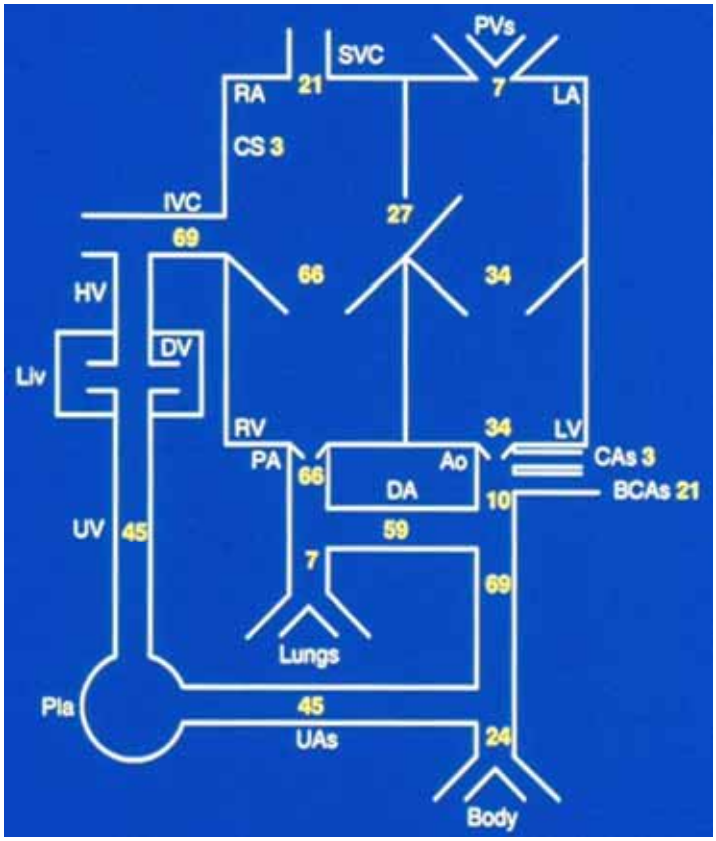

Figure 6. Diagrammatic depiction of fetal circulatory pathways illustrating the percent combined ventricular output for each cardiac/vascular chamber. The numbers indicate percent of combined ventricular output. Ao, aorta; BCAs, brachiocephalic arteries; CAs, coronary arteries; CS, Coronary sinus; DA ductus arteriosus; DV, ductus venosus; HV, hepatic vein; IVC, inferior vena cava; LA, left atrium; Liv, liver; LV, left ventricle; PA, pulmonary artery; Pla, placenta; PVs, pulmonary veins; RA, right atrium, RV, right ventricle; SVC, superior vena cava; UAs, umbilical arteries; UV, umbilical vein.

is 200 ml/kg/minute.[4] The estimates of relative distribution of the CVO based on the data derived from chronically instrumented lambs[13,14] are shown in Figure 6. Oxygen saturations and PO_2s are lower in the fetus than those in the neonates, infants and children.[14] This may be related to lower efficiency of the placenta to transport oxygen than the lungs. However, the fetus adapts to these lower levels by virtue of higher fetal hemoglobin levels; the fetal hemoglobin has low P50 of 18 to 19 torr which facilitates greater oxygen uptake from the placenta. Furthermore, the distribution of the blood to the various organs and the placenta is most advantageous in that the highly saturated blood goes to the heart and brain and low saturated blood to the placenta.

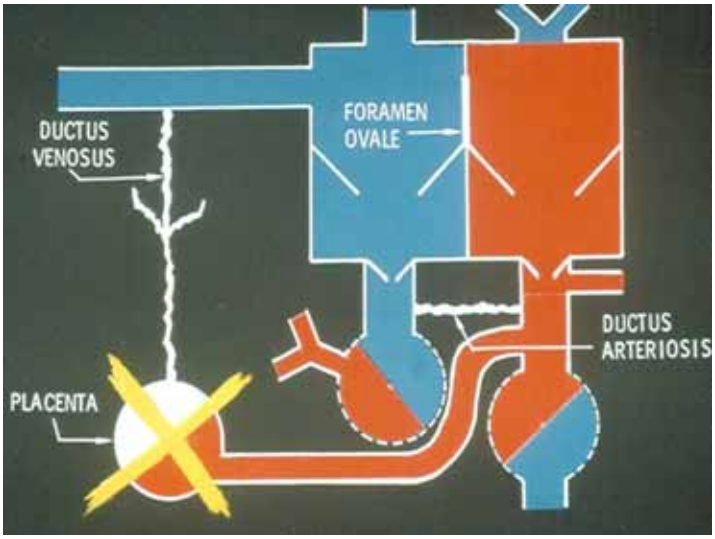

Figure 7. Diagrammatic depiction of changes in fetal circulation at birth. These include removal of placenta, constriction of ductus venosus, closure of foramen ovale and constriction of ductus arteriosus.

MYOCARDIAL FUNCTION IN THE FETUS

The fetal myocardial structure differs significantly from that of the adult. In the adult the myocardial cells are compact with small nuclei and with little or no connective tissue surrounding them. In contradistinction, the fetal myocardial cells are less well organized, have large nuclei (sometimes even multinucleated), and the number of sarcomeres per unit is less. Also, the organization and function of the sarcoplasmic reticulum is incomplete which increases progressively with increasing fetal age. A similar pattern is seen with the development of t-tubule system.[15] The amount of areolar tissue in between the fetal myocardial cells is large [16]. It also appears that the sympathetic innervation of the heart is not completely developed in the fetus.[14,16] There are also differences in the type of substrates utilized, type of contractile protein activated, production and delivery of high energy phosphate, method of calcium delivery, and response of contractible elements to calcium ions between fetal, neonatal and adult myocardium.[15]

The described structural and functional differences result in physiologic effects, namely, greater resting tension at a given muscle length and a lesser tension developed at any resting length in the fetus than in the adult.[16] While the initial studies suggested that the fetal cardiac output is mostly regulated by a change in the heart rate rather than by a change in the stroke volume, subsequent studies indicated that the Frank-Starling mechanism is indeed operative in the fetus, but within the narrow physiologic range.[17] Increase in the afterload adversely affects the fetal heart.[18]

POSTNATAL CIRCULATORY CHANGES

The circulatory changes at birth are elimination of the placenta (Figure 7), maturation of the pulmonary circulation, and closure of fetal circulatory pathways (Figure 7). There is an impressive immediate change at birth followed by a slow change until an adult type of cardiovascular system is achieved; this may occur over varying time periods.

Elimination of the Placenta

At birth, the placenta is removed as a matter of normal birth process and the lungs must assume the gas exchange function acutely. Elimination of placental circulation causes elevation of the systemic vascular resistance because of exclusion of low resistance placental circuit.

Development of Pulmonary Circulation

Soon after the delivery respiration begins and within a few minutes after birth almost complete expansion of the lungs occurs. There is striking decrease in the pulmonary vascular resistance and a distinct increase in the pulmonary blood flow at birth. This is associated with a fall in pulmonary arterial pressures. Expression of the fluid from the alveoli and expansion of the lungs are responsible to a great degree for the fall in the pulmonary vascular resistance.[9,19,20] Other factors that may affect a decrease in the pulmonary resistance are decreased PCO_2, increase in pH and increase in alveolar and blood PO_2. The consensus of opinion is that an increase in PO_2 in the alveoli and blood is the most potent and important pulmonary vasodilator at birth. The alveolar gaseous oxygen diffuses in sufficient quantities into the region of precapillary vessels making themdilate. The mechanism by which the oxygen induces pulmonary arteriolar dilation is not understood. It may directly affect the pulmonary arteriolar smooth muscle cells or its action is mediated through a chemical substance. The oxygen may activate kininogen to bradykinin. Bradykinin is a potent pulmonary vasodilator. The effect of bradykinin itself may be mediated through prostocyclin. A rapid increase in bradykinin levels in the left atrium after ventilation with oxygen supports bradykinin mediated action of oxygen. Since the increased bradykinin levels last for a short period of time one may question the validity of bradykinin mediation as the sole factor responsible for pulmonary vascodilation. Pulmonary vasodilatation induced by oxygen occurs in two phases. The initial rapid phase cannot be inhibited by indomethacin and therefore is not dependent upon prostocyclin-mediation. The subsequent slow phase of the oxygen-medicated pulmonary vasodilatation may be influenced by prostaglandins.[21] Decrease in pulmonary vascular resistance increases the pulmonary blood flow markedly.

Further decrease in the pulmonary vascular resistance and involution of the pulmonary arteriolar medial musculature take place more gradually. The pulmonary vasculature looks very similar to that of the adult by the age of 6 to 8 weeks. Pulmonary parenchymal disease states causing alveolar hypoxia and reduced inspired oxygen such as in high altitude may prevent

normal maturation/involution of pulmonary vasculature. Elevated pulmonary artery pressure associated with congenital heart defects (for example large ventricular septal defect or patent ductus arteriosus) may also retard the normal involution of the pulmonary arterioles.

Closure of the Fetal Circulatory Pathways

Patent foramen ovale. As alluded to in the preceding section, decrease in the pulmonary arteriolar resistance is associated with an increase in the pulmonary flow which in turn increases the volume of blood flow return to the left atrium with consequent increase in the left atrial pressure. Shortly before this, the placenta is eliminated with consequent decrease in the umbilical venous and inferior vena caval flow. This will result in a slight decrease in the right atrial pressure. A combination of increase in the left atrial pressure and decrease in the right atrial pressure will result in apposition of the septum primum and septum secundum causing in functional closure of foramen ovale. This occurs within the first few hours after birth. The functional closure of the foramen ovale is often incomplete, especially if there is an increase in the right atrial pressure (e.g., crying, pulmonary vasoconstriction, severe right atrial or ventricular obstruction), and/or a decrease in the left atrial pressure, with resultant right-to-left interatrial shunting. Severe dilatation of the left atrium secondary to increased pulmonary blood flow (for example patent ductus arteriosus or ventricular septal defect) may stretch the patent foramen ovale, causing left-to-right shunting.

While functional closure of the foramen ovale occurs within hours after birth, anatomic closure may take 2 to 3 months [22,23]. In some subjects, the closure does not take place at all. Several studies have shown persistent patency in nearly 20% of older infants, children, adolescents, and adults.[24]

Ductus venosus. The ductus venosus also closes shortly after birth. The closure may simply be due to lack of blood flow through this structure following elimination of placenta. Or, the mechanism of closure may be similar to that of ductus arteriosus.

Ductus arteriosus. Two stages of ductus arteriosus closure following birth have been described, the first, functional closure by constriction of ductal muscle occurs within 10 to 15 hours of age.[3,19,22,25] The second, anatomic closure occurs by endothelial destruction, subintimal layer proliferation, connective tissue formation over the next two to three weeks. Increase in oxygen tension produces muscular constriction of ductal muscle, causing the ductus to close.[26,27] In contradistinction, situations with low oxygen such as high altitudes or when the neonate is exposed to low oxygen concentrations, the ductal closure is delayed.[28,29] Vasoactive substances such as histamine, 5-hydroxytryptamine, acetylcholine, bradykinin and catecholamine may have a role in ductal closure although their role has not been fully delineated.

The mechanism of action of O_2 in ductal closure is not clearly elucidated, but most authorities suggest that direct stimulation of the

smooth muscle cells of the ductal tissue is responsible for ductal closure. The ductal constriction may also be mediated through cyctocrome and thromboxane systems. Several studies suggest a definitive role of prostaglandins in either initiating ductal constriction or mediating ductal constrictive effect of oxygen.[30] Relaxation property of ductal muscle with prostaglandins seems to develop early in fetal life. The prostaglandin mediated ductal relaxing mechanism is most active at about 0.7 gestation. With increasing gestational age the ductal muscle becomes less responsive to prostaglandins while it acquires increasing sensitivity to oxygen. It would appear that prostaglandins indirectly contribute to ductal closure by becoming less effective after birth and potentiate constrictive action of oxygen.

SUMMARY AND CONCLUSIONS

Fetal circulation is intended to utilize placenta for gas exchange while postnatal circulation uses lungs for gas exchange. Fetal circulatory pathways, namely, umbilical vessels, ductus venosus, foramen ovale and ductus arteriosus, high pulmonary vascular resistance and low placenta resistance facilitate placental gas exchange and promote distribution of oxygenated blood to the vital organs of the fetus. Mechanical factors, prostaglandins and low PO_2 in the lung keep the fetal circulatory pathways open. Postnatal circulatory changes are elimination of the placenta, development of pulmonary circulation, and closure of fetal circulatory pathways. The influence of postnatal circulatory changes on the clinical presentation and clinical course of the neonate with congenital heart defects will be dealt with in Part II of this review to be published in the next issue of Congenital Cardiology Today.

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JUNE MEETING FOCUS

5th World Congress of Paediatric Cardiology and Cardiac Surgery
June 21-26, 2009
Cairns, Australia
www.pccs2009.com

All delegates will be registered for one of the specialty meetings, which will provide a focused start to the World Congress. The "Specialty Meetings" will comprise:

- Interventional (jointly organized with PICS) (3 days: Sun., Mon. and Tue.) "PICS at the World Congress"
- Surgical (jointly organized with WSPCHS) (Mon. and Tue.) "Second Biennial Scientific Meeting of The World Society for Pediatric and Congenital Heart Surgery at the World Congress"
- Pediatric Cardiac Intensive Care (Mon. and Tue.) jointly organized with PICS-AICS (includes perfusion and anesthesia)
- Adult Congenital Heart Disease (Mon. and Tue.) jointly organized with International Society for Adult Congenital Heart Disease (ISACHD)
- Pediatric Electrophysiology / Arrhythmia (Mon. and Tue.) jointly organized with PACES and PEDIRHYTHM
- Imaging (including Fetal Echocardiography / MRI and CT) (Mon. and Tue.)
- Nursing (Mon. and Tue.)
- Pediatric Cardiomyopathy / Transplant (Mon.) Pulmonary Hypertension (Tue.)

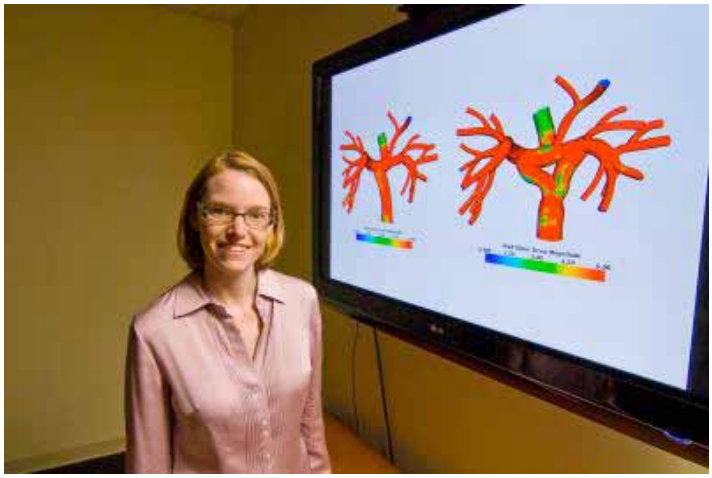
Thereafter, the meeting will be comprised of a series of plenary meetings, each exploring a specific topic, alongside free abstract sessions and educational activities for trainees.

There will be Landmark Lectures by: Robert Anderson (London); Andrew Redington (Toronto); Pascale Vouhe (Paris); Ms. Kathy Mussato (Milwaukee) and Gil Wernovsky (Philadelphia).

Medical News, Products & Information

UC San Diego Engineer Develops Method to Combat Congenital Heart Disease in Children

Congenital heart defects account for five times more deaths annually than all childhood cancers combined. Alison Marsden, an Assistant Mechanical and Aerospace Engineering Professor at the University of California at San Diego, has developed a unique set of computer modeling tools that are expected to enhance pediatric surgeons' ability to perform heart surgery on children. Marsden's work focuses on designing and using simulation tools to provide a way of testing new surgery designs on the computer before trying them on patients, much like, for example, engineers use computer codes to test new designs for airplanes or automobiles.



Alison Marsden, a UC San Diego mechanical and aerospace engineering professor, has developed breakthrough simulation tools to assist pediatric heart surgeons.

Certain severe forms of congenital heart defects leave a patient with only one functional heart pumping chamber. These "single ventricle" defects are uniformly fatal if left untreated, and require a patient to undergo multiple heart surgeries, ending with a Fontan procedure.

In the Fontan surgery, the veins returning blood to the heart from the body are directly connected to the arteries that send deoxygenated blood to the lungs, forming a modified t-shaped junction. This bypasses the heart on the one side so that the resulting circulation puts the single pumping chamber to optimal use. Using models derived from MRI image data, Marsden has come up with a way to optimize a Y-Graft model for the Fontan procedure which can help pediatric surgeons determine whether this procedure will benefit a patient, as well as determine how a patient's heart will perform during moderate exercise. Marsden's research findings on the Y-Graft were published in a paper called, "Evaluation of a novel Y-shaped extracardiac Fontan baffle using computational fluid dynamics," in the February issue of the Journal of Thoracic and Cardiovascular Surgery.

An advantage of Marsden's proposed Y-Graft design is that it can be optimized or modified for an individual patient by custom manufacturing the graft portion prior to surgery.

"Our goal is to provide a set of personalized tools that can be used in collaboration with surgeons to identity the best procedure for patients," Marsden said.

Pediatric surgeons at Stanford University plan to use Marsden's Y-Graft computer models for a Fontan procedure for the first time later this year. One of the pediatric cardiologists working with Marsden is Dr. Jeff Feinstein, an Associate Professor of Pediatrics (Cardiology) at Stanford with a specialization in interventional cardiology, and Director of the Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford.

"Alison's work enables us to look at things we can't look at in any other way," Feinstein said. "The whole concept of simulation based medicine offers opportunities to try things with zero risk to the patients. With this type of computer modeling, you can do 100 simulations before you ever try it in a patient."

Marsden has also been working with Dr. John Lamberti, a Professor in the Department of Surgery at the UC San Diego School of Medicine.

"The research Alison is doing is very relevant to the treatment of the most complex forms of congenial heart disease," said Lamberti, also a Pediatric Cardiac Surgeon and Director of the Heart Institute at Rady Children's Hospital. "This type of computer modeling could provide a patient with better long-term cardiac performance and better exercise tolerance, particularly during the teenage years and into adulthood when conventional-type Fontan procedures begin to fail."

Part of Marsden's work on the Y-Graft includes increasing flow rates to simulate exercise.

"These simulations allow us to obtain information that is difficult to measure in the clinic," Marsden said. "This way we can design something that would allow a patient to perform well at rest but also during exercise."

Marsden – who joined the UC San Diego Jacobs School faculty in 2007 after receiving her Ph.D. at Stanford University – hopes to eventually apply her current research and computer models to a whole range of cardiovascular diseases both in children and adults.

"One of the reasons I came to UC San Diego was because it's a really great place to do this type of work," Marsden said. "We have one of the top bioengineering departments in the country, as well as a top mechanical engineering department and medical school. I had a lot of offers, but I chose UC San Diego because of its strong combination of engineering and medicine expertise. San Diego also has a huge biotech presence, which is a plus for researchers in the region."

Copies of Marsden's paper, "Evaluation of a novel Y-shaped extracardiac Fontan baffle using computational fluid dynamics," are available upon request. For more information: www.ucsd.edu.

Gene Therapy Reversed Heart Damage in Heart Failure

Long-term gene therapy resulted in improved cardiac function and reversed deterioration of the heart in rats with heart failure, according to a recent study conducted by researchers at Thomas Jefferson

University's Center for Translational Medicine. The study was published online in Circulation.

The rats were treated with a gene that generates a peptide called bARKct, which was administered to hearts in combination with recombinant-adeno-associated virus serotype 6 (rAAV6). bARKct works by inhibiting the activation of G protein-coupled receptor kinase 2 (GRK2).

GRK2 is a kinase that is increased in heart failure myocardium. Enhanced GRK enzymatic activity contributes to the deterioration of the heart in heart failure, according to Walter J. Koch, PhD, the W.W. Smith Professor of Medicine and the director of the Center for Translational Medicine at Jefferson Medical College of Thomas Jefferson University. Dr. Koch's research team carried out the study, which was led by Giuseppe Rengo, MD, a post-doctoral fellow.

"The theory is that by inhibiting this kinase, the heart will recover partially due to reversal of the desensitization of the b-adrenergic receptors," Dr. Koch said. "The expression of bARKct leads to a negative neurohormonal feedback that prevents the heart from continuing on the downward slope during heart failure. This was one novel finding of the study."

Dr. Koch and his colleagues used five groups of rats in their study. Two groups received rAAV6 with the bARKct peptide, two groups received rAAV6 with green fluorescent protein (GFP), and the last group received a saline treatment. One of the bARKct groups and one of the GFP groups also received the beta blocker metoprolol concurrently.

Twelve weeks after receiving the treatment, the rats who received the bARKct had a significantly increased left ventricular ejection fraction. The treatment also reversed the left ventricular deterioration and normalized the neurohormonal status. Dr. Koch said that targeting the GRK2 enzyme with bARKct was sufficient to reverse heart failure even without concomitant metoprolol.

The rats that received GFP or saline alone experienced more deterioration of cardiac function during the course of the study. This deterioration was prevented, but not reversed, with the concomitant metoprolol.

In future trials in humans, the bARKct peptide will be administered with beta blockers, which are the standard treatment. However, Dr. Koch said that if a pharmaceutical inhibitor can be developed, then a new class of drugs to treat heart failure could possibly even replace beta blockers.

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For registration questions, contact Amber Maxa at: amaxa@asecho.org.

For housing questions, contact Lindsay Mooring at: lmooring@asecho.org.

Do you or your colleagues have interesting research results, observations, human interest stories, reports of meetings, etc. that you would like to share with the congenital cardiology community?

Submit a summary of your proposed article to Congenital Cardiology Today at: RichardK@CCT.bz

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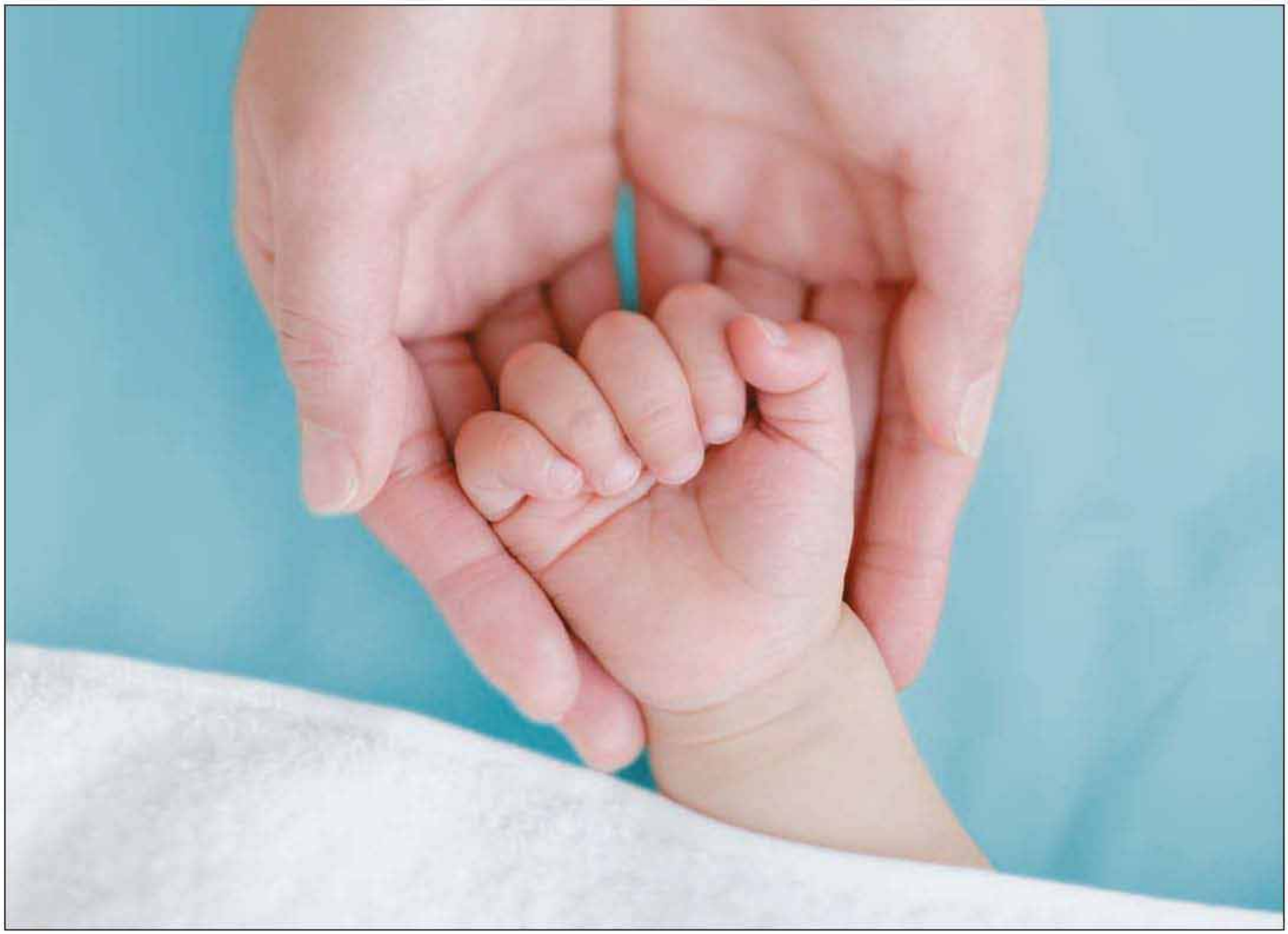

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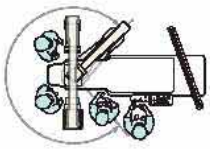

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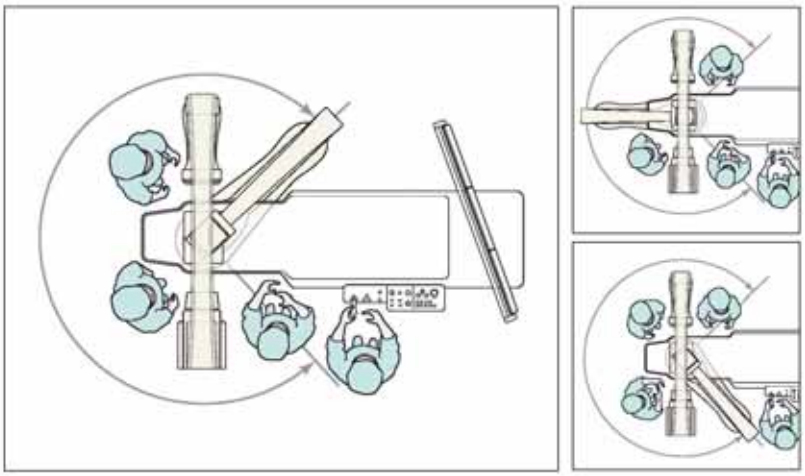

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