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Enhancing the Care of Preterm Infants Undergoing Surgical Ligation of a Patent Ductus Arteriosus

By Afif F. EL-Khuffash, MD; Amish Jain, MD; Patrick J. McNamara, MD

Summary

There is limited consensus on the diagnosis and management of a patent ductus arteriosus (PDA) in preterm neonates. PDA remains one of the most common cardiovascular abnormalities in preterm neonates, occurring in about a third of infants below 30 weeks gestation and up to 60% of infants less than 28 weeks. Shunting from the systemic to the pulmonary circulations, oftentimes referred to as ductal steal, results in systemic hypoperfusion and pulmonary overcirculation with end-organ morbidity. Infants are usually referred for surgical ligation following failure of successful treatment or in the presence of contraindications. The decisions relating to selection for and the timing of referral for surgical ligation remain controversial. In addition, the inherent short- and long-term risks associated with PDA ligation are becoming increasingly recognized. As a result, there is a current shift in opinion and a reluctance to refer infants for the procedure. This article describes the physiological changes occurring before, during, and after PDA ligation; we explore the relationship of these changes to short- and long-term clinical observations in the ligation population. A suggested management approach and future research directions are also discussed.

Introduction

The diagnosis and management of a patent ductus arteriosus (PDA) in preterm neonates poses a major challenge. It is the most common cardiovascular abnormality of prematurity occurring in about a third of infants below 30 weeks gestation and up to 60% of infants less than 28 weeks.[1] The presence of a PDA is associated with morbidities including: feeding intolerance, necrotizing enterocolitis (NEC), severe intra-ventricular haemorrhage (IVH), metabolic acidosis, renal failure, increased ventilator dependence, bronchopulmonay dysplasia (BPD) and pulmonary haemorrhage.[2,3] In addition, a persistent ductus arteriosus failing medical treatment is associated with a four-fold increase in mortality.[4] In a retrospective analysis of 301 infants, mortality rates were higher in infants with a persistent PDA compared to controls (70% vs. 11%). The main cause of death in the PDA population was multi-organ failure. This association remains significant following adjustment for gestation, birth weight, disease severity and co-morbidities including IVH, NEC, and sepsis.[5] It was also noted that infants with moderate to large PDAs had a higher mortality than those with restrictive ducts. However, in spite of these associations, some still advocate leaving the PDA untreated, arguing that it is an innocent bystander. This approach to management is a result of the failure of randomized studies of prophylactic and early PDA treatment to demonstrate a reduction in the above-mentioned morbidities

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or an improvement in neurodevelopmental outcome.[5-8] All of these studies however, treated the PDA as an all-or-none phenomenon, with no consideration of the impact a PDA has on pulmonary or systemic blood flow. This over-simplification of the PDA may explain the negative results of these trials. The PDA in the early life of a premature infant should be regarded as a continuum, from being physiologic, and potentially beneficial, to being pathological (when pulmonary vascular resistance drops), leading to systemic hypoperfusion and pulmonary congestion.

Rationale for Therapeutic Intervention

Prolonged exposure to the effect of left-to-right transductal shunting leads to increased pulmonary blood flow, and, as a consequence, increased pulmonary venous return to the left atrium. The inability of the left ventricle to accommodate the increased blood volume may lead to a rise in LA pressure, and, as a result, pulmonary venous congestion. This explains the association of pulmonary haemorrhage with a significant PDA. The left ventricle begins to dilate, leading to excessive stretching of the muscle fibres, eventually resulting in reduced contractility. Increased LA pressure may also promote increased left-to-right shunting across the atrial septum. The results of this are two-fold: an increase in pulmonary blood flow and a reduction in left ventricular output; therein, in turn, effective systemic blood flow. Echocardiography may be used to characterize the magnitude of the shunt volume indirectly through its effects on the pulmonary and systemic circulation (Figures 1, 2). In addition, infants with a significant PDA have lower regional cerebral oxygen saturation, and higher fractional cerebral oxygen tissue extraction when compared to controls when assessed using near-infrared spectroscopy (NIRS). This implies a reduction in cerebral blood flow in the presence of a significant PD.[9] Prolonged exposure to left-to-right shunting may also compromise coronary perfusion.[10] Cardiac Troponin T (cTnT), a cardio-specific marker of myocardial ischemia / damage, rises significantly in infants with a PDA, and subsequently falls dramatically following successful closure.[11] Higher cTnT values associated with a PDA were also associated with increased morbidity and mortality, along with worse neurodevelopmental outcome at 2 years of age.[2,12]

Timing of treatment remains controversial as there is no clear long-term benefit to either prophylactic or early treatment.[13] Pharmacological closure is only successful in up to 80% of infants treated,[14] with up to 50% in infants less than 25 weeks gestation and less than 750 grams failing to respond to medical therapy.[15] A third of these infants may also relapse following medical closure.[16] Surgical ligation of a PDA is influenced by availability and ease of access to a paediatric cardiothoracic centre. In addition, in some centres surgery may be considered the first-line treatment in infants with NEC, IVH, pulmonary haemorrhage, thrombocytopenia, and severe oliguria. Currently there is no evidence in the literature supporting surgical over medical treatment as a first-line approach.[17] A Cochrane review included one eligible study of prophylactic surgical ligation that enrolled 84 preterm infants. The prophylactic group had ductal ligation performed within 24 hours of life following a pre-specified protocol, while the control group received standard care without indomethacin. Prophylactic surgical ligation of the PDA resulted in a significant reduction of severe stage NEC, [RR 0.25, 95% CI (0.08, 0.83), p value 0.02, NNT 5], but without any survival advantage. The reduction in NEC probably resulted from the timing of PDA treatment rather than the modality, but the findings are somewhat controversial due to the high incidence of NEC in the control group. In general, surgical intervention is contemplated if medical treatment fails. It is possible that delays between attempted medical treatment and surgical ligation may contribute to complications.[4]

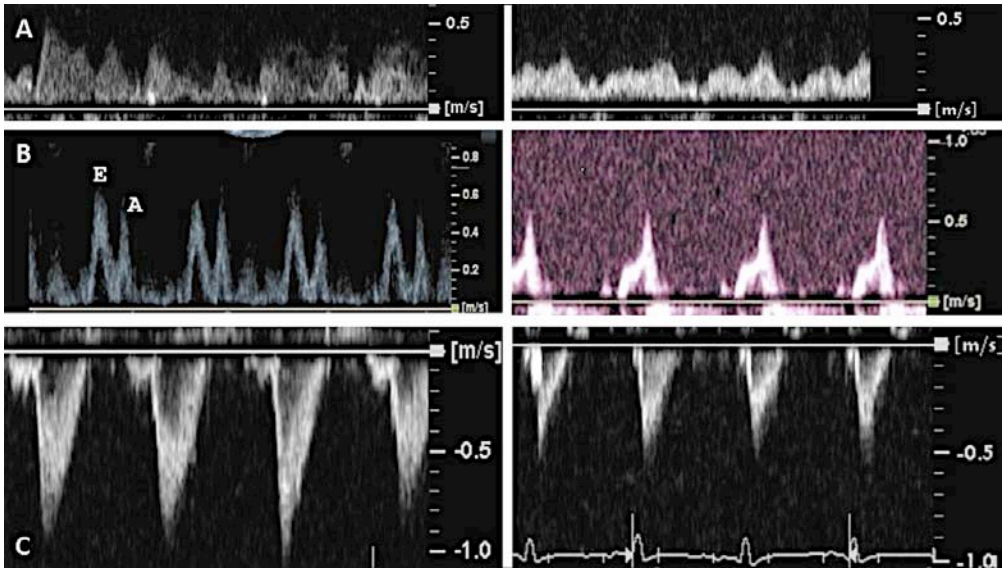

Figure 1. Two-dimensional echocardiography images demonstrating reduction in pulmonary venous peak velocity (Panel A), ratio of passive (E wave) to active (A wave) transmitral flow (Panel B), and left ventricular output (Panel C) after surgical ligation of the ductus arteriosus.

Intra-operative and Immediate Post-operative Consequences of PDA Ligation

Physiology of the Preterm Myocardium

The preterm myocardium is not conditioned to handle substantial changes in preload or afterload. The biological process leading to contraction of the preterm heart muscle is inefficient and relies on L-type calcium channels as a source of calcium contraction, rather than intrinsic calcium stores.[18] Furthermore, the immature myocytes have a higher surface area to volume ratio to compensate for the lack of the T-tubule system necessary for effective calcium entry into the cell. Therefore, the myocardium of preterm infants is poorly tolerant of increased afterload compared to older children.[19] This is supported by animal and preterm human data showing that velocity of circumferential fibre shortening, a load-dependent measure of contractility, is inversely proportional to end-systolic wall stress.[20,21] Furthermore, the immature myocardium contains a higher proportion of non-contractile collagen, lower elastin concentrations, and an inefficient process of calcium extrusion from the myocytes. This leads to impaired relaxation and ventricular filling during diastole contributing to diastolic dysfunction.

There is increasing evidence describing a Post Ligation Cardiac Syndrome (PLCS) occurring in up to 50% of infants undergoing ligation.[22] PLCS is characterised clinically by a fall in systolic blood pressure (usually <3rd centile expected for age) requiring one or more cardiotropic agents, and increasing ventilator requirements, necessitating an increase in mean airway pressure and FiO_2 by at least 20%. This usually becomes apparent 6 to 12 hours post surgery.[23,24] These clinical changes coincide with the physiological sequelae described above, and provide clinical validation to the effect of altering load conditions on myocardial function. One paper reported a significantly higher mortality in infants with PLCS compared to controls (33% vs. 11%).[22]

Several pre-operative risk factors for post-operative PLCS have been identified. Teixeira el al compared 29 preterm infants that underwent ligation within the first 4 weeks of postnatal life (early), versus 36 infants undergoing ligation beyond that period (late).[24] Twenty-seven percent of infants undergoing early ligation required inotropes for low mean BP compared to 5% in the late group. The

presence of NEC or pre-operative shock was also predictive of PLCS. There was a negative correlation between age at ligation and need for cardiotropic support. In a prospective trial, the same group demonstrated that infants weighing less than 1000g were more likely to have post operative LVO less than 170 mls/kg/min, lower shortening fraction, systolic BP less than the third centile, and a higher need for inotropes (30% vs. 4%).[23] Further studies have corroborated these findings. Infants less than 26 weeks gestation, and less than 750 – 1000 grams were more likely to develop PLCS.[25-27] Echocardiography has also been used to facilitate prediction of PLCS. PDA size prior to ligation has a significant negative correlation with post-operative LVO.[28] In addition, there is an inverse correlation between peak velocity across the PDA and ventilator dependence post operatively.[26] Jain et al also demonstrated that a LVO less than 200 min/kg/min at 1 hour post operatively predicted 100% of infants that subsequently developed PLCS at 6 to 12 hours. All the risk factors for PLCS illustrated above highlight the challenges met by the immature myocardium in the face of the dramatic change in loading conditions.

Intra-operative Cerebral Hemodynamic Changes

PDA ligation has been associated with poor neurodevelopmental outcome; therefore, it is important to understand the intra-operative physiological changes that may impact cerebral function. Intra-cerebral hemodynamic changes, and electrical activity during PDA ligation have been studied using several modalities including NIRS, Doppler assessment of cerebral blood flow, and amplitude-integrated electro-encephalography (aEEG). Assessment of Tissue Oxygenation Index (TOI) using NIRS has yielded conflicting results. Zaramella et al examined the effect of PDA clipping on cerebral TOI and cerebral blood flow (CBV) using a combination of NIRS and Doppler assessments at three time points: 35 minutes before ligation, and 14 and 27 minutes post PDA clipping.[29] They found a drop in TOI indicating increased tissue oxygen extraction but no change in CBV, measured by NIRS or Doppler, following clipping of the PDA. In contrast, more recent studies using NIRS during the ligation process demonstrated a sudden surge in CBV immediately post clipping, returning to pre-operative baseline within 5 to 10 minutes.[30,31] One study[31] showed a transient increase in TOI, supporting the observation of increased CBV, lasting up to 20 minutes post ligation. None of the studies demonstrated a change in heart rate or blood pressure during the monitoring period. There are no studies examining the relationship of changes in CBV and TOI to brain injury or long-term neurological outcomes.

Recent studies have demonstrated changes in cerebral electrical activity following surgical ligation. Leslie et al performed continuous amplitude integrated electroencephalography (aEEG) monitoring in a cohort of 17 preterm infants and demonstrated a fall in the lower border of the aEEG trace and decrease in the proportion of patients with aEEG continuity (from 5/17 to 0/17, p=0.04) after PDA ligation. Cerebral background activity recovered to preoperative levels by 24 hours post surgery. Interestingly, lower band width was associated with PDA diameter and gestation on univariate analysis, although the impact of anesthesia was difficult to assess. Lemmers et al performed combined aEEG and NIRS monitoring in 20 preterm infants before and after PDA ligation.[9] They demonstrated lower cerebral oxygen saturations and increased fractional oxygen extraction during the induction phase. Some of these infants had cerebral oxygen saturations as low as 35%, approximating levels that lead to functional and morphological brain damage in animal

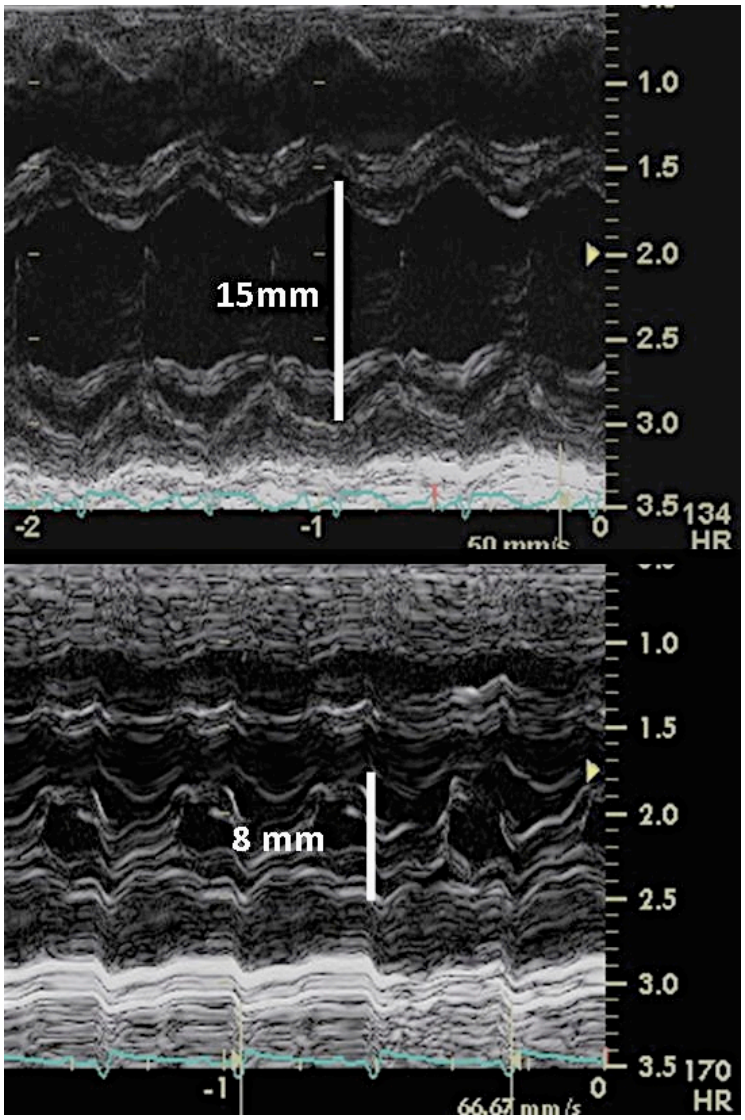

Figure 2. M-mode echocardiography images demonstrating changes in left ventricular cavity size before (Upper Panel) and after (Lower Panel).

experimental models.[32] Cerebral oxygen saturation showed a steady increase in the 24 hours post ligation, with a concurrent decrease in fractional oxygen extraction to values comparable with infants without a PDA. The changes in aEEG background activity were comparable with those seen by Leslie et al,[33] and were most pronounced at 2 hours post clipping. They did note, however, that infants with the most pronounced drop in cerebral oxygen saturations had the most significant drop in brain activity. These changes coincided with a fall in blood pressure post induction.

The reported anaesthetic technique used in the studies seems uniform. Infants usually receive opioids (fentanyl or sufentanil) and a muscle

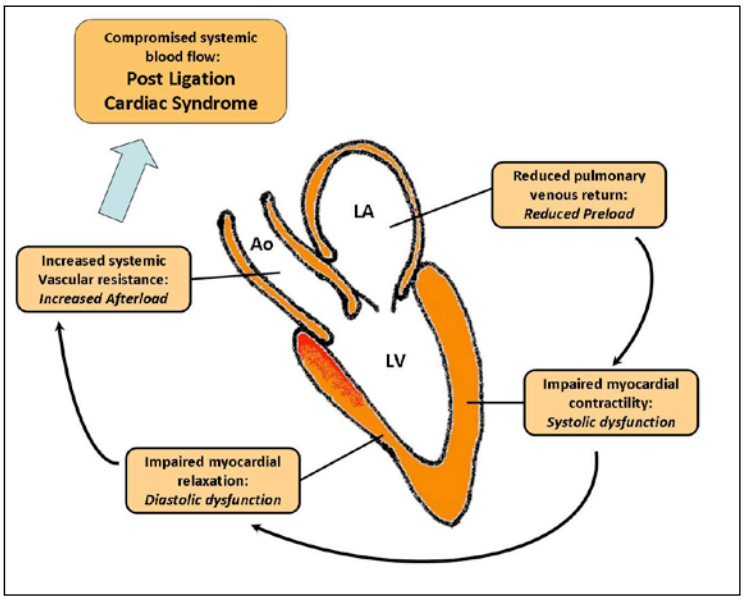

Figure 3. Schematic of cardiovascular physiologic factors contributing to the development of Post-Ligation Cardiac Syndrome.

relaxant (pancuronium) for induction, followed by an opioid infusion to maintain anaesthesia. Inhalation agents are seldom used.[34] It is possible that choice or dose of these agents influences electrical brain activity intra-operatively, although neither study was designed to answer this question. Nevertheless, both studies showed an improvement in aEEG background activity by 24 hours post ligation despite the continuous opioid use. Interestingly, Janvier et al demonstrated that ineffective anaesthesia during ligation is associated with an unstable post-operative respiratory course accompanied by hypotension.[34]

Post-operative Myocardial Adaptation

Surgical ligation of the ductus arteriosus leads to sudden and dramatic changes in cardiovascular physiology of the preterm infant. These changes include a rise in afterload due to the increase in systemic vascular resistance (SVR), and a dramatic fall in preload, due to the sudden reduction in pulmonary blood flow (Figure 3). There has been a recent interest in charactering these changes and assessing myocardial function adaptation resulting from these changes using echocardiography.

Early studies attempting to demonstrate deterioration in ventricular performance following ductal ligation showed equivocal results. Taylor et al noted a temporal relationship between impaired left ventricular performance and increased systemic vascular resistance, coinciding with changes in arterial pressure in a primate model.[35] The first human neonatal study in 1996 by Kimbal et al characterized echocardiography-derived indices of systolic performance, preload and afterload in 14 infants undergoing PDA ligation.[36] They demonstrated a rise in blood pressure and systemic vascular resistance following ligation, but failed to demonstrate any change in left ventricular performance. Further examination of the data revealed a trend towards a reduction in both LVO and shortening fraction immediately after ligation, suggesting that the study was limited by a small sample size.

More recently, Noori et al studied the effect of PDA ligation on myocardial performance.[28] Echocardiography data was obtained 2 hours prior to ligation, 2 hours and 24 hours after ligation in a group of 23 infants (gestation 26.2 ± 2.2 weeks, birth weight 845 ± 280 grams). They demonstrated a significant increase in SVR, accompanied by a significant drop in LVO, and mitral inflow velocities in the immediate post-operative period. These data support the prior suggested physiological changes that accompany PDA ligation: a reduction in preload and an increase afterload. The group also measured the myocardial performance index (MPI), a global myocardial performance indicator which incorporates both systolic and diastolic function and is less influenced by loading conditions.[37] There was deterioration in MPI following ligation, which began to normalise by 24 hours post ligation. Interestingly, there was no difference between the study's time points in the load-dependent measures of systolic function: namely shortening fraction (SF), and the velocity of circumferential fibre shortening (VCFc). This may have resulted from the small sample size, relative insensitivity of these conventional markers of systolic function or the lack of echocardiography evaluation at the time of clinical deterioration. It is worth bearing in mind that the methods used to calculate SVR rely on the following formula: (mean arterial pressure – right atrial pressure) / LVO, therefore, if LVO is significantly compromised due to left heart preload compromise, this formula may overestimate true SVR, although the net rise in diastolic arterial pressure following PDA ligation would suggest otherwise.

Neither of the two described studies assessed myocardial performance at 8 hours post ligation, the time point at which clinical hemodynamic and respiratory deterioration usually become evident in this population. In the largest prospective study to date, including 46 infants (gestation 28.5 ± 11.3, birth weight 1058 ± 272), McNamara et al characterised the effects of PDA ligation on myocardial performance before and after (one, eight, and 24 hours) PDA ligation. The significant decrease in LA: Ao ratio and left ventricular end-diastolic diameter (LVEDD) suggest a fall in left heart preload. In addition, impairment in indices LV systolic performance, namely LV shortening fraction and VCFc, was identified eight hours after surgery coinciding with the clinical deterioration. An increase in the slope of the inverse relationship between end systolic wall stress and VCFc, suggests the changes in myocardial performance were influenced by LV afterload. The overall reduction in LVO is likely to be a consequence of increased LV exposed afterload and decreased preload, although the relative contribution of each is difficult to evaluate. This study provides the best evidence to suggest that myocardial performance post PDA ligation is adversely affected by the altered loading conditions. Interestingly, infants less than 1000 grams were at greatest risk of compromise, further supporting the idea of the vulnerability of the immature preterm myocardium described above.

Pulmonary Mechanics Following PDA Ligation

The presence of prolonged left to right shunting across the PDA leads to altered pulmonary compliance. In animal model experiments, premature newborn baboons [125 d (67%) gestation], exposed to a moderate-size PDA have impaired pulmonary function and arrested alveolar development and surface area when compared with age-matched fetuses (140 d gestation).[38] Several human studies have also demonstrated decreased lung compliance in preterm infants with a PDA compared to controls, but no change in airway resistance. Infants treated with indomethacin also exhibit improved lung compliance following successful medical PDA closure.[39-41] More dramatic changes in lung compliance can be observed in preterm infants undergoing PDA

ligation. In a group of 16 premature infants, dynamic lung compliance improved significantly, coupled by increases in tidal volume and minute ventilation. It should also be noted that baseline lung compliance prior to PDA ligation was lower than expected values normal for matched controls.[42] It is therefore prudent to consider these changes following ligation, as maintaining similar ventilator settings in the post-operative period may lead to lung over-distension. This may further compromise vena caval and pulmonary venous flow leading to impairment in ventricular filling and contributing to lower cardiac output.

Short-term Surgical Complications

Several studies have examined the immediate and short-term sequelae of ligation. Surgery-related complications include: intra-operative bleeding, pneumothorax, vocal cord paralysis, chylothorax, and phrenic nerve injury. The collective incidence of these complications is usually low.[16] The collaborative trial by Gersony et al showed that babies randomized to surgery as primary treatment had a higher incidence of pneumothoraces and retinopathy of prematurity. There was no difference in BPD, IVH, bleeding, sepsis, elevated creatinine, duration of ventilation or duration of stay.[43] Nevertheless, PDA ligation is still considered a relatively uncomplicated procedure; as in a large series of 306 ligations, Mikhial et al reported a 2% incidence of intra-operative bleeding, less than 5% incidence of air leaks and no surgery-related deaths.[44] It is also feasible to carry out the procedure in a neonatal intensive care setting which has the advantage of avoiding transport of sick neonates to a tertiary centre and a delay in ligation. In a series of 115 infants operated on in intensive care, there was no surgical morbidity.[45]

Long-term Complications

The data from the TIPP trial was re-examined to determine whether surgical closure of a PDA is a risk factor for BPD, severe ROP, and neurosensory impairment at 18 months. The clinical course of 426 ELBW infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only with successful PDA closure was reviewed.[46] Of the 95 infants who survived to 18 months after PDA ligation, 50 (53%) had neurosensory impairment, compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy (adjusted odds ratio, 1.98; 95% CI, 1.18-3.30; p = 0.009). Both BPD (adjusted odds ratio, 1.81; 95% CI, 1.09-3.03; p = 0.02) and severe ROP (adjusted odds ratio, 2.20; 95% CI, 1.19-4.07; p = 0.012) were also more common after surgical PDA closure. Death appeared to be less common in infants who underwent surgical PDA ligation (14 vs. 22%, p = 0.09). They concluded that surgical PDA ligation may be associated with increased risks of BPD, severe ROP, and neurosensory impairment in ELBW infants and offered several explanations for this association. First, brain injury secondary to prematurity may have preceded the surgery in some patients; second, infants who underwent surgery may have been sicker with a higher degree of ductal illness severity; third, perioperative or intraoperative events such as hypothermia, cardiorespiratory instability, or exposure to anesthetic drugs may directly contribute to poor outcome. Anesthetic drugs that are routinely used during neonatal surgeries have been shown to cause apoptotic neurodegeneration in the developing rat brain.[47] The latter may be better understood by investigating the impact of anesthesia on neonatal outcomes after other surgical procedures in premature infants.

A major omission from this analysis was the failure to consider duration of exposure to a hemodynamically significant PDA as a potential contributor, particularly in those patients with end-organ blood flow compromise. It is possible that surgical ligation is a surrogate marker for illness severity. It is also possible that the post-operative hemodynamic instability outlined above, may also contribute to the poor neurodevelopmental outcome, but this has not been studied to date.

In a recent study of 446 infants less than 28 weeks gestation, logistic regression analysis was used to examine the effects of several PDA-related variables (presence of a symptomatic PDA, the number of indomethacin doses used, the ductus response to indomethacin, and the use of surgical ligation) on the incidence of ROP, NEC, BPD, death, and neurodevelopmental impairment.[48] The infants' immature gestation accounts for most of the predictive effects that the presence of a patent ductus arteriosus and its treatment had on neonatal morbidity. Use of surgical ligation, however, was significantly associated with the development of chronic lung disease and was independent of immature gestation, other patent ductus arteriosus-related variables, or other perinatal and neonatal risk factors known to be associated with chronic lung disease. These findings add to the growing uncertainty about the benefits and risks of surgical ligation during the neonatal period.

Refining Decision-Making

The optimal timing of surgical ligation is still under debate. The competing risks of PDA related morbidity and surgical complications make this decision difficult in many cases. The staging system, based on clinical and echocardiography criteria, proposed by McNamara and Sehgal has streamlined the decision-making process in Toronto with enhanced patient outcomes.[49] This staging system takes into account clinical characteristics including ventilation, systemic perfusion, along with radiological evidence of pulmonary edema and grades these symptoms in a hierarchical fashion. Similarly, echocardiography criteria to determine myocardial function in addition to markers of pulmonary over circulation and systemic hypoperfusion are also used.[3] This composite approach helps delineate the likely contribution of the ductus arteriosus to the overall clinical state rather than consideration of ductal size alone. In some cases, independent of ductal size, the decision is not to intervene on the basis that the clinical and echocardiography evidence suggests a low volume transductal shunt. Recently Jhaveri et al described a reduction in the incidence of NEC following the introduction of a preoperative stratification system similar to the one described by McNamara.[50] These data support the need for, and potential benefits of, a more comprehensive clinical and echocardiography assessment of infants undergoing PDA ligation. Both approaches recognize that the hemodynamically significant PDA is not a dichotomous variable, but is a physiologic continuum from biological normality to a pathological disease state with clinical instability and varying effects on bodily organs. We believe surgical ligation should still remain as a treatment option for some infants with a hemodynamically significant PDA, but all patients need comprehensive clinical and echocardiography evaluation to determine the nature of the shunt volume and physiologic consequences. It is prudent to ensure adequate anaesthesia intra-operatively with adequate volume support in anticipation of left-heart preload compromise once the ductus arteriosus is ligated. Targeted neonatal echocardiography (TnECHO) should be used to assess post-operative myocardial function. Vasopressors e,g, dopamine and epinephrine should be avoided in the face of increased afterload, and consideration should be given to agents that reduce afterload, e.g. dobutamine, milrinone and improve contractility. Volume replacement should be considered in view of the reduced preload. After the decision to ligate the ductus is made, the approach in our center is as follows: a

cortisol response stress test is performed to assess the infant's stress response and potentially guide post-operative hemodynamic instability. We perform echocardiography assessment one hour post-operatively to assess left ventricular output. Based on the cohort study mentioned above,[51] infants with a LVO less than 200 mls/kg/min are at a high-risk of developing PLCS, and therefore, receive milrinone in an attempt to reduce afterload and improve diastolic dysfunction. A bolus of normal saline is also given to counteract the effect of reduced preload and prevent any fall in diastolic pressure. Further volume replacement is given if there is evidence of volume depletion, especially if there is fluid loss from intra-thoracic drains. Serial blood pressure monitoring is performed to ensure that systolic and diastolic pressures do not fall below the third centiles for any given gestation. Intractable blood pressures should be managed with volume, inotropes and steroids replacement, if the preoperative stimulation test yielded suboptimal results. Weaning the mean airway pressure should also be considered following ligation as the compliance of the lungs invariably improves.

Conclusion

Infants undergoing PDA ligation face several challenges that may contribute to worst neurodevelopmental outcome. The surgical act of ligation of the ductus arteriosus per se is unlikely to contribute to brain injury, but the processes occurring around the event may have more of an impact. Chronic left to right shunting prior to ligation, intra-operative compromise to cerebral oxygen saturation, and post-operative hemodynamic instability may all contribute to brain injury. Further research into characterisation of myocardial function before and after surgery is needed, along with assessment of therapies aiming to improve preload and afterload compromise. The impact of such therapies on neurodevelopment outcome should also be examined.

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A Model for Screening School Children for Congenital Heart Disease in Developing Countries

By Robert Detrano, MD; Da Yi Hu, MD

Introduction

Early detection of congenital heart disease is essential to preventing degeneration of the pulmonary vasculature, chronic damage to the cardiac chambers, and/or early death (see Figure 1). In developed nations, infants are examined at birth, as well as periodically throughout early childhood. At the first sign of pathologic murmur or other signs or symptoms, ultrasound exams are performed to either diagnose or exclude cardiac birth defects. However, in many developing countries, medical personnel are insufficiently aware or trained to perform routine stethoscopic examinations. We of the China California Heart Watch (www.chinacal.org) suggest here a model for mass stethoscope screening of children for congenital heart disease that could be applied throughout the developing world.

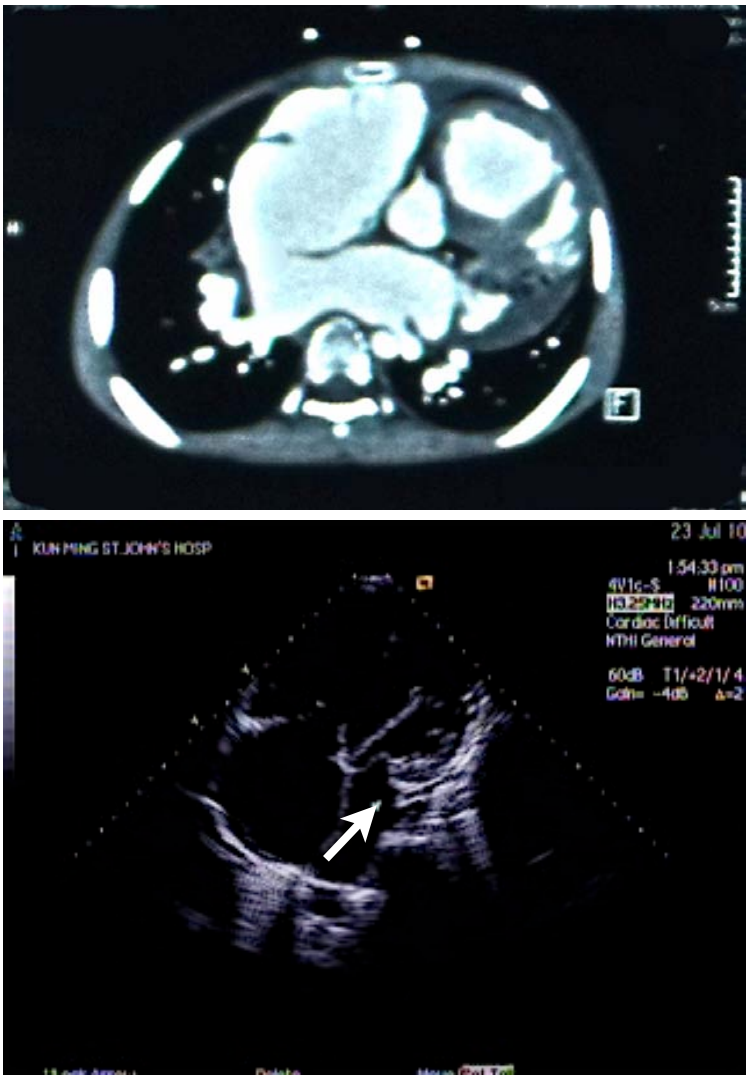

Figure 1. CT and echo frames of a 16 yr. old boy's heart. Arrow shows stenotic mitral valve. There is also an ASD. Right atrium and ventricle are severely dilated due to long-standing undiagnosed and untreated heart disease.

Background

In rural Yunnan Province, China, primary caregivers are not yet sufficiently educated to screen all newborns and young children regularly. Primary caregivers in rural Yunnan are typically village doctors, who undergo a few months to two years of training after graduation from high school. Furthermore, most of their training focuses on infectious diseases, which are still a major source of illness and disability.

In 2005, Jiang et al[1] reported the results of a survey of classroom children in rural Yunnan province. In a single day, the team of cardiologists working with Dr. Jiang trained local village doctors to recognize heart murmurs. These village doctors then stethoscope-screened 48,638 children between the ages of 3 and 18. Children with heart murmurs underwent full examinations by cardiologists, including cardiac ultrasound. Using this method, Dr. Jiang found a prevalence of congenital heart disease ranging from 2.75 to 17 per thousand children in various counties, which is similar to that found in developed nations. What is most telling is that the majority of children diagnosed did not previously know that they had heart disease. Equally interesting, the team reported that most screening personnel (in large part village doctors) were unaware of the proper use of a stethoscope before the training. In short, using screeners who were trained in one day to recognize heart murmurs, Dr. Jiang's team was able to detect the same prevalence of pediatric heart disease as that reported in developed nations where pediatric screeners undergo extensive practical training during medical school, internship and pediatric residency.

Methods

After discussing the methods and results of her study with us, Dr. Jiang inspired us to begin a similar screening program in Yunnan province using both Chinese and foreign undergraduate and medical students as screeners. Our training and screening procedure is as follows:

1. A group of between three and 12 undergraduate and medical student volunteers undergo one half-day of training, divided into two parts: proper use of a simple diaphragm stethoscope and recognition of heart murmurs using electronically recorded murmurs from children and adults. Emphasis is placed on sensitivity (detecting any murmur or abnormally split second sound), rather than on specificity (distinguishing physiologic from pathologic murmurs). Students are tested at the end of the training with ten recordings, three of which are normal. If a student incorrectly reports an abnormality as normal, he/she must repeat the training.
2. After training, students are brought to a local hospital, where they must auscultate the hearts of three or four pediatric or adult patients with heart disease and abnormal auscultatory findings.
3. Students travel with one to three cardiologists to impoverished rural towns where they live and work for 10 to 25 days.
4. Each day, a team of students under the supervision of a cardiologist (one cardiologist to four students) screens classroom children for several hours. Two screeners work in the front of each classroom as the children march up, lift their upper garments and undergo auscultation at four auscultation points.
5. Any child with a heart murmur is referred to a supervising cardiologist. If the cardiologist deems the murmur to be pathologic, he/she with the help of students and nurses perform full exams, including history, physical exam, pulse oximetry, and cardiac ultrasound.
6. Families are notified and referrals are made, if appropriate.

Figure 2. Students stethoscope screen classroom children.

Figure 3. School children wait to be screened.

Figure 4. US medical student takes history from family of child with heart disease

When the family can produce documentation of poverty (income less than $1,500 per year), an offer of financial assistance is arranged.

Results

Since starting the program in March 2009, we have screened about 17,000 children between the ages of four and 16 and detected 78 cases of congenital heart disease (4.6 per thousand). Approximately half of these cases were not previously diagnosed, or the children's families only vaguely remembered being told that the child had congenital heart disease. Only about one fifth had previously undergone corrective procedures. We referred about 25 of these children for corrective procedures, and have reported on some of the results elsewhere.[2] In most of these referred cases, we assisted families with financial support for surgical and non-surgical procedures. Three cases of complex disease were deemed inoperable, in part due to late diagnosis (two double outlet right ventricles and one large VSD with pulmonary hypertension).

Discussion

Based on Dr. Jiang's experience and our own, effective screening of congenital heart disease can be carried out in a developing country using personnel with little prior training in the use of a stethoscope. We have some concerns, but the fact that both Dr. Jiang's program and our own achieved a detection rate close to that in developed nations suggests that sufficient sensitivity is possible in a clinical environment where many children with heart disease would not have been diagnosed at all, had we not intervened.

One concern is related to the detection of atrial septal defects (ASD), that are often missed, even in developed nations. The fixed split of the second sound and the low intensity pulmonic flow murmur of an ASD are difficult to detect even for trained pediatricians. Coarctation of the aorta is another less common defect which can be missed in classroom screenings. However, until the primary caregivers are regularly examining the cardiovascular systems of all children, this method has much to offer to impoverished communities in developing countries.

Another potential drawback is the lack of family and/or community resources needed to treat certain cases of heart disease. This problem is gradually being resolved in rural China with the enactment of new health insurance laws and the activities of large charitable foundations like the Red Cross and the Hua Xia Foundation. However, in some developing nations, awareness of the presence of heart disease is less relevant, due to the lack of treatment funds and resources. We believe that it is much better to know that a problem exists and must be addressed, rather than to ignore it. Knowledge is the first step to a solution. Therefore, we encourage government and non-government groups in all developing nations to consider this approach to screening.

Conclusion

Training local medical, para-medical and even non-medical personnel in classroom screening of children for congenital heart disease is an option that can detect thousands of cases and save thousands of lives. National health departments and the World Health Organization should consider this approach in all developing nations where primary caregivers are not full trained to carefully examine well children.

The international community has appropriately responded with volunteer assistance and funds to address the problem of treating known cases of pediatric heart disease in developing nations. The China California Heart Watch (www.chinacal.org) suggests that similar energy be expended in addressing the problem of early detection using massive classroom screening programs. Thousands of children's lives can be prolonged and much suffering alleviated by applying this simple and inexpensive approach.

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A Tale of Dedication to Humanity: an Amazing Story from Sudan

By Sulafa KM Ali, MD, FRCPCH, FACC

Bahaa is 10 years old, the youngest child of a large Sudanese family with a poor socio-economic background; the father works as a school-guard. "I am very well, I am good at football, the only thing is that when I am about to score a goal I feel dizzy and fall down!" said Bahaa.

The family physician referred him to the cardiologist who found that Bahaa's pulse was completely irregular. An ECG was obtained, and it showed runs of ventricular tachycardia (VT). A 24-hour Holter revealed that VT was present in 90% of his recording (Figure 1). Bahaa was put on amiodarone with a good response, but it was obvious that he needed electrophysiological tests and VT ablation, which were not available in Sudan.

It was a dilemma: where to send Bahaa, how to pay for the cost and how to ensure that the results are good. These were questions that were almost unanswerable. Requests to help Bahaa were made to the neighboring countries. The first response was: sorry we don't accept foreign patients! The second response from Amman/Jordan was very positive: Dr. Muneer Zaqqa, an electrophysiologist recommended Professor Della Bella, from Milan, Italy. "He is the best one to ablate VT!" commented Dr. Muneer. We e-mailed Professor Della Bella, and an immediate response was obtained; after seeing the Holter, the child was accepted for VT ablation. We wanted to know the cost of the procedure in order to look for donations. However Prof. Della Bella and his assistant Dr.

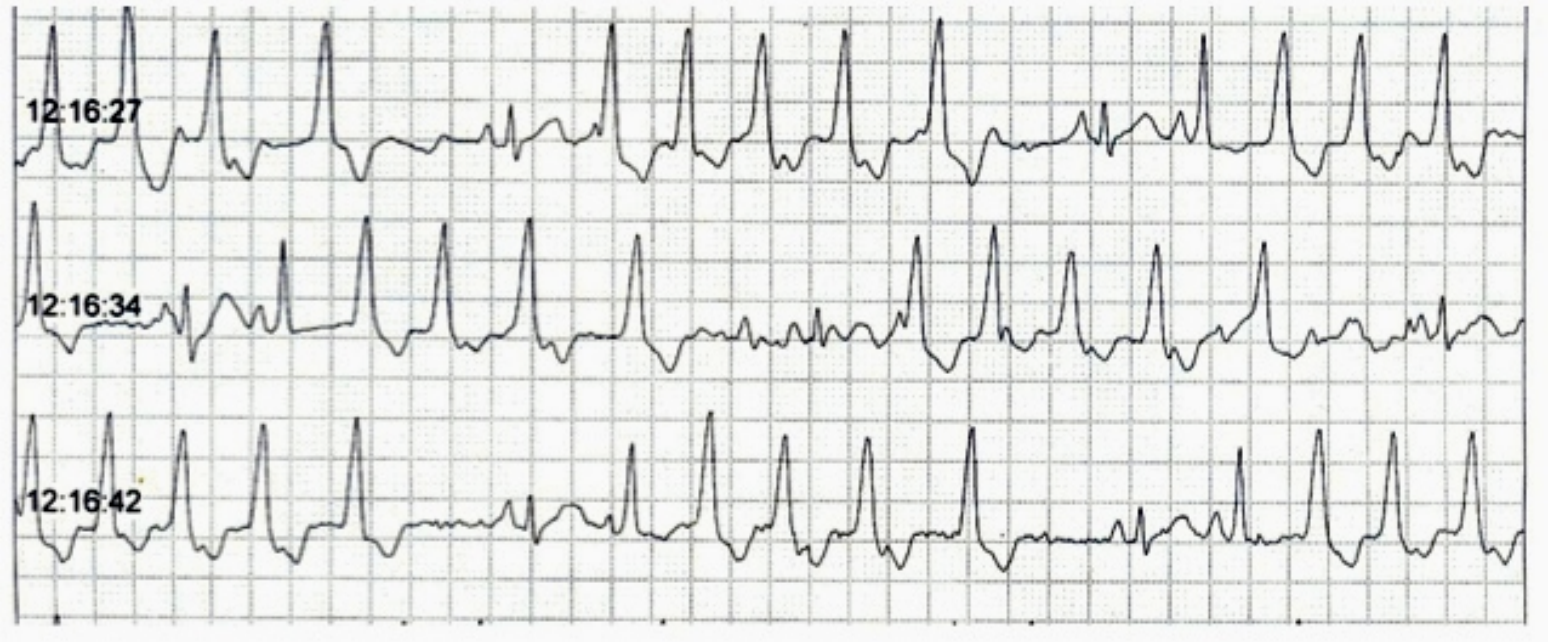


Figure 1. ECG (Holter) showing runs of VT.

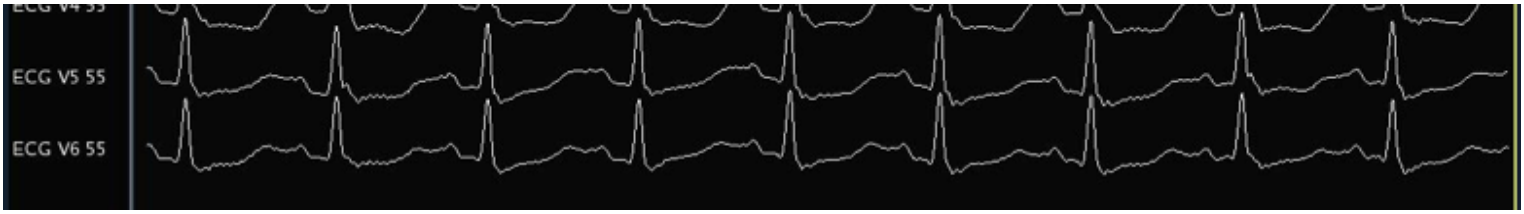
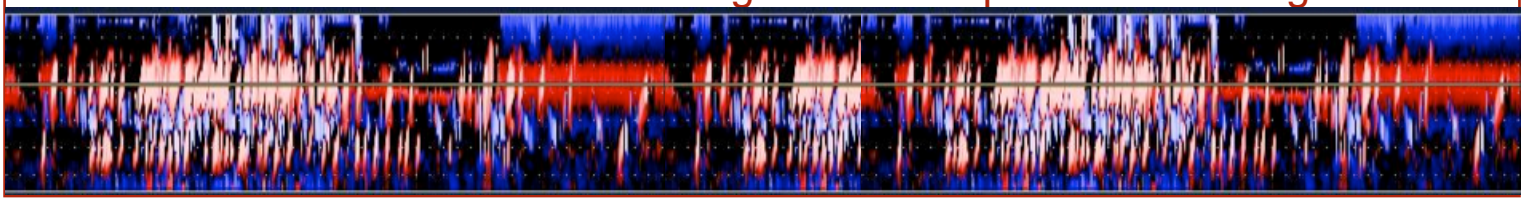


Figure 2. ECG after VT ablation showing sinus rhythm.



The International Children's Heart Foundation (ICHF) is in Urgent Need of an Intensivist for the following trips:

- UAYAQUIL, ECUADOR: Sep. 17- Oct. 6
- SANTIAGO, DOMINICAN REPUBLIC: Sep. 24 - Oct. 8
- QUITO, ECUADOR: Oct. 8 -15
- TEGUCIGALPA, HONDURAS: Oct. 8 -22

ICHF plans to have the 2012 schedule posted by early September. Please email your date and trip preferences for January, February and March of next year to Frank Molloy - frank.molloy@babyheart.org

See the 2011 Mission Trip Schedule and more about ICHF at: http://www.babyheart.org/about-ichf/medical-mission-trips/

Figure 3. Bahaa with Professor Della Bella and Dr. Sora.

Sora Nicoleta decided to help the child, and asked us to wait until they obtain funding from their local charities (Region Lombardia). Six months later, Dr. Sora emailed us saying that the fund was approved, and that Bahaa could come over.

However, it was not easy for Bahaa and his parents to reach Milan. A time-consuming visa process, and the collection of $3000 US had to be completed first. We started to collect money for our boy to travel; however, the Qatar Airways representative in Khartoum, Mr. Nabeel Subhi, a gentleman who appreciates humanitarian needs, decided to donate free tickets to this family.

At last, 8 months after his first visit, Bahaa reached Milan (Foundation Centro San Raffaele del Monte Tabor), and the boy was accommodated by Dr. Sora at her own home. Although amiodarone was discontinued, for the first two weeks Baha had no evidence of VT. "Even after I let him exercise vigorously (bicycle riding, skateboard and kung-fu with the pillows!' said Dr. Sora. But 5 weeks later, the rhythm the ECG started to show trigeminy. Finally, on the 26th of June, Bahaa had ablation of right ventricle outflow tract VT with a very good result.

Dr. Sora admitted that they were impressed by the courage with which Bahaa went through everything. "I never saw his tears except on two occasions: the first time we put him on the operation table (he was alone; his parents were waiting in the ward, and he let escape two silent tears, no crying...) and at the airport," said Dr.Sora. Bahaa returned home in sinus rhythm (Figure 2) with a last hug from Prof. Della Bella (Figure 3).

Words are not enough to say thank you. Thank you to Dr. Sora and Professor Della Bella, and special thanks to Dr. Muneer Zaqqa from Jordan, and Mr. Nabeel Subhi of Qatar Airways in Khartoum. This is an example to be followed in the management of the needy children. As human beings, we are, and must be committed to sharing resources.

CCT

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SCAI Monthly Column: Inaugural M3 International Cardiovascular Conference to Focus on Structural and Valvular Therapies

By Eric Grammer

One of the unique attributes of SCAI's M3 2011 International Cardiovascular Conference is that it brings together the core strengths of two meetings, including the University of Miami's Masters in the Repair of Structural Heart Disease (MIRS) program's focus on structural and valvular heart disease therapies.

As an international conference with faculty from around the globe, attendees will be exposed to data from techniques used in other countries that are just now being evaluated in the United States.

"We'll show some first-in-man, pre-FDA data," says M3 2011 Program Co-director Eduardo de Marchena, MD, FSCAI. "Not only what's available now, but also new and emerging innovations that will give us even more tools to care for patients."

Structural and valvular highlights at M3 2011 will include:

- New and upcoming technologies in the management of valvular heart disease;
- The latest available treatment options for high risk patients with very complex coronary artery disease;
- Strategies for managing patients with 3 vessel coronary disease and left main disease; and
- Much, much more.

For more information, and to register, please visit www.scai.org/M3.

SCAI Fall Fellows Course in CHD/SHD Offers FREE Tuition, Travel and Hotel Stay to Pediatric Fellows-in-Training

Applications are now being accepted for SCAI 2011 Fall Fellows Course in Congenital and Structural Heart Disease taking place December 4-8 at the Mirage Hotel in Las Vegas. SCAI offers complimentary tuition for the course, a complimentary hotel stay (up to four nights), and covers airfare up to $500 to successful applicants. Applicants must be fourth-year interventional cardiology fellows-in-training and third or fourth-year pediatric cardiology fellows-in-training.

Led by Program Director Ziyad M. Hijazi, MD, MPH, FSCAI and a world-class faculty, the course is a can't-miss for any FIT focusing on pediatric, congenital and/or structural interventions. In addition to close access to these leaders in the field, attendees will also be treated to simulations workshops as well as career-focused programs preparing them for graduation from their training programs.

The application deadline is September 15th. For more information, or to apply to attend, please visit www.scai.org/Fellows.

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Medical News, Products and Information

Nationwide Children's Hospital Study Identifies Second Gene Associated with Specific Heart Defects

A gene known to be important in cardiac development has been newly associated with congenital heart malformations that result in obstruction of the left ventricular outflow tract. These are the findings from a study conducted by Nationwide Children's Hospital and appearing in the *Journal Birth Defects Research* Part A.

Left ventricular outflow tract (LVOT) malformations, including aortic valve stenosis, coarctation of the aorta, Hypoplastic Left Heart Syndrome, Shone complex and interrupted aortic arch type A, are responsible for a major portion of childhood death from congenital heart malformations. Yet it is often unclear how these defects develop.

"While 10-15% of people with an LVOT defect have a chromosomal defect such as Turner Syndrome, the causes for most LVOT defects remain unknown," said one of the study's authors Kim McBride, MD, MS, principal investigator in the Center for Molecular and Human Genetics at The Research Institute at Nationwide Children's Hospital.

Recent studies suggest a genetic component to these heart malformations. Aortic valve stenosis, coarctation of the aorta, Hypoplastic Left Heart Syndrome and bicuspid aortic valve have been reported to recur within single families. Nationwide Children's faculty has also identified several chromosomal regions that show evidence of being linked to LVOT malformations.

"It is estimated that there are more than 500 genes that may be important in heart development," said Dr. McBride, also a faculty member at The Ohio State University College of Medicine. "Changes in any of these genes may impact how a child's heart forms."

To identify specific genes, investigators examined the DNA of children treated for LVOT malformations and their parents, enrolled by Dr. McBride at Nationwide Children's Hospital or by Dr. John Belmont and his team in the Department of Molecular and Human Genetics, Baylor College of Medicine at Texas Children's Hospital. Research indicates that LVOT defects share a common developmental mechanism, thus they focused on genes from a signaling pathway shown to be important in cardiac development.

Findings showed an association between the gene ERBB4 and LVOT defects. ERBB4 encodes a protein that serves as an "on" or "off" switch in many cellular functions during heart development. The association with LVOT defects was noted not only for the whole group of defects, but also individually for aortic valve stenosis, coarctation of the aorta and Hypoplastic Left Heart Syndrome.

"The precise defect in this very large gene is not yet known," said Dr. McBride. "ERBB4 now joins a previously identified gene, NOTCH1, as a susceptibility gene for LVOT defects. Replication of these results in other subjects will be required to better determine its role in the development of the heart malformations."

AHA Statement Updates Heart Catheterization Guidelines

Doctors should consider using catheterization as a treatment tool in addition to its established role in diagnosing children with heart defects, according to a new American Heart Association scientific statement.

The statement, published in *Circulation. 2011 Jun 7;123(22):2607-52. Epub 2011 May 2 - Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association* is a major overhaul of the association's last statement released in 1998.

"What we can offer patients now, versus just 10 or 15 years ago, is remarkably different," said Timothy F. Feltes, MD, lead author of the statement and Chief of Pediatric Cardiology and Professor of Pediatrics at The Ohio State University. "There have been tremendous advances in the procedures, devices, experience and the expertise of the physicians who perform the procedures. As physicians caring for patients with congenital heart disease, we have to look at heart catheterizations a little differently than we have in the past."

The statement provides an extensive inventory of diagnostic and interventional techniques that are now considered as options for pediatric patients, noting that catherization procedures carry a degree of risk for patients.

Some of the 22 new therapeutic options for congenital heart disease include catheter-based techniques to: improve blood flow through the heart, repair inborn heart defects such as holes in the heart, repair or replace faulty valves, remove arterial blockages, and many other conditions, such as malformed heart chambers.

In addition, the statement covers several hybrid procedures that use traditional surgical techniques in combination with catherization for treating conditions such as Hypoplastic Left Heart Syndrome (severe under development of the left side of the heart), stent implantation (to widen arteries and keep them open) and others.

The take-home message of this statement, Feltes said, is that "there are numerous conditions that are best served by interventional catheterization procedures."

The statement is key to cardiologists who treat pediatric defects, because there are few other sources of such information. "By virtue of the relatively small number of children and adolescents with congenital heart disease, it is difficult to design clinical trials. Ideally, you need thousands of patients to compare one treatment versus another. Only one child in 100 is born with heart disease, so it is very unlikely that one center will have more than one patient to do a side-by-side comparison," Feltes said.

New Cardiovascular Genetic Testing Guidelines

An international panel of experts from The Heart Rhythm Society and the European Heart Rhythm Association issued new guideline recommendations for all health care professionals about cardiovascular genetic testing at the Heart Rhythm Society's 32nd Annual Scientific Sessions.

Silvia G. Priori, MD, PhD, a leader in the field of inherited cardiovascular diseases and Director of the Cardiovascular Genetics Program at NYU Langone Medical Center, was co-lead author of the *HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies*. The complete guidelines were published in the August 2011 issue of the *HeartRhythm Journa*l and *Europace*.

The new overarching recommendations for cardiac genetic testing include:

(1) Genetic counseling is recommended for all patients and relatives with the familial heart diseases detailed in the document and should include discussion of the risks, benefits and options available for clinical testing and/or genetic testing.

(2) Treatment decisions should not rely solely on his/her genetic test result, but should be based on an individuals' comprehensive clinical evaluation.

(3) It can be useful for pre-genetic test counseling, genetic testing, and the interpretation of genetic test results to be performed in centers experienced in the genetic evaluation and family-based management of the heritable arrhythmia syndromes and cardiomyopathies described in the document.

The goal of the authors was to evaluate the role of genetic testing and ensure that all physicians have the latest knowledge about the potentially life-saving screening for patients with cardiac conditions that may

predispose them to sudden cardiac death and other genetic heart diseases.

The recommendations focus on genetic testing for 13 inherited cardiac conditions including: Long QT Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia, Brugada Syndrome, Progressive Cardiac Conduction Disease, Short QT Syndrome, Atrial Fibrillation, Hypertrophic Cardiomyopathy, Arrhythmogenic Cardiomyopathy/Arrhythmogenic Right Ventricular Cardiomyopathy, Dilated Cardiomyopathy, Left Ventricular Noncompaction and Restrictive Cardiomyopathy. In addition, the statement includes guidance on the use of genetic testing for out-of-hospital cardiac arrest survivors and post-mortem testing in sudden death cases.

"Genetic testing cannot be viewed as a one-size fits all solution, but should be considered for each disease state," said Dr. Priori, who is also director of Molecular Cardiology and Electrophysiology Laboratories at Fondazione Salvatore Maugeri University in Pavia, Italy. "The recommendations outlined in this document can and should be used as guidance on how each potential disease is evaluated with respect to genetic testing, keeping in mind that each patient is different."

Simple Surgical Procedure May Help Prevent Heart Damage in Children

Removing enlarged tonsils and adenoids may help prevent high blood pressure and heart damage in children who suffer from Obstructive Sleep Apnea (OSA), according to a study conducted at Cincinnati Children's Hospital Medical Center. In some children with OSA, adenotonsillectomy can result in significantly lower blood pressure within 24 months of the procedure.

The results were presented at the May ATS 2011 International Conference in Denver.

Children with enlarged tonsils and adenoids are particularly prone to developing OSA, said study lead author Lisa Burns, MD, (Pulmonary Fellow at Cincinnati Children's Hospital Medical Center). And, in children and adults, OSA has been linked with elevations in both daytime and nighttime blood pressure. OSA can also interfere with the normal "dip" in blood pressure levels that occur during sleep. Persistent elevations in blood pressure can result in organ damage, including heart damage.

"Our study emphasizes the importance of treating severe sleep apnea in order to prevent persistent elevation in blood pressure and end-organ damage," Dr. Burns said. "We also show that during sleep, diastolic blood pressure, the measurement of your blood pressure when the heart is relaxing, is more sensitive to the effects of sleep apnea than other measures of blood pressure."

Dr. Burns and colleagues evaluated 115 children between the ages of 7 and 13 years, including 28 patients with mild OSA, 27 with severe OSA and 60 healthy controls. The subjects were evaluated for level of OSA using polysomnography, a diagnostic test used to measure breathing during periods of sleep. All OSA subjects had enlarged adenoids and tonsils and underwent adenotonsillectomy. Blood pressure, rest and activity levels, and heart size were measured at the beginning of the study and during follow-up at 12 to 24 months.

At follow-up, researchers found blood pressure levels during sleep decreased following adenotonsillectomy when compared with measurements at baseline. The procedure also restored the normal nighttime "dip" in blood pressure relative to daytime blood pressure, Dr. Burns said.

In addition, in a subset of children with moderate to severe sleep apnea, there was a decrease in heart size after adenotonsillectomy.

Dr. Burns said the results are similar to those obtained from studies of adults with OSA.

"We expected to see changes based on what we know about adults with sleep apnea and its effect on blood pressure," she said. "We know that children with sleep apnea tend to have higher blood pressures than children without sleep apnea, even if these elevations still fall within a normal range. However this is the first study to evaluate how treatment of sleep apnea impacts blood pressure and heart size in a pediatric population who are free from other diseases, which may also contribute to elevations in blood pressure.

Treating OSA in childhood is especially critical, Dr. Burns noted.

"Children who have elevated blood pressure throughout childhood will often go on to develop high blood pressure in adulthood," she said. "Adults with high blood pressure are at risk for other cardiovascular diseases, such as heart attacks, stroke, and heart failure. By identifying and treating elevations in blood pressure at an earlier age through treatment of OSA, we hope to prevent development of cardiovascular disease in childhood and later in life."

Future studies should investigate the mechanisms leading to blood pressure changes with sleep apnea, she added.

Please note that numbers presented here may differ slightly from those in the abstract. Many of these investigations are ongoing; the above information represents the most up-to-date data available at press time.

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