Sex-Specific Pediatric Percentiles for Ventricular Size and Mass as Reference Values for Cardiac MRI: Assessment by Steady-State Free-Precession and Phase-Contrast MRI Flow

Summary: The present study examined a healthy pediatric group large enough to serve as a reference for volumetric cardiac magnetic resonance imaging (MRI). Age- and sex-specific percentiles for right and left ventricular volumes and mass of healthy children and adolescents from 8 to 20 years of age were established to serve as reference values in the evaluation of acquired and congenital heart disease. Significant sex differences were noted when indexing volumes to body surface area or height. In contrast, indexing ventricular volumes (but not mass) to body weight largely eliminated the sex differences and may therefore be attractive for daily use in pediatric cardiology. An individual patient’s progression of ventricular size in relation to these percentile curves may inform the timing of, or the response to, medical or surgical treatment. This potentially will facilitate a more accurate diagnosis of ventricular dilatation and ventricular hypertrophy by cardiac MRI in this age group, with potential impact on management decisions.

Conclusions: Percentiles for ventricular volumes and mass in healthy children have been established to serve as reference values in pediatric heart disease. Significant sex differences were noted when indexing volumes to body surface area or height. Unisex centiles related to weight may be considered for chamber volumes albeit not for mass.

Editor's Comment: With increasing access and utilization of advanced cardiac MR and computed tomography imaging in pediatric care, in general, and, more specifically, in congenital heart disease, knowledge about the development of ventricular volumes and mass becomes increasingly important. This paper provides an initial impression of sex-specific developments of these measurements in children between 8 and 15 years of age and 16 to 20 years of age. While definite normative values need to be established in larger populations, these data could be used as an additional measure to assess severity of congenital heart disease, as well as to assess success of therapy, and may have prognostic implications.1

Multimodality Noninvasive Imaging for Assessment of Congenital Heart Disease

Summary: Major advances in the field of pediatric cardiology and cardiac surgery over the last several decades have led to a dramatic improvement in survival rates for most forms of congenital heart disease (CHD). For example, hypoplastic left heart syndrome (HLHS), a previously lethal defect, now has early survival rates of up to 90% at major centers. These improved outcomes have produced a growing population of survivors with complex CHD who are now reaching adulthood. During this period, improvements in surgical and medical treatments have been accompanied by developments in diagnostic modalities. Echocardiography has replaced catheterization as the primary diagnostic modality, and it is now uncommon for newborn infants to undergo catheterization for purely diagnostic purposes. Although echocardiography remains the bedrock of noninvasive cardiac imaging, the array of diagnostic modalities and techniques available continues to grow, and this has spawned the specialty of “noninvasive cardiac imaging” and the need for the “cardiac imager” to be adept in all the different modalities.2

Conclusions: Simultaneous advances in several noninvasive imaging techniques have significantly affected the care of children and adults with CHD. Despite the emergence of other imaging modalities, echocardiography remains the first-line technique in most cases. To choose the best techniques for an individual patient, imagers today must have detailed knowledge of the various modalities available. This has major implications for the training of future noninvasive cardiologists.

Editor’s Comment: There is growing awareness that single modality approaches are often insufficient to provide a complete understanding of cardiovascular pathophysiology, refine diagnosis, and, more importantly, to guide management. No disease entity exemplifies this better than CHD. Because of the remarkable successes in pediatric cardiology and cardiac surgery, there is a growing population of patients with CHD reaching adulthood. The complex interplay between anatomy and function of the congenital defect itself is often compounded by diseases of adulthood, which pose great diagnostic and management challenges. This review provides a comprehensive and authoritative discussion of the strengths and weaknesses of each modality as it relates to CHD, with in-depth insights into specific clinical conditions, while also providing recommendations on how to incorporate multimodality imaging in diagnosis and management.2

Vasoreactive Response to Maternal Hyperoxegenation in the Fetus With Hypoplastic Left Heart Syndrome

Summary: Infants with HLHS and a restrictive or intact atrial septum have a particularly poor prognosis. Obstruction to left atrial egress leads to marked changes in the pulmonary vasculature, which
may persist despite successful opening of the atrial septum after birth. A mechanism for evaluating the prenatal status of the pulmonary vasculature in the fetus with HLHS would be of great value, as it could identify the fetus that could benefit from either prenatal intervention or immediate, urgent postnatal care. In this novel, prospective study, the authors sought to investigate the pulmonary vasculature in the fetus with HLHS by assessing for changes in the Doppler-derived pulsatility index, a surrogate measure of vascular impedance, within the branch pulmonary arteries in response to maternal hyperoxygenation (MH). In the authors’ HLHS cohort, maternal hyperoxygenation led to a significant decrease in the pulsatility index within the pulmonary artery (PA) in fetuses with an open atrial septum (P < 0.001); however, there was no significant change in the pulsatility index at any of the PA sites in fetuses that required immediate intervention on the atrial septum at birth. Indeed, MH testing predicted the need for immediate intervention on the interatrial septum at birth (sensitivity, 100%; specificity, 94%; positive predictive value, 71%; negative predictive value, 100%). The authors conclude that MH testing accurately identifies HLHS fetuses requiring urgent postnatal intervention at birth and may be used to select candidates for fetal atrial septoplasty.

Conclusions: PA vasoreactivity to MH occurs in the fetus with HLHS. MH testing accurately identifies fetuses requiring urgent postnatal intervention at birth and may be used to select candidates for fetal atrial septoplasty.

Editor’s Comment: Infants with HLHS may have pulmonary vasculopathy, particularly if there is an intact or restrictive interatrial septum, arguably because of the impact of obstruction to left atrial emptying on the pulmonary vascular bed. Since infants with pulmonary vasculopathy are more likely to require prenatal or urgent postnatal intervention, it would be useful to have a tool for evaluating pulmonary vasoreactivity in utero. In this paper, the authors report the use of the echo-Doppler-derived pulmonary arterial pulsatility index (PI = (peak systolic velocity-end-diastolic velocity)/mean velocity) and its response to MH for this purpose. Absence of a reduction in the PI with MH was 100% sensitive and 94% specific in predicting the need for an urgent atrial septal procedure, suggesting a role for this technique in the prenatal evaluation of fetuses with HLHS.

An Echocardiographic Model Predicting Severity of Aortic Regurgitation in Congenital Heart Disease

Summary: Echocardiographers have had difficulty accurately predicting the severity of aortic regurgitation (AR), and, consequently, >20 different echocardiographic measures have been suggested to quantify AR. This study defined 2 independent predictors of AR severity by 2-dimensional echocardiography in a population of patients with CHD, using cardiovascular magnetic resonance imaging (CMR) as a reference standard. The 2 parameters, parasternal vena contracta-derived area divided by body surface area (based on the parasternal vena contracta width) and abdominal aorta Doppler retrograde velocity-time integral divided by antegrade velocity-time integral, are relatively easy to obtain and can be measured in nearly any patient with CHD. Furthermore, these metrics adjust for changes in body size and are more relevant to the pediatric population. Using these 2 parameters, the authors defined a prediction model that estimates the percentage of AR in a prospective subset of patients, the predicted AR values had a mean bias ± standard deviation of 0.4 ± 7.3% (P = 0.80). The interobserver variability in measurements of parasternal vena contracta width increased substantially at higher AR fractions, potentially limiting the ability of the model to predict percentage of AR at higher degrees.

Conclusions: A model using the 2 variables parasternal vena contracta-derived area divided by body surface area and abdominal aorta Doppler retrograde velocity-time integral divided by antegrade velocity-time integral can predict AR severity in patients with a wide variety of CHD.

Editor’s Comment: The echocardiographic quantitation of AR remains a challenge, despite the availability of the American Society of Echocardiography/European Association of Echocardiography guidelines recommending an integrated approach. Variability arises since component indices may not always provide consistent estimates of severity, and weighting of individual measures may vary from reader to reader and patient to patient. In this study, using MRI-determined regurgitant fraction as a reference standard, the authors developed, and then validated, an approach based on 2 variables selected from a larger group of candidate variables. The variables selected were vena contracta-derived jet area (as imaged on the parasternal short axis views) divided by body surface area and abdominal aorta Doppler retrograde velocity-time integral divided by antegrade velocity-time integral. It is notable that the study group was one of patients with CHD (mean age 19.8 ± 12.1 years), 40% of whom had unicuspid or bicuspid aortic valves. Thus, additional study would be required to determine whether this approach would be equally successful in those with degenerative aortic disease in whom, for example, it may be more difficult to measure the vena contracta.

Quantification of Diffuse Myocardial Fibrosis and Its Association With Myocardial Dysfunction in Congenital Heart Disease

Summary: There is growing recognition that progressive myocardial dysfunction in patients with CHD contributes substantially to clinical heart failure, arrhythmia, and mortality. MRI with late gadolinium enhancement has been demonstrated to demonstrate diffuse fibrosis in several subgroups of CHD, confirming that myocardial fibrosis is a likely final common pathway in these patients; however, late enhancement identifies dense replacement fibrosis and is not as amenable to detecting smaller amounts of diffuse, microscopic fibrosis. To quantify myocardial fibrosis, the authors used a modified Look-Locker sequence to quantify a “fibrosis index” based on T1 for a single short-axis plane of the systemic ventricle before and after administration of gadolinium-based contrast. In 50 patients with CHD, the fibrosis index was significantly elevated in patients compared with normal controls and especially elevated in patients with a systemic right ventricle (RV) and those with cyanosis. The fibrosis index correlated with the end-diastolic volume index and ventricular ejection fraction but not with age. Values for patients with CHD were largely similar to patients with cardiomyopathy. The findings lay the groundwork for further investigation on pathophysiology and treatment of heart failure, specifically in CHD.

Conclusions: Patients with acute CHD have evidence of diffuse, extracellular matrix remodeling similar to patients with acquired heart failure. The fibrosis index may facilitate studies on the mechanisms and treatment of myocardial fibrosis and heart failure in these patients.

Editor’s Comment: The traditional technique for imaging myocardial fibrosis with T1-weighted cardiac magnetic resonance, late gadolinium enhancement, performs well in demonstrating discrete infarct scar or replacement fibrosis. Broberg and colleagues applied the emerging technique of T1 mapping, a quantitative approach that may better demonstrate diffuse interstitial fibrosis in a cohort of CHD patients. A fibrosis index, based on T1 measurements adjusted for hematocrit, was found to be higher in patients compared with healthy controls and was particularly elevated in the myocardium of systemic RVs and patients with cyanotic CHD. Further studies are warranted to understand the predictive value of this index for clinical sequelae such as systemic RV failure and ventricular arrhythmia.

Validation of 3D Echocardiographic Assessment of Left Ventricular Volumes, Mass, and Ejection Fraction in Neonates and Infants With Congenital Heart Disease: A Comparison Study With Cardiac MRI

Summary: Determination of left ventricular (LV) volumes in small, young patients, especially those with complex CHD, is integral to
Pulmonary Vascular Resistance as Assessed by Bicycle Stress Echocardiography in Patients With Atrial Septal Defect Type Secundum

**Summary:** By measuring pulmonary artery pressures (PAPs) and cardiac output during bicycle stress echocardiography, a PAP-flow relationship can be constructed for each patient. The slope of the PAP-flow plot represents the response of the pulmonary vasculature to increased flow and may identify patients with altered pulmonary hemodynamics, which would have been missed at rest. This study showed steeper PAP-flow plots in patients with altered pulmonary hemodynamics, which would have been missed at rest. This study showed steeper PAP-flow plots in patients with cardiomyopathy, possibly general anesthetic, and because breath-holding may be required, the accuracy of 3D echo allows a less-complex technique to be used in these very young patients.

**Conclusions:** In neonates and infants with CHD and small LVs (age-appropriate or hypoplastic), matrix-array 3D echo measurements of mass and volumes compare well with MRI, providing an important modality for ventricular size and performance analysis in these patients, particularly in those with left-side heart obstructive lesions.

**Editor's Comment:** This study confirms the accuracy of matrix-array 3D echocardiography in measuring LV volume and mass when compared with cardiac MRI. The important new information is that 3D echocardiography is reliable in infants with very small LVs, based on the age of the patient, as well as the complexity of his or her CHD. Since cardiac MRI may be challenging in some infants because of the need for sedation, possibly general anesthetic, and because breath-holding may be required, the accuracy of 3D echo allows a less-complex technique to be used in these very young patients.

X-Ray Magnetic Resonance Fusion to Internal Markers and Utility in Congenital Heart Disease Catheterization

**Summary:** Fluoroscopy is the main imaging modality used to guide catheterization procedures; however, several limitations (including poor soft tissue definition, the use of ionizing radiation, and lack of 3D data) make this imaging modality suboptimal. In the x-ray magnetic resonance fusion (XMRF) modality, 3D MRI data are overlaid onto live fluoroscopic images during the catheterization procedure. This takes advantage of the high spatial and temporal resolution provided by fluoroscopy and the good soft-tissue 3D anatomic information provided by MRI; however, to date, there has been no simple method to overlay MRI data onto fluoroscopy data. Current XMRF technology requires the use of external fiducial markers, specialized radiograph systems, or 3D rotational radiographic runs, which makes it impractical to perform XMRF on a routine clinical basis. The authors report on a new XMRF method that can now be done quickly with commercially available software, without the need for contrast, customized radiograph systems, or external fiducial markers. Furthermore, the method only uses minimal radiation, making it feasible to routinely perform XMRF during catheterization procedures. The authors have used this modality during CHD catheterization in 23 patients. The authors have found XMRF useful for roadmapping, angiographic camera angle selection, and device-positioning. This catheterization modality has the potential to significantly reduce radiation exposure and improve catheterization outcomes.

**Conclusions:** Internal marker-based registration can be performed quickly, with minimal radiation, without the need for contrast, and with clinically acceptable accuracy, using commercially available software. The authors have also demonstrated several potential uses for XMRF in routine clinical practice. This modality has the potential to reduce radiation exposure and improve catheterization outcomes.

**Editor's Comment:** Imaging methodologies play a pivotal role in the clinical management of patients with cardiovascular disease. While the main applications of imaging continue to be in diagnosis, timing of interventions, and monitoring response to therapy, imaging techniques are also being increasingly applied to guide interventions. This study provides rigorous phantom and in vivo validation of an integrated approach that combines the high spatial and temporal resolution of fluoroscopy with the superb anatomic details and tissue characterization of MRI. This approach not only offers the potential to reduce fluoroscopy time, and thus radiation, but also provides the basis for a wide range of potential applications, especially in electrophysiology.

Echocardiographic Evaluation Before Bidirectional Glenn Operation in Functional Single-Ventricle Heart Disease: Comparison to Catheter Angiography

**Summary:** There has been increasing interest in noninvasive evaluation alone in patients with single-ventricle circulation before undergoing bidirectional Glenn operation. The authors studied the ability of echocardiography to visualize and assess the relevant vascular anatomy in this patient population. Echocardiography was found to perform poorly compared with catheter angiography. The branch pulmonary arteries were successfully imaged by echocardiography in less than two thirds of patients, and the majority of PA stenoses found at catheterization were not visualized by echocardiography. The aortic arch was imaged more readily by echocardiography, with the majority of arch obstructions identified. Sedation did not appear to improve the performance of echocardiography for assessment of the pulmonary arteries. Given the clinical importance of identification and treatment of obstructions to pulmonary blood flow in the single

medical and surgical management; however, because of the abnormal shape of these ventricles, formulas that rely on geometric assumptions based on 2-dimensional echocardiography may be inaccurate. In this study, the authors demonstrate that matrix-array 3-dimensional (3D) echocardiography can reliably measure small LV volumes and mass in neonates and infants with complex CHD, using summation of discs methodology. This methodology has the potential to be applied to a variety of outcome studies to best determine medical and surgical strategies, particularly in pediatric patients with LV hypoplasia.

**Conclusions:** In patients with open versus closed ASDs and those able to demonstrate differences in the PVR response to exercise in patients with open versus closed ASDs and those closed later in life. This study showed steeper PAP-flow plots in patients with altered pulmonary hemodynamics, which would have been missed at rest. This study showed steeper PAP-flow plots in patients with ASDs develop pulmonary hypertension while others with seemingly similar shunts do not. This study uses Doppler echocardiography during bicycle stress echocardiography to calculate PVR, using the slope of the PA systolic pressure flow plot. The authors are able to demonstrate differences in the PVR response to exercise in patients with open versus closed ASDs and those closed later in life. The study does not elucidate any new mechanisms for the development of pulmonary hypertension in patients with ASD, but the relationship of the PAP-flow plot to peak oxygen consumption provides an opportunity to help time ASD closure and also to use this technique in other conditions associated with pulmonary hypertension.
ventricle circulation, the authors conclude that echocardiography alone before bidirectional Glenn operation is insufficient to image the relevant vascular anatomy.

**Conclusions:** In a large cohort of patients presenting for BDG, evaluation by echocardiography frequently failed to image the PAs and missed the majority of PA stenoses. Sedation did not appear to improve the performance of echocardiography for evaluation of the PAs. Echocardiography cannot be relied on as the sole investigation before BDG.

**Editor’s Comment:** There has been increasing interest in noninvasive evaluation alone in patients with single-ventricle circulation before undergoing bidirectional Glenn operation. This study evaluated the ability of echocardiography to assess the pulmonary arteries and aorta in this patient population and reported that it performed poorly compared with invasive angiography particularly with regards to PA stenoses. Thus, echocardiography is not a substitute for invasive angiography in patients being evaluated for bidirectional Glenns.

**Pulmonary Vascular Resistance, Collateral Flow, and Ventricular Function in Patients With a Fontan Circulation at Rest and During Dobutamine Stress**

**Summary:** The pathophysiologic causes for failure of the Fontan circulation are multifactorial. Therefore, diagnostic tools are warranted that permit a differential analysis of ventricular and pulmonary vascular function. In this study, an MRI catheterization technique that enables simultaneous pressure and volume measurement in the single ventricle was used. From these measurements, parameters of global pump, myocontractile, and diastolic function can be derived. In addition, MRI catheterization allows determination of aortopulmonary collateral (APC) flow in conjunction with pulmonary vascular resistance. The authors found that pharmacologic stress by dobutamine improved contractility, although without substantial augmentation of stroke volumes. At the same time, the single ventricle showed signs of abnormal diastolic performance. In the absence of a subpulmonary ventricle, these findings should be seen in the light of pulmonary vascular function. In the studied patients, blood flow through APCs contributed substantially to the total pulmonary blood flow. In addition, its proportion increased during stress; however, augmented total pulmonary blood flow was not associated with increased pulmonary vascular resistance, implying that resistance did not contribute to a limited preload reserve and, thus, impaired diastolic filling of the systemic ventricle. The method described in this study provides detailed and differential information of the cardiovascular function in Fontan, which will potentially improve the planning of individual treatment strategies. The findings of this descriptive study of preselected patients require further study in larger groups of patients with different types of Fontan circulation.

**Conclusions:** In patients with a Fontan circulation, APC flow contributes substantially to enhanced pulmonary flow during stress. The authors’ data indicate that pulmonary vascular resistance to augmented cardiac output was adequate, but decreased diastolic compliance was identified as an important component of ventricular dysfunction.

**Editor’s Comment:** Please refer to the comment following article entitled, “Coil Occlusion of Aortopulmonary Collateral Arteries Before Arterial Switch Procedure in an Infant With Transposition of the Great Arteries.”

**Noninvasive Quantification of Systemic-to-Pulmonary Collateral Flow: A Major Source of Inefficiency in Patients With Superior Cavopulmonary Connections**

**Summary:** This research presents and validates a method of quantifying the systemic-to-pulmonary collateral flow in the single-ventricle population with superior cavopulmonary anastomoses. It used cardiac MRI through-plane velocity mapping to calculate 2 independent estimators of collateral flow (the difference between the aortic and caval flow and the difference in pulmonary vein and PA flow). The authors found good agreement between the 2 estimators. In addition, this collateral flow was on average more than half of the total pulmonary blood flow and more than one third of the cardiac output (aortic flow), and ventricular end-diastolic volume correlated with collateral flow. This suggests that collateral flow can be a significant hemodynamic burden in this population. The proposed methodology could identify patients who may benefit from collateral embolization and determine whether embolization significantly affects total collateral flow and cardiac output. The implications of these findings for clinical outcomes of single-ventricle patients require further studies.

**Conclusions:** The authors present a noninvasive method for systemic-to-pulmonary collateral flow quantification in patients with superior cavopulmonary connections. It should provide an important clinical tool in treating these patients. Furthermore, the authors show that systemic-to-pulmonary collateral flow is a significant hemodynamic burden in many patients with bidirectional Glenn shunt physiology. Future investigations will allow objective study of the impact of collateral flow on outcome.

**Editor’s Comment:** Please refer to the comment following article entitled, “Coil Occlusion of Aortopulmonary Collateral Arteries Before Arterial Switch Procedure in an Infant With Transposition of the Great Arteries.”

**Aortopulmonary Collaterals After Bidirectional Cavopulmonary Connection or Fontan Completion: Quantification With MRI**

**Summary:** APCs are frequent in patients with a so-called single-ventricle physiology. On the basis of previous reports that linked the presence of APCs to a higher incidence of complications after the Fontan completion, foremost prolonged pleural effusions, most institutions coil-occlude large APCs. Recently, however, this practice has been challenged by studies that did not confirm a deleterious effect of these channels. The contradicting nature of these reports may be related to the difficulty in assessing the magnitude of blood flow through collaterals angiographically. The authors show that APC flow volumes can be measured accurately and noninvasively in the majority of patients before and after Fontan completion. An increasing number of institutions are obtaining an MRI in their patients before proceeding to the Fontan completion. Artifacts from metallic implants, which prevented APC-flow measurement in 5 of our patients, will become less important and less frequent as MRI-compatible devices are introduced. Phase-contrast MRI can quantify the degree of left-to-right shunting through APCs. From this pilot study, it is still unclear whether a large APC-flow volume is associated with a worse clinical outcome. Even now, however, awareness of the hemodynamics, including the ratio of pulmonary-to-systemic blood flow and collateral blood flow, will help the clinician in obtaining a complete picture of the patient’s status. Confirmation about a large left-to-right shunt can potentially guide therapy in a patient with single-ventricle physiology and heart failure. Therefore, the authors believe that APC-flow assessment should be performed in every patient with bidirectional cavopulmonary connections or Fontan circulation who undergoes an MRI.

**Conclusions:** APC blood flow can be noninvasively measured in patients with bidirectional cavopulmonary connections and Fontan, using MRI in the majority of patients, and results in a significant left-to-right shunt.

**Editor’s Comment:** Please refer to the comment following article entitled, “Coil Occlusion of Aortopulmonary Collateral Arteries Before Arterial Switch Procedure in an Infant With Transposition of the Great Arteries.”
Coil Occlusion of Aortopulmonary Collateral Arteries Before Arterial Switch Procedure in an Infant With Transposition of the Great Arteries

Summary: Major APC arteries or enlarged bronchial arteries are well-described in transposition of the great arteries and can present problems on cardiopulmonary bypass with flow from the collaterals returning to the left atrium, resulting in blood in the surgical field and the potential for poor organ perfusion. The additional flow can also present problems in the postoperative period, with high pulmonary blood flow and cardiac volume overload requiring closure of collaterals.

Conclusions: The images in this article illustrate the detection of these vessels by echocardiography before corrective surgery, allowing interventional catheter embolization of these vessels in advance of an arterial switch procedure. Thus, the risk of complications during cardiopulmonary bypass and the risk of high-postoperative pulmonary blood flow were avoided. Although postoperative embolization of major APC arteries has been described, this is the first report of embolization before a corrective surgical intervention in a patient with transposition of the great arteries.

Editor's Comment: APCs develop as embryonic splanchnic arteries to provide PA flow rather than regress in the face of congenital anomalies such as pulmonary atresia that negatively impact native PA development and flow. The long-term sequelae of chronic left-to-right shunting through these vessels and their potential management were addressed in this series of papers. Schmitt and colleagues demonstrated the hemodynamic importance of increased APC flow using dobutamine stress CMR and immediate post-CMR invasive pressure measurements. Whitehead and colleagues showed that collateral flow represents more than one third of aortic flow (ie, cardiac output in patients with superior cavopulmonary anastomoses). Using a different quantification approach, Grosse-Wortmann and colleagues also found a significant volume load via APCs on the functionally single ventricle. These techniques hold promise in (1) better understanding of APCs' long-term significance and (2) improved patient selection and procedural planning for their treatment, given advances such as those demonstrated by Jowett and colleagues in transcatheter occlusion.

Laboratory Measures of Exercise Capacity and Ventricular Characteristics and Function Are Weakly Associated With Functional Health Status After Fontan Procedure

Summary: As mortality rate has declined dramatically for repair of even the most complex CHD patients, clinical care will focus increasingly on preventing and treating morbidities and improving functional health status. Patients with a functional single ventricle who have had the Fontan procedure are at high risk for suboptimal functional health status. Determination of associations of functional health status with laboratory measures, which may suggest pathophysiological mechanisms, is important for planning interventions and outcome measures for clinical trials. The authors performed a cross-sectional assessment of patients 6 to 18 years of age who had undergone the Fontan procedure. The results showed that laboratory measures of exercise capacity and ventricular characteristics and function (as assessed objectively by brain natriuretic peptide levels, exercise testing, echocardiography, and MRI) were only weakly associated with results from a validated questionnaire measure of physical and psychosocial functional health status. This suggests that strategies aimed at preserving indices of ventricular form and function (as assessed by laboratory testing) may have little effect on current functional health status. The impact of treatment strategies targeted toward those with important laboratory abnormalities in the pathological range may influence functional health status to an unknown degree but should be an important component of future studies. Strategies targeting functional health status and its noncardiac determinants directly, such as through rehabilitation programs and by addressing psychosocial morbidities, may have a greater impact on health-related quality of life. Such programs should be developed and evaluated for these high-risk and complex patients.

Conclusions: In relatively healthy patients who had the Fontan procedure, laboratory measures account for a small proportion of the variation in functional health status and therefore may not be optimal surrogate end points for trials of therapeutic interventions.

Editor's Comment: Functional health status is an important component of assessing patient’s functional performance, and, in this instance, the detailed survey has been applied to patients who have had the Fontan procedure. In an era of constrained resources, it is important that we evaluate outcomes in an objective way, and this approach has been used here. Nonetheless, despite the rigors of the multimodality approach, the correlation of objective survey information to echo, MR, exercise testing, and laboratory values is relatively weak. It is a little surprising that exercise testing did not correlate better with the Functional Health Status, and the authors rightfully suggest that the correlation will need to be improved so that resources that track with outcome can be incorporated into future trials and patient management.

Relationship of Intraoperative Cerebral Oxygen Saturation to Neurodevelopmental Outcome and Brain Magnetic Resonance Imaging at 1 Year of Age in Infants Undergoing Biventricular Repair

Summary: This study explored whether intraoperative cerebral oxygen saturation ($rSO_2$), measured by near-infrared spectroscopy, was associated with neurodevelopmental outcomes at age 1 year among infants undergoing biventricular repair without aortic arch reconstruction. The Lower Psychomotor Development Index of the Bayley Scales was modestly associated with lower $rSO_2$ during the 60-minute period after cardiopulmonary bypass and at the time points of 10 minutes of cooling, off-cardiopulmonary bypass and 60 minutes after cardiopulmonary bypass. Lower $rSO_2$ from postinduction to 60 minutes after cardiopulmonary bypass and for the 60-minute period after cardiopulmonary bypass was associated with hemosiderin foci on qualitative MRI analysis. No relationship could be demonstrated between $rSO_2$ and the Mental Development Index of the Bayley Scales, neurological examination, or head circumference. The relationship of lower $rSO_2$ with lower Psychomotor Development Index score and greater risk of hemosiderin on brain MRI, even after adjustment for age ≤30 days or diagnosis group, suggests that periods of intraoperative and early postoperative decreased cerebral oxygen delivery are associated with adverse longer-term neurodevelopmental outcomes.

Conclusions: Perioperative periods of diminished cerebral oxygen saturation, as indicated by $rSO_2$, are associated with 1-year Psychomotor Development Index and brain MRI abnormalities among infants undergoing reparative heart surgery.

Editor's Comment: This is another excellent example of using brain MRI-based findings as a surrogate marker for clinical outcomes in a large group of infants undergoing biventricular repair without aortic arch reconstruction. Intraoperative cerebral oxygen saturation, measured by near-infrared spectroscopy, was associated with neurodevelopmental outcomes at age 1 year among infants undergoing biventricular repair without aortic arch reconstruction. This study underlines the significant importance to maintain normal intraoperative and early postoperative cerebral oxygen delivery and may also be useful to identify candidates for screening and therapy early on and possibly prevent adverse longer-term neurodevelopmental deficits.
Maladaptive Aortic Properties in Children After Palliation of Hypoplastic Left Heart Syndrome Assessed by Cardiovascular Magnetic Resonance Imaging

Summary: In children with HLHS, the status of the reconstructed aorta after the Norwood operation is of potential prognostic importance. Dilatation and an impaired distensibility of the neoaorta have already been reported in previous echocardiographic and angiographic studies; however, comprehensive data on the anatomic and functional properties of the reconstructed aorta and their potential influence on RV function in HLHS are still lacking. The present study used CMR to evaluate the anatomy, bioelastic properties, viability of the aorta, and RV ejection fraction in 40 patients with HLHS. Compared with control subjects, patients with HLHS had an increased aortic size and reduced aortic bioelasticity (distensibility and pulse-wave velocity). Fibrosis was detected with CMR in the proximal aorta, using the well-proven late gadolinium enhancement technique. Aortic late gadolinium enhancement correlated inversely with reduced RV ejection fraction and distensibility in the ascending aorta. These findings suggest unfavorable aortic-ventricular coupling, which may contribute to a higher risk for later RV failure. This study may help improve our understanding of aortic bioophysical properties after extensive surgical reconstruction of the aorta. The results may serve as baseline data for further longitudinal studies in children with HLHS to establish the prognostic value of anatomic and bioelastic aortic properties measured by CMR.

Conclusions: Adverse aortic properties postpalliation of HLHS manifest themselves by aortic dilatation, decreased distensibility, and increased volume of nonviable aortic wall tissue. The negative association between aortic late gadolinium enhancement and RV ejection fraction suggests unfavorable aortic-ventricular coupling. The potential impact of these findings on long-term RV function should be evaluated in future studies.

Editor’s Comment: The physiological connections between the heart and the aorta remain poorly understood, yet may offer novel insights into diseases as varied as hypertension, coronary atherosclerosis, and, now, complex CHD. Voges and colleagues applied a CMR protocol that integrated measurements of aortic pulse wave velocity, cardiac function, and aortic wall late gadolinium enhancement imaging in a cohort of children with HLHS and similarly aged controls. Decreased aortic function occurred with greater aortic fibrosis and reduced systemic RV function. The authors’ approach warrants extension to better understand aortoventricular interactions as markers of, and treatment targets for, a spectrum of cardiovascular diseases.

Total Anomalous Pulmonary Venous Connection: Morphology and Outcome From an International Population-Based Study

Summary: Totally anomalous pulmonary venous connection is a cyanotic CHD with ongoing morbidity and mortality particularly related to pulmonary venous obstruction (PVO). This study is the largest population-based study of the disease to date and reports on the incidence, morphology, outcome, and factors predictive of poor outcome for all babies born with this anomaly in a fixed geographic area (United Kingdom, Ireland, and Sweden). Importantly, the report represents an exhaustive collaborative effort of all pediatric cardiac centers in the United Kingdom, Ireland, and Sweden. Unlike other studies, the population-based nature of these data reflects the entire spectrum of morphology, as well as contemporary practice. The authors have identified a cohort of patients with PVO after surgical repair and identified risk factors for this. After reading the article, the clinician should be aware of the wide spectrum of complexity in this condition, should be better able to predict outcome for an individual patient with total anomalous pulmonary venous connection, and should understand which patients are particularly at risk of developing postoperative PVO.

Conclusions: Preoperative clinical and morphological features are important risk factors for postoperative PVO and survival.

Editor’s Comment: Totally anomalous pulmonary venous connection is an uncommon form of cyanotic CHD. In this multinational study, the largest to date, the authors report the incidence, morphology, outcome, and factors predictive of poor outcome in infants with this anomaly. Risk factors for PVO after surgical repair, which is associated with post-op morbidity and mortality, are identified. In aggregate, this paper provides a valuable resource for those caring for patients with total anomalous pulmonary venous drainage, particularly with regards to risk stratification.

Heart Rate Response During Exercise and Pregnancy Outcome in Women With Congenital Heart Disease

Summary: Women with moderate and complex forms of CHD are at increased risk for adverse cardiac events during pregnancy. Risk stratification in this population remains incompletely defined. Prepregnancy exercise testing with measures of cardiac endurance and chronotropic response has been recommended to improve risk assessment; however, to date, the relationship between stress test results and pregnancy outcome has not been evaluated. The purpose of the present study was to assess the predictive value of cardiopulmonary exercise testing on pregnancy outcome in women with CHD. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with a higher risk for maternal cardiac and neonatal adverse events. Peak oxygen consumption was not associated with adverse outcomes. Stress testing with measures of chronotropic response is a promising tool for the practicing clinician that, when considered in the context of other clinical and hemodynamic factors, may further improve risk stratification of women with CHD who are considering pregnancy.

Conclusions: Abnormal chronotropic response correlates with adverse pregnancy outcomes in women with CHD and should be considered in refining risk stratification schemes.

Editor’s Comment: Pregnancy in women with CHD exposes the mother and the baby at increased risk of complications. Prepregnancy stress testing has been advocated as a useful tool to identify patients at increased risk. This retrospective study evaluated the predictive value of chronotropic and metabolic parameters from cardiopulmonary exercise stress testing to identify patients with complex CHD at risk for maternal and neonatal complications. The study identified chronotropic incompetence, as defined by the chronotropic reserve index (a measure that is independent of age, resting heart rate, and functional state), as an important marker of risk, which was independent from other established prognostic variables. The mechanism underlying the blunted heart rate response to exercise in women with CHD remains unknown; however, this parameter is simple and inexpensive to measure and offers another potentially valuable tool to identify at-risk patients, which may enhance informed decisions regarding pregnancy and potentially improve medical surveillance of pregnant women with complex CHD.

Increased Vertebral Artery Tortuosity Index Is Associated With Adverse Outcomes in Children and Young Adults With Connective Tissue Disorders

Summary: Historically, cardiac surgical management of children and young adults with Marfan syndrome and related connective tissue disorders has been based primarily on aortic root size and rate of aortic growth. With the discovery of Loeys-Dietz syndrome and its reported aortic dissection at smaller dimensions and younger age, clinicians have begun to consider underlying genetic diagnosis when making decisions about timing of surgical intervention. The authors
observed vertebral arterial tortuosity in patients with Marfan syndrome and Loeys-Dietz syndrome and sought to investigate if the degree of arterial tortuosity was related to cardiovascular outcomes. In this study, the authors developed a vertebral artery tortuosity index based on magnetic resonance angiography to assess arterial tortuosity in both controls and connective tissue disorder patients. The measurement was simple to calculate from standard magnetic resonance angiography, taking 1 to 2 minutes. The authors found that higher tortuosity is independently associated with earlier cardiac surgery, arterial dissection, and death. In this study, a high vertebral artery tortuosity index was more strongly associated with early adverse outcome than a diagnosis of Marfan syndrome. The vertebral artery tortuosity index may offer helpful information about prognosis in connective tissue disorder patients and may ultimately play an additive role in surgical decision-making.

Conclusions: Arterial tortuosity measured by magnetic resonance angiography is a reproducible marker of adverse cardiovascular outcomes in connective tissue disorders.

Editor’s Comment: The authors introduce a novel but simple MR-based measure of vertebral artery tortuosity that predicts earlier cardiac surgery, arterial dissection, and death independently of traditionally used aortic root diameter in children and young adults with Marfan and Loeys-Dietz syndrome. The vertebral artery tortuosity index takes 1 to 2 minutes to measure and can be implemented easily into clinical routine.

Adolescents With D-Transposition of the Great Arteries Corrected With the Arterial Switch Procedure: Neuropsychological Assessment and Structural Brain Imaging

Summary: Advances in the management of CHD have improved the survival of individuals with even the most complex heart lesions, unmasking significant neurodevelopmental risk among survivors. Assessments conducted in early childhood have provided early data on the frequency and severity of neurodevelopmental morbidity; however, few studies have evaluated the neuropsychological and neuroimaging outcomes of adolescents with CHD. The authors evaluated 139 children, 16 years of age, with d-transposition of the great arteries, who were enrolled as infants in the Boston Circulatory Arrest Study, a randomized trial comparing the outcomes associated with 2 vital organ support strategies: deep hypothermia with total circulatory arrest or with continuous flow-flow cardiopulmonary bypass. Adolescents in the 2 groups generally performed similarly; however, compared with the general population, adolescents in the combined treatment groups had lower, and more variable, scores on academic achievement, memory, attention, executive functions, visual-spatial skills, and social cognition. Almost two thirds had received remedial academic or behavioral services. Postoperative seizure, detected clinically or by continuous electroencephalogram recording, was the strongest predictor of poor outcomes. Structural MRI abnormalities were found in one third of the adolescents and were more frequently focal than diffuse, consisting of mineralization or iron deposits. Greater exposure to catheterization and longer time on cardiopulmonary bypass were independent risk factors for brain mineralization. Although most adolescents had satisfactory neuropsychological outcomes, a significant minority performed below the expected level. The results suggest that children with d-transposition of the great arteries should remain under surveillance into adolescence to permit identification of neurocognitive and behavioral difficulties.

Conclusions: Adolescents with d-transposition of the great arteries who have undergone the arterial switch operation are at increased neurodevelopmental risk. These data suggest that children with CHD may benefit from ongoing surveillance to identify emerging difficulties.

Editor’s Comment: This unique report describes significant neurodevelopmental risk among survivors of d-Transposition of the great arteries corrected with the arterial switch procedure, based on qualitative and quantitative neuropsychology and brain MRI assessment. Such data will be useful and important to tailor surveillance into adolescence to permit identification of neurocognitive and behavioral difficulties.

Mutations in the Sarcomere Gene MYH7 in Ebstein Anomaly

Summary: Ebstein anomaly is a rare congenital heart malformation affecting both the tricuspid valve and RV and is characterized by adherence of the septal and posterior leaflets of the tricuspid valve to the underlying myocardium. Ebstein anomaly is more common in patients with a family history of CHD, but most cases are sporadic and familial. Ebstein anomaly is rare. Associated abnormalities of LV morphology and function have been observed. A possible association between Ebstein anomaly with left ventricular noncompaction (LVNC) and mutations in MYH7 encoding β-myosin heavy was previously shown in 1 family with multiple affected members. In the present study, the authors describe that Ebstein anomaly is within the diverse spectrum of cardiac morphologies triggered by a sarcomere gene defect. The authors performed mutational analysis of MYH7 in a cohort of 141 unrelated probands with Ebstein anomaly. Mutations were identified in 8 of 141 probands (6%), the largest resequencing study of Ebstein anomaly thus far. Mutation-positive probands and family members showed various congenital heart malformations as well as LVNC. Significant pleiotropy and reduced penetrance were characteristic of MYH7-mutation–positive congenital heart malformations. In 6 of 8 probands with MYH7 mutations, LVNC was identified in addition to Ebstein anomaly, whereas among 133 MYH7-mutation–negative probands, none had LVNC. The authors provide further evidence for a link between structural proteins, cardiomyopathy, and congenital heart malformations. MYH7 mutations are predominantly found in Ebstein anomaly associated with LVNC and may warrant genetic testing and family evaluation in this subset of patients.

Conclusions: Ebstein anomaly is a congenital heart malformation that is associated with mutations in MYH7. MYH7 mutations are predominantly found in Ebstein anomaly associated with LVNC and may warrant genetic testing and family evaluation in this subset of patients.

Editor’s Comment: While classically thought of as a right heart disease, Ebstein anomaly may often present with abnormalities of LV structure and function. Postma and colleagues identified MYH7 mutations that predicted associated LV noncompaction in a large cohort of unrelated probands with Ebstein anomaly. This discovery is significant for many reasons, not the least of which are the implications on natural history and outcomes in this condition. Such genotype-phenotype studies underscore the complementary roles of genetic analysis and cardiac imaging in defining the functional significance of suspected disease-causing mutations in structural heart disease.

Sarcomere Gene Mutations in Isolated Left Ventricular Noncompaction Cardiomyopathy Do Not Predict Clinical Phenotype

Summary: LVNC is a cardiomyopathy with a genetic etiology, and autosomal-dominant transmission is common. The morphological, echocardiographic characteristics include a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses. The clinical features range from asymptomatic individuals to symptomatic patients with progressive deterioration of cardiac function, thromboembolic events, and arrhythmias, including sudden cardiac death. LVNC is genetically heterogeneous, and prior reports indicate that mutations in genes encoding sarcomere proteins are associated with LVNC. In the present study, the authors evaluated the potential clinical impact of genetic analysis of sarcomere genes in patients with isolated LVNC. The authors describe mutations in cardiac myosin-binding protein C.
The mutations in MYBPC3 and α-tropomyosin (TPM1) in a cohort of unrelated adult probands with isolated LVNC. The mutations in MYBPC3 and TPM1 and in 6 other previously reported sarcomere genes in this cohort resulted in a total of 18 (29%) heterozygous mutations in 63 probands. Beta-myosin heavy chain (MYH7) was the most prevalent disease gene, accounting for 13% of cases, followed by MYBPC3 (8%). Although mutations in sarcomere genes account for a significant proportion of cases of isolated LVNC, patients who are mutation-positive could not be distinguished from those who are mutation-negative by their clinical characteristics; however, the authors provide insight into how mutations of different sarcomere genes lead to diverse clinical phenotypes, with implications for diagnosis, genetic testing, and follow-up. Genetic testing of sarcomere genes is a valuable diagnostic tool for the probands and their relatives who may be at high risk of inheriting the cardiomyopathy.

Conclusions: Mutations in sarcomere genes account for a significant (29%) proportion of cases of isolated LVNC in this cohort. The distribution of disease genes confirms genetic heterogeneity and opens new perspectives in genetic testing in patients with LVNC and their relatives at high risk of inheriting the cardiomyopathy. The presence or absence of a sarcomere gene mutation in LVNC cannot be related to the clinical phenotype.

Editor’s Comment: LVNC is a genetically determined cardiomyopathy, commonly associated with autosomal-dominant transmission. As prior reports have indicated that mutations in genes encoding sarcomere proteins are associated with LVNC, the current study evaluated 18 such mutations, reporting both their prevalence and clinical significance. Notably, patients who were gene-positive versus those who were gene-negative did not differ from one another with regards to a number of clinical characteristics. This study adds important information to our understanding of the genetic basis for LVNC, with the expectation that additional causative gene mutations will be identified.

Magnetic Resonance-Guided Cardiac Interventions Using Magnetic Resonance-Compatible Devices: A Preclinical Study and First-in-Man Congenital Interventions

Summary: MR-guided diagnostic catheterizations for patients with CHD were pioneered in our institution around a decade ago; however, performance of interventional procedures was still only made possible with the use of radiograph-ionsizing radiation, either on its own or in combination with MR-imaging guidance. Within that time period, several research workers performed MR-guided interventions in animals successfully, but translation into humans was not made possible because of the lack of fully MR-compatible devices. The emergence of a new MR-safe and compatible guide wire enabled us to perform the 2 first-in-man cardiac interventions reported here, solely under MR guidance. Future study will be needed to determine whether the outcomes for MR-guided procedures are comparable with those guided by fluoroscopy.

Conclusions: The described preclinical study and case reports are encouraging that with the availability of the new MR-compatible and safe guide wire, certain percutaneous cardiac interventions will become feasible to perform solely under MR guidance in the future. A clinical trial is underway in the authors’ institution.

Editor’s Comment: Given the increasing ionizing radiation exposure in medicine, the development of alternative strategies such as MR-guided cardiac interventions become increasingly attractive if they are as effective and efficient compared with radiograph-based guidance. This paper provides an example, demonstrating near-real time monitoring of a new MR-compatible and safe guide wire first in pigs and then in 2 humans. Although attractive, many challenges remain before certain percutaneous cardiac interventions will become feasible to perform solely under MR guidance.

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