C O N G E N I T A L
C A R D I O L O G Y T O D A Y

Timely News and Information for BC/BE Congenital/Structural Cardiologists and Surgeons

Volume 7 / Issue 10
October 2009
International Edition

IN THIS ISSUE

CONGENITAL CARDIOLOGY TODAY

Editorial and Subscription Offices
16 Cove Rd, Ste. 200
Westerly, RI 02891 USA
www.CongenitalCardiologyToday.com

ISSN: 1544-7787 (print); 1544-0499 (online). Published monthly.

UPCOMING MEDICAL MEETINGS

11th Brazilian Congress of Pediatric Intensive Care
Nov. 3-7, 2009; Belo Hironzonte, Brazil
www.ctip2009.com.br

ICI 2009 - Innovations in Cardiovascular Interventions
Dec. 6-8, 2009; Tel-Aviv, Israel
www.congress.co.il/ici2009

5th Charleston Symposium on Interventional Pediatric Electrophysiology
Dec. 13-15, 2009; Charleston, SC USA
musckids.com/heart/conferences/

Evolving Concepts in the Management of Complex Congenital Heart Disease II:
Jan. 14-16, 2010; San Diego, CA USA
www.chsd.org/body.cfm?id=1753

Cardiology 2010
Feb. 10-14, 2010; Lake Buena Vista, FL USA
www.chop.edu/cardiology2010

Hypertension in the Adult Congenital Heart Disease Population: A Review of the Literature

By Mark Townsend, MD; Robert Battle, MD; Alexander Ellis, MD; Sam Lee, MD; and William Moskowitz, MD

As medical and surgical techniques to repair or palliate congenital heart lesions continue to improve, the number of patients surviving to adulthood continues to expand rapidly. The total adult congenital heart disease (ACHD) population surpassed one million in 2005.[1] As the number of patients with ACHD increases, so, too, does the likelihood that adult cardiologists and primary care physicians are involved in their care. Familiarity with the anatomy and physiology of the individual lesions as well as late-onset complications is vital for all physicians caring for this group of patients. Medical management of adult comorbidities in the ACHD population however, lacks uniformity in basic health issues such as hypertension, which is still often considered to be a "psychosocial issue."[2]

As younger patients with congenital heart disease grow up, the onset of 'typical' adult diseases further complicates their care, adding additional variables to already complicated cardiovascular profiles. Risk factors for hypertension are amplified in this population by the usual lifestyle choices confounded by intrinsic physical limitations in some patients. Exercise intolerance and activity restriction are known to increase the risk for obesity, which in itself is a significant risk factor for the development of hypertension. Emotional challenges such as anxiety and mood disorders are also prevalent in the ACHD population. The link between depression and enhanced sympathetic activation cannot be ignored in the ACHD population with hypertension.[3] Lastly, even elements as basic as target blood pressures for a given congenital heart lesion and its surgical repair remain poorly understood.

We undertook a systematic review of the current literature for information pertaining to the diagnosis and management of hypertension in the ACHD population.[4, 5] We discuss hypertension care within the limitations of relevant evidence-based data in the current literature.

Methods

Medline / PubMed was searched for citations with the keywords "hypertension" or "systemic hypertension" paired with all keywords listed in the appendix. Available MeSH headings were then used to search for all congenital conditions and pharmacologic classes discussed. Given the scarcity of pertinent literature, all citations were reviewed and included based on relevant content, regardless of format or trial design. References of included articles were scanned for additional publications to check the completeness of our review. No other review articles were available for analysis. Only articles written in English and French were reviewed. Articles were not excluded based on date of publication.

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

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

Announcing Expanded Labeling

Improved Outcomes. Real-Time Data Accuracy.

Based on clinical evidence, INVOS® System labeling for site-specific blood oxygen monitoring has been expanded. This makes it the only commercially-available cerebral/somatic oximeter to be backed by the following claims.

- Improved outcomes after cardiac or major general surgery in patients > 2.5 kg
- On-label treatment of patients at any weight
  - o > 2.5 kg: real-time data accuracy
  - o < 2.5 kg: trend monitoring
- Noninvasive indication of O_2 changes in the cerebral and peripheral circulatory systems
  - o Often providing an early warning of O_2 deficits associated with impending shock and anaerobiosis

Labeling claims not applicable to other devices as data was derived using the INVOS System and its proprietary algorithm.

CEREBRAL/SOMATIC INVOS OXIMETER
REFLECTING THE COLOR OF LIFE®

Tetralogy of Fallot: Natural History and Late Complications

The ACHD population with TOF is adversely affected by the natural history of the resultant pulmonary insufficiency. The late morbidity of pulmonary insufficiency has been increasingly appreciated in recent years, such as progressive right ventricular dilation and fibrosis or scar around the ventriculotomy predisposing to lethal arrhythmias.[6] Patients are "asymptomatic" until RV dysfunction is severe and irreversible; sudden death may be the presenting feature in up to 6% of patients.[7] Right ventricular dysfunction is further compounded by preexisting pulmonary hypertension created by the use of various central shunts as an early bridging procedure before a complete repair, in an era before early primary repair was possible. Central shunts often distort the architecture of the pulmonary arteries, leading to distal pulmonary arterial obstruction.

Biventricular failure is not uncommon in this group, and is not well tolerated. Predisposition for left ventricular failure in this population is partially driven by the kinetics of abnormal right ventricular function, the association of which is not well understood.[8,9] In addition, an association between TOF and aortic medial abnormalities exists which can lead to progressive aortic root dilation and aortic insufficiency.[10,11] Given this underlying vascular medial abnormality, systemic hypertension serves as an additional insult in this population.

"The significance of adult onset comorbidities in the congenital heart disease population as it ages has been predicted and lamented for years."

Our review of the literature found no studies that addressed the prevalence or management of hypertension in patients with repaired TOF at any age. However, the natural history of this disease indeed suggests a predisposition to systemic hypertension. In an uncontrolled series of 147 uncorrected TOF adults evaluated with cardiac catheterization, 9.5% of patients had overt systemic hypertension.[12] This population shares histological similarities to systemic hypertension at baseline in terms of myosin composition of ventricular myocardium, the significance of which is not completely clear.[13] Patients with surgically repaired ventricular septal defects and TOF were shown together to have a mildly higher, but significant systolic blood pressure during exercise than age-matched controls.[14]

The use of calcium channel blockers for hypertension in TOF has been suggested, given the possible benefit of simultaneously reducing pulmonary vascular resistance. The post-operative use of nicardipine has been reported to be efficacious in children after cardiothoracic surgery, including TOF repair, with a target systolic blood pressure of ≤ 110 mm Hg in patients 5 years or older. No adverse effects were noted in a total of 337 hours of intravenous use.[15] The risk of using calcium channel blockers is that sinus node slowing may be significant enough to precipitate hemodynamically-significant bradycardia or the emergence of an ectopic atrial pacemaker.[16] This is especially germane given that underlying sinus node dysfunction may occur in one third of

TOF patients, increasing the potential complications with use of calcium channel blockers in this population.[17] Thus, in practice, calcium channel blockers are not often used in patients with repaired TOF.

Both beta-1 and beta-2 receptors are down-regulated in TOF. The use of beta blockers is known to increase both types of beta receptors.[18, 19, 20] Beta blockers are often used for aortic root dilation in Marfan Syndrome without clear consensus; by extension, there is no current consensus on their use in TOF.[21, 22] Research needs to be done to establish the potential role of beta blockers in the populations with: (1) pre-clinical and, (2) overt alterations of right and left sided structures and function, including aortic root dilation. The effects of beta blockers on right ventricular function in addition to potential modification of RV mediated arrhythmias in this population remain relative unknowns, and require investigation. In practice, beta blockers are often used in the management of hypertension in TOF given the associated aortopathy and the risk of ventricular arrhythmias precipitating sudden death.

Coarctation of the Aorta

The association between coarctation of the aorta and hypertension is well established in an extensive body of literature. Regardless of timing or method of repair, it is recognized that this population is plagued by persistent arterial stiffness despite a widely patent repaired aorta. This is well-demonstrated by ambulatory blood pressure monitoring studies.[23] In the current adult population, late hypertension is observed in at least 25% of patients.[24, 25] Almost two thirds of patients have been reported to be hypertensive 15-30 years after coarctation repair.[26, 27] Age at the time of initial repair is the most important predictor of late hypertension, which is relevant to the adult population since later repair occurred more frequently in the past.[28, 29] Of interest, the presence of a commonly associated bicuspid aortic valve does not appear to effect blood pressure, but does pose a risk for general aortic complications such as aneurysms, dissection and rupture.[30, 31] Risk factors for the late onset of hypertension are listed in Table 1.

Table 1. Risk Factors for the Late Onset of Hypertension in Coarctation in the Absence of Re-coarctation

- "Gothic" geometry of the aortic arch[32] - limited by difficult reproducibility[33]
- Residual descending aortic narrowing[34]
- Repair with a subclavian patch[35]
- Polytetrafluoroethylene patch aortoplasty[36]
- Reduced vascular reactivity[37]
- Late repair[38, 39, 40]
- Maximum exercise systolic BP > 193 mm Hg[41]

The etiology of hypertension after coarctation repair is multifactorial. Decreased baroreflex sensitivity to changes in arterial pressure has been shown in 6 control matched children after repair.[42] Histologic changes of the carotid wall with increased intima medial thickness has been reported.[43, 44] Renin levels were shown to increase after captopril challenge in a small number of coarcation patients when compared to patients with essential hypertension, suggesting a renin mediated effect.[45] A follow-up study, however, showed antidotal evidence that in spite of the extensive activation of the renin-angiotensin-aldosterone axis in this population, the effect of angiotensin-converting enzyme (ACE) inhibition is quickly lost.[46] This has not been reproduced in a large trial.

In spite of the clear predisposition of this population to systemic hypertension, the benefits of medical intervention have not yet been studied on a large scale. Large registries still have not been designed to standardize treatment regimens.[47] Many patients with a history of previous coarctation repair are not receiving optimal care.[48]

Per ACC/AHA guidelines, beta blockers, ACE inhibitors and angiotensin receptor blockers should be used as first-line medications with the choice of medication influenced in part by aortic root dimensions, aortic insufficiency and valvar aortic stenosis.[49] In tandem with medical management, hypertensive patients should be evaluated for possible recoarctation defined as a peak gradient of more than 20 mm Hg across the coarctation repair site via cardiac catheterization.[50, 51] Screening for hypertension is performed by measuring the blood pressure in both arms and a leg keeping in mind the historical use of subclavian flaps for surgical repair.

Single Ventricle Physiology with a Morphologic Left Ventricle

Tricuspid atresia makes up the large majority of patients with single ventricle physiology, a morphologic left ventricle and a Fontan anastamosis. Adult patients who have undergone some variation of a Fontan procedure are prone to atrial arrhythmias, protein-losing enteropathy, and thrombus formation.[52] Specifically, patients with a Fontan for tricuspid atresia have a 10 to 20% risk of atrial tachycardia or flutter-fibrillation, and a 13% risk of developing protein-losing enteropathy as a result of elevated systemic venous pressures. NYHA class is I or II in as many as 90% of patients. There is a low incidence of left ventricular dysfunction.[53, 54, 55]

Neurohormonal activation after a Fontan occurs both acutely and chronically with elevation of renin, angiotensin II, vasopressin and endothelin-1.[56, 57, 58] This cascade theoretically predisposes this population to ventricular hypertrophy, which in the setting of a Fontan is poorly tolerated because forward flow through the lungs is passive and dependent on good diastolic function of the single ventricle. A small series of 23 patients with a mean age of 19.4 years looked for LV hypertrophy but reported normal LV masses as assessed by MRI, albeit with diminished ejection fractions compared to a normal control population.[59] The elucidation of the risk of hypertrophy and hypertension will be a requisite as this population ages.

Medical management in this population is often first initiated for Fontan dysfunction with minimal attention paid to blood pressure ranges. The use of ACE inhibitors has been widespread as a front line agent along with diuresis in patients with Fontan dysfunction, in spite of the fact that this management does not affect pulmonary vascular resistance significantly.[60] Data on the use of ACE inhibitors is limited. Two very small trials have compared patients with Fontans who are treated with ACE inhibitors to untreated patients, with the outcome being response to exercise. There was no change in cardiac autonomic or hemodynamic response to exercise with the addition of ACE inhibition.[61, 62] This topic deserves a more thorough investigation. The use of other classes of medications is limited, but the potential role of newer medications is exciting. For example, endothelin-1 is believed to play a significant role in the elevation of pulmonary vascular resistance as evidenced by muscularization of the pulmonary arterioles, but has not yet been applied clinically to this population.[63, 64]

The range of normative blood pressures for this population is unknown, and needs to be established with large, multi-center trials. The incidence and effect of systemic hypertension in this adult population is undocumented. In our practice, an LV mass index of 90 to 100 g/m2 measured by trans-thoracic echocardiography is arbitrarily used as an independent indication for medical management, rather than blood pressure alone.

Systemic Morphologic Right Ventricles

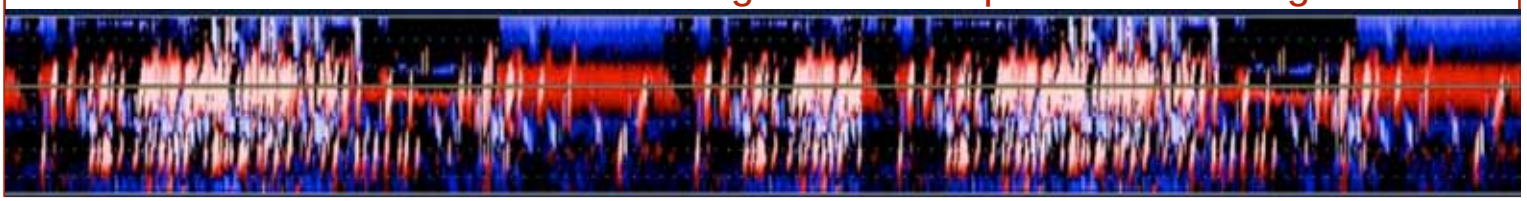
Three conditions account for the majority of patients with systemic right ventricles: congenitally corrected transposition of the great arteries (L-TGA), atrial switch operations (Senning and Mustard repairs) for transposition of the great arteries (D-TGA), and Hypoplastic Left Heart Syndrome (HLHS). The relevance of the ability of systemic right ventricles to generate systemic hypertension as defined by left ventricular standards is an unknown since normal systemic right ventricular (RV) pressure ranges have not been defined.

Replete in the hypertension literature is the improvement of hypertension and left ventricular function with exercise. Systemic right ventricular function after a Mustard repair does not, however, improve with exercise.[65, 66] Patients with either L-TGA or atrial switch operations were noted to have chronotropic incompetence and an impaired stroke volume response during exercise.[67] It is not clear whether this information can be extrapolated to other systemic right ventricles given our lack of understanding of their natural history.

Congenitally Corrected Transposition of the Great Arteries (L-TGA)

Nature's corollary to surgically created systemic right ventricles is L-TGA. The natural history of this condition is not benign, even in the absence of associated conditions. These patients are prone to systemic RV dysfunction, systemic / tricuspid valve regurgitation, conduction abnormalities, complete heart block, arrhythmias and sudden death.[68, 69, 70] The morphologic RV is usually supplied by a morphologic right coronary. As the myocardium hypertrophies to accommodate its work load, it is prone to ischemia, further worsening ventricular oxygenation and inducing further hypertrophy.[71, 72] Surgical options depend on associated conditions. The double switch operation (incorporating an atrial switch along with a great artery switch) has been used, but is not widely implemented as the standard of care and is a high risk procedure in adult populations.[73]

Defining acceptable blood pressure ranges that strike a balance between compensatory and excessive hypertrophy will be important in the future. With the assertion that 90 – 97% of these 'systemic' tricuspid valves are abnormal and prone to regurgitation, the preload of the morphologic right ventricle is rarely normal.[74] Afterload reduction with ACE inhibition as of yet has no proven role in the management of L-TGA. In the face of moderate tricuspid regurgitation, preload alteration in the form of diuresis is often added, also without proven benefit. If systemic AV valve regurgitation is severe, valve replacement is performed before the onset of right ventricular failure. No large clinical trials to date have studied the medical management of L-TGA. The balance between management of preload and afterload reduction



needs to be investigated, along with the definition of goal blood pressure ranges.

Hypoplastic Left Heart Syndrome

The afterload of a systemic right ventricle in HLHS is not normal on several accounts, even in the presence of a normal blood pressure. The pathophysiology of HLHS entails aortic arch hypoplasia, and presumably invokes the natural history of coarctation itself. Surgical correction via completion of a Fontan operation, (putting the pulmonary and systemic circulations in series), inherently increases afterload on a single ventricle by increasing the vascular length of the circuit, and decreasing the vascular cross-sectional area.[75] Neurohormonal activation after a Fontan occurs both acutely and chronically as discussed above, including activation of endothelin-1. Forearm vascular resistance has been shown to be increased along with diminished vascular endothelin function in these patients.[76, 77] Under normal circumstances, an increase in left ventricular afterload leads to an increase in ventricular contractility, but in patients with a Fontan, this compensatory mechanism is altered and does not occur. These patients are left with a mismatch in ventricular contractility and afterload with resultant reduction in mechanical efficiency and limitation in ventricular functional reserve.[78]

Afterload reduction therapy should be considered in all patients with a systemic right ventricle as a result of HLHS, although the benefit remains unproven. Cardiac dysfunction in this population is poorly tolerated, evidenced by gradual elevation of Fontan pressures and eventual Fontan dysfunction. The corollary use of ACE inhibitors to prevent myocardial remodeling and hypertrophy of the left ventricle is an established tenant in general practice, the significance of which is not clear in HLHS.[79, 80] Diastolic dysfunction secondary to compensatory hypertrophy is difficult to accurately quantitate in an outpatient setting, but if left to progress unchecked, will inevitably be detrimental.

Research needs to be done in this field beginning with a definition of a normal blood pressure range in a Fontan patient with HLHS. The potential use of newer drugs such as endothelin receptor antagonists in this population is an exciting option that may be beneficial in maximizing pulmonary blood flow, thereby further improving Fontan hemodynamics.[81]

Atrial Switch Operations

The coronary circulation of the systemic RV in both the Mustard and Senning procedures is supplied by a right coronary system, creating the potential for a myocardial perfusion supply / demand mismatch. This population is known to be at a significant risk for supraventricular tachyarrhythmias, notably atrial flutter which is associated with CHF.[82] In a series of 448 survivors of the Mustard procedure, only 40% remained in sinus rhythm at 20 years post surgery.[83] Patients have been reported to have a 2.4% loss of sinus rhythm per year.[84] The risk of sudden death is as high as 7% without identifiable risk factors in a series of 113 patients with Mustard repairs.[85]

Systemic vascular resistance (SVR) after an atrial switch has been shown to be abnormally increased during exercise.[86] Empiric use of losartan in a small number of patients with a mean systolic blood pressure of 117 showed improvement in systemic RV ejection fraction, tricuspid regurgitation and functional capacity in terms of exercise time. The mean systolic blood pressure dropped to 107 mm Hg on 50 mg/day.[87] Enalapril may not affect SVR in this population. In a study of 8 patients, blood pressure decreased over one year on enalapril without a decrease in systemic vascular resistance, exercise capacity and cardiac index at peak exercise.[88] A pilot study of a similar patient population before and after ACE inhibitor therapy for > 6 months showed no difference in exercise and MRI determined variables.[89] The benefit of the seemingly widespread and routine use of ACE inhibitors or angiotensin receptor blockers remains controversial and unproven after an atrial switch.

Conclusion

The significance of adult onset comorbidities in the congenital heart disease population as it ages has been predicted and lamented for years. However, the ongoing inadequacy of our current knowledge base as it pertains to the ACHD population is evidenced by the paucity of research that has been conducted on one of the most basic of adult health concerns, hypertension. Our review of the literature in common subpopulations with ACHD reveals little in terms of the incidence, prevalence, and implications of hypertension. Without a full understanding of the natural history of hypertension in the ACHD population, evidence based management algorithms seem frustratingly distant. Future research at its most basic level needs to consist of defining normal blood pressure ranges specific to the congenital cardiac malformation and the variations of each surgical correction.

Appendix

Keywords used along with “hypertension” and “systemic hypertension:”

- Adult Congenital
- Grown Up Congenital Heart Disease
- GUCH
- Tetralogy of Fallot
- coarctation of the aorta
- tricuspid atresia
- congenitally corrected transposition
- L-TGA
- atrial switch
- Mustard
- Senning
- systemic right ventricle
- right ventricle
- hypoplastic left heart

Relevant MeSH terms available that were used:

- aortic coarctation
- hypoplastic left heart syndrome
- transposition of great vessels
- Fontan
- Tetralogy of Fallot
- tricuspid atresia
- angiotensin converting enzyme inhibitors
- adrenergic beta-antagonists
- calcium channel blockers

References

1. Williams, RG et al. Report of the National Heart, Lung, and Blood Institute Working Group on Research in Adult Congenital Heart Disease. JACC 2006; 47(4):701-7.
2. Warnes C et al. ACC/AHA Guidelines for the Management of Adults with Congenital Heart Disease: Executive Summary. JACC 2008;52(23):1890-947.
3. Stefan MA, Hopman WM, Smythe JF. Effect of activity restriction owing to heart disease on obesity. Arch Pediatr Adolesc Med, 2005;159:477-81.
4. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J, 2005;150(2): 193-201.

5. Green, A. Outcomes of congenital heart disease: a review. Pediatr Nurs, 2004;30 (4):280-4.
6. Firer SK, Gomes JA, Love B, Mehta D. Mechanism and therapy of cardiac arrhythmias in adults with congenital heart disease. Mt Sinai J Med 2005;72(4):263-9.
7. Warnes, CA. The Adult With Congenital Heart Disease. Born to be Bad? JACC, 2005;46(1):1-8.
8. Geva, T et al. Factors Associated With Impaired Clinical Status in Long-Term Survivors of tetralogy of Fallot Repair Evaluated by Magnetic Resonance Imaging. JACC 2004;43(6):1068-74.
9. Ascah KJ et al. The effects of right ventricular hemodynamics on left ventricular configuration. Can J Cardiol 1990;Apr 6(3):99-106.
10. Chong WY, Wong WH, Chiu CS, Cheung YF. Aortic root dilation and aortic elastic properties in children after repair of tetralogy of Fallot. Am J Cardiology 2006;97(6):905-9.
11. Tan J, Davlouros P, McCarthy K, Gatzoulis M, Ho S. Intrinsic histological abnormalities of aortic root and ascending aorta in tetralogy of Fallot: Evidence of causative mechanism for aortic dilation and aortopathy. Circ 2005;112:961-8.
12. Abraham KA et al. Tetralogy of Fallot in adults. A report on 147 patients. Am J Med, 1979;66(5):811-6.
13. Schiaffino S et al. Myosin changes in hypertrophied human atrial and ventricular myocardium. A correlated immunofluorescence and quantitative immunochemical study on serial cryosections. Eur Hear J, 1984;5 Suppl F:95-102.
14. Matthys D, Verhaaren H. exercise hypertension in children after surgical repair of treated ventricular and atrial septal defects. Arch Mal Coeur Vaiss, 1990;83(5):697-700.
15. Tobias JD. Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children.; American Journal of Therapeutics, 2001;8:3-6.
16. Bolens Me et al. Electrophysiologic effects of intravenous Verapamil in children after operations for congenital heart disease. Am J Cardiol. 1987;60 (8):692-6.
17. Roos-Hesselilnk J et al. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Circulation 1995;91 (2214-19.
18. Brodde OE et al. Drug and disease induced changes of human cardiac beta 1 and beta 2 adrenoceptors. Eur Heart J, 1989;10(B):38-44.
19. Steinfath M et al. Changes in cardiac beta-adrenoceptors in human heart diseases: relationship to the degree of heart failure and further evidence for etiology-related regulation of beta 1 and beta 2 subtypes. J Cardiothorac Vasc Anesth 1993;7(6):668-73.
20. Khamssi M, Brodde OE. The role of cardiac beta1- and beta 2-adrenoceptor stimulation in heart failure. J Cardiovasc Pharmacol 1990;16 (5):S133-7.
21. Niwa K. Aortic root dilation in tetralogy of Fallot long term after repair-histology of the aorta in tetralogy of Fallot: evidence of intrinsic aortopathy. Int J Cardiology 2005;103:117-19.
22. Niwa K, Gatzoulis MA et al. Progressive aortic root dilation in adults late after repair of tetralogy of Fallot. Circulation 2002;106:1374-78.
23. Kaemmerer H, Oelert F, Bahlmann J, Blucher S, Meyer GP, Mugge A. Arterial hypertension in adults after surgical treatment of aortic coarctation. Thorac Cardiovasc Surg. 1998;46(3):121-5.
24. Tor-Salazar OH et al. Long term follow up of patients after coarctation of the aorta repair. Am J Cardiol, 2002;89:541-47.
25. Beerman LB et al. Coarctation of the aorta in children. Late results after surgery. Am J Dis Child. 1980;134(5): 464-6.
26. Presbitero P, Demaire D et al. Long term results (15-30 years) of surgical repair of aortic coarctation. Br Heart J 1987;57(5):462-7.
27. Ou P, Mousseaux E, Szezepanski I, Aggoun Y, Bonnet D. Does hypertension need treatment following correction of coarctation in childhood? Arch Mal Coeur Vaiss, 2006;99(10): 924-7.
28. Cohen M, Fuster V, Steele P, Driscoll D, McGood D. Coarctation of the aorta; long term follow up and prediction of outcome after surgical correction. Circulation, 1989; 80:840-45.
29. Shinebourne EA et al. Coarctation of the aorta in infancy and childhood. Br Hear J, 1976;38:375-80.
30. De Divitiis et al. Ambulatory blood pressure, left ventricular mass, and conduit artery function late after successful repair of coarctation of the aorta. JACC, 2003;41(12):2259-65.
31. Oliver JM, Gellego P, Gonzalez A, Aroca A, Bret M, Mesa JM. Risk factors for aortic complications in adults with coarctation of the aorta. JACC 2004;44 (8):1641-47.
32. Ou P, Bonnet D, Auriacombe L, Pedroni E, Balleaux F, Sidi D, Mousseaux E. Late systemic hypertension and aortic arch geometry after successful repair of coarctation of the aorta. Eur Hear J, 2004:25:1853-59.
33. Lashley D et al. Aortic arch morphology and late systemic hypertension following correction of coarctation of aorta. Congenit Heart Dis, 2007;2(6):410-5.
34. Vriend JW et al. Predictive value of mild, residual descending aortic narrowing for blood pressure and vascular damage in patients after repair of aortic coarctation. Eur Hear J, 2005:26(1)84-90.
35. Giordano U et al. the influence of different surgical procedures on hypertension after repair of coarctation. Cardiol Young, 2005:15(5):477-80.
36. Walhout R et al. Comparison of polytetrafluoroethylene patch aortoplasty and end-to-end anastamosis for coarctation of the aorta. J Thorac Cardiovasc Surg 2003;126(2):521-8.
37. De Divitiis M et al. Arterial hypertension and cardiovascular prognosis after successful repair of aortic coarctation: a clinical model for the study of vascular function. Nutr Metab Cardiovsc Dis, 2005;15(5):382-94.
38. Vriend J, Mulder B. Late complications in patients after repair of aortic coarctation: implications for management. Int J Cardiol, 2005;101:399-406.
39. Shinebourne EA et al. Coarctation of the aorta in infancy and childhood. Br Hear J, 1976;38:375-80.
40. Clarkson PM et al. Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 year follow-up with particular reference to late systemic hypertension. Am J Cardiol, 1983;51(9): 1481-8.
41. Vriend J, Montfrans G, Romkes H, Vliegen H, Veen G, Tijssen J, Mulder B. relation between exercise-induced hypertension and sustained hypertension in adult patients after successful repair of aortic coarctation. J Hypertension, 2004:22(3):501-9.
42. Beekman RH et al. Altered baroreceptor function in children with systolic hypertension after coarctation repair. Am J Cardiol, 1983;52(1):112-7.
43. Heath D et al. The carotid bodies in coarctation of the aorta. Br J Dis Chest, 1986;80(2):122-30.
44. Aggoun Y et al. Arterial dysfunction after treatment of coarctation of the aorta. Arch Mal Coeur Vaiss, 2001;94(8): 785-9.
45. Fallo F et al. Effect of captopril on blood pressure and on the renin-angiotensin-aldosterone system in coarctation of the aorta. Clin Exp Hypertens A, 1983;5(3): 321-8.
46. Fallo F et al. Resistance to Captopril in hypertension of coarctation of the aorta. Int J Cardiol, 1985;9(1)111-3.
47. Reinhard W et al. Grown-up congenital heart disease: a problem to take care of. European Heart Journal, 2005;26:8-10.
48. Gono J, Freeman L. Aortic coarctation repair – lost and found: 'The role of local long term specialised care. Int J Cardiol, 2005;104:176-83.
49. Warnes C et al. ACC/AHA Guidelines for the Management of Adults with

Congenital Heart Disease: Executive Summary. JACC 2008;52(23):1890-947.
50. Therrien J, Warnes C, Daliento L et al. Canadian Cardiovascular society consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease part III. Can J Cardiol 2001;17:1135-58.
51. Vriend JW, Zwinderman AH, de Groot E, Kastelein JJ, Bouma BJ, Mulder BJ. Predictive value of mild, residual descending aortic narrowing for blood pressure and vascular damage in patients after repair of aortic coarctation. Eur H Jour 2004;26:84-90.
52. Kaulitz R, Hofbeck M. Current treatment and prognosis in children with functionally univentricular hearts. Arch Dis child 2005:90:757-62.
53. Mair DD et al. The Fontan procedure for tricuspid atresia: early and late results of a 25 year experience with 216 patients. JACC 2001, 37(3):933-39.
54. Mastalir ET et al. Late clinical outcomes of the Fontan operation in patients with tricuspid atresia. Arq Bas Cardiol, 2002; 79(1):56-60.
55. Girod EA, Fontan F et al. Long term results after the Fontan operation for tricuspid atresia. Circulation 1987;75:605-10.
56. Mainwaring RD et al. Comparison of the hormonal response after bidirectional Glenn and Fontan procedures. Ann Thorac Surg 1994;57:59-64.
57. Hiramatsu T et al. Time course of endothelin-1 and adrenomodullin after the Fontan procedure. Ann Thorac Surg 1999;68:169-72.
58. Hjortdal VE et al. Neurohormonal activation late after cavopulmonary connection. Heart 2000;83:439-43.
59. Eicken A et al. Hearts late after Fontan operation have normal mass, normal volume, and reduced systolic function. JACC 2003;42(6):1061-65.
60. Momma K. ACE inhibitors in pediatric patients with heart failure. Paediatr Drugs, 2006;8(1):55-69.
61. Ohuchi H et al. Severely impaired cardiac autonomic nervous activity after the Fontan operation. Circulation, 2001;104:1513-18.
62. Kouatli AA et al. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 1997;96:1507-12.
63. Yamagishi M et al. The role of plasma endothelin in the Fontan circulation. J Cardiovasc Surg (Torino), 2002;43(6): 793-7.
64. Levy M et al. Endothelial vasoactive factors: predictive markers of the results of the Fontan intervention? Arch Mal Coeur Vaiss, 2004;97(5): 515-21.
65. Gelatt M et al. Arrhythmia and mortality after the mustard procedure: a 30 year single center experience. JACC 1997;29(1):194-201.
66. Vogel M et al. Long term results of mustard operation in transposition of the great arteries. Angiographic and nuclear medicine study of ventricular function. Herz 1992;17(3):190-7.
67. Ohuchi H et al. Comparison of the right and left ventricle as a systemic ventricle during exercise in patients with congenital heart disease. American Heart J, 1999;137:1185-94.
68. Webb GD et al. Transposition complexes. Cardiol Clin 1993;11(4): 651-64.
69. Mark Egloff L et al. Congenitally corrected transposition of the great arteries: a clinical and surgical study. Thorac Cardiovasc Surg 1980;28(4): 228-32.
70. Bjarke BB, Kidd BS. Congenitally corrected transposition of the great arteries. A clinical study of 101 cases. Acta Paediatr Scand, 1976;65(2): 153-60.
71. Mark Hornung TS et al. Myocardial perfusion defects and associated systemic ventricular dysfunction in congenitally corrected transposition of the great arteries. Heart 1998;80:322-26.
72. Sharma S et al. Dynamic changes of gene expression in hypoxia induced right ventricular hypertrophy. Am J Physiol Heart Circ Physiol 2004:286:H1185-92.
73. Poirier NC, Mee RB. Left ventricular reconditioning and anatomical correction for systemic right ventricular dysfunction. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu, 2000;3:198-215.
74. Dyer K, Graham TP. Congenitally corrected transposition of the great arteries: current treatment options. Current Treatment Options in Cardiovascular Medicine 2003;5:399-407.
75. Bridges ND et al. Baffle Fenestration with Subsequent transcatheter closure. Modification of the Fontan operation for patients at increased risk. Circulation, 1990;82:1681-89.
76. Kelley JR et al. Diminished venous capacitance in patients with univentricular hearts after the Fontan procedure. Am J Cardiol 1995;76:158-63.
77. Mahle WT et al. Endothelial function following the Fontan operation. Am J. Cardiol 2003;91:1286-88.
78. Shaddy RE, Wernovsky G. Pediatric Heart Failure. Boca Raton Fl, Taylor and Francis. 2005
79. Senzaki H, Masutani S, Ishido H, Taketazu M, Kobayashi t, Sasaki N, Asano H, Katogi T, Kyo S, Yokote Y. Cardiac rest and reserve function in patients with Fontan Circulation. JACC, 2006;47(12):2528-35.
80. Bonnet D. Plasticity of the myocardium in pediatric cardiology. Arch Pediatr 1996;(3)1273-75.
81. Oishi P et al. Nitric oxide-endothelin-1 interactions after surgically induced acute increases in pulmonary blood flow in intact lambs. Am J Physiol-Heart 2006;290:1922-32.
82. Puley G et al. Arrhythmia and survival in patients > 18 years of age after the mustard procedure for complete transposition of the great arteries. Am J Cardiol, 1999;83(7):1080-4.
83. Gelatt M et al. Arrhythmia and mortality after the Mustard procedure: a 30 year single center experience. JACC 1997;29 (1):194-201.
84. Gatzoulis MA et al. Diagnosis and Management of Adult Congenital Heart Disease. Edinburgh, Churchill Livingstone. 2003
85. Wilson NJ et al. Long term outcome after the Mustard repair for simple transposition of the great arteries, 28 year follow up. JACC 1998;32(3): 758-65.
86. Ensing GJ et al. Cardiovascular response to exercise after the Mustard operation for simple and complex transposition of the great vessels. Am J Cardiol 1988:62;617-22.
87. Lester SJ et al. Effects of Losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries. Am J Cardiol 2001;88:1314-16.

88. Robinson B, Heise CT, Moore JW, Anella J, Sokoloski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transpositiom of the great arteries. Pediatr Cardiol 2002:23;618-23.
89. Hechter S, Fredriksen P, Lieu P, Veldtman G, Merchant N, Freeman M, Therrien J, Benson L, Siu S, Webb G. Angiotensin-converting enzyme inhibitors in adults after Mustard procedure. Am J Cardiol, 2001:87;660-63.

CCT

Corresponding Author

Mark Townsend, MD
The Cardiovascular Group
Centra Stroobants Heart Center
2410 Atherholt Rd.
Lynchburg, VA 24501 USA
P (434) 200-5252; F (434)544-2312
Mark.Townsend@centrahealth.com

Robert Battle, MD
University Of Virginia Medical Center
Charlottesville, VA USA

Alexander Ellis, MD
Children's Hospital of The King's Daughters
Norfolk, VA USA

Sam Lee, MD
The Children's Heart Center, Medical College of Virginia, VCU
Richmond, VA USA

William Moskowitz, MD
The Children's Heart Center, Medical College of Virginia, VCU
Richmond, VA USA

United States and Canada Pediatric Cardiologists, Congenital Heart Surgeons in Hospitals Providing Open Heart Surgery for Children 2008/2009

Complied by Dilip R. Bhatt. MD, FAAP; Kenneth Jue, MD, FAAP; Janice Stillwell (Project Manager)

This Directory is available in a PDF file:
www.CongenitalCardiology.com/DIR2008.pdf:

Published by
CONGENITAL CARDIOLOGY TODAY

BioSTAR®

Bioabsorbable Septal Repair

Introducing an Important Advance
in Structural Heart Repair

NMT Medical, Inc.

27 Wormwood Street
Boston, MA 02210-1625 USA
+1-617-737-0830 ext. 304
Fax: +1-617-737-1084
www.nmtmedical.com

CE 0086

Medical News, Products and Information

Novel Gene Found for Dilated Cardiomyopathy

Researchers in the Heart Institute at Cincinnati Children's Hospital Medical Center have discovered a novel gene responsible for heart muscle disease and chronic heart failure in some children and adults with dilated cardiomyopathy (DCM).

Mutations in the ANKRD1 gene may cause DCM, which is the most common cause of chronic heart failure in young people and the most common reason for heart transplant. ANKRD1 is a gene that encodes a protein that plays a role in the structure and functional ability of the heart.

The internationally conducted study was published in the July 21, 2009 issue of the *Journal of the American College of Cardiology.*

"Our study indicates that variants in ANKRD1 result in dysfunction of the contraction apparatus and signaling machinery of the heart – the method by which cells communicate to influence heart function," says Jeffrey Towbin, MD, Co-Director of the Heart Institute and Director of Cardiology at Cincinnati Children's. "This clarifies the mechanisms by which these inherited mutations cause disease in a subset of DCM patients."

DCM is a condition in which the heart becomes weakened and enlarged and cannot pump blood efficiently. The decreased heart function can affect the lungs, liver, kidneys and other body systems. DCM is one of the cardiomyopathies, a group of diseases that primarily affect the heart muscle. Cardiomyopathies have different causes and affect the heart in a variety of ways. In DCM the major pumping chamber of the heart, the left ventricle, is dilated, often without any obvious cause.

DCM occurs more frequently in men than in women and is most common between the ages of 20 and 60 years, although it also occurs in fetuses, newborns and children. About one in three cases of congestive heart failure is due to DCM, which also occurs in children.

Dr. Towbin and his colleagues screened 208 patients, mostly children and young adults, with DCM for gene mutations. They found three, disease-associated variants of the ANKRD1 gene. All four patients carrying the variants were male. This prevalence rate is consistent with prevalence data for most of the other known genes associated with DCM. This finding confirms previous gene discoveries by Dr. Towbin's group. It also "provides us with a better understanding of the causes and mechanisms involved in the development of this disease and will enable better genetic testing and new treatments to be devised to improve outcomes of this serious disease," according to Dr. Towbin.

The study was funded by grants from the National Institutes of Health, the Children's Cardiomyopathy Foundation and the Abby Glaser Children's Heart Fund. Collaborating institutions included Texas Children's Hospital and Baylor College of Medicine in Houston, the Medical Faculty Mannheim at the University of Heidelberg in Germany, the Institute of Cardiovascular Science and University College in London in the United Kingdom, and the Tokyo Medical and Dental University in Japan.

Dr. Towbin is co-author of another study in the same issue of *JACC* showing that the ANKRD1 gene also causes a different clinical form of cardiomyopathy.

Registration is Open for Cardiology 2010

Cardiology 2010 will take place February 10-14, 2010 at the Contemporary Resort and Convention Center, Walt Disney World, Lake Buena Vista, Florida, USA.

This annual post-graduate course is designed for physicians, nurses, perfusionists, administrators, clinical pharmacists, respiratory therapists, and all others involved in the care of neonates, infants, children and young adults with cardiovascular disease.

The International course faculty will present over 300 talks in Plenary Sessions, as well as small group and subspecialty breakout sessions covering all areas necessary for comprehensive care of patients. Each year, the course faculty, topics and format are chosen following a careful assessment of prior attendee's comments and reviews. *Cardiology 2010* also invites new young investigators from around the globe to present new science and ideas.

Based upon the positive feedback they received following *Cardiology 2009* in Nassau last year, they have modified the course format to allow attendees the opportunity to enjoy more free time without a strict meeting agenda. In addition, in response to the realities of the current economic climate, they have reduced the cost of the meeting for all attendees, while still providing over 30 contact hours including hot topics, basic reviews, subspecialty breakouts and much more!

Abstract Submission Deadline is October 19th, 2009; Notification of Acceptance will be October 30, 2009. Course participants are encouraged to submit abstracts for consideration for the *Annual Outstanding Investigator and Nursing Scientist Awards*. The top six abstracts will be presented as oral presentations; the remaining will be presented in one of three poster sessions. The international course faculty will select the recipients of the *7th Annual Outstanding Investigator Award*, and the *5th Annual Nursing Scientist Awards*; the winners will receive an award at the featured plenary session on February 13th, 2010, of a complimentary registration for *Cardiology 2011* and a $500 travel grant.

Abstracts will be accepted in all aspects of cardiovascular care, including cardiac issues in the neonatal and pediatric intensive care units, cardiovascular nursing, inpatient and outpatient cardiology, surgical, anesthesia and perfusion research, as well as basic cardiovascular science.

There is a Special Track for Residents, Fellows and Junior Faculty, Including a Pre- and Post-Conference Seminar. Expanding on a very popular feature in previous years, a special course-long track is planned for trainees and junior faculty early in their career to provide guidance on career choices, financial security, work-life balance and other practical guidelines for long-term success in cardiovascular medicine.

For more information, to download the program, to submit abstracts, or to register, go to: www.chop.edu/cardiology2010.

MRI Simulation of Blood Flow Helps Plan Child's Delicate Heart Surgery

Researchers at the Georgia Institute of Technology, collaborating with pediatric cardiologists and surgeons at The Children's Hospital of Philadelphia, have developed a tool for virtual surgery that allows heart surgeons to view the predicted effects of different surgical approaches. By manipulating three-dimensional cardiac magnetic resonance images of a patient's specific anatomy, physicians can compare how alternative approaches affect blood flow and expected outcomes, and can select the best approach for each patient before entering the operating room.

"This tool helps us to get the best result for each patient," said co-author Mark A. Fogel, MD, an Associate Professor of Cardiology and Radiology, and Director of Cardiac MRI at The Children's Hospital of Philadelphia. "The team can assess the different surgical options to achieve the best blood flow and the optimum mixture of blood, so we can maximize the heart's energy efficiency."

In the August issue of the *Journal of the American College of Cardiology: Cardiovascular Imaging*, the researchers describe the surgical planning methodology, detailing how the tool helped them to plan the surgery of a four-year-old girl who was born with just one functional ventricle, or pumping chamber, instead of two.

Two in every 1,000 babies in the United States are born with this type of single ventricle heart defect. These children typically suffer from low levels of oxygen in their tissues because their oxygen-rich and oxygen-poor blood mix in their one functional ventricle before being redistributed to their lungs and body.

To correct this, the children undergo a series of three open-heart surgeries – called the staged Fontan reconstruction – to reshape the circulation in a way that allows oxygen-poor blood to flow from the limbs directly to the lungs without going through the heart. While these vascular modifications can eliminate blood mixing and restore normal oxygenation levels, surgeons and cardiologists must ensure that the lungs will receive proper amounts of blood and nutrients after the surgery so that normal development occurs.

"Preoperatively determining the Fontan configuration that will achieve balanced blood flow to the lungs is very difficult and the wide variety and complexity of patients' anatomies requires an approach that is very specific and personalized," said Ajit Yoganathan, PhD, Regents' Professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "With our surgical planning framework, the physicians gain a better understanding of each child's unique heart defect, thus improving the surgery outcome and recovery time."

The patient described in this paper, Amanda Mayer, age four, of Staten Island, NY, had previously undergone all three stages of the Fontan procedure at The Children's Hospital of Philadelphia, but developed severe complications. Her oxygen saturation was very low – only 72%, compared to normal levels of at least 95% – which indicated the possibility of abnormal connections between the veins and arteries in one of her lungs. Normally, the liver releases hormonal factors that prevent these abnormal connections, so the presence of the malformations indicated a low supply of hepatic blood to the lung.

To improve the distribution of these hormonal factors to both lungs, the surgeons needed to re-operate and reconfigure the patient's cardiovascular anatomy. Georgia Tech's surgical planning framework helped Thomas L. Spray, MD, Chief of the Division of Cardiothoracic Surgery at Children's Hospital, to determine the optimal surgical option.

"MRI acquires images of the child's heart without using radiation," said Spray. "Then we use the computerized technology to model different connections to simulate optimum blood flow characteristics, before we perform the surgery."

The image-based surgical planning consisted of five major steps: acquiring magnetic resonance images of the child's heart at different times in the cardiac cycle, modeling the preoperative heart anatomy and blood flow, performing virtual surgeries, using computational fluid dynamics to model the proposed postoperative flow, and measuring the distribution of liver-derived hormonal factors and other clinically relevant parameters as feedback to the surgeon.

Fogel collected three different types of magnetic resonance images, and Yoganathan, along with graduate students Kartik Sundareswaran and Diane de Zélicourt, generated a three-dimensional model of the child's cardiovascular anatomy. From the model they reconstructed the three-dimensional pre-operative flow fields to understand the underlying causes of the malformations.

For this particular patient, the team saw a highly uneven flow distribution – the left lung was receiving about 70% of the blood pumped out by the heart, but only five percent of the hepatic blood. Both observations suggested left lung malformations, but closer examination of the flow structures in that particular patient revealed that the competition between different vessels at the center of the original Fontan connection effectively forced all hepatic factors into the right lung even though a vast majority of total cardiac output went to the left lung.

To facilitate the design of the surgical options that would correct this problem, Jarek Rossignac, PhD, a professor in Georgia Tech's School of Interactive Computing, developed Surgem, an interactive geometric modeling environment that allowed the surgeon to use both hands and natural gestures in three-dimensions to grab, pull, twist and bend a three-dimensional computer representation of the patient's anatomy. After analyzing the three-dimensional reconstruction of the failing cardiovascular geometry, the team considered three surgical options.

The research team then performed computational fluid dynamics simulations on all three options to investigate for each how well blood would flow to the lungs and the amount of energy required to drive blood through each connection design. These measures of clinical performance allowed the cardiologists and surgeons to conduct a risk/benefit analysis, which also included factors such as difficulty of completion and potential complications.

Of the three choices, Spray favored the option that showed a slightly higher energy cost, but exhibited the best performance with regards to hepatic factor distribution to the left and right lungs. Five months after the surgery, Mayer showed a dramatic improvement in her overall clinical condition and oxygen saturation levels, which increased from 72% to 94%. Mayer is breathing easier, and is now able to play actively like other children, according to her cardiologist, Donald Putman, MD, of Staten Island, NY.

"The ability to perform this work is a team effort," Fogel added. "State-of-the-art three-dimensional cardiac MRI married to modern biomedical engineering and applied anatomy and physiology enabled this approach. With the advanced pediatric cardiothoracic surgery we have here at The Children's Hospital of

Philadelphia, patients can benefit from this new method."

Additional authors on the paper include Shiva Sharma from Pediatric Cardiology Services, Kirk Kanter from the Division of Cardiothoracic Surgery at Emory University, and Fotis Sotiropoulos from the Department of Civil Engineering at the University of Minnesota.

This work was funded by grant number HL67622 from the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

First-Degree Relatives of Patients with the Most Common Cardiac Birth Defect Should be Screened for Larger-Than-Normal Aortas

Bicuspid Aortic Valve (BAV), a condition in which patients' aortic valves have just two leaflets instead of the normal three, is the most common cardiac anomaly, affecting up to 2% of the general population. The defect can result in calcification deposits on the heart valve, leakage of the valve and may results in a feeling of tightness in the chest as well as shortness of breath. The condition is easily diagnosed; often physicians can hear a "click" or a murmur when they listen to a BAV patient's heart with a stethoscope.

Studies have shown that BAV is likely genetic, although the gene has not been identified, and in some families, incidence of this defect could run as high as 20%.

A study, published in the June 8, 2009, *Journal of the American College of Cardiology*, suggests that nearly a third of first-degree relatives (siblings, children or parents) of BAV patients are likely to have enlarged aortas, a potentially serious condition that can only be detected by undergoing transthoracic echocardiograms. This was found even in the absence of any abnormalities of the heart valve itself.

According to the study, 325 of first-degree relatives with no heart valve abnormality had significantly larger aortas that expected for age, gender and body size as compared to no enlargement seen in control patients. Also, the study found that the aortas of the first-degree relatives had abnormal stiffness similar to the patients with congenital bicuspid valve. Generally, when aortas are 50 millimeters in diameter, surgery is recommended in order to prevent a rupture of the aorta.

"If you know that a relative does have bicuspid aortic valve, then you know that you should be screened," said study author Kirsten Tolstrup, MD, Assistant Director of the Cardiac Noninvasive Laboratory at the Cedars-Sinai Heart Institute. "BAV appears to be a genetic condition that has many different manifestations, so we will be studying the genes."

Kirsten Tolstup, MD, Assistant Director of the Cardiac Noninvasive Laboratory at the Cedars-Sinai Heart Institute, is available to discuss the study's findings and provide additional details.

This study, conducted among 54 patients with bicuspid aortic valve and 48 first-degree relatives of those patients as well as 45 matched controls found:

- 32 % of apparently healthy first-degree relatives have enlarged aortas
- 53 % of BAV patients had enlarged aortas
- 9.4 % of first-degree relatives had BAV

The findings suggest that patients with bicuspid aortic valve and their first-degree relatives should have a screening echocardiogram to be evaluated for dilated aorta and bicuspid aortic valve.

The study abstract can be accessed at: http://content.onlinejacc.org

---

Comprehensive Cardiogenetic Testing for Families of Sudden Unexplained Death Victims Can Save Lives

Relatives of a young person who dies suddenly should always be referred for cardiological and genetic examination in order to identify if they too are at risk of sudden death, a scientist told the annual conference of the (26 May 2009). Dr. Christian van der Werf, a research fellow at the Department of Cardiogenetics, Academic Medical Centre, Amsterdam, The Netherlands said that, although his team's research showed that inherited heart disease was present in over 30% of the families of sudden unexplained death (SUD) victims, the majority of such relatives were currently not being referred for examination.

When an individual aged 1-50 years dies suddenly, autopsy reveals an inheritable heart disease in the majority of the victims. But in approximately 20% autopsy does not reveal the cause of death. "We thought that cardiological and genetic examination of surviving first degree relatives of these SUD patients might reveal an inherited heart disease," said Dr. van der Werf.

In the largest such study to date, the team looked at the outcome of first degree relative screening in 127 families who had suffered an SUD and where either there had been no autopsy (53.8%), or the autopsy did not reveal a cause of death. The average age at death of the SUD victims was only 29.8 years old.

The initial examination of the relatives consisted of taking personal and family medical history and a resting ECG. A second cardiac autopsy of the SUD victim was undertaken if tissue had been stored and was available. Additional cardiological examinations of the relatives were performed where necessary. Genetic analysis of the associated candidate gene(s) was performed in material obtained from the deceased person or in those relatives who showed clinical abnormalities.

The researchers found inherited heart disease in 36 (32%) of the families. These results meant that doctors were able to treat affected relatives and try to prevent their succumbing to sudden cardiac death. "The scale of heart disease that we found in such families underlines the necessity for general practitioners to refer first degree relatives of SUD victims to a specialised cardiogenetics department as soon as possible", said Dr. van der Werf. "Currently we estimate that only 10% of SUD families are being examined for inherited heart conditions.

The study is the second report from the registry of families who attended the Amsterdam centre's cardiogenetics department because of unexplained sudden death of a relative aged 1-50 years. The scientists intend to continue to report the yield of family screening in an increasing number of families.

"At present we are conducting a study to stimulate general practitioners and other involved physicians to request autopsy and DNA-storage for SUD patients and to refer relatives to a cardiogenetics department after a case of sudden death at young age. We hope this will lead to identification of more families at risk of sudden cardiac death, in which preventive measures then can be taken" said Dr. van der Werf.

"Relatives of young sudden death victims are often referred to cardiologists for cardiological examination. We believe relatives should instead be referred to cardiogenetics

departments, where clinical geneticists, cardiologists and psychosocial workers cooperate. These professionals specialise in inherited heart diseases and their clinical and psychosocial implications, and can provide a better quality of care. Additionally, cardiologists should receive more education in inherited heart diseases. By taking these measures we can save lives and avoid further distress for families who have already suffered enough," he said.

Stem Cells and Embryonic Heart Development

Biologists have long wondered why the embryonic heart begins beating so early, before the tissues actually need to be infused with blood. Two groups of researchers from Children's Hospital Boston, Brigham and Women's Hospital, and the Harvard Stem Cell Institute (HSCI) - presenting multiple lines of evidence from zebrafish, mice and mouse embryonic stem cells - provide an intriguing answer: A beating heart and blood flow are necessary for development of the blood system, which relies on mechanical stresses to cue its formation.

Their studies, published online by the journals *Cell* and *Nature*, respectively, on May 13, 2009 together offer clues that may help in treating blood diseases such as leukemia, immune deficiency and sickle cell anemia, suggesting new ways scientists can make the types of blood cells a patient needs. This would help patients who require marrow or cord blood transplants, who do not have a perfect donor match.

One team, led by Leonard Zon, MD, of the Division of Hematology/Oncology at Children's and Director of its Stem Cell Research Program, used zebrafish, whose transparent embryos allow direct observation of embryonic development.

Publishing in *Cell*, Zon and colleagues discovered that compounds that modulate blood flow had a potent impact on the expression of a master regulator of blood formation, known as Runx1, which is also a recognized marker for the blood stem cells that give rise to all the cell types in the blood system.

Confirming this observation, a strain of mutant embryos that lacked a heartbeat and blood circulation exhibited severely reduced numbers of blood stem cells. Further work showed that nitric oxide, whose production is increased in the presence of blood flow, is the key biochemical regulator: Increasing nitric oxide production restored blood stem cell production in the mutant fish embryos, while inhibiting nitric oxide production led to reduced stem cell number.

Zon and colleagues went on to demonstrate that nitric oxide production was coupled to the initiation of blood stem cell formation across vertebrate species. Suppression of nitric oxide production in mice, by either genetic or chemical means, similarly reduced the number of functional Runx1-expressing blood stem cells.
"Nitric oxide appears to be a critical signal to start the process of blood stem cell production," says Zon, who is also affiliated with the HSCI. "This finding connects the change in blood flow with the production of new blood cells."

The second team, publishing in *Nature*, was led by George Q. Daley, MD, PhD, Director of the Stem Cell Transplantation Program at Children's Hospital Boston, and Guillermo García-Cardeña, Director of the Laboratory for Systems Biology of the Center for Excellence in Vascular Biology at Brigham and Women's Hospital, along with scientists from the Indiana University School of Medicine. Intrigued by the appearance of blood progenitors in the wall of the developing aorta soon after the heart starts beating, they investigated the effects of mechanical stimulation on blood formation in cultured mouse embryonic stem cells.

They showed that shear stress – the frictional force of fluid flow on the surface of cells lining the embryonic aorta – increases the expression of master regulators of blood formation, including Runx1, and of genetic markers found in blood stem cells. Shear stress also increased formation of colonies of progenitor cells that give rise to specific lineages of blood cells (red cells, lymphocytes, etc.). These findings demonstrate that biomechanical forces promote blood formation.

Daley, García-Cardeña and colleagues also studied mouse embryos with a mutation that prevented initiation of the heartbeat. These embryos had a sharp reduction in progenitor blood cell colonies, along with reduced expression of genetic markers of blood stem cells. When specific cells from the mutant embryos were exposed in vitro to shear stress, markers of blood stem cells and numbers of blood cell colonies were restored.

Finally, the team showed that when nitric oxide production was inhibited, in both cell cultures and live mouse embryos, the effects of shear stress on blood progenitor colony formation were reduced.

"In learning how the heartbeat stimulates blood formation in embryos, we've taken a leap forward in understanding how to direct blood formation from embryonic stem cells in the petri dish," says Daley, who is also affiliated with the HSCI.

The authors of the two papers speculate that drugs that mimic the effects of embryonic blood flow on blood precursor cells, or molecules involved in nitric oxide signaling, might be therapeutically beneficial for patients with blood diseases. For example, nitric oxide could be used to grow and expand blood stem cells either in the culture dish or in patients after transplantation.

CONGENITAL CARDIOLOGY TODAY

Headquarters
9008 Copenhaver Dr. Ste. M
Potomac, MD 20854 USA

Publishing Management
Tony Carlson, Founder & Senior Editor
TCarlsonmd@gmail.com
Richard Koulbanis, Publisher & Editor-in-Chief
RichardK@CCT.bz
John W. Moore, MD, MPH, Medical Editor
JMoore@RCHSD.org

Associate Editorial and Web Support Staff
Chris Carlson, Caryl Cornell, Virginia Dematatis, and Loraine Watts

Editorial Board
Teiji Akagi, MD
Zohair Al Halees, MD
Mazeni Alwi, MD
Felix Berger, MD
Fadi Bitar, MD
Jacek Bialkowski, MD
Philipp Bonhoeffer, MD
Mario Carminati, MD
Anthony C. Chang, MD, MBA
John P. Cheatham, MD
Bharat Dalvi, MD, MBBS, DM
Horacio Faella, MD
Yun-Ching Fu, MD
Felipe Heusser, MD
Ziyad M. Hijazi, MD, MPH
Ralf Holzer, MD
Marshall Jacobs, MD
R. Krishna Kumar, MD, DM, MBBS
Gerald Ross Marx, MD
Tarek S. Momenah, MBBS, DCH
Toshio Nakanishi, MD, PhD
Carlos A. C. Pedra, MD
Daniel Penny, MD
James C. Perry, MD
P. Syamasundar Rao, MD
Shakeel A. Qureshi, MD
Andrew Redington, MD
Carlos E. Ruiz, MD, PhD
Girish S. Shirali, MD
Horst Sievert, MD
Hideshi Tomita, MD
Gil Wernovsky, MD
Zhuoming Xu, MD, PhD
William C. L. Yip, MD
Carlos Zabal, MD

FREE Subscription: Congenital Cardiology Today is available free to qualified professionals worldwide in pediatric and congenital cardiology. International editions available in electronic PDF file only; North American edition available in print. Send an email to Subs@CCT.bz. Include your name, title, organization, address, phone and email.

Contacts and Other Information: For detailed information on author submission, sponsorships, editorial, production and sales contact, current and back issues, see website.

TINY HEARTS INSPIRED HYBRID LABS WITH ACCESS FOR BIG TEAMS.

Fixing a heart from birth through adulthood takes big teams working together. So we examined the needs of leading clinicians when designing our hybrid solutions. The result: our Infinix™-i with 5-axis positioners and low profile detectors, stays out of the way, but right where needed, providing the best possible access to patients. To lead, you must first listen.

medical.toshiba.com

TOSHIBA
Leading Innovation