Sudden Cardiac Death in Adult Congenital Heart Disease

Summary: Sudden cardiac death (SCD) is a major cause of mortality in adults with congenital heart disease (CHD). As this population ages, the population at risk and the risk factors associated with SCD may be changing. Therefore, we conducted a multicenter case-control study to determine the adult CHD population at risk of SCD and the clinical parameters associated with SCD. From 3 databases including 25,790 adults with CHD, 1,189 deaths (5%) were identified, of which 213 patients (19%) died suddenly. The cause of sudden death was proven or presumed arrhythmia in 171 of 1,189 patients (14%; 64% male; mean age, 36±15 years). Most cases of SCD occurred at rest (69%) or during sleep (11%). The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. We have identified several clinical parameters associated with SCD in adults with CHD that may be helpful in identifying high-risk patients and may guide clinicians in their treatment strategy. The identified clinical parameters are similar to the risk factors for SCD in ischemic cardiomyopathy and include documented supraventricular tachycardias, impaired ventricular function, prolonged QRS duration, and increased QT dispersion. Although patients with repaired cyanotic and left-sided outflow tract lesions have been identified previously as at risk for SCD, this study reveals that a broader spectrum of adults with CHD, even those with cardiac lesions traditionally considered mild, are potentially at risk for SCD. This highlights the need for further prospective studies as well as vigilant ongoing follow-up of the adult with CHD.

Conclusions: The clinical parameters found to be associated with SCD in adults with a broad spectrum of CHD, including systemic right ventricles, are similar to those in ischemic heart disease. Moreover, even those patients with mild cardiac lesions are potentially at risk for SCD. This highlights the need for further prospective studies as well as vigilant ongoing follow-up of the adult with CHD.

Cocartation of the Aorta and Coronary Artery Disease: Fact or Fiction?

Summary: Aortic coarctation is reported to predispose to the development of coronary artery disease (CAD). Despite recent advances in surgical and percutaneous management of these patients, recent data indicate that patients with aortic coarctation still die at a much earlier age than the general population. The number 1 cause of death in this population is thought to be CAD. These data raise the question of whether coarctation of the aorta is an independent risk factor for the development of CAD. Our main objectives were to describe the prevalence of CAD among adults with aortic coarctation and to determine whether aortic coarctation is an independent predictor of CAD. Using a population-based congenital heart disease database with longitudinal follow-up of >20 years, we found, not surprisingly, that traditional cardiovascular risk factors independently predicted for the development of CAD in our cohort. However, the presence of aortic coarctation did not independently predict for the development of CAD. To the best of our knowledge, this is the first study to attempt to examine whether coarctation of the aorta is an independent risk factor for the development of CAD. Our results are significant because they are actionable. Our findings suggest that cardiovascular outcomes of patients with coarctation of the aorta may be improved with tighter risk factor control.

Conclusions: Although traditional cardiovascular risk factors independently predicted for the development of CAD, the diagnosis of CoA alone did not. Our findings suggest that cardiovascular outcomes of these patients may be improved with tight risk factor control.
Conclusions: Surgery for primary cardiac tumors in children has good early and long-term outcomes, with low recurrence rate. Rhabdomyomas are the most frequent surgical histotypes. Malignant tumors negatively affect early and late survival. Heart transplant is indicated when conservative surgery is not feasible. Lack of recurrence after partial resection of benign cardiac tumors indicates that a less risky tumor debulking is effective for a subset of histotypes such as rhabdomyomas and fibromas.

Left Ventricular Longitudinal Function Predicts Life-Threatening Ventricular Arrhythmia and Death in Adults With Repaired Tetralogy of Fallot

Summary: Sudden cardiac death and life-threatening ventricular arrhythmia are a major concern in adults after repair of tetralogy of Fallot. Accurate risk stratification of patients who may benefit from implantable cardioverter-defibrillators would be crucial in this context. Previous studies have focused on the predictive value of surgical history, ECG parameters, inducible arrhythmia, exercise intolerance, and burden of myocardial fibrosis. More recently, left ventricular (LV) systolic dysfuncion and diastolic dysfunction have been reported to carry prognostic information. Recent studies, however, suggest that longitudinal LV function, measured by speckle tracking echocardiography, is more sensitive in detecting early myocardial damage compared with LV ejection fraction. We assessed the relation between measures of LV longitudinal systolic function on speckle tracking (global LV strain) and on M-mode echocardiography (mitral annular plane systolic excursion) and outcome (sustained ventricular tachycardia, resuscitated sudden cardiac death, or appropriate implantable cardioverter-defibrillator discharge) in 413 tetralogy of Fallot patients (median follow-up, 2.9 years). Univariable Cox analysis, mitral annular plane systolic excursion and global LV strain were significantly related to the combined end point, whereas LV ejection fraction and echocardiographic estimates of LV diastolic dysfunction were not. An echocardiographic model was constructed using global LV strain or mitral annular plane systolic excursion, right ventricular fractional area change, and right atrial area, identifying tetralogy of Fallot patients with a higher risk of sudden cardiac death and life-threatening ventricular arrhythmias. The results of this study suggest that longitudinal measures of LV systolic function outperform LV ejection fraction in providing information on outcome and should be considered a useful adjunct to established markers such as QRS duration in the estimation of prognosis in this challenging population.

Conclusions: LV longitudinal dysfunction was associated with greater risk of sudden cardiac death/life-threatening ventricular arrhythmias. In combination with echocardiographic right heart variables, also available from routine echocardiography, these measures provide important outcome information and should be considered a useful adjunct to established markers such as QRS duration in the estimation of prognosis in this challenging population.

Early Developmental Outcome in Children With Hypoplastic Left Heart Syndrome and Related Anomalies: The Single Ventricle Reconstruction Trial

Summary: Survival to adulthood is becoming a reality for patients with hypoplastic left heart syndrome and related single right ventricle anomalies treated with staged palliation from the Norwood operation to the Fontan procedure. We assessed neurodevelopment at age 14 months in the 15-center, randomized Single Ventricle Reconstruction trial by using the Psychomotor Development Index and Mental Development Index of the Bayley Scales of Infant Development-Second Edition. We found a high prevalence of neurodevelopmental impairment in patients with hypoplastic left heart syndrome and related single right ventricle anomalies. Lower Bayley Scales of Infant Development-Second Edition scores at age 14 months were predicted by both innate patient factors and measures of greater severity of illness. Patient factors that portended greater risk included the presence of genetic syndromes or other anomalies, lower maternal education, and lower birth weight. Patients with a more complicated postoperative course following the Norwood procedure also had worse outcomes, as indicated by independent risk factors of longer postoperative mechanical ventilation or hospital stay. Between Norwood discharge and age 12 months, a greater number of complications were also associated with worse development, a novel finding that highlights ongoing brain vulnerability and opportunities for intervention. Neither the type of systemic-to-pulmonary-artery shunt nor bypass-related variables were predictors of Bayley Scales of Infant Development-Second Edition scores in multivariable analyses. Thus, patient characteristics and indices of greater severity of illness were the factors most highly associated with later neurodevelopmental outcome. Substantial improvement in neurodevelopmental outcome in this vulnerable population is thus likely to require inclusion of interventions that occur outside the operating room.

Conclusions: Neurodevelopmental impairment in Norwood survivors is more highly associated with innate patient factors and overall morbidity in the first year than with intraoperative management strategies. Improved outcomes are likely to require interventions that occur outside the operating room.

White Matter Protection in Congenital Heart Surgery

Summary: The most common neurological deficits in children after surgery for congenital heart disease are fine and gross motor deficits. Recent MRI studies have demonstrated a significant number of newly developed white matter (WM) lesions in infants after surgery. The present study describes region-specific WM development in the juvenile porcine brain, which is similar in developmental stage to the human newborn. Acute and long-term cellular responses to cardiopulmonary bypass in oligodendrocyte lineages and neuronal elements, which are the most prominent cell populations in WM, have been observed. A uniquely susceptible cellular target of cardiopulmonary bypass–induced WM injury in the oligodendrocyte lineage, as well as maturation-dependent vulnerability of developing WM, was found. Oligodendrocyte progenitor cells, which mediate WM recovery function, are highly resistant to cardiopulmonary bypass–induced injury. Interestingly, oligodendrocyte progenitor cell number decreases with age, which suggests that immature WM is vulnerable but also retains a significant endogenous cellular potential for recovery. Therefore, the optimal time window for congenital heart disease repair is the period during which WM contains the largest number of oligodendrocyte progenitor cells. Importantly, it was identified that under conditions of higher cerebral oxygenation and lower inflammation, the maturation stage was not a crucial determinant of cardiopulmonary bypass–induced WM injury. Together with the recent clinical finding that newborns with congenital heart disease have delayed brain development due to abnormal cerebral circulation in utero, the present study suggests that earlier normalization of cerebral circulation by primary congenital heart disease repair using higher cerebral oxygenation and lower inflammation should improve WM development in this population.
Conclusions: Primary repair in neonates and young infants potentially provides successful WM development in congenital heart disease patients. Cardiac surgery during this susceptible period should avoid ischemia-reperfusion injury and minimize inflammation to prevent long-term WM-related neurological impairment.6

Functional Variant in Methionine Synthase Reductase Intron-1 Significantly Increases the Risk of Congenital Heart Disease in the Han Chinese Population

Summary: Over the past 20 years, a series of clinical studies have shown that periconceptional folic acid supplementation prevents congenital heart disease, although the underlying molecular mechanism is still unknown. However, the declining prevalence of congenital heart disease at birth reveals a “floor effect,” which clearly shows that the effect of folic acid administration is influenced by the individual genetic background. The present study provides certain theoretical support for personalization of folic acid supplementation to prevent birth defects. We found that the MTRR c.56+781 A>C variant results in functionally reduced MTRR expression and reduces the activity of MTRR in the homocysteine remethylation pathway. It made susceptible fetuses vulnerable to the challenge of maternal insufficiency of folic acid. Thus, it is necessary for the pregnant woman to take folic acid and vitamin B12 and B6, especially when the fetus is genotyped as susceptible MTRR. Furthermore, the present study also emphasizes why folic acid should be supplemented periconceptionally and especially in the first trimester: At early stages of embryonic development, particularly between days 15 and 32, which is a critical phase of heart development, embryonic homocysteine is almost exclusively removed by the activity of the dominantly expressed MTR/MTRR pathway. Therefore, the discovery of regulatory polymorphisms in the MTRR gene provides new insight into risk assessment for common birth defects and sheds light on the molecular mechanism underlying the prevention of embryonic abnormalities by supplementation of folic acid.

Conclusions: We have demonstrated that the MTRR c.56+781 A>C variant is an important genetic marker for increased CHD risk because this variant results in functionally reduced MTRR expression at the transcriptional level. Our results accentuate the significance of functional single-nucleotide polymorphisms in noncoding regions of the homocysteine/folate metabolism pathway core genes for their potential contributions to the origin of CHD.7

Ulinastatin, a Urinary Trypsin Inhibitor, for the Initial Treatment of Patients With Kawasaki Disease: A Retrospective Study

Summary: The present study is the first report demonstrating that ulinastatin (UTI), a urinary trypsin inhibitor, is associated with fewer patients requiring additional rescue treatment and reduction of coronary artery lesions in the treatment of Kawasaki disease (KD). UTI, which protects tissues and organs against neutrophil-mediated injury, has been clinically used for the treatment of circulatory shock, septic shock, and acute respiratory distress syndrome. The results of our retrospective study suggested the usefulness of UTI as an initial treatment of KD, although UTI has been used mainly as an additional rescue treatment for patients refractory to initial treatment. Considering the pathological finding of neutrophils in the early stage of KD, clinical use of UTI may be more beneficial in initial treatment than in additional rescue treatment. Moreover, initial treatment with a combination of intravenous immunoglobulin and UTI may reduce not only the occurrence of coronary artery lesions but also the number of patients requiring additional rescue treatment, leading to possible benefits in total cost. No adverse events associated with UTI were observed in the present study. We consider that UTI is an effective candidate for intensive initial treatment to improve the clinical course and coronary outcome among patients with KD. Further study and a randomized prospective trial are needed to confirm the clinical benefits of UTI.

Conclusions: UTI was associated with fewer patients requiring additional rescue treatment and reduction of coronary artery lesions in this retrospective study.8

Randomized Trial of Cutting Balloon Compared With High-Pressure Angioplasty for the Treatment of Resistant Pulmonary Artery Stenosis

Summary: Children born with congenital heart disease not uncommonly require cardiac catheterization to treat congenital and acquired malformations such as pulmonary artery stenosis, replacing or complementing surgical techniques. In this study of Cutting Balloons compared with high-pressure balloon angioplasty for resistant pulmonary artery stenosis, we have shown superior efficacy with the Cutting Balloon technology and an equivalent safety profile. This finding has important clinical application for a population with previously untreatable disease. Although few studies have evaluated the performance of devices developed for adults but used in children, in this study, we have demonstrated that some of the unique study design and execution difficulties met in the pediatric population can be overcome. We hope that future studies will continue to rigorously evaluate the performance of devices used to treat children with rare diseases relative to more common adult indications.

Conclusions: Cutting balloon therapy for pulmonary artery stenosis not responsive to low-pressure balloon is more effective than high pressure balloon therapy and has an equivalent safety profile.9

Surgery in Adults With Congenital Heart Disease

Summary: A significant proportion of patients with congenital heart disease require surgery in adulthood. In the Congenital Gorvita (CONCOR) national registry of adults with congenital heart disease, one fifth required surgery during 15 years of follow-up, and in nearly 40%, surgery was for reoperations. This is the first study showing that men with congenital heart disease have a 40% higher chance of undergoing first surgery and a 20% higher chance of undergoing reoperations in adulthood compared with women. Furthermore, men have a 2-times-higher risk of mortality after reoperations in adulthood compared with women. This study supports the existing evidence for sex differences in the prognosis of adults with congenital heart disease, and these findings underscore the need for further research on the mechanisms underlying these differences.

Conclusions: Of predominantly young adults with congenital heart disease, one fifth required cardiovascular surgery during a 15-year period; in 40%, the surgery was a reoperation. Men with congenital heart disease have a higher chance of undergoing surgery in adulthood and have a consistently worse long-term survival after reoperations in adulthood compared with women.10

Isolated Atrioventricular Block in the Fetus: A Retrospective, Multinational, Multicenter Study of 175 Patients

Summary: Isolated congenital complete atrioventricular block in the fetus is a rare but potentially lethal condition, most frequently associated with transplacental passage of maternal anti-Ro/
abnormalities consistent with antibody-associated disease beyond the neonatal lupus die of complications predicted by echocardiographic years, and 4 children underwent cardiac transplantation. Data from minorities compared with whites, who were at a lower risk of hydrops and impaired left ventricular function at diagnosis were associated with an increased risk of death. The presence of ≥1 of these risk factors was associated with a 10-fold increase in mortality before birth and a 6-fold increase in the neonatal period independently of treatment. Except for a slightly lower gestational age at diagnosis in treated than untreated patients, risk factors were equally distributed between groups. Reversion of incomplete atrioventricular block was seen in 5 steroid-treated patients, but only 2 of them remained in sinus rhythm at 1 and 2.7 years of age. Our results do not support universal treatment with steroids for antibody-exposed fetuses with complete atrioventricular block, but because of the retrospective design, we cannot rule out a possibly beneficial, or even harmful, effect of steroids.

Conclusions: Risk factors associated with a poor outcome were gestation ≤20 weeks, ventricular rate ≤50 bpm, hydrops, and impaired left ventricular function. No significant effect of treatment with fluorinated corticosteroids was seen.11

Maternal and Fetal Factors Associated With Mortality and Morbidity in a Multi–Racial/Ethnic Registry of Anti-SSA/Ro–Associated Cardiac Neonatal Lupus

Summary: The cardiac manifestations of neonatal lupus include advanced conduction disease and rarely an isolated cardiomyopathy. This study, which included 325 offspring exposed to maternal anti-SSA/Ro antibodies with cardiac neonatal lupus, was used to determine the mortality, morbidity, and associated risk factors in a multi–racial/ethnic US-based registry. The case fatality rate was 17.5%. A third of the cases died in utero. The cumulative probability of survival at 10 years for a child born alive was 86% (most dying within a year of birth). Fetal echocardiographic risk factors associated with a statistically significant increase in mortality in a multivariate analysis included hydrops, endocardial fibroelastosis, an earlier diagnosis of cardiac neonatal lupus, and a lower ventricular rate. Overall, isolated advanced heart block was associated with a 7.8% case fatality rate, whereas the concomitant presence of dilated cardiomyopathy or endocardial fibroelastosis more than quadrupled the case fatality rate. There was a significantly higher case fatality rate in minorities compared with whites, who were at a lower risk of hydrops and endocardial fibroelastosis. Pacing was required in 70% by 10 years, and 4 children underwent cardiac transplantation. Data from this cohort reveal that nearly one fifth of fetuses who develop cardiac neonatal lupus die of complications predicted by echocardiographic abnormalities consistent with antibody-associated disease beyond the atrioventricular node.

Conclusions: Nearly one fifth of fetuses who develop cardiac neonatal lupus die of complications predicted by echocardiographic abnormalities consistent with antibody-associated disease beyond the atrioventricular node. The disparity in outcomes observed between minorities and whites warrants further investigation.12

Congenital Heart Defects and Developmental and Other Psychiatric Disorders: A Danish Nationwide Cohort Study

Summary: Studies focusing on a wide range of congenital heart defects (CHDs) have reported associations with mild cognitive impairment, speech and language difficulties, impaired motor skills, attention deficit hyperactivity disorder, and autism-like disabilities. These disabilities may cross the boundaries of many clinical disciplines including neurology, pediatrics, and psychiatry, depending on referral practices. In this study we examined the incidence of psychiatric hospitalization or outpatient visits among Danish patients with CHD compared with a general population cohort. We focused on psychiatric admissions and outpatient contacts overall and on contacts for specific mental disorders in accordance with the overall pattern of neurobehavioral sequelae described in the CHD population, as well as relevant genetic risk factors. The overall risk of a first-time psychiatric diagnosis was elevated compared with the general population cohort, whether or not a cardiac therapeutic intervention had occurred. In the age range for potential pediatric cardiac follow-up (<15 years of age), the risk was increased for both male and female patients. Among those aged 15 to 30 years who receive treatment in an adult cardiac clinic, only males were at increased risk for a first-time psychiatric diagnosis compared with the general population cohort. Because our study only considered first-time psychiatric diagnoses, our results cannot exclude the possibility that more adult female CHD patients may have mental health issues at a given time (prevalent disease) compared with females in the general population. Our study indicates the importance of addressing mental health issues in optimal CHD follow-up and care.

Conclusions: Congenital heart disease patients with or without invasive therapeutic interventions are at increased risk of developmental and other psychiatric disorders, which seem to develop earlier than in patients with diabetes mellitus or asthma.13

Peak Oxygen Uptake Correlates With Survival Without Clinical Deterioration in Ambulatory Children With Dilated Cardiomyopathy

Summary: In adults, cardiopulmonary exercise testing is an integral part of the decision-making process for heart transplantation listing. However, experience with using cardiopulmonary exercise test as a prognostic tool in children is very limited. In the present study, using cardiopulmonary exercise testing, we studied 82 ambulatory children with dilated cardiomyopathy and found that lower peak oxygen uptake was associated with a higher rate of death (without transplantation) and clinical deterioration requiring urgent listing for transplantation. Children with a peak oxygen uptake ≤62% of the predicted value were at particularly high risk. The study provides supportive evidence for the use of cardiopulmonary exercise test for risk stratification of pediatric dilated cardiomyopathy and suggests that exercise test variables may become part of the standard clinical risk assessment of older children with dilated cardiomyopathy.

Conclusions: We have demonstrated that a cardiopulmonary exercise test is feasible in ambulatory children with dilated cardiomyopathy who are ≥120 cm height and for the first time have linked peak VO2 with outcome in children.14
Risk, Clinical Features, and Outcomes of Thrombosis Associated With Pediatric Cardiac Surgery

Summary: Thrombosis in the context of pediatric cardiac surgery is usually considered a clinically important but somewhat rare complication. Thus, awareness has been limited, likely resulting in a failure to identify this potentially important clinical problem, reporting biases, inappropriate/insufficient use of diagnostic tests, and a lack of prospective clinical studies. This topic has not been a major research focus in the past. In a review of 1542 pediatric cardiac surgeries, we found that 171 (11%) were associated with incident thrombosis, with multiple subpopulations at substantially higher risk. There were no systematic detection protocols in place during the study period; thus, it is very likely that our estimated thrombosis prevalence of 11% is an underestimation and that this is a much more prevalent problem than reported here. Thrombosis was associated with a high degree of serious complications (28%), with increased morbidity and worse postoperative clinical outcomes compared with surgeries without thrombosis. Both thrombus and patients’ characteristics were associated with increased odds of serious complications and thrombus resolution, and these factors could be used for future risk stratification. Further research is necessary to determine the mechanisms by which the identified factors are associated with thrombosis and its outcomes by focusing on pathways of coagulation and platelet activation. This study establishes thrombosis in the context of pediatric cardiac surgery as an important clinical problem and will, we hope, form the basis of further research aimed at better prevention, detection, and treatment of those complications.

Conclusions: Thrombosis affects a high proportion of children undergoing cardiac surgery and is associated with suboptimal outcomes. Increased awareness and effective prevention and detection strategies are needed.

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. We 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, we 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. We found that higher tortuosity is independently associated with earlier cardiac surgery, arterial dissection, and death. In our study, a high vertebral artery tortuosity index was more strongly associated with early adverse outcome than a diagnosis of Loeys-Dietz syndrome compared to 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.

Long-Term Prognosis of Patients With Kawasaki Disease Complicated by Giant Coronary Aneurysms: A Single-Institution Experience

Summary: Kawasaki disease, a systemic vasculitis with unknown cause, is the most frequent acquired cardiovascular disease in children and a major public health problem. Despite appropriate treatment, including high-dose intravenous immunoglobulin infusion and aspirin, a certain number of patients develop giant coronary aneurysms (>8 mm) that would undergo remodeling, leading to ischemic heart disease. In the last 15 years, we have developed catheter and surgical interventions for this ischemic heart disease and proposed indications of these treatments. As a result, the long-term survival of patients with giant coronary aneurysms is moderately good, ie, 90% at 20 years and 87% at 30 years after onset. However, the result of catheter and surgical coronary intervention may not be satisfactory in this setting because many patients require repeat procedures. In addition, it is still difficult to treat small children with ischemic heart disease caused by Kawasaki disease. Further research should focus on medical treatment to prevent coronary vascular remodeling and the indications for and effectiveness of catheter and surgical coronary interventions.

Conclusions: The long-term survival of patients with Kawasaki disease complicated by giant coronary aneurysms is moderately good with multiple catheter and surgical interventions. Further research should focus on the prevention of coronary vascular remodeling and the indications for and effectiveness of percutaneous and surgical coronary interventions.

Congenital Heart Defects in Europe: Prevalence and Perinatal Mortality, 2000 to 2005

Summary: Information on prevalence and fetal and perinatal mortality associated with Congenital Heart Defects (CHD) in Europe is needed as a baseline from which to monitor future progress in primary prevention, to monitor the impact of termination of pregnancy for fetal anomaly (TOPFA) on prevalence, to plan for high-quality services, and to allow individual regions to compare their rates with the European average and range. We analyzed data from 29 population-based congenital anomaly registries in 16 European countries covering 3.3 million births from 2000 to 2005. The total prevalence of CHD was 8.0 per 1000 births, and live birth prevalence was 7.2 per 1000 births, varying between countries. The total prevalence of nonchromosomal CHD was 7.0 per 1000 births, of which 3.6% were perinatal deaths and 5.6% TOPFA. Severe nonchromosomal CHD (ie, excluding ventricular septal defects, atrial septal defects, and pulmonary valve stenosis) occurred in 2.0 per 1000 births, of which 8.1% were perinatal deaths, 40% were prenatally diagnosed, and 14% were TOPFA. The TOPFA proportion for severe CHD varied from 0 to 32% between countries. The live-birth prevalence of Down syndrome with CHD (average 0.5 per 1000) varied >3-fold between countries because of differences in maternal age profile of births and differences in TOPFA rates for Down syndrome. There are an estimated 36 000 children live born with CHD in the European Union each year and 3000 TOPFA, stillbirth, or early neonatal deaths with CHD. Investing in primary prevention and in cardiac services from in utero to adulthood is essential.

Conclusions: Annually in the European Union, we estimate 36 000 children are live born with CHD and 3000 who are diagnosed with CHD die as a TOPFA, late fetal death, or early neonatal death.
Investing in primary prevention and pathogenetic research is essential to reduce this burden, as well as continuing to improve cardiac services from in utero to adulthood.14

Characterization and Functionality of Cardiac Progenitor Cells in Congenital Heart Patients

Summary: Visionaries in the field of cardiac therapeutics have long looked to a future when damaged hearts could be rebuilt from the cellular level. Reports on bone marrow–derived stem cells and, more recently, endogenous cardiac progenitor cells have focused on their function and utility in rebuilding the hearts of adults. In the pediatric population, the majority of potential clinical applications would involve patients with cardiomyopathy or congenital lesions rather than adulthood ischemic injury. Our study investigated the presence of a resident pool of human cardiac progenitor cells and demonstrated how it changes during postnatal maturation in the nondiseased myocardium of young patients with congenital heart disease. We showed that resident human cardiac progenitor cells are present in the young myocardium and are most abundant during the neonatal period. Furthermore, these cells can be isolated from a wide range of congenital heart patients, including neonates and adolescents, as well as those with cyanosis. Our study suggests that the best source of human cardiac progenitor cells is the right atrium, from which small, clinically relevant myocardial specimens can be obtained. These isolated cells can be expanded in vitro and therefore provide a large number of cells for therapeutic applications. Our functional findings with these cells could enhance the development of novel cell-based regenerative approaches not yet explored in congenital heart patients.

Conclusions: Resident human cardiac progenitor cells (hCPCs) are most abundant in the neonatal period and rapidly decrease over time. Human cardiosphere-derived cells can be reproducibly isolated and expanded from young human myocardial samples regardless of age or diagnosis. hCPCs are functional and have potential in congenital cardiac repair.19

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

Summary: Women with moderate and complex forms of congenital heart disease 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 congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease. In the cohort of 89 pregnancies in 83 women, a blunted heart rate response during exercise was associated with congenital heart disease.

Conclusions: Abnormal chronotropic response correlates with adverse pregnancy outcomes in women with congenital heart disease and should be considered in refining risk stratification schemes.20

Left Ventricular Remodeling and Improvement in Diastolic Function After Balloon Aortic Valvuloplasty for Congenital Aortic Stenosis

Summary: Chronic pressure load on the left ventricle due to aortic stenosis results in ventricular hypertrophy, myocardial fibrosis, and abnormal myocardial mechanics. These processes can result in both systolic and diastolic dysfunction. Diastolic function and noninvasive measures of left atrial pressure improve in the majority of patients after effective relief of aortic stenosis with balloon aortic valvuloplasty.

Conclusions: After balloon aortic valvuloplasty, LV remodeling characterized by an increase in end diastolic volume and decrease in LV mass/volume occurs and echocardiographic measures of diastolic function and LV end-diastolic pressure improve in most patients. Risk factors for persistent diastolic dysfunction include higher pre-BAVP LV mass z-score and worse pre-BAVP diastolic function.21

Videoscopic Left Cardiac Sympathetic Denervation for Patients With Recurrent Ventricular Fibrillation/Malignant Ventricular Arrhythmia Syndromes Besides Congenital Long-QT Syndrome

Summary: Left cardiac sympathetic denervation is useful in some patients with long-QT syndrome, but its role in controlling life-threatening ventricular arrhythmias in other arrhythmogenic disorders is less clear. We report the use of left cardiac sympathetic denervation in 27 patients with a spectrum of arrhythmia syndromes, including catecholaminergic polymorphic ventricular tachycardia, idiopathic ventricular fibrillation, and cardiomyopathies. Left cardiac sympathetic denervation was performed as primary preventive therapy in 5 patients who had a high-risk profile and β-blocker intolerance, and all are free of arrhythmic events thus far. In 22 patients with previous arrhythmias, 18 are free of recurrent arrhythmias and the frequency of recurrences was reduced in 4. Thus, left cardiac sympathetic denervation may represent a substrate-independent antifibrillatory treatment option for some patients with life-threatening ventricular arrhythmia syndromes other than long-QT syndrome.

Conclusions: Left cardiac sympathetic denervation may represent a substrate-independent antifibrillatory treatment option for patients with life-threatening ventricular arrhythmia syndromes other than long-QT syndrome. The early follow-up seems promising, with a marked reduction in the frequency of cardiac events postdenervation.22

Genetic Modifiers Predisposing to Congenital Heart Disease in the Sensitized Down Syndrome Population

Summary: Our investigation supports a “threshold model for congenital heart disease (CHD),”2 in which CHD occurs owing to small genetic contributions by multiple genes that each increase the risk to some degree. The presence of trisomy 21 dramatically increases the frequency of CHD, thus Down syndrome (DS) is a sensitizing condition and a major risk factor. We confirmed that a disomic modifier, Creld1, can greatly increase the frequency of CHD in a mouse model of DS when its expression is reduced. Further, disomic modifiers Creld1 and Hey2, which have no effect on heart development when either is heterozygous alone, result in a significantly increased frequency of CHD in doubly affected mice. Our study identifies candidate modifiers using the sensitized DS population that can be
used to build a catalogue of modifier genes that may potentially help understand the pathogenesis of CHD. Such knowledge is essential for future work aimed at the prevention of CHD.

Conclusions: Using mouse models of Down syndrome and of genes associated with congenital heart disease, we demonstrate a biological basis for an interaction that supports a threshold hypothesis for additive effects of genetic modifiers in the sensitized trisomic population.23

Exome Analysis of a Family With Pleiotropic Congenital Heart Disease

Summary: Congenital heart defects constitute a major portion of clinically significant developmental abnormalities with a frequency of 3% to 6%. Based on twin studies and familial clustering, congenital heart diseases are highly heritable but most occur through multifactorial mechanisms with complex inheritance. To accurately predict the risk of congenital heart disease and to intervene or eventually prevent these defects, we need to identify the causative genes. Although strides have been made in the identification of congenital heart disease genes, current efforts using candidate gene screening only identify mutations in approximately 10% of patients. The present investigation represents the first reported use of next-generation sequencing to analyze a family with diverse but highly penetrant congenital heart disease. Through exome analysis, we identified Myh6 Ala230Pro as the most likely causative variant in this family and catalogued other less penetrant but potentially pathogenic variants that may modify the phenotype. Next-generation sequencing combined with family-based analysis has the potential to unravel the complex genetics of congenital heart disease. The development of a catalog of variants that affect the expression and severity of congenital heart defects has the potential to allow individualized screening and/or therapies for patients, that is, the advent of personalized genetic-based medicine in patients with congenital heart disease.

Conclusions: It is likely that next-generation sequencing will become the method of choice for unraveling the complex genetics of CHD, but information gained by analysis of transmission through families will be crucial.24

Implantable Cardioverter Defibrillator Therapy in Adults With Congenital Heart Disease: Who Is at Risk of Shocks?

Summary: Sudden cardiac death is a major cause of mortality in adults with congenital heart disease (CHD) and might be prevented by implantable cardioverter defibrillator (ICD) therapy. The number of patients with CHD who receive an ICD is steadily increasing. However, in this population, contrary to the patients with ischemic or nonischemic cardiomyopathy, the indication for ICD implantation is poorly defined and little is known about the efficacy of ICD therapy. Therefore, we conducted a multicenter study to determine the long-term outcome of ICD therapy in adults with CHD and developed a simple risk score model for appropriate ICD discharges. Overall, 136 adults with CHD and ICD (mean age ± SD, 41±13 years; 67% male) were identified. The indication for ICD implantation was primary prevention in 50% of patients. Thirty-nine patients (29%) received effective appropriate ICD shocks during a median follow-up of 4.6 years. Patients with a secondary prevention indication, coronary artery disease (CAD), and symptomatic nonsustained ventricular tachycardias were at highest risk of receiving appropriate shocks. Based on these clinical features, a risk score was developed to evaluate the likelihood of appropriate ICD shocks. The 8-year Kaplan-Meier curve to first appropriate shock was 94%, 57%, and 26% for low-, intermediate-, and high-risk patients, respectively. More important, morbidity was considerable because of the relatively high rate of inappropriate shocks (30%) and implantation-related complications (29%). Therefore, the risk/benefit ratio of ICD therapy should be carefully assessed in individual patients. In patients with supraventricular tachycardias, ablation before ICD implantation should be considered because this reduced the risk of inappropriate shock by 25%. In addition, because the population of adults with CHD is growing and aging, assessment of CAD might be warranted.

Conclusions: Adults with CHD and ICDs receive high rates of appropriate and effective shocks. Patients with secondary prevention indication, coronary artery disease, and symptomatic nonsustained ventricular tachycardia are at highest risk of receiving appropriate ICD shocks. ICD implantation is accompanied by considerable morbidity, including inappropriate shocks and procedure-related complications.25

Outcomes After Stent Implantation for the Treatment of Congenital and Postoperative Pulmonary Vein Stenosis in Children

Summary: Intraluminal pulmonary vein stenosis is a progressive condition that is frequently lethal in children. Treatment approaches for relief of luminal stenosis are acutely successful, but with limited long-term benefit. Although intravascular stents are successful in the relief of luminal stenosis, the rates of restenosis are high. Stents implanted at a larger diameter appear to remain patent longer with lower risk of reintervention.

Conclusions: Transcatheter stent implantation can acutely relieve pulmonary vein stenosis in children, but reintervention is common. Larger stent lumen size at implantation is associated with longer stent patency and a lower risk of reintervention.26

Impaired Mitochondrial Biogenesis Precedes Heart Failure in Right Ventricular Hypertrophy in Congenital Heart Disease

Summary: Right ventricular (RV) pressure and/or volume overload represents a common clinical scenario in patients with congenital heart disease (CHD). Physiological mechanisms can compensate even for decades. However, chronic maintenance of this overload may lead to the development of severe ventricular hypertrophy, dilatation and dysfunction, ventricular arrhythmias, and ultimately, heart failure. Several clinical reports indicate that when severe RV dilatation, dysfunction, and/or arrhythmias occur, the outcomes of these patients are poor even if a successful surgery with relief of the hemodynamic burden is carried out. Nevertheless, the appropriate timing for intervention is not standardized. Our study demonstrates an impairment in mitochondrial biogenesis in patients with CHD and chronic RV overload. Specifically, we observed a decrease in the quantity of mitochondrial DNA in myocardial samples obtained from patients with CHD undergoing cardiac surgery when compared with control subjects. This decrease was seen early and progressed during the transition from compensated RV overload to decompensated RV failure. The decrease in mitochondrial DNA was more pronounced in patients with significantly elevated RV systolic pressure. Our results suggest that in patients with CHD and RV overload, cellular changes start early, before the development of clinical signs or symptoms of heart failure. These changes were more marked in patients with high RV pressures. Prompt intervention to relieve the hemodynamic load on the RV may improve outcomes in this challenging population.
Conclusions: Impaired mtDNA replication causes early and progressive depletion of mtDNA in the RV of the patients with congenital heart disease during the transition from hypertrophy to failure. Decreased mtDNA content probably is a sensitive marker of mitochondrial injury in this patient population.27

Detection of Extra Components of T Wave by Independent Component Analysis in Congenital Long-QT Syndrome

Summary: The main ECG criteria for the diagnosis of long-QT syndrome (LQTS) include abnormal T-wave morphology as well as prolonged QT interval. We hypothesized that additional components related to the abnormally long myocardial repolarization process are included in the T wave of LQTS and investigated whether independent component analysis (ICA) can extract such abnormal repolarization components. Digital ECG data were obtained as time series in 22 patients with genetically confirmed LQTS type 1 (LQT1) and 30 normal subjects. In each case, the T-wave area was analyzed by radical ICA after noise reduction by the wavelet thresholding method. Furthermore, inverse ICA was applied to determine the origin of each independent component (IC). ICA revealed that a T wave consisted of 4 basic ICs in control subjects, whereas ≥5 (mostly 6) ICs were identified in all 22 patients with LQT1. The extra ICs, which were not evident in normal subjects, were assumed to contribute to the formation of abnormal T-wave morphology. The extra ICs were identified even in patients with normal QTc values and in those taking ß-blockers. Inverse ICA indicated that the additional ICs originate predominantly from the late phase of the T wave of the left ventricle. These results mean that ICA is a potentially useful multivariate statistical method to differentiate patients with LQTS from normal subjects. Further studies are needed to validate the clinical usefulness of the method in a large number of subjects, including patients with other mutations of LQTS, especially LQT2 and LQT3.

Conclusions: Extra ICs appear during repolarization in all patients with LQT1 but not in normal subjects. ICA is a potentially useful multivariate statistical method to differentiate patients with LQT1 from normal subjects.28

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 by the wavelet thresholding method. Furthermore, inverse ICA was applied to determine the origin of each independent component (IC). ICA revealed that a T wave consisted of 4 basic ICs in control subjects, whereas ≥5 (mostly 6) ICs were identified in all 22 patients with LQT1. The extra ICs, which were not evident in normal subjects, were assumed to contribute to the formation of abnormal T-wave morphology. The extra ICs were identified even in patients with normal QTc values and in those taking ß-blockers. Inverse ICA indicated that the additional ICs originate predominantly from the late phase of the T wave of the left ventricle. These results mean that ICA is a potentially useful multivariate statistical method to differentiate patients with LQTS from normal subjects. Further studies are needed to validate the clinical usefulness of the method in a large number of subjects, including patients with other mutations of LQTS, especially LQT2 and LQT3.

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References


