The Cardiac Patient from Birth to Adulthood
21-22 February 2019 in Stockholm Sweden
The symposium is arranged by Journal of Internal Medicine and Acta Paediatrica

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Berzelius symposium 99  
The Cardiac Patient from Birth to Adulthood

Welcome to the symposium and the Swedish Society of Medicine!
Cardiovascular diseases originate to a considerable extent during fetal life and childhood. The causes of congenital cardiac diseases often seem to be unknown, but genetic factors are thought to be important. Acquired diseases like coronary heart disease, hypertension and stroke may also originate during fetal and early postnatal life, due to environmental factors. These cause metabolic and developmental programming, which affect later blood pressure and metabolic homeostasis. That is why it is important to prevent and treat cardiovascular diseases as early as possible, even before conception.
Surgical treatment of congenital heart diseases in newborn infants have resulted in a remarkable increase in the survival of such children and treating the fetus may lead to further improvements in outcome in the near future.
Up until the end of the 20th century, many of these children used to die before adulthood. Although most adults with congenital heart disease seem to enjoy a relatively good quality of life, they still face numerous residual problems. In many cases their long-term prognosis remains unknown and this is a new challenge for physicians specialising in adult medicine.
The aim of this symposium is to explore topical areas such as state-of-the-art treatment for adult congenital heart disease, the early development of atherosclerosis and arrhythmia and the cardiovascular outcomes of prematurity. In particular, we will explore the transition from paediatrics to adult cardiology and this will be illustrated by clinical case presentations. We will also discuss how to prevent cardiovascular diseases in the womb and during early childhood.
This symposium is jointly organized by Acta Paediatrica and the Journal of Internal Medicine and some of the lectures will be published as reviews.

Organising committee
Bengt Johansson, Hugo Lagercrantz, Annika Rydberg, Magnus Domellöf, Per Dahlqvist, Ulf de Faire, Ulf Thilén
Program

Thursday 21 February 2019

09.15–09.30  Welcome and introduction
Hugo Lagercrantz, Stockholm, Sweden, Ulf de Faire, Stockholm Sweden and Bengt Johansson, Umeå, Sweden

09.30–10.00  Session 1 - Chairs: Annika Rydberg, Umeå, Sweden and Helge Skulstad, Oslo, Norway
Adult congenital heart disease – past, present and future
Michael Gatzoulis, London, UK

10.00–10.30  The changing epidemiology in congenital heart disease
Ariane Marelli, Montreal, Canada

10.30–11.00  Coffee

11.00–11.30  Session 2 - Chair: Mikael Dellborg, Göteborg, Sweden
Atherosclerosis in patients with congenital heart disease
Eero Jokinen, Helsinki, Finland

11.30–12.00  Arrhythmia interventions in complex congenital heart disease
Sabine Ernst, London, UK

12.00–12.30  Single ventricle physiology
Marc Gewillig, Leuven, Belgium

12.30–13.30  Lunch

13.30–14.00  Session 3 - Chairs: Bengt Johansson, Umeå, Sweden and Ingegerd Östman-Smith, Göteborg, Sweden
Physical capacity in adults with congenital heart disease
Gerhard-Paul Diller, Münster, Germany

14.00–14.30  Quality of life in adult patients with congenital heart disease
Philip Moons, Leuven, Belgium

14.30–15.00  Persistent foramen ovale in cryptogenic stroke
Lars Søndergaard, Copenhagen, Denmark

15.00  Coffee

15.30–16.30  Poster presentation
Chairs: Christina Christersson, Uppsala, Sweden and Annika Rydberg, Umeå, Sweden

16.30–17.00  Session 4 - Chair: Hugo Lagercrantz, Stockholm, Sweden
Evolutionary aspects on the origin of cardiac disease
Johan Frostegård, Stockholm, Sweden

19.00  Reception at the Stockholm City Hall hosted by a member of the Presidency of the City Council and co-hosted by Stockholm’s County Council. (Pre-reservation is necessary.)
Friday 22 February 2019

08.30–09.00  **Session 5** - Chairs: Magnus Domellöf, Umeå, Sweden and Ulf de Faire, Stockholm, Sweden
The inheritance of cardiovascular disease risk
**Mark Hanson**, Southampton, UK

09.00–09.30  Early life origins of adult cardiovascular disease
**Atul Singhal**, London, UK

09.30–10.00  Preterm birth and cardiovascular risk
**Mikael Norman**, Stockholm, Sweden

10.00–10.30  Coffee

10.30–12.45  Clinical case management – expert discussion
Chair: Ulf Thilén, Lund, Sweden Bengt Johansson, Umeå, Sweden
Magnus Domellöf, Umeå, Sweden Mats Synnergren, Göteborg, Sweden
David Ley, Lund, Sweden

- Pulmonary insufficiency. **Peder Sörensson**, Stockholm, Sweden
- Liver disease in univentricular physiology. **Joanna Hlebowicz Frisén**, Lund, Sweden
- Borderline hypertension in aortic coarctation. **Johan Ljungberg**, Umeå, Sweden
- The fullterm SGA baby – risk management. **Staffan Berglund**, Umeå, Sweden
- Persistent ductus – management in early life. **Stefan Johansson**, Stockholm, Sweden
- Coronary artery function after arterial switch.
- Ross surgery – when? **Peter Eriksson**, Göteborg

12.45–13.00  Concluding remarks
**Bengt Johansson** and **Annika Rydberg**

13.00  Buffet-lunch

**Twitter:** #theCardiacPatient
General information

When and where?

Lunches and coffee
Lunches coffee and refreshments are included in the participation cost and will be served on the premises at the Swedish Society of Medicine.

Social programme
Reception at the Stockholm City Hall on Thursday 21 February at 7 p.m. We will arrange for a joint walk from SSM to the City Hall at 6.30 p.m. (sharp!)
Address: Hantverkargatan 1 in Stockholm (Pre-reservation is necessary).

The Stockholm City Hall is one of Sweden’s most famous buildings, and one of the capital’s most visited tourist attractions. It is famous for its grand ceremonial halls and unique pieces of art and is the venue of the Nobel Prize banquet held in December each year.
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Mikael Norman
Adult Congenital Heart Disease: Past, Present and Future

Michael A. Gatzoulis and Margarita Brida, Royal Brompton Hospital and National Heart & Lung Institute, Imperial College, London, England

The diagnosis and management of congenital heart disease (CHD), the most common inborn and global defect, have been a tremendous success story of modern medicine. Back in the 1950s survival of children born with CHD was only approximately 15%. Thanks to remarkable advances in paediatric cardiology, cardiac surgery and catheter interventions, including radical and innovative procedures such as the Fontan operation for “single ventricle”, atrial/arterial switch for transposition of great arteries, percutaneous pulmonary valve implantation and others more than 90% of children survive now well into adulthood.1 Many patients, however, are afflicted by residual and progressive haemodynamic lesions, exercise intolerance, arrhythmias, heart failure and premature death.2 Beyond CHD, adult patients face additional challenges and/or opportunities such as pregnancy, acquired heart disease, non-cardiac pathology etc., necessitating integrated care and all medical disciplines. Furthermore, there is a pressing need to understand better the late pathophysiology of CHD and provide evidence regarding drug therapy, devices and transplantation.3 We are truly faced with a “tsunami” in terms of ACHD numbers, disease heterogeneity and complexity and we must work together,4 beyond age and geographic boundaries to provide for it, which is the noble aim of the February 2019 Stockholm Symposium. It is only then that we can secure necessary resources, welcome more people in our field, learn from “marching with our patients”, and educate all involved so that every single patient with CHD, born anywhere in the world, reach their full life potential.5

Reference:


The Changing Epidemiology in Congenital Heart Disease

Ariane Marelli, McGill University Health Center, Canada

The lecture will discuss the changing epidemiology of congenital heart disease and the impact of demographic shifts in health care delivery and research directions. The lecture will align closely with the congress theme by demonstrating that congenital heart disease is a lifespan condition requiring special consideration in how we deliver care and in terms of the knowledge gaps we need to address. Learning points will center around how alignment of pediatric and adult cardiology missions will have the highest yield in mitigating the challenges that lay ahead in the next decade.

Key references:


Atherosclerosis in Patients with Congenital Heart Disease

Eero Jokinen, Children's Hospital, University of Helsinki, Finland

Cardiovascular disease has the same meaning for health care today as the epidemics of centuries had for medicine in earlier times: half of the population in developed countries die of cardiovascular disease. Coronary heart disease by itself is the single most common cause of death before the age of 55 in Europe. Moreover, the prevalence of CHD is increasing rapidly in countries e.g. in India where it previously has been a rare disease.

Children and adolescents with acyanotic congenital heart disease have the same risk profile as their healthy peers: physical inactivity, obesity and increased insulin resistance. There is one exception to this rule: patients with cyanotic heart defects are protected against atherosclerosis. The risk possibly returns to the average level after the defect has become acyanotic after correction.

AHA considers patients with congenital heart disease to be at high risk as consequences of early coronary heart disease might be more fateful in young adults with corrected congenital heart disease than in his/her peers. Therefore, prevention of risk factors for coronary heart disease should start early in patients with coronary heart disease.

Reference:
Bauer et al. Int J Cardiol. 18:2018
Duffels et al. Circ J 74:1436–41; 2010
Perkoff JK Int J Cardiol 97:79–86; 2004
Arrhythmia Interventions in Complex Congenital Heart Disease

Sabine Ernst, Royal Brompton Hospital, London, England

Patients with congenital heart disease (CHD) may initially present with paroxysmal arrhythmia symptoms and therefore early ECG documentation of a given arrhythmia is key. As some arrhythmias have a propensity to degenerate into more difficult to treat arrhythmias (eg. atrial tachycardia into atrial fibrillation) timely referral to an electrophysiologist with expertise in arrhythmia management of CHD patient is important. In the management of sustained tachycardia in CHD patients catheter ablation has been recognized now as one of the pillars. Recent improvements in mapping and ablation technology such as three-dimensional (3D) electroanatomical mapping, 3D image integration and advanced techniques such as remote magnetic navigation and non-invasive mapping have improved ablation outcomes substantially in this complex patient cohort. The majority of arrhythmia substrates in CHD patients is re-entrant in nature and frequently caused by the preceding surgical interventions which result in scar tissue (eg. atriotomy scars) that can serve as anchors for critical isthmuses. However, also patients with non-palliated CHD can suffer from sustained arrhythmias, mostly caused by significant chamber dilatation. The success of atrial (AT) or ventricular (VT) tachycardia ablation in CHD is influenced by the underlying cardiac anatomy and surgical repair, along with the current hemodynamic sequelae of the anatomy and repairs. The presentation will focus on state-of-the-art ablation techniques for both atrial and ventricular arrhythmia in various cohorts of CHD patients.
Single Ventricle Physiology

Marc Gewillig KU Leuven, Belgium

After five decades, the Fontan operation remains the final palliation for patients with complex congenital heart disease and thousands of patients have been operated. However, mortality and morbidity in these patients remain high. Standard paradigms of management have religiously been pursued with minimal effect on outcome. Exercise intolerance, acute and chronic heart failure, cyanosis, arrhythmias, thromboembolism, protein losing enteropathy, plastic bronchitis, liver disease, renal dysfunction and premature death have become major determinants of outcome.

When creating the Fontan circuit, the surgeon puts the Fontan-portal system like a dam upstream of the ventricle. By doing so, he shifts the critical bottleneck outside and upstream of the heart itself: the dam will control overall flow and the degree of congestion upstream. Technically, the Fontan operation is created without touching the ventricle; therefore all changes observed at ventricular level such as hypocontractility, diastolic dysfunction etc., are downstream secondary phenomena and therefore of little relevance – a fact well-known by all intensivists. The ventricle, while still the engine of the circuit, no longer controls the flow but it will pump the (reduced) amount that is offered: this explains why treatments that target heart rate, contractility and afterload reduction, when within physiological range, have no effect on Fontan hemodynamics. Only decreasing the ventricular filling pressure (which is the end of the new bottleneck) will increase overall flow; however the ventricle cannot generate such suction to compensate for the damming, and we have no lusitropic drugs that might help, especially not in a volume deprived ventricle.

Decrease of the the venous congestion and increase of overall flow in the new Fontan circuit is obtained by a fenestration: such fenestration will bypass the Fontan-portal system, thereby illustrating or even proving that this system has become the new critical bottleneck. Lowering the pulmonary vascular resistance (vasodilators, negative pressure ventilation) can also help, but to a lesser extent as overall resistance can only lowered by less than 10%.

Pulmonary vascular resistance is known to increase with time, but more so in a Fontan circulation because of chronically decreased flow, minimal to mild desaturation, increased collateral flow, suboptimal mixing of inferior and superior caval flow, absence of pulsatility, endothelial dysfunction, and absence of flushing by episodes of high flow and high pressure as are normally seen during exercise in subjects with a normal right ventricle.

The ventricular filling pressure is also known to increase with age, but much more so in a Fontan circulation because of the chronic volume deprivation with reduced to absent exercise-induced ventricular stretch. Any muscle that is underused and poorly or never stretched above its operating length will become more stiff; in the ventricle this will result in increasing filling pressures.
Flow in FPC over time: “good” Fontan – circulatory failure with “preserved” ventricular function

Flow (cardiac output) in normal human (thin solid line) whilst minimal output to remain functional is indicated by the dotted line. Immediately after establishment of a Fontan circuit, the Fontan portal complex FPC is the main controller of flow (thick solid line). Ventricular function is normal (extra cardiac operation) at the start, but gradually declines due to ageing, underuse and rising VEDP (thick dotted line). However, over time due to rise in pulmonary vascular resistance (PVR) and ventricular end-diastolic pressure (VEDP), cardiac output steadily declines. Up to this stage the FPC is the only determinant of cardiac output but once it reaches the minimal viable flow, the ventricle takes over with demise.
Acute changes of the ventricle such as severe bradycardia or tachycardia, ventricular dysfunction or acute excessive afterload may shift the critical bottleneck towards the ventricle. Such an episode will severely compromise the patient and may kill him if the ensuing rise of ventricular filling pressure reaches the level of systemic venous pressure. Treating the underlying ventricular problem may re-shift the bottleneck and restore the prior output.

Flow in FPC over time: acute changes

Flow in FPC over time: Interlocked bottleneck (circulatory failure with poor ventricular function)

There are intermediate situations where deterioration in the FPC and ventricle occur simultaneously. The effect is that the two lines converge and may become interlocked. Treatment of the one and neglecting the other will inevitably lead to treatment failure. Once the two lines become interlocked, a vicious negative spiral ensues.
Physical Capacity in Adults with Congenital Heart Disease

Gerhard-Paul Diller, Universitätsklinikum Münster, Germany

Exercise capacity is reduced in adults with congenital heart disease. In addition, various studies have demonstrated the association between depressed objective exercise capacity and poor outcome in the midterm as well as for cardiac procedures in this population. While it is not entirely clear if these patients stand to benefit from exercise training, international recommendations encourage regular exercise. Data from cardiopulmonary exercise testing suggest a relatively low risk of adverse events during exercise in adults with congenital heart disease. This is also supported by studies investigating the mode of death in this patient group, reporting that only a minority of patients die during exercise. The presentation will summarize the data on exercise capacity in congenital heart disease, its prognostic implication as well as aspects of exercise prescription and risk of sport activities in this emerging population.
Quality of Life in Adult Patients with Congenital Heart Disease

Philip Moons, University Hospital Leuven, Belgien

The first study on quality of life (QoL) in patients with congenital heart disease was published more than 40 years ago. Since then, the number of QoL articles on these patients has grown exponentially. However, most of the published studies present with substantial methodological and conceptual limitations. Furthermore, geographic differences in QoL have been observed. In this presentation, APPROACH-IS will be presented as an exemplar for QoL studies that are based on sound conceptual grounds and allow international comparisons. Key learning points are: i) There are different conceptual approaches in QoL research that should be taken into account in the interpretation of study findings; ii) overall QoL in adults with congenital heart disease is good and can be better than that of healthy individuals, if measured in terms of satisfaction with life; iii) country-specific factors can predict QoL above and beyond patient-related factors.

Key references:


Persistent Foramen Ovale in Cryptogenic Stroke

Lars Søndergaard, Rigshospitalet Copenhagen, Denmark

Despite therapeutic advances for secondary prevention of ischemic stroke, the incidence of recurrent stroke remains high. Many of these strokes are labelled cryptogenic due to any causal findings. However, the link between ischemic stroke and paradoxical embolism via patent foramen ovale (PFO) has been studied extensively. There are now four international randomized clinical trials that have demonstrated a therapeutic benefit with percutaneous PFO closure in addition to anti-platelet therapy compared to anti-platelet therapy alone in reducing the risk of recurrent ischemic stroke in this cryptogenic population. These studies prove that in many cases there is a causal relationship between PFO and ischemic stroke of “unknown” aetiology. Subsequent guidelines from national societies should be updated to focus on management of patients with PFO-associated stroke.
Evolutionary Aspects on the Origin of Cardiac Disease

Johan Frostegård, Karolinska Institutet, Stockholm, Sweden

Atherosclerosis is an inflammatory condition, characterized by activated immune competent cells, a necrotic core of dead cells, and oxidized low density protein (OxLDL) in the plaques. Oxidized phospholipids especially phosphorylcholine (PC) and its role in OxLDL-induced immune activation has been in focus of our research since the mid 90s. Atherosclerosis is the major underlying cause of cardiovascular disease (CVD) and thus a major cause of death. It generally gives symptoms rather late in life, and since evolution is much related to reproduction, could there be any evolutionary aspects on atherosclerosis of relevance? In my opinion, the answer is yes. Why do humans live so long, and why is there menopause? One explanation which is credible, is the “grandmother” hypothesis, according to which it has been an evolutionary advantage to live long enough after the reproductive years (more or less) to educate the young generation. There could thus be some protection against atherosclerosis, due to this. However, this is most likely only a minor mechanism.

There are other possibilities, which are more indirect. One is related to blood lipids and LDL, where an example is familial hypercholesterolemia, FH. This condition could have been beneficial in previous times, when infections especially among children was a major cause of death and LDL is known to interact with bacteria and endotoxin. It is possible that high LDL could provide some protection, which is supported by genealogic studies where survival among FH was not decreased in the 1800s. A side-effect could thus be that very high LDL is detrimental now when atherosclerosis has become a major killer.

We have proposed a hypothesis, which is an extension of the Old friends/hygiene hypothesis, which has evolutionary implications. This is focused on PC which is exposed and recognized by the immune system on OxLDL, but also on dead cells, and is a danger-associated molecular pattern (DAMP). Interestingly PC is also a pathogen-associated molecular pattern (PAMP) and is exposed on some microorganism including nematodes and bacteria. We also determined that antibodies against PC (anti-PC), especially IgMs, are associated with protection in atherosclerosis development, CVD, autoimmune diseases including SLE, and others. We studied anti-PC among individuals from Kitava, New Guinea who then lived a traditional life as hunter-gatherers and horticulturalists, where CVD and autoimmune disease are virtually unknown, and anti-PC was very high there as compared to Swedish controls. High levels there could be caused by infectious agents we are not exposed to in Sweden but which have been with humanity for millions of years. We therefore hypothesize that an immune deficient state with low anti-PC levels could contribute to chronic inflammatory conditions such as atherosclerosis, CVD and autoimmune disease.

Underlying potential mechanisms are relevant for atherosclerosis: in our studies anti-PC increases clearance of dead cells, inhibits uptake of OxLDL in inert macrophages/foam cells, promotes T regulatory cells, and has anti-inflammatory properties.

There are other non-mutually exclusive possibilities. One example is heat shock proteins (HSP), which are important in OxLDL-immunity and such induced HSP could trigger an immune reaction which is beneficial in infections but not in the vascular wall. Taken together, evolutionary factors could play both a direct and indirect role in atherosclerosis. There could be a reproduction and survival advantage according to the grandmother hypothesis, though this is not likely to be strong. Very high LDL is an example of indirect mechanisms, which could have been beneficial when infections where major causes of death. Low levels of anti-PC due to a lack of exposure to microorganisms which have co-evolved with humans for millions of years, leads to an immune deficient...
of indirect mechanisms, which could have been beneficial when infections were major causes of death. Low levels of anti-PC due to a lack of exposure to microorganisms which have co-evolved with humans for millions of years, leads to an immune deficient state, predisposing to atherosclerosis and thus another example of evolutionary aspects on atherosclerosis.
The Inheritance of Cardiovascular Disease Risk

Mark Hanson, Institute of Developmental Sciences and NIHR Southampton Biomedical Research Centre, University Hospital Southampton, UK

Cardiovascular disease (CVD) is foremost among the non-communicable diseases (NCDs) which account for more than 70% of deaths globally each year. CVD is also prominent among the pre-existing conditions still accounting for nearly 25% of maternal deaths, and is linked to gestational diabetes and preeclampsia. It thus affects women of reproductive age. We and others have reported markers of CVD risk even in young children, related to prenatal factors such as mother’s diet or body composition (1,2,3). The underlying mechanisms include epigenetic changes (4) which can alter the trajectory of risk across the life course. Preventive interventions need to commence before conception, to reduce transmission of CVD risk by promoting healthy behaviours in prospective parents, as well as in pregnancy and postpartum. Surprisingly, these opportunities are not included in the 2018 United Nations Political Declaration on NCDs (see 5).

NCDs such as CVD have communicable risk components transmitted across generations by socio-economic as well as biological factors, although the former can also become embodied in the offspring by epigenetic mechanisms. The inheritance of CVD risk, and social inequalities in such risk, thus raise wider questions about responsibility for the health of future generations at societal as well as individual levels.

Mark Hanson is supported by the British Heart Foundation


Early Life Origins of Adult Cardiovascular Disease

A. Singhal, Childhood Nutrition Centre, UCL GOS Institute of Child Health, London, UK

The idea that nutrition may act during a critical window in development to permanently affect, or ‘program’, long-term health is strongly supported by the benefits of breast-feeding for later risk of obesity and cardiovascular disease (CVD)\textsuperscript{1–4}. Early experimental (randomised) studies showing lower risk factors for CVD (leptin resistance, dyslipidaemia, high blood pressure, and insulin resistance) in preterm infants randomly assigned to human milk\textsuperscript{1} are now strongly supported by several systematic reviews showing a protective effect of breast-feeding on later obesity \textsuperscript{2} and CVD\textsuperscript{3}. The mechanisms for these effects may include benefits of human milk on long-term cardiac structure and function, and the concept that the advantages of breast-feeding are related to slower growth and relative undernutrition of breast-fed compared to formula-fed infants - the ‘Growth Acceleration Hypothesis’. This hypothesis is now supported by 45 studies\textsuperscript{3} (summarised in 5 systematic reviews\textsuperscript{4}), an individual patient meta-analysis in 47,661 individuals, 6 randomised trials and, most recently, by an RCT of infants predominantly breast-fed\textsuperscript{5}.

This presentation will give an overview of the early origins of obesity and CVD, and the mechanisms involved. It will emphasise the need for experimental studies in nutrition, and the implications of nutritional programming for nutritional, clinical and public health practice.

References:


Preterm Birth and Cardiovascular Risk

Mikael Norman, Karolinska Institutet, Stockholm, Sweden

An estimated 15 million babies (11% of all livebirths worldwide) are born preterm each year, and infant survival is nowadays the most probable outcome in high resource settings. Preterm infants are small because of shortened gestation, sometimes complicated by fetal (and postnatal) growth restriction. Considering that an increased risk of cardiovascular disease has been repeatedly reported in people born small, it is important to understand potential contributions from preterm birth to adverse cardiovascular health in adult life. Follow-up studies of children and young adults born preterm suggest some alterations in the structure and function of the cardiovascular system, elevated blood pressure and glucose intolerance. Whether or not these changes in physiology reflect early adaptations after preterm birth or genetic traits remain to be established. And if and how preterm birth results in a significant risk increase for cardiovascular disease late in life are still unresolved questions.
Poster presentation on Thursday 22nd February at 15.00-15.30

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Study of changes in heart rate variability during surgical stages to completed Fontan circulation

Jenny Alenius Dahlqvist\textsuperscript{1}, Urban Wiklund\textsuperscript{2}, Marcus Karlsson\textsuperscript{2}, Annika Rydberg\textsuperscript{1}

\textsuperscript{1}Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden
\textsuperscript{2}Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden

Objectives: In patients with Fontan circulation, arrhythmia is a serious complication contributing to morbidity and mortality. Arrhythmia is related to heart rate variability (HRV), which reflects autonomic nervous regulation of the heart. Our hypothesis was that autonomic nervous ganglia, located at the junction of the superior vena cava’s entrance to the heart, may be affected during the bidirectional Glenn procedure (BDG), resulting in reduced HRV.

Methods: 24-hour ECG recordings were obtained before BDG (n=47), after BDG (n=47) and after total cavopulmonary connection (TCPC) (n=45) in patients, and in 38 healthy controls. HRV was analysed by spectral and Poincaré methods. Age-related z-scores were calculated and compared using linear mixed effects modeling.

Results: Total spectral power (P\textsubscript{tot}) and the Poincaré index SD\textsubscript{2} were significantly lower in patients before BDG when compared to healthy controls, but no difference was found in RR interval. The RR interval and SD\textsubscript{2} were significantly increased in patients post BDG compared to pre BDG. Compared to healthy controls; patients operated with BDG had significantly longer RR intervals and reduced P\textsubscript{tot}. Patients post TCPC showed longer RR intervals and lower P\textsubscript{tot} compared with healthy controls.

Conclusions: Heart rate was reduced after BDG procedure, and further reductions of HRV were seen post-TCPC. Our results indicate that autonomic regulation of cardiac rhythm is affected both after BDG and again after TCPC. This may be reflected as, and contribute to, postoperative arrhythmic events.
Impaired skeletal muscle endurance in adults with complex congenital heart disease is associated with local muscle oxygenation kinetics

Sandberg C1,2, Crenshaw AG3, Elçadi GH3, Christersson C4, Hlebowicz J5, Thilén U5, Johansson B1

1 Heart center and Department of Public Health and Clinical Medicine, Umeå University, Sweden
2 Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University, Sweden
3 Centre for Musculoskeletal Research, Department of Occupational and Public Health Sciences, University of Gävle, Sweden
4 Department of Medical Sciences, Uppsala University, Sweden
5 Department of Cardiology, Clinical Sciences, Lund University, Sweden

Background: Adults with complex congenital heart disease show reduced aerobic exercise capacity and impaired skeletal muscle function compared to healthy peers. Peripheral muscle factors are presumed to be important contributors, but the mechanisms are poorly understood.

Purpose: To investigate if muscle oxygenation is associated with reduced skeletal muscle endurance in adults with complex CHD.

Method: Sixty-four adults with complex congenital heart disease (mean age 36.9±14.8 years, females n=19) were recruited from centers specialized in congenital heart disease. Seventy-four age and gender matched healthy peers were recruited as controls. Muscle oxygen saturation was successfully determined on the anterior portion of the deltoid muscle using near-infrared spectroscopy for 57 patients and 71 controls. Measurements were made at baseline, during isotonic shoulder flexions (0–90°) to exhaustion, and during 60 seconds of recovery.

Results: The adults with complex CHD performed fewer shoulder flexions (38±15 vs. 69±40, p<0.001), had lower muscle oxygen saturation at rest (58±17% vs. 69±18%, p<0.001), a slower desaturation rate at exercise onset (-9.5±5.9%/sec vs. -15.1±6.5%/sec, p<0.001), and a slower resaturation rate post exercise (3.9±2.8%/sec vs. 5.4±3.6%/sec, p=0.008) compared to the controls.

Conclusion: A distinct association was found between muscle oxygenation kinetics and early muscle fatigue for adults with complex CHD. Our findings may give insight to the underlying mechanisms for the reduced aerobic exercise capacity for these patients, and therefore provide implications for design of exercise training protocols in this population.
Parents’ experience of uncertainty related to transfer from pediatrics to adult care in adolescents with congenital heart disease

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Parents play a crucial role for their adolescent during the transition before transfer to adult care. Many parents acknowledge the struggling of feeling secure in handing over the responsibility and letting go of control. Well-prepared and informed parents who feel secure are most likely better skilled to support their adolescent and to hand over the responsibility.

Purpose
The purpose of this cross-sectional study was to study parent’s levels of uncertainty related to the transfer from pediatric to adult care in adolescents with Congenital Heart Disease (CHD) and to identify potentially correlating factors.

Methods
A total of 351 parents (53.8% mothers) to adolescents, 16–18 years old, born with CHD were included (35% response rate). Parental uncertainty was assessed using a Linear Analogue Scale (Range 0–100). Data was collected between January and August 2016. Potential correlates were assessed using the readiness for transition questionnaire (RTQ) (including adolescents transition readiness, adolescents responsibility and parental involvement) and a questionnaire for sociodemographic data.

Results and Outcomes
The mean parental uncertainty score was 42.5 (SD 30.1). Twenty-four percent of the parents had a very low level of uncertainty (score 0–10) and 7% had a very high level (score 91–100).

An ICC analysis showed a good agreement between the matched parents (0.737, 95% confidence interval 0.58–0.84, p = 0.005). Mothers generally had a significantly higher uncertainty level than fathers (p = 0.03). This difference, however, was not clinically meaningful given the low Cohen’s d of 0.15.
The univariate regression analysis indicated that increased levels of perceived overall readiness (p = 0.005) and a lower level of parental involvement (p=0.005) were associated with a lower level of uncertainty. Adolescent age, sex, CHD complexity, adolescents’ responsibility and parental age were not associated with the level of uncertainty. Twenty six percent of the mothers and 36% of the fathers reported that they had not started thinking of the transfer yet. This did not differ between being a parent of a boy or a girl, nor did the complexity of the disease display any significant differences for mothers, although it did for fathers. With increasing age of the adolescent, parents reported a decrease in “I have not thought about the transfer”.

Conclusion
A wide range in levels of uncertainty was seen. There was a good agreement in the mothers and fathers perceived level of uncertainty. The level of uncertainty was not associated with the adolescent’s age, gender, or disease complexity. Parents who perceived their adolescent as more ready for the transition felt less uncertain with the upcoming transfer. The result also showed that a high level of parental involvement might indicate a high level of uncertainty. Still, thirty percent of the parents had not started to think about the transfer to adult care. These results suggest that it might be important for healthcare providers to start up an early discussion with parents about their important role when their child is transitioning and preparing for transfer to adult care.
Unraveling the role of healthcare system factors for continuing care of adolescents with congenital or rheumatic heart disease: Rationale and methods of the international Adole7C-project

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Background:
Although lifelong follow-up is recommended for most people with congenital (CHD) or rheumatic heart disease (RHD), up to 76% present with care gaps, which are associated with increased morbidity and healthcare utilisation. Prior research on predictors was limited to patient-related factors, leaving hospital-related and healthcare system-related predictors unaddressed. The Adole7C-project (AdolesCents reCeiving Continuous Care for Childhood-onset Chronic Conditions) is an international research project that aims (i) to investigate the prevalence of care gaps in adolescents with CHD and RHD in
South Africa, Sweden and Belgium; (ii) to identify hospital-related and healthcare system factors that predict discontinuation of cardiac follow-up; and (iii) to determine the impact of care gaps on mortality, morbidity and healthcare utilisation.

Methods:
We employ an integrative study, combining quantitative and qualitative research approaches. The quantitative study comprises an international, multicentre study in 2 centres in South Africa (Cape Town, Port Elizabeth), 7 centres in Sweden (Gothenburg, Lund, Stockholm, Umeå, Uppsala, Linköping, Örebro), and 2 centres in Belgium (Leuven, Gent). Patients are selected from the paediatric cardiology outpatient clinic visit lists 2005–2011. Overall, 1500 patients will be included. Patient data on predictors and outcomes are collected through patient hospital registers and medical files. If data are missing, a personal contact with the patient will be made. For hospital- and health-care system factors, a dedicated research form will be completed by the heads of paediatric cardiology departments. Multilevel analyses will be undertaken. The qualitative study comprises an ethnographic approach, using individual interviews and focus group discussions with patients who either presented with care gaps or not, to understand the barriers and facilitators for continuing medical follow-up.

Conclusion:
The Adole7C-project is designed to provide evidence on the impact of healthcare system factors on continuing cardiac care for adolescents with CHD or RHD.
Asking the expert

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Background

The Norwegian Association for Children with Congenital Heart Disease in 2013 established an internet-based service, Ask the expert, offering patients with heart disease, their parents and others to submit questions to a paediatric cardiologist (AM). The aim of the present study was to evaluate data from this service.

Methods

Questions (no formal structure required) were submitted by email to a contact person (HWP) at the Association’s office, anonymized, and forwarded to the cardiologist. Answers were returned through the contact person. All questions and answers were stored (April 2013 through December 2018). Data for who put forward questions (parents, patient, others), the heart diseases involved, topics addressed and recommendations given in the answers were systematized.

Results

289 emails were submitted including a total of 313 separate questions. 214 (74%) of the emails were put forward by parents, 33 (11%) by patients (young or adults) and 10 (3%) by health care personnel, students, journalists etc. 32 (11%) could not be classified. In 107 (37%) of the emails the heart defect was explicitly given. Presumed severe defects (coarctation of the aorta, tetralogy of Fallot, aortic stenosis, hypoplastic left heart syndrome) were overrepresented compared to population-based data (1), while more moderately severe defects (atrial and ventricular septal defects, patent ductus arteriosus) were underrepresented (p < 0.05). Questions most often referred to symptoms (43; 14%), interventions (38; 12%), infections (26; 8%), function of the health care system (23; 7%), physical activity (21; 7%), nutrition (19; 6%) and sources for information (15; 5%). In the answers, 57 (20%) patients were recommended consultation with authorized health care personnel (general practitioner, district nurse, paediatrician, cardiologist, others).

Conclusions

There is a (major) need for supplementary information to what is given by the authorized health care system to patients with heart disease and their parents. A broad spectrum of topics is addressed (it is asked about “everything”). Severe heart defects were over- and moderately severe ones underrepresented. In a substantial percentage contact with the authorized health care system was recommended.

Reference

Enablers and barriers for physical activity in adults with congenital heart disease

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Background: A majority of adults with congenital heart disease (CHD) have reduced exercise capacity and do not reach the recommended level of physical activity. A physically active lifestyle is essential to maintain health and counteract acquired cardiovascular disease. This study illuminates aspects that may be relevant for performing physical activity.

Purpose: To describe what adults with CHD considered as enablers and barriers for physical activity.

Methods: Semi-structured interviews were performed individually with fourteen adults (age 19–68 years, women=7) with complex CHD. The interviews were analyzed using qualitative content analysis.

Results: Aspects that may enable or inhibit physical activity were found in four categories: Physical, psychological, psychosocial and environmental aspects.

This can be exemplified by the category physical aspects; where persons expressed being limited by the CHD to perform physical activity, but also that improved aerobic fitness allows for being more active, and in the category psychosocial aspects; the person’s previous negative experiences and lack of support constituted barriers while encouragement from others and being active as a child enabled an active lifestyle in adult age.

Conclusion: The present study identifies barriers and enablers for being physically active in adults living with CHD. It is essential to identify prerequisites for supporting and promoting physical activity and thereby hopefully prevent long-term adverse outcomes. Barriers can potentially be transformed to enablers through increased knowledge in both the adult with CHD and the healthcare provider.
Low birth weight and risk of atypical development of cardiac specialised tissue in children.

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Low birth weight (LBW) has been reported to be linked with increased risk of cardiovascular pathology emerging later in life, including hypertension, dyslipidaemia, hypercoagulation, coronary heart disease, and stroke. Meanwhile, little is known on the possible association between LBW and further risk of cardiac arrhythmias, although the conduction system of the heart undergoes intensive growth and remodelling during the foetal period and after birth. As a consequence, retarded intrauterine growth may cause atypical development of cardiac specialised tissue with arrhythmogenic effect.

Our previous study (Kelmanson I.A. et al., 1998) encompassed 31 children aged 1–15 years (12 boys, 19 girls), in whom the persistence of accessory pathways of conduction tissue in the heart and inducible reciprocating supraventricular tachycardia were confirmed by means of programmable transoesophageal pacing, constituted the study group. None of them exhibited signs of either inborn or acquired heart disease causing arrhythmia; their parents and siblings did not suffer cardiac arrhythmias. The control group was formed of 62 apparently healthy children (two controls for each case) matched to cases for sex, age, date and place of birth. Information on infant perinatal and maternal characteristics was collected retrospectively. Risk of arrhythmia was increasing with diminishing birth weight, and the highest and statistically significant values were associated with weight at birth less than 2500 g: odds ratio was equal to 14.6 (95% CI: 1.7–127.9; p= 0.015), and it remained significant after adjustment for major potential confounders. In addition, children with arrhythmia were more often born with retarded intrauterine growth (birth weight < 10 percentile), preterm (<37 weeks of gestation), of higher birth order, and they had lower Apgar scores at 1 and 5 min. Their mothers more often had diagnosed gynaecological diseases.

Infants born light were shown to have mild degree of cellular deficit within the heart, and our previous findings were that birth weight had an impact on the growth capacity of the heart in infants (Kelmanson I.A., 1998). Along with cardiac growth, conduction system of the heart is subject to intensive remodelling. During early cardiac development, there is direct physical continuity between the atrial and ventricular myocardium. This physical continuity, and, by implication, electrical continuity, is normally lost during fetal and perinatal development when junctional conduction system (atrophic atrioventricular node and His bundle) undergoes a ‘resorptive degeneration’ of its peripheral parts, especially in the fibrous body and the fibrous septum. Whenever this physiological process fails or slows down, some peripheral bundles of the conduction system remain connected to the common myocardial tissue of the ventricular septum. Remnants of conducting tissue may be present in infants born at term, and sometimes even in adults. Under particular conditions, they may cause potentially malignant junctional arrhythmias. The findings are indicative that retarded fetal growth may be closely linked not only with retarded growth of the heart, but also with delayed maturation of its conduction system thus increasing risk of cardiac arrhythmias later in life.
High prevalence of ascending aortic dilation in adults with repaired coarctation of the aorta

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**Background:** Ascending aortic dilation is common in adults with repaired coarctation of the aorta (CoA). The condition is associated with life-threatening complications such as aortic dissection and rupture, but the data are currently limited regarding factors associated with ascending aortic dilation in these patients.

**Methods and results:** From the national register of congenital heart disease, 165 adult patients (≥ 18 years old) with repaired CoA, and echocardiographic data on aortic dimensions, were identified (61.2 % male, mean age 35.8 ± 14.5 years). Aortic dilation (aortic diameters > 2SD above reference mean) was found in 55 (33.3 %) of the 165 included patients, and was associated with aortic valve disease in univariate logistic regression analysis (p = 0.010, OR 2.44 [1.23–4.83]).

**Conclusions:** In conclusion, aortic dilation is common in this study population of adult patients post repair of CoA, and is strongly associated with aortic valve disease. It is worth noting that no association was found between aortic dilation and age or blood pressure, suggesting that the aortic diameter is fairly static in this young cohort, and that ascending aortic dilation in adults with repaired CoA does not primarily result from hypertension.
Lower systolic blood pressure at 7 years of age in marginally low birth weight children who received early iron supplementation

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Background: The prevalence of hypertension, followed by cardiovascular diseases, is increasing and the need to early detect those at risk as well as to find ways to prevent the progression is crucial. Studies have found that low birth weight (LBW; <2500 g) could be a risk factor to later high blood pressure (BP). However, results alter and the risk magnitude in different settings is still unclear. Also, several pathways have been suggested, although knowledge regarding mechanisms as well as potential treatments is still a relatively unexplored area.

Approximately 60% of all children born with LBW are born with a birth weight between 2000–2500g, here referred to as marginally LBW. This large subgroup of children is rarely the primary focus in studies.

Aim: In this study, we investigated the effect of early iron supplementation on later BP in LBW infants.

Method: This was a randomized double-blinded controlled trial including 285 marginally LBW children stratified into three intervention groups receiving placebo, 1 mg Fe/kg/day or 2 mg Fe/kg/day between 6 weeks and 6 months of age.

At 3.5 and 7 years of age, BP was measured and compared between the groups. Three measurements were performed and mean systolic and diastolic BP as well as heart rate was registered. Mean values were compared between the groups in crude analyses as well as analyses adjusted for covariates (sex, age, height and heart rate). Also, anthropometric measures as well as blood samples and body composition were assessed and have been reported elsewhere.

Results: According to intention to treat principle, 207 and 189 marginally LBW children were assessed for BP at 3.5 and 7 years respectively (dropout rate until age 7 was 29%).

There was no significant difference in diastolic BP at any measuring point.

At 3.5 years, mean systolic BP was higher in the placebo group compared to the two iron supplemented group (p=0.074, adjusted p=0.026). The adjusted mean systolic difference was 2.1 mmHg (95% CI: 0.1; 4.1 mmHg) lower in the combined iron supplemented groups (1 or 2 mg Fe/kg/day), compared to the placebo group.

At the 7-year control, the mean ± SD systolic BP was 103 ±8.1, 101 ±7.5 and 101 ±7.8 mmHg in the children who received placebo, 1 and 2 mg Fe/kg/day respectively (p=0.322, adjusted p=0.076). When combining the iron supplemented groups, the adjusted mean difference was 2.2 mmHg (95% CI: 0.3; 4.2 mmHg) lower in the iron supplemented children.

Conclusion: We found that early iron supplementation given to marginally LBW children reduced later systolic BP both at 3.5 and 7 years of age. To our knowledge, these results are novel and suggest that early micronutrient intervention could modify the risk of later high BP and hence, reduce the risk of cardiovascular diseases.
Quality of Life in adults with repaired tetralogy of Fallot

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Introduction: Thanks to improved medical and surgical care, the numbers of patients with tetralogy of Fallot (ToF) increase. However, long-term morbidity is a concern and potentially affects quality of life (QoL).

Methods: Patients with ToF and data on EuroQol-5 dimensions questionnaire (EQ-5D) were identified in Swedcon (the national Swedish register on congenital heart disease). The EQ-5D index was dichotomized into best possible health related QoL (EQ-5D index = 1) or differed from 1.

Results: 288 patients were studied. Univariate logistic regression showed a positive association between low NYHA class (NYHA I) (odds ratio [OR] 8.3, 95% confidence interval [CI] 3.8 to 18.2), self-reported physical activity >3 h/week (OR 3.3, 95% CI 1.7 to 6.7) and good right ventricular function (OR 2.6, 95% CI 1.1 to 6.0). A negative association between a composite of symptoms (OR 0.2, 95% CI 0.1 to 0.4), ongoing cardiovascular medication (OR 0.3, 95% CI 0.2 to 0.5), age (OR 0.97, 95% CI 0.96 to 0.99), and EQ-5D index was observed. In a multivariate logistic regression model, low NYHA class (OR 7.3, 95% CI 3.3 to 16.1) and self-reported physical activity >3 h/week (OR 2.3, 95% CI 1.1 to 4.8) remained associated with best possible health related QoL. NYHA and symptoms were interchangeable in the model.

Conclusion: Self-reported physical activity, NYHA class and absence of symptoms were strongly associated with QoL measured by EQ-5D. Physical activity level is a potential target for intervention to improve QoL in adults with repaired ToF.
Postnatal nutritional intakes and hyperglycemia as determinants of blood pressure at 6.5 years of age in children born extremely preterm

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Background and aims
Children born extremely preterm (EPT) have higher blood pressure (BP) than term-born children. This might be attributed to adverse developmental programming by altered early-life exposures. We assessed associations between nutrition, growth and hyperglycemia early in infancy, and BP at 6.5 years of age in children born EPT.

Methods
Data regarding perinatal exposures including nutrition, growth and glycemia status were collected from the Extremely Preterm Infants in Sweden Study (EXPRESS), a population-based cohort including infants born <27 gestational weeks during 2004–2007. At follow-up at 6.5 years of age, three BP measurements were performed at resting conditions and height and weight measured in a sub-cohort of 171 children. Z-scores for systolic (SBP) and diastolic (DBP) blood pressures were calculated as outcomes.

Results
Higher mean daily protein intake (+1 g/kg/d) during postnatal weeks 1 to 8 was associated with 0.40 (±0.18) SD higher DBP. Higher mean daily carbohydrate intake (+1 g/kg/d) during the same period was associated with 0.18 (±0.05) and 0.14 (±0.04) SD higher SBP and DBP, respectively. No associations were found between infant growth (weight, length) and later BP. Hyperglycemia and its duration during postnatal weeks 1 to 4 were associated primarily with higher DBP z-scores.

Conclusions
Increased protein and carbohydrate intakes during the first weeks of life, as well as occurrence and duration of hyperglycemia, were associated with higher BP at 6.5 years of age in children born EPT, whereas weight gain and linear growth during the same period were not. These findings emphasize the importance of modifiable early-life exposures, such as nutrition and hyperglycemia, in determining long-term outcomes in children born preterm.
Jöns Jacob Berzelius, one of the most prominent natural scientists of the 19th century, was born in 1779 in Väversunda, in the county of Östergötland in southern Sweden, a region with rich cultural traditions. Orphaned at an early age, he went to several foster-homes and received his schooling in nearby Linköping. After graduating in medicine at the University of Uppsala, he moved to Stockholm, where he became assistant master without pay at the so-called »Surgical School«, and worked as a doctor for poor people. At the age of 28 he became professor of medicine and pharmacy.

In 1808 Berzelius was one of the seven men who founded the Swedish Society of Medicine »For the perfection of science through mutual mediation of knowledge and collective experience, for the promotion of friendly confidence between doctors«.

Berzelius have enriched our knowledge of nature of life phenomena, established the atomic weights of most of the known elements, presented his electrochemical theory for the understanding of the nature of chemical compounds and laid the foundation for the sciences of the chemistry of rock types. He also found that elements combine with each other according to fixed numerical relationships. In addition to this, in his striving for order and method, with his talent for simplicity and clarity in expression, he created the chemical symbolic language in 1813, which since that time has been an essential instrument of chemistry.

With time he became a practised lecturer but preferred to express himself in writing and this he did superbly. Impressive are the great scientific works where he also demonstrated his interest and ability to spread knowledge about the latest advances of natural sciences. Berzelius delight in research and debate was united with a great humility before the great scientific questions. Both his attitude and artistry of formulation is illustrated by the following passage in his Manual of Chemistry (vol 3, 1818):

»All our theory is but a means of consistently conceptualizing the inward processes of phenomena, and it is presumable and adequate when all scientifically known facts can be deduced from it. This mode of conceptualization can equally well be false and, unfortunately, presumable is so frequently. Even though, at a certain period in the development of science, it may match the purpose just as well as a true theory. Experience is augmented, facts appear which do not agree with it, and one is forced to go in search of a new mode of conceptualization within which these facts can also be accommodated; and in this manner, no doubt, modes of conceptualization will be altered from age to age, as experience is broadened, and the complete truth may perhaps never be attained. But even if the goal can never be reached, let us never abandon our endeavor to get closer to it.«

Parts of this text is found in: Berzelius – Creator of the chemical language, by Carl Gustaf Bernhard, the Royal Swedish Academy of Sciences
History of the SSM building

In 1879, the Swedish Society of Medicine moved from what was then the home of Karolinska Institutet at Norr Mälarstrand to its own premises in Jakobsgatan in Stockholm. It soon outgrew this location and a search for new premises was resumed.

On Walpurgis night in 1889, six men were inside the Katarina lift at Slussen in Stockholm. A fault developed in the machinery, causing the lift cage to fall. One of the passengers, Carl Westman, was injured, but a fellow passenger, Johan Rissler, a surgeon and member of the building committee of the Society of Medicine, immediately assisted him.

In 1904, the Society announced an architectural competition for a building on a site it had purchased in Klara Östra Kyrkogata. The winner was Carl Westman, and the building was finished two years later.

The Society's building which dates from 1906, was a breakthrough for the architect Carl Westman and the national romantic style architecture he favoured.

The building itself is work of art – from its facade of handmade brick and Christian Eriksson’s granite reliefs in the entrance to its mosaic floors, carved balustrades, chandeliers, and ventilation grilles – all Westman signatures. The building today is a Swedish, turn of the century architectural treasure.