Congenital Heart Disease: A Lifelong Journey

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Congenital heart disease: A Success Story

Survival rate


15% \( \rightarrow \) >90%

Cardiac surgery

PDA-Closure \( \rightarrow \) BT-Shunt \( \rightarrow \) Fontan-Operation

Fallot correction

Cardiovascular imaging

ECG \( \rightarrow \) Fluoroscopy \( \rightarrow \) Angiography \( \rightarrow \) Echo \( \rightarrow \) Valvular interventions ...

(Paediatric-)Cardiology

Rashkind
Lillehei used ‘Human Cross-Circulation’
First Case 31\textsuperscript{st} August 1954

The first 10 patients died – How could he carry on?
The only operation described with a potential mortality of 200%
A parent could lost not only their child but also their spouse!
Fontan Evolution: CHD a Very Dynamic Field
Percutaneous Valves
Transcatheter PV implantation in Tetralogy

Major advance
Size of the valve and PV “annulus” may be a problem for the adult patient.
Long-term survival after surgery for CHD

13,876 operations in 10,976 patients with CHD
Between 1953 to 2009

Repair now performed much earlier

Peri-op mortality from 7% \( \downarrow \) 3%

FU 98% complete

Late survival from 70% \( \uparrow \) 86%

Raissadati et al. Circulation 2015

Figure 1. Patient age at operation and the number of operations and birth rate by decade. Bars are divided according to different age groups. The continuous line represents the number of children born in the general population during each decade.
Mortality in Adult Congenital Heart Disease

- 6,969 adult patients (age 29.9±15.4 years)
- FU between 1991 and 2013, mean of 9.1 years
- 524 patients died
- Patients with Fontan physiology, Eisenmenger syndrome and complex CHD had much poorer survival.
Our Research:

- Chronic Heart Failure (CHD is a lifelong disease)
Neurohormonal Activation and the Chronic Heart Failure Syndrome in Adults With Congenital Heart Disease

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Background—Neurohormonal activation characterizes chronic heart failure, relates to outcome, and is a therapeutic target. It is not known whether a similar pattern of neurohormonal activation exists in adults with congenital heart disease and, if so, whether it relates to common measures of disease severity or whether cardiac anatomy is a better discriminant.

Methods and Results—Concentrations of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin-1 (ET-1), renin, aldosterone, norepinephrine, and epinephrine were determined in 53 adults with congenital heart disease, comprising 4 distinct anatomic subgroups (29 female; 33.5±1.5 years of age; New York Heart Association class 2.0±0.1, mean±SEM) and 15 healthy control subjects (8 female; 32.3±1.3 years of age). Systemic ventricular function was graded by a blinded echocardiographer as normal or mildly, moderately, or severely impaired. Adults with congenital heart disease had elevated levels of ANP (56.6 versus 3.1 pmol/L), BNP (35.8 versus 5.7 pmol/L), ET-1 (2.5 versus 0.7 pmol/L, all P<0.0001), renin (147 versus 16.3 pmol/L), norepinephrine (2.2 versus 1.6 pmol/L, both P<0.01) and aldosterone (546 versus 337 pmol/L, P<0.05). There was a highly significant stepwise increase in ANP, BNP, ET-1, and norepinephrine according to New York Heart Association class and systemic ventricular function, with even asymptomatic patients having evidence of significant neurohormonal activation. In contrast, there was no direct relationship between the 4 anatomic subgroups and any of the neurohormones studied.

Conclusions—Neurohormonal activation in adult congenital heart disease bears the hallmarks of chronic heart failure, relating to symptom severity and ventricular dysfunction and not necessarily to anatomic substrate. Neurohormonal antagonism across this large and anatomically diverse population should be considered. (Circulation. 2002;106:92-99.)

Key Words: heart diseases ■ heart failure ■ heart defects, congenital
Neurohormonal activation in ACHD
Relation to cardiac anatomy

**Log ANP**

ANOVA p=0.30

**Log BNP**

ANOVA p=0.48

**ET-1 (pmol/L)**

ANOVA p=0.12

**Ne (nmol/L)**

ANOVA p=0.24

Bolger et al Circulation 2002
Neurohormonal activation

Logrank p<0.0001

Cumulative mortality (%)

BNP > 78pg/ml

BNP ≤ 78pg/ml

P > 78pg/ml 20 15 14 12 11 10 9 9 3
P ≤ 78pg/ml 29 29 29 29 29 29 29 19

Giannakoulas G. Am J Cardiol 2010
Exercise capacity in adults with CHD
MVO2 and underlying diagnosis

Aortic coarctation
Tetralogy of fallot
VSD
Mustard-operation
Valvular disease
Ebsteins anomaly
Pulmonary atresia
Fontan-operation
ASD (late closure)
ccTGA
Complex anatomy
Eisenmenger

Mean ± SD
28.7 ± 10.4
25.5 ± 9.1
23.4 ± 8.9
23.3 ± 7.4
22.7 ± 7.6
20.8 ± 4.2
20.1 ± 6.2
19.8 ± 5.8
19.2 ± 6.2
18.6 ± 6.9
14.6 ± 4.7
11.5 ± 3.6

ANOVA p<0.0001

Diller et al. Circulation 2005
PEAK VO2 PREDICTS COMBINED END-POINT OF HOSPITALIZATION OR DEATH

Diller et al, Circulation 2005
DISTRIBUTION OF PEAK VO2
IN ASYMPTOMATIC ACHD PATIENTS (NYHA class I)

Diller et al, Circulation 2005
Heart failure – increasing with age

Cardiac mortality by cause

Diller et al  Circulation 2015
Aging population

Numbers European Union (Population 497 Mll. in 2008)

Prevalence 5.1%* - 5.2% ** (2012/13)

ACHD Patients > 60 years

Estimated prevalence 11% (2030)

ACHD Patients < 60 years

Children with CHD

** German Competence Network for Congenital Heart Disease (data on file)

Extrapolation

Baumgartner H EHJ 2014
Non-Cardiac Mortality – increasing with age

Diller et al  Circulation 2015
ACHD mortality

Standardized mortality ratio

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SMR (95%CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PDA</td>
<td>0.42 (0.10–1.78)</td>
<td>0.20</td>
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<tr>
<td>ASD</td>
<td>1.13 (0.86–1.48)</td>
<td>0.32</td>
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<tr>
<td>VSD</td>
<td>1.36 (0.82–2.27)</td>
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<tr>
<td>Valvar disease</td>
<td>1.39 (1.09–1.78)</td>
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<tr>
<td>Aortic Coarctation</td>
<td>1.73 (1.22–2.46)</td>
<td>&lt;0.001</td>
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<tr>
<td>AVSD</td>
<td>1.86 (1.05–3.30)</td>
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<td>Marfan syndrome</td>
<td>2.24 (1.41–3.57)</td>
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<tr>
<td>Tetralogy of Fallot</td>
<td>2.34 (1.73–3.17)</td>
<td>&lt;0.001</td>
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<td>TGA arterial switch</td>
<td>2.61 (0.77–8.82)</td>
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<td>Ebstein anomaly</td>
<td>3.30 (1.99–5.49)</td>
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<td>Systemic RV</td>
<td>4.88 (3.33–7.16)</td>
<td>&lt;0.001</td>
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<tr>
<td>Eisenmenger syndrome</td>
<td>12.79 (9.67–16.91)</td>
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<td>Complex CHD</td>
<td>14.13 (10.71–18.64)</td>
<td>&lt;0.001</td>
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<tr>
<td>Fontan–circulation</td>
<td>23.40 (15.97–34.29)</td>
<td>&lt;0.001</td>
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(∗) d’Udekem et al., Circulation, 2015 (Australia & NZ, n=1089)
(ª) Pundi et al., Circulation, 2015 (Mayo, n=1052)
(‘) Khairy et al., Circulation, 2008 (Boston, n=261)
What can we do… Medical therapy?

Focus on
Single Ventricles/Fontan & the Systemic RV
Cardiac resynchronization in ‘real life’

Patients with CRT/multisite pacing (N=65)

No structural congenital heart disease N=10

Primary CRT Implantation (N=7)

- Aortic coarctation with dilated cardiomyopathy (N=2)
- Tetralogy of Fallot (N=2)

Indication for antibradycardia pacing or ICD

- congenitally corrected TGA (N=2)
- TGA after atrial switch (N=1)

Diller GP, ESC 2017
Ventricular Assist Devices

Problems With Existing Devices

- Many mechanical moving parts, valves -> prone to failure
- Thrombus formation
- Hemolysis
- Infection caused by connection to external lead
- Used by patients in critical conditions/bridge to transplantation
- Large external battery

*Currently, no VAD designed specifically for Fontan patients
Transplantation?
Figure 6. Comparison of survival after transplantation in Fontan patients, based on whether they had a history of protein-losing enteropathy (PLE) or not (No PLE) before listing. There was no difference in survival between these two groups.
Is life worth living? It all depends on the liver...

William James (1842–1910)
American philosopher and psychologist
Exercise & Exercise Training

Becker-Grünig et al, *Int J Cardiol* 2013
The Future:

- How can we do better?
End-Stage CHD: More Trials needed!

Figure 2 Adult congenital heart disease subgroups prone to heart failure: drug therapy and potential impact on prognosis. Green box and green line indicates established prognostic benefit and blue box and dotted line indicates prognostic benefit uncertain. ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; HTx, heart transplantation; PAH, pulmonary arterial hypertension; RV, right ventricle; TGA, transposition of the great arteries.
1098 patients (median age 34.4 years) with ES between 2000-2015

Over a median FU of 3.1 years 278 patients died; 6 had a Tx

12 predictors of death on univariable analysis including advanced therapy for PAH (HR 0.75, 95%CI 0.59-0.95, P=0.017)
The MUSES Study:
Type of Shunt and Outcome

Kempny et al Circulation 2017
### 5 Year Mortality Prediction in Eisenmenger Syndrome (n=1,098)

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<tr>
<th>6MWT distance</th>
<th>Pre-tricuspid shunt</th>
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**SO₂ at rest (%)**

**Color scale for 5-years mortality:**
- ≤10%
- (10%-20%)
- (20%-30%)
- (30%-40%)
- (40%-50%)
- >60%

*Kempny et al Circulation 2017*
Bosentan reduces pulmonary vascular resistance indexed

Change from baseline

Placebo (n=17) Bosentan (n=36)

T.E. = -472 dyn.sec.cm\(^{-5}\)
p=0.04

Galie et al for Breathe-5, Circulation 2006
Bosentan increases exercise capacity

6MWD (m) Change from baseline

T.E. = 53.1 m p=0.008

Galie et al for Breathe-5, Circulation 2006
End-Stage CHD: More Trials needed!

Evaluation of Macitentan in Patients With Eisenmenger Syndrome
Results From the Randomized, Controlled MAESTRO Study

BACKGROUND: Eisenmenger syndrome describes congenital heart disease-associated severe pulmonary hypertension accompanied by right-to-left shunting. The multicenter, double-blind, randomized, placebo-controlled, 16-week, phase III MAESTRO study (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity) evaluated the efficacy and safety of the endothelin receptor antagonist macitentan in patients with Eisenmenger syndrome.

METHODS: Patients with Eisenmenger syndrome aged ≥12 years and in World Health Organization functional class II–IV were randomized 1:1 to placebo or macitentan 10 mg once daily for 16 weeks. Patients with complex cardiac defects, Down syndrome and background PAH therapy were eligible. The primary end point was change from baseline to week 16 in 6-minute walk distance. Secondary end points included change from baseline to week 16 in World Health Organization functional class. Exploratory end points included NT-proBNP (N-terminal pro-B-type natriuretic peptide) at end of treatment expressed as a percentage of baseline. In a hemodynamic substudy, exploratory end points included pulmonary vascular resistance index (PVRi) at week 16 as a percentage of baseline.
RV LAX, mm

LV LAX, mm

PRF, %

RVESVi, ml/m²

RVEF, %

LVEF, %

ANP, pmol/L

BNP, pmol/L

VO₂max, ml/kg/min

Ramipril

Placebo

P=0.04

P=0.01

P=0.94

P=0.66

P=0.08

P=0.12

P=0.15

P=0.25

P=0.32

Babu-Narayan et al IJC 2010
End-Stage CHD: More Trials needed!

Figure 2: Adult congenital heart disease subgroups prone to heart failure: drug therapy and potential impact on prognosis. Green box and green line indicates established prognostic benefit and blue box and dotted line indicates prognostic benefit uncertain. ccTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; HTx, heart transplantation; PAH, pulmonary arterial hypertension; RV, right ventricle; TGA, transposition of the great arteries.
Congenital Heart Disease: How Can We do Better?

- Provide for the ever growing clinical need:
  - Patient numbers
  - More complex work
  - Tertiary, multi-disciplinary expertise necessary
Congenital Heart Disease: How Can We do Better?

- **Provide for the ever growing clinical need:**
  - Patient numbers
  - More complex work
  - Tertiary expertise necessary
  - Empower the patient
  - Be their advocate
- Fontan pregnancy possible
- Best end patients low risk
- Miscarriages are common
- Premature birth
- Small for dates babies expected
- Anticoagulation
- Family planning (best time to have children between 25-35)
- Tertiary care
- Long-term impact unknown
Ventilation \quad Q_p/s \quad O_2 \text{ carrying capacity} \quad \text{Muscle}

Iron Therapy: ACHD patients wonderful and stoic… They are the true Heroes

Tay et al. Int J Card July 2010
Congenital Heart Disease: How Can We do Better?

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  - Patient numbers
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  - Be their advocate
  - Engage and support general cardiologist and the wider profession
21st Century Adult CHD Pathway

Patient access routes
- Transition pathway from paediatric cardiology
- 'Lost to follow up' referrals from pt/GP/other HCP
- Transfer from other ACHD network
- New diagnosis from general cardiology/other medical service
- Emergency via A&E with cardiac or non-cardiac problem
- Patients from Overseas

Triage
- All pts seen at least once at the ACHD Hub (NHSE standard)

Initial assessment
- ACHD Hub “One Stop, Unique Patient Experience”
  - On a single-day/visit:
    - Physiology (Echo, CMR, CPET etc*)
    - Risk stratification AI
    - Consultant review (care planning)
    - CNS review (counselling/lifestyle*)
    - Consent to research

Treatment/Procedure
- Other investigations
- MDT
- Surveillance
- Medical Tx
- Intervention (EP/pacing/catheter)
- Surgery/Assist Devices/Tx

Personalized Follow up
- High Risk
  - At specialist centre Tech based monitoring Trials participation
- Medium Risk
  - Routine as outreach Periodically at specialist centre
- Low Risk
  - Level 2/3 ACHD centre CNS outreach Periodic risk assessment AI

* According to CHD lesion

Provided at specialist centre
Provided at network

Palliative Care
Congenital Heart Disease: How Can We do Better?

Provide for the ever growing clinical need:

- Patient numbers
- More complex work
- Tertiary expertise necessary
- Empower the patient
- Be their advocate
- Engage and support general cardiologist and the wider profession

Harness technology:
- Monitoring
- Risk stratification
- Education
Predictive Model:

Diller et al, under review EHJ 2018
Automatic heart chamber recognition and measurements
Own results

Patient with Tetralogy of Fallot
A comprehensive risk stratification model for CHD:
Adult congenital heart disease: education, education, education

Michael A Gatzoulis

Adult patients with congenital heart disease (CHD) are the beneficiaries of successful pediatric cardiac surgery and cardiology programs around the world. Over half of them would have died before reaching adulthood had it not been for surgical intervention in infancy and childhood. This success in treatment is exemplified by the fact that 96% of children with CHD who survived infancy will live to at least 15 years of age. It has been estimated that there are currently over 250,000 adults with CHD in the UK, approximately 1,000,000 in the US and similar numbers in proportional terms in Europe and the rest of the world. The prevalence will continue to grow exponentially as more patients survive early interventions and adult patients with CHD live longer. Although the outlook for obstetricians, other hospital specialists, family doctors and health allied professionals. While the CHD aficionados will continue to educate themselves using the endless opportunities for continuing medical education, we need to expand our educational portfolio and extend our efforts to reach a wider audience. Although high-level, sophisticated and somewhat esoteric material has been the main academic drive for many individuals or teams working in the field, and remains essential for maintaining and improving tertiary practice, a change in emphasis is required—towards educational efforts at a more-basic level, which are accessible and clear to this broader target audience. Widely available guidelines, more-basic textbooks and more publications in general cardi-
DISEASES
OF THE
HEART
AND
CIRCULATION

Second, revised and enlarged edition
Third impression

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