Disclosures

• Research Support
  • Actelion
  • United Therapeutics
  • Gilead
  • Pfizer
  • Amplatzer
  • NIH
• Canadian Heart Research Centre
• Chair, ABIM ACHD Subspecialty Board and Exam Committee
CHD POPULATION
Congenital Heart Disease Population

- 40,000 infants born with CHD/year.
- THE most common birth defect
- What is successful outcome?

Surviving to Adulthood
Survival to 18 yrs of age with CHD

Decade Born with CHD

- 1940: 20%
- 1960: 40%
- 1970:
- 1980: 80%
- 1990: 90%

Percent Survival to 18 Years Old

CHD - Population

Surviving to Adulthood is Now Expected
Congenital Heart Disease Population

- PEDIATRIC: 50%
- ADULT: 50%

2000

Congenital Heart Disease Population

2010

PEDIATRIC: 40%
ADULT: 60%

ADULTS are now \(\frac{2}{3}\) of the CHD Population

![Graph showing lifetime prevalence of congenital heart disease (CHD) from 2000 to 2010. The data indicates a significant increase in the number of adults with CHD, from 22,291 in 2000 to 24,851 in 2005, and further to 1,500,000 by 2010. The percentage of adults with CHD also increased, from 54% in 2000 to 66% in 2010, while the percentage of children with CHD decreased, from 46% to 34%.](image-url)
Adult vs Pediatric Complex CHD Populations in Canada

The Prevalence of SEVERE CHD has Increased 85% for Adults vs 22% for Children

ACHD Patients Reaching Adulthood

2/3 have moderate and complex CHD

20,000 new pts/yr
PROBLEM
CHD Patients Reaching Adulthood

ACHD Patients

20,000 new pts/yr

- 1970: 325,000
- 1980: 500,000
- 1990: 750,000
- 2000: 1,000,000
- 2012: 1,300,000
Temporal Trends in Survival to Adulthood Among Patients Born With Congenital Heart Disease From 1970 to 1992 in Belgium

Philip Moons, PhD, RN; Lore Bovijn, MSc, RN; Werner Budts, MD, PhD; Ann Belmans, MSc; Marc Gewillig, MD, PhD
Mortality in adult congenital heart disease

Non Cardiac (23%)

Arrhythmia (21.9%)

Vascular (14.3%)

Peri-Operative (7.1%)

Cardiac, Other (5.1%)

Heart Failure (24.5%)

Mean Age of Death ≈ 30 yrs

n = 6,933
Died 197
24,865 pt yrs

Verheugt CL et al. EHJ 2010.31:1220-29.
Hospital Admission Rate
General Population vs ACHD

Admission Rate (%)

General population
ACHD population

Age Groups (years)

20-30 30-40 40-50 50-60 60-70 70-80

Verheugt CL et al. Heart 2010.96:872-78
Once Reaching ACHD

- Survival is not as expected
- HF and arrhythmia (~45%)
- Morbidity is substantial
Adults with Congenital Heart Disease

- Arrhythmias
- Heart Failure
- Valvular Disease
- Residual Shunts
- Vascular Lesions
- Right Heart Failure
- Left Heart Failure
- Systolic
- Diastolic
- Pulmonary Hypertension
- Atrial
- Ventricular
- Sudden Death
- Systolic
- Diastolic
- Pneumonia
- Renal and Hepatic Insufficiency

Long –Term Complications

Adult Co-Morbidities
- CAD, PVD
- DM
- OSA, COPD
- Renal and Hepatic Insufficiency
Adults with Congenital Heart Disease

- Arrhythmias
  - Atrial
  - Ventricular
  - Sudden Death

- Heart Failure
  - Right Heart Failure
  - Left Heart Failure
    - Systolic
    - Diastolic
    - Pulmonary Hypertension

- Vascular Lesions

- Residual Shunts

- Valvular Disease

Long-Term Complications
Montreal CHD Database: Outcomes of Patients with PHT-CHD

PHT Prevalence in Montreal 1983-2005 CHD Database

2000/36000 ACHD = 5.8%

- 2X Increase in Mortality
- 3X Increase in Morbidity

PHT, pulmonary hypertension; CHD, congenital heart disease
How Does CHD Lead to PAH?
Understand CHD Anatomy
SHUNT
Systemic to Pulmonary
SHUNT
ANATOMY

Secundum ASD Defect

Modified from http://www.yale.edu/imaging/chd/e_asd/index.html. Pat Lynch
Atrial Septal Defect
Muscular VSD
Subpulmonic VSD
Atrioventricular Septal Defect
Single Ventricle Anatomy

HLHS  TA  DORV  DILV  Unbalanced AVC  PA  Ebstein
Truncus Arteriosis

PA
Transposition of the Great Arteries with VSD
Understanding Shunt Physiology
ASD Physiology Left to Right Shunt

Shunt Magnitude
- Size of Defect
- Ventricular Diastolic Compliance
A different view on predictors of pulmonary hypertension in secundum atrial septal defect

Charlien Gabriels a, Pieter De Meester a, Agnes Pasquet b, Julie De Backer c, Bernard P. Paelinck d, Marielle Morissens e, Alexander Van De Bruaene a, Marion Delcroix a, Werner Budts a, *

- 295 pts
- Defect closed > 55yo, lead to PH in 34%
- PH group higher AF, RHF
PAH – Congenital Heart Disease

Left to Right Shunt

↓

Increase PBF and Pressure

↓

Progressive Microvascular Changes
Development of PAH with a VSD

\[ \text{PVR} = \frac{\text{mPA} - \text{LA}}{\text{Qp}} \]

\[ \text{PVR} \ll \text{SVR} \]

\[ \text{Qp:Qs} = 4:1 \]
VSD
Mid (2-7 yrs)

PVR << SVR

Qp:Qs = 1.5:1
VSD

PVR $\gg$ SVR

Qp:Qs = 0.9:1

Eisenmenger Syndrome
Successful Reversal of Pulmonary Hypertension in Eisenmenger Complex

Randas J. V. Batista, José L. V. Santos, Noriaki Takeshita, Lise Eocchino, Paulo N. Lima, Marilu Goehr, Marco A. Cunha, Akira T. Kawaguchi, Tomas A. Salerno

Campina Grande do Sul, PR - Brazil

1. PRESSURE
2. FLOW
3. SHEAR STRESS
4. 1,2,3 + GENETICS
5. SOMETHING ELSE
Late End Stage

PVR $\geq$ SVR

Qp:Qs = 0.9:1

Eisenmenger Syndrome
Successful Reversal of Pulmonary Hypertension in Eisenmenger Complex

Randas J. V. Batista, José L. V. Santos, Noriaki Takeshita, Lise Eocchino, Paulo N. Lima, Marilu Goehr, Marco A. Cunha, Akira T. Kawaguchi, Tomas A. Salerno

Campina Grande do Sul, PR - Brazil
What is the Prevalence of CHD PH?
PAH Distributions in the US: REVEAL Registry

Overall

- Idiopathic (46.2%)
- Associated (50.7%)
- Heritable (2.7%)
- Pulmonary veno-occlusive (0.4%)
- Drugs/Toxins (10.5%)
- Portopulmonary (10.6%)
- Connective tissue/collagen vascular (49.9%)
- Heritable (2.7%)
- Pulmonary veno-occlusive (0.4%)

Based on Venice Clinical Classification (2003); 2967 patients. Adapted from Badesch DB et al. *Chest.* 2010;137:376-387.
CONCOR Registry of Adult Congenital Heart Disease (CHD) Patients (N=5970)*

60% of CHD patients are not at increased risk for PAH

40% of CHD patients had systemic-to-pulmonary shunts and are at risk for PAH

10% developed PAH (4% overall)

PAH, pulmonary arterial hypertension; CHD, congenital heart disease
At-risk patients include 357 adult patients with a surgically created systemic-to-pulmonary shunt.
*CONCOR: CONgenital COR vitia registry of adult patients with congenital heart disease from 86 tertiary and regional hospitals in the Netherlands. 5970 patients enrolled as of November 2005
Adapted from Duffels MGJ et al. *Int J Cardiol*, 2007;120:198-204.
Total Number of Patients \((n = 1824)\) per Type of Septal Defect in the CONCOR Registry

### Table 2

Baseline characteristics of patients with a septal defect and PAH

<table>
<thead>
<tr>
<th></th>
<th>Eisenmenger syndrome ((n=65))</th>
<th>Non-Eisenmenger ((n=112))</th>
<th>Closed defect ((n=30))</th>
<th>Total ((n=112))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>40%</td>
<td>41%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>36 (18–70)</td>
<td>57 (23–80)</td>
<td>37 (21–81)</td>
<td>38 (18–81)</td>
</tr>
<tr>
<td><strong>Underlying diagnosis (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>31 (48)</td>
<td>8 (47)</td>
<td>8 (27)</td>
<td>47 (42)</td>
</tr>
<tr>
<td>ASD II</td>
<td>8 (12)</td>
<td>8 (47)</td>
<td>12 (40)</td>
<td>28 (25)</td>
</tr>
<tr>
<td>ASD I</td>
<td>3 (5)</td>
<td>1 (6)</td>
<td>5 (17)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>AVSD</td>
<td>23 (35)</td>
<td>0 (0)</td>
<td>5 (17)</td>
<td>28 (25)</td>
</tr>
<tr>
<td><strong>Mean PAP, mm Hg (±SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>89 (±21)</td>
<td>58 (±19)</td>
<td>49 (±12)</td>
<td>71 (±26)</td>
</tr>
<tr>
<td><strong>NYHA classification (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (12)</td>
<td>4 (29)</td>
<td>13 (48)</td>
<td>23 (25)</td>
</tr>
<tr>
<td>II</td>
<td>15 (29)</td>
<td>8 (57)</td>
<td>8 (30)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>III</td>
<td>28 (54)</td>
<td>0 (0)</td>
<td>6 (22)</td>
<td>34 (37)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (6)</td>
<td>2 (14)</td>
<td>0 (0)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

Concor patients with a SD

11% 8% 7% 41% 27%

Sinus Venosus Defect

- Patch Closure
- Re-routing Pulmonary Veins

Modified from http://www.yale.edu/imaging/chd/e_asd/index.html. Pat Lynch
ASD and Risk for Pulmonary Hypertension

FACTORS
- Type of Defect
- Size of Defect
- Shunt Magnitude
- Age at Repair
- Patient Age
- PA pressure

Montreal CHD Database: Outcomes of Patients with PHT-CHD

PHT Prevalence in Montreal 1983-2005 CHD Database

2000/36000 ACHD = 5.8%

- 2X Increase in Mortality
- 3X Increase in Morbidity

• 91 patients w CHD/PH
• Started on PH specific therapy
• Evaluating predictors for Mortality and Clinical Events

Events
• HF
• Arrhythmias
• Worsening FC
• Hemoptysis
New predictors of mortality in adults with congenital heart disease and pulmonary hypertension: Midterm outcome of a prospective study

Mark J. Schuuring a,b, Annelieke C.M.J. van Riel a,b, Jeroen C. Vis a, Marielle G. Duffels a, Arie P.J. van Dijk c, Rianne H.A.C.M. de Bruin-Bon a, Aeilko H. Zwinderman d, Barbara J.M. Mulder a,b,*, Berto J. Bouma a

a Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
b Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

t NT-pro-BNP serum level < 500 ng/L and TAPSE ≥ 15 mm
p = 0.034

either NT-pro-BNP serum level ≥ 500 ng/L with TAPSE ≥ 15 mm
or NT-pro-BNP serum level < 500 ng/L with TAPSE < 15 mm
p = 0.001

NT-pro-BNP serum level ≥ 500 ng/L and TAPSE < 15 mm

Follow up (years)

n = 85 69 48 32
RV Function Predicts Outcome

46 yo with VSD/ES
RVEF 42%

28 yo with closed ASD
RVEF 18%
Know the Medical Therapies for CHD PH
5th World Symposium on PH: Modified Classification of PH

1. Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK1, ENG, Smad 9, CAV1, KCNK3
      1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      **1.4.4 Congenital heart diseases**
      1.4.5 Schistosomiasis

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1’’. Persistent PH of the newborn

2. PH due to left heart disease
   2.1 LV systolic dysfunction
   2.2 LV diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases (update)

4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Classification of CHD and PH

ES- Right to Left
Mechanisms of Action of Approved Therapies for PAH

**Endothelin Pathway**
- Pre-proendothelin → Proendothelin
- Endothelin-1
  - Endothelin receptor A
  - Endothelin receptor B
- Vasoconstriction and proliferation
  - Endothelin receptor antagonists

**Nitric Oxide Pathway**
- Nitric Oxide
  - L-arginine → L-citrulline
- Exogenous nitric oxide
  - SGC stimulator
- Phosphodiesterase type 5
  - cGMP
- Phosphodiesterase type 5 inhibitor
  - Vasodilation and antiproliferation

**Prostacyclin Pathway**
- Prostacyclin (prostaglandin I₂)
  - Arachidonic acid → Prostaglandin I₂
- Prostacyclin derivatives
  - cAMP
  - Vasodilation and antiproliferation

5th World Symposium on PH: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

Expert Referral (I-C)

Cardiac Cath/Vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
  - APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

VASOREACTIVE

- WHO FC I-III
- CCB (I-C)

Sustained response (WHO FC I-II)

- YES: Continue CCB
- NO: INITIAL THERAPY WITH PAH-APPROVED DRUGS

NON-VASOREACTIVE

Hemodynamic Evaluation
Shunt Physiology

PVR = \frac{PA\ mean - PCWP}{CO\ (TD,\ Fick)}

Shunt pts CO = Qp

Qp:Qs = 2.5:1
PVR 5.2U
PVR:SVR = 0.19:1
Hemodynamic Evaluation
Shunt Physiology

\[ \text{PVR} = \frac{\text{PA mean} - \text{PCWP}}{\text{CO (TD, Fick)}} \]

Shunt pts CO = Qp

Qp:Qs = 1.2:1

PVR 13.5U

PVR:SVR = 0.4:1
Hemodynamic Evaluation
Shunt Physiology

CHD and PH

Qp:Qs = 1.2:1
PVR:SVR = 0.4:1

CO (TD, Fick)
Shunt pts CO = Qp

Close Defect
No MEDS

Close Defect + MEDS

Open Defect + MEDS

Open Defect
No MEDS

PVR = PA mean – PCWP

CHD and PH

Close Defect
No MEDS

Close Defect + MEDS

Open Defect + MEDS

Open Defect
No MEDS
### 5th World Symposium on PH: 2013 PAH Treatment Algorithm

#### INITIAL THERAPY WITH PAH-APPROVED DRUGS

**YELLOW: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined)**

Level of evidence based on WHO-FC of majority of patients of studies

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
<th>WHO FC II</th>
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<tbody>
<tr>
<td>I</td>
<td>A or B</td>
<td>• Bosentan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ambrisentan</td>
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<tr>
<td></td>
<td></td>
<td>• Macitentan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Riociguat</td>
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<tr>
<td></td>
<td></td>
<td>• Sildenafil</td>
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<tr>
<td></td>
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<td>• Tadalafil</td>
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<tr>
<td>Ia</td>
<td>C</td>
<td>• Epoprostenol IV</td>
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<td>• Iloprost inh</td>
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<td>• Macitentan</td>
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<td>• Riociguat</td>
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<td>• Sildenafil</td>
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<td></td>
<td></td>
<td>• Treprostinil SC, inh*</td>
</tr>
<tr>
<td>Iib</td>
<td>B</td>
<td>• Beraprost*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>• Initial Combination Therapy</td>
</tr>
</tbody>
</table>

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*Not approved in US
Bosentan Therapy in Patients With Eisenmenger Syndrome
A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

Nazzareno Galiè, MD; Maurice Beghetti, MD; Michael A. Gatzoulis, MD; John Granton, MD; Rolf M.F. Berger, MD; Andrea Lauer, PhD; Eleonora Chiossi, MSc; Michael Landzberg, MD; for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators

- 54 pts randomized 2:1 to Bosentan
  - 37 Bosentan
  - 17 Placebo
- After 16 wks of therapy
  - PVRi was reduced in Bosentan grp (- 472 dynes.sec.cm-5)
  - 6 MWD was increased in Bosentan (+34m)

Galie N et al. Circ 2006;114;48-54.
Change In Indexed Pulmonary Vascular Resistance (PVRi)

Change In Exercise Capacity From Baseline

BREATHE-5

6MWD (m)

Change from baseline

Placebo (n=17)  Bosentan (n=37)

T.E. = 53.1 m
p=0.008

A Retrospective Look at Eisenmenger Syndrome Patients from the UK with and without Advanced PAH Therapies

Adjusted survival rate curves, based on the propensity score–adjusted Cox model, of patients within the third propensity score quartile, with and without advanced therapy. Quartiles of propensity score are based on the average propensity scores from the 10 imputed databases. $P$ value refers to Cox model.


N = 219 with no therapy and 68 on PAH specific therapy
Successful Reversal of Pulmonary Hypertension in Eisenmenger Complex

Randas J. V. Batista, José L. V. Santos, Noriaki Takeshita, Lise Eocchino, Paulo N. Lima, Marilu Goehr, Marco A. Cunha, Akira T. Kawaguchi, Tomas A. Salerno

Campina Grande do Sul, PR - Brazil
21 yo with Large Secundum ASD

- Exercise saturation from 94 to 72%.
- Baseline hemodynamics

Qp:Qs = 1.4:1
PVR 7.7 U
21 yo with Large Secundum ASD

- Nitric Oxide 40ppm, 100% FiO2

Qp:Qs = 2.1:1

PVR 6.5 U
Amplatzer ASO device

iCAST covered stent
Final Result
Discharge

• Echocardiogram showed the following:
  ➢ Stable device position in the inter-atrial septum
  ➢ Small net left to right shunt, significantly smaller than previous exam
  ➢ Estimated SPAP 56 mm Hg

• Started on endothelin receptor antagonist

• Exercise saturation 1 month later: 88-90%
Sequential Combination Therapy (I-A)

ERAs

Prostanoids + PDE-5 I or SGCs

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

INITIAL THERAPY WITH PAH-APPROVED DRUGS

Inadequate Clinical Response on Maximal Therapy

Balloon Atrial Septostomy (IIa-C)

### 5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

<table>
<thead>
<tr>
<th><strong>Functional Class</strong></th>
<th>• I or II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamics</strong></td>
<td>• Normalization of RV function (RAP &lt; 8 mm Hg and CI &gt; 2.5-3.0 L/min/m²)</td>
</tr>
<tr>
<td><strong>Echocardiography/ MRI</strong></td>
<td>• Normal/near normal RV size and function</td>
</tr>
<tr>
<td><strong>BNP level</strong></td>
<td>• ‘Normal’</td>
</tr>
<tr>
<td><strong>6MWD</strong></td>
<td>• 380-440 m, may not be aggressive enough</td>
</tr>
</tbody>
</table>
| **CPET**             | • Peak VO₂ >15 mL/kg/min  
                      • VE/VCO₂ @ AT <45 |

IT’S ALL ABOUT THE RIGHT VENTRICLE
Sequential Combination Therapy (I-A)

ERAs

Prostanoids + PDE-5 I or SGCs

Initial Therapy with PAH-Approved Drugs

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

* Referral for Lung Transplantation (I-C)

Inadequate Clinical Response on Maximal Therapy

Balloon Atrial Septostomy (IIa-C)

SUMMARY

• PAH occurs in about 4-6% of CHD patients and 10% of those at highest risk

• Developing PH with a background of CHD dramatic increases morbidity and mortality

• Early expert evaluation is important to make the right decision regarding closing a defect, medical therapy or combination of therapies

• RV is key to prognosis

• Need more research as to the etiology and genetics

• ALL CHD patients require long-term follow up
Congenital Heart Disease & Pulmonary Hypertension

Update for 2015

Curt J Daniels, MD, FACC
Shepard Endowed Chair for Cardiovascular Medicine
Professor, Internal Medicine and Pediatrics

Director, COACH Program Columbus Ohio Adult Congenital Heart Disease and Pulmonary Hypertension Programs

COACH
Columbus Ohio Adult Congenital Heart Program