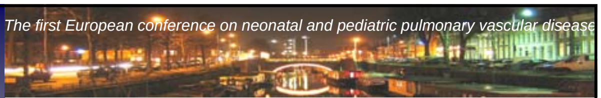
Centrum Congenitale Hartafwijkingen



Echocardiography in Pediatric Pulmonary Arterial Hypertension

M.T.R. Roofthooft
Pediatric cardiologist
Beatrix Children's Hospital
Center for Congenital Heart Disease
University Medical Center Groningen
The Netherlands

Netwerk Kinder Pulmonale Hypertensie

Centrum Congenitale Hartafwijkingen

Historical Milestones PAH


a postmortem (1891) to a clinical observation (1897)


clinical syndrome (Ayerza's disease, 1901) to the syphilis theory (1900s)

"coupling" of heart and lungs; diseases of the lungs may affect the heart and diseases of the heart may affect the lungs

concept of "passive and reactive" PH and the different response of pulmonary vascular resistance

Centrum Congenitale Hartafwijkingen

Geneva 1973 *Evian 1998* *Venice 2003* *Dana Point 2008* *Nice 2013*

TABLE 1. Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK-1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3. Unknown
   1.3. Induced by drugs and toxins
   1.4. Associated with PAH
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5. Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns
   3.4. Sleep-related breathing disorder
   3.5. Alveolar hypoventilation disorders
   3.6. Chronic exposure to high altitudes
   3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear or multifactorial mechanisms
   5.1. Hematologic disorders: Myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic kidney failure on dialysis

ALK-1 indicates activin receptor-like kinase 1 gene; BMPR2, bone morphogenetic protein receptor, type 2; PAH, pulmonary artery hypertension; HIV, human immunodeficiency virus.

Centrum Congenitale Hartafwijkingen

Goal Oriented Treatment Strategy in Adults

ESC/ERS Guidelines PAH 2009

Pros of Echocardiography

- *widespread availability*
- *clues for differential diagnoses*
- *first-line tool to detect PH*
- *assessment of RV function*
- *role in guiding treatment of PAH patients*

Pediatric PAH

- *feasible, also in young children*
- *non-invasive*
- *good quality of echo-windows*
- *allowing repetitive measurements/longitudinal follow-up*

Centrum Congenitale Hartafwijkingen

Echocardiography: prognostic value of right heart parameters in PAH

Parameter	Correlation	Study design	First author [ref.]
Pericardial effusion	Mortality	Retrospective, multi-	Zhang [24]
Tricuspid valve regurgitation	Survival	Prospective, single centre, n=59	Ghio [29]
	Mortality; transplantation	Prospective, single centre, n=25	Bustamante-Labarta [27]
Eccentricity	Survival	Prospective, single centre, n=59	Ghio [29]
	Composite end-point of death/transplantation	Prospective, multi-centre, n=81	Raymond [25]
Right ventricular free wall systolic strain	Disease severity, disease progression and mortality	Prospective, single centre, n=80	Sachdev [33]
Right ventricular dyssynchrony	WHO FC; eccentricity index; hospitalisations due to PH/heart failure	Prospective, single centre, n=52	López-Candales [34]
Right ventricular systolic to diastolic duration ratio	Clinical outcomes; 6MWD; death or transplantation; right ventricular fractional area of change	Retrospective, single centre, n=47	Alkon [35]
Right ventricular myocardial performance (Tei) index	[illegible]	[illegible] centre, n=53	[illegible]
	Degree of pulmonary regurgitation; left ventricular eccentricity index; presence of pericardial effusion	Retrospective, single centre, n=93	Grapsa [32]

Adapted from: Vonk Noordergraaf A, Galie N, The role of the right ventricle in Pulmonary Arterial Hypertension Eur Resp Rev 2011

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

Echocardiography in Pediatric PAH

- *The Toronto-study* *Canada, 2010*
- *The Graz-study* *Austria, 2012*
- *The Denver-study* *USA, 2012*
- *The Groningen-study* *the Netherlands, 2013*

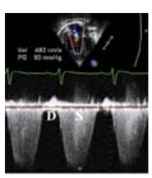
University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Toronto-study Canada, 2010

RV systolic to diastolic duration, using doppler flow of tricuspid regurgitation

- *Association with:*
  - *RV performance*
  - *Hemodynamics*
  - *6MWT*
  - *Clinical outcome / survival*



Alkon et al. Usefulness of thr RV systolic to diastolic duration ratio to predict functional capacity and survival in children with PAH; Am J Cardiol 2010: 106:430-436

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Toronto-study Canada, 2010

47 children with PAH (503 serial echocardiograms)

S/D ratio was significant higher in patients than controls

higher S/D ratio was associated with:
worse RV fractional area of change
worse hemodynamics
shorter 6MWT
worse clinical outcome (independent to Ppap and PVR)

increase of 0.1 was associated with a 13% increase in yearly risk for LungTX/death

S/D ratio 1-1.4: associated with moderate risk
S/D ratio>1.4 associated high risk of negative outcome

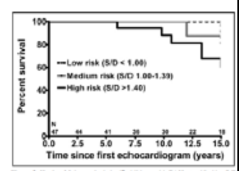
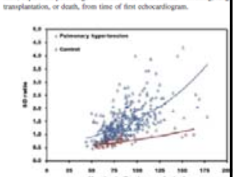


Figure 2. Kaplan-Meier analysis in 47 children with PAH, stratified by S:D ratio, depicts the percentage of children free from clinical worsening, lung transplantation, or death, from time of first echocardiogram.



University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Graz-study *Austria, 2012*

Tricuspid Annular Peak Systolic Velocity (S') (TDI) in children/young adults with pressure (PAH-CHD) or volume-overload (corrected Fallot)

Background
Systolic velocity of the tricuspid annulus of RV free wall is a reliable indicator for global RV systolic function

cut-off values in adults predict RV impairment

For children: normal values S' in healthy recently published

Koestenberger et al.Tricuspid Annular Peak Systolic Velocity (S') in Children and Young Adults with Pulmonary Arterial Hypertension Secondary to Congenital Heart Diseases, and in those with repaired tetralogy of Fallot: echocardiography and MRI data. JASE 2012:25; 1041-49

University Medical Center Groningen

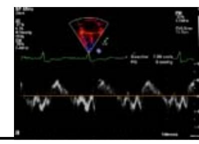
Centrum Congenitale Hartafwijkingen

The Graz-study *Austria, 2012*

Tricuspid Annular Peak Systolic Velocity (S')

Compared with
RV ejection rate and RV end-diastolic volume index (RVEDVi) (cardiac MRI)

- *Change in S' value earlier in PAH-CHD (n=31, < 18 years)*
- *S' value: limited correlation with TAPSE in study population (r=0.260)*
- *Impaired S' with increasing age in both PAH-CHD (n= 55) and Fallots (n=183)*
- *Positive correlation S' with RV ejection rate in both groups*
- *Negative correlation S' with RVEDVi in both groups*



University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Denver-study *USA, 2012*

Tissue doppler imaging in children with IPAH

Study clinical utility of TDI in assessment of disease severity and prognostic value

Background:
reduced peak systolic and diastolic TDI velocities (TV, IVS, MV) in adult IPAH
+ correlation Sm of TV-annulus with Ppap and PVRi
- correlation with cardiac index

TDI velocities
systolic myocardial velocity
early diastolic myocardial relaxation velocity (Em)
late diastolic myocardial velocity associated with atrial contraction

related to BNP, NYHA FC and hemodynamics

Takatsuki et al. Tissue doppler imaging predicts adverse outcome in children with IPAH. J Pediatrics 2012;161:1126-31

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Denver-study *USA, 2012*

Table III. Tissue Doppler velocity in children with idiopathic PAH and healthy controls

Variables	Idiopathic PAH (n = 51) mean ± SD	Healthy control (n = 51) mean ± SD	*P* value
Mitral			
Em velocity (cm/s)	12.7 ± 5.5	20.5 ± 3.4	<.001
Am velocity (cm/s)	6.9 ± 2.7	6.9 ± 2.3	.85
Em/Am ratio	1.8 ± 0.2	3.3 ± 1.2	<.001
E/Em ratio	6.7 ± 2.3	4.8 ± 1.0	<.001
Sm velocity (cm/s)	8.3 ± 2.8	10.1 ± 2.5	<.001
Septal			
Em velocity (cm/s)	8.1 ± 3.7	15.5 ± 3.0	<.001
Am velocity (cm/s)	6.7 ± 2.4	6.8 ± 1.8	.85
Em/Am ratio	1.3 ± 0.6	2.4 ± 0.8	<.001
E/Em ratio	10.3 ± 3.6	6.4 ± 1.6	<.001
Sm velocity (cm/s)	6.7 ± 1.8	8.6 ± 1.2	<.001
Tricuspid			
Em velocity (cm/s)	10.2 ± 4.3	17.3 ± 3.1	<.001
Am velocity (cm/s)	11.4 ± 3.2	9.5 ± 3.3	.01
Em/Am ratio	0.9 ± 0.4	2.0 ± 0.9	<.001
E/Em ratio*	5.9 ± 2.6	3.8 ± 1.1	<.001
Sm velocity (cm/s)	11.3 ± 2.4	13.6 ± 2.8	<.001

- *no correlation Sm and Em of MV-annulus with hemodynamics*
- *TV Em cut-off values (<8cm/sec) correlated with worse oucome*
- *Tricuspid Em marker for detecting RV diastolic dysfunction*

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Denver-study *USA, 2012*

TV Em associated with hemodynamics and outcome

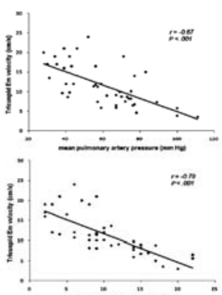


Figure 1. Linear correlation between tricuspid Em velocity and mean pulmonary artery pressure, RV end-diastolic pressure in 45 children with idiopathic PAH.

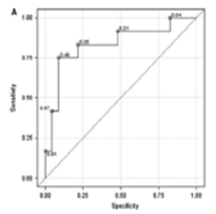


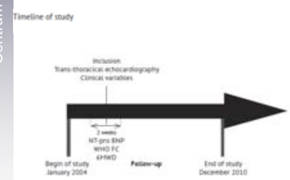
Figure 3. A, Logistic regression was used to evaluate the cutoff at 8 cm/s of initial tricuspid Em velocity for prediction of adverse events including death, hospitalization, and lung transplantation. This receiver-operating characteristic curve corresponded to a c-index (area under the curve) of 0.83. The cutoff value of 8 cm/s corresponds to a sensitivity of 75% and a specificity of 87%. B, Plot of the relationship between the

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

The Groningen-study 2013

Retrospective study of the potential of echocardiography for the assessment of disease Severity and prognosis in pediatric PAH



children with PAH (confirmed by RHC)

standardized follow up visits at least twice a year

Data concerning RHC, six-minute-walk-distance (6MWD), echo-data and biological serum markers collected in a registry

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

Echocardiographic windows and parameters

2D-Dimenional variables and Functional variables

Echocardiographic parameters		Code	Echo - window	N=48
Functional variables				
Pulmonary valve regurgitation (colour doppler)		PR (grade)	Parasternal short-axis	45
PR maximum velocity		PR Vmax	Parasternal short-axis	28
PR end-diastolic velocity		PR Ved	Parasternal short-axis	22
TAPSE (tricuspid annular plane systolic excursion)		TAPSE	Apical four chamber	45
Tricuspid valve regurgitation (colour doppler)		TR (grade 0-3)	Apical four chamber	45
TR maximum velocity		TR Vmax	Apical four chamber	33
lateral tricuspid annulus (TVI)				
Tei-index (TVI)		Tei tvi	Apical four chamber	34
Tricuspid valve early diastolic e-wave		TVe	Apical four chamber	29
Tricuspid valve diastolic a-wave		TVa	Apical four chamber	27
Tricuspid valve e deceleration time		TVe dec	Apical four chamber	25
E;/A Tissue Doppler (TVI)		Ea TVI	Apical four chamber	25
E/E' = e top pulsed / e-top tissue doppler		ee	Apical four chamber	26
Tricuspid valve systolic velocity (TVI)		TVs	Apical four chamber	32
Tricuspid valve systolic duration		TVs duration	Apical four chamber	11
E/A ratio pulsed Doppler Tricuspid valve		Ea pulsed	Apical four chamber	26
Pericardial effusion	Yes/no	PE (y/n)	Subcostal	48
Pericardial effusion	mm fluid	PE (mm)	Subcostal	48

RV = right ventricle, LV = left ventricle, IVS = interventricular septum, IVRT = isovolumetric relaxation time, PR = pulmonary regurgitation, TR = tricuspid regurgitation, TVI = tissue velocity imaging

Centrum Congenitale Hartafwijkingen

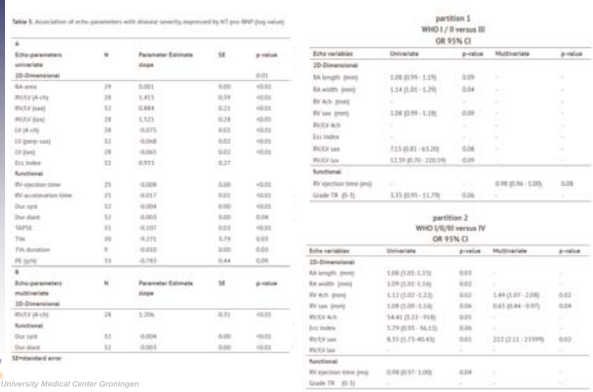
Study Population

		Patients	Death or need for LTx	Survivors	P-value
		N=48	N=22	N=26	
Female	n (%)	27 (56)	13 (59)	14 (54)	0.78
Incident cases	n (%)	29 (60)	15 (68)	14 (54)	0.38
Age of echo-study	(yrs)	8.0 (4.6-13.4)	8.1 (3.4-12.9)	7.5 (4.6-14.2)	0.84
Follow-up	(yrs)	3.3 (0.8-6.5)	0.8 (0.1-3.2)	5.4 (3.2-7.4)	<0.001
BSA	(m^2)	0.9 (0.6-1.3)	1.0 (0.6-1.3)	0.9 (0.6-1.4)	0.56
PAH-CHD	n (%)	18 (38)	6 (27)	12 (46)	0.24
mortality	n (%)	22			
WHO-FC		2.9 ± 0.8	3.0 (3.0-4.0)	3.0 (2.0-3.0)	0.02
I + II		12 (25)	3 (14)	9 (35)	0.18
III		28 (58)	12 (55)	16 (62)	0.77
IV		8 (17)	7 (32)	1 (4)	0.02
NT-pro-BNP	log value n	2.9 (2.2-3.6) 33	3.5 (2.9-4.0) 15	2.3 (1.9-3.0) 18	0.01

University Medical Center Groningen

Centrum Congenitale Hartafwijkingen

Disease Severity

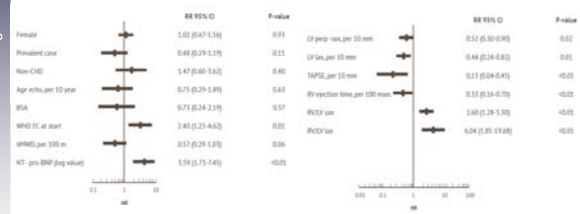


Centrum Congenitale Hartafwijkingen

Outcome

(transplant-free survival)

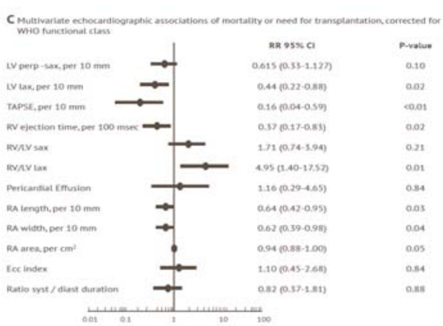
Demographic and echo-variables



Centrum Congenitale Hartafwijkingen

Outcome

demographic and echo-variables



Centrum Congenitale Hartafwijkingen

Proposal Goal Treatment Strategy in pediatric PAH

Better prognosis	Determinants of prognosis	Worse prognosis
improvement / I-II	WHO-FC	III-IV
NO	Syncope	Yes
Normal to nearly normal	Plasma levels NT pro-BNP	Very elevated and rising
adequate RV-function RA dimensions Small RV/LV ratio Smaller RV S/D ratio (1-1.4) TPSV (S') TV Em (>8cm/sec)	Echocardiography	RV-failure RA dimensions Large or increasing RV/LV ratio Smaller LV S/D ratio (>1.4) TPSV (S') TV Em (<8cm/sec)
Improved distance	6 MWT	Decreased distance
Decreased PVRI, mPAP/mSAP, RAP Increased CI, MVSO2 Acute response +	Hartcatheterization	Increased PVRI, mPAP/mSAP, RAP decreased CI, MVSO2 Acute Response -

Centrum Congenitale Hartafwijkingen

Conclusions Echocardiography Pediatric PAH

- *Emerging knowledge, especially focused on outcome*
- *Need to investigate the value in therapy-effect*
- *Need further comparison to other techniques (CMRI)*
- *Relative small patient numbers / single center studies ask for further collaboration*

University Medical Center Groningen