2010년 순환기관련학회 춘계통합학술대회

세종병원
Sejong General Hospital

Debate in Congenital Heart Disease

: Pulmonary Vasodilator in Fontan

Kim, Soo-Jin

Sejong General Hospital, Sejong Cardiovascular center

12 yrs, s/p Fontan

- NYHA class II(worse than before)

  : the earliest sign of failing Fontan circulation
- Intermittent history of Atrial Flutter
- Exercise cardiopulmonary test : VO2max-2/3 of normal
- CVP 15 mmHg
- Live cirrhosis on abdominal CT

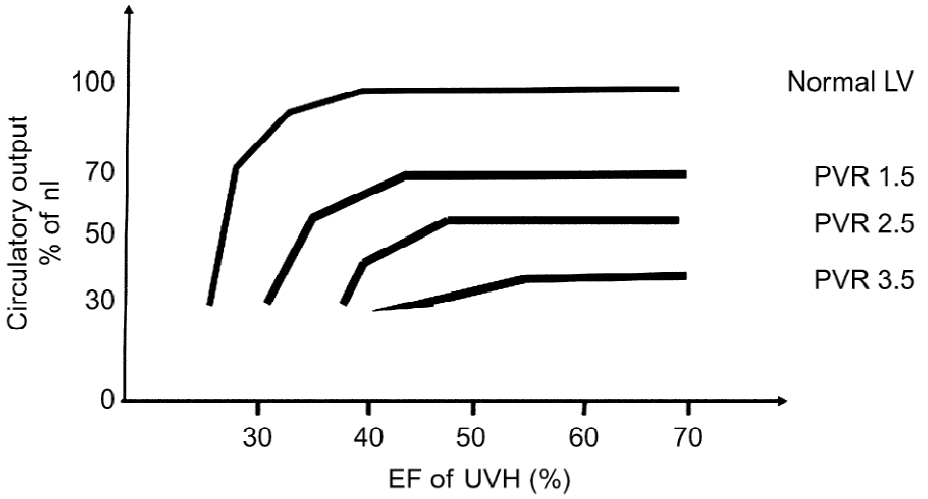
My opinion is medical observation for the patient.

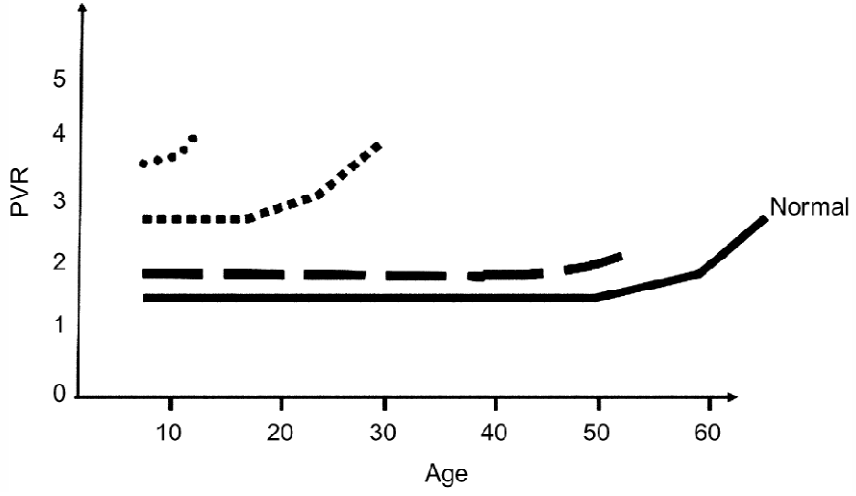
My Dilemma

- 처음에 나의 주장이 'trial of pulmonary vasodilator'인 것으로 잘못 알고 있었다.
- 내 의견 역시 'trial of pulmonary vasodilator' 이다.
- 최근에 나온 대부분의 연구들은 'trial of pulmonary vasodilator'을 지지하는 내용들이다. (왜냐면 전통적인 치료방법을 새로 연구하는 경우는 드무니까 ---)
- 대부분의 의사들은,심한 질환에 대하여 아무것도 안하는 것보다는 해롭지 않고 덜 침습적이라면, 뭔가 시도하는데 점수를 준다.

PVR in Fontan circulation

- CO is determined by PVR
- increasing PVR or progression of PVOD as the age increase.





Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure

Max B. Mitchell, MD[a]
David N. Campbell, MD[a]
Dunbar Ivy, MD[b]
Mark M. Boucek, MD[b]
Henry M. Sondheimer, MD[b]
Biagio Pietra, MD[b]
Bibhuti B. Das, MD[b]
Joseph R. Coll, PhD[b]

Objectives: Elevated pulmonary vascular resistance may contribute to late Fontan circulation failure but is difficult to assess in such patients. Our aims were to assess outcomes of patients with failed Fontan circulation after heart transplantation and to determine whether elevated pulmonary vascular resistance might have contributed to the failure.

Methods: Fifteen patients (14 Fontan circulations, 1 Kawashima circulation) underwent transplantation. The most common indication was ventricular dysfunction (mean ventricular end-diastolic pressure 12.5 mm Hg). Patients with early failures (n = 4) required transplantation less than 1 year after the Fontan operation. Those with late failures (n = 11) underwent transplantation at least 1 year after the Fontan operation. Mean age at transplantation was 11.6 years. Mean Fontan-transplantation interval was 7.4 years. Mean pulmonary arterial pressure, transpulmonary gradient, and pulmonary vascular resistance before and after transplantation were assessed.

TABLE 4. Paired pretransplantation versus posttransplantation pulmonary hemodynamic comparisons

Variable	n	Before	After	Mean difference	SD	*P* value
All patients						
PAP (mm Hg)	13	17.0 ± 3.7	19.7 ± 3.3	2.7	4.8	.064
TPG (mm Hg)	12	5.3 ± 2.3	12.0 ± 2.1	6.8	3.5	<.0001
PVR (Wood units · m^2)	6	1.8 ± 1.1	2.7 ± 1.0	0.8	1.7	.296
Late Fontan failures						
PAP (mm Hg)	9	17.0 ± 3.4	20.6 ± 2.5	3.6	4.8	.057
TPG (mm Hg)	8	4.9 ± 2.5	12.8 ± 2.0	7.9	3.6	.0004
PVR (Wood units · m^2)	3	1.5 ± 0.9	3.5 ± 0.7	2.0	1.5	.155

J Thorac Cardiovasc Surg 2004;128:693-9

Histomorphometric analysis of pulmonary vessels in single ventricle for better selection of patients for the Fontan operation

Marilyne Lévy, MD, PhD[a]
Claire Danel, MD[b]
Daniel Tamisier, MD[a]
Pascal Vouhé, MD[a]
Francine Leca, MD[a]

Objective: In cases of single-ventricle physiology, the Fontan procedure often fails even when the usual selection criteria are strictly respected. We analyzed specimens from intraoperative open lung biopsies performed on 40 patients with single-ventricle physiology who were considered to be good candidates for the Fontan procedure. Histomorphometric study was performed to determine histologic factors predictive of failure of the Fontan procedure.

Methods: Histomorphometric studies were performed on samples from 40 patients aged 6 months to 23 years with single-ventricle physiology, either tricuspid atresia (n = 14) or univentricular heart (n = 26). The preoperative pulmonary arterial pressure was 18 mm Hg or less in 35 cases and greater than 18 mm Hg in 5 cases.

TABLE 2. Relationship of histologic evaluation of pulmonary arterial structure and preoperative PAP

		Histologic examination	
PAP (mm Hg)	No.	Normal	Abnormal
≤18	35	17 (49%)	18 (51%)
>18	5	0	5

J Thorac Cardiovasc Surg 2002;123:263-70

Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients

Alessandro Giardini*, Anna Balducci, Salvatore Specchia, Gaetano Gargiulo, Marco Bonvicini, and Fernando Maria Picchio

Pediatric Cardiology and Adult Congenital Unit, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

Received 22 August 2007; revised 22 April 2008; accepted 6 May 2008; online publish-ahead-of-print 4 June 2008

Aims We sought to assess the effects of sildenafil on exercise capacity and haemodynamic response to exercise in Fontan patients.

Methods and results We prospectively studied 27 patients with Fontan circulation (age 22.8 ± 4.9 years). All patients underwent a baseline exercise test with non-invasive measurement of cardiac index (CI) and pulmonary blood flow (PBF) index, and peak exercise oxygen uptake (VO_2). After the baseline test, patients were randomly assigned to receive either a single 0.7 mg/kg body weight oral dose of sildenafil citrate ($n = 18$) or no treatment (control group, $n = 9$). After 1 h of rest, all patients performed a second exercise test. All patients completed the study protocol. The dose of sildenafil ranged from 25 to 50 mg. The change in peak VO_2, the primary endpoint, was greater in the sildenafil group (9.4 ± 5.2%) than in the control group (0.3 ± 4.1%, $P < 0.05$). Sildenafil increased rest and peak exercise PBF index ($P < 0.01$ and $P < 0.05$ vs. control group, respectively), as well as rest and peak exercise CI ($P < 0.001$ and $P < 0.05$ vs. control group, respectively), without altering rest or peak exercise transcutaneous arterial blood oxygen saturations ($P > 0.05$ vs. control group for both). No patient reported serious adverse events after sildenafil.

Conclusion In Fontan patients, oral administration of a single dose of sildenafil improves exercise capacity and haemodynamic response to exercise.

Keywords Fontan • Cardiac output • Oxygen uptake • Exercise

Eur Heart J 2008;29:1681-7

Successful clinical trials of pulmonary vasodilators

Resolution of Protein-Losing Enteropathy and Normalization of Mesenteric Doppler Flow With Sildenafil After Fontan

Orhan Uzun, MD, Joon Kwang Wong, MBBS, Vinaj Bhole, MRCP, and Oliver Stumper, PhD, MD

Department of Pediatric Cardiology, University Hospital of Wales, Cardiff, United Kingdom; Department of Pediatric Cardiology, Birmingham Children's Hospital, Birmingham, United Kingdom

Ann Thorac Surg 2006;82:e39-40

Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome

Keiji Haseyama, MD, Gengi Satomi, MD, Satoshi Yasukochi, MD, Hikoro Matsui, MD, Yorikazu Harada, MD, and Shunji Uchita, MD, Nagano, Japan

J Thorac Cariovasc Surg 2006;132(5):1232-3

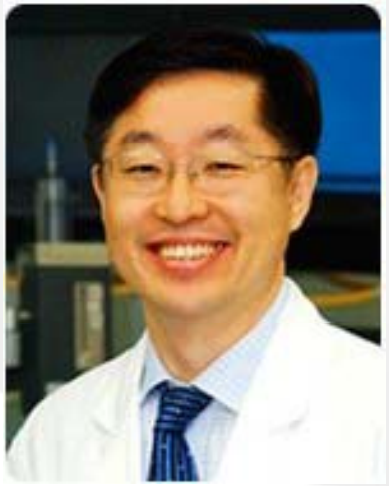
The effect of bosentan in patients with a failing Fontan circulation

Caroline Ovaert,[1] Daisy Thijs,[2] Daniel Dewolf,[3] Jaap Ottenkamp,[4] Hugues Dessy,[5] Philip Moons,[6] Marc Gewillig,[2] Luc Mertens[2]

[1]Department of Pediatric Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [2]Department of Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium; [3]Department of Pediatric Cardiology, Universitair Ziekenhuis Gent, Gent, Belgium; [4]Department of Pediatric Cardiology, University Medical Centre, Leiden, Netherlands; [5]Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium; [6]Center for Health Services and Nursing Research, University Hospitals Leuven, Leuven, Belgium

Cardiol Young 2009;19:331-9

What will you do for this patient?



He will say …

- Good circulatory output and thus good long-term outcome in a Fontan patient requires a low PVR.

" So I will use the pulmonary vasodilators."

What leads to Fontan failure?

- Pathway obstruction
- Arrhythmia
- Valve or ventricular dysfunction , increasing afterload
- Thromobosis, PLE …
- Increasing PVR

  : Pulmonary endothelial dysfunction due to loss of pulsatility

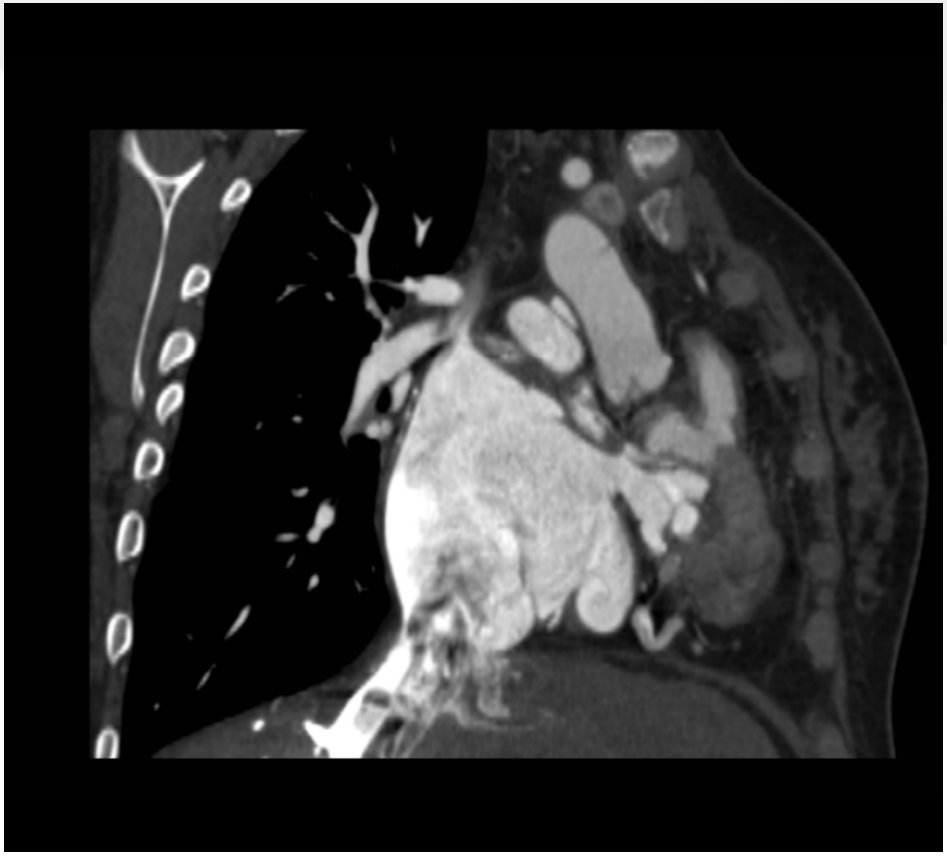
What we need to manage this patient ?

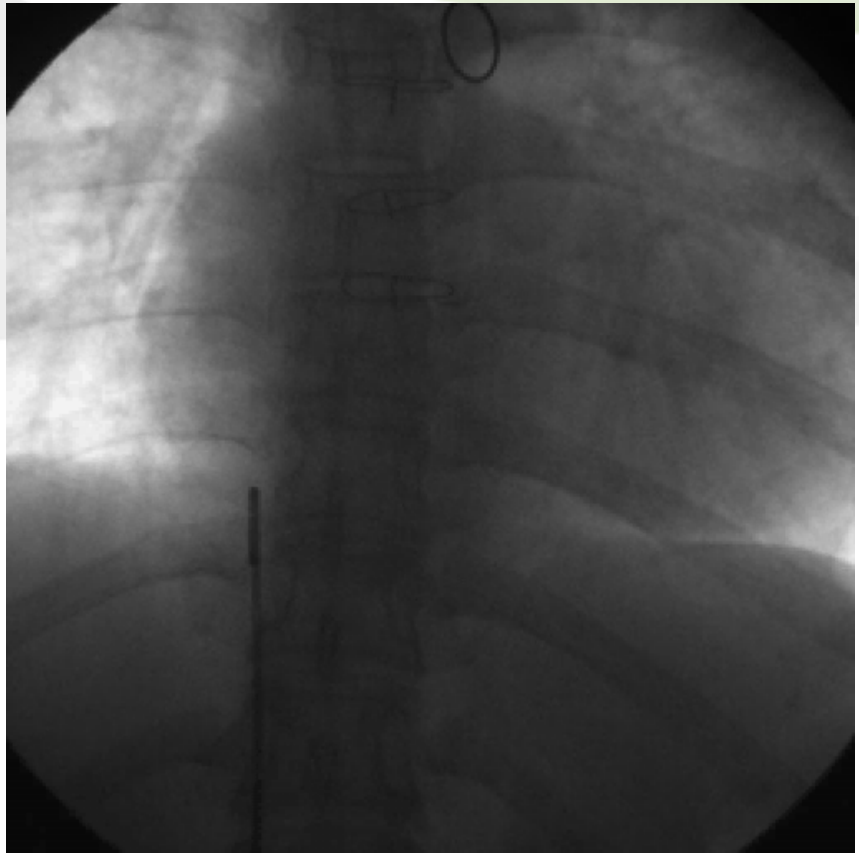
- A detailed hemodynamic assessment of the Fontan circulation including meticulous imaging.

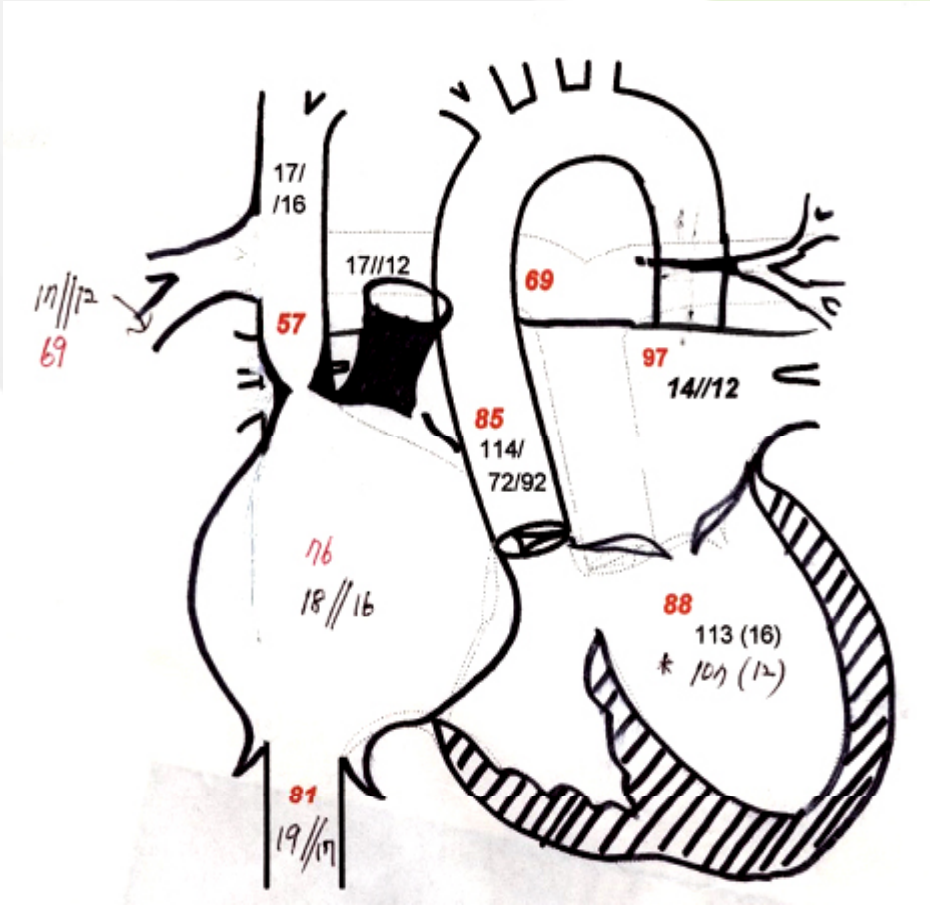
Case

42y/female, s/p AP Fontan (other hospital, at 12y)

- worse FC(II-III) & DOE
- paroxsamal atrial arrhythmia





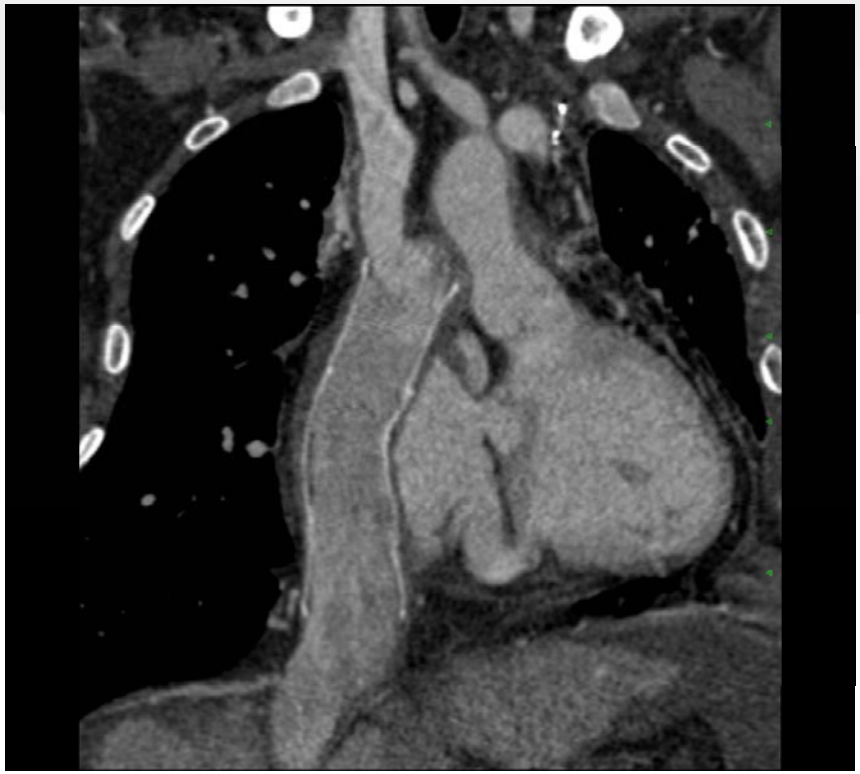


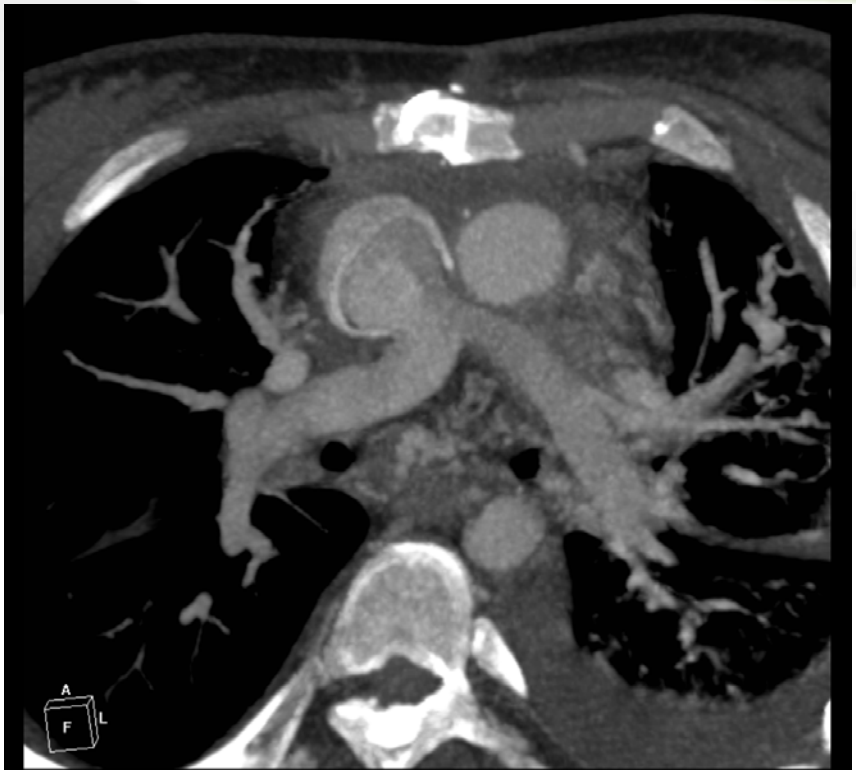
- Interrupted LPA
- Stenotic SVC-RA junction
- Marked dilatedRA

- Qp/Qs : 1
- Qp : 1.7
- Qs : 1.7
- Rp/Rs : 0.1
- TPG : 4
- Rp : 2.4

Operation

- Conversion to Extracardiac Fontan
- LPA angioplasty
- Maze procedure with Pacemaker implantation
- Reduction of RA wall



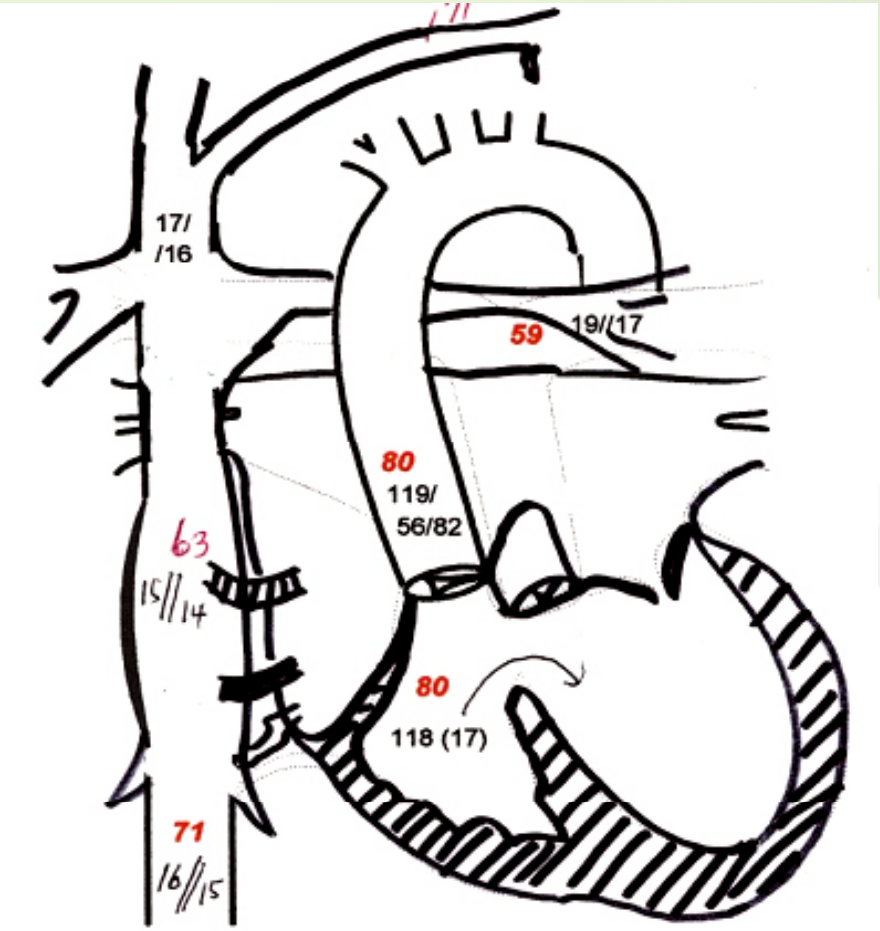


FU cath 4m after op.

- Improved FC & Symptoms.

  No arrhythmia

- Qp/Qs : 0.4
- Qp : 2.9
- Qs : 7.7 ↑
- TPG : 4
- Rp : 1.4 ↓



Long-term limitation in Fontan physiology

- Loss of pulsatile flow

  → down regulation of endothelial NO synthesis

  → attenuation of endothelial dependent vasodilatation

  → increased PVR

K. Klimes
H. Abdul-Khaliq
S. Ovroutski
W. Hui
V. Alexi-Meskishvili
B. Spors
R. Hetzer
R. Felix
P. E. Lange
F. Berger
M. Gutberlet

Pulmonary and caval blood flow patterns in patients with intracardiac and extracardiac Fontan: a magnetic resonance study

Received: 16 January 2006
Accepted: 20 October 2006
Published online: 22 December 2006

Katrin Klimes, MD (✉)
Hashim Abdul-Khaliq, MD, PhD
Stanislav Ovroutski, MD · Wei Hui, MD
Peter E. Lange, MD, PhD
Felix Berger, MD, PhD
Department of Congenital Heart Defects/
Paediatric Cardiology
Deutsches Herzzentrum Berlin
Augustenburger Platz 1
13353 Berlin, Germany
Tel.: +49-30/4593-2800
Fax: +49-30/4593-2900
E-Mail: klimes@dhzb.de

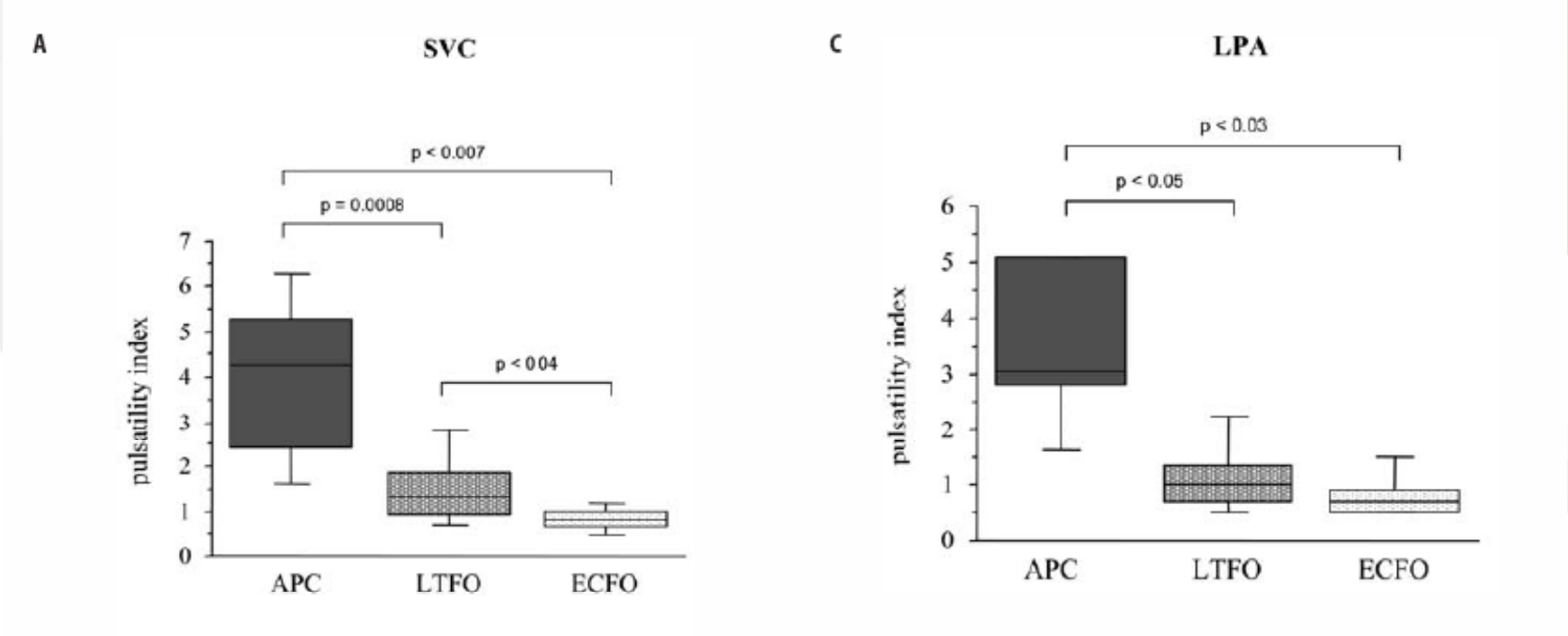
Vladimir Alexi-Meskishvili, MD, PhD
Roland Hetzer, MD, PhD
Department of Cardiothoracic
and Vascular Surgery
Deutsches Herzzentrum Berlin
Augustenburger Platz 1
13353 Berlin, Germany

Birgit Spors, MD · Roland Felix, MD, PhD
Matthias Gutberlet, MD, PhD
Department of Radiology
and Nuclear Medicine
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin, Germany

Summary *Aims* We compared in vivo blood flow and pulsatility after different types of Fontan operation using magnetic resonance imaging. *Material and methods* A total of 37 consecutive patients (mean age 19±7.9 years, 7.3±3.2 years after Fontan operation), 7 with atriopulmonary anastomosis (APC), 18 with intra-atrial lateral tunnel (LTFO) and 12 with extracardiac Fontan (ECFO) were studied using magnetic resonance phase-contrast velocity mapping. Blood flow (volume flow) in the superior vena cava (SVC), inferior vena cava (IVC) and both pulmonary arteries were measured and a pulsatility index was calculated for each vessel. *Results* For all modifications, the blood flow distribution between the SVC and IVC was normal (1:2). Patients with APC had a normal pulsatility, a dilated right atrium, partial backward flow in the IVC and physiological blood flow distribution between the pulmonary arteries. LTFO and ECFO patients had no retrograde flow in the IVC, equal blood flow distribution between the pulmonary arteries and very low or absent pulsatility. *Conclusions* MRI allows hemodynamic quantification and characterization of various types of Fontan modifications and may be a valuable tool to predict Fontan failure. Despite showing normal pulsatility, patients with APC have right atrial dilatation and partial backward flow in the IVC, demonstrating suboptimal Fontan circulation. LTFO and ECFO both produce unidirectional antegrade flow in the IVC but pulsatility is very low or absent, which may promote poor pulmonary artery growth and increase of pulmonary vascular resistance contributing to late Fontan failure.

Key words
Fontan procedure –
congenital heart defects –
magnetic resonance imaging

Pulsatility Index in Fontan



- Patients with AP Fonatn have a normal or supernormal pusatility but also significant backward flow in the IVC and a dilated right atrium, which is know to cause thromboembolism and arrhythmia.

Clin Res Cardiol 2007;96:160-7

Basal Pulmonary Vascular Resistance and Nitric Oxide Responsiveness Late After Fontan-Type Operation

S. Khambadkone, MD, MRCP; J. Li, MBBS; M.R. de Leval, MD, FRCS;
S. Cullen, MB, BCh, BaO, FRCPI; J.E. Deanfield, FRCP; A.N. Redington, FRCP

Background—The pulsatile nature of pulmonary blood flow is important for shear stress–mediated release of endothelium-derived nitric oxide (NO) and lowering pulmonary vascular resistance (PVR) by passive recruitment of capillaries. Normal pulsatile flow is lost or markedly attenuated after Fontan-type operations, but to date, there are no data on basal pulmonary vascular resistance and its responsiveness to exogenous NO at late follow-up in these patients.

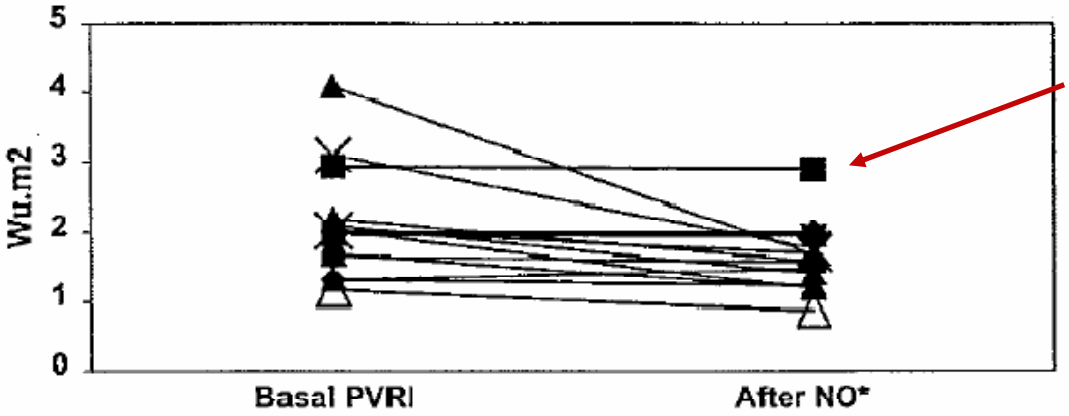
Methods and Results—We measured indexed PVR (PVRI) using Fick principle to calculate pulmonary blood flow, with respiratory mass spectrometry to measure oxygen consumption, in 15 patients (median age, 12 years; range, 7 to 17 years; 12 male, 3 female) at a median of 9 years after a Fontan-type operation (6 atriopulmonary connections, 7 lateral tunnels, 2 extracardiac conduits). The basal PVRI was 2.11±0.79 Wood unit (WU) times m^2 (mean±SD) and showed a significant reduction to 1.61±0.48 (P=0.016) after 20 ppm of NO for 10 minutes. The patients with nonpulsatile group in the pulmonary circulation dropped the PVRI from 2.18±0.34 to 1.82±0.55 (P<0.05) after NO inhalation.

Conclusions—PVR falls with exogenous NO late after Fontan-type operation. These data suggest pulmonary endothelial dysfunction, related in some part to lack of pulsatility in the pulmonary circulation because of altered flow characteristics. Therapeutic strategies to enhance pulmonary endothelial NO release may have a role in these patients. (***Circulation***. **2003;107:3204-3208.**)

Key Words: Fontan procedure ■ pulmonary vascular resistance ■ endothelial dysfunction

Circulation 2003;107:3204-8

Effect of NO on PVR in Fontan patients



Presence of no Vasoreactivitly

- The patents with PVR <2 showed no significant change .
- NO responsiveness is correlated with the residual pulsatility.

(the non-pulsatile group respond to NO with significant drop of PVR, compared with pulsatile group)

What we have to do before trial of pulmonary vasodilator ?

- First, treat with possible ***medical and surgical procedure***
  - Surgical correction of pathway obstruction
  - Fenestration to increase CO
  - Optimization of rhythm
  - Fontan conversion
  - Medication : ACE inhibitor or ARB, beta blocker, diuretics

- Trial of pulmonary vasodilator after the ***Vasoreactivity test***

Conclusions

- The management strategy for Fontan failure includes revision of surgically amenable obstruction, optimization of rhythm, fenestration and medication.
- Pulmonary Vasodilator therapy can be part of this management.

Will you use the pulmonary vasodilator ?

Now, No !

Thank you !

Sejong General Hospital
Sejong Cardiovascular Center