Unresolved issues (in Fontan state)

Management of Grown Up Congenital Heart Disease (EHJ 2003;24:1035)

- indications for and results of Fontan conversion
- outcome of TCPC in modern era
- role of anticoagulation
- medical therapy for failing systemic ventricle
- role of ACE inhibitors

Questions to be answered

- 수술 후 5년이 경과한 무증상의 이 Fontan 환자는 현재 어떤 상태이고 앞으로는 어떤 상태로 바뀔까?

→ 지속적으로 현재 상태를 유지할까 혹은 시간 경과에 따라 심기능 저하에 의한 심부전이 발생할까?

↓

  - Long-term outcome of Fontan operation
  - Stress on the ventricle in Fontan state
  - Heart failure after Fontan operation

- ACEi는 이 경우에 심실 기능 저하 방지에 효과적일까?

↓

  - ACEi in heart failure
  - ACEi in prevention of heart failure
  - ACEI in Fontan operation

Effects of angiotensin-II

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease (EHJ 2004;25:1454)

Vessels	Vasoconstriction Stimulates noradrenaline, aldosterone, vasopressin and endothelin-1 release
Heart	Inotropic and chronotropic effects Coronary vasoconstriction
Adrenal gland	Aldosterone and adrenaline release
Brain	Vasopressin release Substance P, LHRH and ACTH release Stimulation of the thirst center Increased sympathetic activation
Kidney	Vasoconstriction (efferent afferent arteriole) Contraction of mesangial cells Increased Na reabsorption in the proximal tubule Increased K excretion in distal nephron Decreased renin release
Platelets	Stimulates platelet adhesion and aggregation
Endothelial cells	Inactivation of NO (inhibits endothelial nitric oxide synthase) Expression of endothelial oxLDL receptor (LOX-1)
Sympathetic outflow	Enhancement of peripheral noradrenergic neurotransmission Catecholamine release from the adrenal medulla
Fibrinolysis	Increased expression of PAI-1 and 2
Inflammation	Activation and migration of macrophages Increased expression of adhesion molecules (VCAM-1, ICAM-1, P-selectin), chemotactic proteins (MCP-1) and cytokines (IL-6)
Trophic effects	Hypertrophy of cardiac myocytes Stimulation of vascular smooth muscle migration, proliferation and hypertrophy Stimulates proto-oncogenes (fos, myc, jun) and MAPKs (ERKs, JNK) Increased production of growth factors (PDGF, bFGF, IGF-1, TGF 1) Increased synthesis of extracellular matrix proteins (fibronectin, collagen type-I and III, laminin- 1 and 2) and metalloproteinases
Atherosclerosis	Stimulation of NADH/NADPH oxidase activity and superoxide anion production, lipid peroxidation

Use of ACE-I in heart failure: guidelines

Ischemic heart

Dilated CMP

Volume overloaded LV

- All patients with symptomatic heart failure and reduced LVEF, functional class II–IV
- LVSD (reduced LVEF, 40–45%) without symptoms

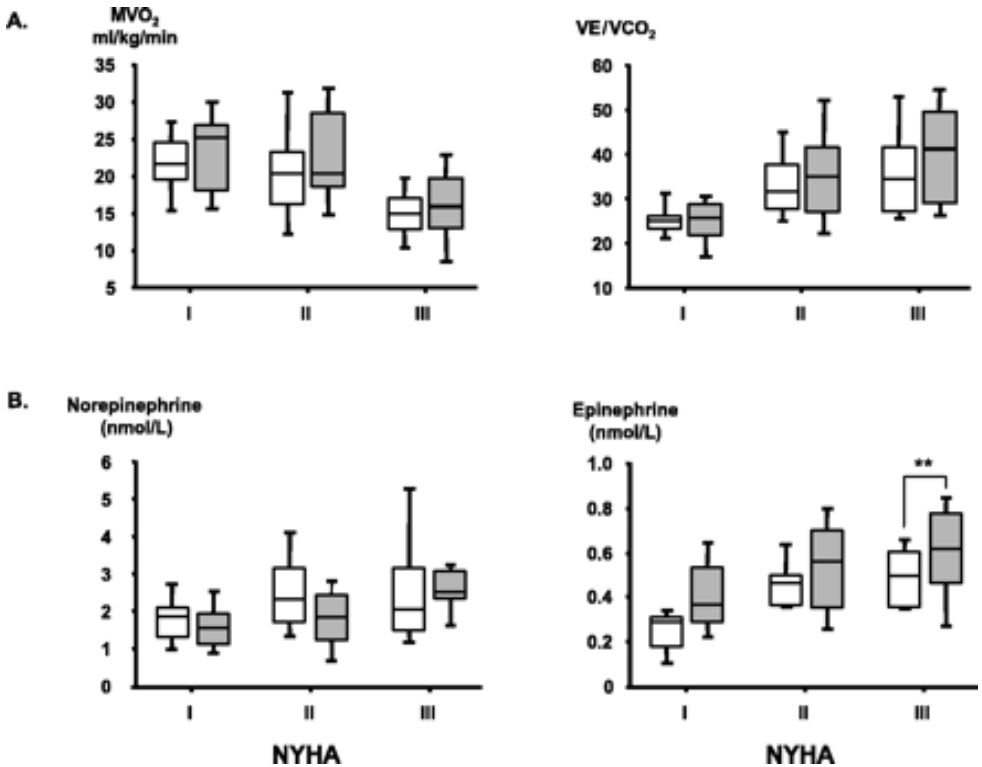
preserved LV function??

Evident: prolong survival, reduce progression of heart failure and improve quality of life

Controversial: improvement in the functional class

Necessary method for Dx of CHF (EHJ 2001;22:1527)

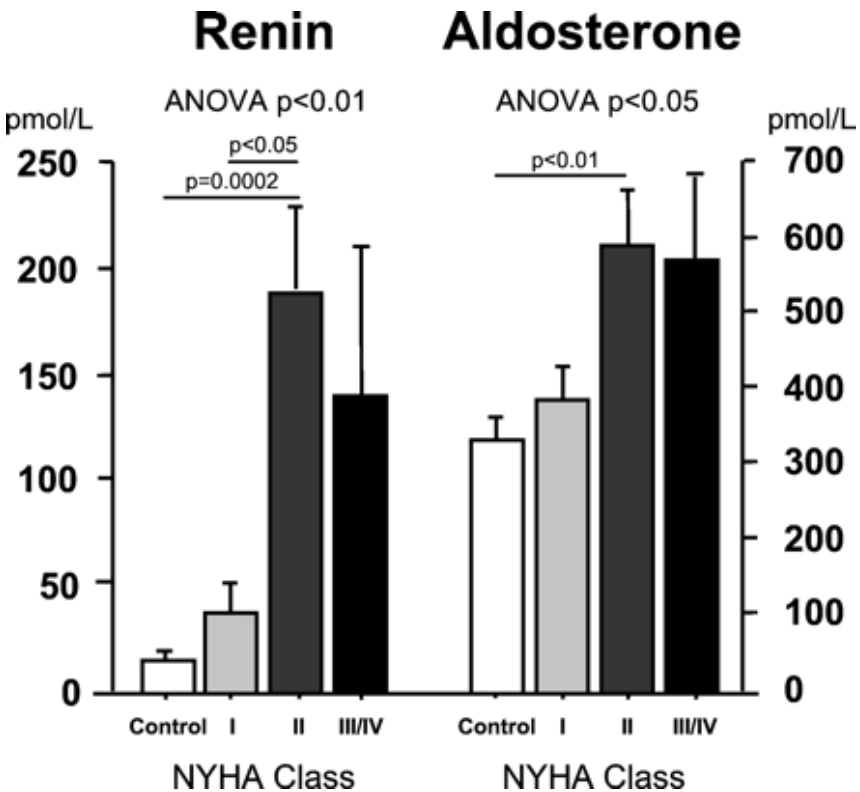
- Symptoms: Dyspnea, fatigue, ankle swelling
- Measurement of cardiac function (echocardiography, nuclear cardiology, cardiac MRI): Ejection fraction <45%, abnormal filling characteristics, valve disease, elevated pulmonary artery pressure, pericardial disease may also be apparent
- Natriuretic peptides: Elevated levels give diagnostic and prognostic information; changes relate to treatment response; normal levels may exclude heart failure

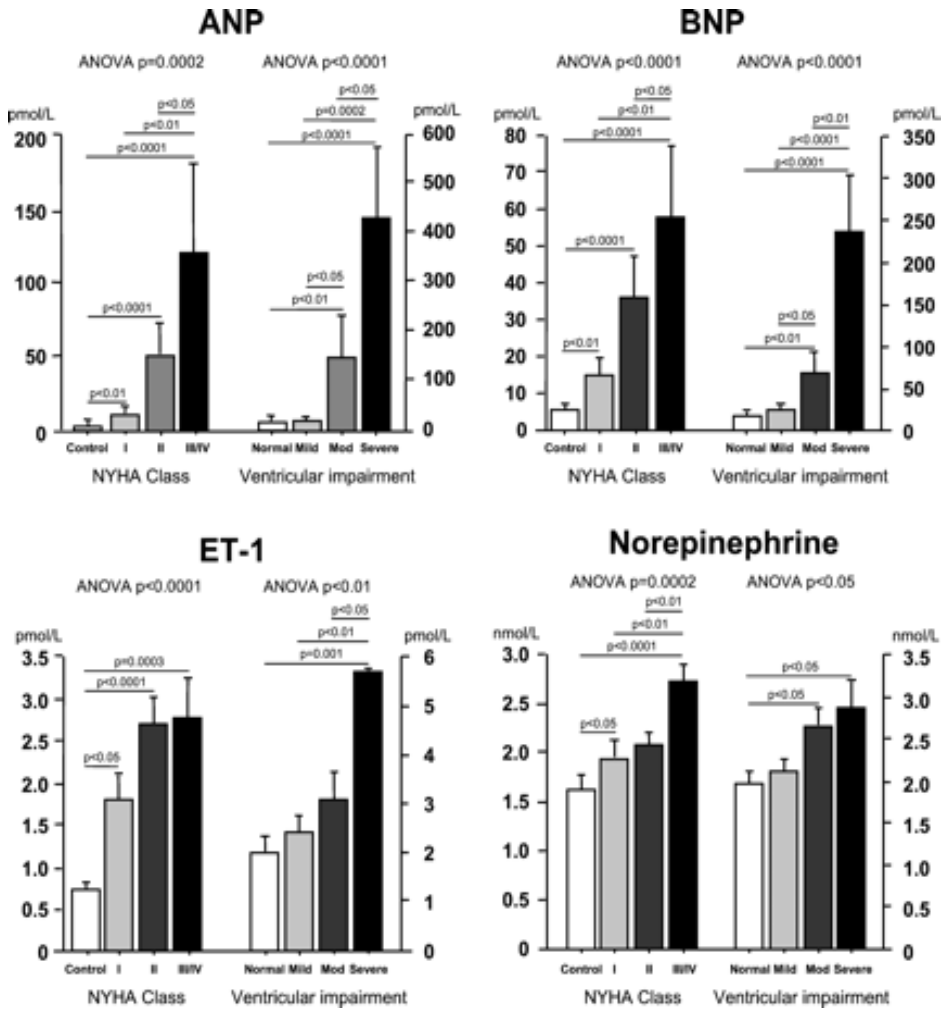


CHF d/t ischemic/dilated HF (white) vs. CHD (gray)

Congenital heart disease: the original heart failure syndrome (EHJ 2003;24:970)

Heart failure in CHD is due to persistent abnormalities in cardiac pressure, volume, tension and flow, hypoxia, etc.

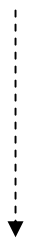




Neurohumoral activation and chronic heart failure syndrome in adults with congenital heart disease (circulation 2002;106:92)

Outpatients with mild symptoms and relatively preserved cardiac function

Stable chronic heart failure



Fontan state can be regarded as stable chronic heart failure

→ Similar strategy to those in chronic heart failure

Outcome after the Fontan op

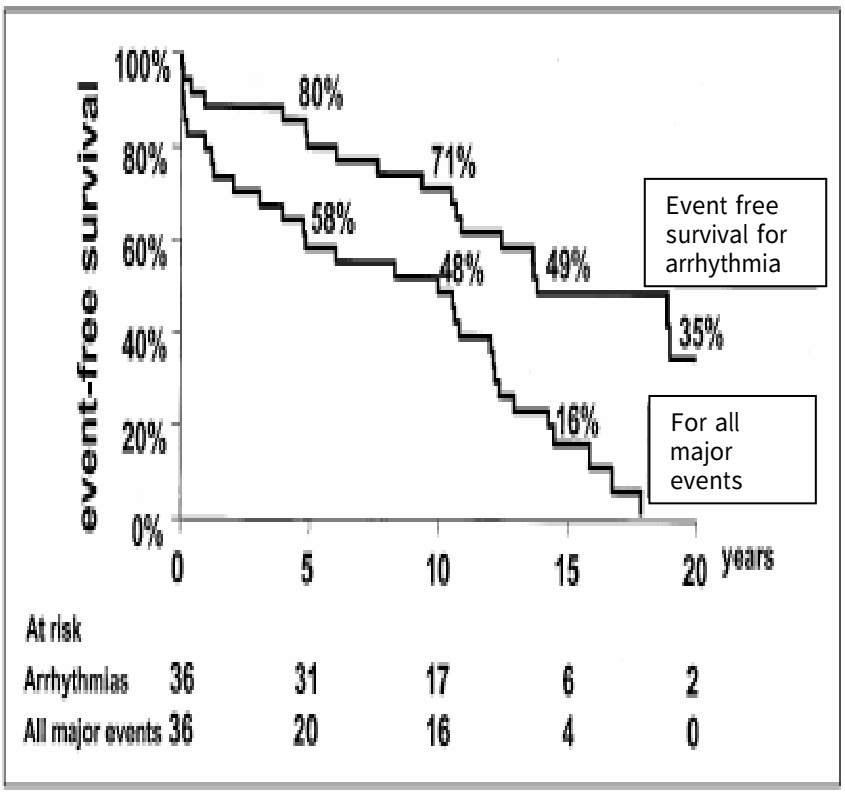


FIGURE 2. Event-free survival rates for all-cause mortality and morbidity, including reoperations, hospitalizations, arrhythmias, and thromboembolic events. There is a separate curve for the incidence of arrhythmias after Fontan operation.

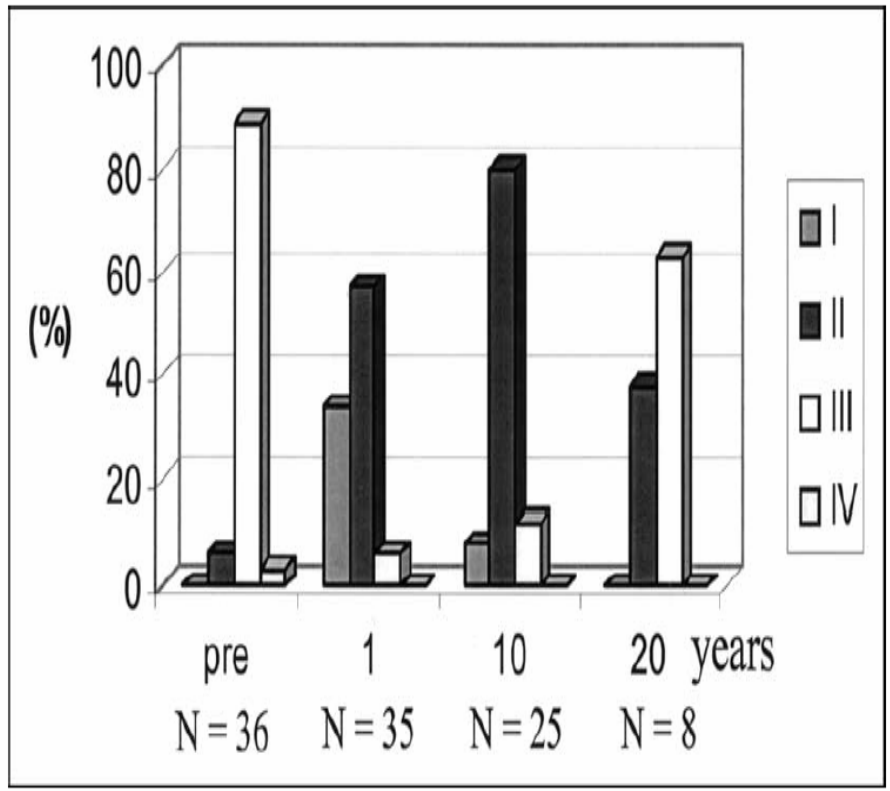


FIGURE 3. New York Heart Association classification before and after Fontan operation. With longer follow-up after Fontan operation, changes in classification indicate a decline in function.

(Bosch et al, Am J Car 2004)

ACEi in Fontan state

variable results

- 18 pts (14±6 yrs of age, 4 -19 yrs after op.), double-blind placebo control
- Enalapril (0.2 to 0.3 mg/kg/d, max.15 mg) for 10 wks.
- Mean percent increase in cardiac index from rest to maximum exercise was slightly but significantly decreased in enalapril groups (102±34% [enalapril] versus 125±34% [placebo]; $P<.02$).
- At maximal exercise, cardiac index, oxygen consumption,minute ventilation and total work were not different.

Enalapril Does Not Enhance Exercise Capacity in Patients After Fontan Procedure.
Kouatil et al, Circulation 1997;96:1507-1512

- 13 Fontan pts; range 8-16 yrs
- Enalapril for 1wk, 0.3 mg/kg/day (max 10 mg/day) and placebo.
- Exercise test and echo. estimation of VESWS after of 1 wk of therapy.
- Oxygen uptake and HR, which in part reflects stroke volume at submaximal work rates, was 7.8 ml O_2 per heart beat in the placebo group vs 9.4 ml O_2 per heart beat in the enalapril group ($p<0.05$).
- The VESWS was higher in the placebo group (65 g/cm^2 vs 56 g/cm^2, $p<0.01$).

Effects of enalapril on exercise and end systolic ventricular wall stress in the Fontan patient. Troutman, et al. Pediatr Res 1996;39(4) Suppl2:39

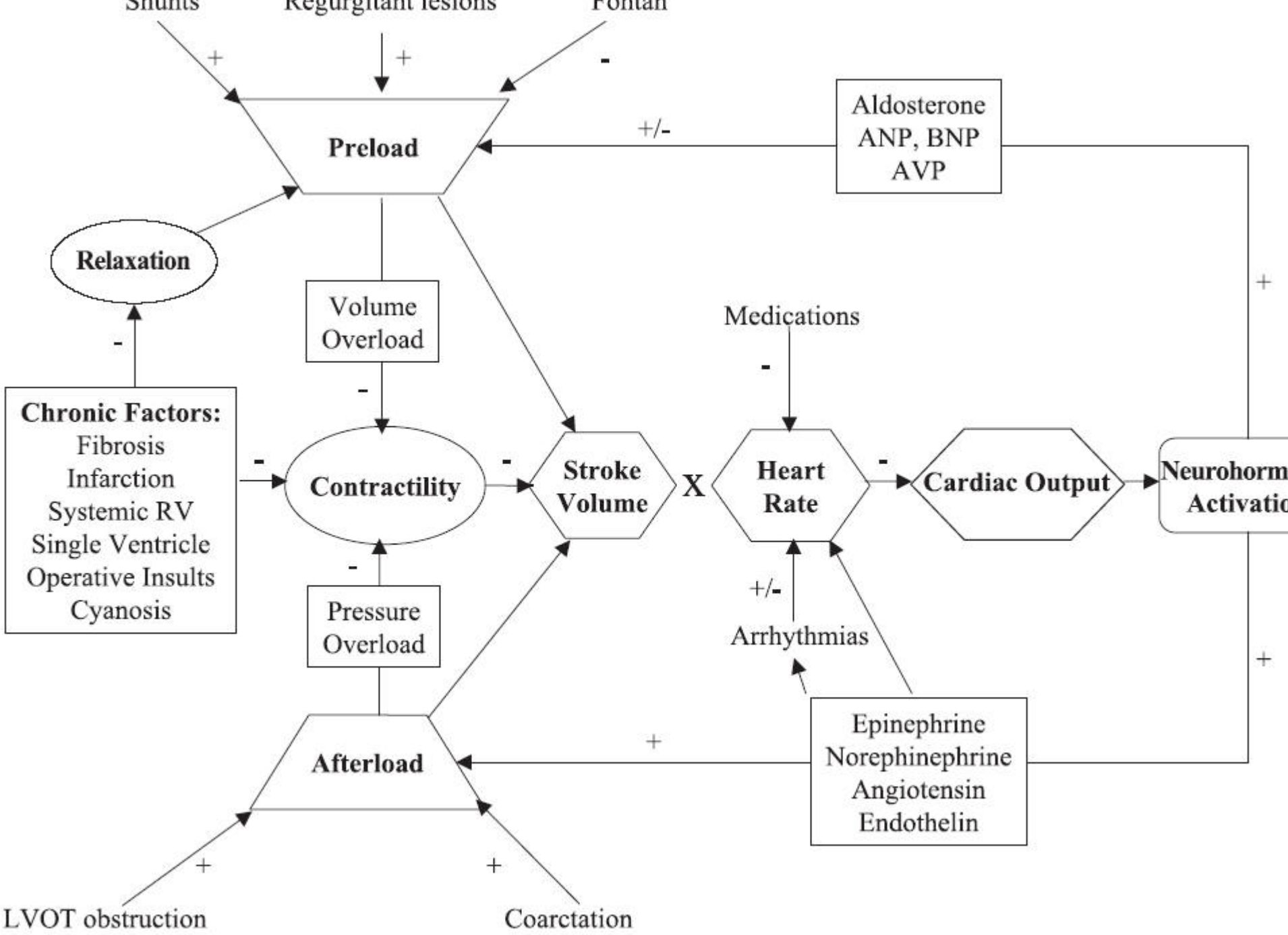
- exercise capacity in Fontan pt-

- 50 Fontan pts vs 15 control
- To elucidate the relation between exercise capacity and peripheral hemodynamics in patients after the Fontan operation
- near-infrared spectroscopy -vastus lateralis

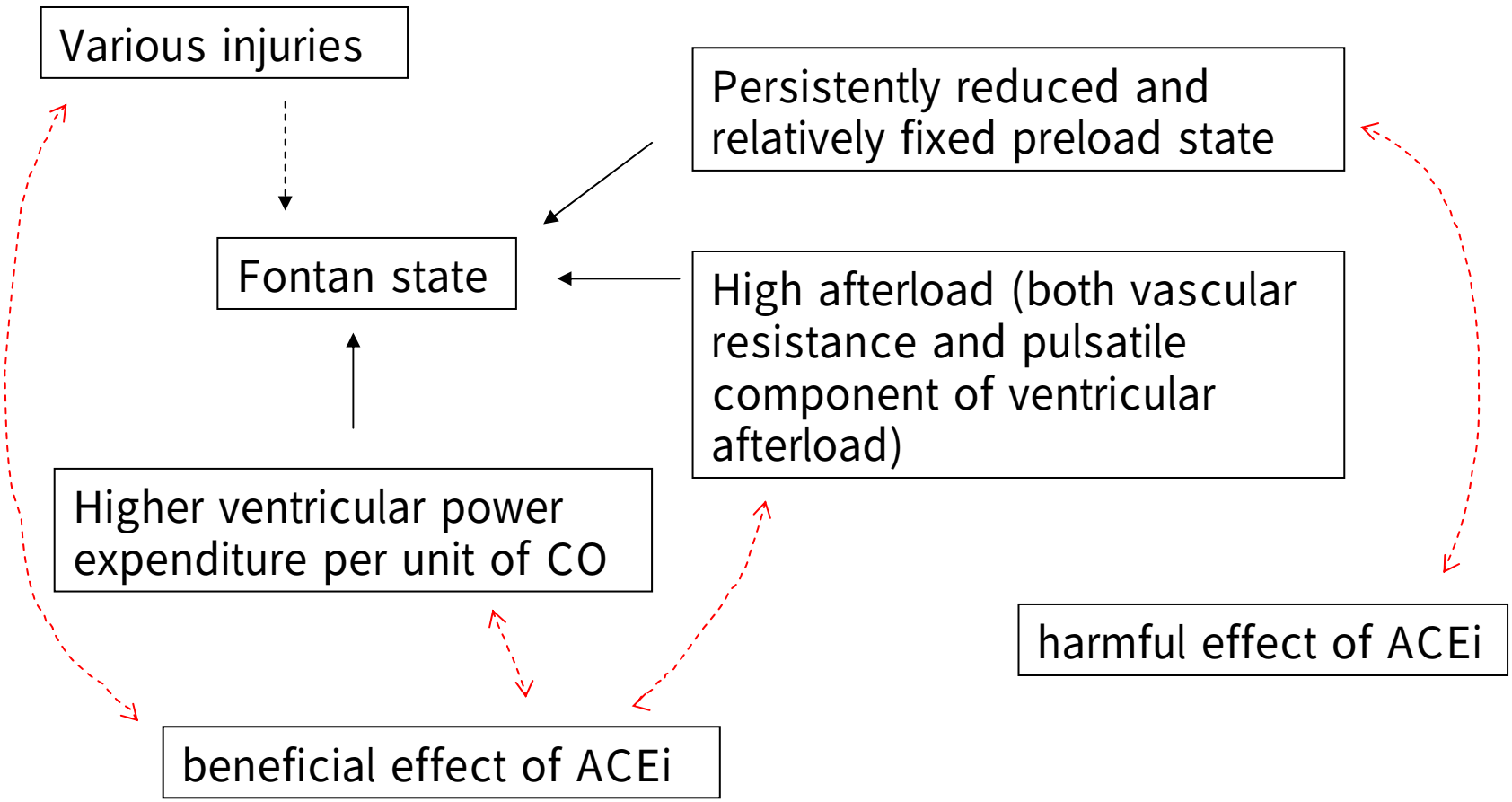
  US - flow-mediated vasodilation of the brachial and posterior tibial aa.
- diminished exercise capacity was related to a reduced blood flow supply and an attenuated post-exercise oxygen resaturation of the working skeletal muscle, which also was related to impaired endothelium-dependent vasodilation.

Am J Cardiol 2004;93(6):792

Suggestion


Shunts
Regurgitant lesions
Fontan
+
+
-
Preload
+/-
Aldosterone
ANP, BNP
AVP
Relaxation
Volume
Overload
Medications
-
-
+
Chronic Factors:
Fibrosis
Infarction
Systemic RV
Single Ventricle
Operative Insults
Cyanosis
-
Contractility
-
Stroke
Volume
X
Heart
Rate
-
Cardiac Output
Neurohorm
Activatio
-
+/-
Pressure
Overload
Arrhythmias
+
Afterload
+
Epinephrine
Norephinephrine
Angiotensin
Endothelin
+
+
LVOT obstruction
Coarctation

Intrinsic defects in Fontan physiology



Current and Potential Treatments for Diastolic Congestive Heart Failure

Pathophysiological Basis	Therapy
Relieve volume overload	Diuretic
	Fluid and sodium restriction
	Dialysis
Decrease heart rate, prolong diastolic filling time	ß-adrenergic blockade
	Calcium channel blockade (verapamil or diltiazem)
	Consider digoxin
Restore atrial contraction (atrial fibrillation)	Antiarrhythmic agents
	Cardioversion
Renin-angiotensin axis blockade	Angiotensin-converting enzyme inhibitors
	Angiotensin receptor antagonists
Aldosterone blockade	Spironolactone
	Investigational agents
Control hypertension	Additional agents if needed
Relieve ischemia	Medical therapy
	Revascularization

improves diastolic distensibility of the ventricle

regression of biopsy-proven myocardial fibrosis

conclusion

- ACEi can be effective if Fontan state is associated with high preload (AV regurgitation or aortic regurgitation) or intrinsic ventricular myocardial dysfunction.
- ACEi in Fontan state without high preload may be harmful due to further decrease in preload induced by the drug.
- Because intrinsic ventricular myocardial dysfunction is very difficult to define, ACEi can be tried cautiously. However, follow-up evaluation after medication should be done to prove beneficial effect.
- In this case, ACEi can be tried if AV regurgitation is thought significant or progressive.
- More specific marker indicating cardiac dysfunction in CHD is needed.