Endothelial dysfunction in Postoperative Congenital Heart Disease and Kawasaki Disease – is it real?

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Introduction

Shear force, Endothelium & Its function

Drug to evaluate vascular function

Endothelial dysfunction in preoperative CHD

Endothelial dysfunction in postoperative CHD

Cardiopulmonary bypass & endothelial injury

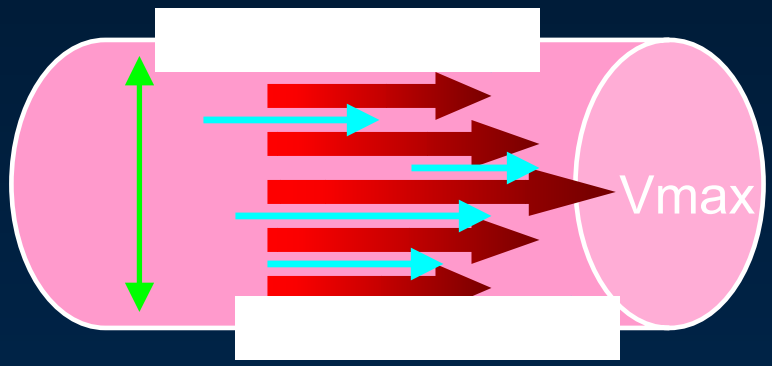
Endothelial dysfunction in Fontan circulation

Endothelial dysfunction in Kawasaki disease

Conclusion

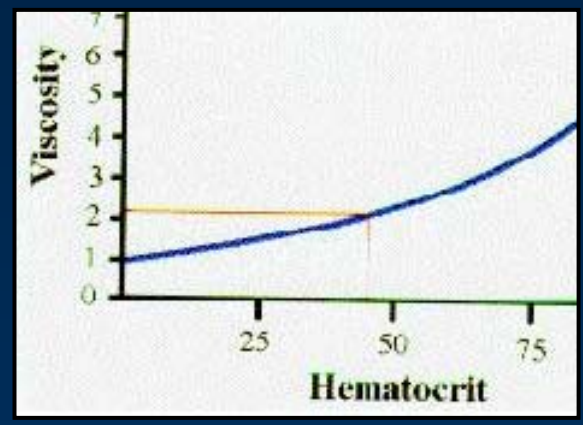
Introduction

Hemodynamics in blood vessel



1) Tensile force

2) Shear force (frictional force) 



∝ viscosity, flow velocity, 1/vessel diameter

Aorta : 15 dyn/cm^2 vs. venule : 0.8~1 dyn/ cm^2

<u>Essential to maintain homeostasis of vessel.</u>

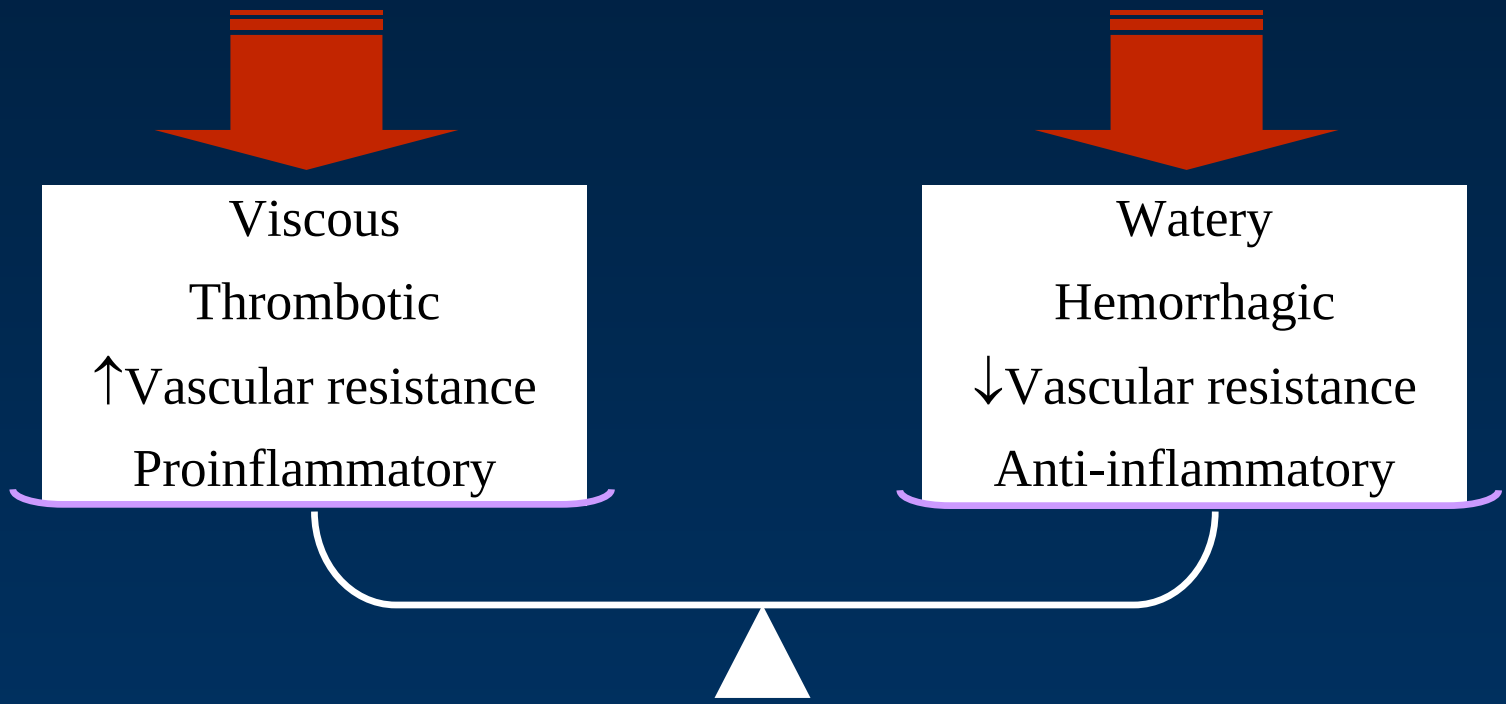
But if excessive or too small, damage to endothelial cell structurally and functionally.

Example) expression of iNOS

Endothelium

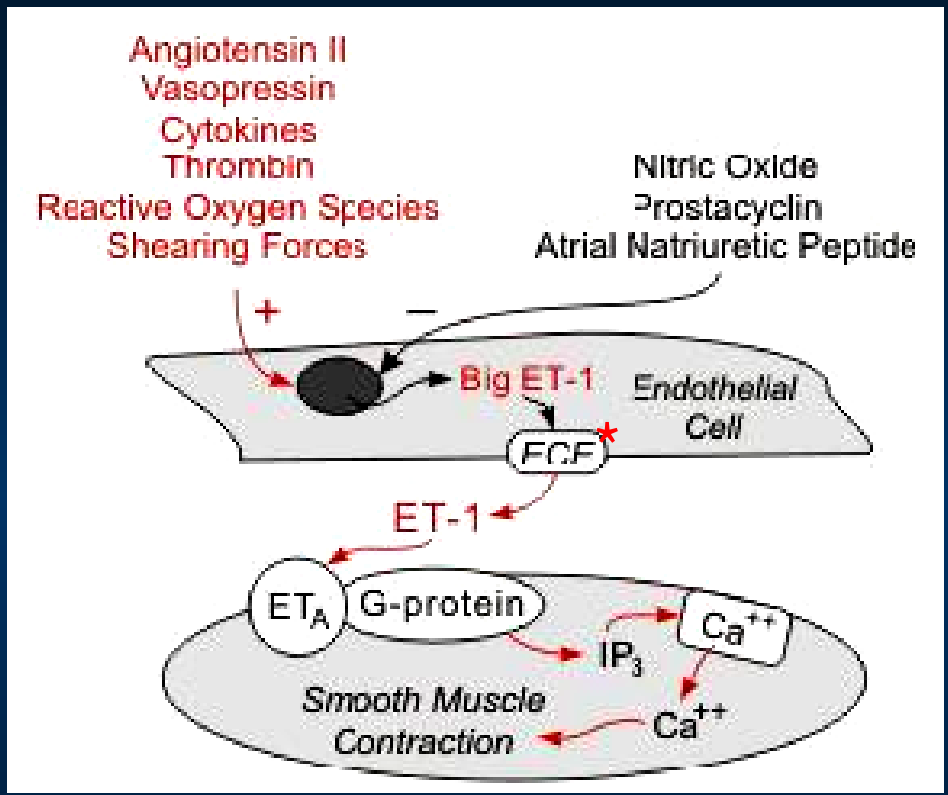
; The thin epithelium lining the blood vessels, lymphatics, and serous cavities.

Endothelin-1, nitric oxide radical, superoxide radical, prostaglandin, von Willebrand factor, adenine nucleotide, kinin, endothelium-derived hyperpolarizing factor, …



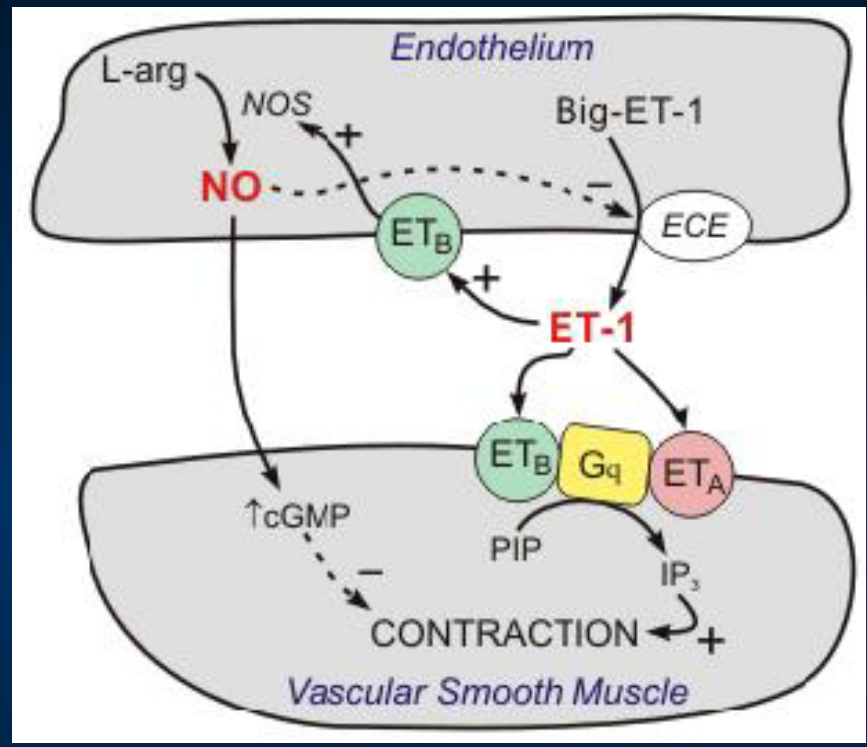
Disease **Homeostasis** **Disease**

Endothelin-1(ET-1)

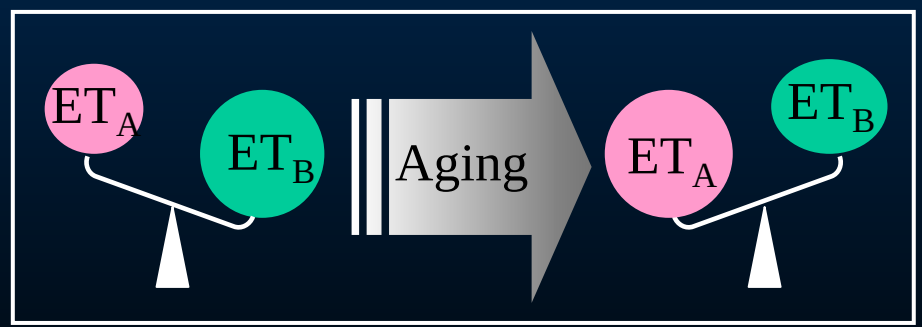


ET-1 production by vascular endothelium and its mechanism for production vascular smooth muscle contraction.

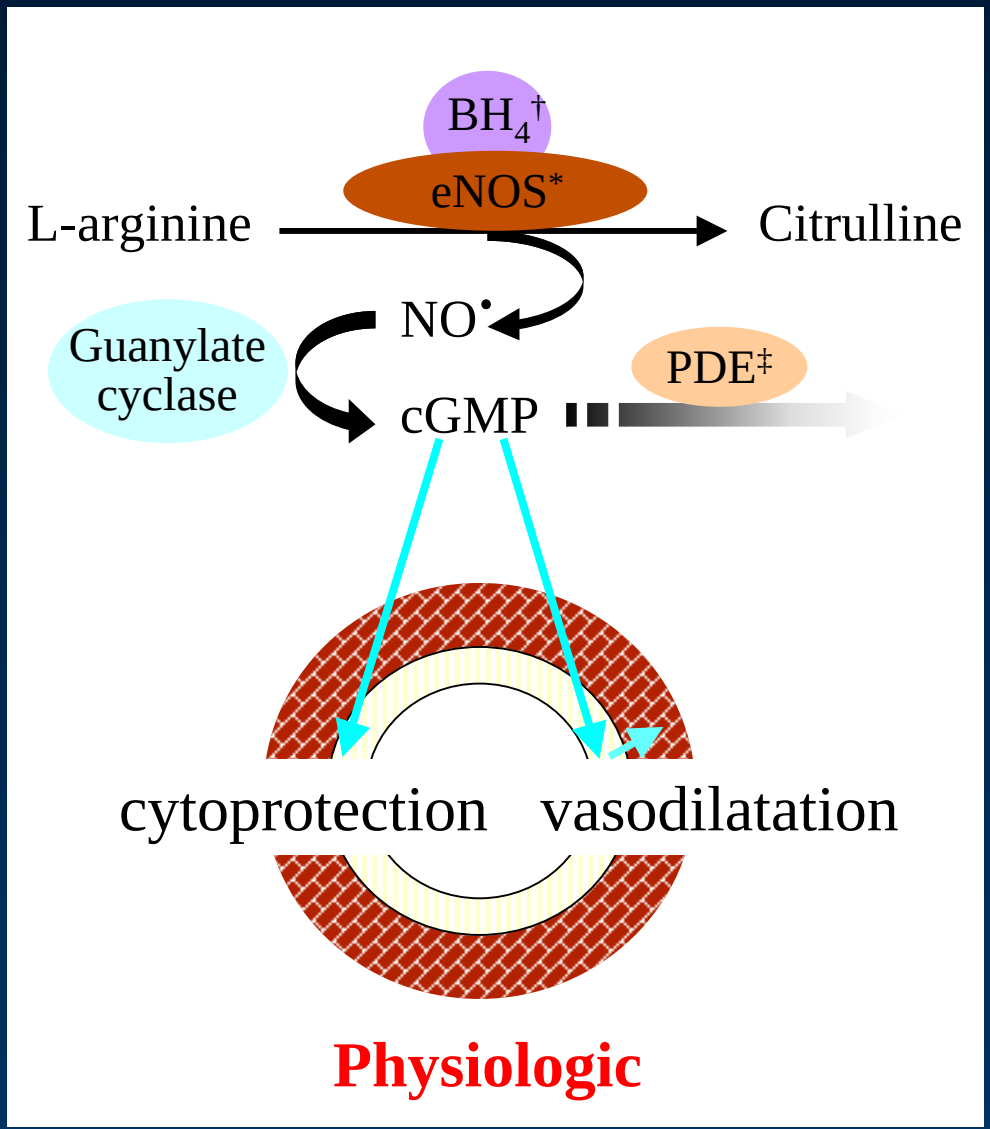
**ECE: endothelin converting enzyme*

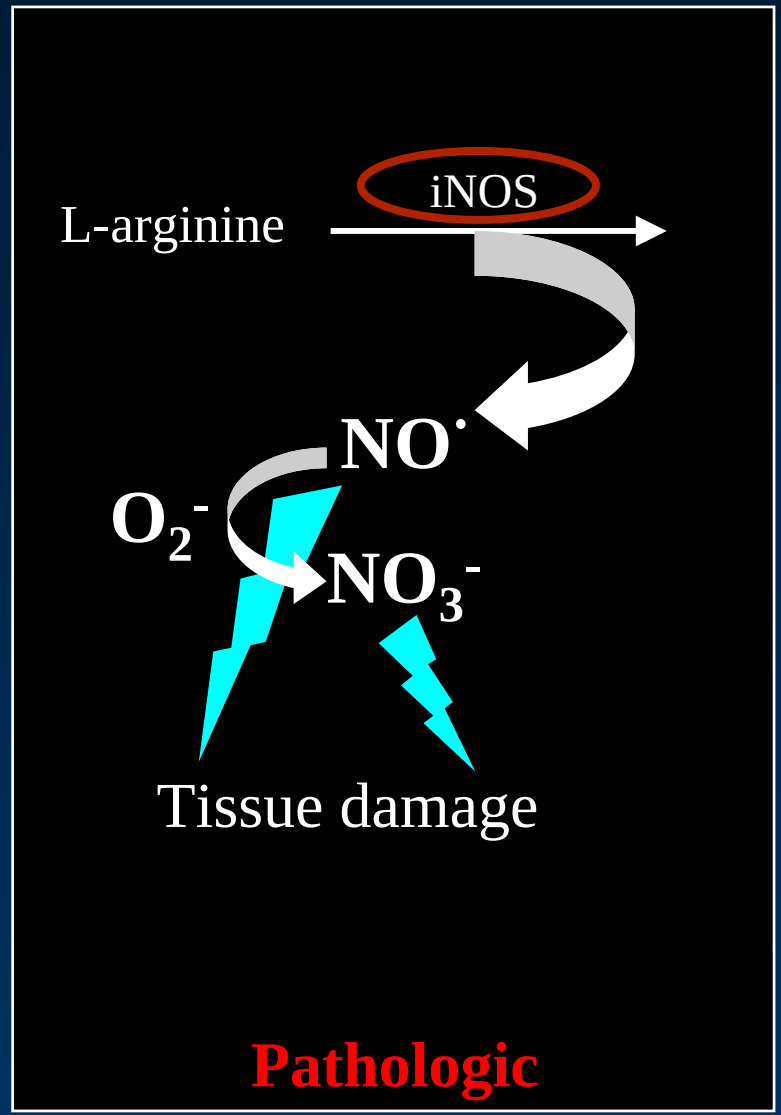


ET-1 and interaction with NO



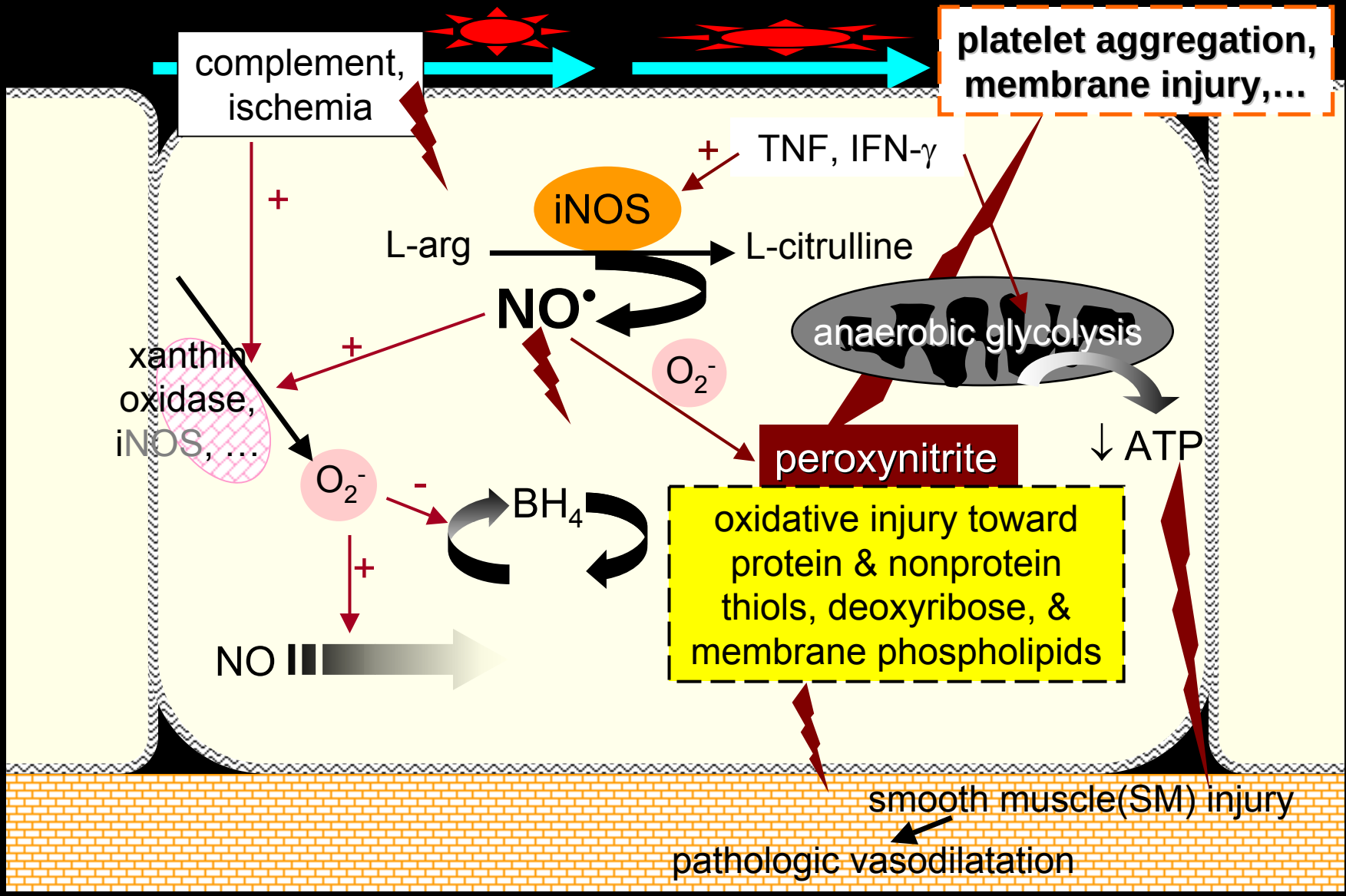
Nitric oxide($NO^{\cdot}$) – a kind of free radicals



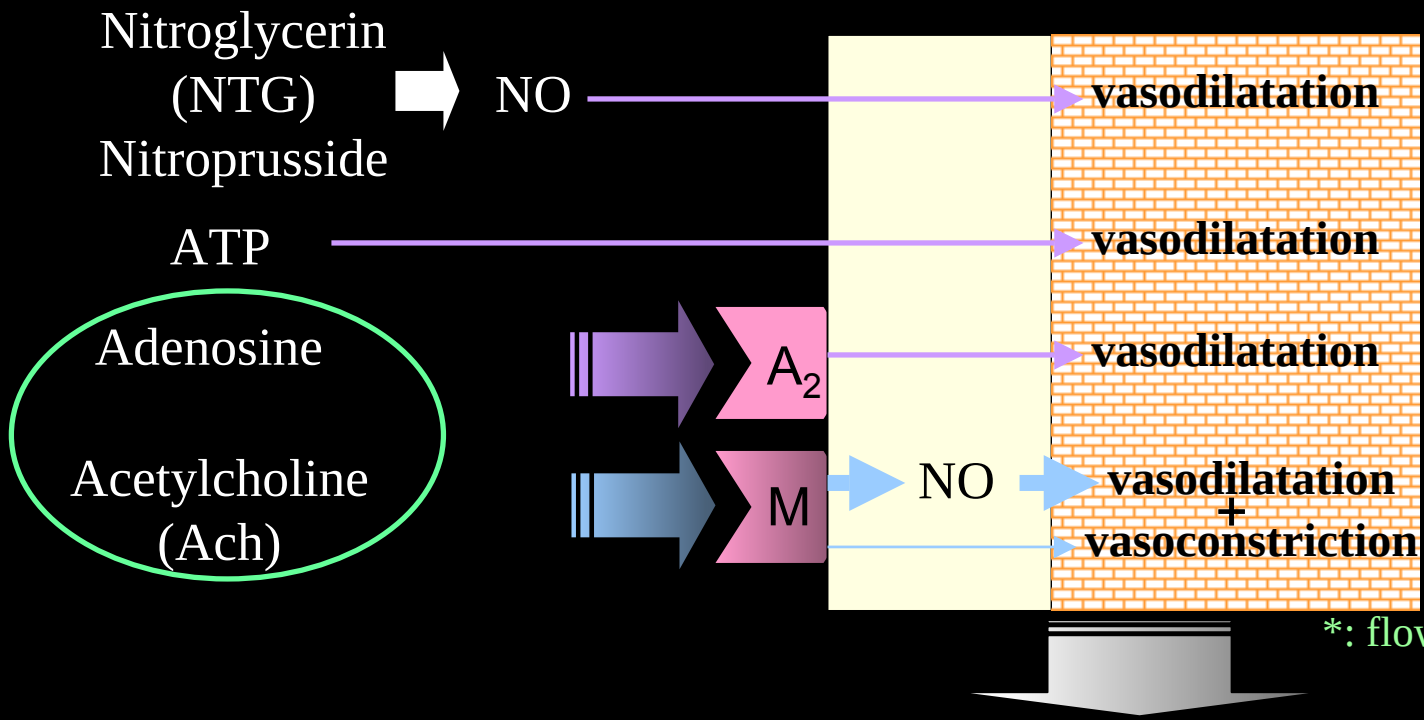


*:e-nitric oxide synthase, †:tetrahydrobiopterin, ‡:phosphodiesterase

Endothelial injury, dysfunction & nitric oxide



Evaluation of vascular function



PET { Myocardial blood flow (MBF)
Coronary flow reserve (CFR)

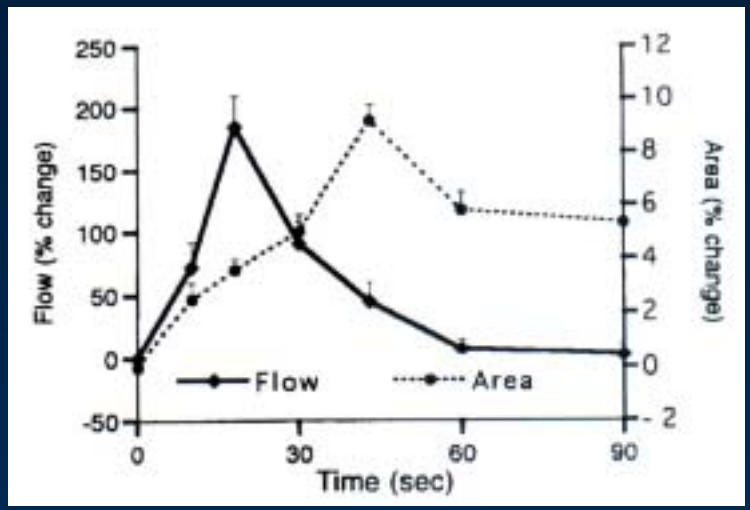
Cardiac angiography { Epicardial coronary arterial (ECA) diameter
Coronary blood flow (CBF)

Sonography, angiography : Blood flow & diameter of systemic artery

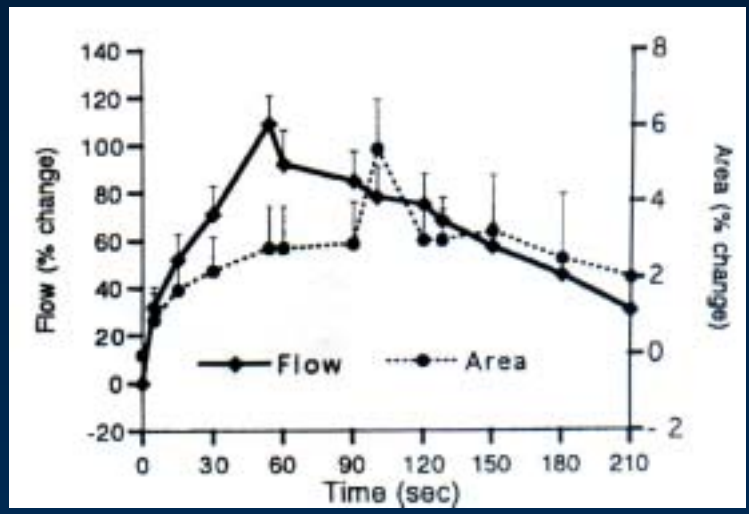
Effect of adenosine vs. Ach. on ECA

Hollenberg SM, Catheter Cardiovasc Interv 1999

Adenosine



Ach



Binding to A_2 receptor on coronary microvascular endothelium

→↑coronary microvascular diameter

→↑coronary blood flow

→↑ECA diameter (by FMD)

Binding to muscarinic receptor on coronary endothelium

→↑ECA & microvascular diameter, coronary blood flow

→Plateau of coronary flow & diameter

→Maximal ↑ ECA diameter (by FMD)

Endothelial dysfunction in CHD with increased L→R shunt By ↑shear stress on pulmonary artery(PA)

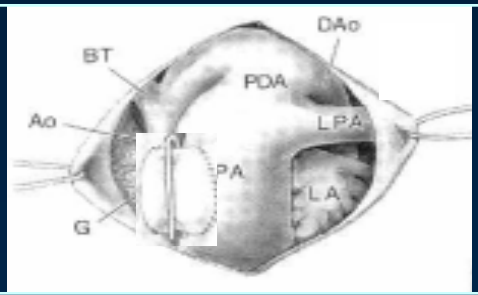
↑Pulmonary blood flow & velocity	Normal to ↑ PA pressure, reversible PHT	Irreversible PHT(Eisenmenger Sd.)
▪↑Shear stress	▪Endothelial adaptation → injury & dysfunction	▪Progression to vascular smooth muscle injury
▪Normal response to vasoactive agent	▪↓Vasodilatory response to Ach.	▪↓Vasodilatory response to adenosine, NTG, nitroprusside, etc. Paradoxic vasoconstriction to Ach.
▪Normal histology on LM, ↑ endothelial metabolism on EM	▪Initiation of PA wall muscularization	▪Hypertrophy of arterial media, proliferative intimal lesion, ↑arterial wall collagen content…

Operable

Inoperable

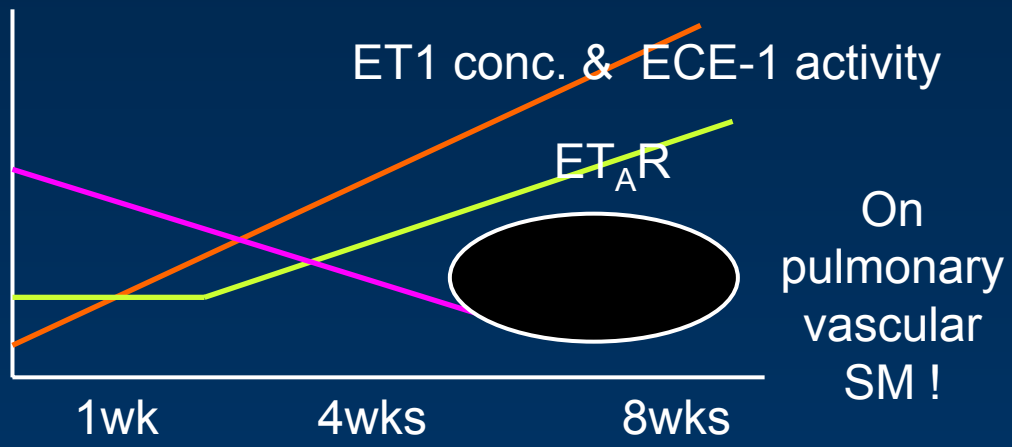
Endothelial dysfunction in CHD with increased L→R shunt, From a molecular point of view. -Ao. to PA shunt model -

Black SM et al., 1998~2002. Artificial AsAo. to PA shunt, in late stage of pregnancy, birth ??

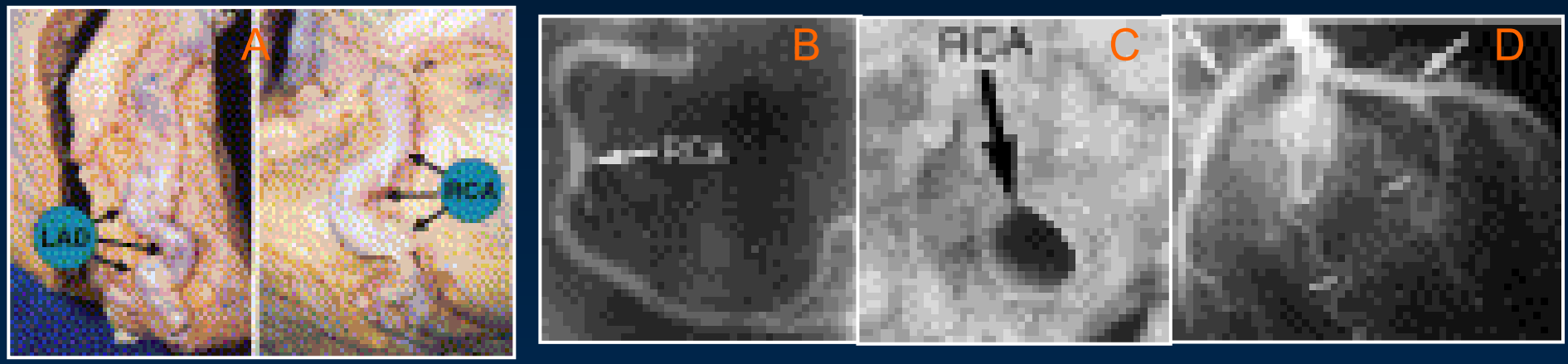


	4wks(reversible change on PA)	8wks(1mo. in human, irreversible change)
PA pressure	normal	↑
eNOS mRNA	↑	No change
NO & cGMP conc.	↑	↓

ET1 conc.
ECE-1 activity
ET_AR
ET_BR



Endothelial dysfunction in cyanotic CHD (CCHD) By ↑shear stress on coronary artery(CA)



A) CAs in a 43-year-old cyanotic woman with Eisenmenger's sd.
B) Selective coronary arteriogram illustrating moderate dilatation of the RCA.
C) Necropsy specimen illustrating moderate dilatated and atheroma free RCA.
D) Selective left coronary arteriogram from a 53-year-old cyanotic man with Eisenmenger's sd. The circumflex and left anterior descending arteries are moderately dilated; the diagonal branches are moderately dilated and tortuous.

↑ viscosity → ↑ shear force → ↑ endothelium derived vasodilating factor, etc. → tortuous dilatation, wall thinning & anti-atherosclerotic change of CA, but, maintain CBF & CFR !!.

Endothelial dysfunction in CCHD & Eisenmenger Sd.

- In functionally univentricular heart & Eisenmenger Sd. :
  Altered levels of endothelial markers →precede intravascular coagulation and thrombosis, ↑vWF & tissue-type plasminogen activator, ↓thrombomodulin
- Hypoxia :
  Shift the endothelial phenotype towards a prothrombotic state.
  Induces exocytosis of the Weibel-Palade bodies (storage site of vWF, tissue-type plasminogen).
- In severe PHT patients, ET_BR gene is overexpressed on pulmonary vascular SM.
  → $ET_{AB}R$ inhibitor (bosentan®) has an positive effect on these patients (in studying).

Endothelial dysfunction in postoperative CHD

Endothelial dysfunction in postoperative CHD

Preexisting endothelial damage & dysfunction + Endothelial injury by cardioplegia & cardiopulmonary bypass (CPB) / Ischemia-reperfusion (I/R) injury → Postop. heart failure !

Activation of complement system & inflammatory cells,
↑ oxidative stress, free radical & NO_3^-, disturbance of Ca^{2+} homeostasis,…

Heart

- iNOS on cardiomyocyte.
- ↑ coronary vascular permeability due to ↑ VEGF, its receptor on CA & prostaglandin by Cycloxygenase-2(COX-2).
- ↑ contractility of cardiomyocyte due to ↑ ET-1.
- ↑ coronary vascular tone or coronary spasm due to ↑ intracellular Ca^{2+}, ET-1 & COX-2.

PA

↑↑ PA pressure (PAP)

PHT, ↓ oxygenation

↓ coronary microvascular circulation & ventricular function

NO and peroxynitrite in postischemic myocardium

Zweier, Antioxidants & redox signaling, 2001

- In Sprague-Dawley rats,

Preischemia —30 min of global ischemia→ Post-reperfusion (~900 sec.)

- Measure $NO^{\bullet}$ & $^{\bullet}O_2^-$ generation, NO_3^- & nitrotyrosine formation, contractile function.

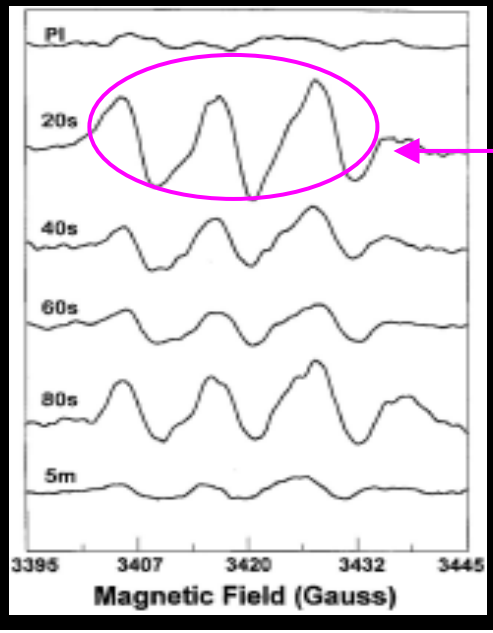
By electron paramagnetic resonance (EPR) spin tapping measurements	*By luminol chemilumine scence*	*By immuno-histochemistry using Ab.*

$NO^{\bullet}$ & $^{\bullet}O_2^-$: Paramagnetic.

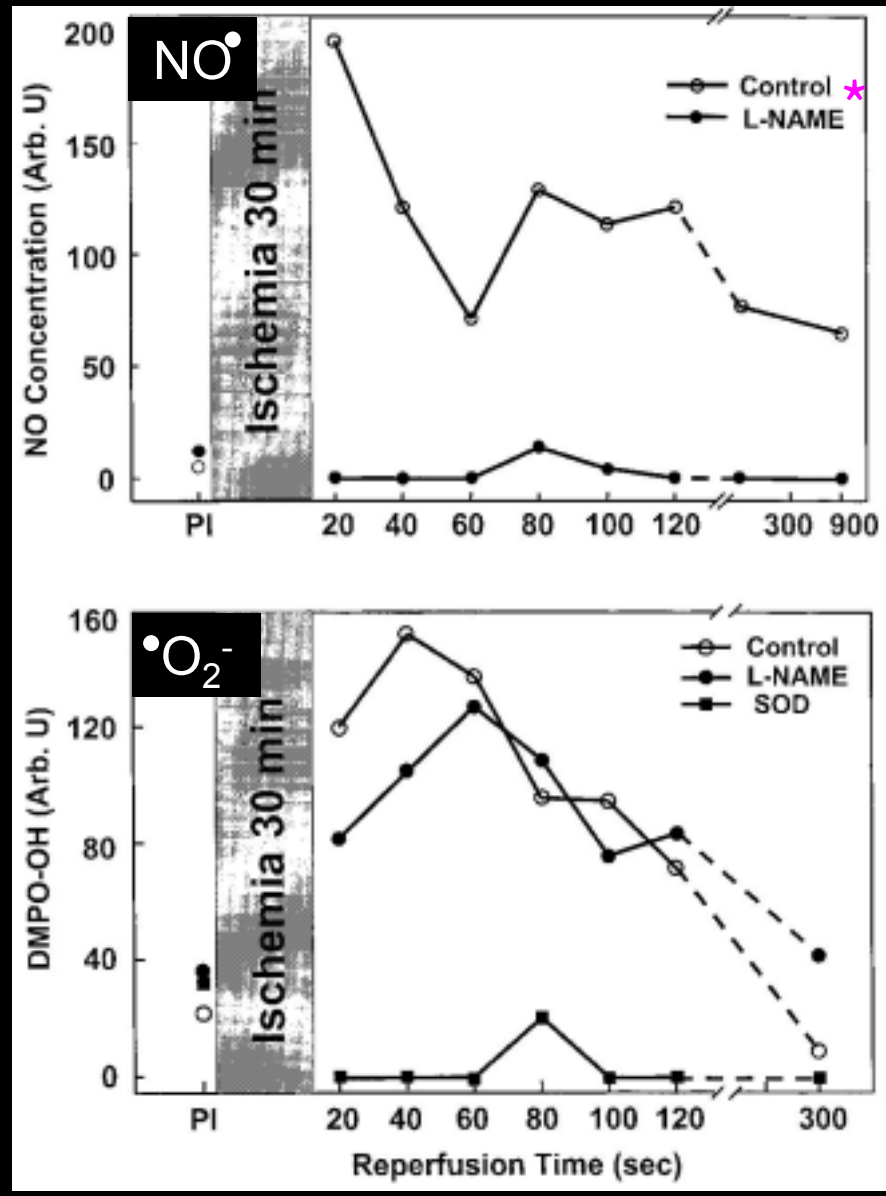
Bind with high affinity to a variety of metal chelates and metalloproteins distinctive EPR spectra of these nitroso complexes. Quantitative measure of free radical generation in living tissue.

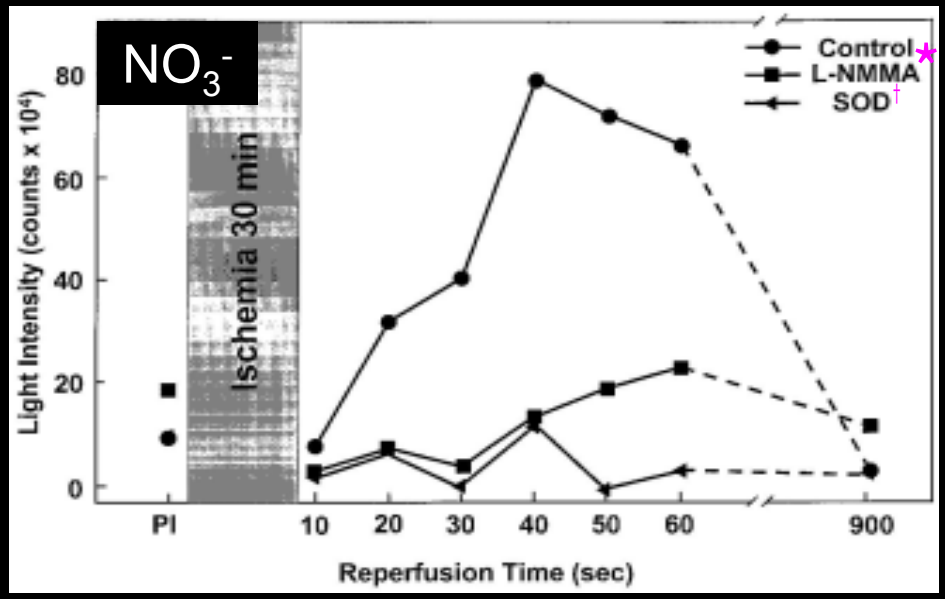
- Fe-MGD(Fe2+-N-methyl-D-glucamine dithiocarbamate) : for $NO^{\bullet}$
- DMPO(5,5-dimethyl-a-pyrroline-N-oxide) : for $^{\bullet}O_2^-$

Zweier, Antioxidants & redox signaling, 2001



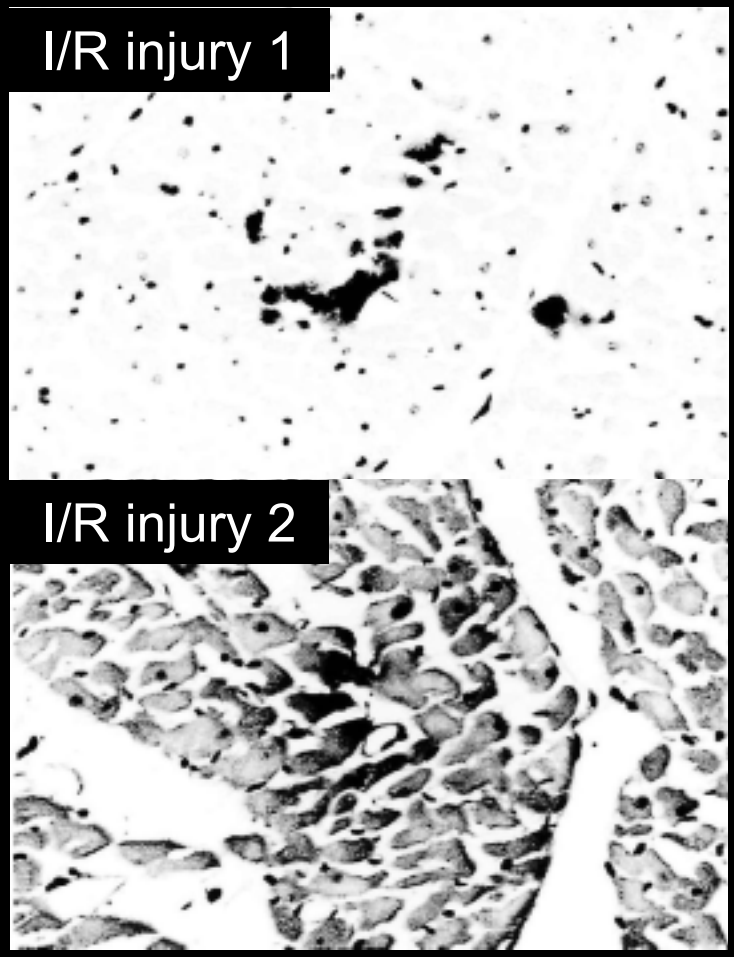
Typical triplet EPR spectrum of NO-Fe-MGD complex



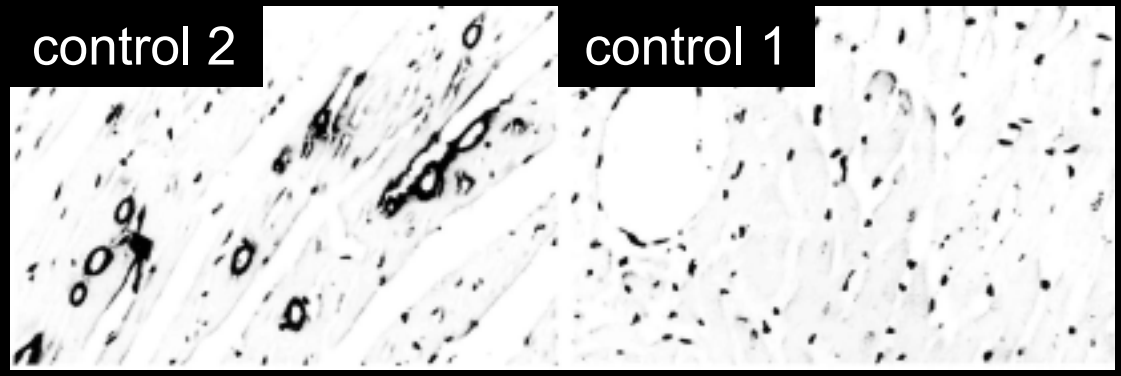


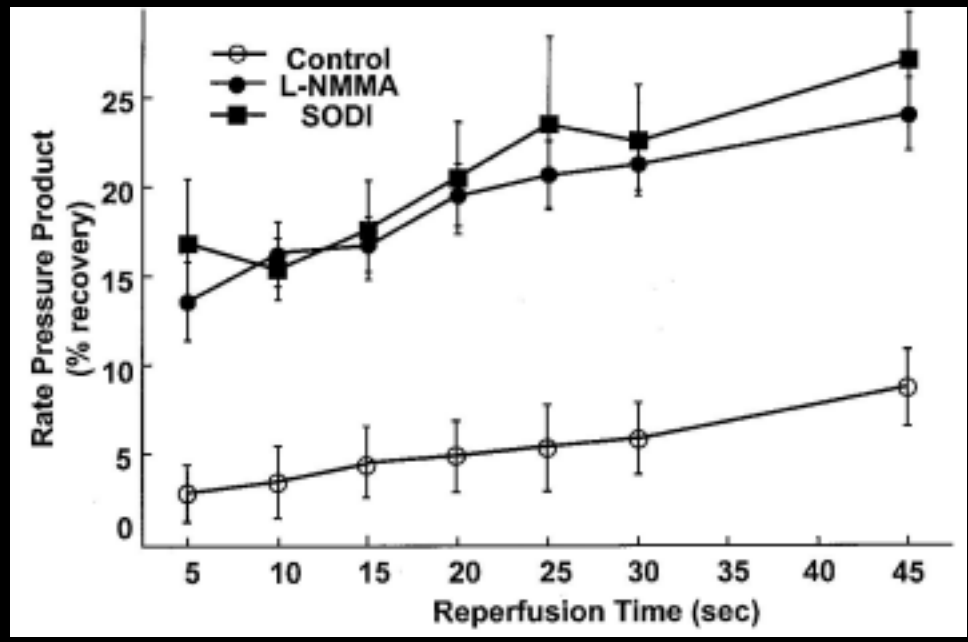
* L-NAME, L-NMMA: NOS inhibitor † SOD: superoxide dismutase

Zweier, Antioxidants & redox signaling, 2001



Immunohistology measurement of the presence and localization of nitrotyrosine formation in normal & postischemic heart tissue.





Measurement of the recovery of RPP, an index of contractile function in untreated control hearts & hearts pretreated L-NMMA or SOD.

Significance of pulmonary vascular endothelial injury

- CPB & cardioplegia aggrevate pre-existing pulmonary endothelial injury.
- Pulmonary hypertensive crisis

; sudden onset of desaturation, hypotension, and increase of PAP $\rightarrow$ directly $\uparrow$ of postop. morbidity, mortality and mechanical ventilation time.

- Factors to aggravate PA injury.

:CPB duration, preoperative diagnosis (AVSD > large VSD > TGA, TA, TAPVR), preoperative pulmonary blood flow, operation time.

- PHT not increase more than mean arterial pressure is clinically not important, but it may be critical to patient of Fontan circulation or RV dysfunction !!

Interventions to reduce endothelial injury

- To reduce the degree of complement activation.

: coating the cardiopulmonary circuit with heparin, using leukocyte filter or monoclonal antibody to adhesion molecule or complement (pexelizumab).

- To remove free radicals.

: add superoxide dismutase, deferoxamine, or N-acetyl cysteine to cardioplegic solution.

- To reduce the degree of intracellular [Ca^{2+}] increase.

: use cardioplegic solution of low [Ca^{2+}] (0.4~1.2mmol/l) or high [Mg^{2+}] (5.0mEq/l).

Local [Mg^{2+}] is high $\rightarrow$ protect endothelial cell

Intracellular [Mg^{2+}] is high $\rightarrow$ inhibit release Ca^{2+} from intracellular calcium store and exhaustion of ATP $\rightarrow$ maintain homeostasis of vascular SM

Treatment of endothelial injury

1. Classic Tx.: vasodilator, inotropics, high O_2 ventilation, induce alkalosis, etc.

2. NO inhalation

   - Benefit: inactivation at the moment of contact to Hb. → no systemic effect.
   - Problem: no consistent response rate, rebound PHT & oxygen desaturation, coagulation inhibition, methemoglobinemia.

   * IV infusion of sildenafil (viagra®, potent & selective PDE-5 inhibitor), prostacyclin.
   → overcome the problem of No therapy, esp. rebound phenomenon.

3. Intravenous infusion of L-arginine, or substance P.

   → produce NO.

4. Intravenous infusion of BQ123 (selective ET_AR inhibitor), Oral medication of bosentan® ($ET_{AB}R$ inhibitor).

Endothelial injury & dysfunction after Fontan op.

Major hemodynamic change: absence of pulsatile pulmonary blood flow

Problems

Endothelial dysfunction in pulmonary & systemic vessel

↓NO, ↑ET-1, ↑VEGF, …

Arrhythmia

.

.

Treatment

NO inhalation

Sildenafil, prostacyclin,… infusion

ACE inhibitor, $ET_{AB}R$ inhibitor medication

Levy et al., J Thorac Cardiovasc Surg 2003

NOS expression:a predictive marker of Fontan procedure outcome?

Satisfactory preoperative hemodynamic data ⇒ op. ⇒ successful, or **failed**

Endothelial dysfunction ? → ↑Intraacinar PA wall thickness

- Group I : successful outcome, 8 cases Group II : failed outcome, 9 cases

	Control	Group I	Group II	*P* value*
%wall thickness of the distal PA(%)		9.6	20.45	<0.01
eNOS immunostaining grade	0.88	0.86	1.86	<0.01
ET-1 immunostaining grade	0.7	0.9	1.3	<0.01

*: P value between Group I and II

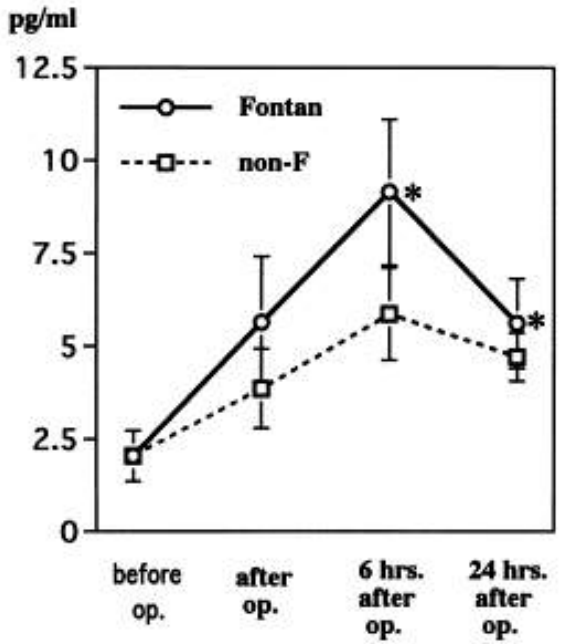
- All pts. of Gr II : a marked expression of NOS & ET-1, despite low PAP.
- Normal wall thickness & ↑↑ NOS (2 pts.) → failed outcome
  ↑↑ wall thickness & ↑ NOS (1 pt.) → successful outcome
- eNOS grade correlated with histomorphometric grade, r=0.71

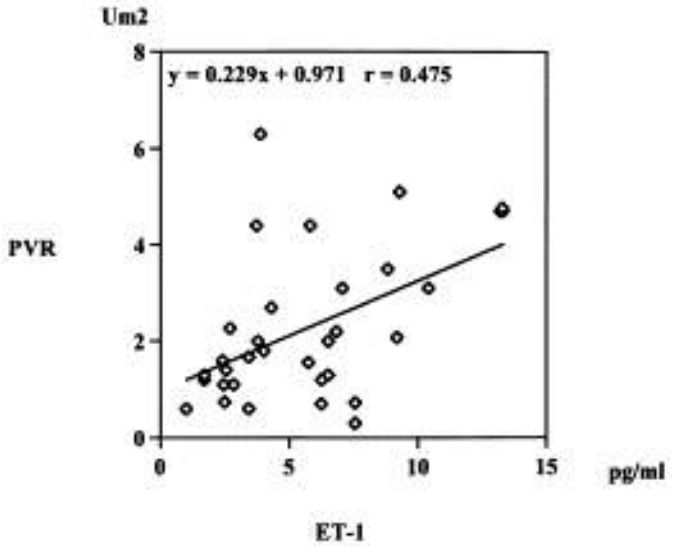
Intraacinar PAs contribute greatly to PVR & failure of the Fontan procedure
∵ an impaired vascular reactivity after a stimulus such as CPB.

Plasma ET-1 after Fontan op.

[Hiramatsu et al., Ann Thorac Surg 1999]

plasma ET-1





Correlation between ET-1 and PVR

[Yamagishi M et al., J Cardiovasc Surg (Torino) 2002]

- POD #1, after ICU care : Plasma ET-1 concentrations were elevated (more than 4 x basal level), and correlated significantly with CVP.
- During postop. Cath. : ET-1 concentrations were decrease, but significantly correlated with CVP.

Treatment after Fontan op.

1. Postop. NO inhalation : immediately ~~~~~ 9yrs after op.

	Yoshimura (2005)		Gamillscheg (1997)	Goldman (1996)	
Pts. number	47		9	15	
NO conc.(ppm)	10 (5~30)		4.1 (1.5~10)	20	
Duration (hours)	48 (5~1248)		12~264 (106)	0.25	
Indication	CVP<15 TPG<8	CVP≥15 TPG≥8	CVP≥20, TPG≥10	SaO_2≤85%	SaO_2>85%
CVP (mmHg)	NS	16 → 14	21 → 17.8		
Transpulmonary ΔP(TPG, mmHg)*	NS	9.9 → 8.4	13.5 → 7.7	12.2→ 9.6	NS
Mean systemic BP	NS	71.9 → 76.8	59 → 65		
SaO_2 (%)	NS	90.1 → 93.3	86 → 94	64 → 82	NS

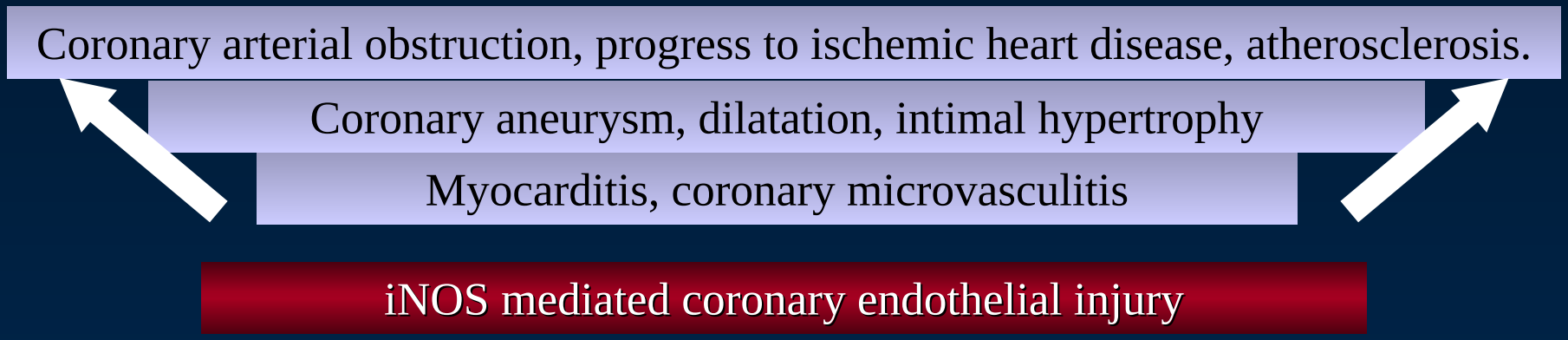
*TPG : PAP-LAP

2. Angiotensin converting enzyme(ACE) inhibitor medication.

;direct vascular SM relaxation, ↓bradykinin degradation, ET-1 secretion, iNOS expression & vascular membrane oxidase acivity,… But, routine administration ?

Endothelial dysfunction in Kawasaki disease

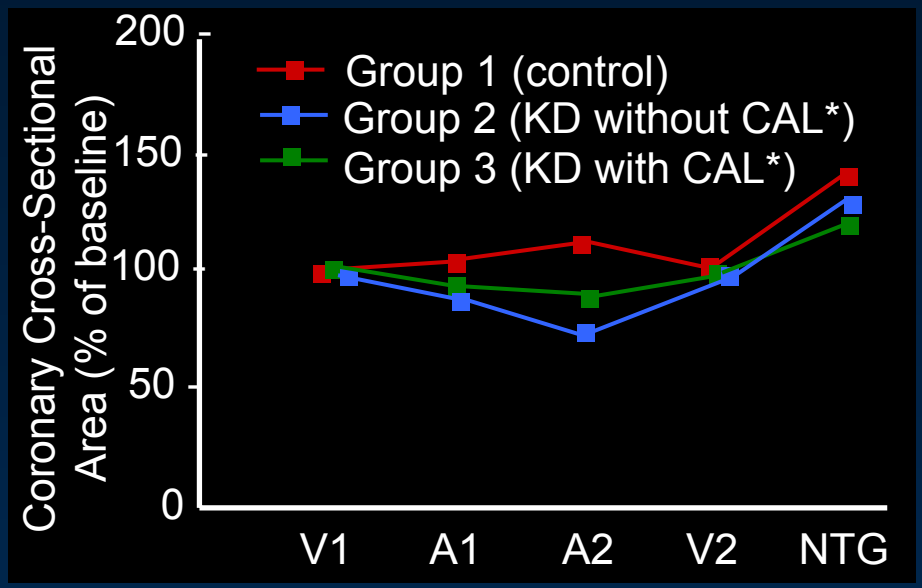
Endothelial dysfunction in Kawasaki disease



- ↑ NO (by downregulation of eNOS & upregulation of iNOS).
- Endothelial iNOS detection even to one year after onset of disease.
- Neutrophil iNOS expression is maximal at the acute stage of disease, vs.

  Monocyte iNOS expression is maximal at the 2 weeks after disease onset.
- IVIG decrease the expression of iNOS on coronary endothelial cell.
- Detection of iNOS & nitrotyrosine on aneurysmal coronary arterial wall.
  (by animal model using intraperitoneal infusion of *Lactobacillus casei* cell wall)
- $NO + O_2^- \rightarrow NO_3^-$ pathway in ischemia-reperfusion model.

Endothelial dysfunction in Kawasaki disease



Angiography & IVUS study

Mitani Y, Circulation 1997

Serial intracoronary infusion of Ach vs. NTG
→ % Change of LAD area

- Ach - Gr.1 vs. 2, Gr.1 vs. 3 : $P<0.05$
- NTG – Gr.1 vs. 3 : $P<0.05$

PET studies

	Muzik O, JACC 1996		*Hauser M, Pediatr Cardiol 2004*	
Duration from disease onset to evaluation (yr)	8 ± 4		10.3 ± 6	
Group (n)	Control (10)	KD without CAL* (10)	Control (10)	KD with resolved CAL (10)
MBF (ml/g/min) At rest	0.77±0.16	0.82±0.14	0.77±0.17	0.86±0.27
MBF (ml/g/min) **Adenosine**†	3.40±0.57	2.63±0.64	3.10±0.80	2.42±0.81
CFR (ml/g/min) †	4.6±0.9	3.2±0.7	4.09±1.01	2.89±0.26

*CAL: Coronary arterial lesion †: $P<0.05$

Conclusion

Endothelial dysfunction in Postoperative Congenital Heart Disease and Kawasaki Disease – is it real?

Yes…