Epidemiology, Physiology and Evaluation of Eisenmenger Syndrome

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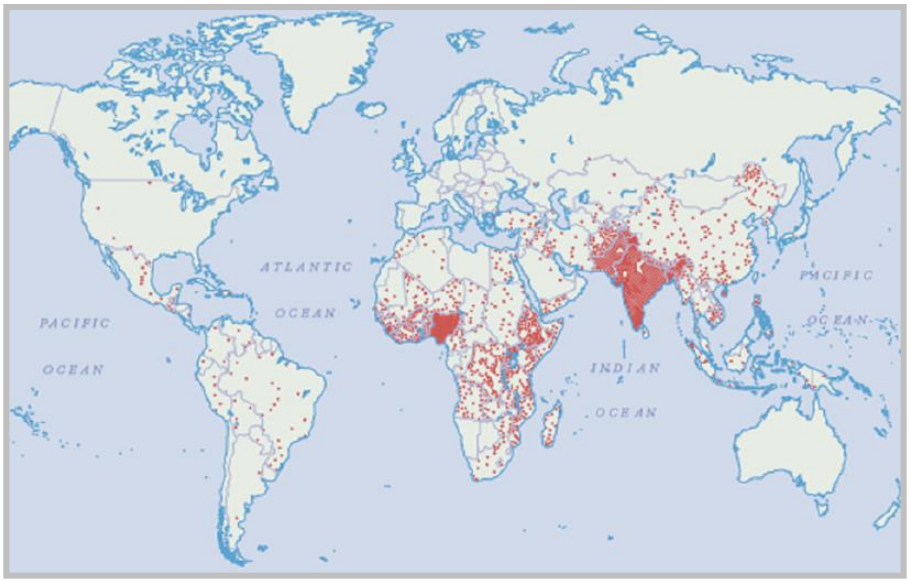
Eisenmenger syndrome

Victor Eisenmenger initially described
the clinical features of a patient with PAH
and a right to left shunt in 1897 A 32-year-old man

The term Eisenmenger syndrome(ES),
coined by Paul Wood in 1958,
embodies PAH Which is consequence of
a systemic to pulmonary arterial connection.

Victor Eisenmenger
1864~1932



Epidemiology

of

Eisenmenger Syndrome

Diagnostic Classification of Pulmonary Hypertension

The 4th World Symposium on PH in Dana Point, California, in 2008

1. PAH: Pulmonary Arterial Hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3. Drug and toxin induced
   - 1.4. Associated with
     - 1.4.1. Connective tissue diseases
     - 1.4.2. HIV infection
     - 1.4.3. Portal hypertension
     - 1.4.4. Congenital heart diseases
     - 1.4.5. Schistosomiasis
     - 1.4.6. Chronic hemolytic anemia
   - 1.5. PPHN

1` PVOD and/or PCH

2. PH owing to left-sided heart disease

3. PH owing to lung diseases and/or hypoxia

4. CTEPH; chronic thromboembolic pulmonary hypertension

5. PH with unclear multifactorial mechanisms

Worldwide Physician Education and Training in Pulmonary Hypertension
Pulmonary Vascular Disease: The Global Perspective

C. Gregory Elliott et al CHEST / 137 / 6 / JUNE, 2010 SUPPLEMENT

Pulmonary hypertension (PH) affects >25 million individuals worldwide and causes premature disability and death for many. The diagnosis and treatment of PH have advanced dramatically through the development of a clearly defined diagnostic classification, an evidence-based treatment algorithm for adults with pulmonary arterial hypertension using life-saving medications, and life-saving surgical procedures. However, worldwide education and training of physicians has lagged behind advances in the management of PH. Expertise in the diagnosis and management of PH is uncommon, even though physicians receive training on PH during their graduate and postgraduate education. Advances in worldwide physician education and training in PH will require substantial organization and work. Organizations working in this field will need to work collaboratively to maximize funding for education and to optimize the achievement of educational goals. Political, economic, and cultural barriers must be identified and overcome as part of any strategic plan. Global education should include training objectives for generalist, non-PH specialist, and PH specialist physicians. ***CHEST 2010; 137(6)(Suppl):85S–94S***

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

Pulmonary hypertension (PH) affects > 25 million individuals worldwide

Korean PAH Registry of PHT (2011)

Classification	case	%
Idiopathic (IPAH)	225	22.2
Congenital systemic to pulmonary shunts	243	24.0
Chronic thrombo-embolic disease	500	49.3
Familial	15	1.5
Miscellaneous	31	3.1
Total	1014	100
Prevalence of PAH : 20.2/million		

Jo Won Jung. Ajou University School of Medicine.

GUCH patients in Samsung Medical Center

	Seoul SMC 2007 (n=256)	%		Seoul SMC 2007 (n=256)	%
1	ASD	36.8	8	Pulmonary stenosis	2.3
2	VSD	17.0	9	AVSD	1.9
3	TOF	14.0	10	0thers	
4	PDA	7.0		Eisenmenger syn.	7.0
5	Pulmonary atresia	4.6		Marfan syndrome	5.8
6	TGA	3.5		Coronary AV fistular	0.7
7	Ebstein`s anomaly	2.7			

Epidemiology of the Pulmonary Arterial hypertension(PAH)

Nation	Age	No. of patients	Incidence of PAH	Prevalence of PAH	% of CHD
France	children	50		3.7/million	24.0%
France	>18years	674	2.4/mill./Y	15.0/million	11.3%
Korea	all	1014		20.2/million	24.0%
Scotland	adult	374	7.6/mill./Y	26.0/million	
Netherlands	children	63			37.0%

Epidemiology of the Eisenmenger Syndrome (ES) in patients with CHD

Nation	Age	No. of patients	% of PAH with CHD	% of ES with CHD
Dutch	>18years	5970 CHD	4.2%	2.4%
Samsung H.	adult	256 CHD		7%
Paul Wood		727 CHD		17.5%
			prevalence	prevalence
Belgium	>18years	91 ES		11/million
Western countries	adult		1.6~12.5/million	

25-50% of PAH affected by ES

The Global Incidence of Pulmonary Vascular Disease associated With CHD

The incidence of CHD at 8 to 12 per 1,000 live births.

Worldwide, about 600,000 babies are born annually with significant CHD,

50% or more will die of infection and heart failure in infancy.

Globally, 80% of the population lives outside the developed countries.

Only 2% to 15% of patients receive curative intervention.

We calculate that
there are approximately 3.2 million children worldwide
with an isolated ASD, VSD, or PDA
who if untreated and surviving infancy would
develop pulmonary vascular disease.

Approximately 30% of children with CHD who do not undergo surgical repair will develop pulmonary vascular disease.

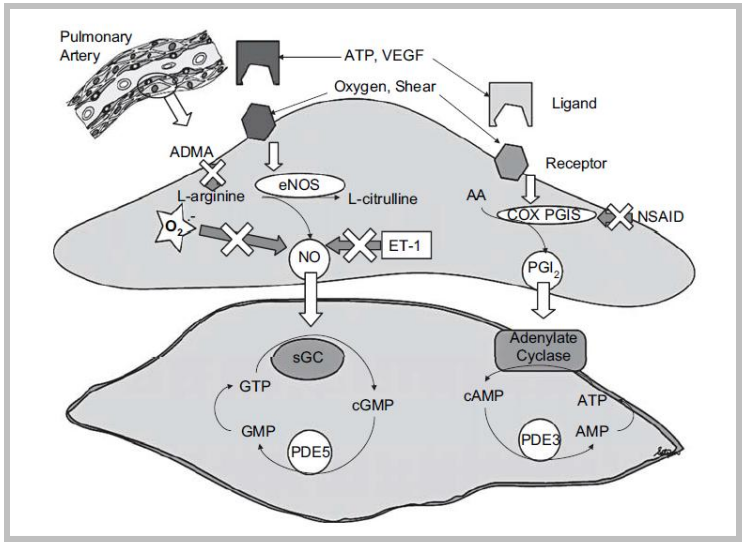
Ian Adatia et al CHEST / 137 / 6 / JUNE, 2010 SUPPLEMENT

Advances in pediatric cardiology/cardiac surgery

1. Increased the number of patients with CHD surviving into adulthood.
2. Decreased the number of patients overall with Eisenmenger syn.

1940~1960	Open heart surgery was confined mainly to some patients with PDA, ASD, PS.
1960~1980	The results of open heart surgery were not particularly good except in a few centers.
1980~2000	Surgical repair of most defects reached high standards and high volume, although for complex lesions the techniques underwent continuous modification
2000~2011	Surgical repair and catheter intervention

Seoul SMC	1996(n=514)	2007(n=256)
Natural survivors	81%	35%
Postoperative survivors	19%	65%



Physiology

of

Eisenmenger syndrome

The physiology of Pulmonary circulation

Pulmonary vascular resistance(PVR) is determined by:

1. The cross sectional area of small muscular arteries and arterioles
2. Blood viscosity
3. Total mass of the lung
4. Stenosis of the blood vessels
5. Extramural compression of the blood vessels

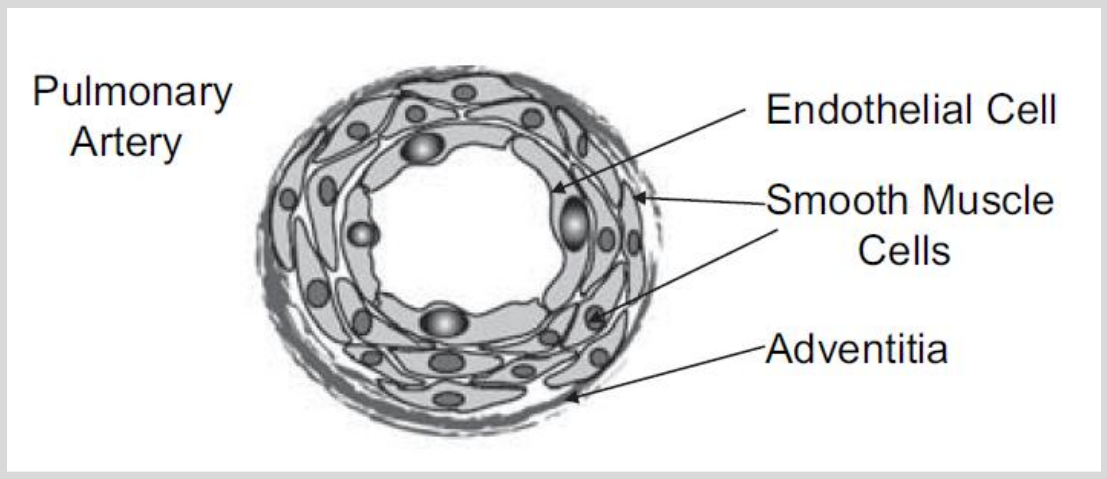
Normal PVR is 1 Wood unit(or 67±23 dyne.sec/cm)

which 1/10 of SVR

Factors in the regulation of the pulmonary vascular tone.

Factor	Pulmonary vascular tone effects	Hemostatic effects	Cellular effects
Endothelin-1	vasoconstrictor		Smooth muscle mitogen
Nitric oxide	vasodilator	Inhibits platelet function	Inhibits proliferation of smooth muscle /endothelial cells
Prostcyclin	vasodilator	Inhibits platelet function	Inhibits proliferation of smooth muscle /endothelial cells
Thromboxan A2	vasoconstrictor	Activates platelet function	

A key factor is balanced release of
Nitric oxide and Endothelin by endotherial cell.

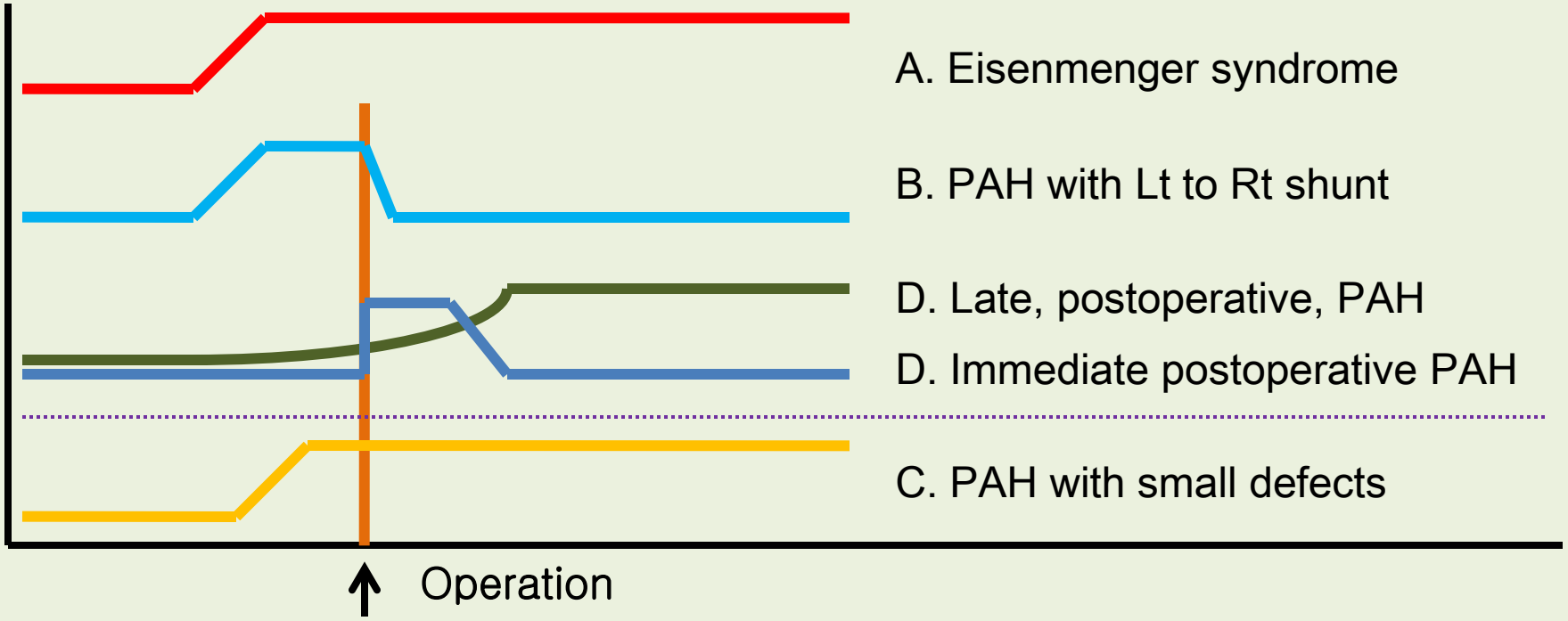


Response of the PA

to Increased Blood Fow

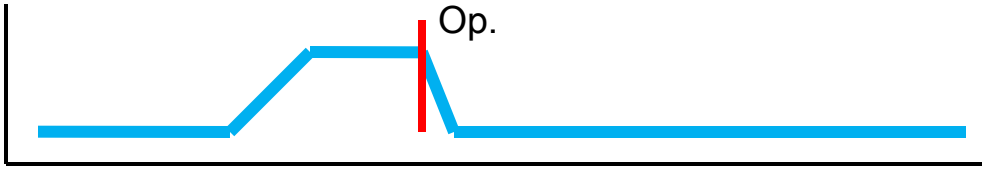
Clinical classification of congenital, systemic-to pulmonary shunts associated with PAH. -ESC/ERS GUIDELINES-

A. Eisenmenger's syndrome
B. PAH associated with systemic-to-pulmonary shunts
C. PAH with small defects : similar to idiopathic PAH.
D. PAH after corrective cardiac surgery



ESC/ERS GUIDELINES. Eur Respir J 2009; 34: 1219–1263

Hyperkinetic PHT

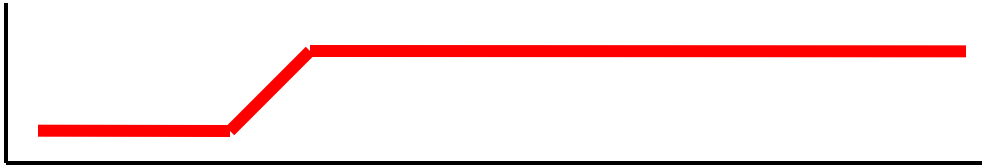


: PHT associated with Large left to right shunt lesions.

- Large left to right shunt
- An increase in PBF
- A direct transmission of the systemic pressure to the PA
- Compensatory pulmonary vasoconstriction
- Increased expression of numerous mediators and receptors
- Increased expression of signaling molecules
- Increase in PVR

Hyperkinetic PH is usually reversible if the cause is eliminated before Permanent change occur in the pulmonary arteries.

Pathologic change : the pathogenesis of chronic PAH



Elevated PA pressure : 3 well characterized vascular change

1. Endothelial dysfunction and vasoconstriction

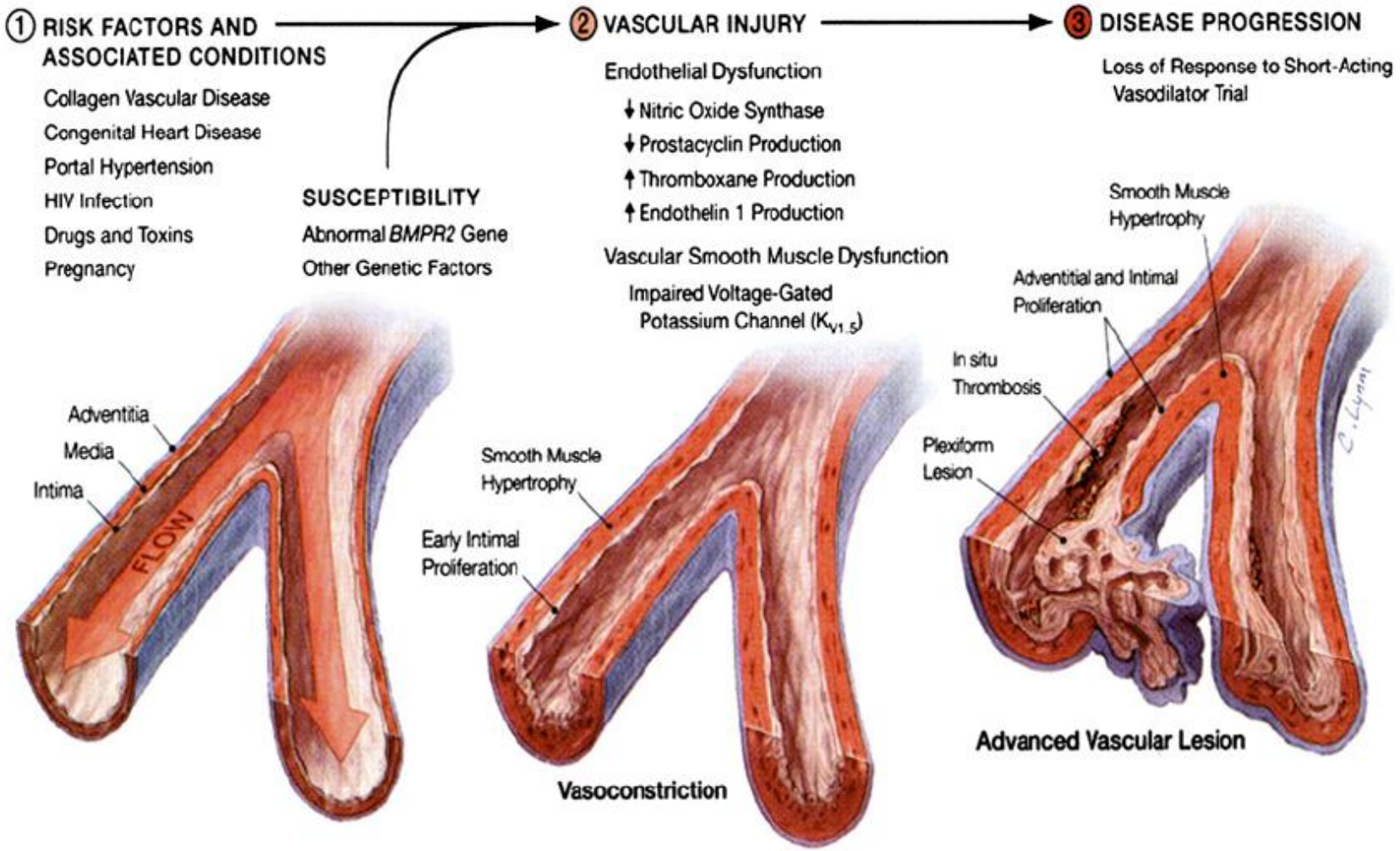
2. Vascular remodeling :

   Proliferation of smooth muscle or epitherial cell

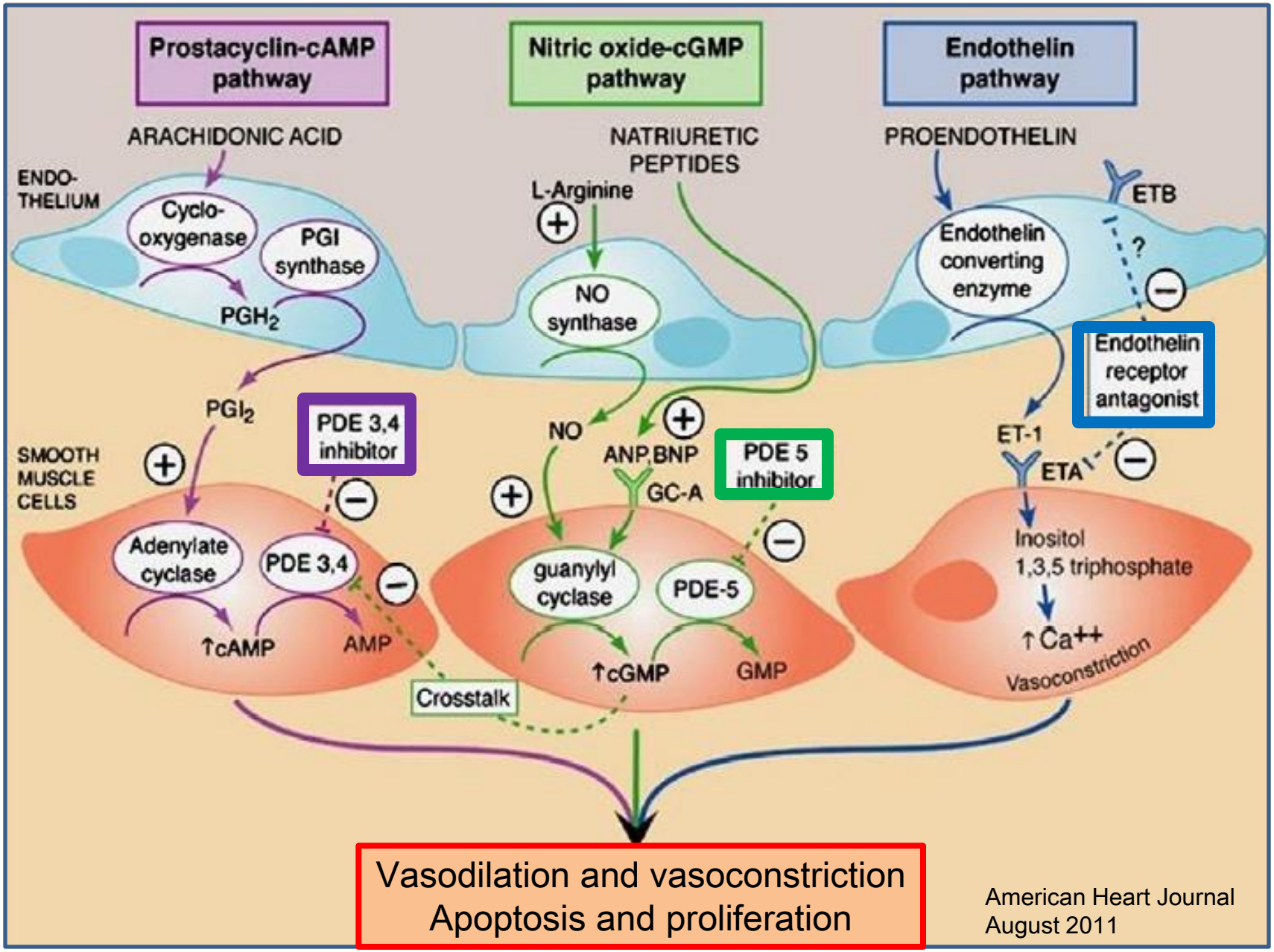
3. In situ thrombosis

Pulmonary arterial hypertension in congenital heart disease. John T. Granton Cardiol Clin 20 (2002) 441–457

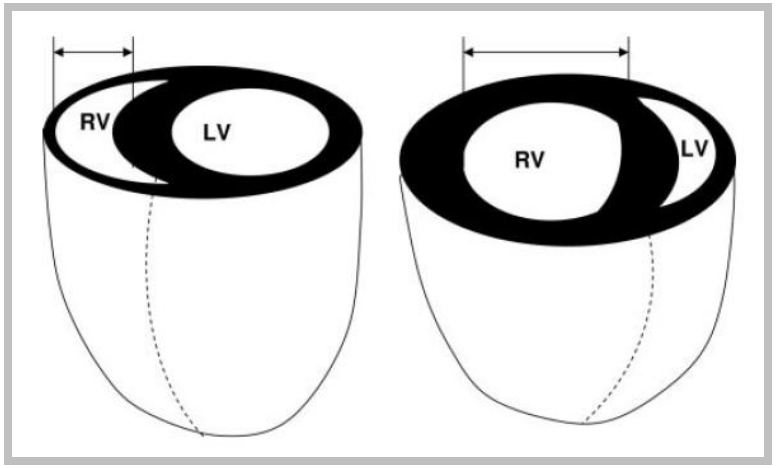
The pathogenesis of chronic PAH



Pathogenesis of pulmonary arterial hypertension.
(From Gaine S. Pulmonary hypertension. JAMA 2000;284(24):3160–8;



The 3 main therapeutic pathways currently emphasized in the treatment of PAH.



Response of the RV

to Increased Afterload

Response of the RV to Increased Afterload

Important determinants

of the response of the RV to increased afterload.

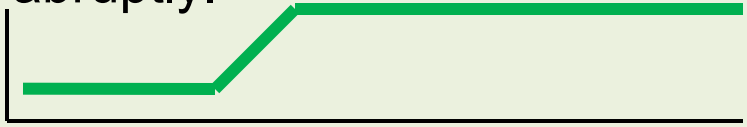
1. The contractile performance of the cardiomyocyte
2. The rate and magnitude of the increase in RV afterload
3. The time of onset of disease

The rate and magnitude of the increase in RV afterload

RV adaptation also depends on
the rapidity and magnitude at which the increase in afterload occurs.

1. If pulmonary hypertension develops abruptly.

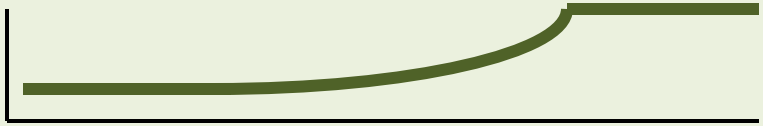
acute right-sided heart failure



thin RV cannot sustain sudden pressure loads over 40 to 50 mmHg.

2. If pulmonary hypertension develops slowly.

the RV hypertrophies



and it can tolerate mild PH without produce clinical problem.

(a compensatory increase in muscle mass)

The rate of the increase in RV afterload : abruptly

1. If pulmonary hypertension develops abruptly.

acute right-sided heart failure

thin RV cannot sustain sudden pressure loads over 40 to 50 mmHg.

RV pressure overload

increase in end-systolic volume / a decrease in ejection fraction

↓

Reduced cardiac output

↓

Systemic hypotension

↓

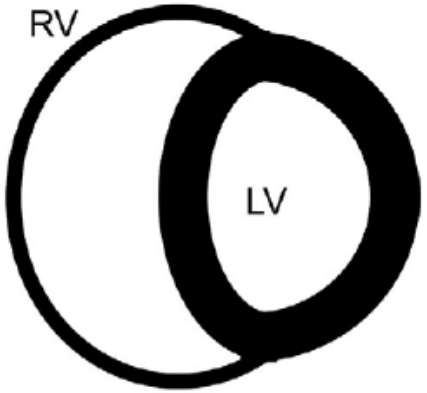
Reduced RV tissue perfusion

decreased ↓ RV coronary perfusion

RV free wall ischemia

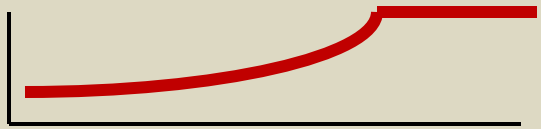
↓

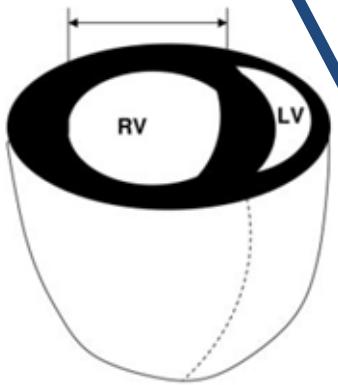
Reduced RV free wall contractility



The rate of the increase in RV afterload : slowly

2. If pulmonary hypertension develops slowly.
   the RV hypertrophies
   and it can tolerate mild PH without produce clinical problem





Left to right shunt

Increased pulmonary blood flow

Endotherial dysfunction
and vascular remodeling

Increase in PVR

RV hypertrophy

Pathophysiology of right ventricular failure. Clifford R. Greyson. Crit Care Med 2008 Vol. 36, No. 1 (Suppl.)

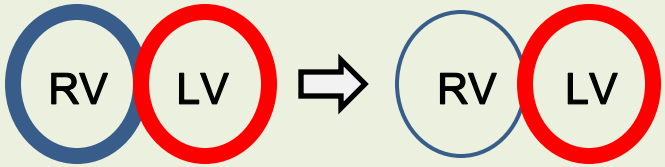
The time of onset of disease

The time of onset of disease is important.

At birth, the ventricles have similar muscle masses as the work required of the ventricles in utero is approximately equal.

After birth, PVR decreases

SVR increases



LV hypertrophic growth outpaces that for the RV.

If the RV is continuously exposed to systemic pressure, its growth and function parallel those for the LV.

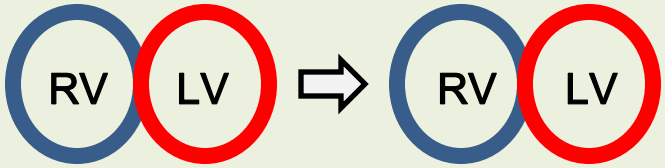
Pathophysiology of right ventricular failure.
Clifford R. Greyson, MD Crit Care Med 2008 Vol. 36, No. 1 (Suppl.) S57

The time of onset of disease

Patients with ES and a defect distal to the TV

1. Regression of RV wall thickness does not occur
   fetal morphology persists throughout infancy, adolescence, and adulthood.
2. RV and LV wall thickness are equal
   independent of age, defect type, PVR, magnitude of shunt flow.

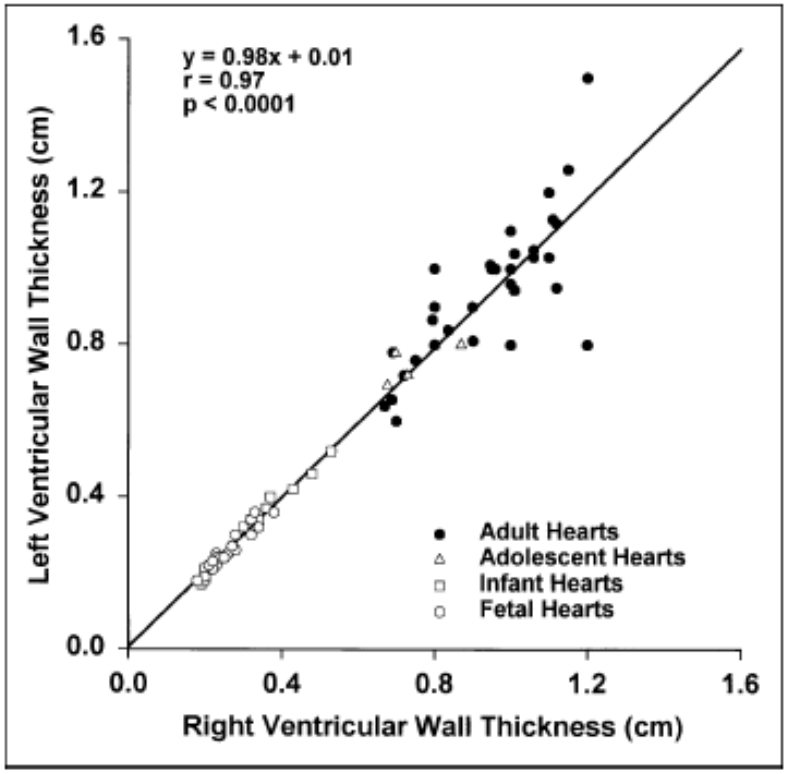
=> Preservation of biventricular function



Preservation of biventricular function
is likely the primary reason patients with ES fare so much better than other adults with severe pulmonary hypertension.

Severe PH without RV failure.

William E. Hopkins Am J Cardiol 2002;89:34-38



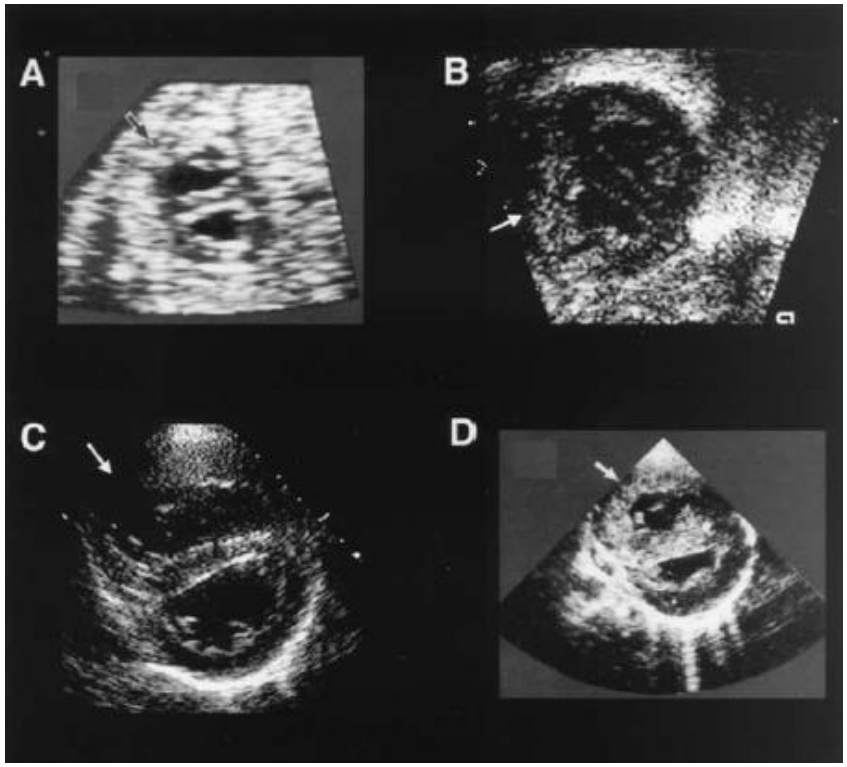
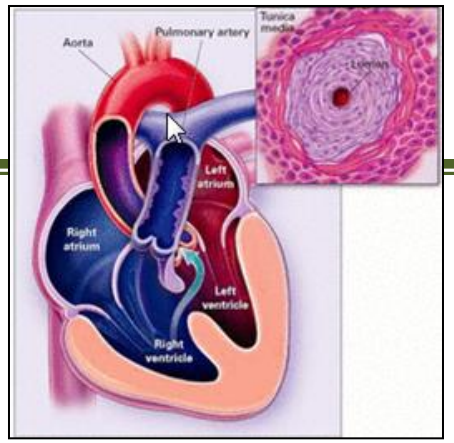


FIGURE 3. Wall thickness. Linear regression analysis of the relation between right and left ventricular wall thickness in fetuses with normal hearts, infants with nonrestrictive VSD and left-to-right shunt (pre-Eisenmenger phase), and adolescents and adults with nonrestrictive post-tricuspid defects and Eisenmenger syndrome.

Pathophysiology of Eisenmenger syndrome



- Left to right shunt
- Increased pulmonary blood flow
- Mechanical stretching in the pulmonary vasculature
- Endotherial dysfunction and Vascular remodeling
- Produces the progressive structural & histologic changes
- Increase in PVR
- RV hypertrophy
- Inverted shunt (Right to left)

Endotherial dysfunction and Vascular remodeling

- Increased expression of numerous mediators and receptors
- Increased expression of signaling molecules

1. Endothelin-1
2. NO
3. Prostacyclin
4. Thromboxan A2

PAH in CHD. John T. Granton. Cardiol Clin 20 (2002) 441–457

Risk factors for pulmonary hypertension in CHD

1. The size of the shunt and subsequent blood flow
   - Small-to-moderate size VSD : only 3%
   - Larger size VSD (greater than 1.5 cm in diameter) : 50%
2. The type of defect
   - Nearly all patients with Truncus arteriosus
   - Approximately 50% of patients with large VSD
   - Only 10% of patients with ASD
3. Particularly in the presence of trisomy 21.

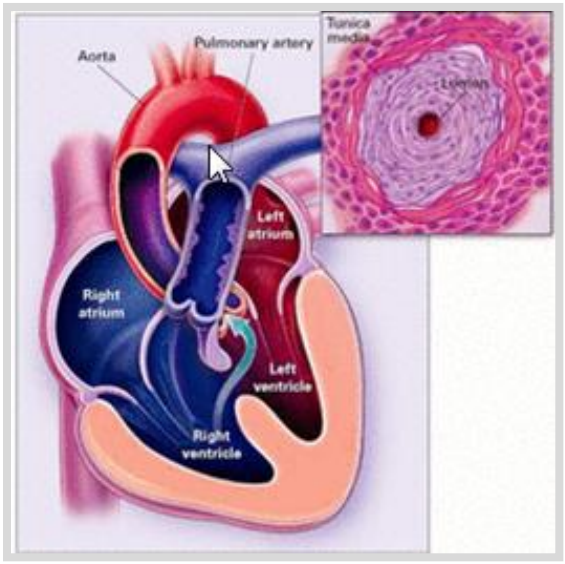
Comparison of the hemodynamics and survival of adult with severe primary pulmonary hypertension or Eisenmenger syndrome

Hopkins WE - J Heart Lung Transplant - 01-JAN-1996; 15(1 Pt 1): 100-5

survival	at 1 year	at 2 years	at 3 years
Eisenmenger Syndrome	97%	89%	77%
Primary PH	77%	69%	35%

1. The progression of the pulmonary vasculopathy is slower .
   Preservation of RV wall thickness
   prevented progressive RV failure in the face of high PA pressures.

2. The second protective mechanism may be the defect itself.
   Unloads RV, and preserves LV cardiac output.
   This effect may be particularly important during exercise to protect RV from a sudden increase in pulmonary vascular pressure that would be expected to occur with an increase in blood flow.



Evaluation of

Eisenmenger Syndrome

Evaluation of Eisenmenger Syndrome

1. History taking and Symptoms
2. Physical examinations
3. Chest X-ray
4. ECG
5. Echocardiography
6. Cardiac catheterization
7. Lung biopsy

The symptoms associated with PAH and ES

Clinical presentations in PAH	Clinical presentations in ES
1. Dyspnea (with exertion)	1. Hemoptysis
2. Fatigue	2. CVA
3. Syncope	3. Hemorrhage
4. Chest pain	4. Brain abscesses
5. Near syncope	5. Secondary erythrocytosis
6. Palpitations	6. Coagulation abnormalities
7. Leg edema	7. Cardiac arrhythmia

Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107(2):216–23.

Physical examination

1. Cyanosis with or without clubbing
2. Distended neck vein
3. A single S2, or it splits narrowly. Loud P2
4. A diastolic murmur of PR
5. A holosystolic murmur of TR
6. Signs of right-sided heart failure: hepatomegaly, ankle edema
7. Arrhythmia

Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107(2):216–23.

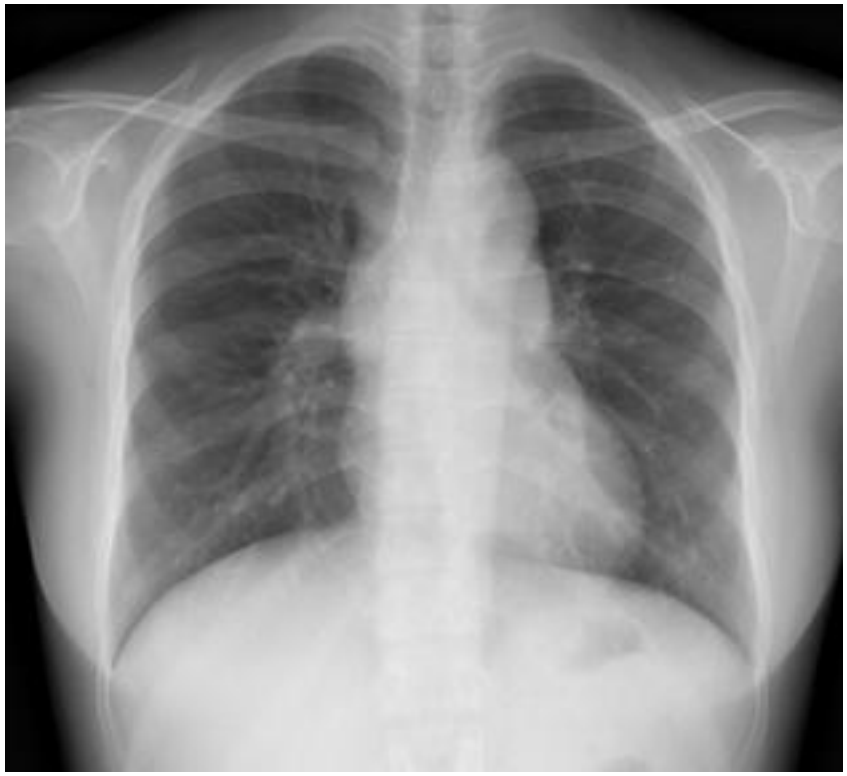
WHO PH functional assessment classification

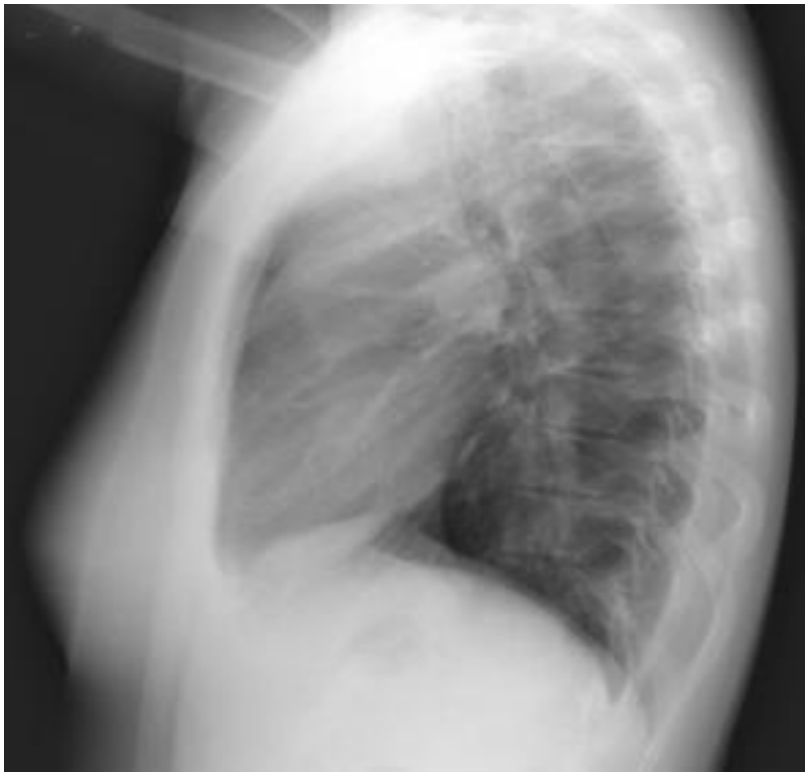
Class I	Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Slight limitation of physical activity; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Marked limitation of physical activity; comfortable at rest, but less-than-ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope; signs of right-sided heart failure may be present.
Class IV	Inability to carry out any physical activity without symptoms; dyspnea and/or fatigue may even be present at rest; discomfort is increased by any physical activity; signs of right-sided heart failure are usually present.

The 2nd World Symposium on PH. 1998 Evian, France

Chest radiography

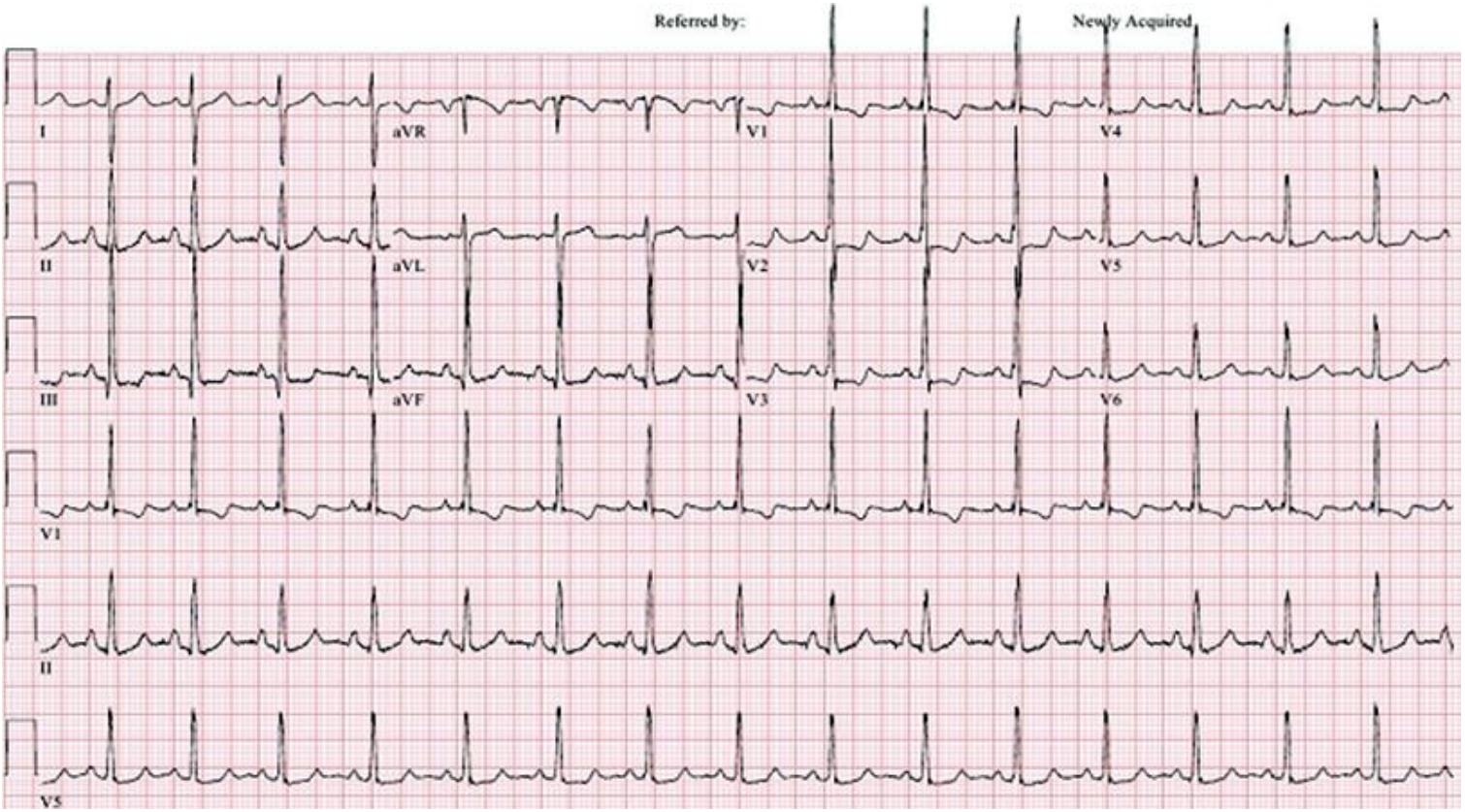
1. Peripheral hypovascularity : attenuated peripheral vascular markings
2. Enlarged main and hilar pulmonary artery shadows
3. RV enlargement :
   obscuration of the retrosternal clear space on a lateral view



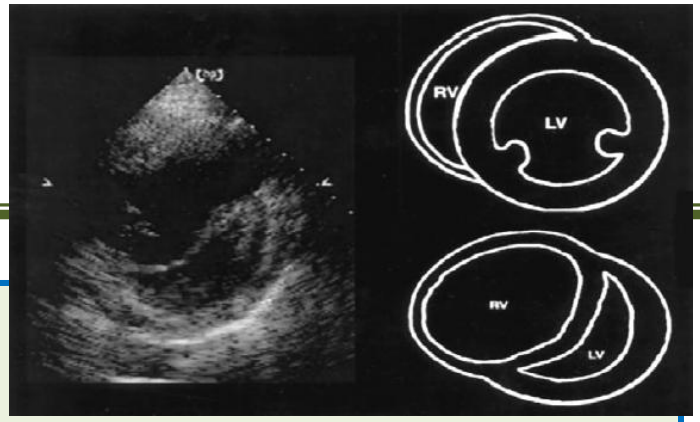


Electrocardiography

Right ventricular hypertrophy
Right-axis deviation
The absence of these findings does not exclude PAH



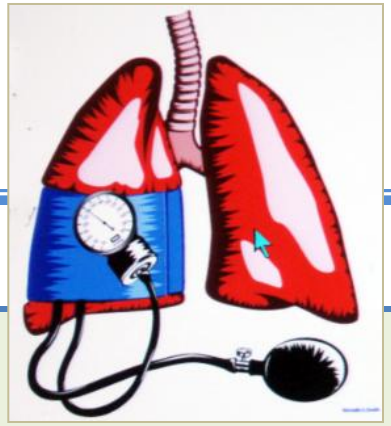
Echocardiography



1. To evaluate cardiac anatomy
2. The estimation of PA pressure :
   is based on the peak velocity of the jet of TR.
3. Other echocardiographic variables
   that might reinforce suspicion of PH include
   1) an increased velocity of PR
   2) short acceleration time of RV ejection into the PA
   3) increased dimensions of RV and RA
   4) abnormal shape and function of the interventricular septum
   5) increased RV wall thickness
   6) dilatation of the MPA

Echocardiographic Indexes for the Non-Invasive Evaluation of Pulmonary Hemodynamics. Alberto Milan, Journal of the American Society of Echocardiography Volume 23 Number 3 2010

Systolic Pulmonary Artery Pressure.



sPAP = RV systolic pressure

in the absence of PV stenosis or outflow tract obstruction.

RV systolic pressure

= RA pressure (RAP) + pressure gradient between RV & RA.

= RAP + $4(TRv)^2$

The modified Bernoulli equation: $\Delta P = 4 \times V^2$

V is the tricuspid regurgitant velocity (TRv).

Echocardiographic Indexes for the Non-Invasive Evaluation of Pulmonary Hemodynamics. Alberto Milan, J Am Soc Echocardiogr 2010;23:225-39

Underestimation or overestimation of the systolic PA pressure

In a recent study, in 48% of 63 patients studied,

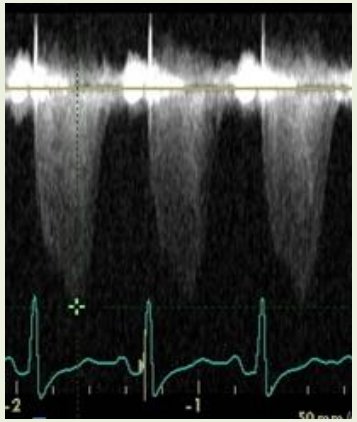
echocardiography-derived sPAP

differed more than 10 mmHg from invasively measured sPAP;

underestimation or overestimation.

due to such factors

1. Inaccuracy of predicted RAP
2. Inaccuracy of angle of interrogation
3. Incomplete signal envelope of regurgitant flow



To minimize error

1. TRv should be measured in multiple views: seeking the maximal TRv.
2. The use of color flow Doppler : to obtain the best alignment

Cardiac catheterization

Right-heart catheterization is the standard for PAH diagnosis.

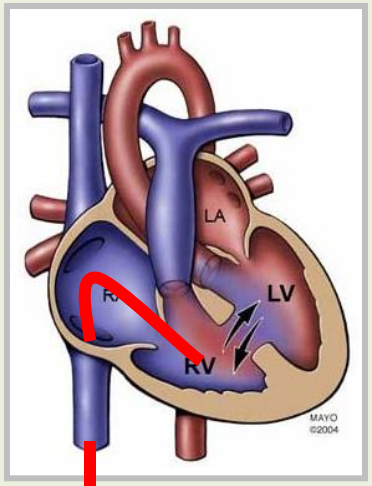
1. Hemodynamic measurements

    Oxygen saturation(IVC, SVC, RV, PA)

    Pressure (RA, RV, PA, PCWP)

    Cardiac output/ index

    Pulmonary vascular resistance



2. Vasodilator testing should be done in all cases of PAH.

3. Angiography:

    to avoid precipitating a pulmonary hypertensive crisis

In pediatric patients, two studies have found that major complications including arrhythmia, pulmonary hypertensive crisis, and cardiac arrest were 5% and 6%. Mary P. Mullen, MD, Pediatr Crit Care Med 2010 Vol. 11, No. 2

Cardiac catheterization : Pulmonary vascular resistance

Pulmonary vascular resistance (PVR)

= (mean PA pressure - mean LA pressure) / pulmonary blood flow (Qp)

Patients were inoperable

if the PVR calculation exceeded 8 Wood's Units,

particularly if resistance did not fall with oxygen administration or

if the PVR/SVR ratio was greater than 0.5.

Cardiac catheterization : Vasodilator testing

Pulmonary vasoreactivity test :

iNO, iv Epoprostenol, iv Adenosine, Oxygen,

Epoprostenol: 2-12 ng/kg per min.

iNO: 20-40 ppm for 5 min.

iv Adenosine: 50-350 ug/kg/minute

A positive response to the vasodilator test

decrease ≥ 10 mmHg in the mean PAP

a mean PAP ≤ 40mmHg

an unchanged or increased cardiac output

Medical Therapy for Pediatric Pulmonary Arterial Hypertension.
Cecile Tissot, MD Vol. THE JOURNAL OF PEDIATRICS 157, No. 4 October 2010

The 6-minute walk test (6 MWT)

The 6-MWT is technically simple, inexpensive, reproducible.

The best test to classify the severity of PAH and estimate prognosis.

Correlates well with cardiopulmonary exercise testing (CPET) measures and should be used to assess exercise capacity at diagnosis as well as serially with treatment of the patient who has PAH.

Diagnosis of Pulmonary Arterial Hypertension. Terence K. Trow. Clin Chest Med 28 (2007) 59–73

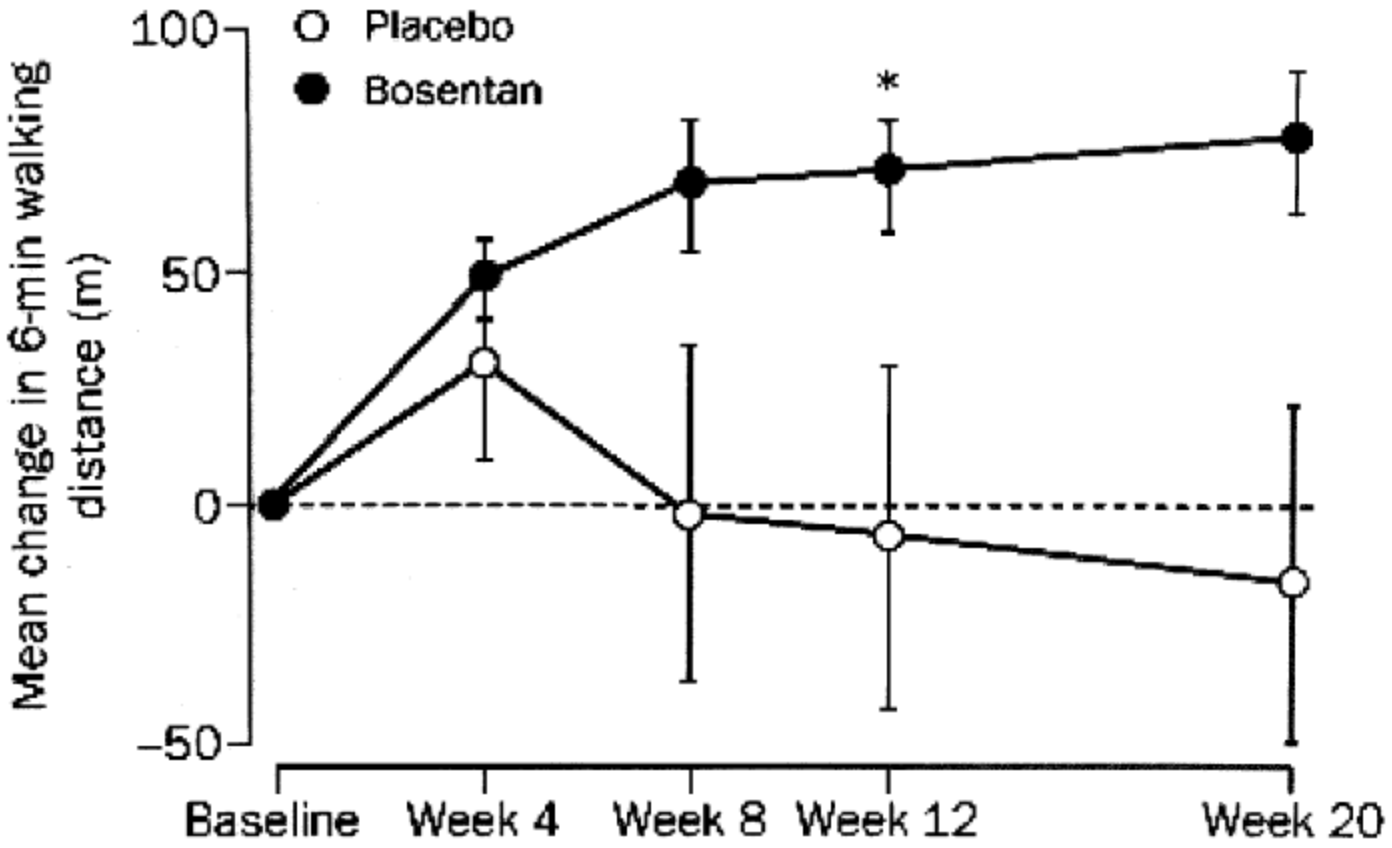


Fig. 6. Bosentan Trial: change in 6-minute walking distance from baseline to week 20.

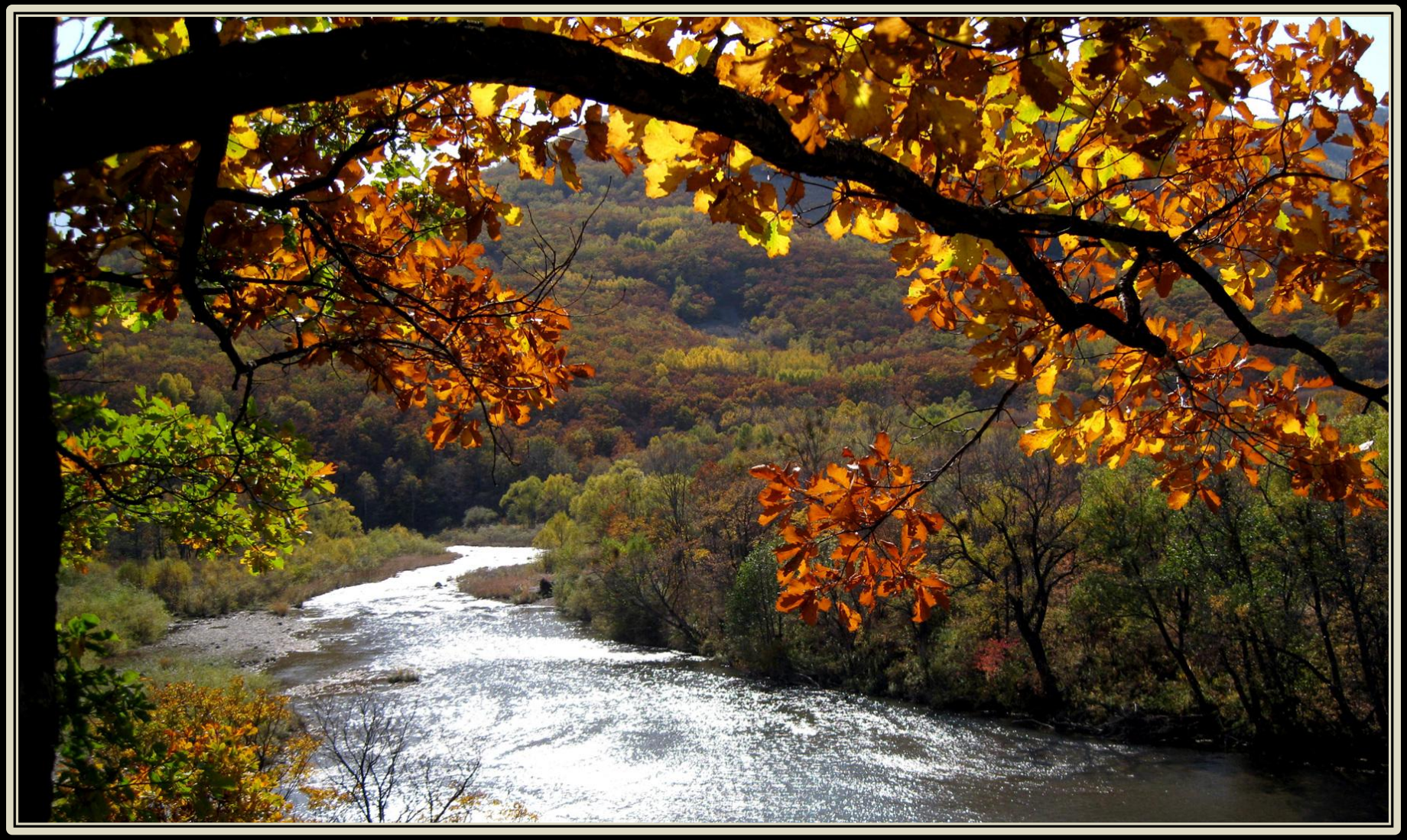
Channick RN, SimonneauG, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosental in patients with pulmonary hypertension: a randomized placebo controlled study. Lancet 001;358:1119–23

Considerations before Initiating Therapy in ES

Evaluation of severity

1. Clinical (WHO-FC)
2. Echocardiographic parameters
3. Hemodynamic parameters on right heart catheterization
4. Exercise capacity (6MWT, cardiopulmonary exercise test)
5. Biochemical markers(NT-pro BNP)

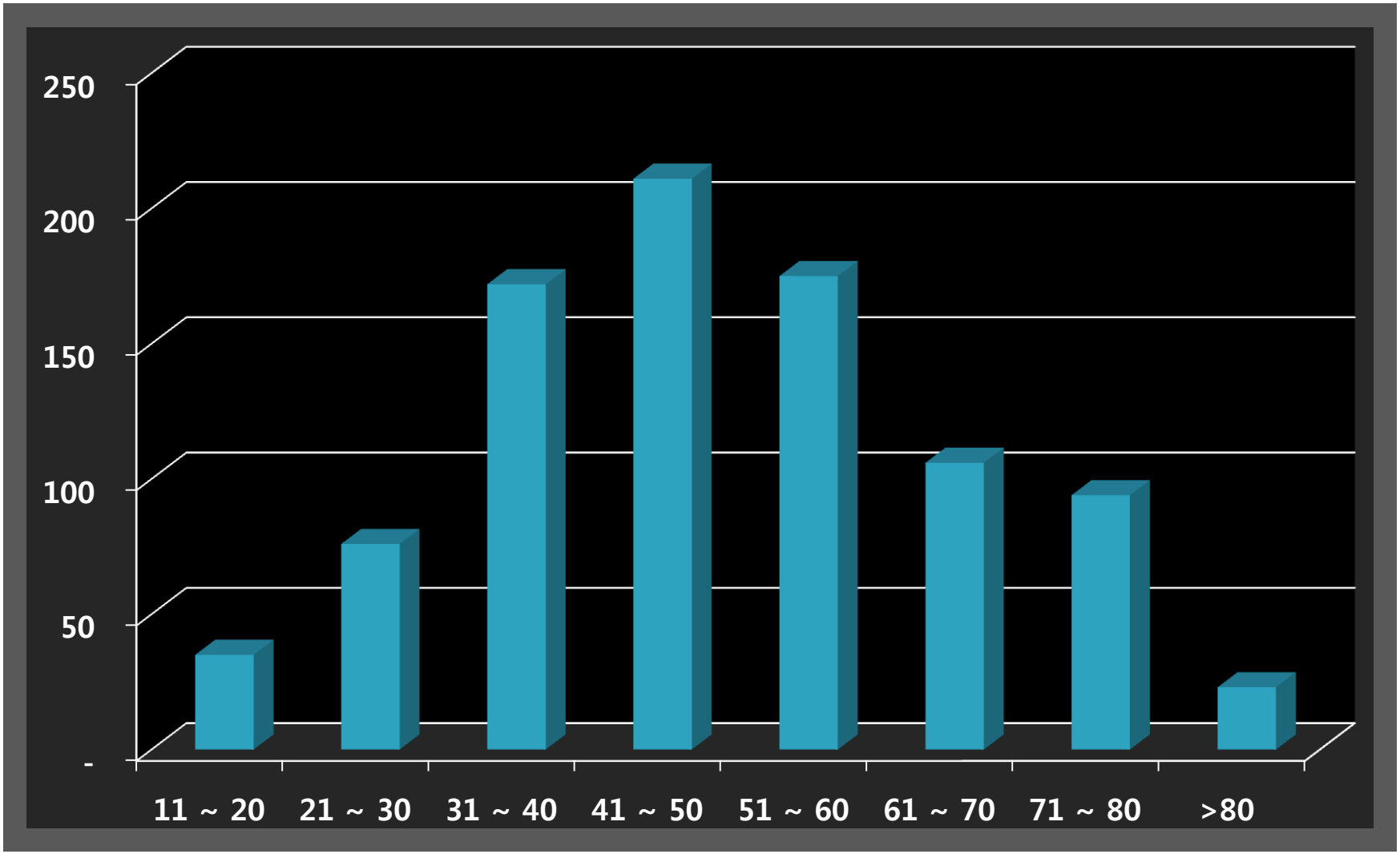
6. Lung biopsy
   is not recommended because it has considerable risks
   a very low likelihood of altering the diagnosis or treatment.



Autumn 2010

Korean PAH Registry of PHT (2011)

Age distribution



Korean PAH Registry of PHT (2011)

Diagnostic Classification

	CHD	CTD	Familial	IPAH	others	Total
Cardio	102	54	2	55	19	232
Ped cardio	134			34	8	176
Pulmo	7	41	13	136	3	200
Rheuma		405			1	406
Total	243	500	15	225	31	1014

Classification and epidemiology of pulmonary hypertension

Vallerie V. McLaughlin, MD

Pulmonary Hypertension Program, Division of Cardiovascular Medicine, University of Michigan, Woman's RM. L3119, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0273, USA

1. The first World symposium on PH in Geneva, Switzerland, in 1973
2. The second World symposium on PH in Evian, France, in 1998.
3. The Third World Symposium on PAH in Venice, Italy, in 2003.
4. The 4th World Symposium on PH in Dana Point, California, in 2008.

ESC/ERS guidelines: arbitrary criteria for estimating the presence of PH based on TR peak velocity and Doppler-calculated systolic PA pressure (Ppa) at rest (assuming a normal RA pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH.

1. Echocardiographic diagnosis: PH unlikely
   TR velocity < 2.8 m/s, systolic Ppa <36 mmHg
   and no additional echocardiographic variables suggestive of PH

2. Echocardiographic diagnosis: PH possible
   TR velocity < 2.8 m/s, systolic Ppa < 36 mmHg,
   but presence of additional echocardiographic variables suggestive of PH
   TR velocity 2.9–3.4 m/s, systolic Ppa 37–50 mmHg
   with/without additional echocardiographic variables suggestive of PH

3. Echocardiographic diagnosis: PH likely
   TR velocity > 3.4 m/s, systolic Ppa > 50 mmHg,
   with/without additional echocardiographic variables suggestive of PH.

Evaluation of various empirical formulars for estimating mean PA pressure using systolic PA pressure in adult.

Chemla D - Chest - 01-MAR-2009; 135(3): 760-8

		Equations
Two-pressure model	F1	dPAP + 0.33 pPAP
	F2	dPAP + 0.41 pPAP
	F3	Square root (sPAP × dPAP)
Single pressure model	F4	0.61 sPAP + 2 mmHg
	F5	2/3 sPAP

The most accurate formula was F4 (mean bias, 0.0 mm Hg).
sPAP > 36 mm Hg could be used to diagnose PH (mPAP > 25 mm Hg) with a 97.9% sensitivity and 98.6% specificity.

Echocardiographic Determination of Mean Pulmonary Artery Pressure

Amr E. Abbas, MD, F. David Fortuin, MD, Nelson B. Schiller, MD,
Christopher P. Appleton, MD, Carlos A. Moreno, BS, and Steven J. Lester, MD

We performed a simultaneous Doppler and invasive study to validate the role of Doppler-derived peak pulmonary regurgitant velocity as a reliable non-invasive measure of pulmonary artery mean pressure. Assessment of right atrial pressure, as shown in this study, enhances the use of this Doppler parameter as a correlate of pulmonary artery mean pressure.
(Am J Cardiol 2003;92:1373–1376)

$$mPAP = 4PRv^2 + RAP$$

Noninvasive Estimation of PVR by Doppler Echocardiography in Patients With PAH.

Hidemichi Kouzu, et al. Am J Cardiol 2009;103:872– 876

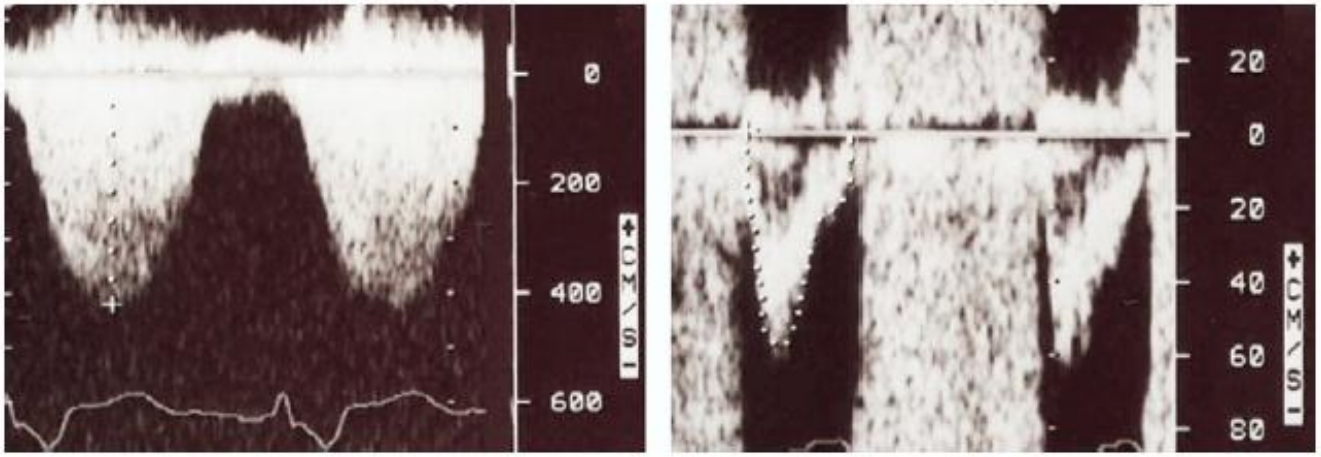


Figure 1. Images showing TRPG (left) and TVI of the RVOT (right) in a patient with idiopathic PAH (TRPG 74.4 mm Hg, TVI 8.6 cm, TRPG 74.4/TVI 8.6= 8.7). This patient's invasive PVR was 1,426 dyne s cm^{-5}.

In conclusion,

TRPG/TVI provides a reliable estimation of PVR

over a wide range in patients with PAH with various underlying causes.

A TRPG/TVI >7.6 showed 85% sensitivity and 92% specificity

for identifying patients in the poor-prognosis group.

The Pathology of the pulmonary vasculature

Pathologic change

systemic-to-pulmonary arterial communication

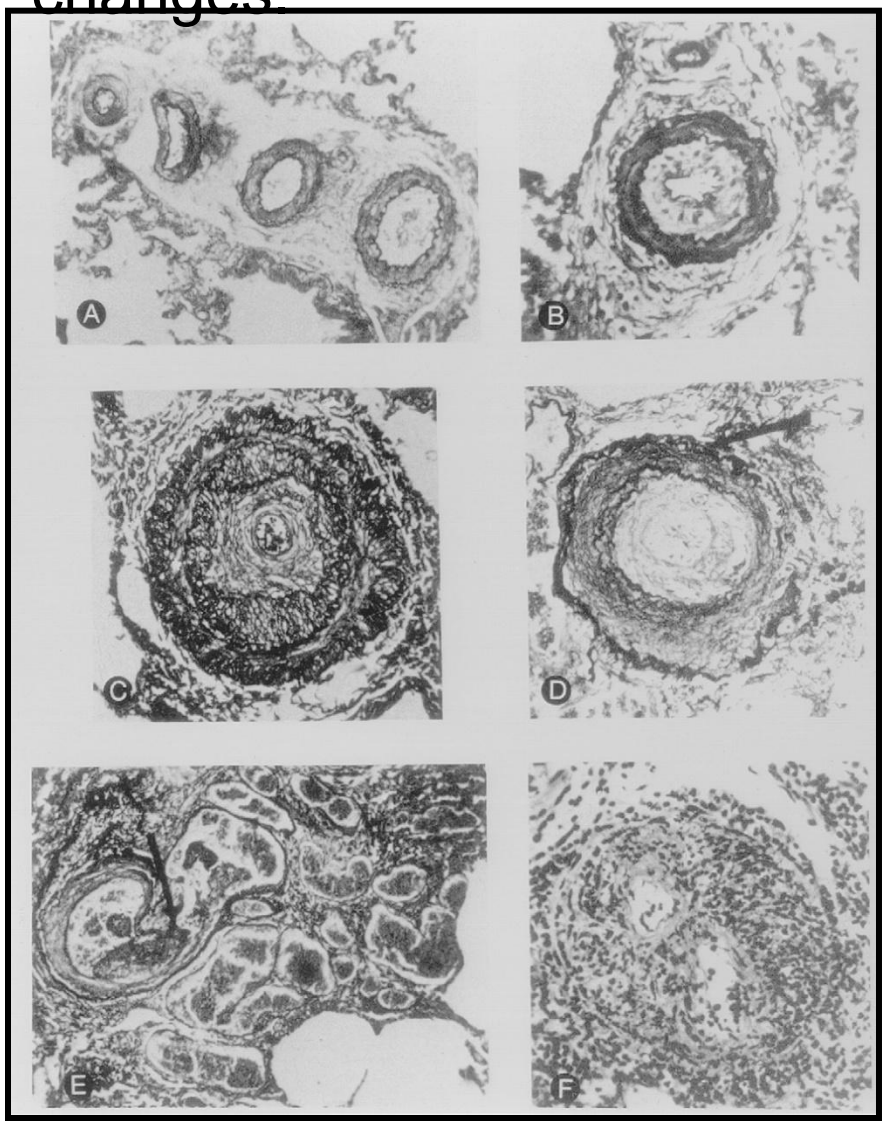
→ an increase in blood flow to the pulmonary circulation

→ mechanical stretching in the pulmonary vasculature

→ produces the progressive structural and histologic changes

1. An extension of muscle into peripheral, normally nonmuscular arteries.
2. Medial hypertrophy of normally muscular arteries occurs.
3. Reduction in arterial concentration due to impaired growth of arterioles.
4. Dilation complexes, plexogenic lesions, fibrinoid necrosis

Heath Edwards classification of pulmonary vascular changes.



1. Grade I: medial hypertrophy.
2. Grade II: cellular intimal proliferation
3. Grade III: occlusive changes.
4. Grade IV: dilatation
5. Grade V: plexiform lesion.
6. Grade VI: acute necrotizing arteritis

Histologic Correlates

The Heath-Edwards classification
is less useful to characterize the earliest changes
frequently seen in infants and children undergoing cardiac surgery.

A morphometric approach was studied by
Rabinovitch et al, Haworth, and Haworth and Hislop.
The morphometric approach quantifies and grades from A to C
the degree of abnormal distal extension of smooth muscle,
the thickness of the medial hypertrophy,
the density of small PAs relative to the number of alveoli.

The results of the morphometric analysis of lung biopsy specimens may be predictive of late outcome,
but lung biopsy is used rarely in the routine assessment of operability.

A morphometric approach was studied by Rabinovitch

Grade		Structural finding	Hemodynamic finding
A		Extension of muscle into peripheral arteries normally non muscular. Associated with a mild increase in the medial wall thickness of the normally muscular arteries(<1.5 times normal)	Increased PBF Normal or minimal increased in mPAP Normal PVR
B		Extension as in Grade A but greater medial hypertrophy	
	mild	1.5 < medial wall thickness < 2	
	severe	2 < medial wall thickness	Increased PBF Increased in mPAP Normal PVR
C		Future of B(severe) with a decrease number of peripheral arteries relative to alveoli and usually decreased arterial size	Increased PBF Increased in mPAP increased PVR
	mild	more than half the normal number of arteries	3.5 Um^2<PVR< 6 Um^2
	severe	Less than half the normal number of arteries	6 Um^2< PVR

The morphometric grading system evloved from correlation with preoperative pulmonary hemodynamic findings.

The Physiologic change of Pregnancy in Patients with PH

When it is complicated by pregnancy,
it is associated with increased mortality, (mortality as high as 60%)

	Cardiac output(CO) increases by 50% from baseline.
During pregnancy	1. Blood volume increases in the early stages, 2. A reduction in afterload secondary to decreased PVR. 3. Later in pregnancy, CO is augmented by an increase in HR.
During delivery	With every uterine contraction, approximately 500 mL of blood is diverted from the uterine to the maternal circulation, with a resultant increase in CO and BP.
After delivery	1. Significant autotransfusion from the uterine circulation. 2. Increase in venous return from the relief of vena caval obstruction by the gravid uterus. 3. With concomitant fluid shifts into the intravascular space,
In addition	Pregnancy is associated with a hypercoagulable state.

C. Randall LaneClin Chest Med 32 (2011) 165–174

ESC/ERS guidelines: hemodynamic definition of PH

Definition	Characteristics	Clinical group(s)
PH	Ppa ≥ 25 mmHg	
Pre-capillary PH	Ppa ≥ 25 mmHg Ppcw ≤ 15 mmHg CO normal or reduced	1. Pulmonary arterial hypertension 2. PH due to lung disease 3. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanism
Post-capillary PH	Ppa ≥ 25 mmHg Ppcw > 15 mmHg CO normal or reduced	2. PH due to left heart disease

TABLE 4 ESC/ERS guidelines: important definitions

PH is a haemodynamic and pathophysiological condition defined as an increase in $\bar{P}_{pa}$ $\geqslant$25 mmHg at rest as assessed by right heart catheterisation (table 3). PH can be found in multiple clinical conditions (table 5).

The definition of PH on exercise as a $\bar{P}_{pa}$ >30 mmHg as assessed by right heart catheterisation is not supported by published data.

The definition of PH on exercise as a Ppa > 30 mmHg

is not supported by published data and

healthy individuals can reach much higher values.

Thus no definition for PH on exercise as assessed by RHC can be provided at the present time.

The Global Perspective Congenital Heart Disease : Pulmonary Vascular Disease: The Global Perspective. Ian Adatia Chest 2010;137;52S-61S

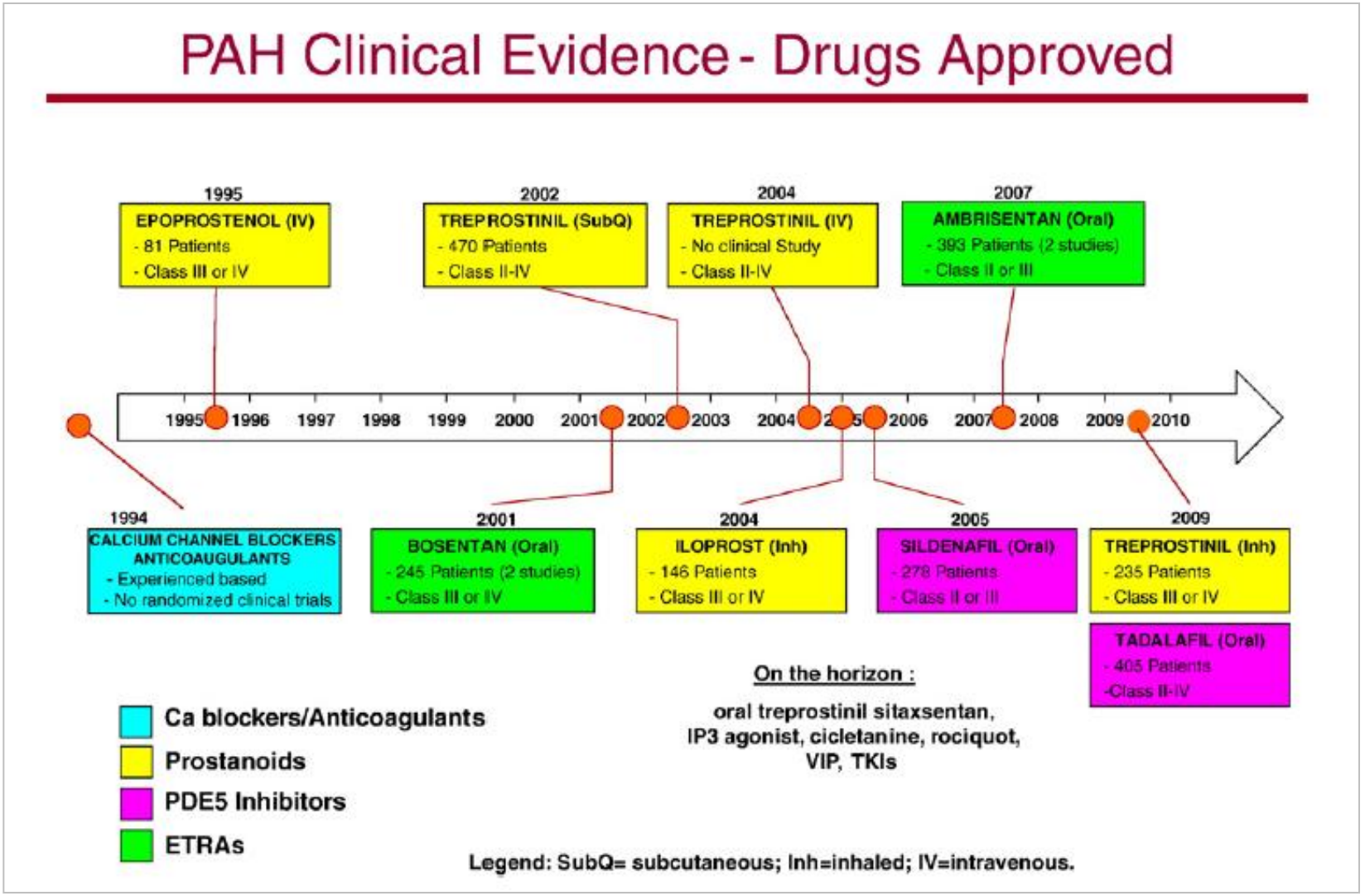


Figure: The timeline of drug approval in PAH is shown here, highlighting the advances in targeted drug therapy since the mid 1990s.
VIP indicates vasoactive intestinal peptide; TKIs, tyrosine kinase inhibitors

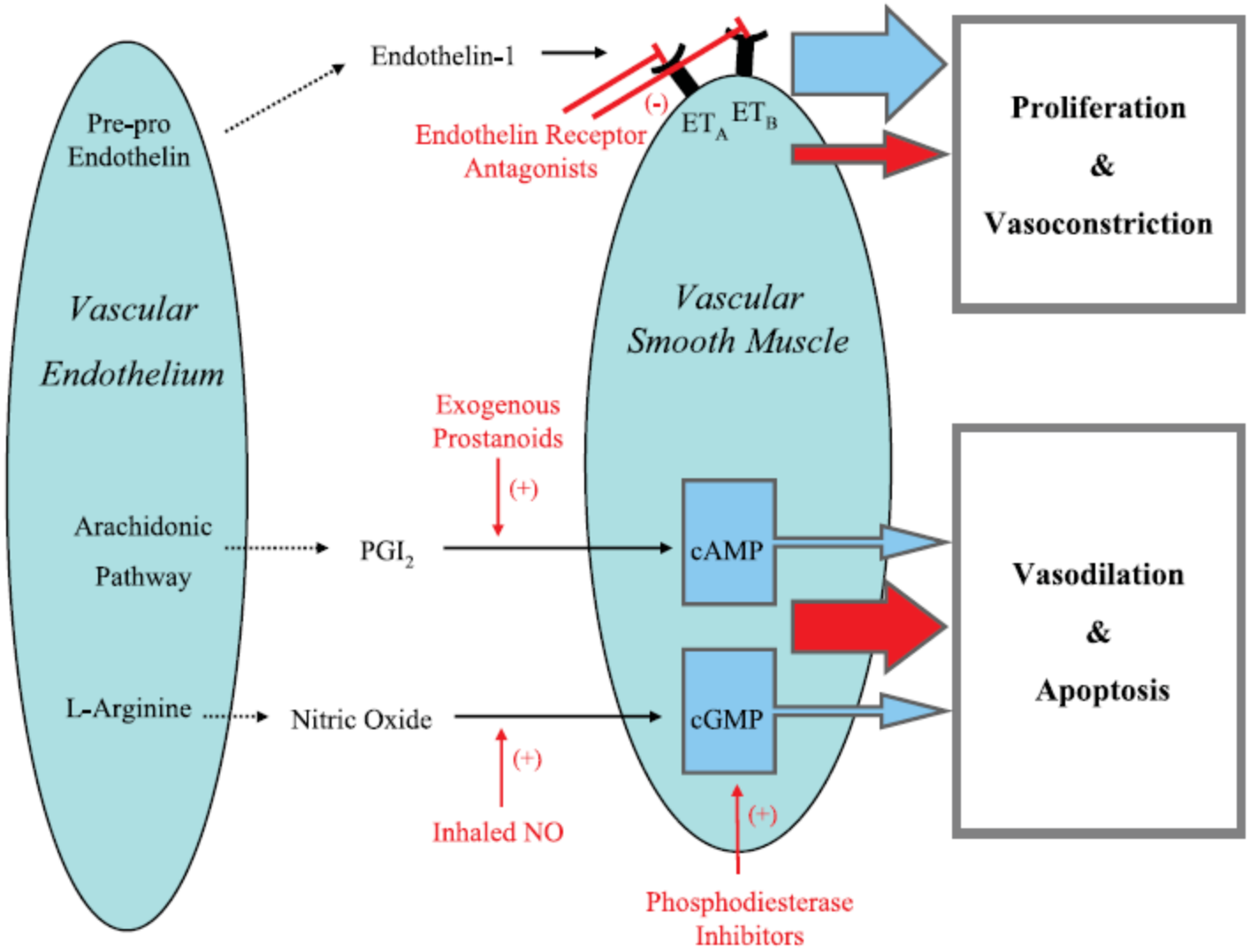


Figure 1. Schematic representation of pathways implicated in pulmonary arterial hypertension, and sites of action of current therapies.

Crit Care Med 2007 Vol. 35, No. 9

Repair of previously inoperable patients who respond to advanced therapy

For	Against
1. Abort R-L shunt	1. Potential conversion of ES to IPHA (and thus worse long-term outcome)
2. Eliminate cerebrovascular event	2. High perioperative risk
3. Prevent cyanosis Increase Exercise capacity Decrease erythrocytosis Decrease hemostatic problem Decrease systemic organ failure	3. Limited experience and no long term data
4. Protective pulmonary circulation	

Prognostic Factors in PAH

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)[a]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[b] >2.0 cm	Echocardiographic findings[b]	Pericardial effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI ≥2.5 L/min/m^2	Haemodynamics	RAP >15 mmHg or CI ≤2.0 L/min/m^2