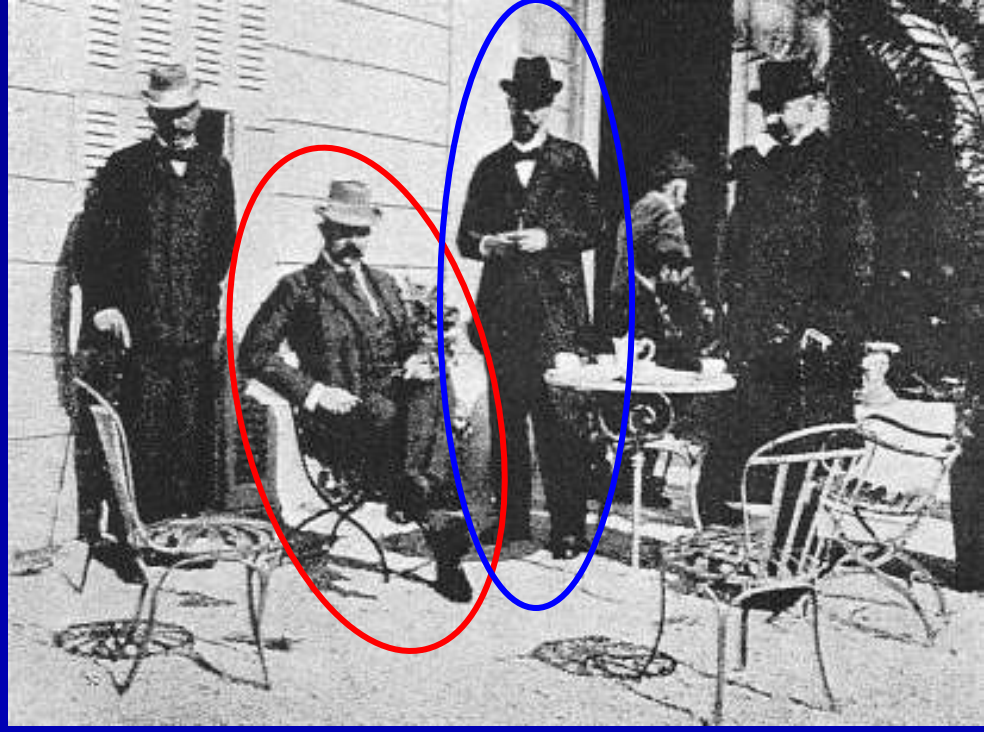
Victor Eisenmenger*

Left to right: Baron Bronn, Archduke Francis Ferdinand, Victor Eisenmenger, Count Cavriani*



Eisenmenger's Syndrome

May 20, 2005

Joe M. Moody, Jr, MD

UTHSCSA and STVAHCS

*Partin C. Am J Cardiol. 2003:92:1187.

Recommended References

- Perloff, JK. Clinical Recognition of Congenital Heart Disease. 5th ed. 2003, Ch 17.
- Mavroudis C et al. Pediatric Cardiac Surgery. 3rd ed. 2003.
- Allen HD et al. Moss and Adams' Heart Disease in Infants, Children, and Adolescents. 6th ed. 2001.
- Braunwald E et al. Heart Disease; a Textbook of Cardiovascular Medicine. 7th ed. 2005.

Eisenmenger's Terminology

- Eisenmenger's Physiology: situation with any shunt usually L to R reversing because of elevated PVR
- Eisenmenger's complex or Eisenmenger's Syndrome: same but only in VSD

Findings in Eisenmenger's Physiology

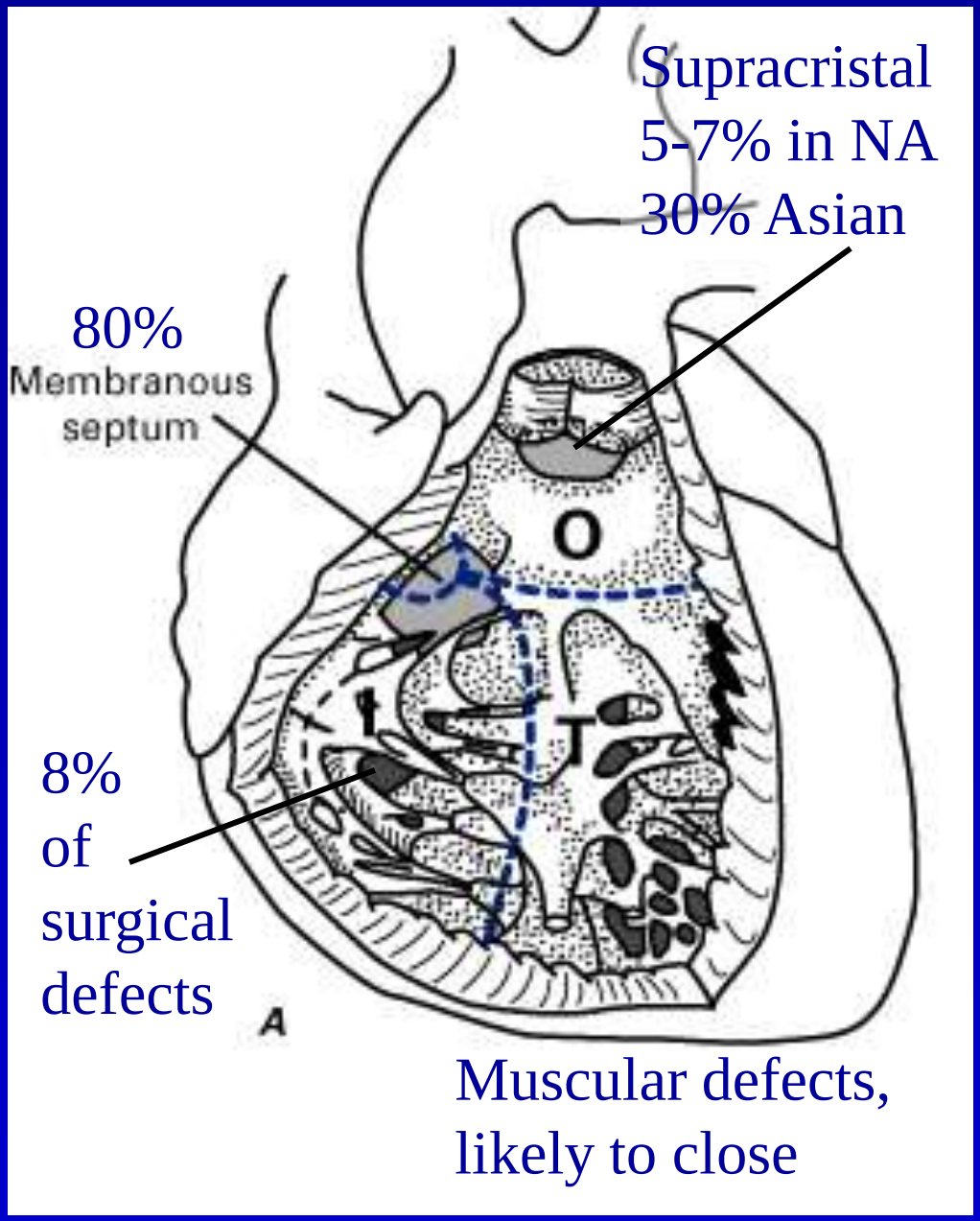
- Examination: Signs of elevated PA pressure; no shunt murmur, only potential valvular regurgitation murmurs
- ECG: RVH
- CXR: Maybe small heart and black lungs
- Echo: Severe RVH, shunt location more by echo than Doppler, since shunt jets are low velocity

Ventricular Septal Defect

- Most common congenital malformation of the heart or circulation except bicuspid aortic valve, 20% of cases of congenital heart disease
- Restrictive defects often close (50-75%)
  - Many before age 1
  - 60% before age 3
  - 90% before age 8
  - Reported as late as age 46

p. 311, Perloff, JK. Clinical Recognition of Congenital Heart Disease. 5th ed. 2003

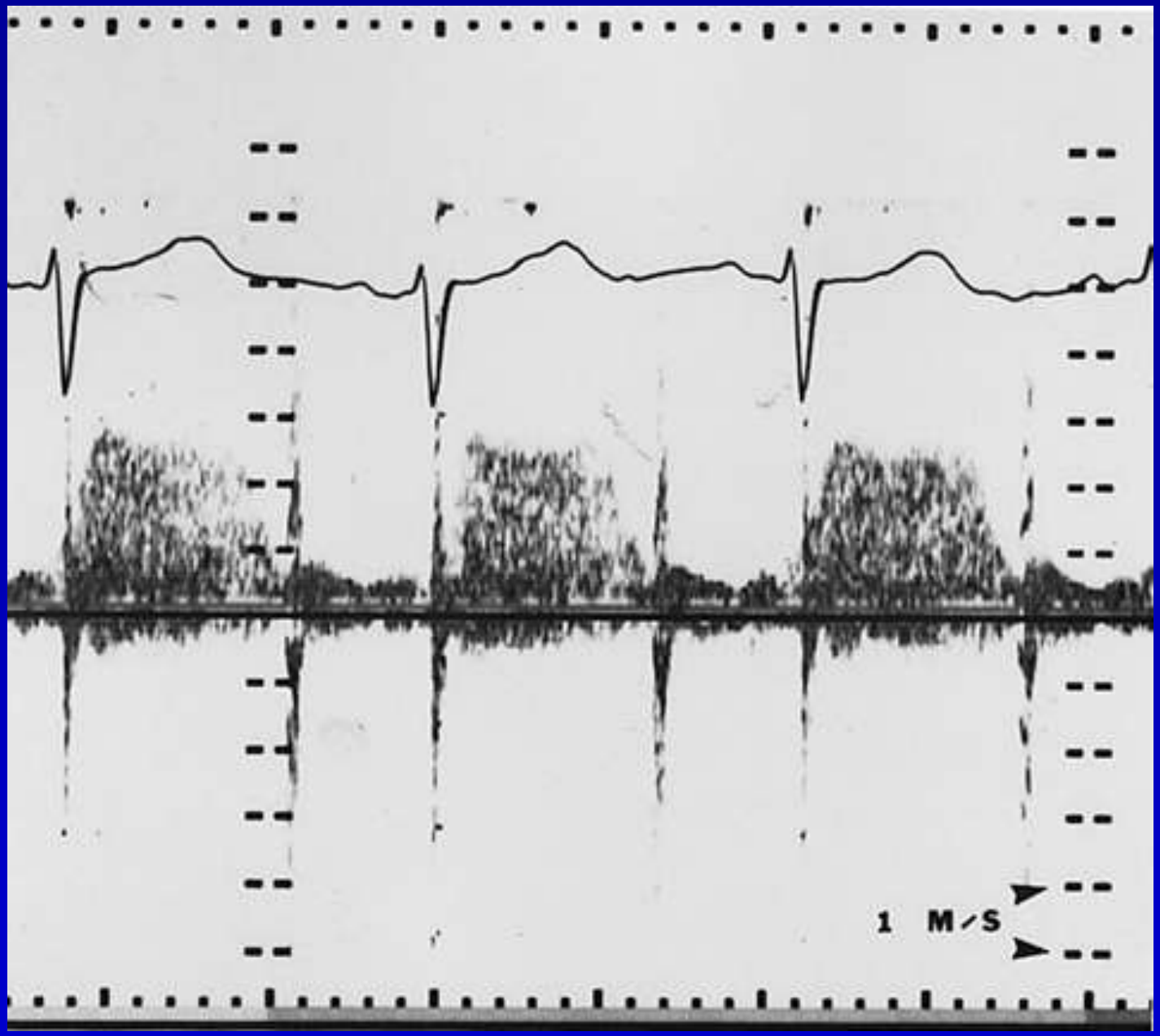
VSD Classification



- Restrictive: defect is small, restricting flow, so normal RV pressure and PAR
- Moderately restrictive: mildly elevated RV pressure and low or variable PAR
- Nonrestrictive: RV pressure = LV pressure and elevated and variable but subsystemic PAR
- Eisenmenger syndrome: nonrestrictive defect with RV pressure = LV and suprasystemic PAR

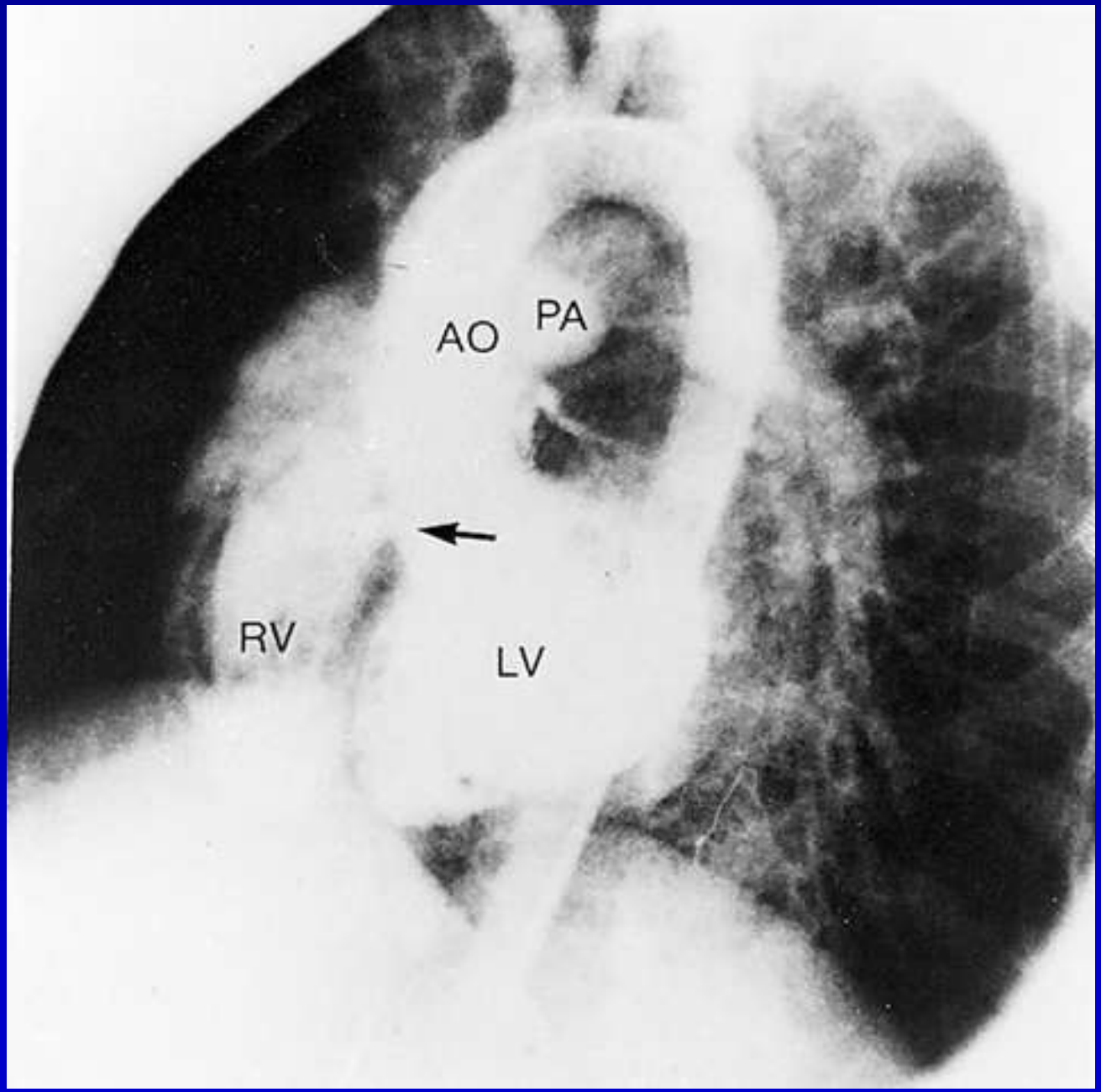
From Hurst, 1999, Ch 70; Perloff p.312-15

CW Doppler, VSD



From Hurst, 1999, Ch 70

LV angiogram
LAO projection
VSD



From Hurst, 1999, Ch 70

History of Eisenmenger's Syndrome

- Eisenmenger, Victor. "Congenital Defects of the ventricular septum" Z. Klin. Med. 1897;32(Suppl):1
- 1932 Maude Abbott referred to VSD and elevated PVR and R to L shunt as "Eisenmenger's Complex"
- Wood, Paul. "The Eisenmenger syndrome, or pulmonary hypertension with reversed central shunt." Br Med J 1958;2:701, 755

p. 318, Perloff, JK. Clinical Recognition of Congenital Heart Disease. 5th ed. 2003

History of Eisenmenger's Syndrome

- "The patient was a powerfully built man of 32 who gave a history of cyanosis and moderate breathlessness since infancy. He managed well enough, until January, 1894 when dyspnea increased and edema set in. Seven months later (August) he was admitted to hospital in a state of heart failure. He improved with rest and digitalis, but collapsed and died more or less suddenly on November 13 following a large hemoptysis. At necropsy, a 2- to 2.5-cm defect was found in the perimembranous septum."

Wood, P. Br Med J 1958;2:701, 755

Eisenmenger's Syndrome

- VSD and Cyanosis – typical of cyanosis as a multisystemic disorder
- RBC mass and hemostasis
- CNS
- Bilirubin kinetics
- Systemic vascular bed
- Coronary circulation
- Myocardium
- Uric acid metabolism and clearance
- Kidneys
- Respiration
- Digits and long bones
- Gynecologic endocrinology

- Management of these influences morbidity and mortality
- Longevity is 10-20 years longer now than in early reports
- RV failure is uncommon unless systemic hypertension

p. 319, Perloff, JK. Clinical Recognition of Congenital Heart Disease. 5th ed. 2003

Risks for Pulmonary Hypertension in Congenital Heart Disease

- Large shunts more than small shunts
- VSD more than ASD, and Truncus also high
- In ASD, sinus venosus more than secundum
- Mortality less than PPH (3 year survival 77% vs 35%) maybe due to thicker RV wall in ES* and maybe due to pop-off valve in ES (PPH with PFO fares better than without, and atrial septostomy is helpful)
- Mortality worse with young age at dx, RVH by ECG, SV arrhythmias and poor functional class (also syncope, surgery, trisomy 21, hemoptysis, elevated RA pressure, lower SAO2, pregnancy)
- Cause of death: SCD (arrhythmia likely), hemoptysis and pulmonary hemorrhage, pregnancy complications, stroke, brain abscess

Granton JT et al. Cardiol Clinics 2002;20:441
*Hopkins WE et al. Am J Cardiol. 2002;89:34

Pulmonary Artery Problems

- Endothelial dysfunction: endothelial contour is abnormal, increased intracellular microfilament bundles; endothelial abnormalities may contribute to VSM cell proliferation and ECM changes
- Vasomotor tone: elevated thromboxane and endothelin, changes in NO
- Genetics play role in PPH but not in ES
  - BMPR-II (bone morphogenic protein receptor)
- Cause of death in some patients is emergent nonresponsiveness to pulm vasodilators and autopsy showing fibrinoid necrosis of the PA small vessels*

Granton JT et al. Cardiol Clinics 2002;20:441
*Daliento L et al. Cardiovasc Pathol. 2002;11:221

Endothelial Pathophysiology

- Endothelial cell produces elastase
- Elastase degrades ECM proteoglycans
- Proteoglycans release their bound growth factors
- FGF-2 and TGF-β can induce VSM hypertrophy and proliferation and stimulate connective tissue protein synthesis (increase in fibronectin and tenascin)
- VEGF is also increased locally

- Antielastase therapy might help

Granton JT et al. Cardiol Clinics 2002;20:441

Eisenmenger Physiology

- "Eisenmenger Syndrome" coined by Paul Wood: PVOD from large left to right shunt with PA pressure ~ systemic, bidirectional shunt
- From ASD, VSD, PDA, AVSD, Truncus, aortopulmonary window, univentricular heart
- Usually high PVR is established in infancy (<2 y.o.), even at birth
- Cyanosis progressive during teens and 20s
- Functional capacity decreases in 20s and after
- Survival 42% at age 25

Braunwald 2005, p. 1496

Eisenmenger Physiology

- Symptoms palpitations in 50% (atrial fibrillation/flutter 35%, VT 10%), hemoptysis 20%, PE, angina, syncope, endocarditis, CHF
- Eisenmenger PDA can have pink right nail beds and cyanosis of left hand
- Management: flu shots, iron replacement, antiarrhythmics, dig, diuretics, bedrest for hemoptysis (O2 not help and not proved in plane flight either)
- Ca blockers and ACE-I unproved, bosentan is under study, sildenafil unproved and provocative
- Lung transplant and repair of defect (55% 1-yr survival), or heart-lung (70% 1-yr survival)
- General anesthesia for noncardiac surgery is high-risk, try local; paradoxic emboli

Braunwald 2005, p. 1497-8

Cyanosis

- Cyanosis is seen with excess concentration of circulating reduced hemoglobin, over 3-4 gm/dl
- Central cyanosis is characteristic of shunt, peripheral cyanosis indicates excessive extraction and peripheral constriction, can have both
- Hypoxemia stimulates renal oxygen sensors to increase erythropoetin, so RBC numberrs and hemoglobin concentration is increased
- Increased hemoglobin concentration compensates for low arterial oxygen saturation (increased oxygen delivery), thus it is adaptive
- Heme breakdown is excessive and increases bilirubin production and biliary unconjugated bilirubin and calcium bilirubinate (insoluble) stones

Braunwald, 2001, p. 1513, 1617; Perloff 2003 p. 319-20.

Treating Cyanosis

- Supplemental O2 has not been shown to help
- Bosentan has shown promise
  - 9 patients on 125 mg bid had increase in O2 saturations from 79% to 88%, and 6/9 improved NYHA class*
- Heart lung transplantation is better than lung transplantation**

*Christensen DD et al. Am J Cardiol. 2004;94:261.
**Waddell TK et al. J Heart Lung Transplant. 2002;21:737 abst

Vascular Responses to Cyanosis

- Systemic vascular dilation is response to endothelial-derived NO and prostaglandins from elevated endothelial shear stress from erythrocytosis – syncope in heat and humidity
- Coronary arterial dilation, elongation, tortuous, ectatic; vasodilator NO and prostaglandins released, increase in coronary blood flow at rest and preserved coronary reserve due to microvascular remodeling

Perloff 2003 p. 319-20.

Coronary circulation

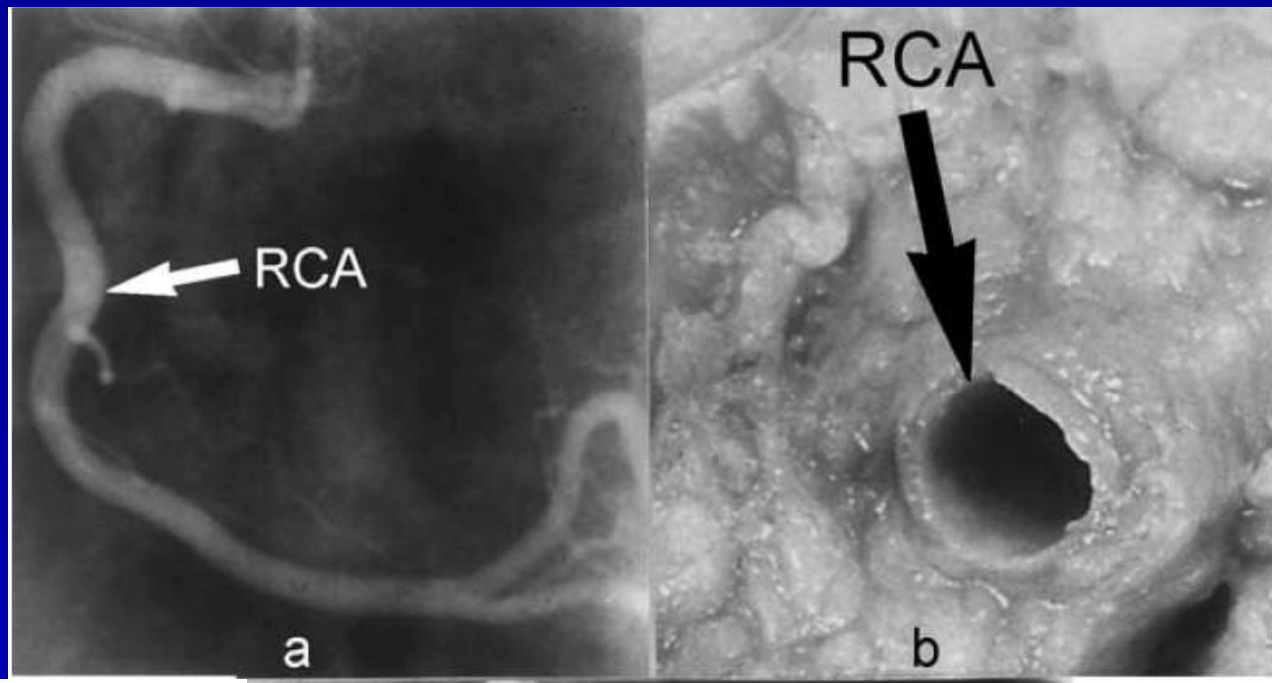
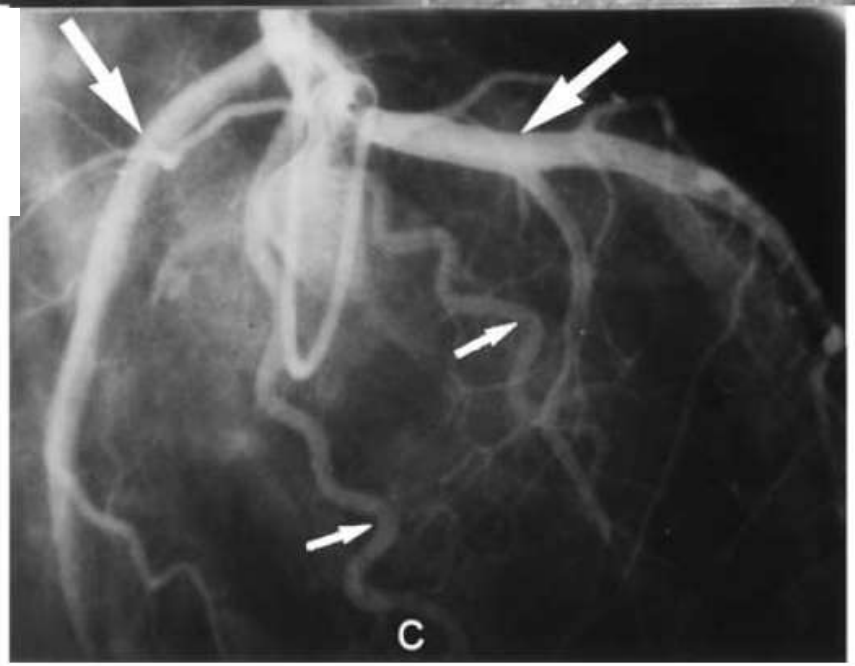


Fig. 1. (a,c) Coronary arteriograms showing a dilated atheroma-free right coronary artery and dilated, tortuous atheroma-free left coronary arteries in a 45 year old man with an Eisenmenger ventricular septal defect. (b) Cross section of a dilated atheroma-free right coronary artery in a 36 year old man with an Eisenmenger ventricular septal defect.



Perloff JK. Int J Cardiol. 2004;97:79.

Exercise Responses in Cyanosis

- Dyspnea: hyperventilation at rest and increases excessively during exercise because right-to-left shunt worsens with exercise and gives higher arterial CO2 and lower pH, stimulating respiratory center
- Hypoxemia may be worsened at even low levels of exercise and more oxygen debt and more anaerobic metabolism
- PREGNANCY: maternal mortality exceeds 50% and risk of *in utero* death is very high (uterine hypoxemia); in cyanotic heart disease OTHER than Eisenmenger maternal complication rate is 32% and 37% fetal prematurity, better if resting O2 saturation >85%

Braunwald 2005, p. 1496; Perloff 2003 p. 319-20.

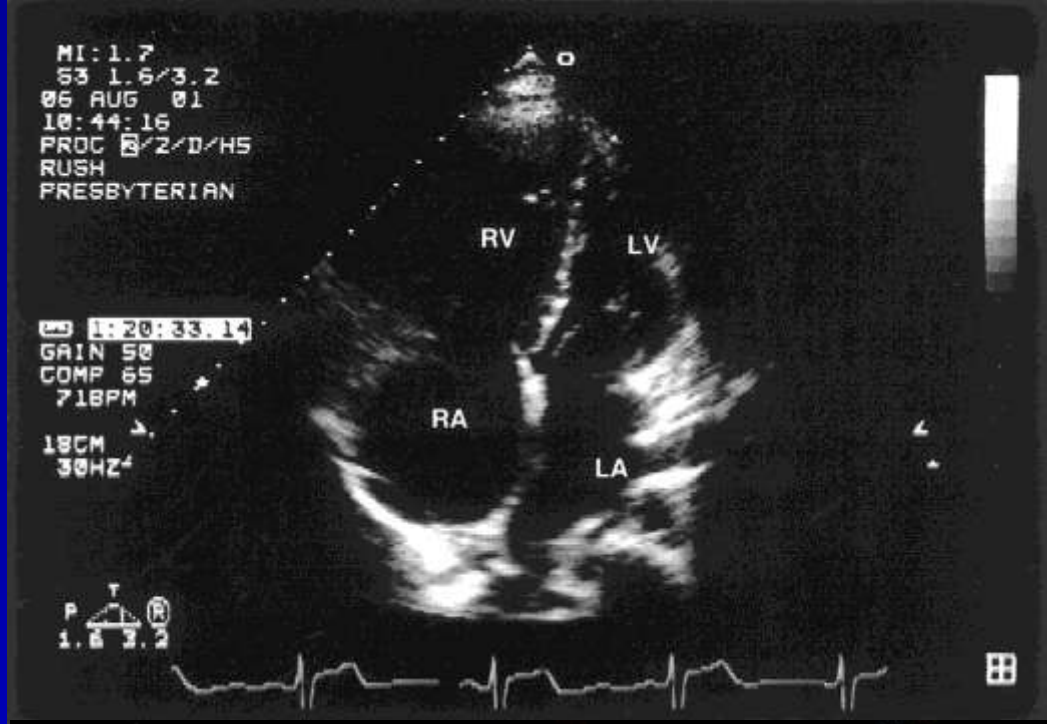
Pregnancy

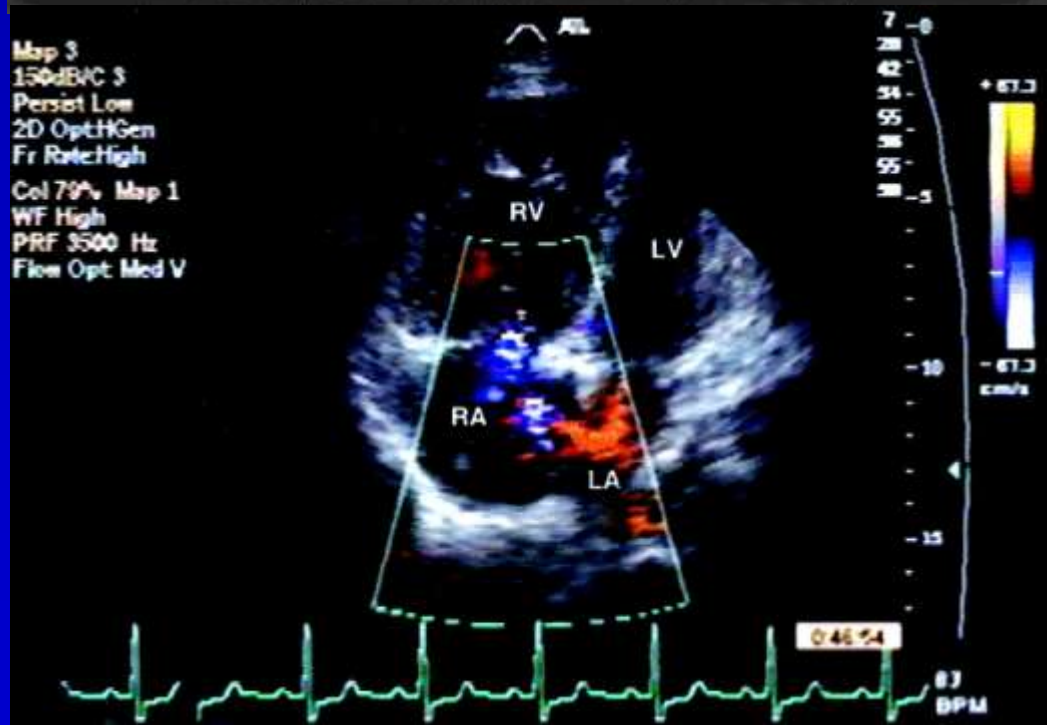
- Eisenmenger's syndrome and primary pulmonary hypertension have similar maternal mortality of 30-50%
- Plasma volume peaks early 3rd trimester at 150% normal, may precipitate RV failure
- Fall in systemic resistance due to placental flow and vasodilation may increase cyanosis
- Hypovolemia (giving acidosis and hypercarbia) during L & D may cause SCD
- Pulmonary embolism or *in situ* infarction is a risk
- Perinatal mortality is 30% and intrauterine growth retardation (1/3) and prematurity (1/2) are very common
- Monitor in hospital for 2 weeks after delivery

Warnes CA. Int J Cardiol. 2004;97:11

Pregnancy and Epoprostenol

- 21 yo gravida 3 para 2, 34 weeks, several weeks of dyspnea and edema and preterm contractions
- O2 sat 80% on 100% nonrebreather, to low 70s on mild exertion; P 107, R 24, BP 134/73, JVP elevated, TR murmur, R sided S3
- Epoprostenol titrated up to 9 ng/kg/min and O2 sat increased to 90%
- Successful delivery by C-section
- Discharged on 12 ng/kg/min





Geohas C et al. Chest. 2003;124:1170.

Metabolic Responses to Cyanosis

- Proteinuria is from increased glomerular hydraulic pressure in response to high viscosity of erythrocytosis
  - Dilated hilar arterioles and glomerular capillaries from NO
  - Increased glomerular cellularity from PDGF and TGF-β in cytoplasm of venous megakaryocytes that get shunted into the arterial circulation and lodge in glomerular tufts

Braunwald 2005, p. 1496; Perloff 2003 p. 319-20.

Metabolic Responses to Cyanosis

- Hyperuricemia from decreased renal clearance and/or increased production of urate, enhanced reabsorption from renal hypoperfusion reinforced by high filtration fraction; gouty arthritis uncommon not rare (treat with colchicine, probenecid, antiinflammatory drugs or allopurinol)
- Uric acid higher with higher PA pressure and higher PAR and lower CI, and had worse prognosis even multivariate*

Braunwald 2005, p. 1496; Perloff 2003 p. 319-20; *Oya H et al. Heart 2000;84:53.

Hyperviscosity Syndrome

- Symptoms: mainly CNS and usually stereotypic - headache, altered mentation, visual disturbances, tinnitus, paresthesias, fatigue, dizziness, and myalgias; relief by phlebotomy is defining
- Usually hematocrit is >65% with symptoms, maybe less if iron deficient, or maybe if dehydration (excessive heat, illness, fever, diarrhea, vomiting)
- Retinal vein occlusion has been reported from hyperviscosity*
- Asymptomatic elevation in hematocrit is not an indication for phlebotomy unless preop and hct >65% because then it reduces bleeding
- Phlebotomy: remove 250-500 ml over 30-45 minutes with simultaneous with volume of NS (Dextran if CHF) infusion; iron supplementation; can repeat QD

Braunwald, 2005, p. 1496. *Rodriguez N et al. Am J Ophthalmol. 2001;132:268.

Hyperviscosity and Retinal vein occlusion

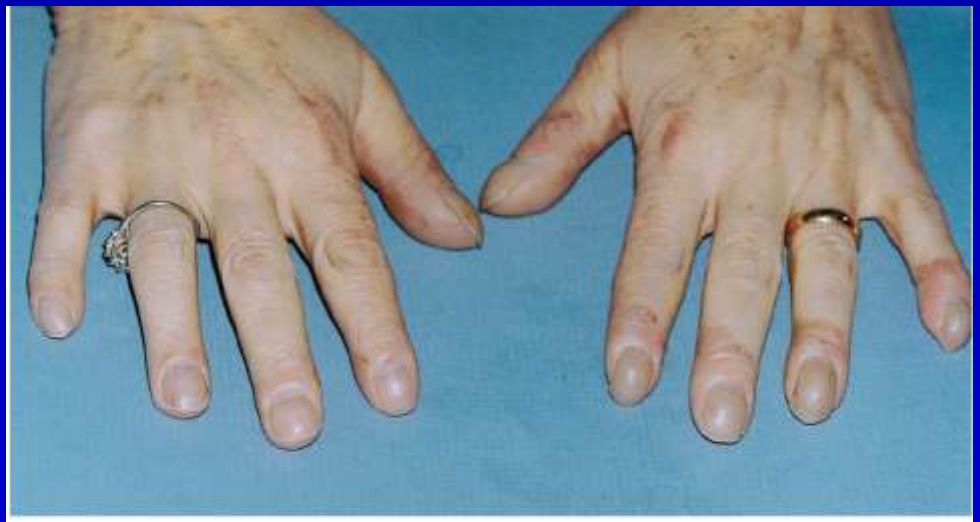
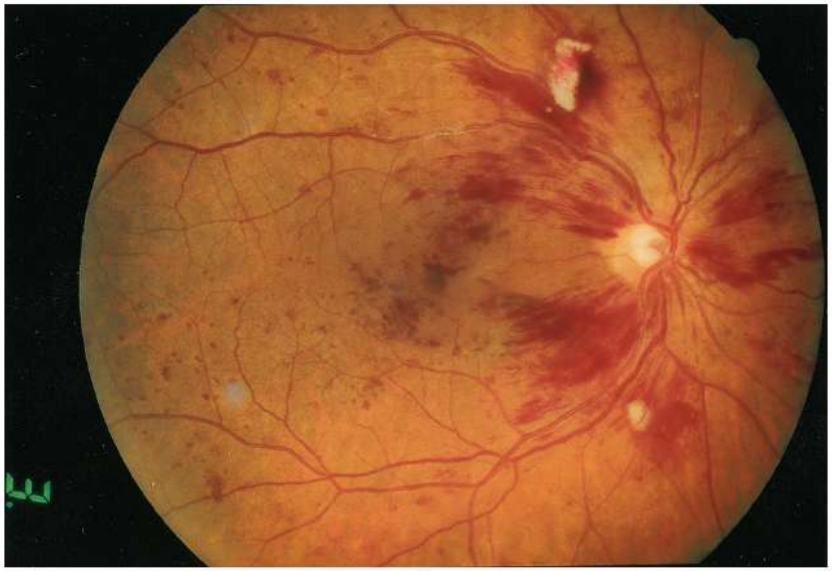


FIGURE 2. Digital erythema and severe clubbing.



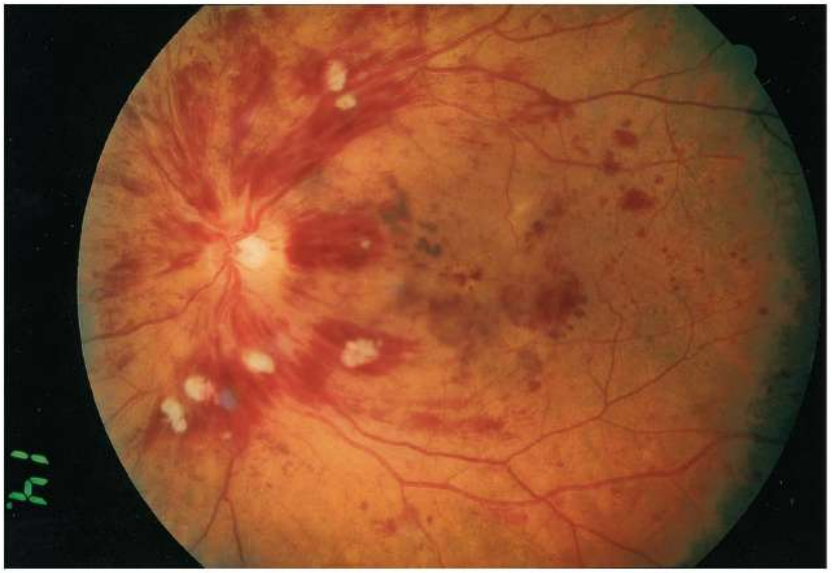


FIGURE 1. Ophthalmoscopic appearance of intraretinal hemorrhages, cotton wool spots, and macular edema (A, right eye; B, left eye).

Rodriguez N et al. Am J Ophthalmol. 2001;132:268.

Iron Deficiency

- Common and important in cyanosis, from hemoptysis, epistaxis, menses, inappropriate phlebotomy
- Microcytosis increases whole blood viscosity (less deformable than biconcave disc)
- Replace iron till hematocrit increases or till iron-replete state, IV iron for oral intolerance

Braunwald, 2001, p. 1617

Abnormality in Hemostasis

- Platelet counts are usually low normal, elevated PT and PTT, decreased factor V, VII, VIII, and IX, including von Willebrand factor, and increased fibrinolysis have been implicated
- Spontaneous superficial bleeding (gums, nosebleed, menorrhagia) can occur in up to 20% of patients and is usually self-limited, but massive intrapulmonary hemorrhage is a common cause of sudden death; avoid ASA, NSAID and heparin
- Preoperative phlebotomy if hematocrit >65%, 500cc/24hr, can save for autologous transfusion
- Anticoagulant usually should be avoided, but in atrial fibrillation or mechanical prosthesis, a risk-benefit dilemma must be addressed
- Treatment: platelet transfusions, FFP, Vitamin K, cryoprecipitate, desmopressin can be used for severe bleeding

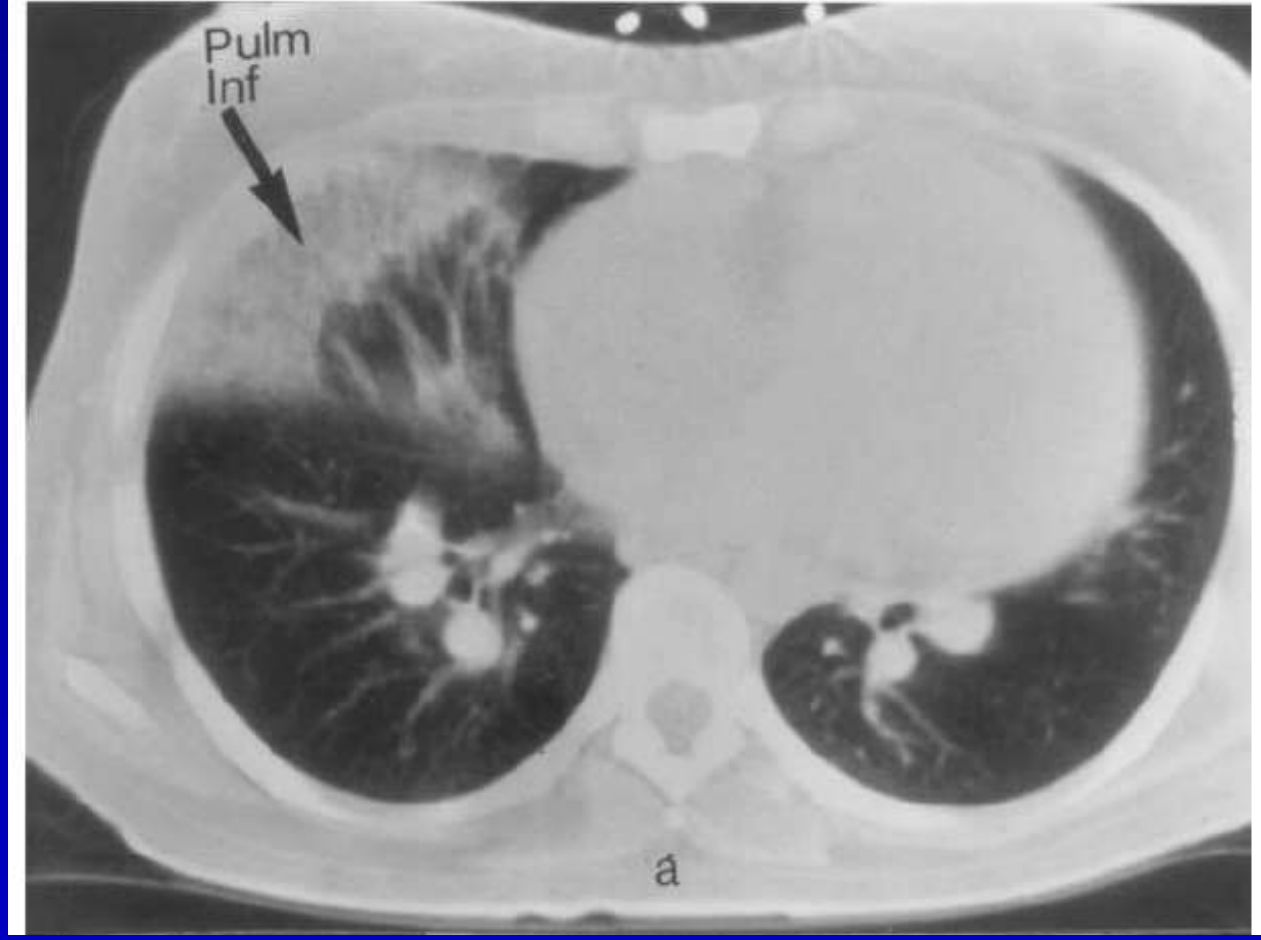
Braunwald, 2005, p. 1496; Perloff 2003, p. 319-20.

Pulmonary Artery Aneurysm

31 pts with cyanotic Pulm vasc dz vs 13 women with PPH

All had enlarged PA's

Cyanotic patients all had thrombus (moderate to massive in 30%); PPH patients without aneurysm or thrombus



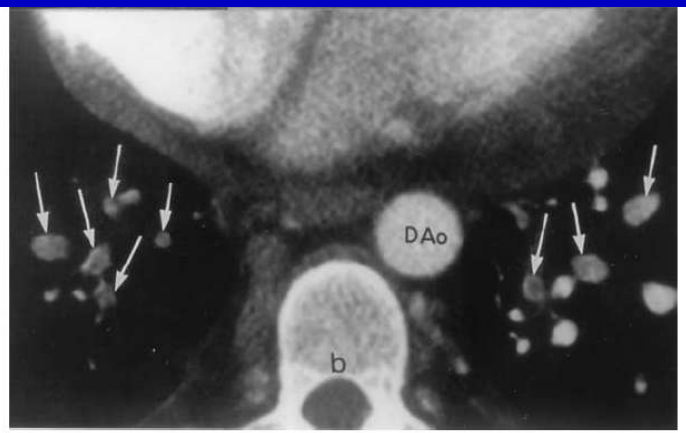
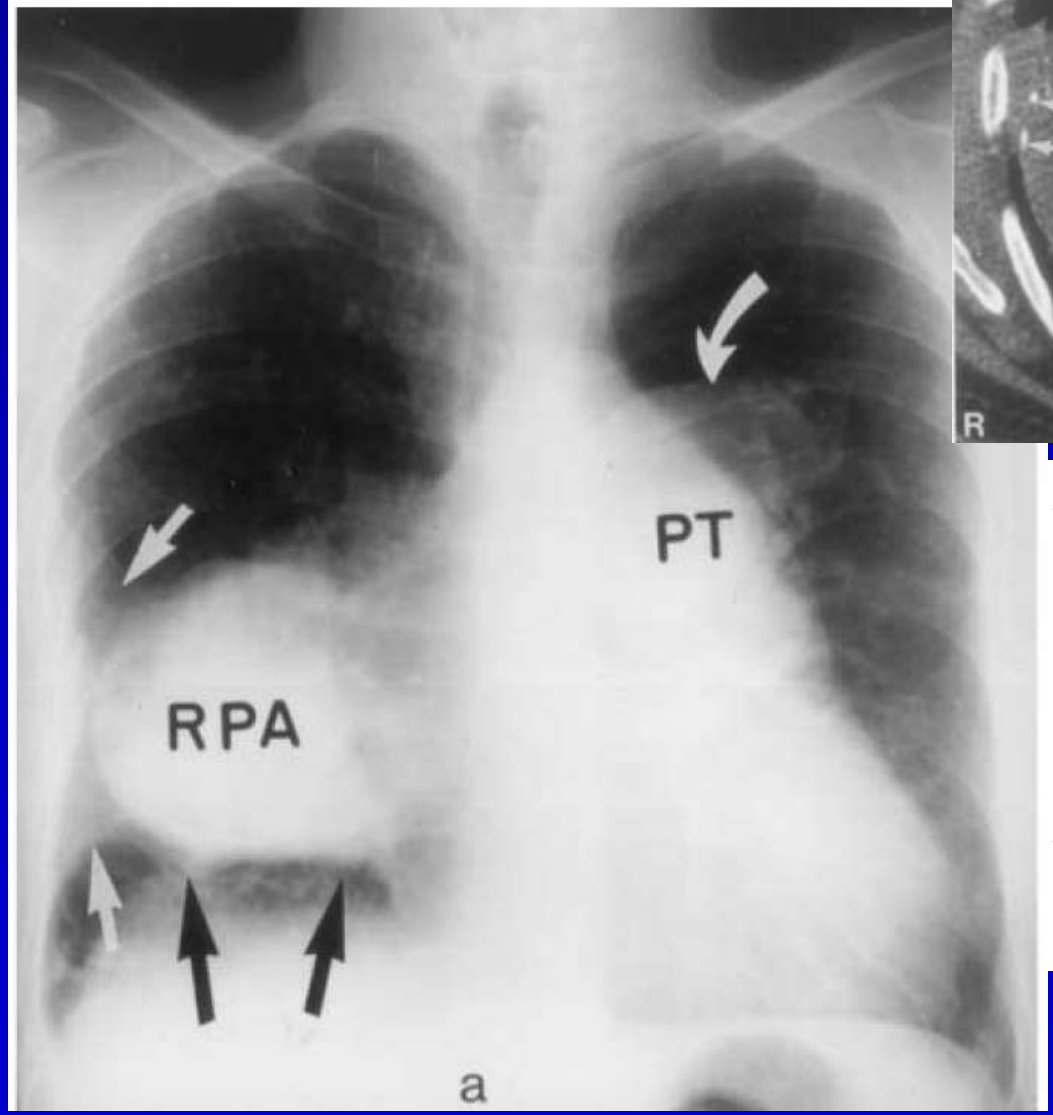


FIGURE 5. *(A)* Transaxial section from the pulmonary CTA of a 38-year-old cyanotic man with Down syndrome, a nonrestrictive inlet VSD, and Eisenmenger syndrome. A hemorrhagic pulmonary infarction (Pulm Inf) was caused by embolization from a large proximal thrombus. *(B) Arrows,* intrapulmonary arteries into which emboli were seeded from the proximal thrombus. Abbreviation as in Figure 1.

Perloff JK et al. Am J Cardiol. 2003;92:182

Pulmonary Artery Aneurysm



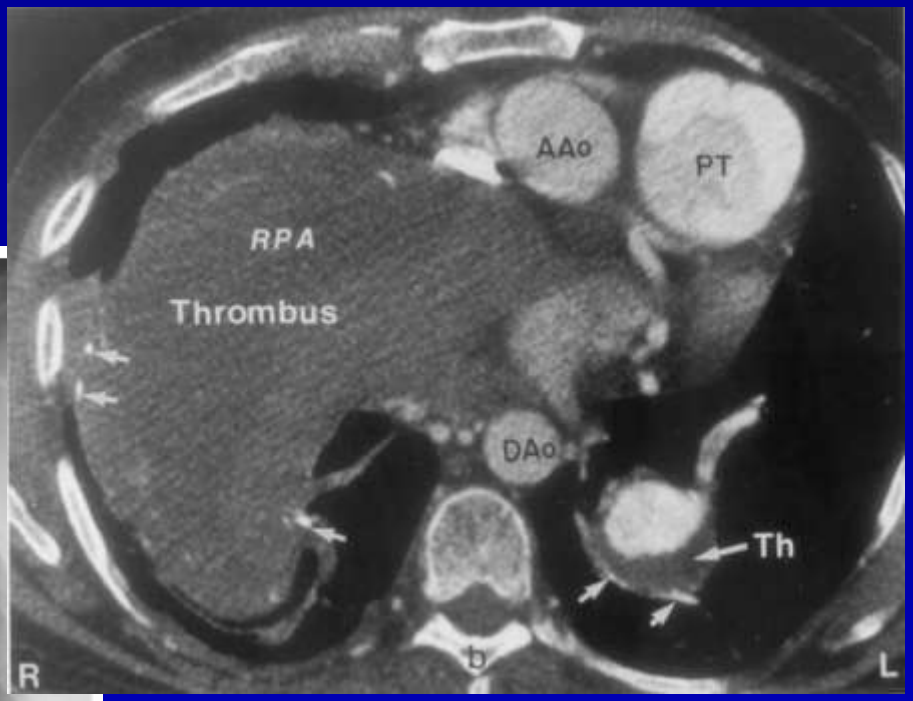


FIGURE 1. Posteroanterior chest x-ray from a 54-year-old man with Eisenmenger syndrome and a nonrestrictive perimembranous VSD. *(A)* An aneurysmal right pulmonary artery (RPA) compressed the middle lobe bronchus causing atelectasis *(paired white arrows)* and elevation of the right hemidiaphragm *(paired black arrows)*. The pulmonary trunk (PT) and left pulmonary artery *(curved white arrow)* are also aneurysmal. *(B)* A transaxial section from the pulmonary CTA of the same patient showing massive thrombus completely occluding the aneurysmal RPA. Extension of thrombus into the right and left branches caused asphyxic death. There is a paucity of calcification *(arrows)* in the wall of the aneurysmal RPA. An enlarged left intrapulmonary artery also contained thrombus (Th) and a thin rim of calcification *(paired arrows)*. AAo = ascending aorta; DAo = descending aorta.

Perloff JK et al. Am J Cardiol. 2003;92:182

Thrombosis and Hemoptysis

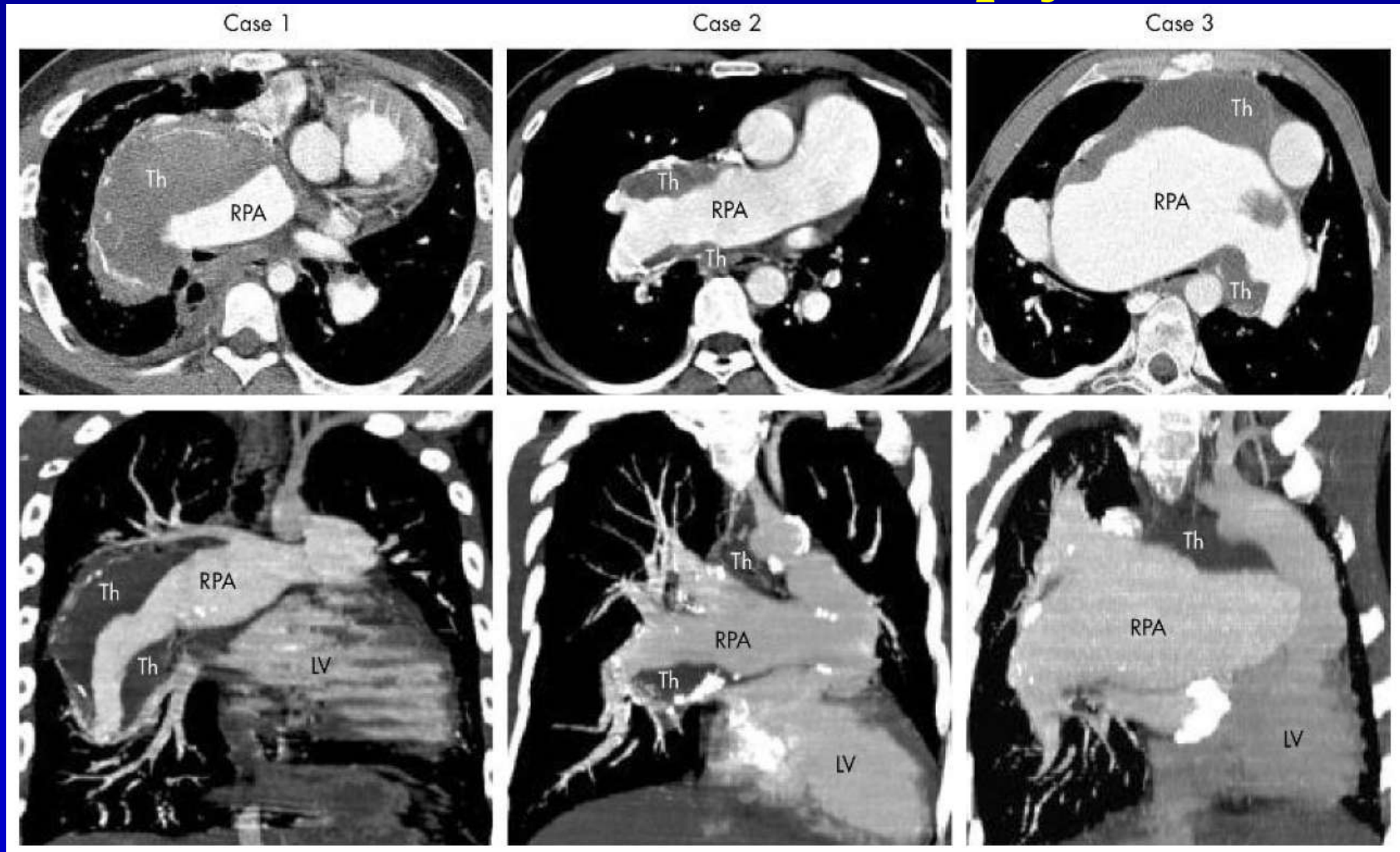


Figure 1 (Top) Computed tomography pulmonary angiography (CTPA) transaxial images and (bottom) oblique coronal reformation with maximum intensity projection for each patient. LV, left ventricle; RPA, right pulmonary artery; Th, thrombus.

Broberg C et al. Heart. 2004;90:63.

Thrombosis

- 34 Eisenmenger patients in Toronto, 22 VSD, 5 ASD, 3 PDA, 5 other
- Age 41+/- 10, O2 saturation 82 +/-9%
- 35% prior bleeding
- 11% prior thrombotic event
- 15% anticoagulant
- 9% antiplatelet
- 56% RV dysfunction echo
- Main PA size 44 mm

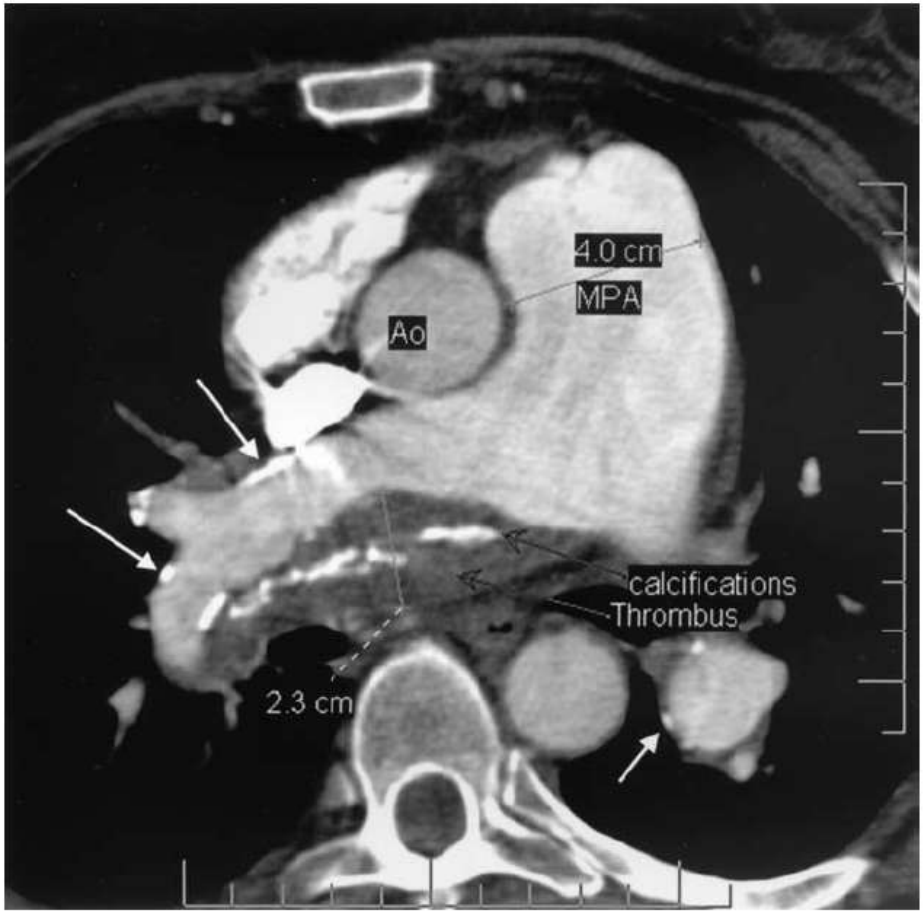


Figure 1. Axial computed tomography angiography image at the level of the main pulmonary artery bifurcation shows dilation of the main pulmonary arteries and an eccentric 23-mm mural thrombus along the posterior wall of the right pulmonary artery. The thrombus is composed of multiple layers of thrombus with embedded linear calcifications suggesting repeated events during formation. Calcifications are also seen along the anterior free wall of the right pulmonary artery and its main branches **(long arrows)** and in the left interlobar artery **(short arrow)**. Ao = ascending aorta; MPA = main pulmonary artery.

Silversides CK et al. JACC. 2003;42:1982.

Thrombosis

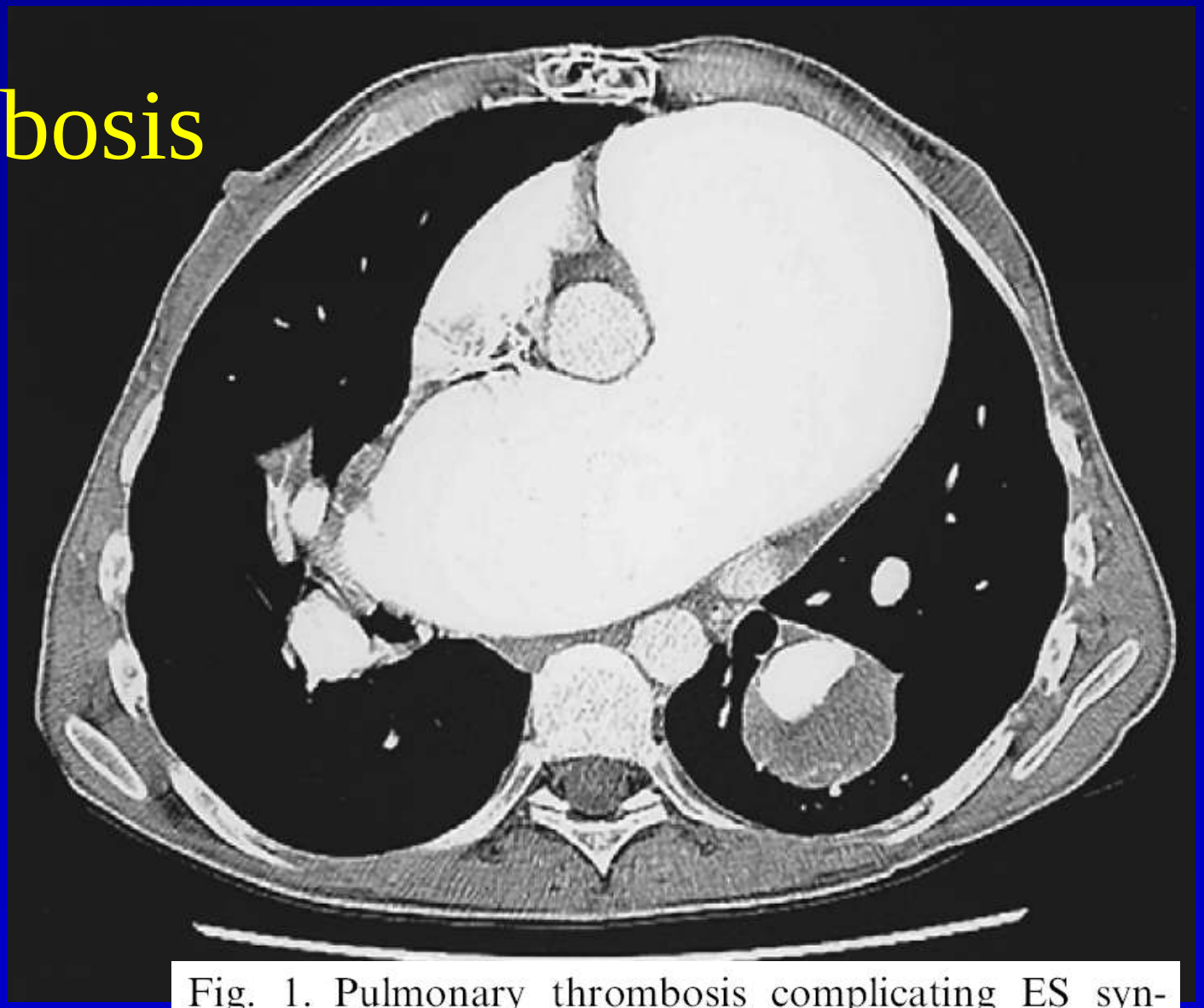
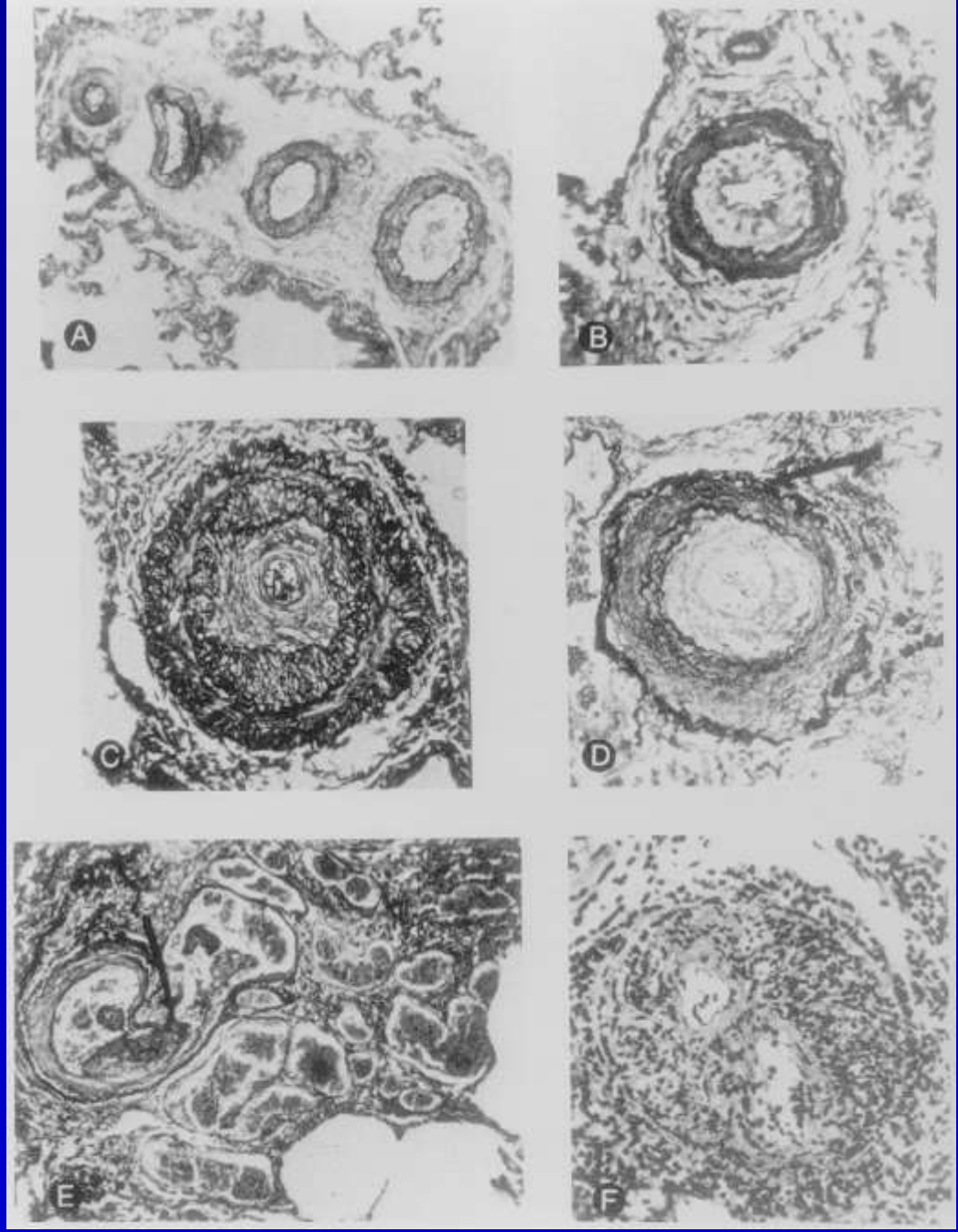


Fig. 1. Pulmonary thrombosis complicating ES syndrome. A large thrombus is identified in the left descending pulmonary artery in a patient with ES secondary to an atrial septal defect.

Granton JT et al. Cardiol Clinics 2002;20:441

Heath Edwards Classification



(A) Grade I: medial hypertrophy. 150x. (B) Grade II: cellular intimal proliferation in an abnormally muscular artery. 250x. (C) Grade III: occlusive changes. The media is thickened due to fasciculi of longitudinal muscle, and vessel is all but occluded by fibroelastic tissue. 150x. (D) Grade IV: dilatation. Vessel is dilated and media is abnormally thin (arrow). Lumen is occluded by fibrous tissue. 150x (E) Grade V: plexiform lesion. There is cellular intimal proliferation (arrow); clustered around are numerous thin-walled vessels that terminate as capillaries in the alveolar wall. 95x. (F) Grade VI: acute necrotizing arteritis. A severe reactive inflammatory exudate is seen through all layers of the vessel. HE 250x. elastin-van Gieson Stain 1964

Granton JT et al. Cardiol Clinics 2002;20:441

Cerebrovascular Events

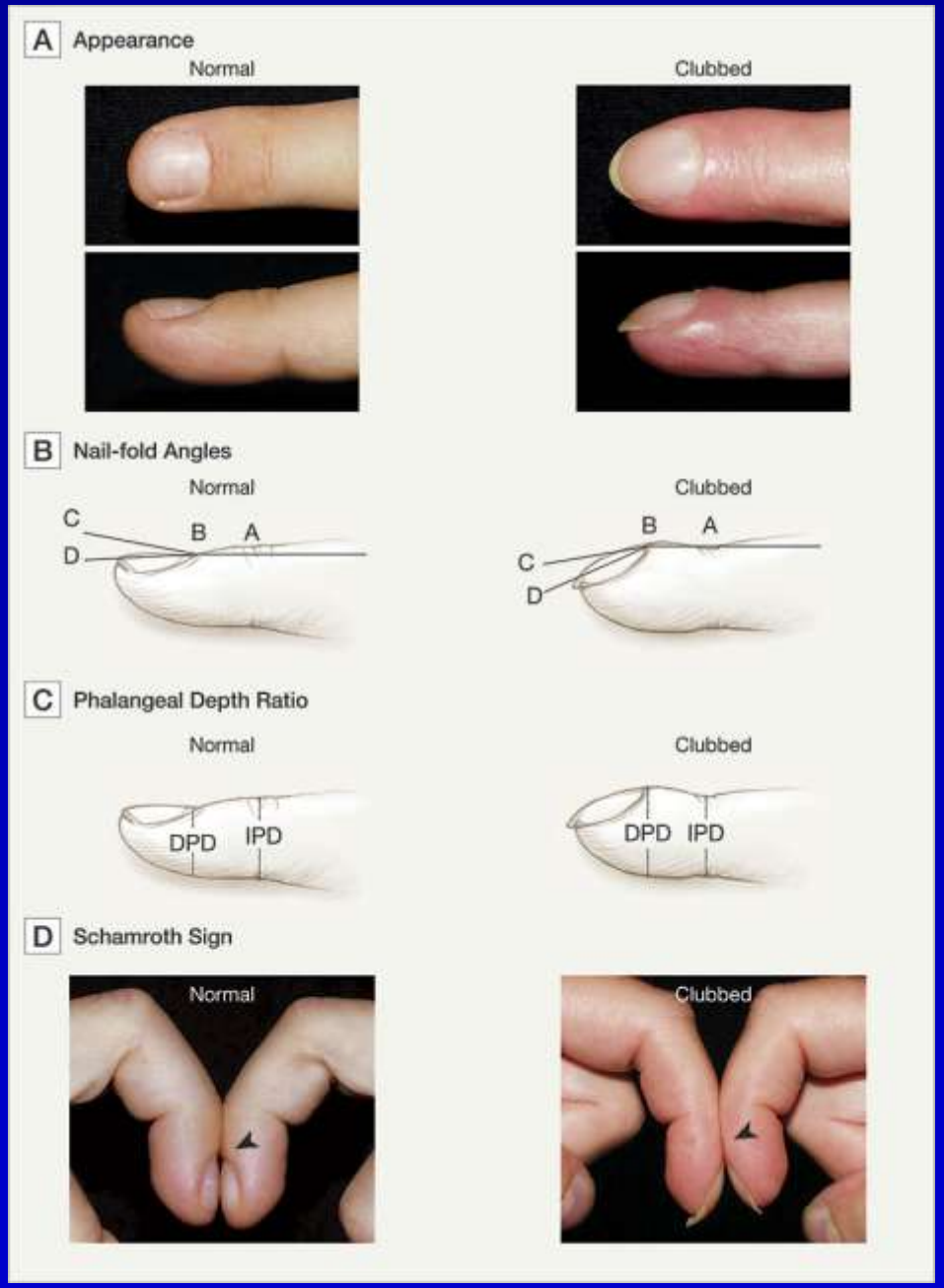
- NOTE: Use air filters in IV lines!
- Stroke from cerebral arterial thrombosis usually seen in patients with iron deficiency or iron depletion (children less than 4 yo have more tenuous iron situation)
- Cerebral hemorrhage with anticoagulant therapy
- Paradoxical emboli occur in R>L shunt, either thrombus or air from IV line without a filter, can present as TIA or stroke or renal or splenic infarcts
- Brain abscess may present with headache and fever and focal finding or seizure

Braunwald, 2005, p. 1496; Perloff 2003 p. 320

Arthralgia and Clubbing

- Megakaryocyte cytoplasm releasing PDGF and TGF-β
  - Cell proliferation, protein synthesis, connective tissue formation, deposition of extracellular matrix
- Arthralgia and bone pain: hypertrophic osteoarthropathy is usual cause (new osseous formation and periostitis)
  - Affects up to 1/3 patients with cyanotic congenital heart disease
  - Mechanism: megakaryocytes from marrow bypass lung and lodge in arterioles and capillaries of subperiosteum
- Clubbing: increased number of capillaries, increased blood flow, extensive AV aneurysms and increase in connective tissue from megakaryocytes in digits
  - PDA and Eisenmenger physiology, clubbed toes, differential cyanosis
  - PDA and TGA and Eisenmenger physiology, clubbed fingers, differential cyanosis

Braunwald, 2005, p. 1496, Perloff 2003, p. 321

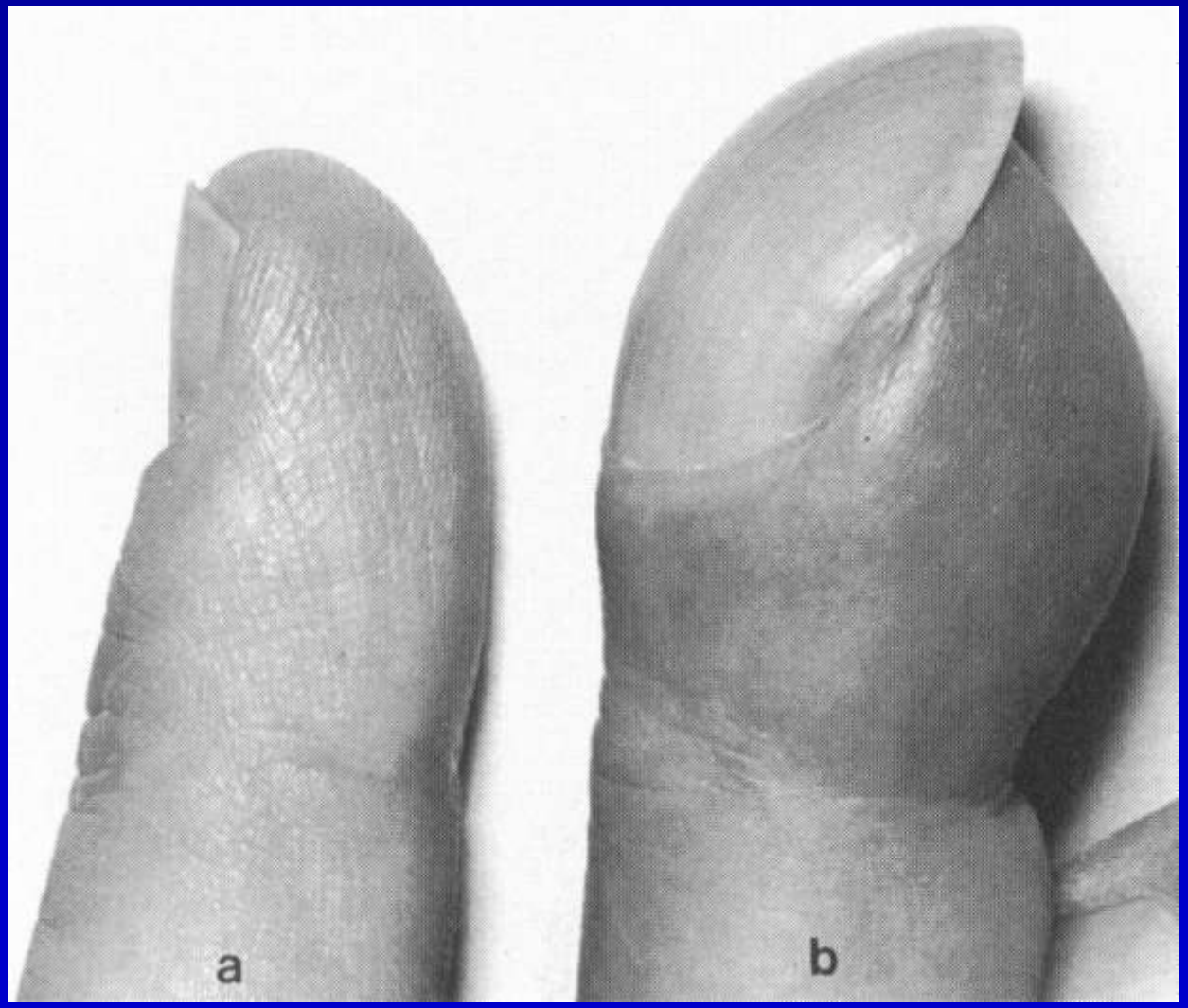


- Neoplastic intrathoracic disease
  - Bronchogenic carcinoma
  - Malignant mesothelioma
  - Pleural fibroma
  - Metastatic osteogenic sarcoma
- Suppurative intrathoracic disease
  - Lung abcess
  - Bronchiectasis
  - Cystic fibrosis
  - Empyema
  - Chronic cavitary mycobacterial or fungal infection
- Diffuse pulmonary disease
  - Idiopathic pulmonary fibrosis
  - Asbestosis
  - Pulmonary arteriovenous malformations
- Cardiovascular disease
  - Cyanotic congenital heart disease
  - Infective endocarditis
  - Arterial graft sepsis*
  - Brachial arteriovenous fistula†
  - Hemiplegic stroke†
- Gastrointestinal disease
  - Inflammatory bowel disease
  - Celiac disease
- Hepatobiliary disease
  - Cirrhosis (particularly biliary and juvenile)
- Metabolic disease
  - Thyroid acropachy

*Associated with clubbing distal to graft sepsis.
†Associated with unilateral clubbing.

Myers KA et al. JAMA 2001;286:341

Normal versus Clubbing



- Proliferation of connective tissue between nail matrix and distal phalanx
- Normal nail bed less than 2 mm thick, clubbing more, and less dense connective tissue
- Primitive fibroblasts present; increased eosinophils and lymphocytes, increased caliber and number of blood vessels

Perloff, 1994, p. 7. Myers KA et al. JAMA 2001;286:341

Clubbing Improvement after Lung Transplant in Cystic Fibrosis

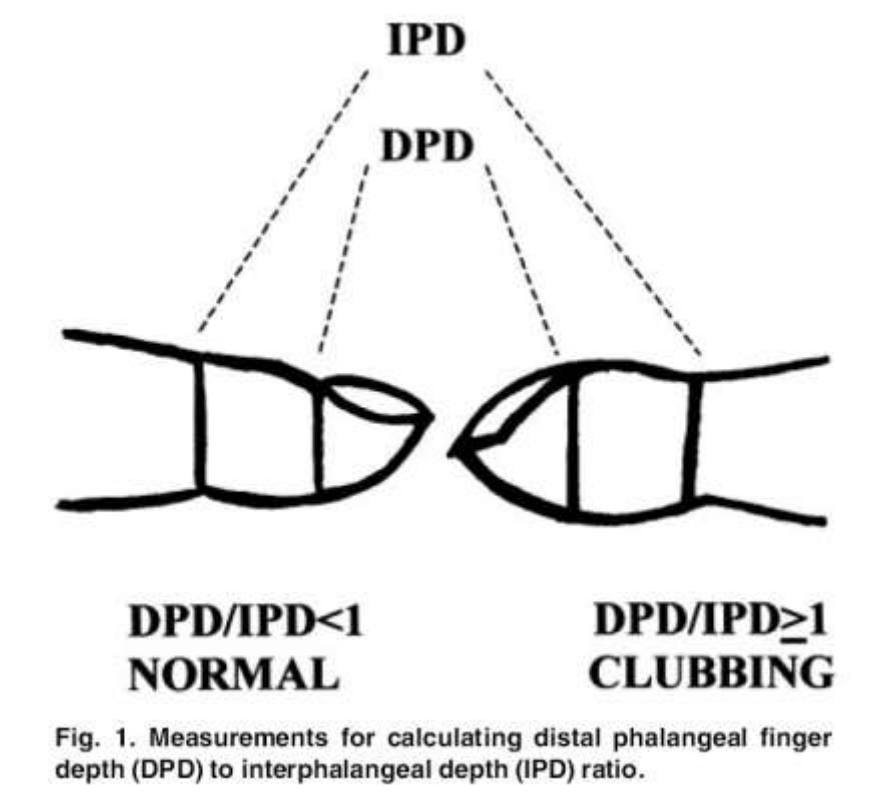


Fig. 1. Measurements for calculating distal phalangeal finger depth (DPD) to interphalangeal depth (IPD) ratio.

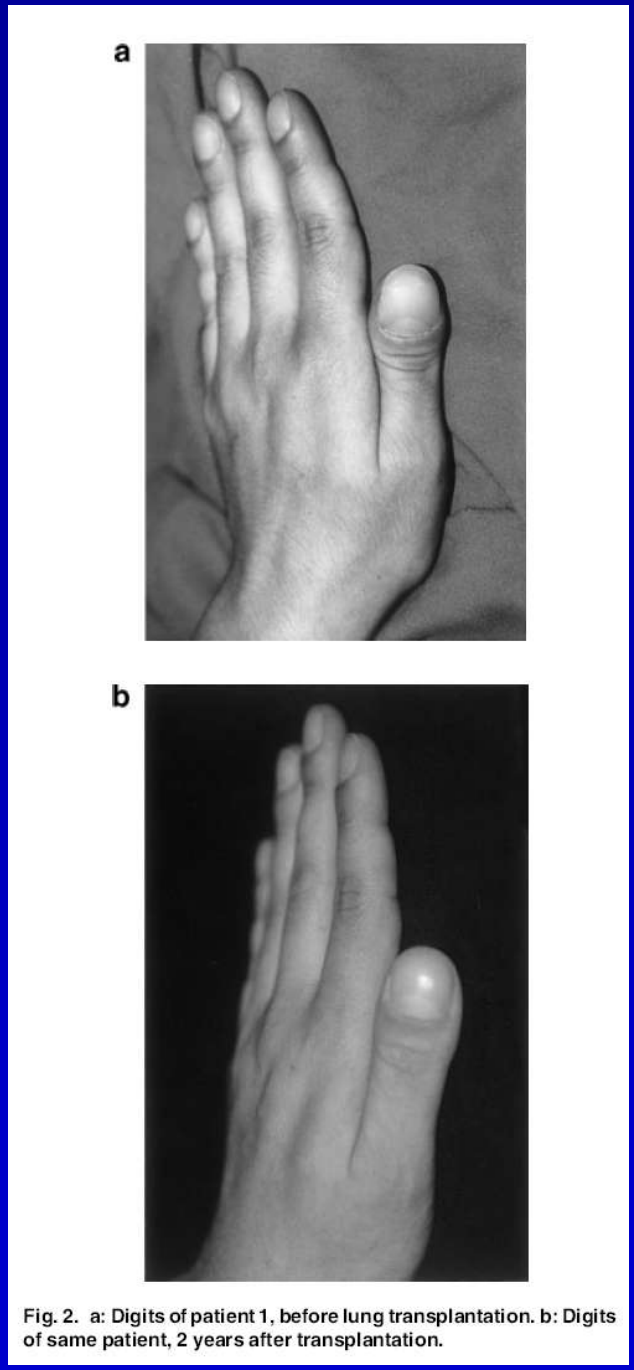


Fig. 2. a: Digits of patient 1, before lung transplantation. b: Digits of same patient, 2 years after transplantation.

Augarten A et al. Pediatr Pulmonol. 2002;34:378

Clubbing Improvement after Lung Transplant in Cystic Fibrosis

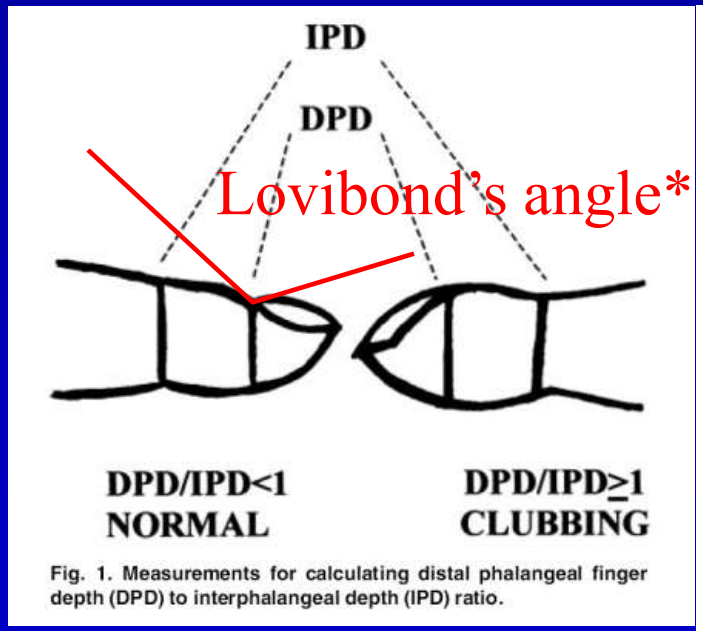


Fig. 1. Measurements for calculating distal phalangeal finger depth (DPD) to interphalangeal depth (IPD) ratio.

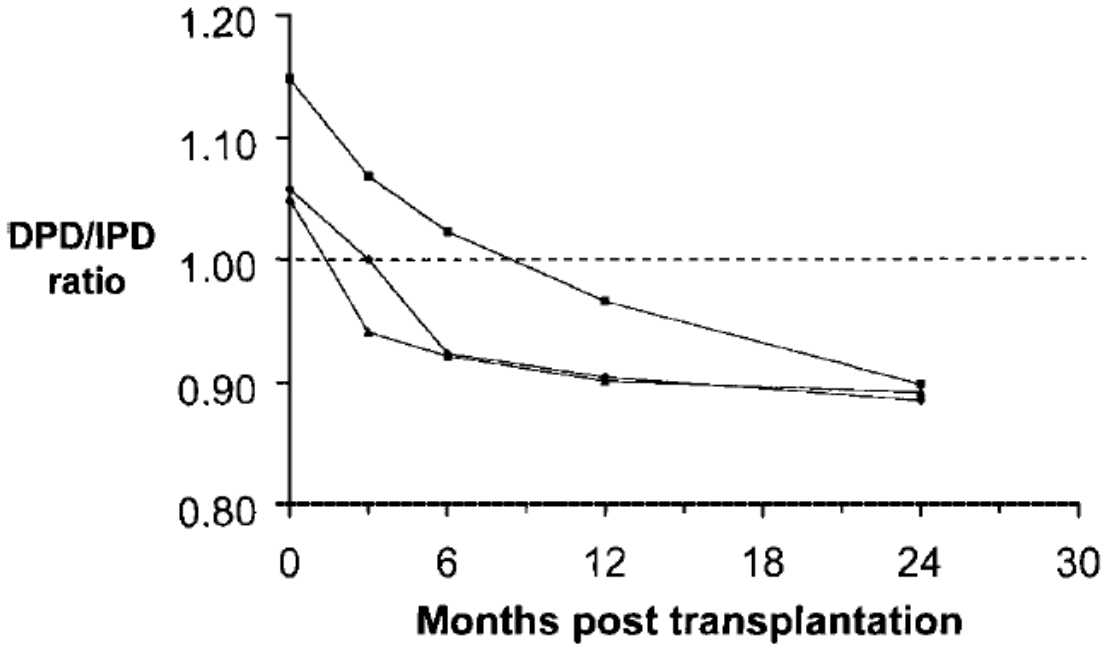
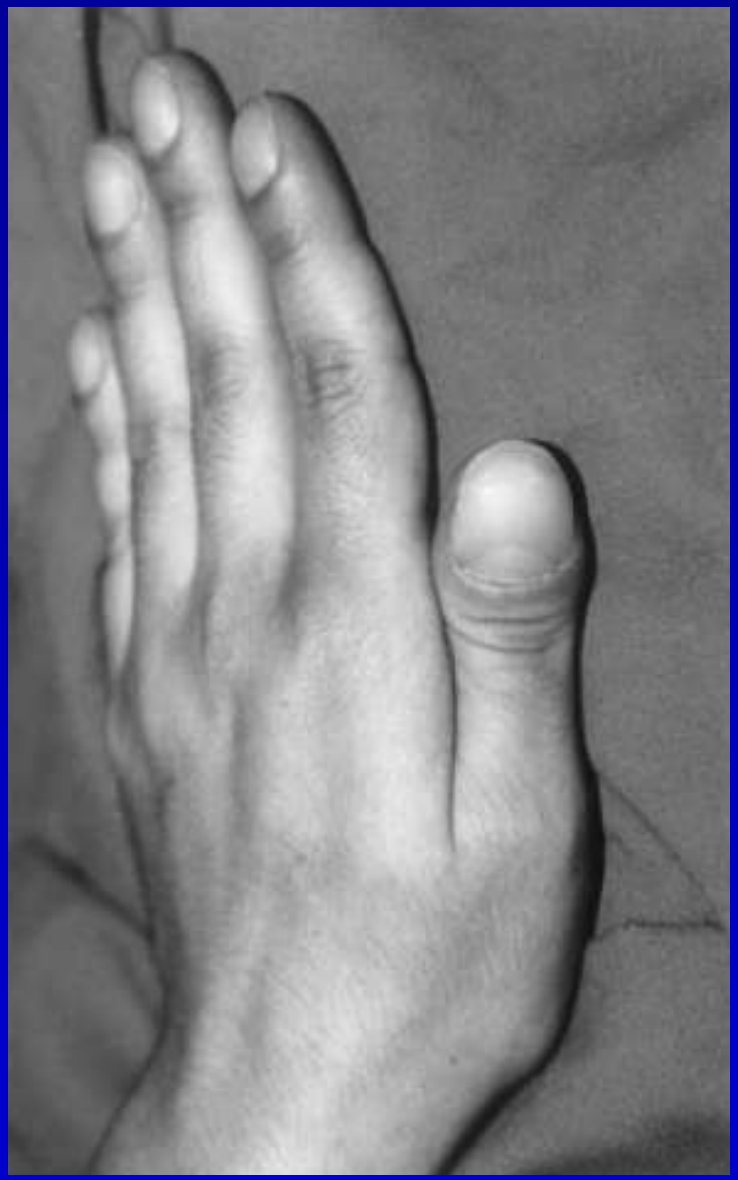
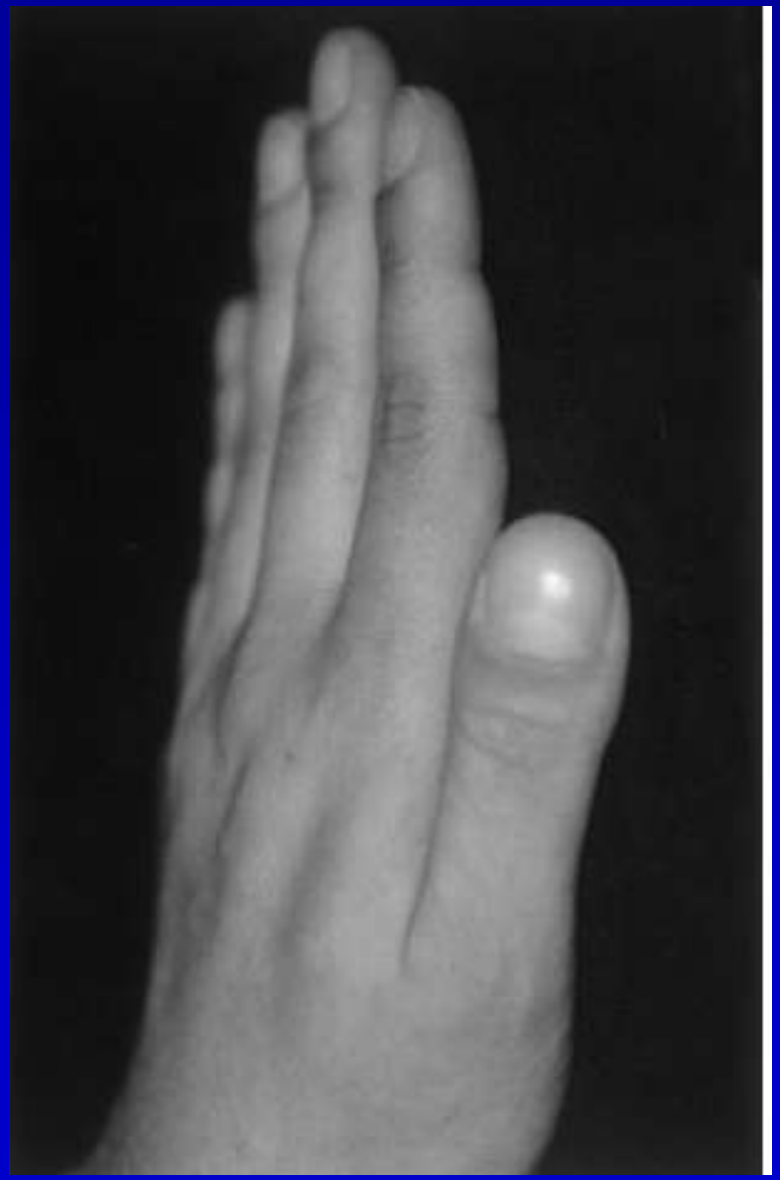


Fig. 3. DPD/IPD ratio in 3 patients prior to and following transplantation. Horizontal dashed line represents upper limit of normal DPD/IPD ratio.

Augarten A et al. Pediatr Pulmonol. 2002;34:378.
*McDonnell JK. Dermatol Clin. 2002;20:503

Clubbing Improvement





Augarten A et al. Pediatr Pulmonol. 2002;34:378

Clubbing and Hypervascularity MRI

Figure 1. Photograph of the patient's left hand showing clubbing.

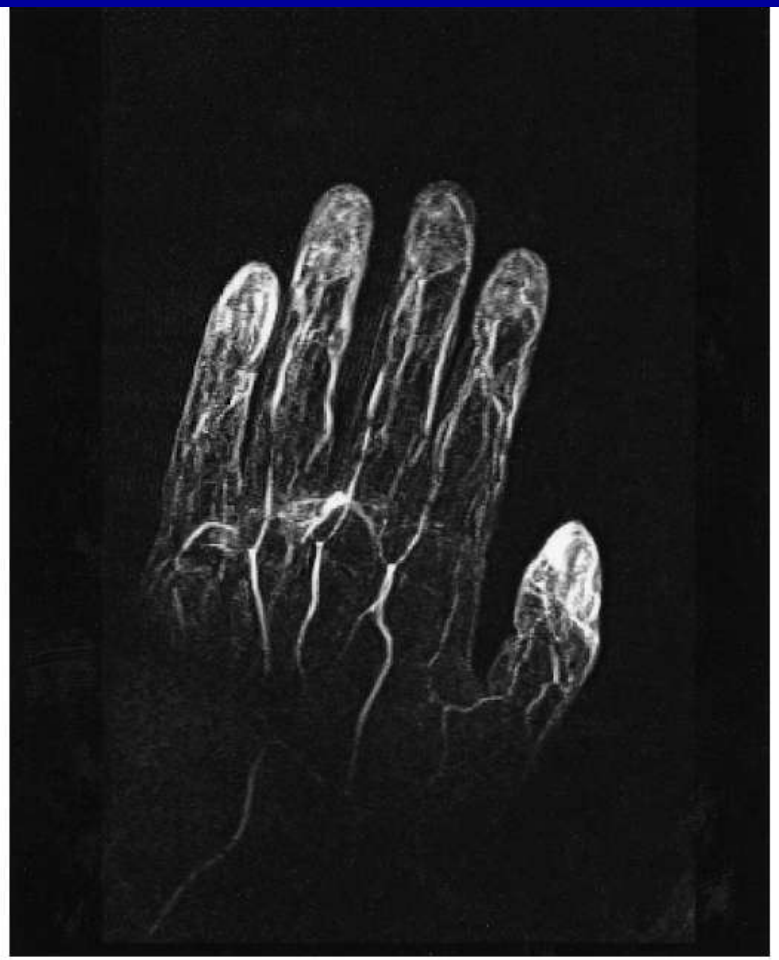


Figure 2. Maximum intensity projection reconstruction of a 3D, contrast-enhanced magnetic resonance angiogram of the patient's left hand. Note the peripheral hypervascularization in the terminal digits, particularly of the first, fourth, and fifth fingers. There is no evidence of vasculitis or arterial stenosis or occlusion.

Weisman F et al. Circulation. 2001;104:2503

Cardiovascular System in Cyanosis

- Patients with cyanotic heart disease have lower than normal total body water
- Patients have elevated ANP and BNP despite low RA pressure and low body water
- These things are true without regard to presence of PHTN (both Eisenmenger and Tetralogy)
- Oxytocin (produced by pituitary) can cause myocytes to release natriuretic peptides, but oxytocin levels are not elevated in cyanotic patients
- In experimental animals a hypoxia response element for promoter site of ANP gene has been found
- So, hypoxia may directly stimulate ANP and BNP secretion
- This raises some question about specificity of BNP elevation for heart failure

Hopkins WE et al. Circulation. 2004;109:2872

Table 2—*Results of CPX*

Variables	$\dot{V}O_2$, mL O_2/kg/min		$\dot{V}E$, L/min	$\dot{V}E/\dot{V}CO_2$ Ratio	$\dot{V}E$ vs $\dot{V}CO_2$ Slope
	AT	Peak	Rest	Rest	Exercise
Patients					
Mean	12.8	16.7	16.0	69.6	57.5
± SD	4.9	6.6	3.9	17.9	30.1
Control subjects					
Mean	20.7	36.1	12.8	52.5	26.2
± SD	5.1	7.7	3.1	11.2	4.1
p Value	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005

Stress Testing in Cyanotic Heart Disease

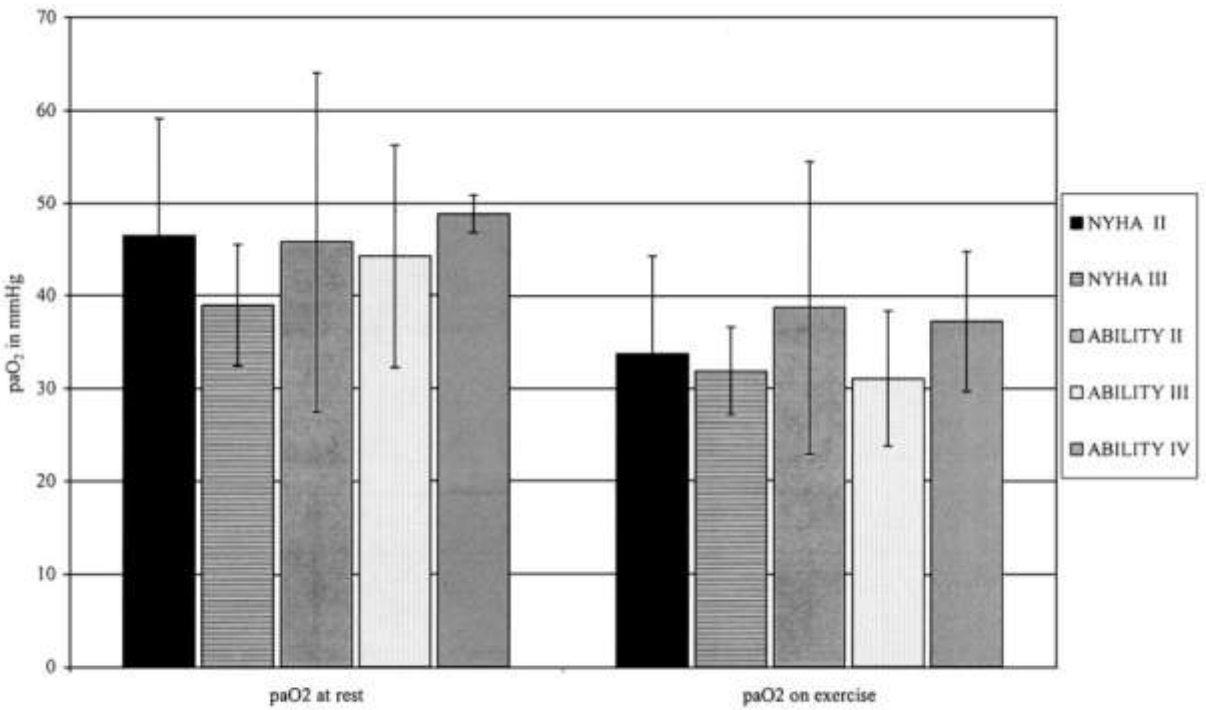


FIGURE 1. Mean PaO_2 at rest and under maximal exercise for groups in different NYHA and ability classes.

Glaser S et al. Chest. 2004;125:368.

Stress Testing in Cyanotic Heart Disease

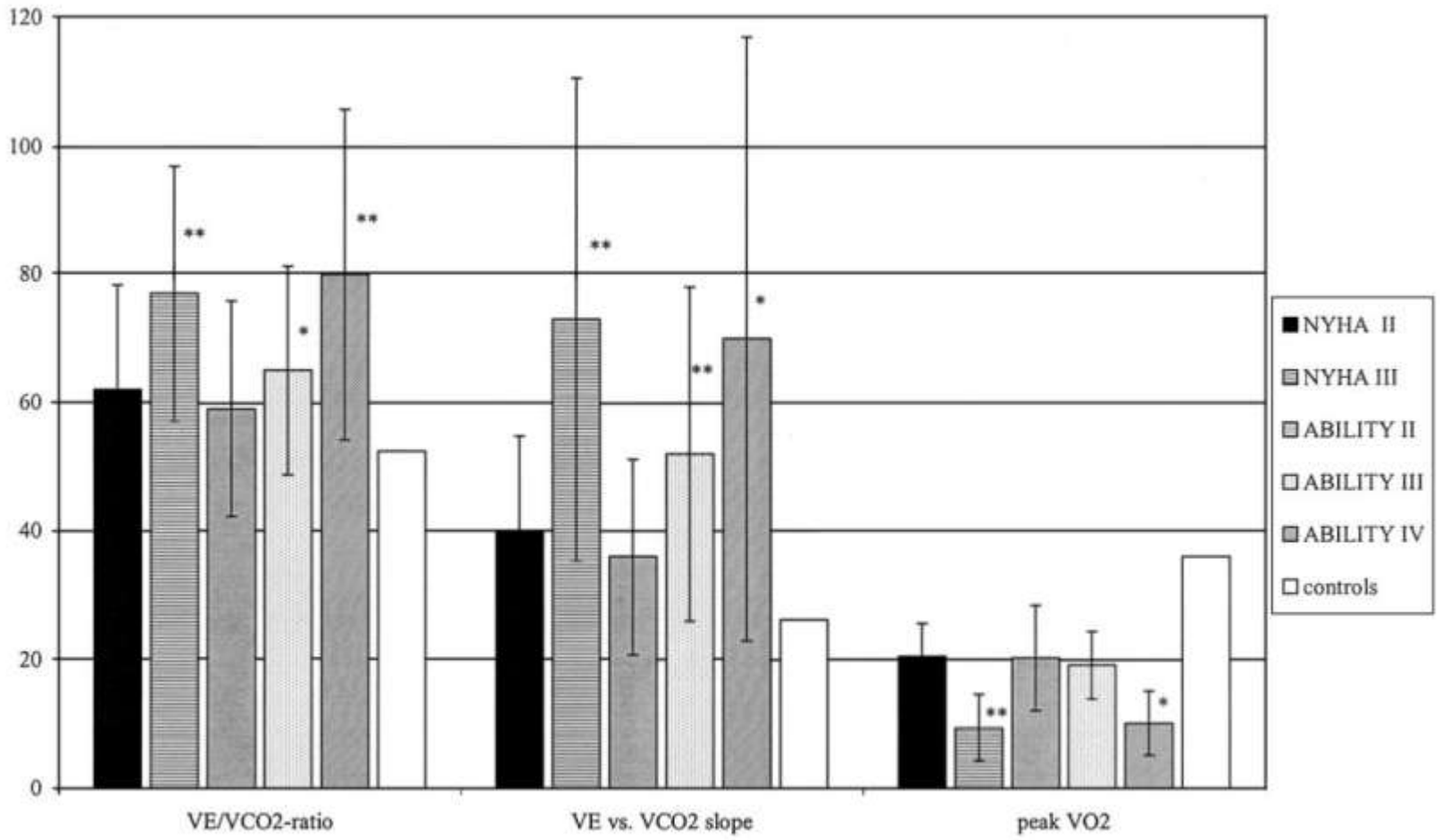


FIGURE 2. Mean CPX results for groups in different NYHA and ability classes compared to control subjects. Peak $\dot{V}O_2$ is shown as milliliters of oxygen per kilogram per minute. *$p < 0.05$, compared to lower class; **$p < 0.005$, compared to lower class.

Glaser S et al. Chest. 2004;125:368.

Abnormal Developmental Mechanisms

- Conus and great vessel development
- Intracardiac blood flow
  - Valve stenosis, atresia
  - ASD, VSD
- Cell death abnormality
- Extracellular matrix
- Abnormal targeted growth
- Abnormal situs and looping

TABLE 5.3. PATHOGENETIC CLASSIFICATION OF SOME CONGENITAL CARDIOVASCULAR MALFORMATIONS BASED ON COMMON DEVELOPMENTAL MECHANISM RATHER THAN ANATOMIC DETECT

Ectomesenchymal tissue migration abnormalities
- Conotruncal septation defects
  - Subarterial, type I ventricular septal defect
  - Double-outlet right ventricle
  - Tetralogy of Fallot
  - Pulmonary atresia with ventricular septal defect
  - Aorticopulmonary window
  - Truncus arteriosus communis
- Abnormal conotrucal cushion position
  - Transposition of the great arteries (–d)
- Branchial arch defects
  - Interrupted aortic arch type B
  - Double aortic arch
  - Right aortic arch with mirror-image branching

Abnormal intracardiac blood flow
- Perimembranous ventricular septal defect
- Left heart defects
  - Biscuspid aortic valve
  - Aortic valve stenosis
  - Coarctation of the aorta
  - Interrupted aortic arch type A
  - Hypoplastic left heart, aortic atresia:mitral atresia
- Right heart defects
  - Biscuspid pulmonary valve
  - Secundum atrial septal defect
  - Pulmonary valve stenosis
  - Pulmonary valve atresia with intact ventricular septum

Cell death abnormalities
- Muscular ventricular septal defect
- Ebstein's malformation of the tricuspid valve

Extracellular matrix abnormalities
- Endocardial cushion defects
  - Ostium premium atrial septal defect
  - Type III, inflow ventricular septal defect
  - Atrioventricular septal defect
- Dysplastic pulmonary or aortic valve

Abnormal targeted growth
- Anomalous pulmonary venous return

Abnormal situs and looping
- Heterotaxia, L-loop

?PDA

Moss and Adams, 2001, p. 68

TABLE 5.5. PREVALENCE OF SELECTED CONGENITAL CARDIOVASCULAR MALFORMATIONS PER 10,000 LIVE BIRTHS FROM CASES REGISTERED IN THE BALTIMORE–WASHINGTON INFANT STUDY, 1981–1989

	Defect	Prevalence per 10,000 live births					
7	*Transposition of the great arteries	7	*	2.64	T	8	4
	*Truncus arteriosus		*	0.69	T	9	2
	*Double-outlet right ventricle		*	0.49	*		
8	*Tetralogy of Fallot	8	*	2.60	T	7	6
6	AV septal defect	6		3.27			
10	Trisomy 21	10		2.32			
	Euploid			0.97			
	*Total anomalous pulmonary venous return		*	0.66	T		
5	*Tricuspid valve atresia, normal great vessels	5	*	3.6	T	10	1
	Ebstein's anomaly of the tricuspid valve			0.52			
11	*Hypoplastic left heart syndrome	11	*	1.78[a]	*		
4	Pulmonary valve stenosis	4		3.78[b]		4	7
2	*Pulmonary valve atresia, intact IVS	?2	*	5.8	*		
	Aortic valve stenosis, bicuspid aortic valve			0.81/0.74		6	6
13	Coarctation of the aorta	13		1.39		5	7
	Ventricular septal defect			15.57		1	30
1	Perimembranous	1		9.87			
3	Muscular	3		4.7[b]			
9	Atrial septal defect (isolated secundum type)	9		2.35		2	10
	Patent ductus arteriosus			0.88		3	10
12	*Laterality and looping including LTGA	12	*	1.44	*		

Moss and Adams, 2001. P. 69; Braunwald, 2001, p. 1506

Rank Order Percent