La sindrome di Eisenmenger

Sono pazienti che devono essere lasciati a sé stessi o oggi possediamo nuove opzioni terapeutiche ?

Dr.A.Donti

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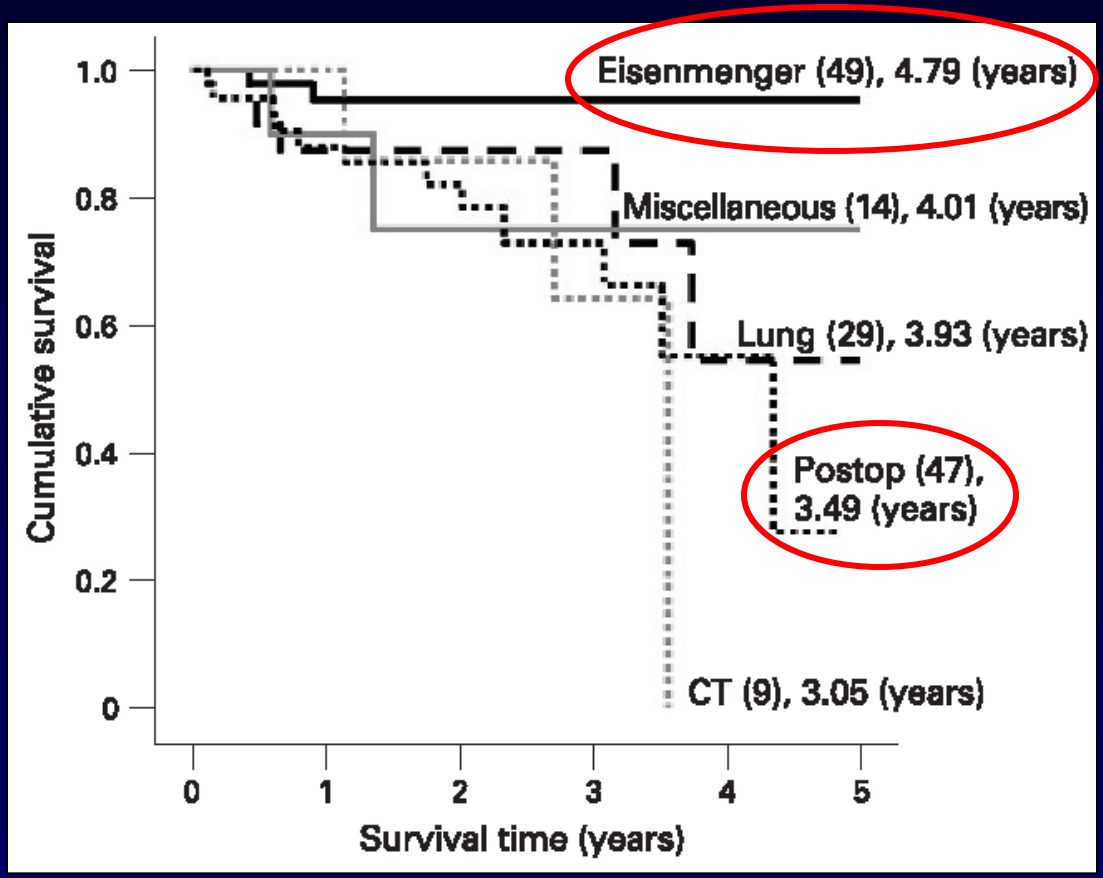
Centro Regionale per il cardiopatico congenito adulto
Policlinico S.Orsola-Malpighi
Università di Bologna

Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006

S G Haworth, A A Hislop

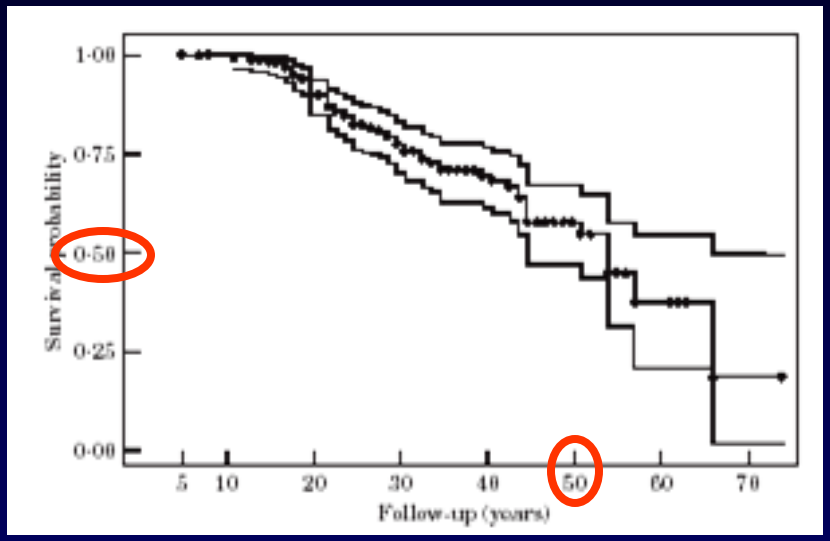


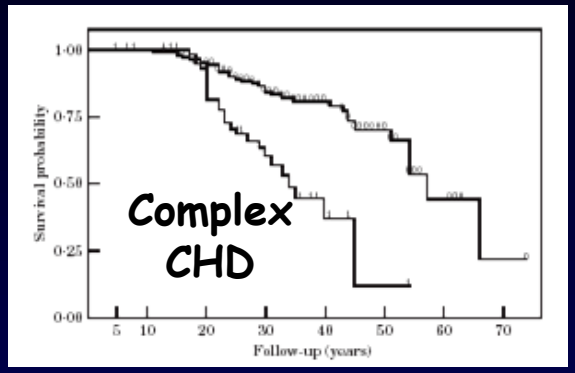
Haworth et al. Heart 2009;95:312-317

Eisenmenger syndrome

Factors relating to deterioration and death

(Eur Heart J 1998; 19: 1845–1855)





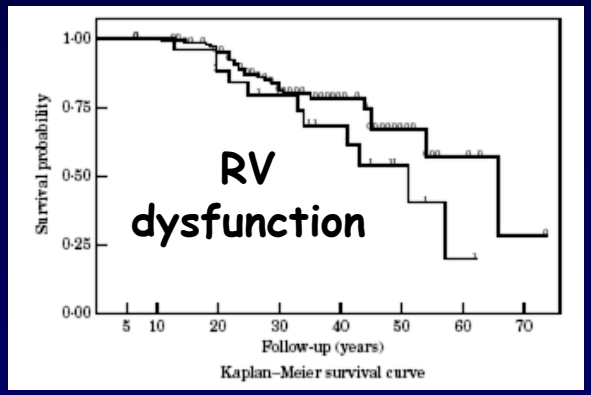


Table 4 Predictive factors of survival

Parameters	Hazard ratio	Standard error	*P*	95% confidence interval
Complex CHD	4·91	3·67	0·03	1·09–22·01
Creatinine	1·01	0·003	0·002	1·00–1·01
RV dysfunction	3·24	1·51	0·01	1·27–8·27
Age at onset of symptoms	0·83	0·02	<0·001	0·77–0·88

CHD=congenital heart defect; RV=right ventricular.

Il paziente con sindrome di Eisenmenger va ……accudito !

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Table 22 Risk reduction strategies in patients with cyanotic congenital heart disease

Prophylactic measures are the mainstay of care to avoid complications. The following exposures/activities should be avoided:
• Pregnancy
• Iron deficiency and anaemia (no routine, inappropriate phlebotomies to maintain a pre-determined haemoglobin)
• Dehydration
• Infectious disease: annual influenza vaccination, pneumovax (every 5 years)
• Cigarette smoking, recreational drug abuse including alcohol
• Transvenous PM/ICD leads
• Strenuous exercise
• Acute exposure to heat (sauna, hot tub/shower)

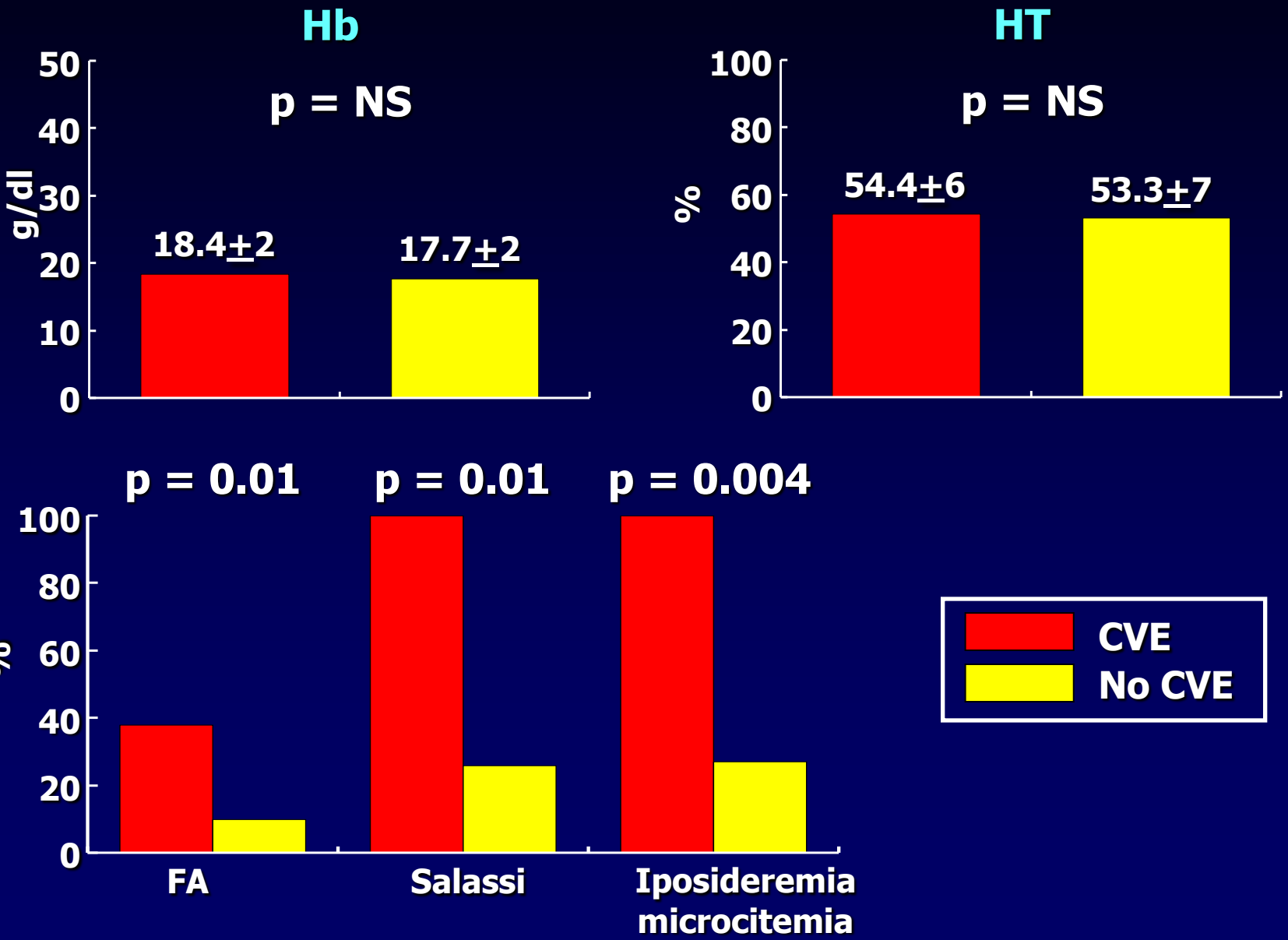
Other risk reduction strategies include:
• Use of an air filter in an intravenous line to prevent air embolism
• Consultation of a GUCH cardiologist before administration of any agent and performance of any surgical/interventional procedure
• Prompt therapy of upper respiratory tract infections
• Cautious use or avoidance of agents that impair renal function
• Contraceptive advice

Il salasso nel paziente cianotico : quando e perchè ??

Ogni volta che Ht > 60%
per prevenire il rischio di eventi cerebrovascolari ??

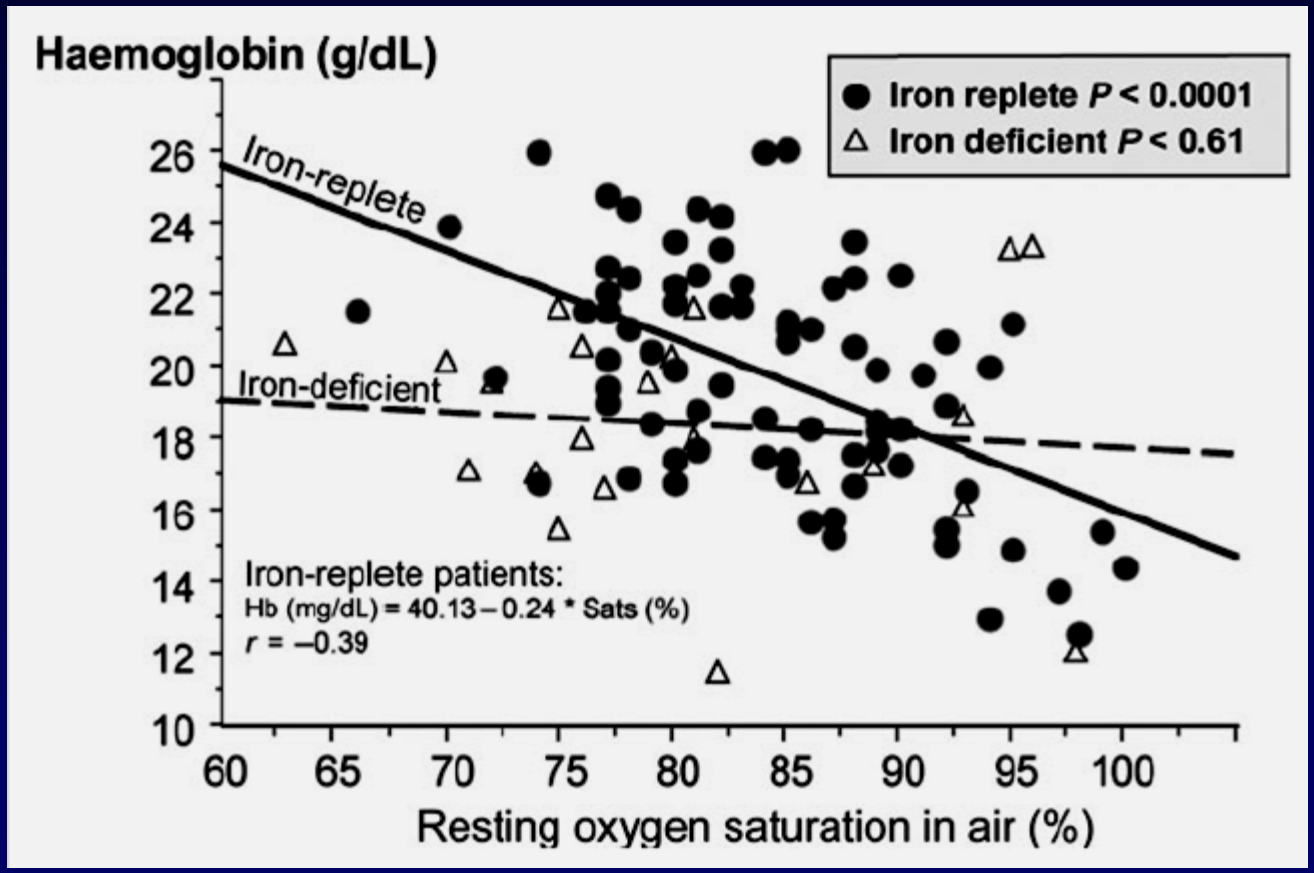
Cerebrovascular Events in Adult Patients With Cyanotic Congenital Heart Disease

N. Ammash et al., J Am Coll Cardiol 1996; 28: 768-772



Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case–control study

Gerhard-Paul Diller[1,2], Konstantinos Dimopoulos[1,2], Craig S. Broberg[1], Mehmet G. Kaya[1], Utpal Singh Naghotra[1], Anselm Uebing[1,3], Carl Harries[1], Omer Goktekin[1], J. Simon R. Gibbs[2,4], and Michael A. Gatzoulis[1,2*]



Eur Heart J 2006; 27: 1737-42

Il salasso nel paziente cianotico :

- 1) Ht > 65% o Hb > 20g/dl + sintomi da iperviscosità (esclusa disidratazione)

Prelievo di 300-400 ml di sangue
+ infusione contemporanea o precedente di SF 700-1000 ml

ESC Guidelines for the management of grown-up congenital heart disease (new version 2010)

The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric Cardiology (AEPC)

- Blood transfusion may be required in the presence of iron-replete anaemia (haemoglobin inadequate to oxygen saturation).
- Iron supplementation should be performed in the presence of iron deficiency (MCV <80 fL) and carefully followed (rebound effect).

Es : Fe trivalente 62.5 mg/die per 2-3 settimane seguito da controllo
HB – MCV – Fe - %sat transferrina - ferritina

Il salasso nel paziente cianotico :

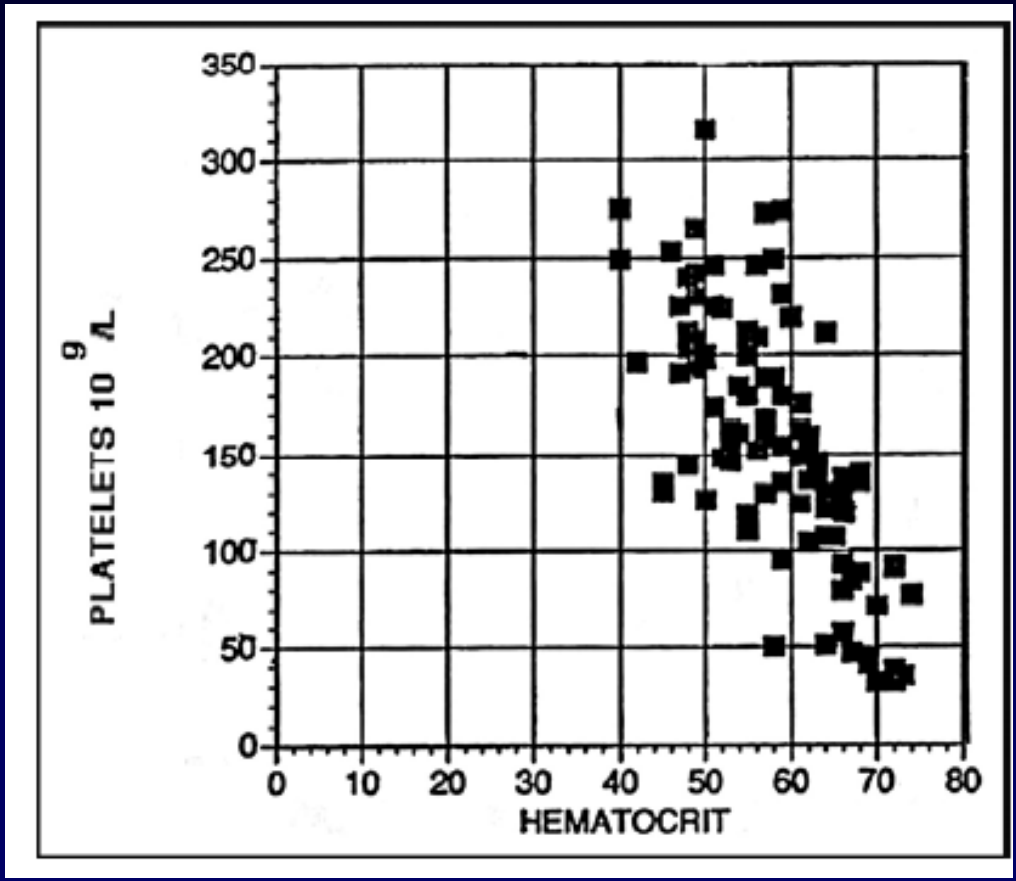
- 2) Ht > 60% in caso di intervento chirurgico **(colecistectomia , …..)**

Per ridurre il rischio emorragico (+ autotrasfusione)

Pathogenesis of Thrombocytopenia in Cyanotic Congenital Heart Disease

Michael C. Lill, MD, Joseph K. Perloff, MD*, and John S. Child, MD

Am J Cardiol 2006; 98: 254 - 58



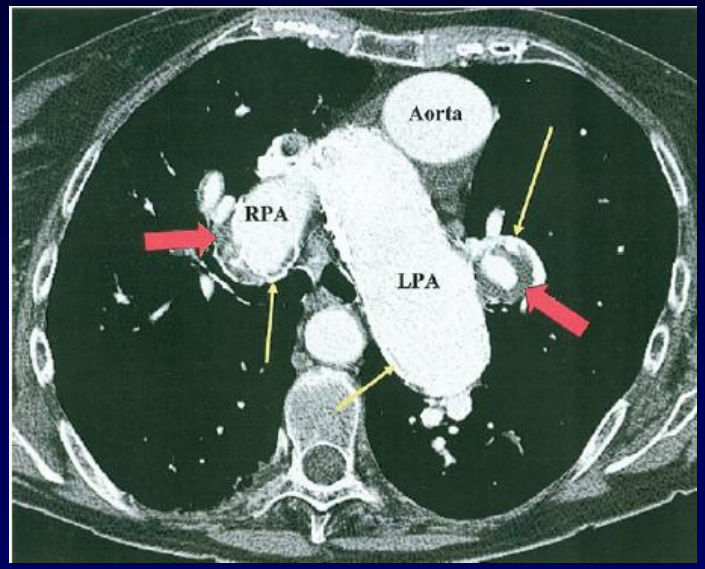
Eisenmenger
Terapia anticoagulante si o no ?

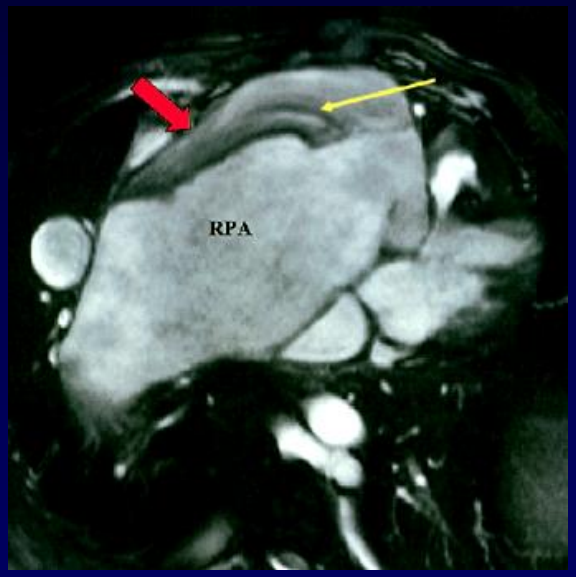
PRO	CONTRO
↑ rischio trombotico	↑ rischio emorragico
❖ stasi ematica (AP)	❖ piastrinopenia/patia
❖ disfunzione endoteliale	❖ deficit fattori K dip.
❖ aterosclerosi	❖ > attività fibrinolitica
❖ materiali protesici	❖ < fatt. Von Willebrand
❖ aritmie (FA)	
↓	↓
Trombosi arterie polmonari TIA/Ictus	***Emottisi Altre emorragie***

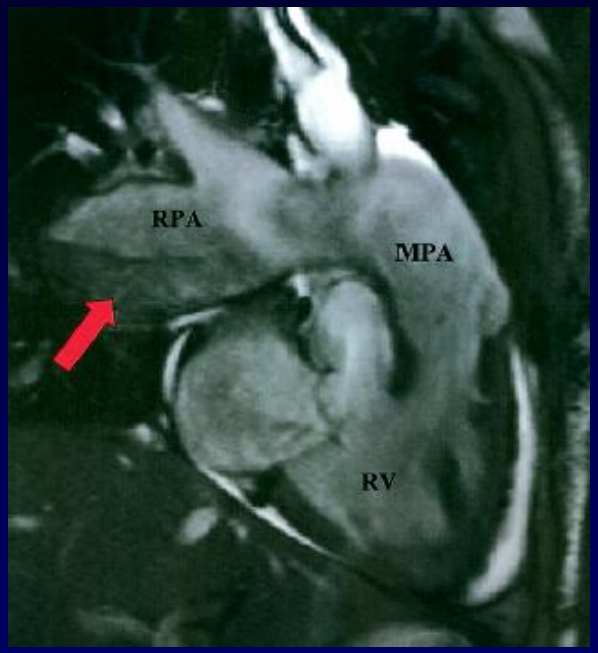
Pulmonary Arterial Thrombosis in Eisenmenger Syndrome Is Associated With Biventricular Dysfunction and Decreased Pulmonary Flow Velocity

Craig S. Broberg, MD,*† Masuo Ujita, MD,‡ Sanjay Prasad, MD,§ Wei Li, MD, PHD,*
Michael Rubens, FRCR,‡ Bridget E. Bax, PHD,‖ Simon J. Davidson, FIBMS, CSCI,¶
Beatriz Bouzas, MD,* J. Simon R. Gibbs, MD,# John Burman, MD,¶
Michael A. Gatzoulis, MD, PHD*

JACC 2007; 50: 634 - 42



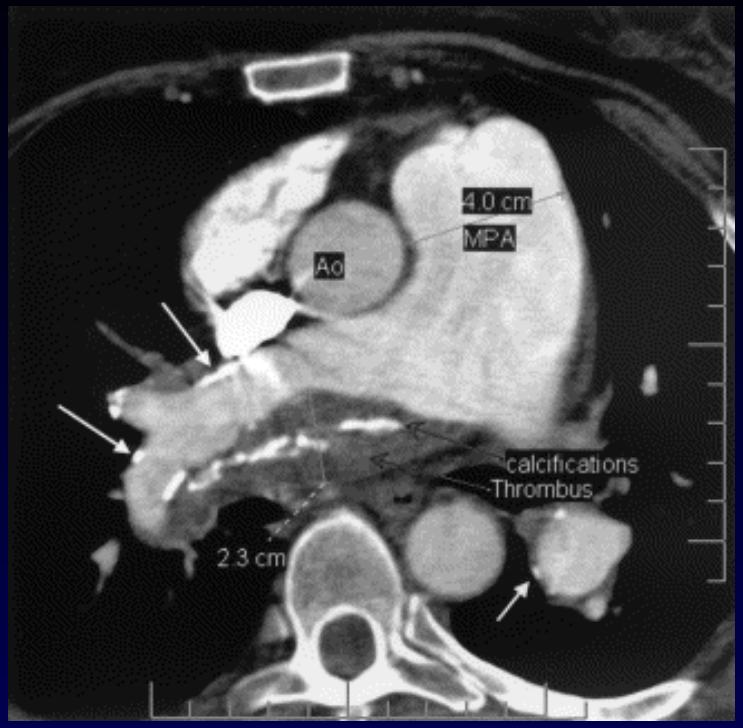


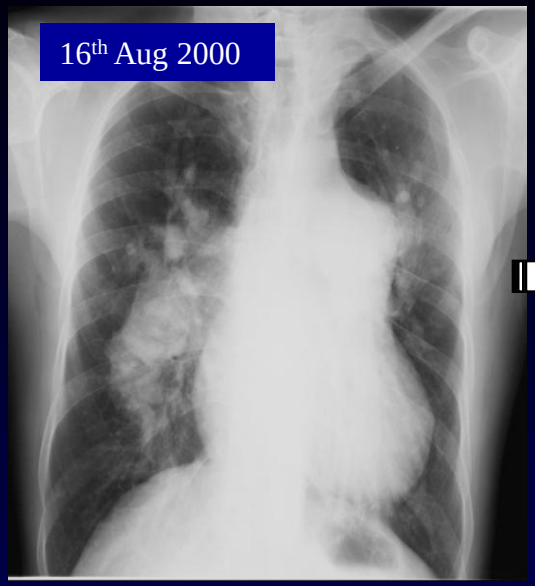


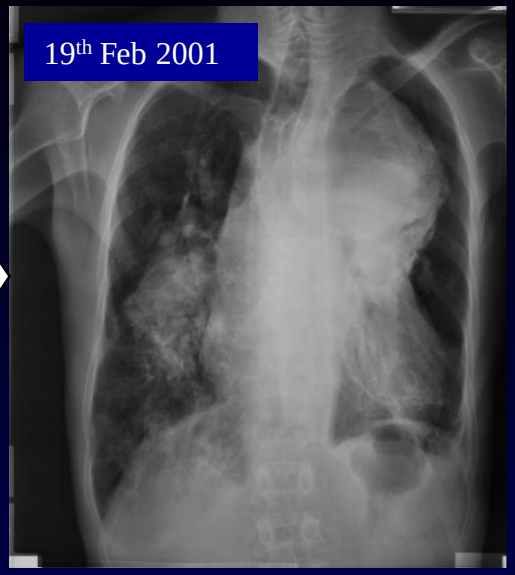
~20% dei pz Eisenmenger

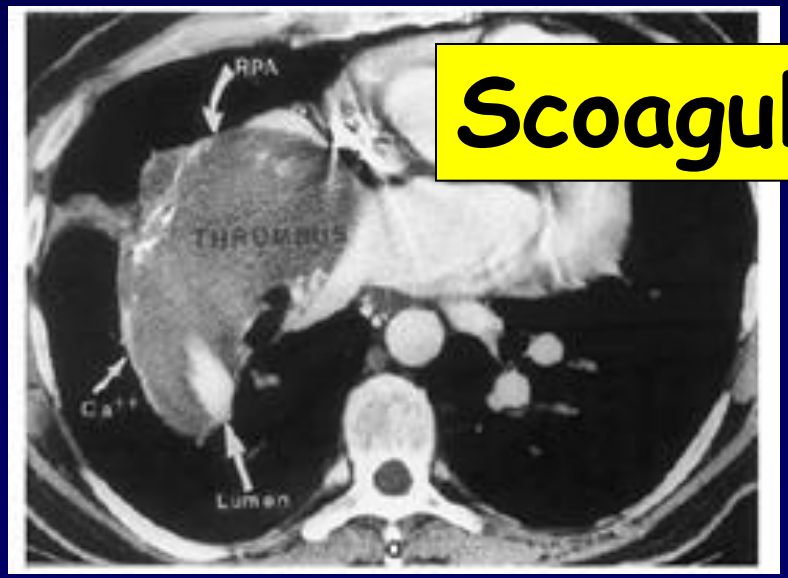
Rischio aumenta se :

Età avanzata – dilatazione severa AP – disfunzione VDx e VSn

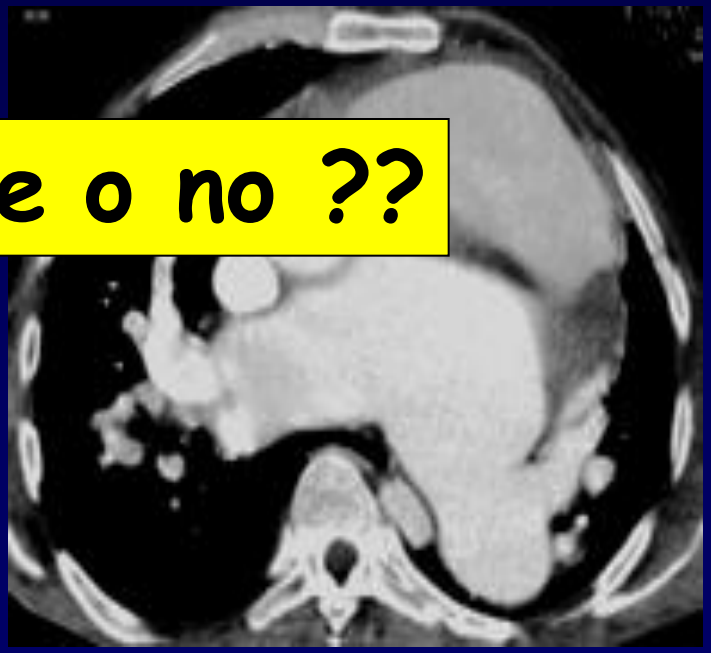








Scoagulare o no ??



Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Table 25 **Recommendations for PAH associated with congenital cardiac shunts**

Statement	Class[a]	Level[b]
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C

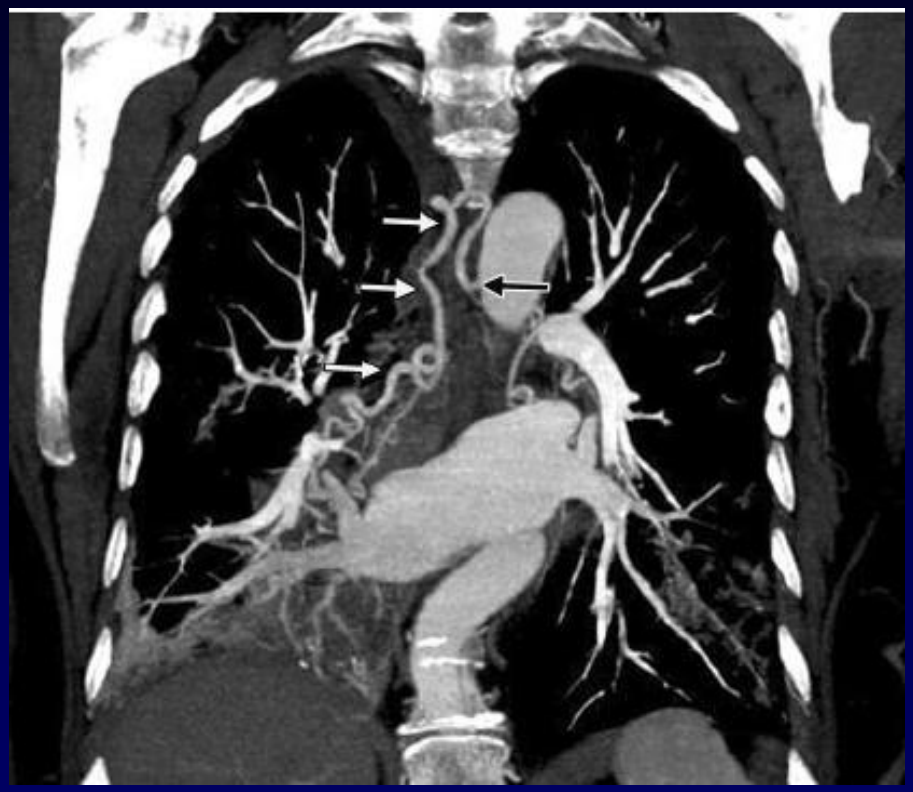
Blood Samples

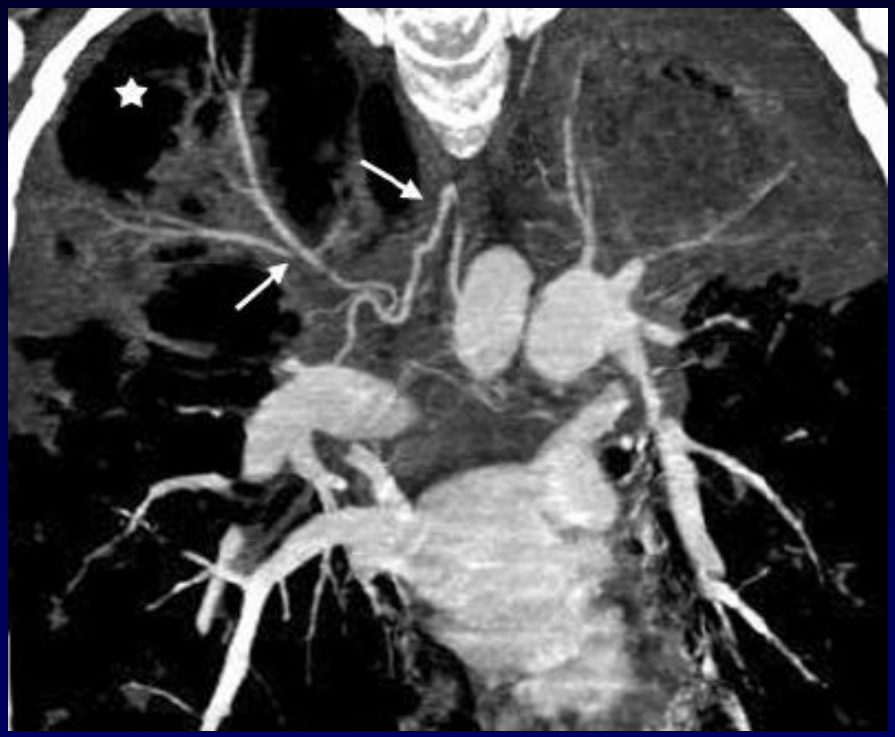
Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma *[B]*, *[R]*.

- The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient's hematocrit is greater than 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted *[R]*.
- Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing *[R]*.

Correggere la quantità di citrato in base ai valori di Ht se Ht > 55% !!

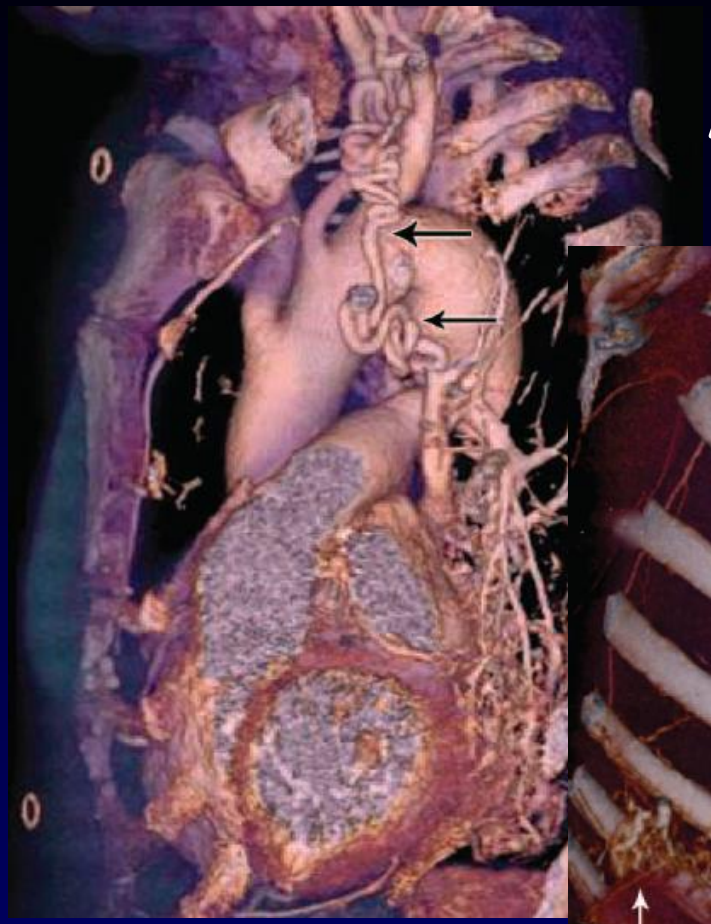
Emottisi
l'importanza della TC multistrato

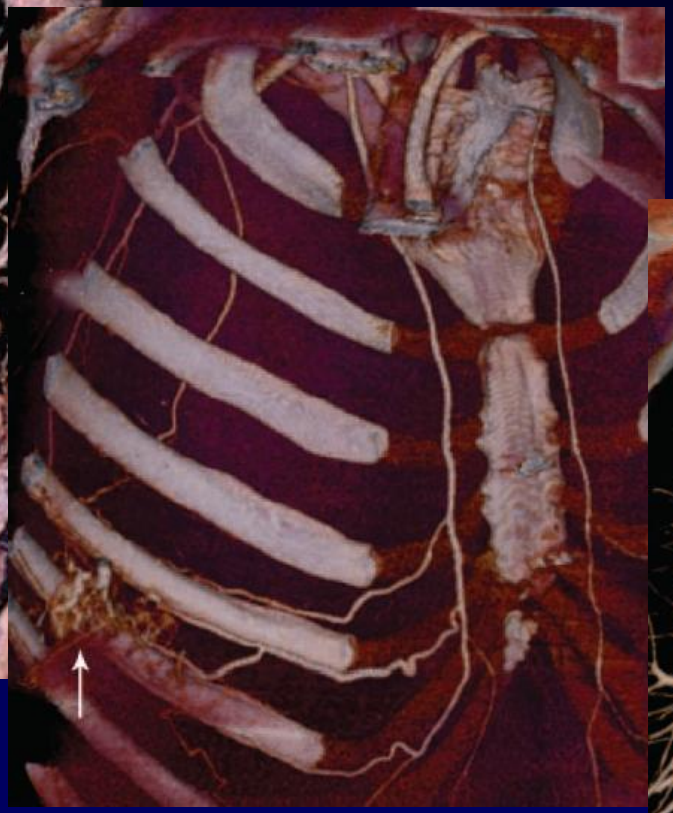


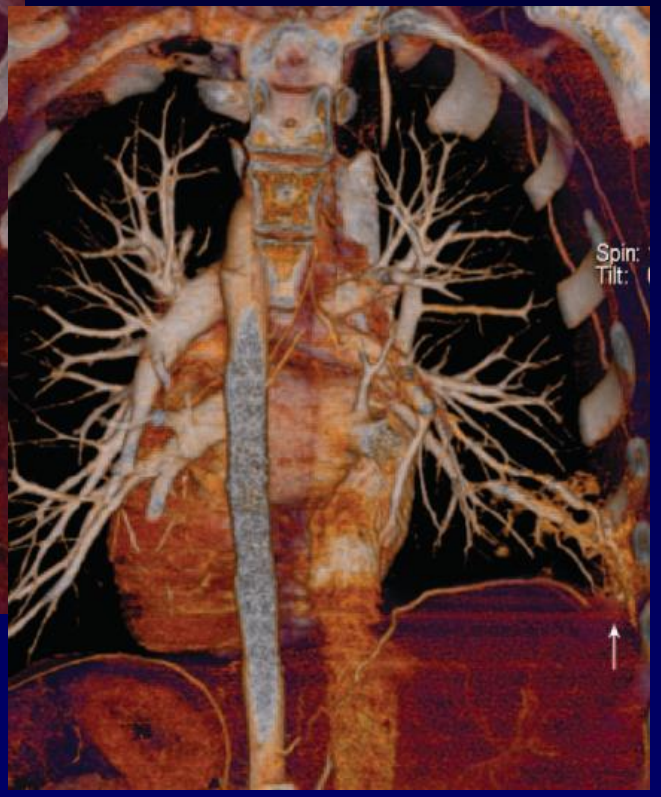


Arterie bronchiali

Emottisi
l'importanza della TC multistrato

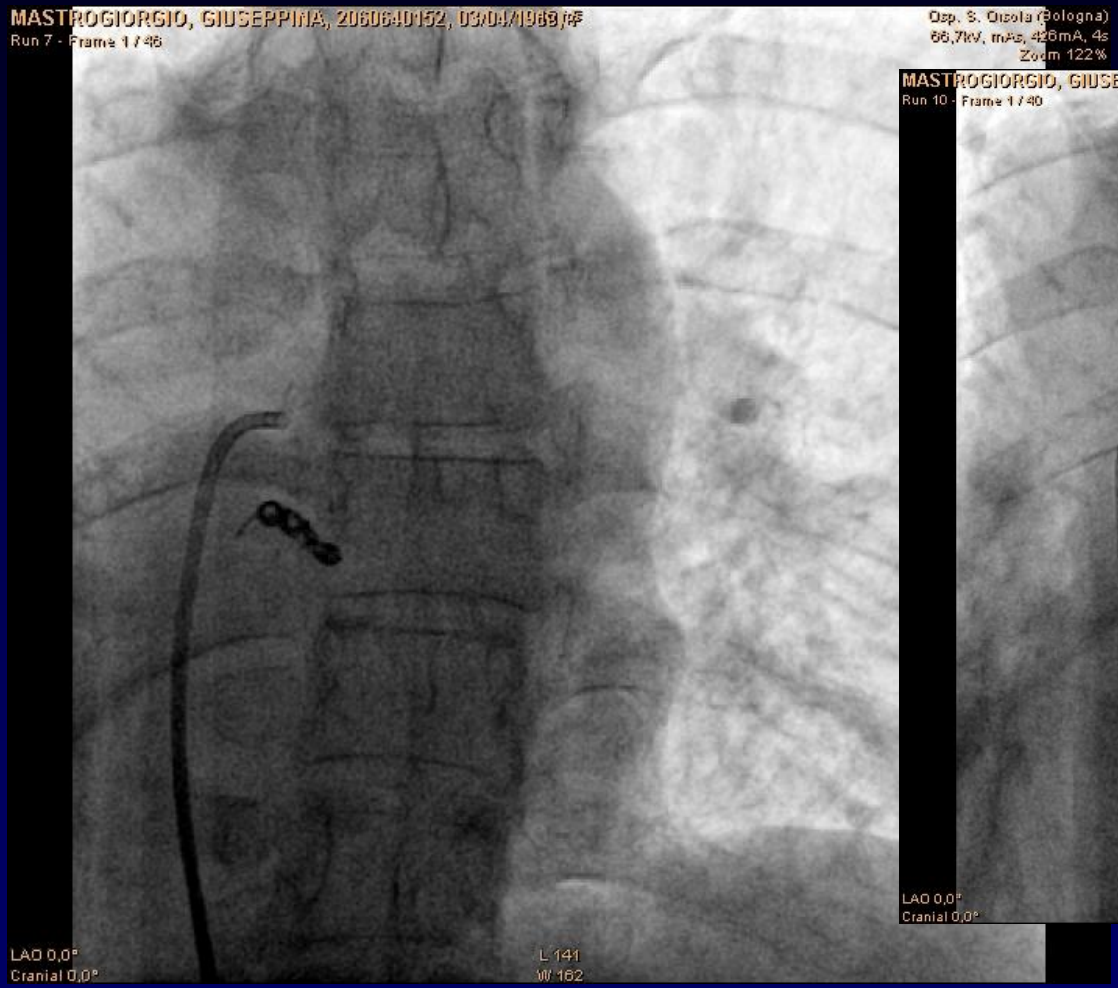


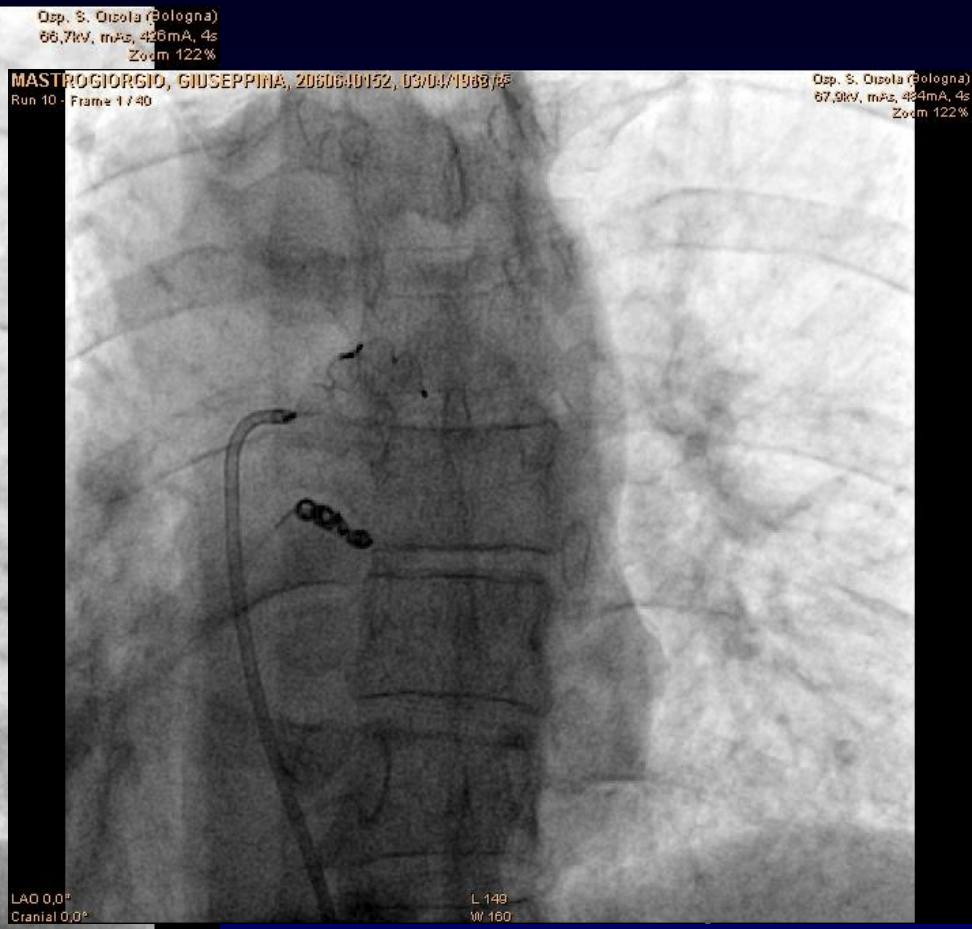




Collaterali sistemico-polmonari

M.G. ♂ 51aa
Isomerismo sn. Cardiopatia complessa in storia naturale

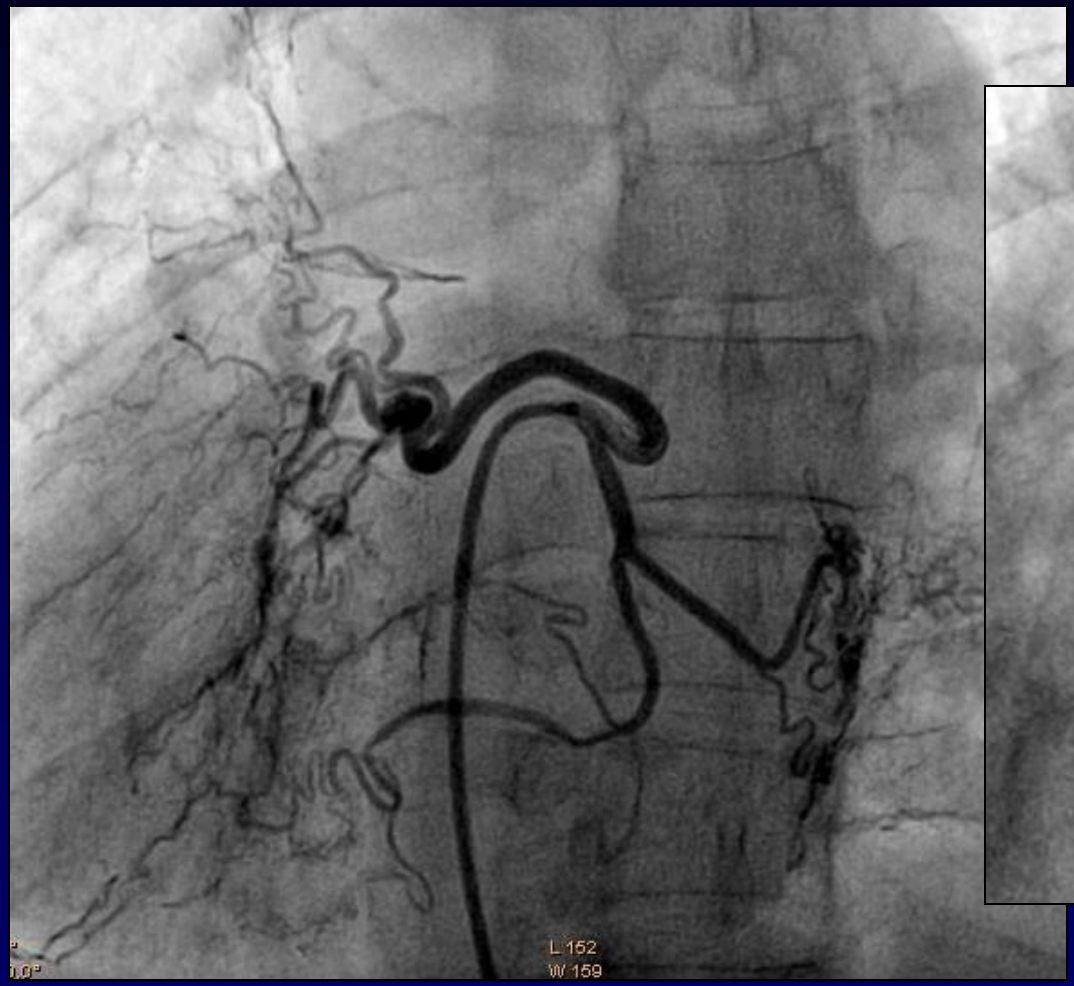


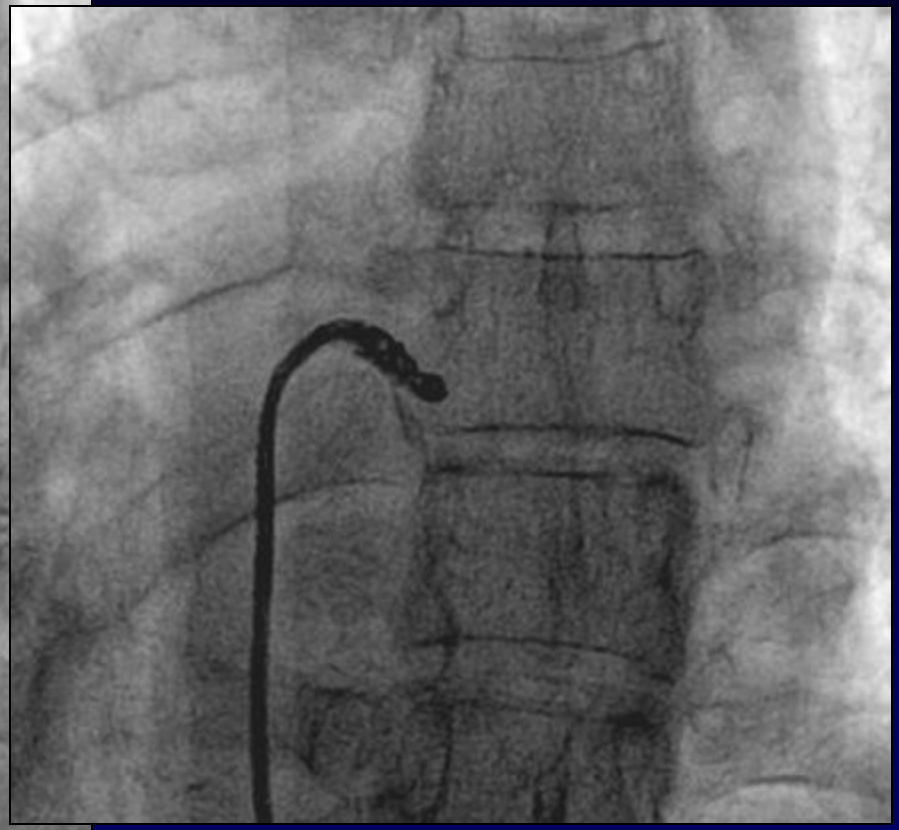


Sat.O2 80% + emottisi recidivanti

M.G. ♂ 51aa

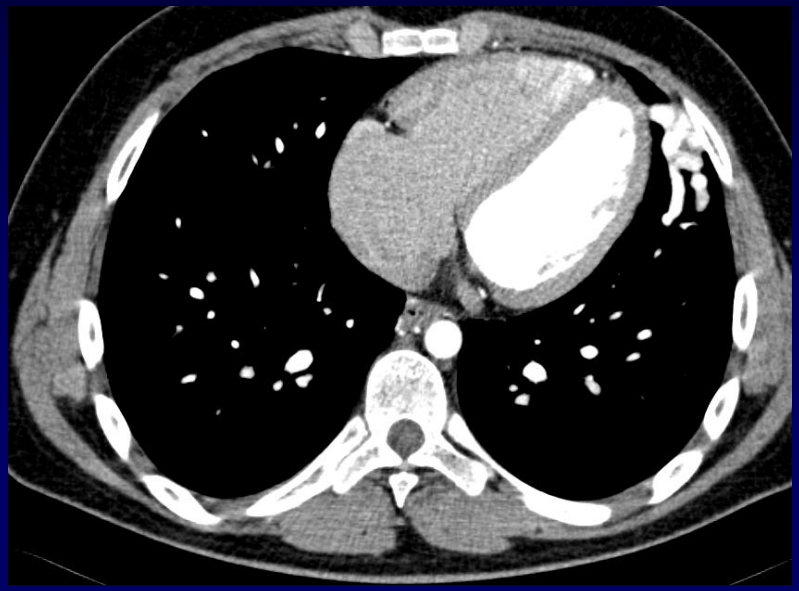
Isomerismo sn. Cardiopatia complessa in storia naturale

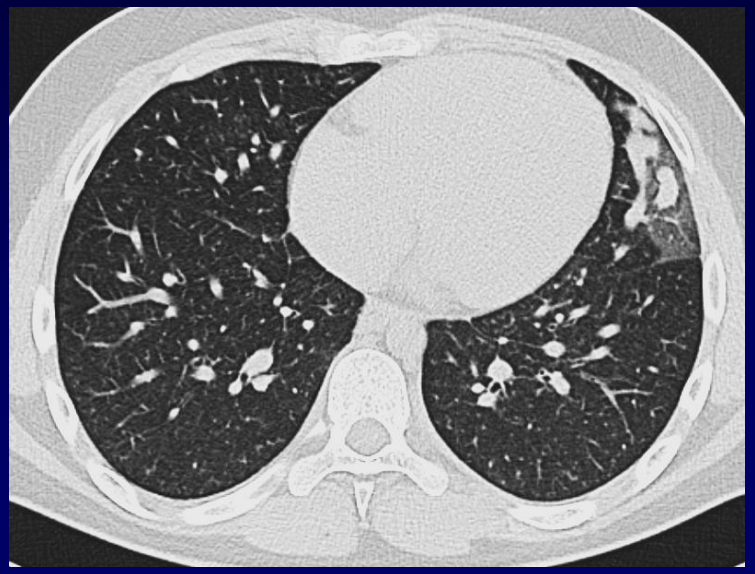


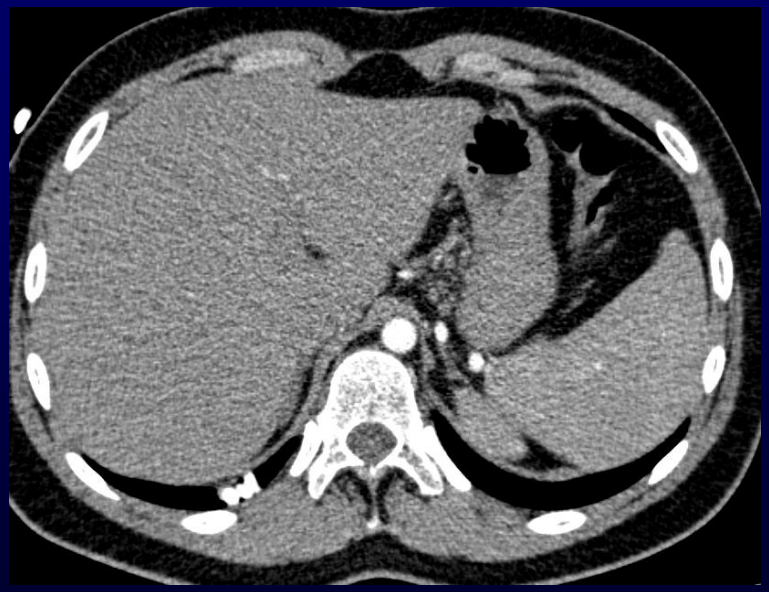


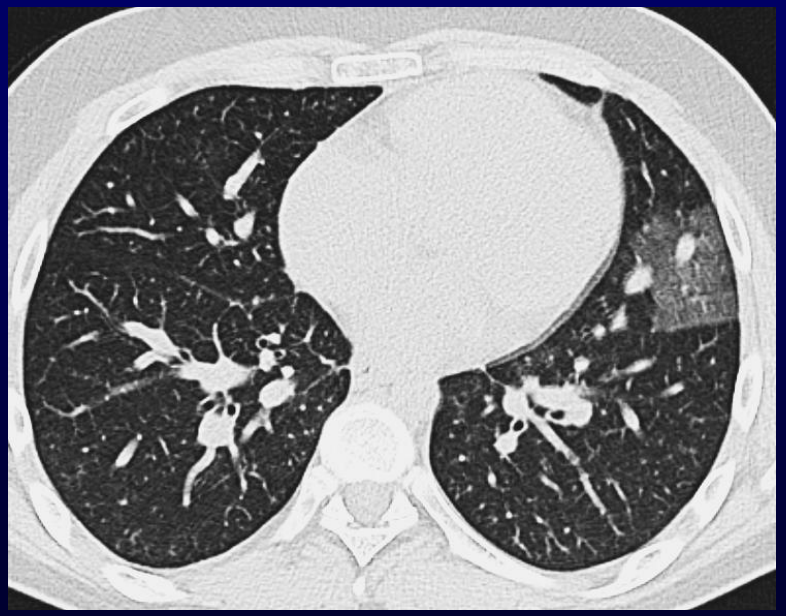
Sat.O2 80% + emottisi recidivanti

M.C. 20 aa. IAP idiopatica
Emottisi recidivante : qual'è la sorgente?

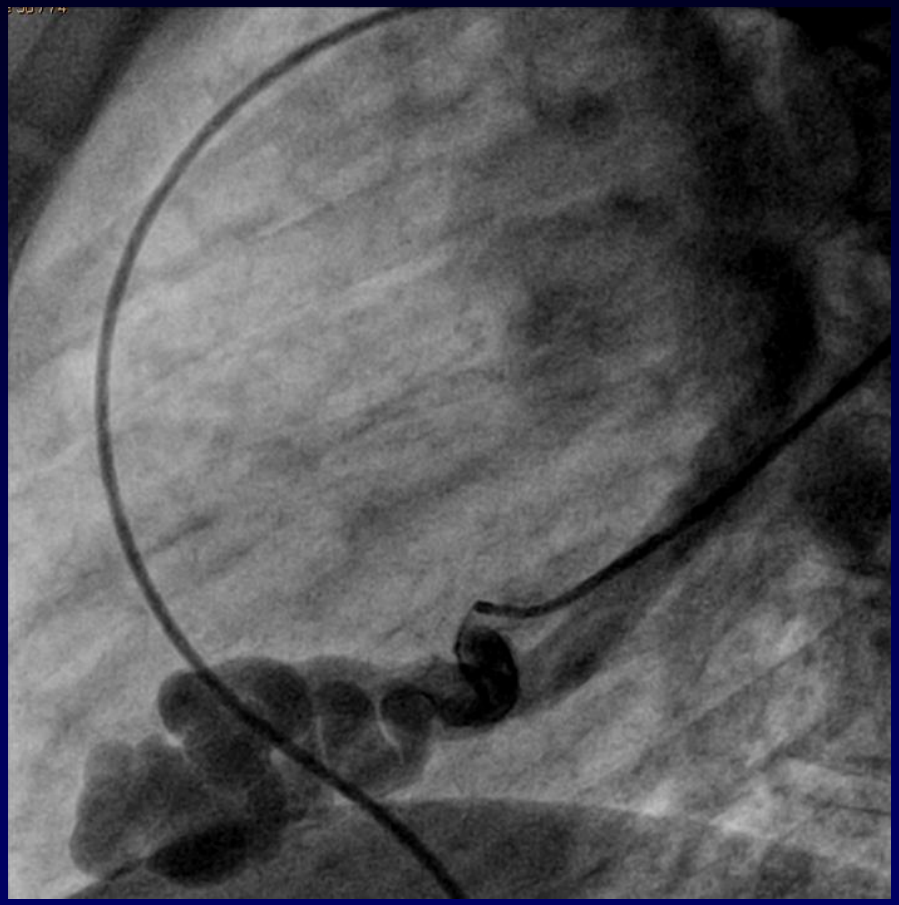


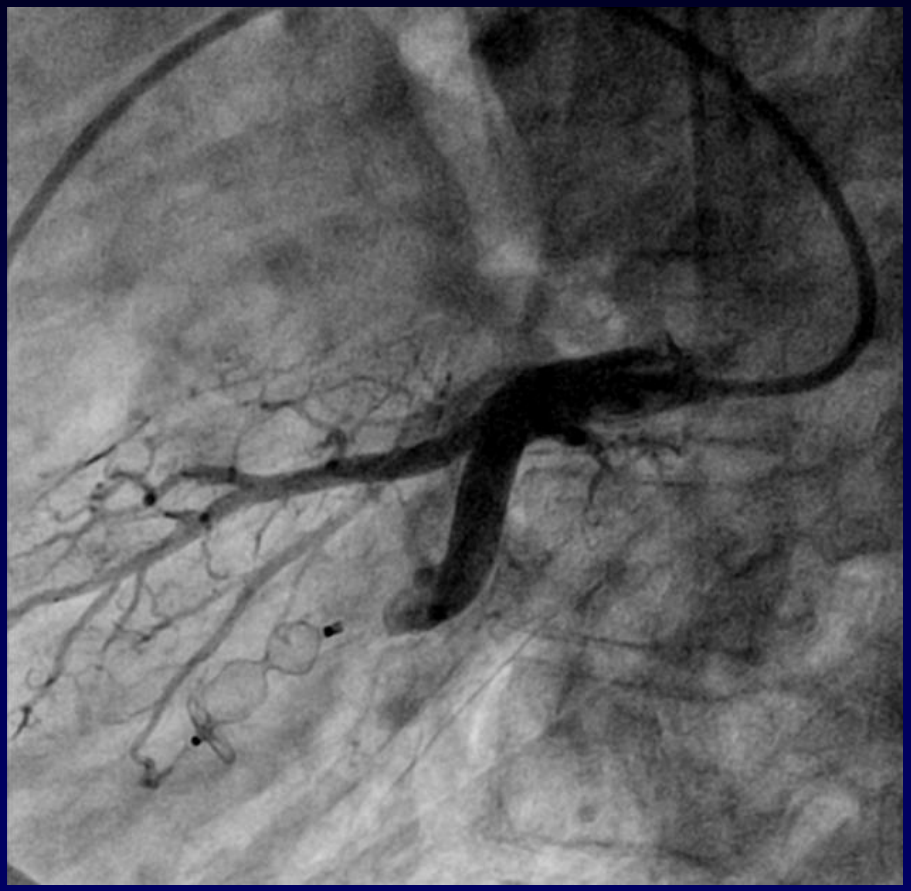




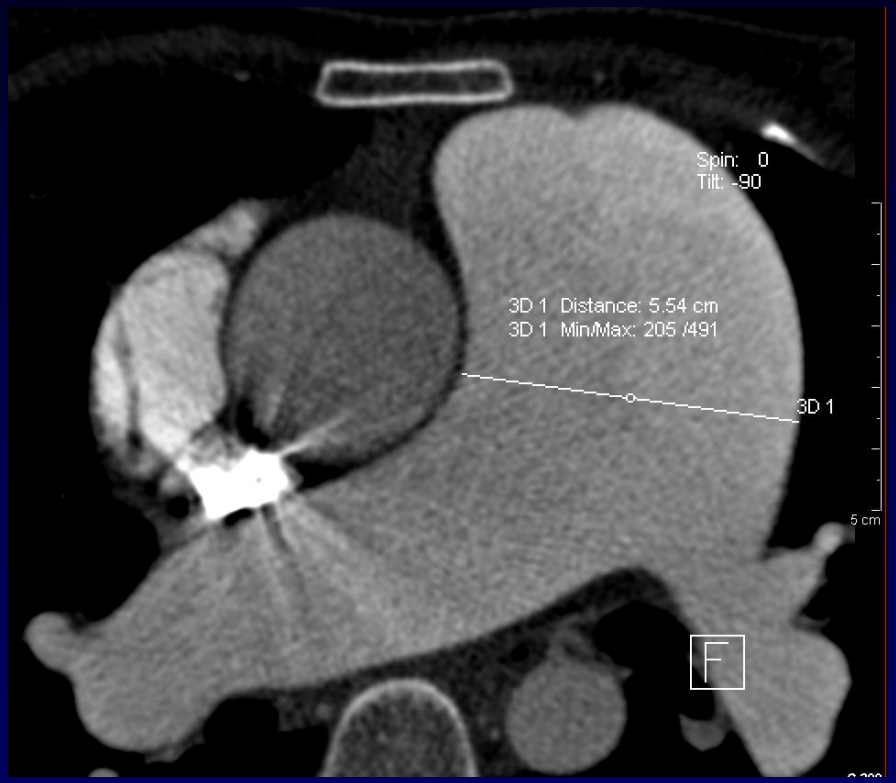


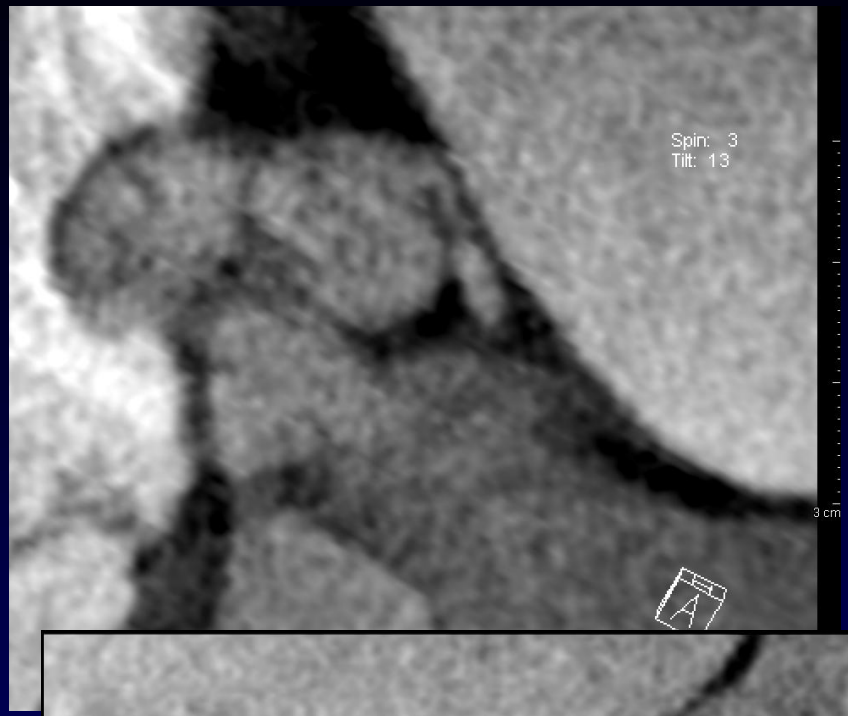
M.C. 20 aa. IAP idiopatica
Emottisi recidivante

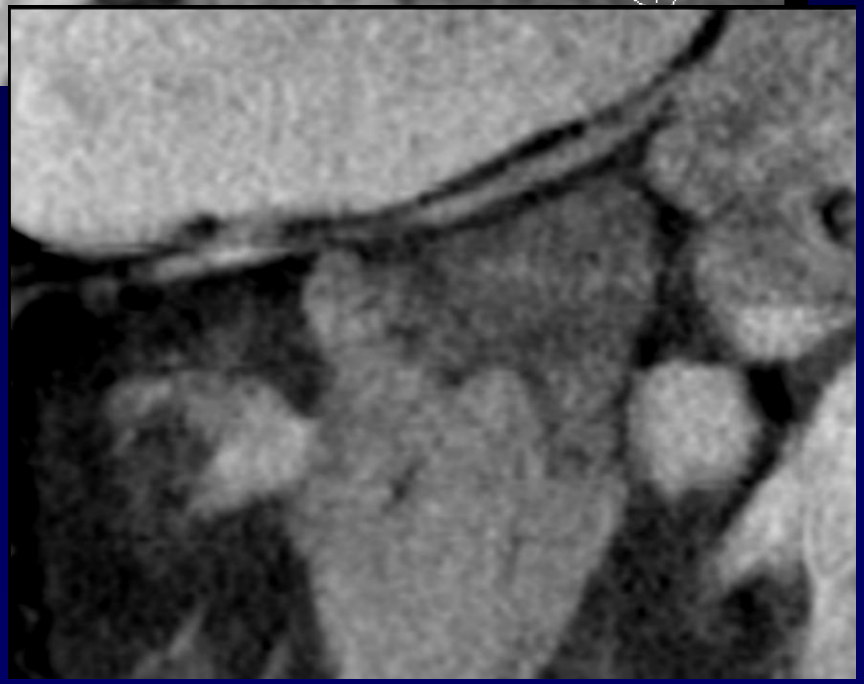




Dolore toracico/sincope da sforzo
Attenzione alla coronaria sinistra !!
Compressione TC

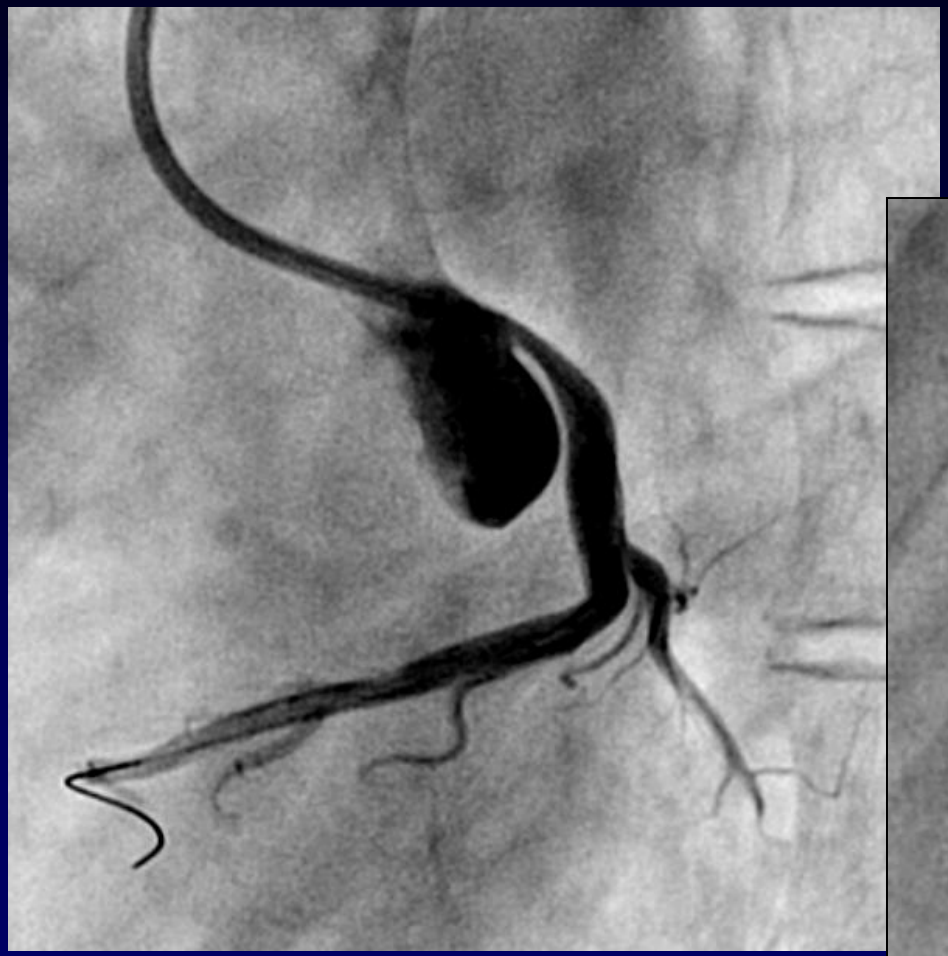


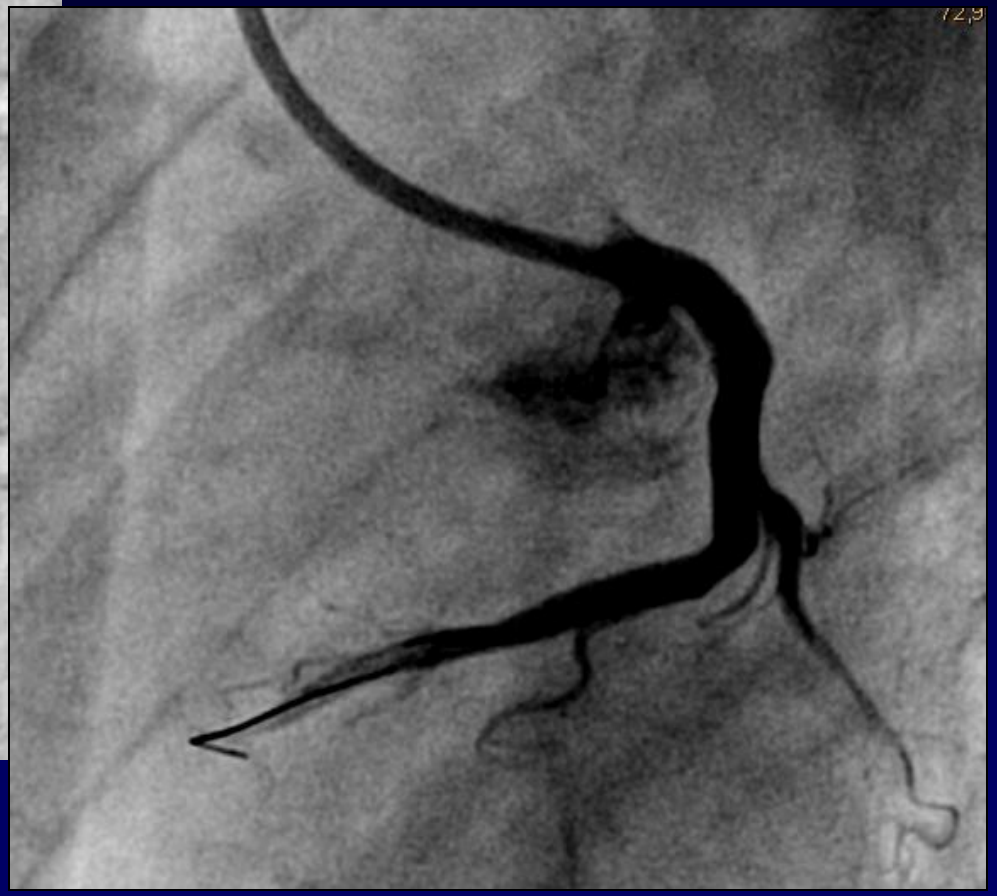




D.S. 38 aa
DIV-Eisenmenger
Sincope da sforzo

D.S. 38 aa
DIV-Eisenmenger
Sincope da sforzo





Guidelines for the diagnosis and treatment of pulmonary hypertension

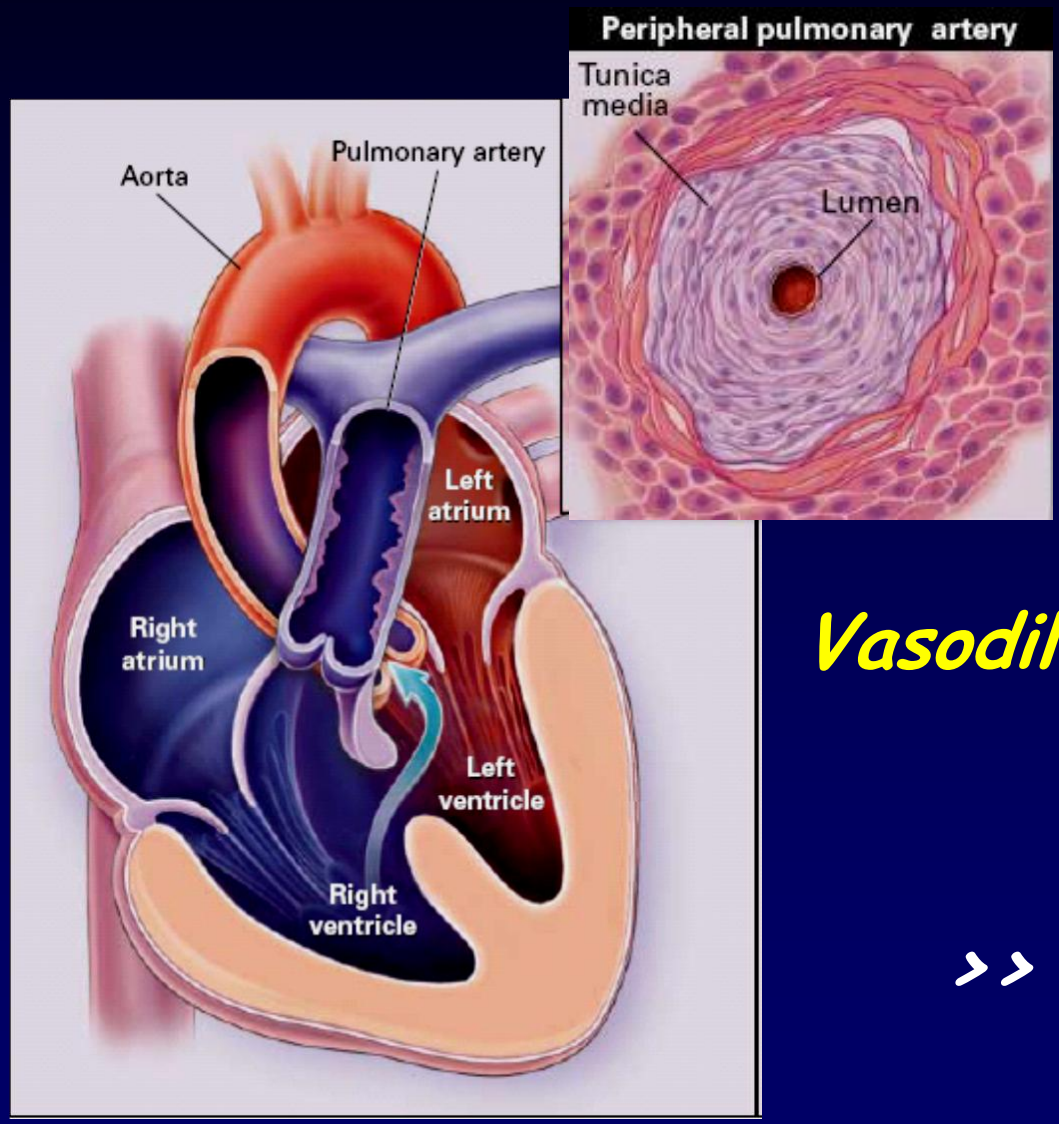
The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1	**Pulmonary arterial hypertension (PAH)**
1.1	Idiopathic
1.2	Heritable
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3	Unknown
1.3	Drugs and toxins induced
1.4	Associated with (APAH)
1.4.1	Connective tissue diseases
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.4.6	Chronic haemolytic anaemia
1.5	Persistent pulmonary hypertension of the newborn
1′	**Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**

- Epoprostenolo e prostanoidi
- Inibitori PDE5
- Antagonisti recettori Endotelina

Ventricolo destro sistemico : la sindrome di Eisenmenger



Vasodilatatore polmonare

>> shunt dx/sn ??

Bosentan Therapy in Patients With Eisenmenger Syndrome

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

Nazzareno Galiè, MD; Maurice Beghetti, MD; Michael A. Gatzoulis, MD; John Granton, MD; Rolf M.F. Berger, MD; Andrea Lauer, PhD; Eleonora Chiossi, MSc; Michael Landzberg, MD; for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators

54 pazienti - classe WHO III- F.Up 16 sett.

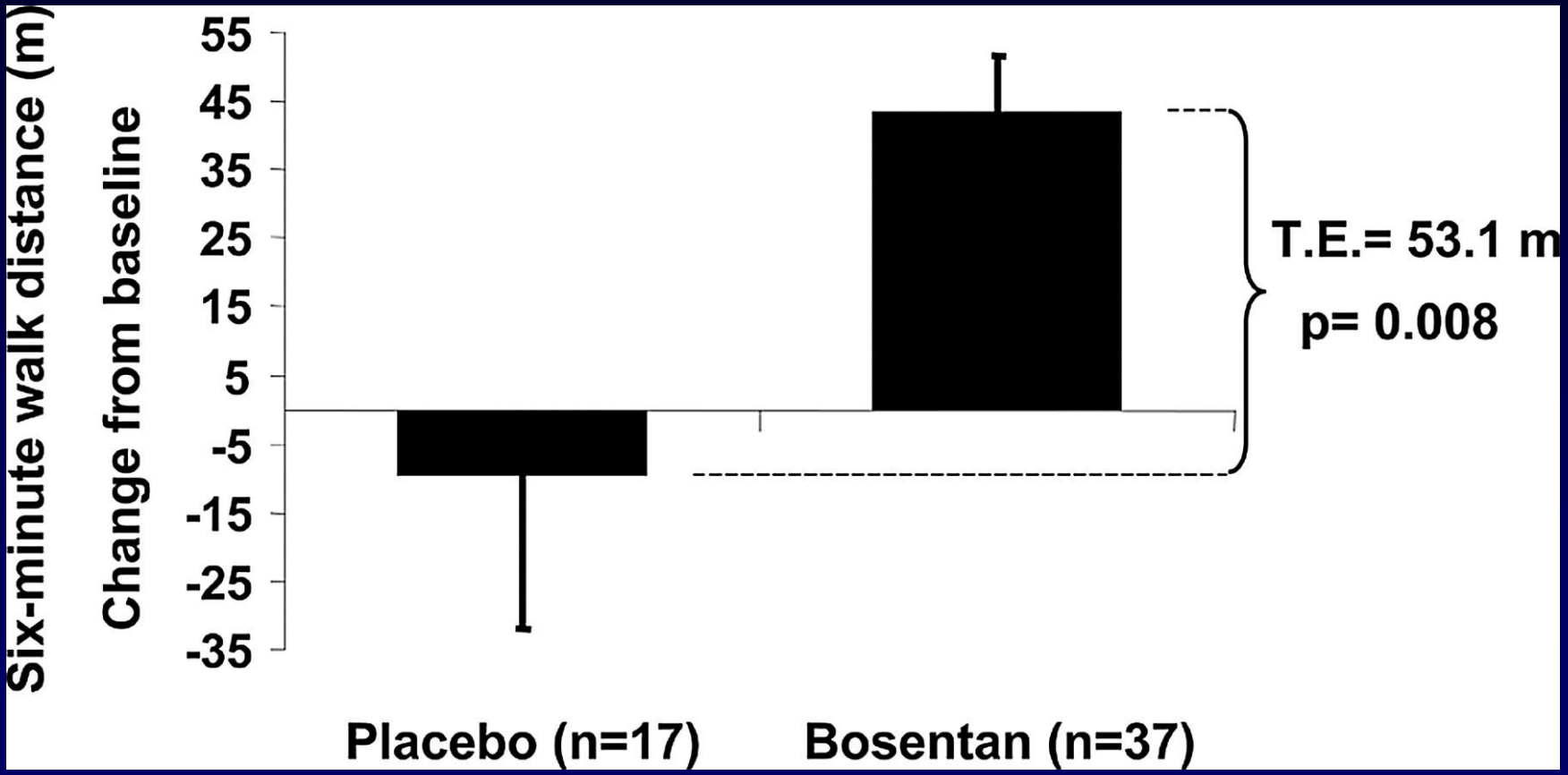
	Change From Baseline		Treatment Effect	
Parameter	Placebo (n=17)*	Bosentan (n=37)*	(Bosentan–Placebo)	*P*
Heart rate, bpm	–0.8 (2.7)	–2.0 (1.9)	–1.2 (3.4)	0.7329
Mean pulmonary arterial pressure, mm Hg	0.5 (1.4)	–5.0 (1.6)	–5.5 (2.5)	0.0363
Mean left atrial pressure,† mm Hg	0.5 (1.2)	0.4 (0.6)	–0.2 (1.3)	0.8862
Pulmonary flow index, $L \cdot min^{-1} \cdot m^{-2}$	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.4675
Pulmonary vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	155.1 (134.0)	–316.9 (138.3)	–472.0 (221.9)	0.0383
Mean systemic arterial pressure, mm Hg	2.5 (2.2)	–3.8 (1.6)	–6.3 (2.8)	0.0282
Mean right atrial pressure, mm Hg	0.4 (0.9)	0.3 (0.5)	–0.1 (1.0)	0.9448
Systemic flow index, $L \cdot min^{-1} \cdot m^{-2}$	–0.2 (0.1)	0.9 (0.8)	1.1 (1.1)	0.2981
Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	378.9 (246.8)	–372.9 (244.6)	–751.8 (388.4)	0.0595

Galie'et al. Circulation 2006

Bosentan Therapy in Patients With Eisenmenger Syndrome

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

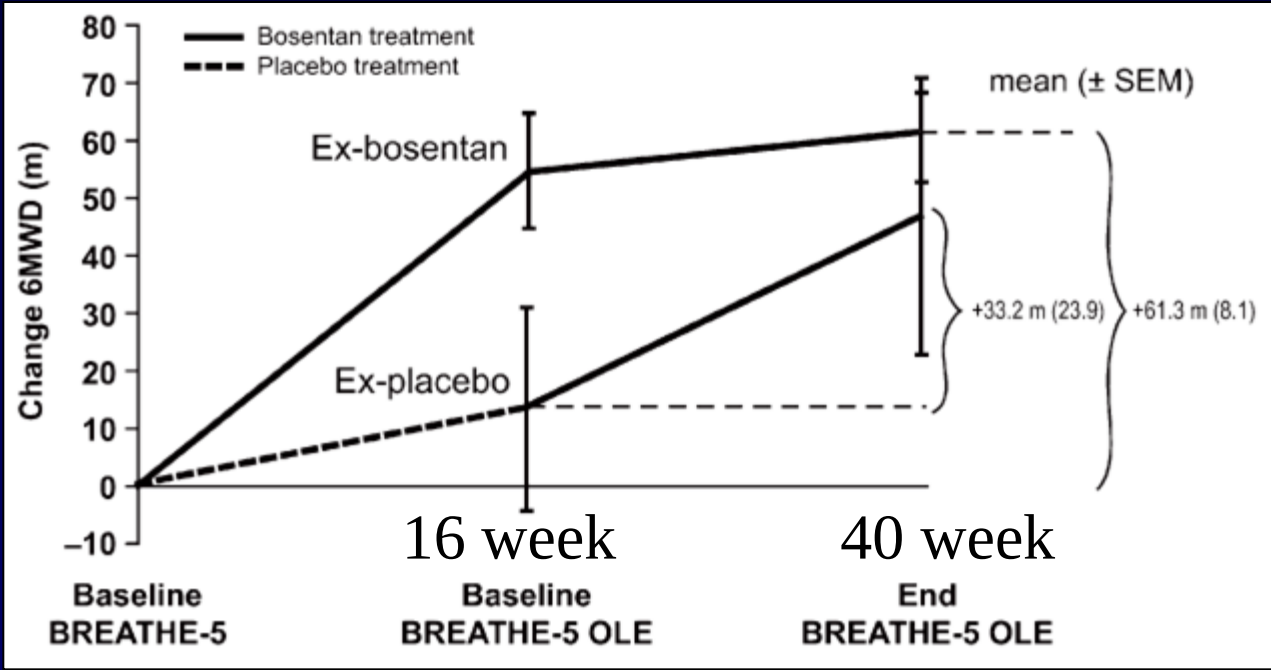
Nazzareno Galiè, MD; Maurice Beghetti, MD; Michael A. Gatzoulis, MD; John Granton, MD; Rolf M.F. Berger, MD; Andrea Lauer, PhD; Eleonora Chiossi, MSc; Michael Landzberg, MD; for the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators



Galie' et al. Circulation 2006

Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: Results of the BREATHE-5 open-label extension study

Michael A. Gatzoulis [a,*], Maurice Beghetti [b], Nazzareno Galiè [c], John Granton [d], Rolf M.F. Berger [e], Andrea Lauer [f], Eleonora Chiossi [f], Michael Landzberg [g]
on behalf of the BREATHE-5 Investigators



Int J Cardiol 2008;127:27-32

ESC Guidelines for the management of grown-up congenital heart disease (new version 2010)

The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric Cardiology (AEPC)

European Heart Journal 2010 ; 31:2915-57

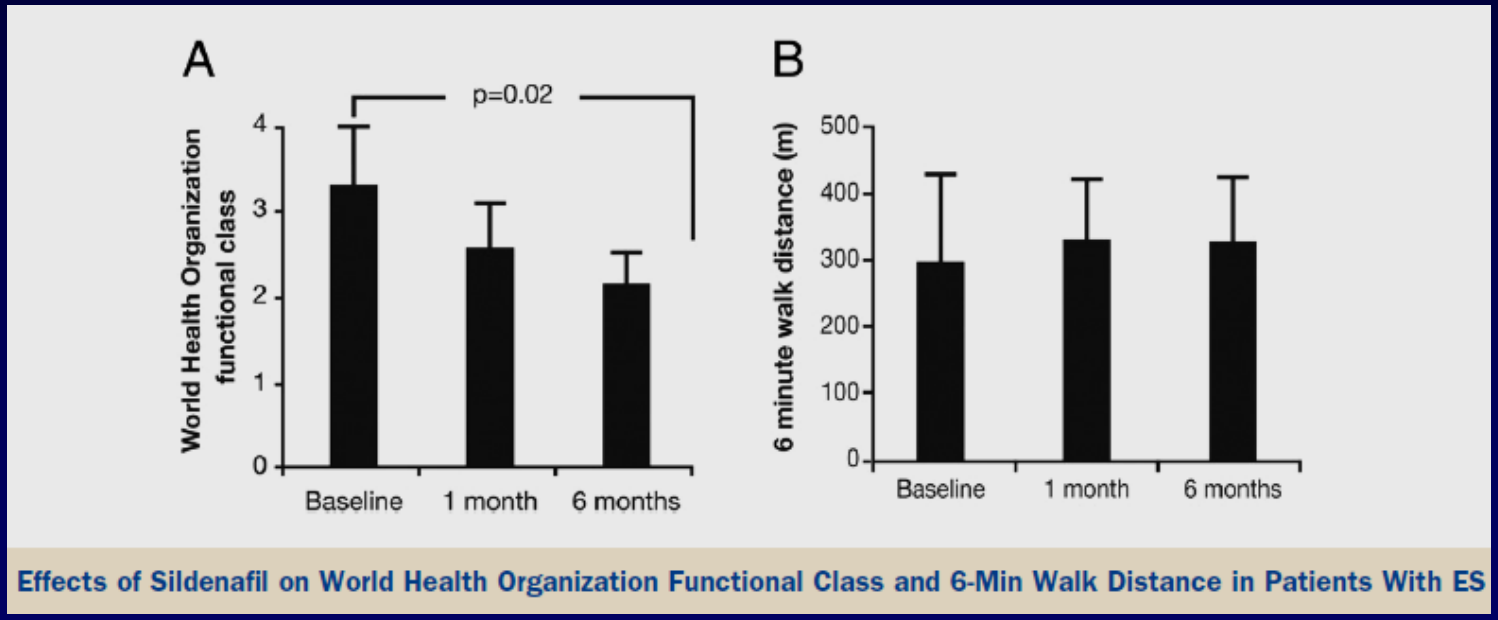
Recommendations	Class[a]	Level[b]
Targeted PAH therapy in CHD should only be performed in specialized centres	I	C
The ERA bosentan should be initiated in WHO-FC III[c] patients with Eisenmenger syndrome	I	B

Eisenmenger Syndrome

A Clinical Perspective in a New Therapeutic Era of Pulmonary Arterial Hypertension

Maurice Beghetti, MD,* Nazzareno Galiè, MD†
Geneva, Switzerland; and Bologna, Italy

J Am Coll Cardiol 2009;53:733-40



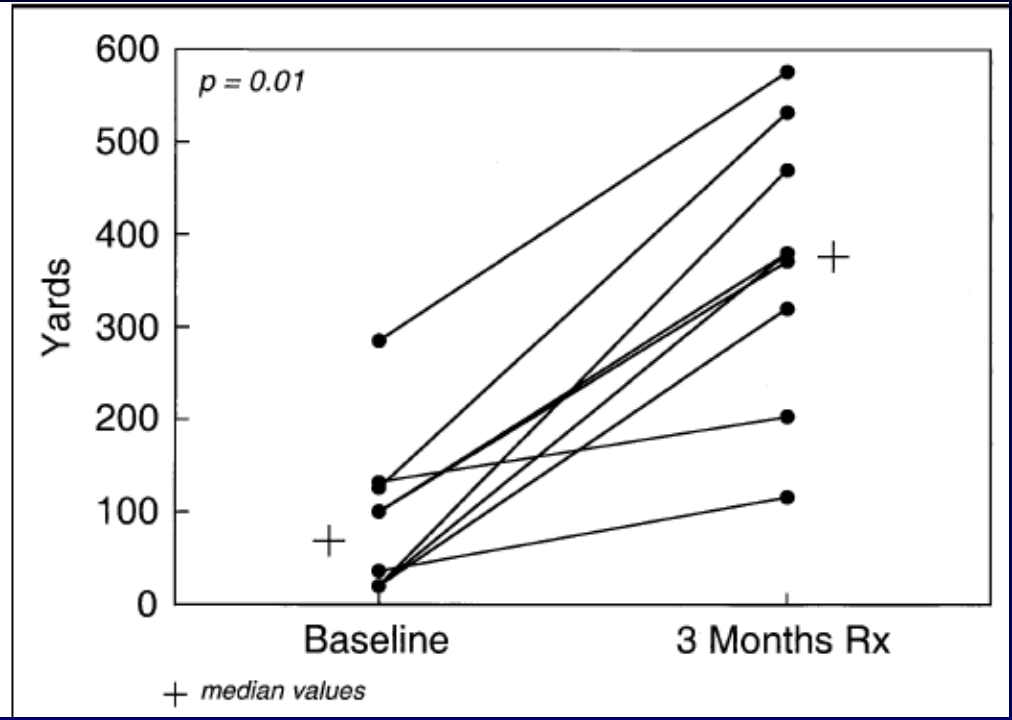
Effects of Sildenafil on World Health Organization Functional Class and 6-Min Walk Distance in Patients With ES

Inibitori della fosfodiesterasi 5

Usefulness of *Epoprostenol* Therapy in the Severely Ill Adolescent/Adult With Eisenmenger Physiology

Susan M. Fernandes, MHP, PA-C, Jane W. Newburger, MD, MPH, Peter Lang, MD, Dorothy D. Pearson, PA-C, Jeffrey A. Feinstein, MD, MPH, Kimberlee Gauvreau, ScD, and Michael J. Landzberg, MD

Am J Cardiol 2003 ;91(5):632-5



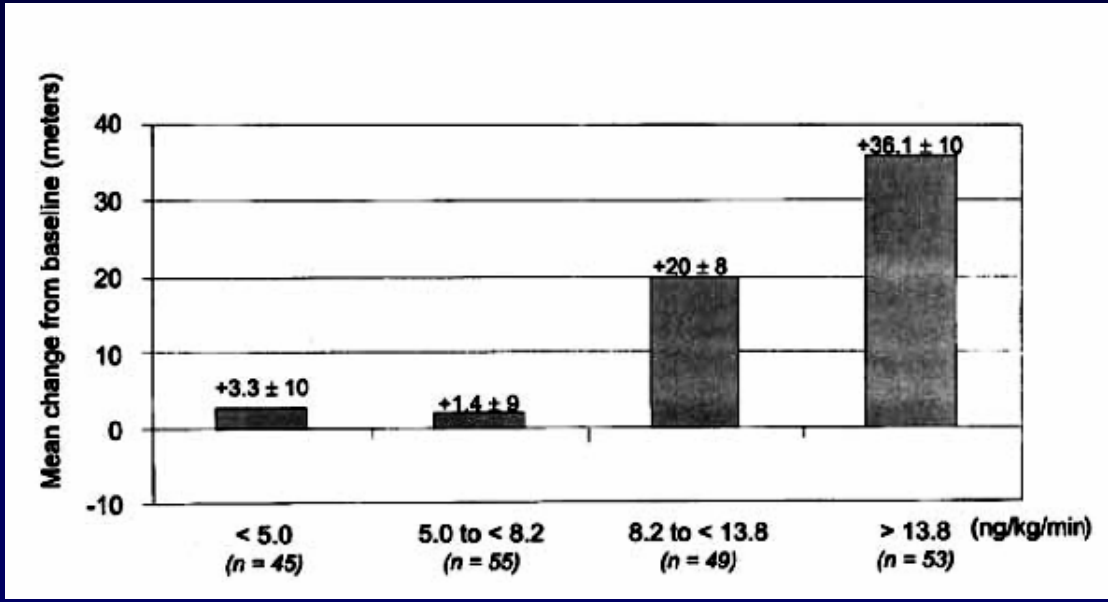
Epoprostenolo : Broviac ➡ rischio embolia paradossa

Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

GERALD SIMONNEAU, ROBYN J. BARST, NAZZARENO GALIE, ROBERT NAEIJE, STUART RICH, ROBERT C. BOURGE, ANNE KEOGH, RONALD OUDIZ, ADAANI FROST, SHELMER D. BLACKBURN, JAMES W. CROW, and LEWIS J. RUBIN, for the Treprostinil Study Group

Am J Respir Crit Care Med 2002 ;165:800-4



Treprostinil : dolore in sede di infusione (85%)

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

European Heart Journal 2010 ; 31:2915-57

Recommendations	Class[a]	Level[b]
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in WHO-FC III[c] patients with Eisenmenger syndrome	IIa	C

Guidelines for the diagnosis and treatment of pulmonary hypertension

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European Heart Journal 2010 ; 31:2915-57

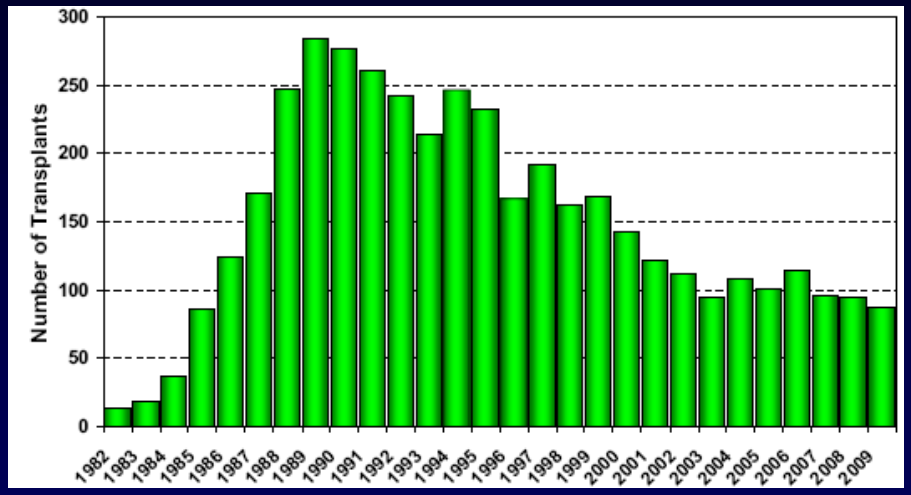
Recommendations	Class[a]	Level[b]
Combination therapy may be considered in WHO-FC III[c] patients with Eisenmenger syndrome	IIb	C
The use of calcium channel blockers should be avoided in patients with Eisenmenger syndrome	III	C

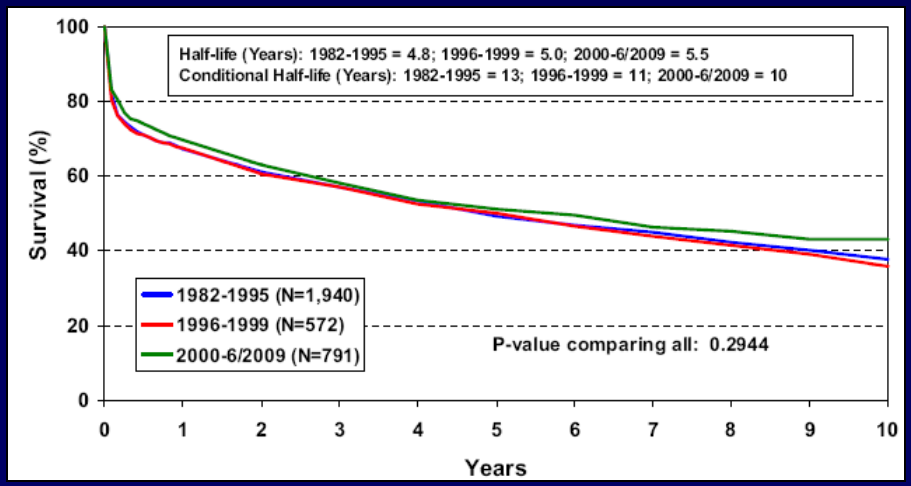
Test di vasoreattività non indicato

The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report—2011

Jason D. Christie, MD, MS, Leah B. Edwards, PhD, Anna Y. Kucheryavaya, MS, Christian Benden, MD, Fabienne Dobbels, PhD, Richard Kirk, MA, FRCP, FRCPCH, Axel O. Rahmel, MD, Josef Stehlik, MD, MPH, and Marshall I. Hertz, MD

J Heart Lung Transplant 2011 ; 30(10):1104-22





- Inserimento in lista ?
- Complessità tecnica
- Pregressi interventi chirurgici (toracotomie)
- Rischio emorragico (collaterali pluero-polmonari)
- Scarsità di donatori

Nuove tecnologie

Nuovi farmaci

Esperienza
Team multidisciplinare

Heart—lung and lung transplantation in grown-up congenital heart disease: long-term single centre experience☆

Heidi Goerler*, Andre Simon, Bernhard Gohrbandt, Christian Hagl, Petra Oppelt, Juergen Weidemann, Axel Haverich, Martin Strueber

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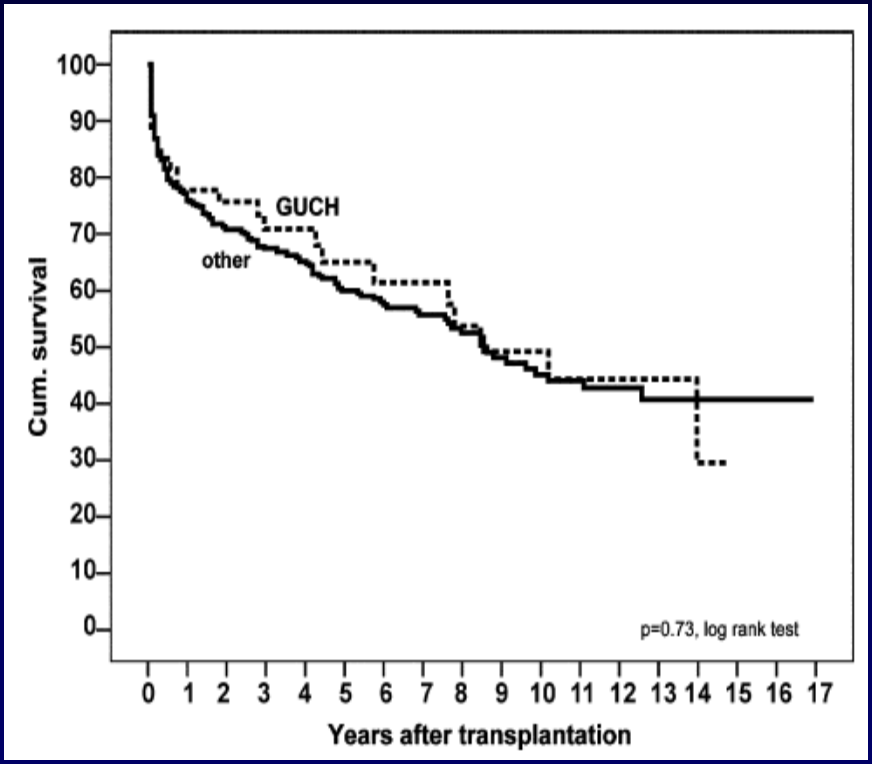
Received 6 April 2007; received in revised form 10 July 2007; accepted 24 August 2007; Available online 27 September 2007

Eur J Cardiothorac Surg 2007 ; 32:926-31



- Inserimento in lista
- Complessità tecnica
- Pregressi interventi chirurgici (toracotomie)
- Rischio emorragico (collaterali pluero-polmonari)

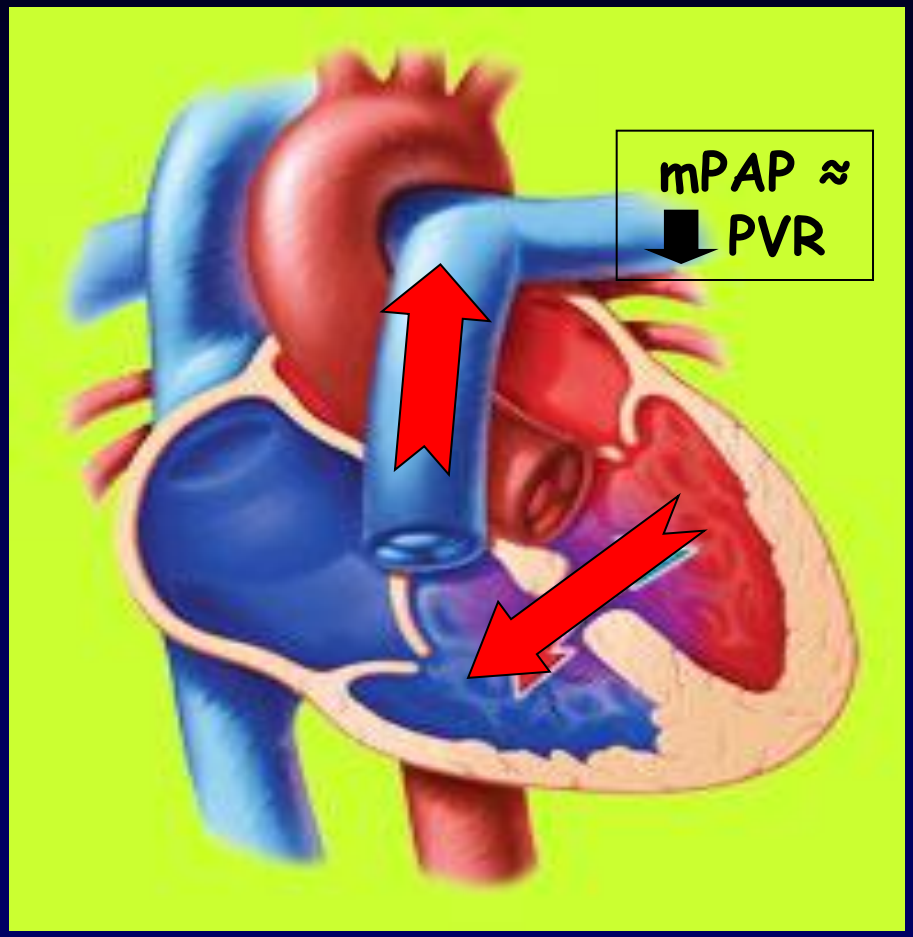
Test di vasoreattività polmonare: *posso usare il Ca antagonista?*

Drug	Route	Half-life	Dose range[a]	Increments[b]	Duration[c]
Epoprostenol	Intravenous	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min
Adenosine	Intravenous	5–10 s	50–350 μg/kg/min	50 μg/kg/min	2 min
Nitric oxide	Inhaled	15–30 s	10–20 ppm	–	5 min[d]

Responder:

- ❑ riduzione PAP media ≥ 10 mmHg
- ❑ PAP media ≤ 40 mmHg
- ❑ CO invariata o aumentata

Eisenmenger ???



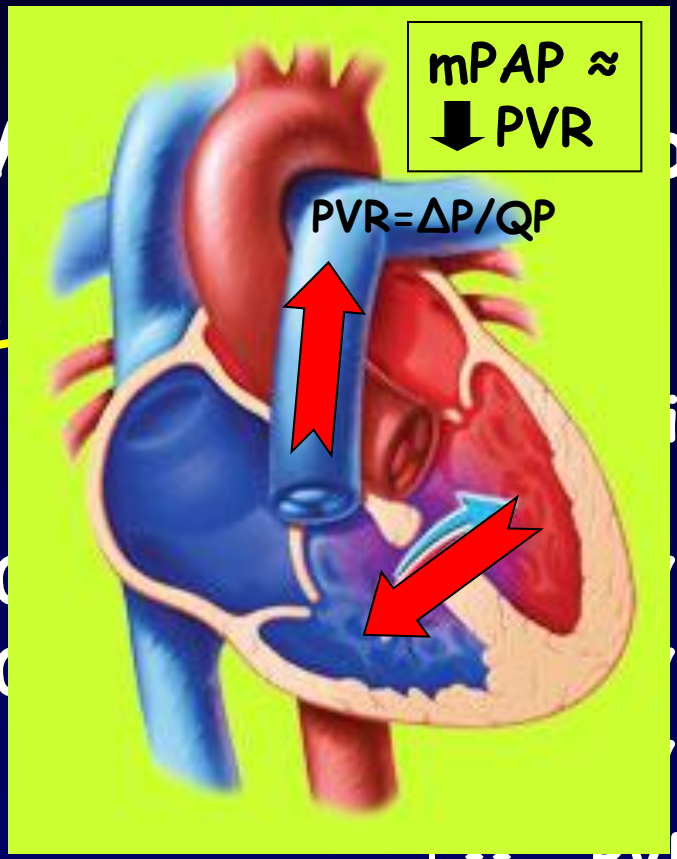
Chi è responder ?

- PVRi≥20%
- PVR/SVR≥20%
- PVRi<6WU.m²
- PVR/SVR<0.3

Valutazione di operabilità nel Pre-Eisenmenger

Operability Assessment

Vasoreactivty test ?



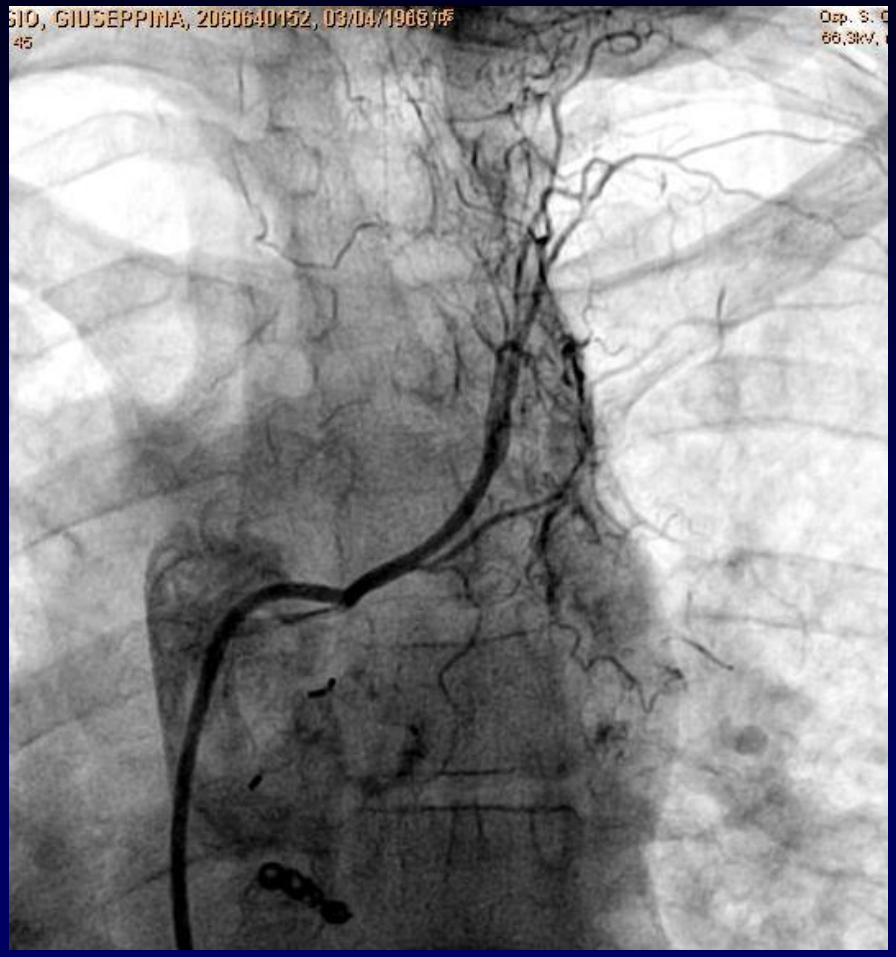
❑ V… …der ?

PAH … CHD

(Established … …ique criteria)

- ❖ ⬇ mPAP≥1… …RI≥20%
- ❖ mPAP≤4… …R/SVR≥20%
- ❖ CO =/⬆ … …RI<6WU.m²
- ❖ … …PVR/SVR<0.3

M.G. ♂ 51aa
Isomerismo sn. Cardiopatia complessa in storia naturale



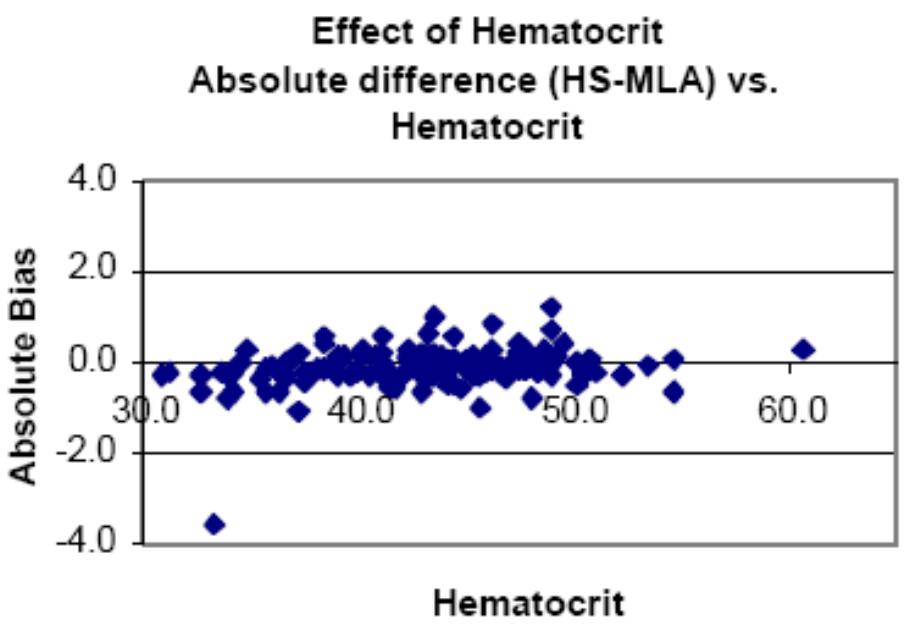
Sat.O2 80% + emottisi recidivanti

INRATIO

Technical Bulletin

TECHNICAL BULLETIN 104

Effect of Hematocrit



Accurate results were obtained on samples with hematocrits ranging from 30 to 55%.

Congenital heart diseases and Pulmonary Hypertension
The 4 phenotypes

Table 6 **Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension**

A. Eisenmenger's syndrome

Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.

B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts

In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. Pulmonary arterial hypertension with small[a] defects

In cases with small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. Pulmonary arterial hypertension after corrective cardiac surgery

In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.