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U.O. Cardiologia Pediatrica
Ospedale Santo Bambino CT
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MASTER UNIVERSITARIO
DI II LIVELLO IN
CARDIOLOGIA PEDIATRICA
ANNO ACCADEMICO 2014—2015

Ipertensione Polmonare

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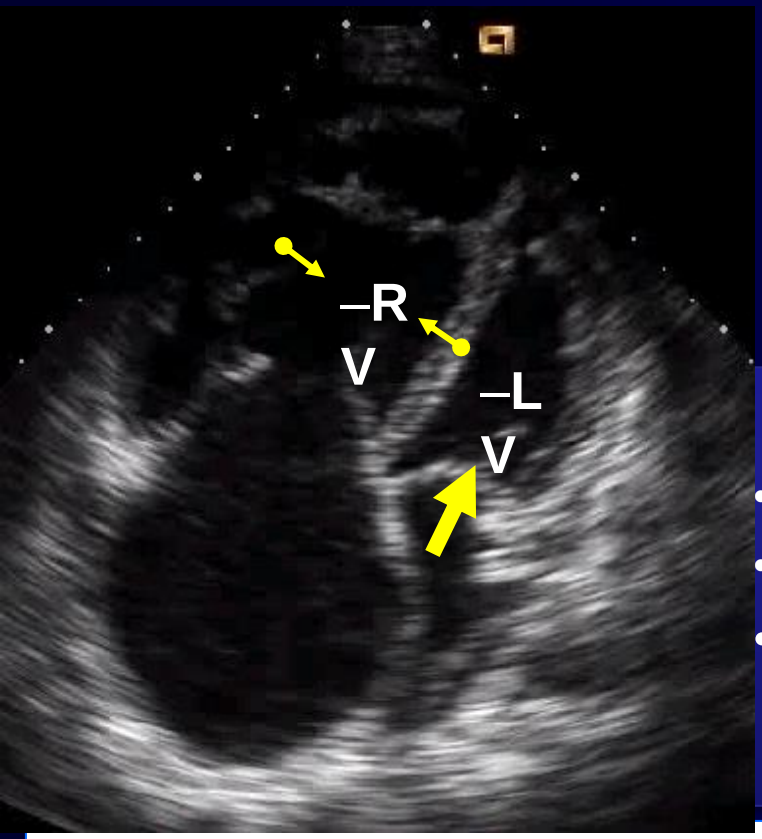
Ipertensione Polmonare

1. Ipertensione Polmonare e cardiopatie congenite
2. Gestione Terapeutica
3. Ecocardiografica come diagnostica strumentale

Ipertensione Arteriosa Polmonare IAP

malattia rara – cronica - causa di morbilità/mortalità in età pediatrica/adulta caratterizzata dall'aumento della pressione in arteria polmonare



SINTOMI:

dispnea, affaticabilità, debolezza, angina, sincope, anoressia, distensione addominali, ritardo di crescita

Prevalenza stimata

- Adulti 15-50/per milione
- bambini 0.7-15.6/per milione
- maschi/femmine 1/1.4
  - 88% IAPidiopatica/familiare (57%)/associata a cc (36%)
  - 12% IAP altri sottogruppi

Dati del «Il REVEAL» The Registry to Evaluate Early and Long-Term PAH (un grande studio osservazionale di bambini e di adulti con diagnosi di PAH Stati) Uniti Circulation. 2012;125:113-122.

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Updated Clinical Classification of Pulmonary Hypertension

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - **2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*Modified as compared with the Dana Point classification. Reprinted with permission from Simonneau G, Gatzoulis MA, Adatia I. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34–41.

BMPR2 = bone morphogenetic protein receptor type II; CAV1 = caveolin 1; ENG = endoglin; KCNK3 = potassium channel K3; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PPHN = persistent pulmonary hypertension of the newborn.

Pediatric Pulmonary Hypertension

The updated Nice classification for PH

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egies. In group 2, congenital and acquired left heart inflow and outflow tract obstruction has been added (22). Lesions in this category include pulmonary vein stenosis, cor triatriatum, supravalvular mitral ring, mitral stenosis, subaortic stenosis, aortic valve stenosis, and coarctation of the aorta associated with an increased left ventricular end-diastolic pressure. In group 3, developmental lung diseases have

Table 2 Developmental Lung Diseases Associated With Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Alveolar capillary dysplasia (ACD)
ACD with misalignment of veins
Lung hypoplasia (“primary” or “secondary”)
Surfactant protein abnormalities
Surfactant protein B (SPB) deficiency
SPC deficiency
ATP-binding cassette A3 mutation
thyroid transcription factor 1/Nkx2.1 homeobox mutation
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

nosis and management. In group 5, the category of segmental PH has been added to PH with unclear multifactorial mechanisms. Examples of segmental PAH include pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries and branch pulmonary arterial stenosis of variable severity.

Definizione Emodinamica di Ipertensione Polmonare

Definizione	Caratteristiche	Gruppi Clinici
Ipertensione Polmonare (IP) *dopo i due mesi di età*	**PAP media ≥ 25 mmHg** *V.N. 14+3 max 20*	Tutti
Pre-capillare (IP)	PAP media ≥ 25 mmHg **PWP media ≤15 mmHg** RVP> 3WU (v.n. ≤ 2WU) CO normale o ridotta	1. **Ipertensione arteriosa polmonare** 3. IP secondaria a malattia polmonare 4. IP tromboembolica cronica 5. IP con non chiari e/o multifattoriali meccanismi
Post-capillare IP	PAP media ≥ 25 mmHg **PWPmedia >15 mmHg** CO normale o ridotta	2. IP secondaria a malattia del cuore sinistro
Post-capillare (IP) passiva	GTP ≤ 12 mmHg	
Post-capillare (IP) reattiva	GTP > 12 mmHg	

PAP= Pressione Arteriosa Polmonare

PWP= Pressione Polmonare Wedge

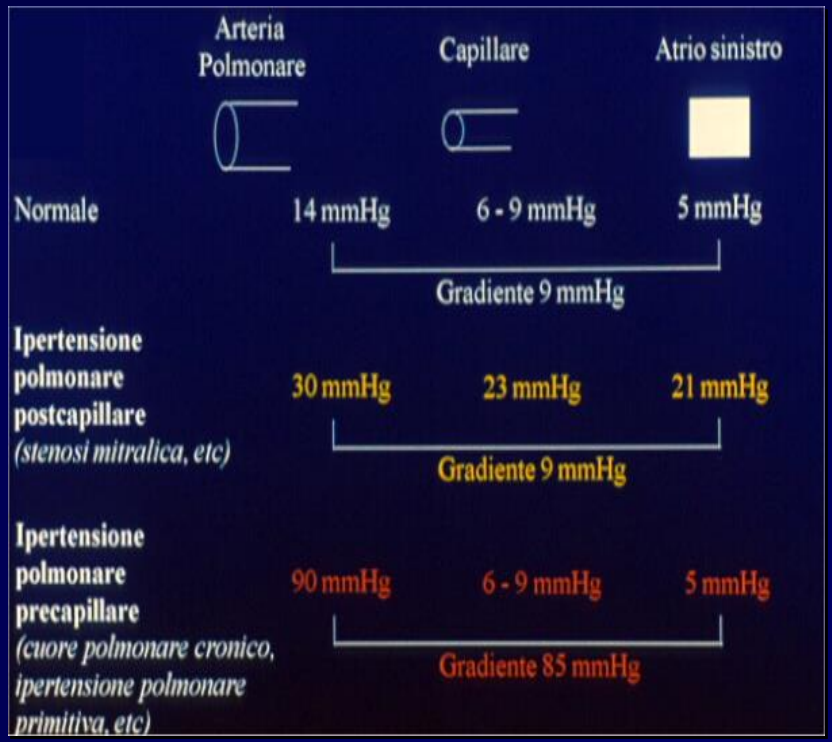
GTP= Gradiente transpolmonare (PAPmedia-PWP media)

Ipertensione Arteriosa Polmonare (IAP)

L'IAP può complicare il corso di molte cardiopatie congenite (c.c.) in bambini e adulti

Forme di IAP associata a c.c.

precapillare	• se secondaria ad aumentato flusso in arteria polmonare e trasmissione di pressione (cc con shunt sn/dx)
postcapillare	• se secondario a patologia del cuore sinistro e conseguente aumento della pressione venosa polmonare



UPDATED CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION

(DEFINITA NEL MEETING DI DANA POINT 2008 LINEE GUIDA 2009-2013)

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la diagnosi eziologica deve essere corretta perché ad eziologie diverse corrispondono diversi approcci terapeutici

Esistono Farmaci approvati specificamente per l'IAP è riguardano solo i pazienti affetti da IAP del Gruppo I

Gli altri gruppi possono, non solo, non trarre beneficio ma addirittura possono essere danneggiati

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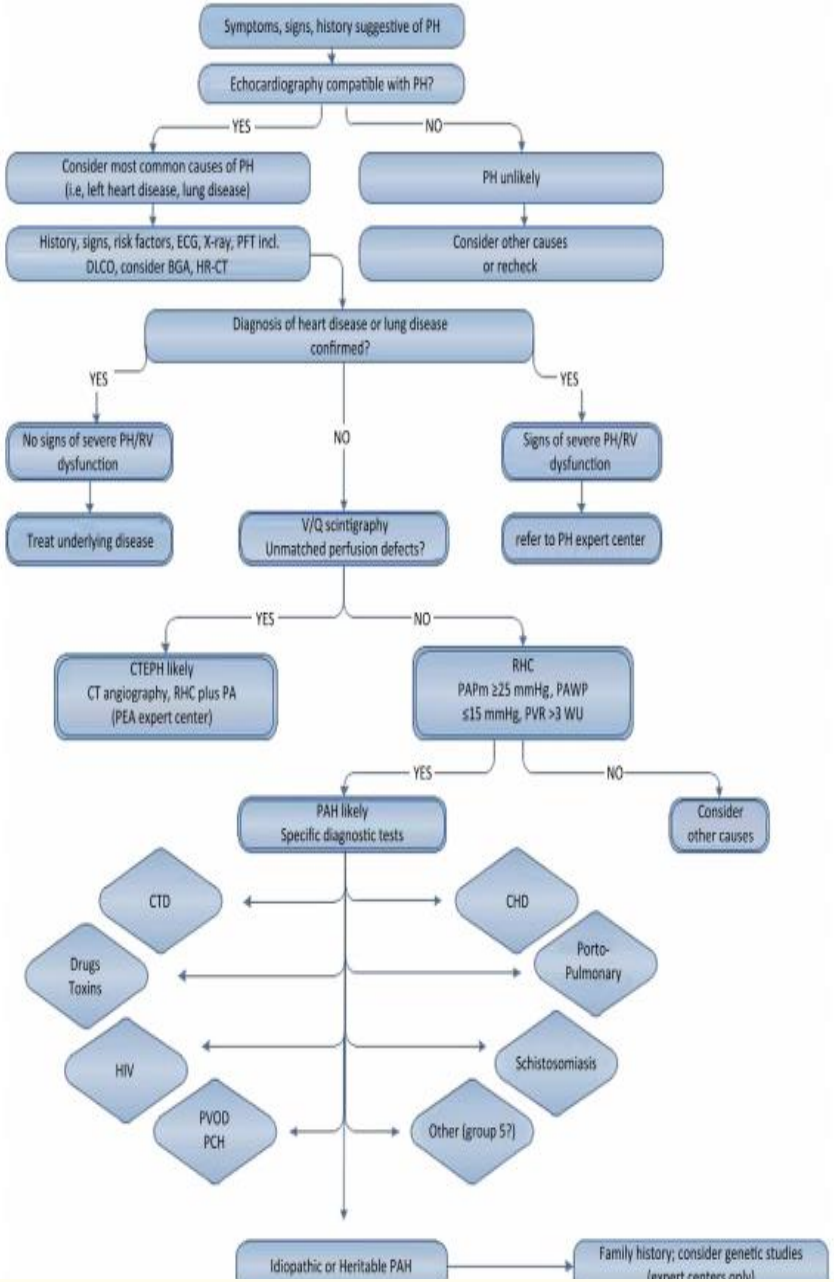
Definitions and Diagnosis of Pulmonary Hypertension



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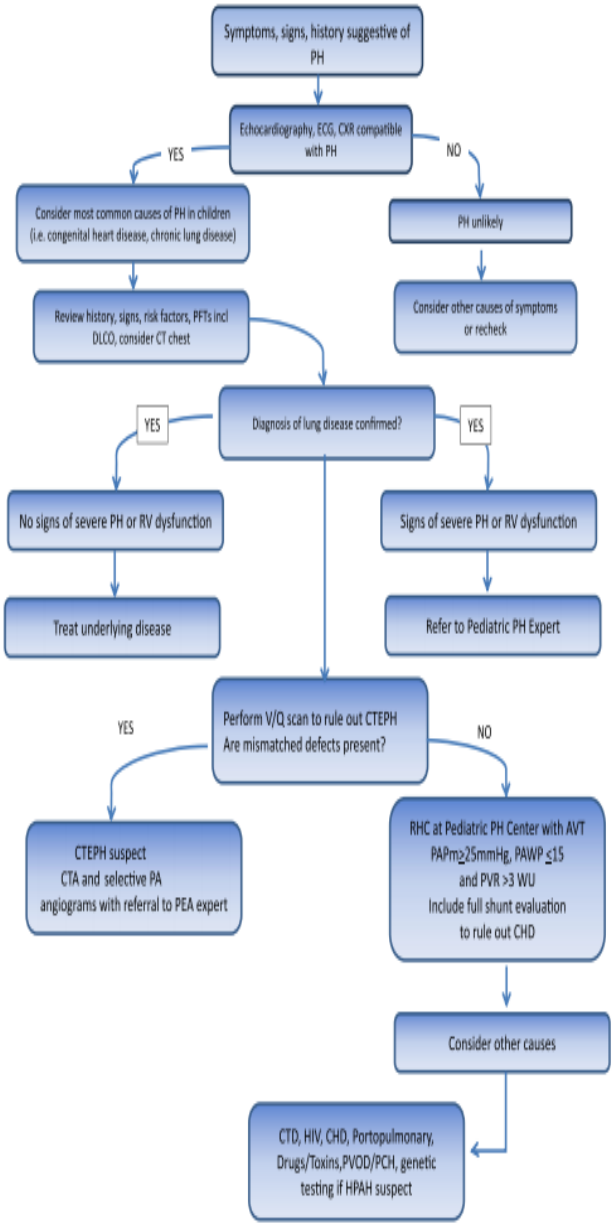
Pediatric Pulmonary Hypertension



BGA = blood gas analysis; CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; HR-CT = high-resolution computed tomography; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PCH = pulmonary capillary hemangiomatosis; PEA = pulmonary endarterectomy; PFT = pulmonary function testing; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheter; RV = right ventricle; V/Q = ventilation/perfusion; x-ray = chest radiograph.

Ipertensione Artetiosa Polmonare e c.c. con shunt

1. tipo di cardiopatia semplice/complessa/palliata 2.dimensione/sede del difetto

CARDIOPATIE SEMPLICI
Ampio difetto senza ostruzione all'efflusso destro
Pre-tricuspidali

1. Difetto Interatriale (O.P., O.S., Seno-venoso)
2. Ritorno Venoso Polmonare Anomalo Parziale/Totale Senza Ostruzione

Ampio ≥ 20 mm
IAP 15-20%
Peggioramento quadro clinico dopo i 50 anni

CARDIOPATIE SEMPLICI
Ampio difetto senza ostruzione all'efflusso destro
Post-tricuspidali

1. Difetto Interventricolare
2. Dotto Arterioso

Restrittivo/non Restrittivo
Ampio ≥ 10 mm
IAP 50-70%
Peggioramento del quadro clinico dopo i 25 anni

CARDIOPATIE COMPLESSE
Shunt sn-dx senza ostruzione all'efflusso destro

1. Canale Atrioventricolare
2. Cuore Univentricolare
3. Ventricolo destro a Doppia Uscita
4. Trasposizione Grossi Vasi Con DIV
5. Truncus Arterioso

IAP 100%
Peggioramento quadro clinico in media a 18 anni

AMPIE CONNESSIONI AORTO-POLMONARI

1. Finestra Aorto-polmonare,
2. Connessioni Sistemico-Polmonari Post-chirurgiche

IAP 100%
Peggioramento quadro clinico in media a 18 anni

Ipertensione Artetiosa Polmonare e c.c.

Incidenza stimata, paesi occidentali, 2.2-15.6/1.000.000, di cui il 25-50% presentano la S.E. *forma più avanzata di IAP associata a CC*

Systemic-to-pulmonary shunt

↓

Increased pulmonary blood flow and pressure

↓

Endothelial dysfunction *

↓

Increase in pulmonary vascular resistance ^

↓

Inverted shunt: pulmonary-to-systemic

↓

Cyanosis (Eisenmenger's syndrome)

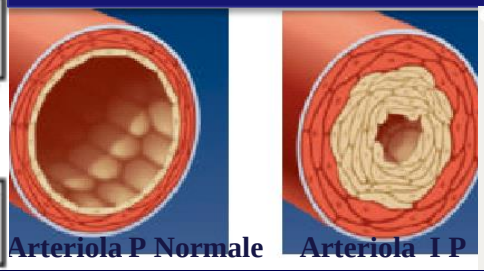
European Heart Journal 2004; 25:2253

*Lo shear stress e stress circonferenziale sull'endotelio vascolare polmonare determina arteriopatia ostruttiva

^ per riduzione dell'area di sezione delle arterie di piccolo calibro

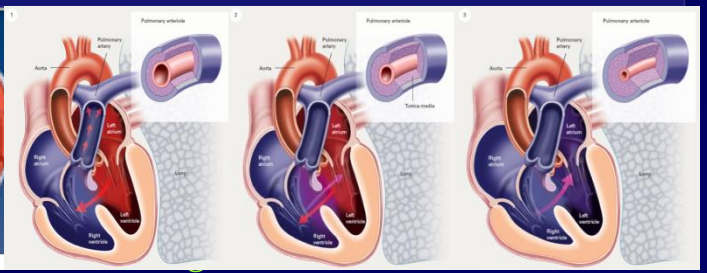
Aumenta anche la pressione arteriosa polmonare per mantenere la stessa portata cardiaca

Quando RVP e PAP superano quelle sistemiche



Arteriola P Normale

Arteriola I P



Fisiopalogia dell'IAP nelle CC

Meccanismi di IAP

1. Vasocostrizione Arteriolare

2. Rimodellamento Vascolare

3. Trombosi Endoluminale

1. Vasocostrizione Arteriolare inizialmente dinamica poi fissa

Alterazioni dell'equilibrio ionico nelle cellule muscolari lisce canali del potassio

Perpetuano la vasocostrizione

Disfunzione Endoteliale alterazione delle tre vie biochimiche principali
1.Prostaciclina,
2. Ossido Nitrico
3.Endotelina

Deficitaria produzione di: Prostaciclina, Ossido Nitrico (vasodilatatori e antiproliferativi)

sovrapproduzione di: endotelinala e trombossano A2 (vasocostrittori e promotori di proliferazione cellulare vasale e rimodellamento)

Fisiopalogia dell'IAP Associata a c.c.

2. Rimodellamento Vascolare:

obliterazione dei vasi polmonari di piccolo/medio calibro

1. Fibrosi laminare concentrica dell'intim
2. Ipertrofia della media
3. Fibrosi dell'avventizia
4. Aree di necrosi fibrinoide e di trombi ell nel contesto della parete vasale

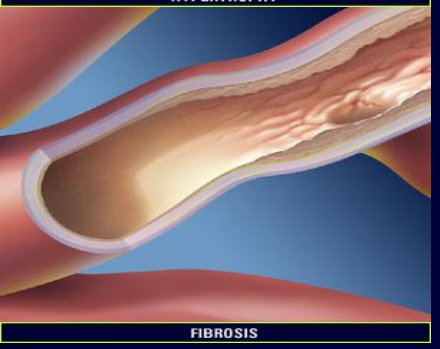
Nessuna differenza tra adulti e bambini

3. Trombosi Endoluminale

Alterazione Della Coagulazione

Elevati livelli di fattore di von Willerbrand e fibrinogeno

Diminuita attività fibrinolitica



Rimodellamento vascolare « Caratteristica del letto polmonare» ***cambiamenti istopatologici e patobiologici simili all' IAP e tutte le forme del Gruppo I***

Grado	Alterazioni Strutturali	Destino
I	Ipertrofia Della Media	Reversibile
II	Proliferazione Cellulare Intimale	Reversibile
III	Fibroelastosi Intimale Occlusiva	Parz.Reversibile
IV	Dilatazione Vascolare Atrofia della Media	Scars. Reversibile
V	Angiomi Avventiziali	Non Reversibile
VI	Necrosi Fibrinoide	Non Reversibile

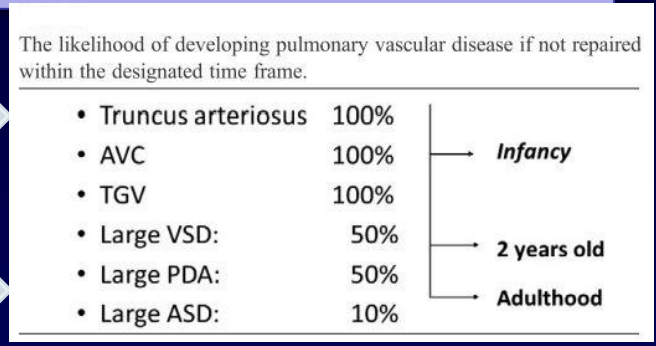
Class. di Heath e Edwards alteraz. strutturali dei vasi arteriosi polmonari sec. c.c. 1958

IAP cardiopatie congenite

3. tempi alla correzione della cc la reazione vascolare polmonare, negli shunt ampi non restrittivi, si instaura normalmente nei primi 12-18 mesi

Ottimizzazione dei tempi di correzione classe racc. **I** liv ev. **B**

se riparazione entro **il primo anno primi mesi**	RVP suscettibile di reversibilità, normale entro 1 anno
se correzione **entro i due anni**	RVP scendono, ma livelli normali non sempre raggiunti
correzione **successiva** quando l'IAP strutturata	la progressione della malattia e insufficienza ventricolare destra può essere accelerata



Trisomia 21

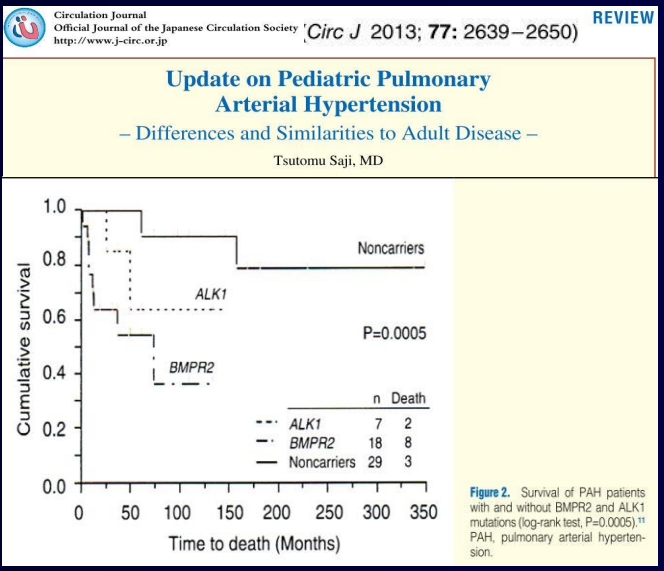
- ipoplasia polmonare,
- immaturità alveolare
- ridotta produzione e secrezione di surfattante polmonare,
- ipotiroidismo,
- malattie ostruttive delle vie aeree, glossite, apnea del sonno

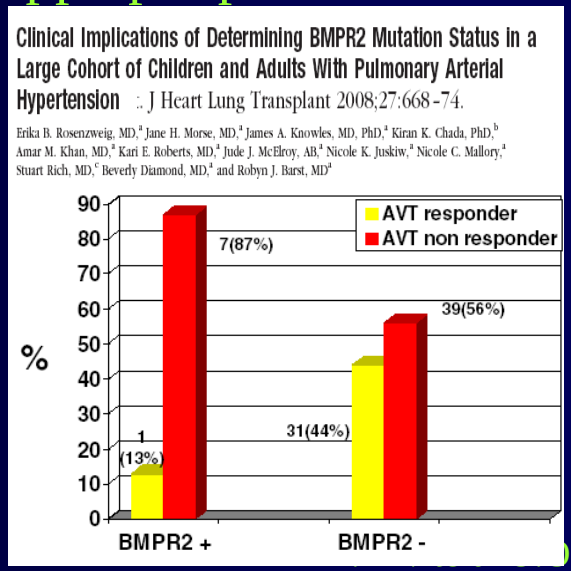
4. Fattori associati entro i 6 mesi: shunt con desaturazione (TGA+DIV) cromosomopatie (trisomia 21), nei primi 6 mesi

ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension

236. Roberts KE, McElroy JJ, Wong WP, et al. BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J. 2004;24:371–4.

- È stato osservato che con la stessa complessità di cardiopatia
  - Alcuni sviluppano precocemente e rapidamente l'IAP irreversibile
  - Altri mantengono livelli accettabili di resistenza vascolare polmonare per anni
- È stato dimostrato la presenza della mutazione BMPR2 in pazienti con CC che svilupparono più precocemente IAP
  - Mutazione presente nel 50% dell' IAPF e nel 25% dell'IAPI
- Si è ipotizzato, quindi, che una predisposizione genetica possa contribuire allo sviluppo più precoce della vasculopatia polmonare





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Pediatric Pulmonary Hypertension

The updated Nice classification for PH

1. Eisenmenger syndrome

   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.

2. Left-to-right shunts
   - Correctable†
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease

   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.

4. Post-operative PAH

   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

*Nice 2013.

Gruppo A
la diagnosi è semplice ed esistono raccomandazioni per il trattamento

Gruppo B
il difetto cardiaco non può essere chiuso senza rischi elevati e le opzioni di gestione sono attualmente limitate

Gruppo C
hanno quadro clinico simile a IAPI idiopatica con il vantaggio di uno shunt

Gruppo D
sviluppano IAP in assenza di shunt residui (cambiamenti nella vascolarizzazione polmonare erano in una fase di irreversibilità o hanno avuto andamento progressivo, nonostante correzione)

Sindrome Di Eisenmenger Gruppo I

Rappresenta la forma più avanzata di IAP associata con C.C.

In termini di tolleranza all'esercizio sono più compromessi rispetto alle altre cc
Anche se sottostimano i loro sintomi poiché adattano lo stile di vita alle loro capacità

Hanno bassa aspettativa di vita terza-quarta decade, solo alcuni la settima

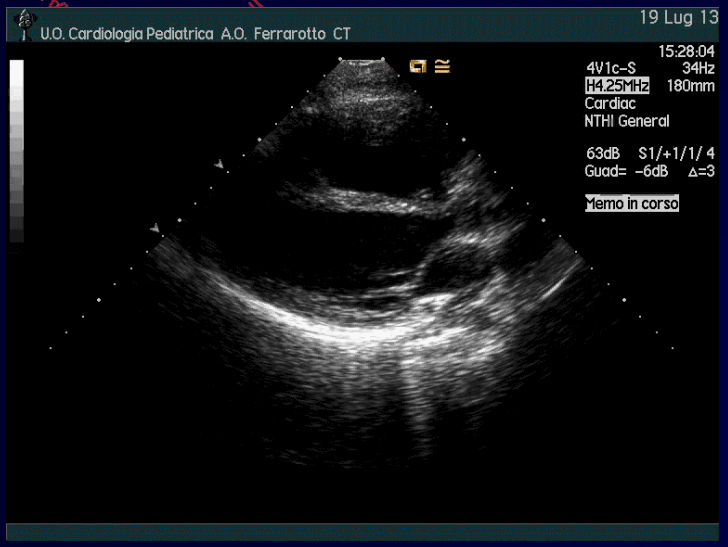
I segni e sintomi sono il risultato di bassi livelli di ossigeno nel sangue:
cianosi, dispnea, stanchezza, vertigini, sincope e aritmia

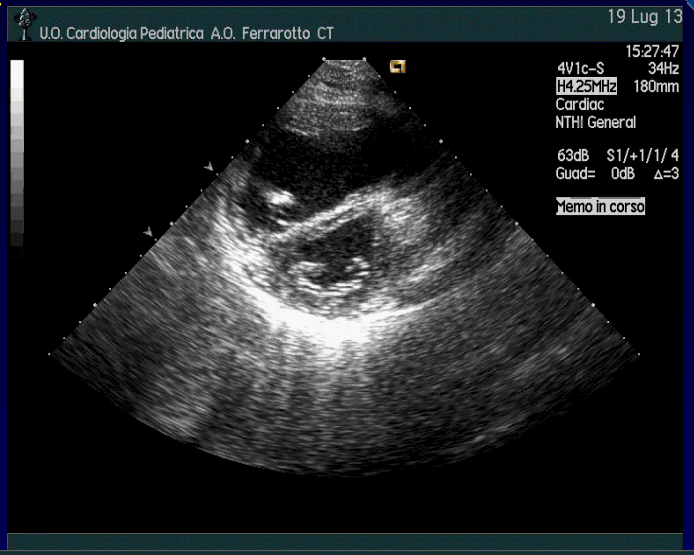
Nell'Eisenmenger rispetto alla IAPI sintomi sono più tardivi

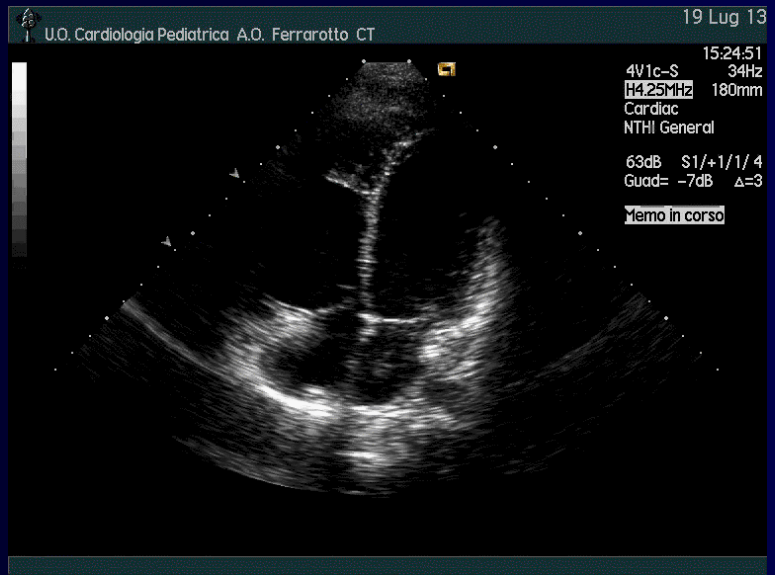
- La morfologia del cuore destro mantiene caratteristiche del cuore fetale
  - Più adatto a sostenere pressioni sistemiche
  - meno predisposto allo scompenso
- La portata cardiaca di base è normale e con l'esercizio aumenta
  - La comunicazione intracardiaca agisce come valvola di sicurezza preservando la funzione ventricolare destra a scapito della cianosi

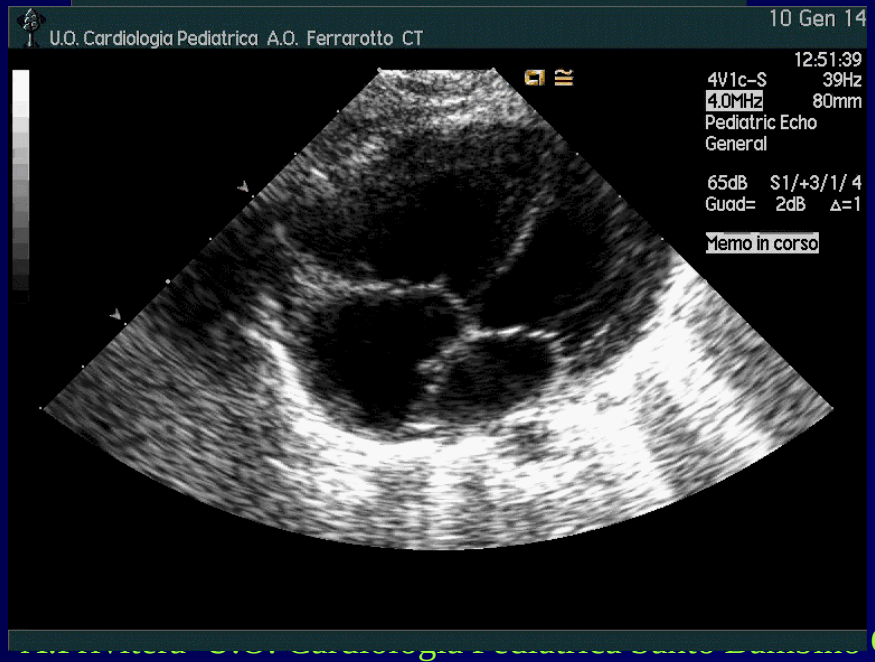
Pazienti	IAP I	S.E.
Dispnea	53%	30%
Pre/sincope	36%	4%
Sopravvivenza a 5aa ultima terza decade	74%	74%

IAP-Idiopatica



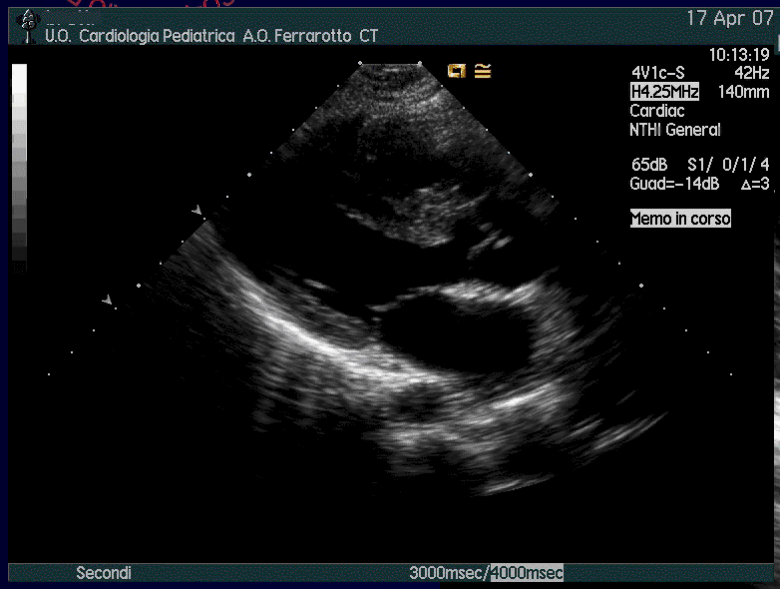


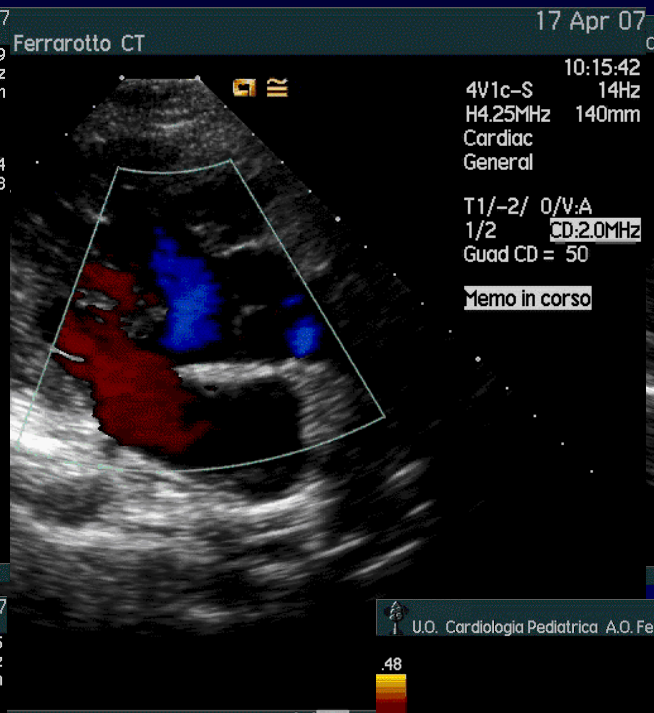


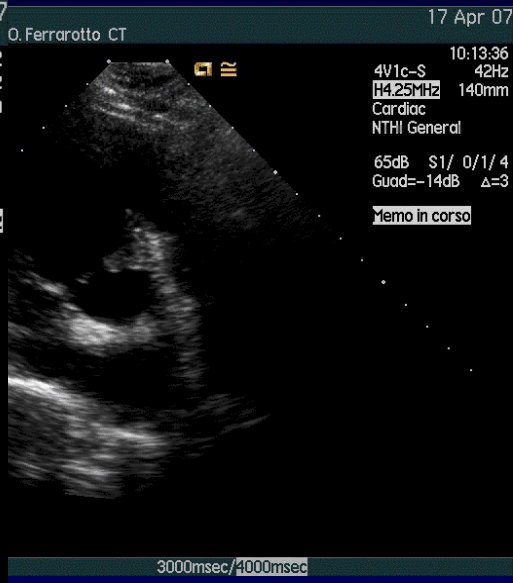


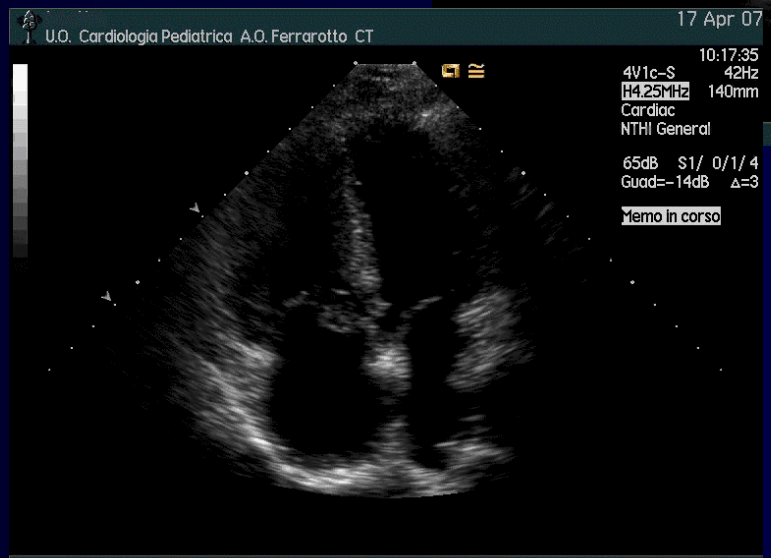
CT

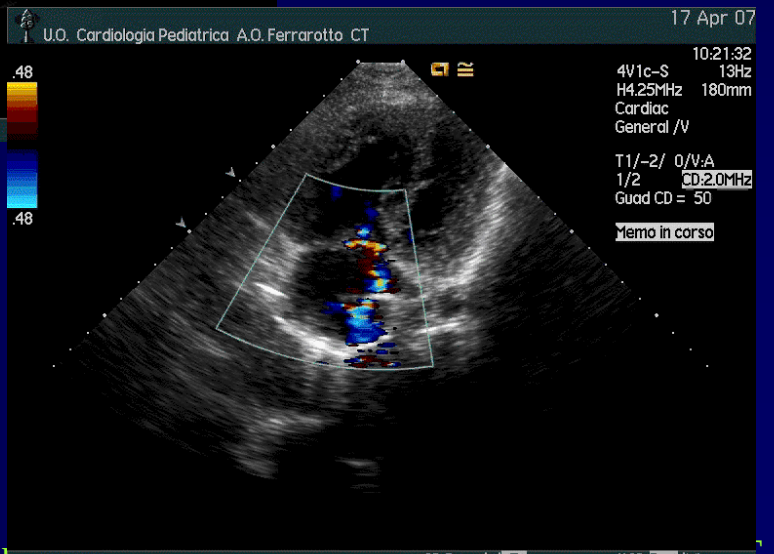
Eisenmenger





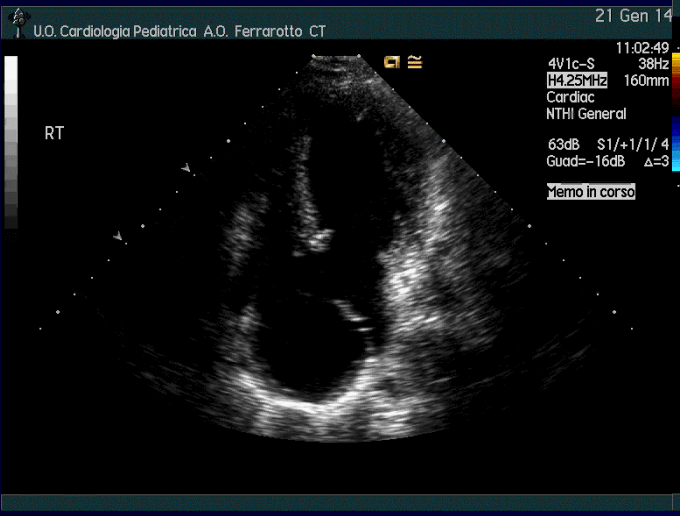


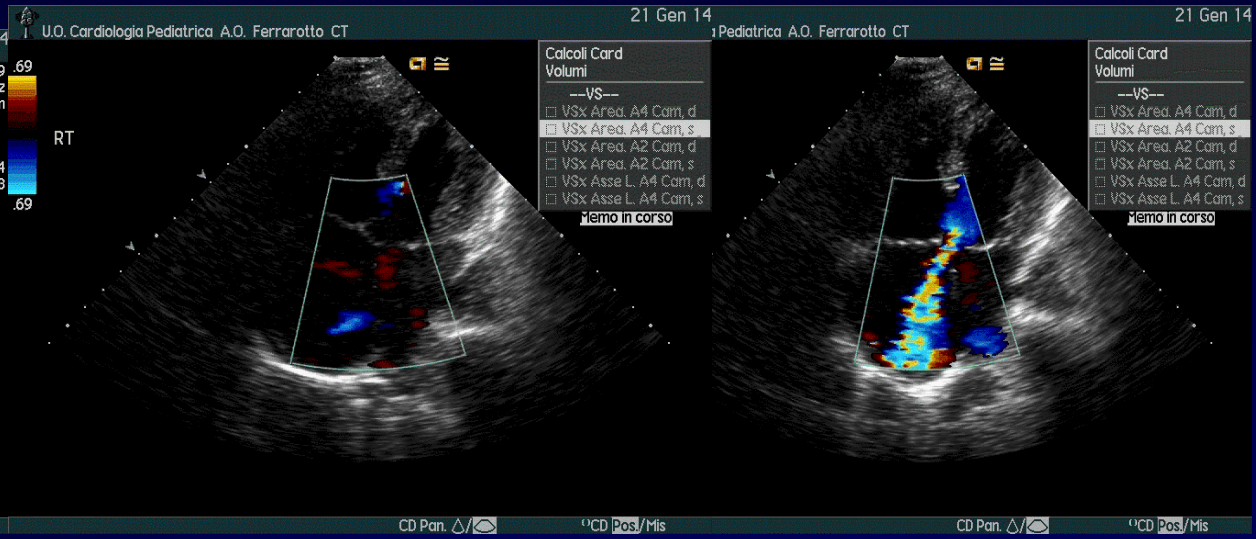


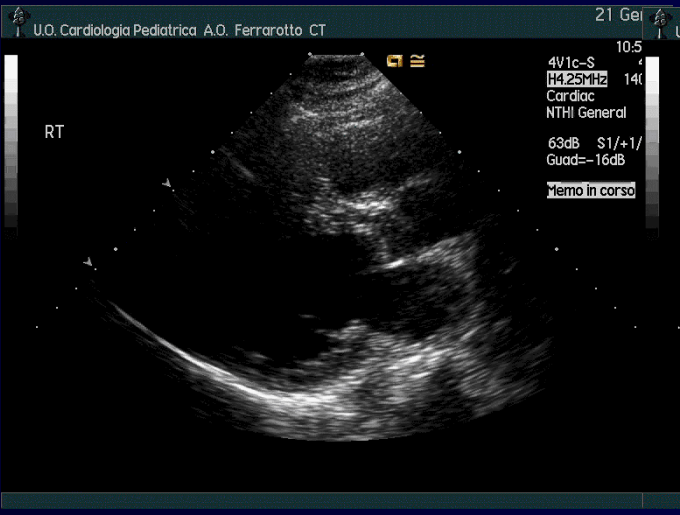


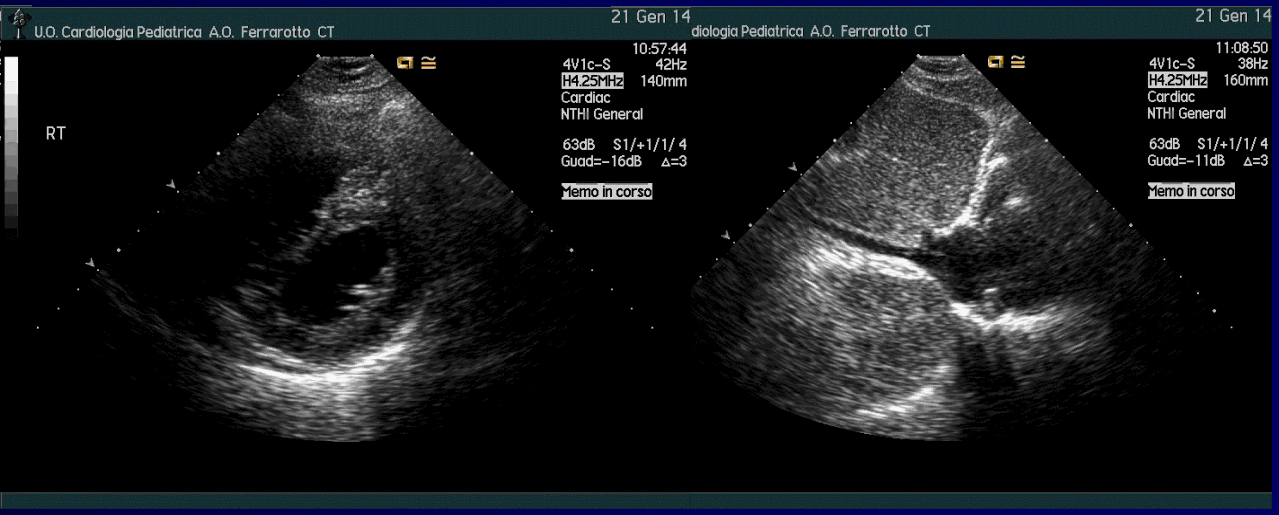
A.Privitera

CAV Eisenmenger









Sindrome di Eisenmenger

Disfunzione multiorgano

Cianosi produzione renale di eritropoietina > eritropoiesi

eritrocitosi secondaria

Isolato aumento dei globuli rossi da compenso alla cianosi cronica

essenziali per mantenere un adeguata ossigenazione dei tessuti e prevenire danni d'organo ipossici

diversa dell'eritrocitosi primitiva dove proliferano tutte le linee cellulari

Emottisi incidenza tra il 11% e il 100%, aumenta con l'età non sembra essere predittivo di mortalità

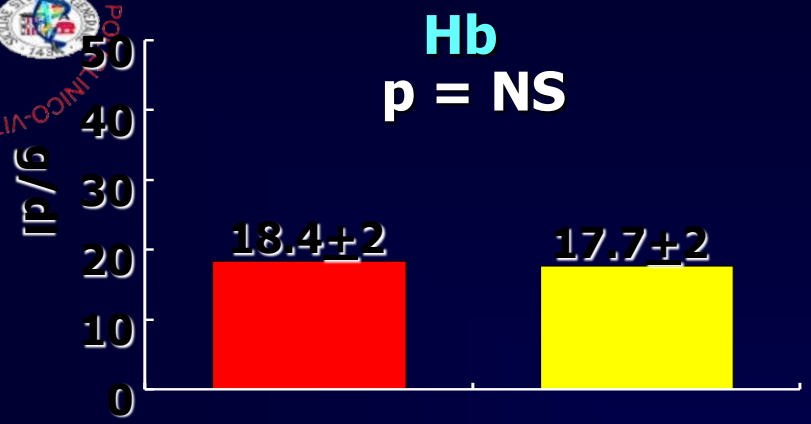
- Alterazioni piastrine (trombocitopenia)
- Alterazioni fattori coagulativi: ridotti i fattori vitamina K dipendenti (II,VII,IX,X) e fattore V
- Aumento dell'attività fibrinolitica

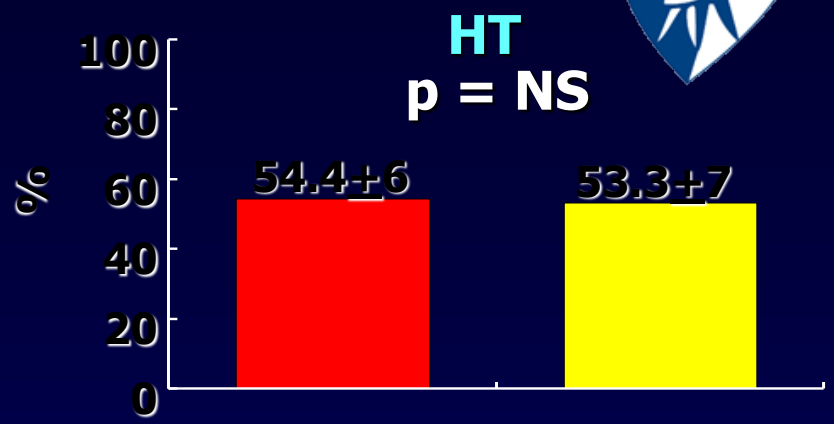
Trombosi della polmonare e Accidenti cerebrovascolari

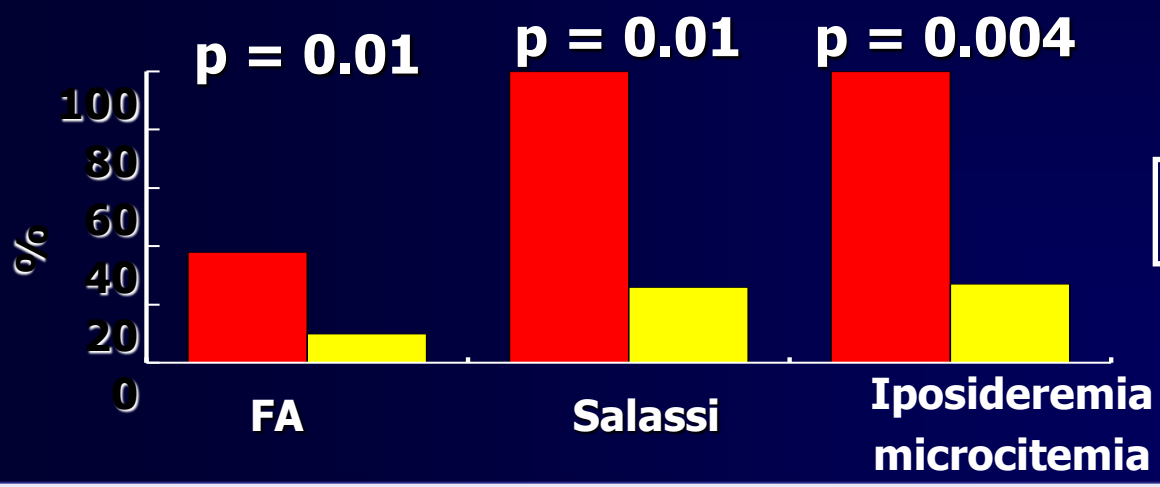
- Disfunzione endoteliale
- Embolia/e. paradossa: secondaria ad aritmie o da elettrodi o cateteri transvenosi
- fattori reologici- carenza di ferro (emorragie o flebotomie inappropriate) microcitosi (globuli rossi sferici non deformabili)

Cerebrovascular Events in Adult Patients With Cyanotic Congenital Heart Disease

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







Esami di laboratorio:

emoglobina, emocromo, ferritina, transferrina, vitamina B12 ed acido folico

Porre attenzione al volume corpuscolare medio (VCM)

- Se inferiore a 80 (sospettare anemia sideropenica)
- Se aumentato (sospettare carenza di vitamina B12, acido folico)

Sindrome di Eisenmenger

Disfunzione multiorgano
complicanze tardive

- Causa Morte
  - Morte improvvisa 30%,
    Insufficienza cardiaca 23%
    Emottisi massiva 11%
- Aritmie ipercinetiche sopraventricolari e ventricolari
  - Mantenere il ritmo sinusale quando possibile
  - Terapia: amiodarone o ablazione
    PM/DIC epicardico (evitare uso di elettrodi transvenosi)
- Sintomi da iperviscosità ematocrito > 65%
  - Cefalea, debolezza, vertigine, affaticabilità, acufeni, disturbi del visus, parestesie labbra e dita, mialgia
  - Escludere carenza di ferro e disidratazione

Terapia di ordine generale Sindrome di Eisenmenger

Trasfusione/supplemento di ferro

- Anemia sideropenica
  VCM <80 fl
- Vitamina B12, acido folico quando aumentato VCM

Flebotomia

Ogni 400-500 ml di sangue rimosso integrare con

750-1000 ml soluzione salina isotonica

- Sintomi da iperviscosità ematica (ematocrito > 65%) in assenza di disidratazione e carenza di ferro
- in caso di intervento chirurgico e Ht > 60%

Emottisi

- Sospendere aspirina,anticoagulanti, antinfiammatori non steroidei, ridurre, attività fisica, sedare la tosse
- Trattare ipovolemia e anemia
  Embolizzazione selettiva arterie bronchiali
  se emorragia/emottisi intrapolmonare refrattaria

Sindrome di Eisenmenger e IAPI

Gravidanza Controindicata
raccomandazione I, evidenza C

- Morte materna45%
  - Durante il parto o la prima settimana successiva (tromboembolia, ipovolemia e preclampsia)
- Alta incidenza di aborto spontaneo
- Solo il 25% arriva a termine
  - Ritardo di crescita e alta mortalità perinatale

Contraccezione

- Consigliata la terapia progestinica, efficace nel 95%
- Controindicata per rischio trombosi la terapia combinata estroprogestinica

Attività Fisica
raccomandazione 1, evidenza A

- Incoraggiare ad essere attivi entro i limiti dei sintomi Da evitare l'esercizio fisico strenuo moderato-intenso e competitivo
- Utile esercizio riabilitativo supervisionato nei pz fisicamente decondizionati

Misure Generali

- Indicata la profilassi contro endocardite batterica (linee guida 2009) Vaccinazione annuale antinfluenzale, ogni 5 anni pneumovax
- A rischio l'anestesia generale, preferire l'epidurale
- Sconsigliato (fumo, alcol, droghe)
- Evitare esposizione ad alte quote >2500m specie se improvvise

Annals of Thoracic Medicine - Vol 9, Supplement 1, July-September 2014

Saudi Guidelines on the Diagnosis an Treatment of Pulmonary Hypertensio

Pulmonary arterial hypertension associated with congenital heart disease

Lopes and Alnajashi: Saudi guidelines for pulmonary hypertension 2014

Table 2: Major steps in the management of the eisenmenger syndrome

Counseling, therapeutic measures and parameter control	Rationale	Class of rec of evidence
Lifestyle: Appropriate occupations and avoidance of dehydration (particularly in long flights)	Prevention of hyperviscosity-related complications	I/C
Contraception and avoidance of pregnancy	Reduction of maternal and fetal mortality	I/B
Infections: Vigilance, prophylaxis and immunization	Prevention of influenza and pneumococcal infections, endocarditis and brain abscess	I/B
Control of hematocrit, blood viscosity and iron stores (replenishment). Mild isovolemic hemodylution in symptomatic patients	Prevention and treatment of hyperviscosity-related symptoms and thrombosis	I/B
Chronic anticoagulation with warfarin	Management of intrapulmonary thrombosis	IIa/B
Oxygen therapy	Improvement of symptoms and oxygen saturation	IIa/B
Advanced therapies for patients with class III/IV symptoms	Improvement of the physical capacity, quality of life, hemodynamics and survival	I/B
Transplantation in highly symptomatic patients	Improvement of symptoms and quality of life	IIa/B
Antiarrhythmic drugs and implantable defibrillators	Prevention of hemodynamic disturbances/ deterioration and sudden death	IIa/B

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

Table 18 Recommendations for general measures

Statement	Class[a]	Level[b]
It is recommended to avoid pregnancy in patients with PAH	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C
Physically deconditioned PAH patients should be considered for supervised exercise rehabilitation	IIa	B
Psychosocial support should be considered in patients with PAH	IIa	C
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently less than 8 kPa (60 mmHg)	IIa	C
Epidural anaesthesia instead of general anaesthesia should be utilised, if possible, for elective surgery	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in patients with PAH	III	C

[a]Class of recommendation.
[b]Level of evidence.

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   - Correctable†
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

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   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

*Nice 2013.

Gruppo A
la diagnosi è semplice ed esistono raccomandazioni per il trattamento

Gruppo B
il difetto cardiaco non può essere chiuso senza rischi elevati e le opzioni di gestione sono attualmente limitate

Gruppo C
hanno quadro clinico simile a IAPI idiopatica con il vantaggio di uno shunt

Gruppo D
sviluppano IAP in assenza di shunt residui (cambiamenti nella vascolarizzazione polmonare erano in una fase di irreversibilità o hanno avuto andamento progressivo, nonostante correzione)

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

D. Pulmonary arterial hypertension after corrective cardiac surgery

Ipertensione, in acuto, immediato post operatorio

- «**crisi ipertensive polmonari**», nel post-operatorio
  - aumenti improvvisi di PAP e RVP con conseguente insufficienza acuta del ventricolo destro e morte

- L'ipertensione polmonare, oggi, complica solo l'1% dei pazienti sottoposti a cardiochirurgia per:
  - ottimizzazione del tempo all'intervento
  - miglior controllo della portata cardiaca, ipossia, acidosi
  - utilizzo standard di Ossido Nitrico e/o sildenafil nel post operatorio

Classe di raccomandazione I livello di evidenza B

La mortalità in coloro che presentano la crisi rimane elevata 10%

Uso di vasodilatatori polmonari nell'immediato post operatorio

Cardiology Journal
2012, Vol. 19, No. 4, pp. 387–394
10.5603/CJ.2012.0070

ISSN 1897–5593

VIA MEDICA

ORIGINAL ARTICLE

Comparison of inhaled nitric oxide and aerosolized iloprost in pulmonary hypertension in children with congenital heart surgery

Conclusions: *Both inhaled NO and aerosolized iloprost were found to be effective and comparable in the management of pulmonary hypertension.* (Cardiol J 2012; 19, 4: 387–394)

Intensive Care Med (2011) 37:502–509
DOI 10.1007/s00134-010-2065-4

ORIGINAL

Alain Fraisse
Ghazwan Butrous
Mary B. Taylor
Michael Oakes
Maria Dilleen
David L. Wessel

Intravenous sildenafil for postoperative pulmonary hypertension in children with congenital heart disease

sildenafil. *Conclusion:* Intravenous sildenafil reduced pulmonary artery pressure and shortened time to extubation and intensive care unit stay in ch

ELSEVIER

European Journal of Cardio-thoracic Surgery 38 (2010) 71–77

www.elsevier.com/locat

Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children☆

Shintaro Nemoto [a,*], Tomoyasu Sasaki [a], Hideki Ozawa [a], Takahiro Katsumata [a], Kanta Kishi [b], Kenichi Okumura [b], Yasuhiko Mori [b], Osamu Umegaki [c]

Abstract

Objective: Sildenafil is a strong pulmonary vasodilator that increases the intracellular cyclic guanosine monophosphate concentration through inhibition of phosphodiesterase-5. We assessed the benefit of oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in paediatric patients. **Methods:** Sildenafil was administered at a starting dose of 0.5 mg kg^{-1} following admission to the intensive care unit. With careful monitoring of haemodynamics, the dose was increased stepwise by 0.5 mg kg^{-1} every 4–6 h up to a maximum of 2 mg kg^{-1}. After successful weaning from a ventilator and from other vasodilators, sildenafil was gradually discontinued over the next 5–7 days. **Results:** A retrospective review of medical records showed an age distribution of <1 month (n = 26), ≥1 – <6 months (n = 36), ≥6 – <12 months (n = 19), 1–3 years (n = 8), 4–9 years (n = 9) and >10 years (n = 2) at the time of surgery. The surgeries were performed for ventricular septal defect closure (n = 17), arterial switch (n = 30), truncus arteriosus repair (n = 10), complete atrioventricular septal defect repair (n = 12), total anomalous venous drainage repair (n = 9), and other open-heart surgery (n = 22). The aforementioned concomitant inhaled nitrous oxide treatment was performed in 66 patients. Pulmonary arterial pressure decreased in 28, was unchanged in five and elevated in one patient out of the total of 34 cases for which data from continuous pressure monitoring were available. Bosentan was added in three cases with persistent symptoms due to pulmonary hypertension despite sildenafil treatment. After sildenafil administration, modest oxygen desaturation occurred in seven cases, but no 'rebound' pulmonary hypertension occurred. There were no significant adverse events during sildenafil treatment. **Conclusions:** Our results suggest that oral sildenafil is a safe and effective alternate for persistent pulmonary hypertension following congenital heart surgery in children.

Neth Heart J (2011) 19:509–513
DOI 10.1007/s12471-011-0218-x

SPECIAL ARTICLE

Advanced therapy for pulmonary arterial hypertension due to congenital heart disease: a clinical perspective in a new therapeutic era

M. J. Schuuring · S. M. Boekholdt · A. Windhausen · B. J. Bouma · M. Groenink · M. Keijzers · R. J. De Winter · D. R. Koolbergen · N. A. Blom · B. J. M. Mulder

Finally, advanced therapy might be useful in CHD patients who undergo cardiac surgery, who tend to have a decline in right ventricular function [15]. Treatment with an endothelin-1 receptor antagonist might reduce perioperative pulmonary vasoconstriction induced by the endothelin-1 release initiated by the cardiopulmonary bypass [16]. In a small study, perioperative treatment with a selective endothelin-1 receptor antagonist led to a significant decrease in PVR compared with the control group [17]. However, trials are needed to confirm this hypothesis and to show clinical benefit in CHD patients. In our centre we are

Ipertensione, post operatorio, a distanza

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

D. Pulmonary arterial hypertension after corrective cardiac surgery

L'ottimizzazione dei tempi alla chirurgia e il trattamento in acuto con vasodilatatori ha aumento la sopravvivenza nell'immediato postoperatorio, ciò non significa che il problema IAP sia risolto nel tempo:

- L'IAP può persistere anche dopo la correzione chirurgica, in assenza di shunt
- Oppure il paziente può star bene per i primi 3-5 anni successivi l'intervento e divenire progressivamente sintomatico per progressivo sviluppo della malattia vascolare polmonare

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

D. Pulmonary arterial hypertension after corrective cardiac surgery

L'emodinamica presentata da questo gruppo è simile all'IAP idiopatica

UPDATE Rev Esp Cardiol. 2010;63(10):1179-93

The Right Heart and Pulmonary Circulation (X)

Pulmonary Hypertension in Congenital Shunts

Maurice Beghetti and Cecile Tissot

Pediatric Cardiology Unit, Children's University Hospital of Geneva, Geneva, Switzerland

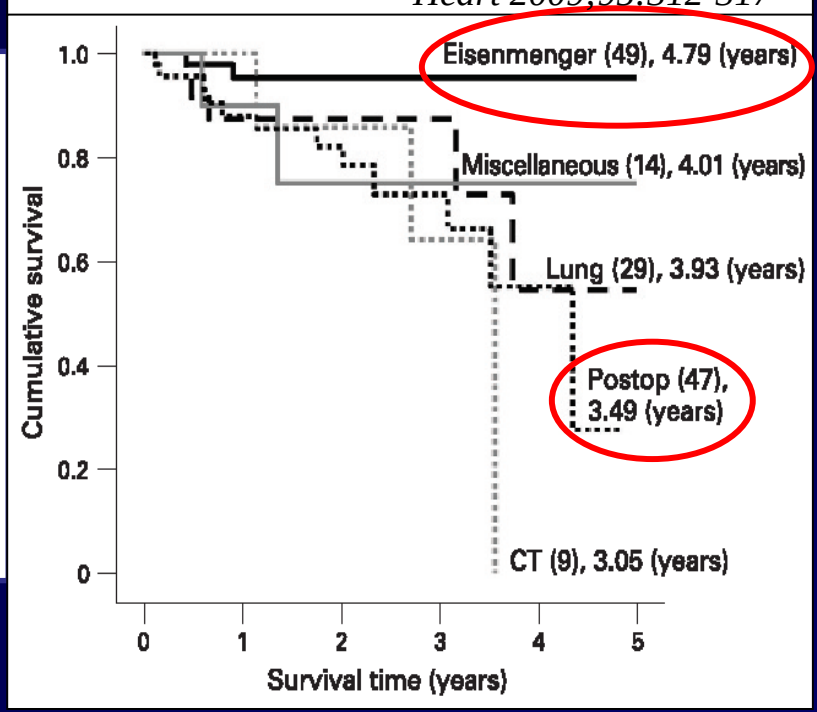
uno studio retrospettivo di 5 anni eseguito nel Regno Unito: bambini con IAP la sottopopolazione che ha sviluppato IAP nel postoperatorio è andata peggio rispetto a quelli con IAPcc non operate che ha sviluppato la SE

- 1/4 di questi bambini sono morti (11/47)
- I bambini con SE avevano una maggiore sopravvivenza

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

S G Haworth, A A Hislop

Heart 2009;95:312-317



La riparazione chirurgica non è sempre l'opzione migliore

Guidelines

Annals of Thoracic Medicine - Vol 9, Supplement 1, July-September 2014

Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary arterial hypertension associated with congenital heart disease

Antonio Lopes, Khalid Alnajashi[1]

Gradi di severità al cateterismo destro

grado	lieve	moderata	severa
PAPmedia ≥25 mmHg	**25-35**	**35-45**	**≥ 45**
RVP	< 2.3	2.3-4.6	> 4.6
RVPI	**< 4**	**4-8**	**> 8**
RVP/RVS	**< 0.3**	**0.3- 0.5**	**≥ 0.5**
QP/QS	> 2	2-1.5	< 1.5
operabilità	**SI (IC)**	**Vasoreattività**	NO (IC)

Valutazione clinico-strumentale Operabilità Classe di raccomandazione I livello di evidenza C

	Correzione- pro	Correzione- contro
Età	< 1 anno	> 2 anni
Tipo di CC	semplice	complessa
Saturazione O2	> 95%	< 90%
Congestione polmonare	Presente	Assente
Rx Torace	Cardiomegalia > vascolarizzazione polmonare	Cuore normale Barrage
Clinica	Insufficienza cardiaca	Cianosi

CT

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International Journal of Cardiology 129 (2008) 163–171
www.elsevier.com/locate/ijcard

Review

Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy

Konstantinos Dimopoulos *, Ana Peset, Michael A. Gatzoulis

Evaluating operability of cardiac defects in adults with CHD and PAH

For	Against
– Abort right-to-left shunting	– Potential conversion of Eisenmenger physiology to iPAH physiology (and thus worse long-term outcome)
– ↓ Cerebrovascular events (stroke /abscess)	
– Prevent cyanosis	
↑ Exercise capacity	– High perioperative risk
↓ Erythrocytosis	
↓ Hemostatic problems	– Very limited experience and no long-term data available
↓ Systemic organ failure	
– Protect pulmonary circulation	

CHD = Congenital heart disease, PAH = pulmonary arterial hypertension, iPAH = idiopathic pulmonary arterial hypertension.

Guidelines

Annals of Thoracic Medicine - Vol 9, Supplement 1, July-September 2014

Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary arterial hypertension associated with congenital heart disease

Antonio Lopes, Khalid Alnajashi[1]

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)

Funzione del cateterismo destro e i test di vasoreattività (classe IIA livello ev. C)

Definizione di Ipertensione Polmonare

grado	lieve	moderata	severa
PAPmedia ≥25 mmHg	**25-35**	**35-45**	**> 45**
RVP (UW)	< 2.3	2.3-4.6	> 4.6
RVPI (UW/m2)	**< 4**	**4-8**	**> 8**
RVP/RVS	**< 0.3**	**0.3- 0.5**	**≥ 0.5**
QP/QS	> 2	2-1.5	< 1.5
operabilità	**SI**	**Vasoreattività**	NO

Test di occlusione con palloncino:

RIDUZIONE della G.C.

AUMENTO della pressione di riempimento Vdx

Suggeriscono

bassa probabilità di beneficiare della chiusura permanente maggiore rischio perioperatorio

Test di Vasoreattività criteri di Barst

	PAPmedia	RVPI	RVP/RVS
Moderata	**35-45**	**>4- ≤ 8**	**0.3- 0.5**
Riduzione del 20% PAPm e RVP e del RVP/RVS		**< 4**	**< 0.3**

non consenso assoluto, operabilità con esito favorevole probabile (classe IIa, evid. B)

Cardiopatie Semplici
DIA, DIV, DAP

chiusura in asintomatici/sintomatici con impegno ventricolare e

PAP e RVP < 2/3 di PAS e RVS

Table 3 Indications for intervention in atrial septal defect

Indications	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR <5 WU should undergo ASD closure regardless of symptoms	I	B[26]
Device closure is the method of choice for secundum ASD closure when applicable	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention	IIa	C
Patients with PVR ≥5 WU but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L–R shunt (Qp:Qs >1.5) may be considered for intervention	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology	III	C

[a]Class of recommendation.
[b]Level of evidence.
ASD = atrial septal defect; L–R shunt = left-to-right shunt; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp:Qs = pulmonary to systemic flow ra… vascular resistance; WU = Wood units.

Table 4 Indications for intervention in ventricular septal defect

Indications	Class[a]	Level[b]
Patients with symptoms that can be attributed to L–R shunting through the (residual) VSD and who have no severe pulmonary vascular disease (see below) should undergo surgical VSD closure	I	C
Asymptomatic patients with evidence of LV volume overload attributable to the VSD should undergo surgical VSD closure	I	C
Patients with a history of IE should be considered for surgical VSD closure	IIa	C
Patients with VSD-associated prolapse of an aortic valve cusp causing progressive AR should be considered for surgery	IIa	C
Patients with VSD and PAH should be considered for surgery when there is still net L–R shunt (Qp:Qs >1.5) present and PAP or PVR are <2/3 of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy)	IIa	C
Surgery must be avoided in Eisenmenger VSD and when exercise-induced desaturation is present	III	C
If the VSD is small, not subarterial, does not lead to LV volume overload or pulmonary hypertension, and if there is no history of IE surgery should be avoided	III	C

[a]Class of recommendation.
[b]Level of evidence.
AR = aortic regurgitation; IE = infective endocarditis; L–… pulmonary arterial hyp… Qs = pulmonary to s…

Table 6 Indications for intervention in patent ductus arteriosus

Indications	Class[a]	Level[b]
PDA should be closed in patients with signs of LV volume overload	I	C
PDA should be closed in patients with PAH but PAP <2/3 of systemic pressure or PVR <2/3 of SVR	I	C
Device closure is the method of choice where technically suitable	I	C
PDA closure should be considered in patients with PAH and PAP >2/3 of systemic pressure or PVR >2/3 of SVR but still net L–R shunt (Qp:Qs >1.5) or when testing (preferably with nitric oxide) or treatment demonstrates pulmonary vascular reactivity	IIa	C
Device closure should be considered in small PDAs with continuous murmur (normal LV and PAP)	IIa	C
PDA closure should be avoided in silent duct (very small, no murmur)	III	C
PDA closure must be avoided in PDA Eisenmenger and patients with exercise-induced lower limb desaturation	III	C

[a]Class of recommendation.
[b]Level of evidence.

Non Indicato

Situazione limite Utili

I test di vosoreattività polmonare

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)

A.Privitera U.O. Cardiologia Pediatrica Santo Bambino CT

Opzione trattamento pre-chiusura

See 1 citation found by title matching your search:

Jpn J Thorac Cardiovasc Surg. 2004 Apr;52(4):213-6.

Atrial septal defect with borderline pulmonary vascular disease: surgery and long-term oral prostacyclin therap for recalcitrant pulmonary hypertension.

Yamauchi H, Yamaki S, Fujii M, Saji Y, Ochi M, Shimizu K.

Division of Cardiovascular Surgery, Department of Surgery II, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.

Abstract

The hemodynamic determination of operability in atrial septal defect (ASD) with severe pulmonary hypertension is problematic. Therefore, we perfor an open lung biopsy prior to the corrective surgery in cases with pulmonary vascular resistance greater than 8 units x m2 and/or pulmonary arterial peak pressure greater than 70 mmHg. We present 4 cases showing occlusion of more than 70% of the small pulmonary arteries and arterioles by musculoelastosis, thromboembolism and mixed-type (musculoelastosis and plexogenic arteriopathy) which was considered borderline in terms of operability. After complete closure of the ASD and postoperative long-term oral prostacyclin (PGI2) therapy, pulmonary artery peak pressure decreased from 110-72 (mean 84) to 105-45 (mean 74) mmHg immediately after operation and 65-40 (mean 57) mmHg after PGI2 therapy. The New York Heart Association functional status of the patients improved from class II-III to class I with oral PGI2 only. Our cases demonstrate that despite more than 70% occlusion of the small pulmonary arteries and arterioles, surgery and long-term PGI2 therapy can reduce pulmonary artery pressure and improve the quality of life.

See 1 citation found by title matching your search:

Int J Cardiol. 2006 Jun 7;110(1):104-7. Epub 2005 Jul 1.

Atrial septal defect closure in a patient with "irreversible" pulmonary hypertensive arteriopathy.

Schwerzmann M, Zafar M, McLaughlin PR, Chamberlain DW, Webb G, Granton J.

Abstract

The presence of irreversible pulmonary hypertension in patients with atrial septal defect (ASD) is thought to preclude shunt closure. We report the case of a woman with plexiform pulmonary arteriopathy secondary to an ostium secundum ASD who was able to successfully undergo percutaneous shunt closure following therapy with chronic intravenous prostacyclin (Flolan). One year after closure, the patient was weaned off Flolan over a period of 7 months following the institution of oral Bosentan therapy. Our case illustrates how aggressive vasodilator therapy with prostaglandins may be capable of reducing pulmonary artery pressure and permitting shunt closure in a patient once considered to have "inoperable" pulmonary arteriopathy.

Interactive CardioVascular and Thoracic Surgery 17 (2013) 963–968
doi:10.1093/icvts/ivt353 Advance Access publication 28 August 2013

ORIGINAL ARTICLE – CONGENITAL

Perioperative sildenafil therapy for pulmonary hypertension in infants undergoing congenital cardiac defect closure†

Ashraf A.H. El Midany[a,*], Ezzeldin A. Mostafa[a], Sherif Azab[a] and Ghada A. Hassan[b]

OBJECTIVES: Pulmonary hypertension in paediatric patients with ventricular septal defect remains one of the most important determinants of perioperative morbidity and mortality. Sildenafil is an oral, well-tolerated pulmonary vasodilator with few drug interactions. We studied the effect of oral sildenafil, when given before and after surgical closure compared with starting it postoperatively, on the pulmonary artery pressure and patients' outcome.

RESULTS: Overall hospital mortality was 4.9%. Mean pulmonary artery pressure decreased significantly at all time points of recording in both groups ($P < 0.0001$). In the sildenafil group, it decreased preoperatively after sildenafil administration from 75.4 to 59.4 mmHg and postoperatively from 50.4 mmHg immediate post-cardiopulmonary bypass to reach 44.2 mmHg before discharge. In the control group, it decreased from 74.6 mmHg to 51 mmHg immediate post-cardiopulmonary bypass to reach 42.7 mmHg before discharge. No adverse effects have been recorded. Although there was no difference in the duration of mechanical ventilation and hospital stay between the two groups, intensive care unit stay was significantly shorter in the sildenafil group. Dobutamine doses were significantly higher in the sildenafil group; however, milrinone and epinephrine have been used more significantly in the control group.

CONCLUSIONS: The low cost, the oral availability and the good tolerability of sildenafil make it a suitable and simple alternative therapy for secondary pulmonary hypertension including persistent postoperative pulmonary hypertension associated with ventricular septal defect in resource limited places. However, starting sildenafil early before surgery does not add a great benefit in terms of improving postoperative pulmonary hypertension or patients' outcome.

J Thorac Cardiovasc Surg. 2009 Mar;137(3):760-1. doi: 10.1016/j.jtcvs.2008.03.064. Epub 2008 Sep 9.

Atrial septal defect repair after a 10-month treatment with bosentan in a patient with severe pulmonary arterial hypertension: a case report.

Hoetzenecker K, Ankersmit HJ, Bonderman D, Hoetzenecker W, Seitelberger R, Klepetko W, Lang IM.

We conclude that bosentan treatment of a patient with type II ASD and severe pulmonary hypertension results in an amelioration of pulmonary hypertension that may allow surgical correction according to standard operating procedures of pulmonary hypertension units.

Considerazioni

UPDATE Rev Esp Cardiol. 2010;63(10):1179-93

The Right Heart and Pulmonary Circulation (X)

Pulmonary Hypertension in Congenital Shunts

Maurice Beghetti and Cecile Tissot

Pediatric Cardiology Unit, Children's University Hospital of Geneva, Geneva, Switzerland

Pre-trattamento **NO**

- Il pre-trattamento può essere d'insulto sulla circolazione polmonare
  - Il calo delle RVP indotte dalle terapie viene annullato dall'incremento del flusso ad alta pressione attraverso il difetto, con aumento dello shear stress nella circolazione polmonare.
  - L'inversione del rimodellamento vascolare portando ad una diminuzione iniziale delle RVP potrebbe ulteriormente danneggiare il letto vascolare polmonare

ELSEVIER International Journal of Cardiology 129 (2008) 163–171 www.elsevier.com/locate/ijcard

Review

Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy

Konstantinos Dimopoulos *, Ana Peset, Michael A. Gatzoulis

Pre trattamento **SI**

- La non uniforme risposta alla terapia avanzata
  - alcuni pazienti dimostrano un forte beneficio, altri ne mostrano poco o nessuno
- Il pre-trattameto serve a valutare l'emodinamica, la risposta sintomatica e la tolleranza alla somministrazione a lungo termine della terapia avanzata ed è consigliabile prima della chiusura

Khan SA, Gelb BD, Nguyen KH. Evaluation of pulmonary artery banding in the setting of ventricular septal defects and severely elevated pulmonary vascular resistance. Congenit Heart Dis 2006;1:244–50.

Strategia Alternative

- Bendaggio dell'arteria polmonare, trattamento con vasodilatatori polmonari, chiusura del difetto e de-bendaggio dell'arteria polmonare quando le resistenze sono diminuite
- chiusura parziale del difetto lasciando uno shunt residuo

Cateterismo destro e Test di Vasoreattività Polmonare

Table 6. Essential Components of Invasive Hemodynamic Assessment

Oxygen saturations (SVC, IVC, RV, PA, SA)
Right atrial pressure
Right ventricular pressure
Pulmonary artery pressure, systolic, diastolic, mean
Pulmonary arterial wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure
Cardiac output/index
Pulmonary vascular resistance
Systemic blood pressure
Heart rate
Response to acute vasodilator

IVC indicates inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SA, systemic artery; and SVC, superior vena cava.

La Risposta Vasodilatatore Acuta (RVA)

Nell'IAPI e nell'IAPF seleziona i responder al trattamento con calcio-antagonisti (CCB)

Nei pazienti con CC il test è utilizzato per:

- stabilire la prognosi in termine di sopravvivenza
- valutare la progressione/reversibilità della malattia vascolare polmonare al fine di stabilire l'operabilità del difetto cardiaco

Table 10 Route of administration, half-life, dose ranges, increments, and duration of administration of the most commonly used agents for pulmonary vasoreactivity tests

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 p.p.m	–	5 min[d]

[a]Initial dose and maximal tolerated dose suggested (maximal dose limited by side effects such as hypotension, headache, flushing, etc.).
[b]Increments of dose by each step.
[c]Duration of administration on each step.
[d]For NO, a single step within the dose range is suggested.

Responder Adulti	Riduzione PAPm ≥ 10 mmHg fino a raggiungere PAPm ≤ 40 mmHg Gittata Cardiaca (GC) aumentato/invariata assenza di riduzione
ESC/ERS Guidelines 2009	Criteri di Sitbon 2005
Responder Bambini	Riduzione PAPm ≥ 20% Indice cardiaco (IC) aumentato/invariato; RVP/RVS riduzione/invariato
REVEAL Circulation. 2012;125:113-122	Criteri di Barst 1986

IAP in età pediatrica

Riduzione sopravvivenza	Incremento Sopravvivenza
> Tempo diagnosi > RVPindicizzate	Test vasoreattività positivo < BNP e NT-proBNP

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

Circ J 2013; **77**: 2639–2650)

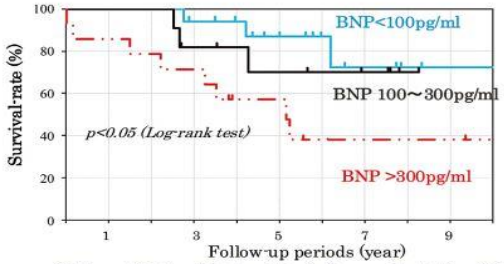
Update on Pediatric Pulmonary Arterial Hypertension

– Differences and Similarities to Adult Disease –

Tsutomu Saji, MD

BNP level at baseline and survival rate

	5 year-survival rate
BNP<100pg/ml	86.9%
BNP100～300pg/ml	70.1%
BNP>300pg/ml	57.1%



47th Annual Meeting of the Association for European Paediatric and Congenital Cardiology

Figure 5. Brain natriuretic peptide (BNP) and survival. The 5-year survival was worse among patients with BNP >300 pg/ml at treatment start than among those with BNP <100 pg/ml.

European Heart Journal (2006) **27**, 1485–1494
doi:10.1093/eurheartj/ehi891

EUROPEAN SOCIETY OF CARDIOLOGY®

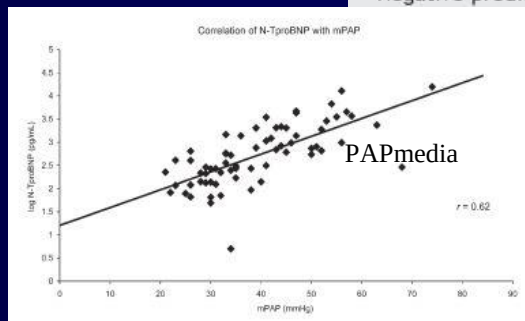
Clinical research
Vascular medicine

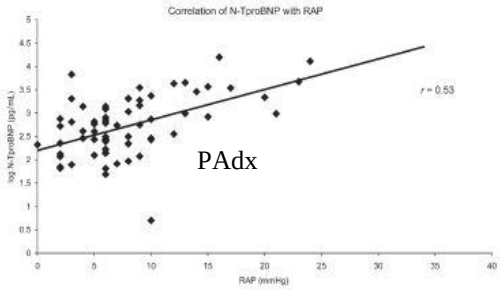
Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension

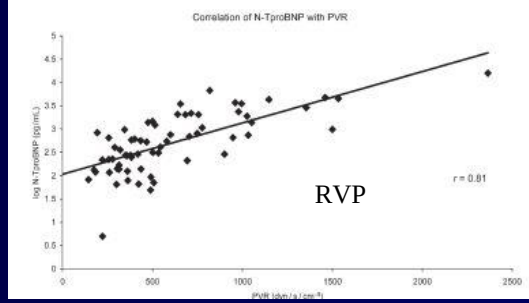
Sensitivity, specificity, positive, and negative predictive value of N-TproBNP for predicting SSc-PAH

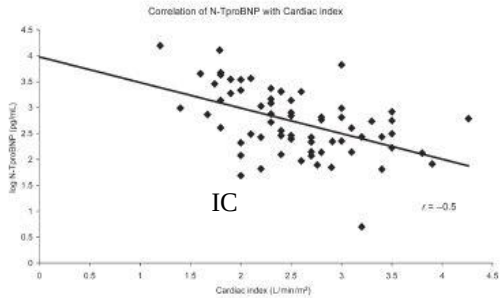
	Level of BNP		
	>395 units	≤395 units	Total
PAH present (cases)	38	30	68
PAH absent (controls)	2	39	41
Total	40	69	109

Sensitivity: 38/68 = 55.9% (95% CI 44.1, 67.4%).
Positive predictive value: 38/40 = 95.1% (95% CI 83.9, 98.7%).
Specificity: 39/41 = 95.1% (95% CI 83.9, 98.7%).
Negative predictive value: 39/69 = 56.5% (95% CI 44.8, 67.6%).









Terapia

Al momento non esiste una cura definitiva per l'ipertensione polmonare

Le attuali terapie mirano a migliorare e/o stabilizzare parametri emodinamici e sintomi

(dispnea, capacità di esercizio, morbilità, sopravvivenza)

Gli obiettivi da raggiungere dipendono dallo stato della malattia al momento della diagnosi

- **Nelle fasi iniziali** — **Prevenire la progressione**
- **Negli stati avanzati** — **Migliorare il quadro clinico**

Terapia di ordine generale nell'IAPI e S.E.

Anticoagulanti

- Eisenmenger (INDICATI)
  In assenza di emostasi: se fibrillazione atriale/trombi arteria polmonare/se insufficienza cardiaca **(IIa-C)**
- IAP Idiopatica (INDICATI INR 1.5-2.5) Rischio tromboembolico venoso per insufficienza cardiaca e immobilità

Diuretici

- Eisenmenger solo quando scompenso destro Attenzione disidratazione
- IAPidiopatica INDICATI Ritenzione di liquidi secondaria ad insufficienza cardiaca destra

Ossigeno

- S.E. non dati su benefici a lungo termine consigliato quando evidenza di beneficio sintomatico e dopo esercizio per correggere desaturazione
- IAPI quando la pressione di O2 è < 60 mmHg

Oral anticoagulants:
IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
APAH (IIb–C)
Diuretics (I-C)
Oxygen (I-C)
Digoxin (IIb-C)

Digossina

- S.E. per rallentare la frequenza ventricolare in caso di tachiaritmie atriali
- IAPI azione inotropa positiva sul ventricolo destro

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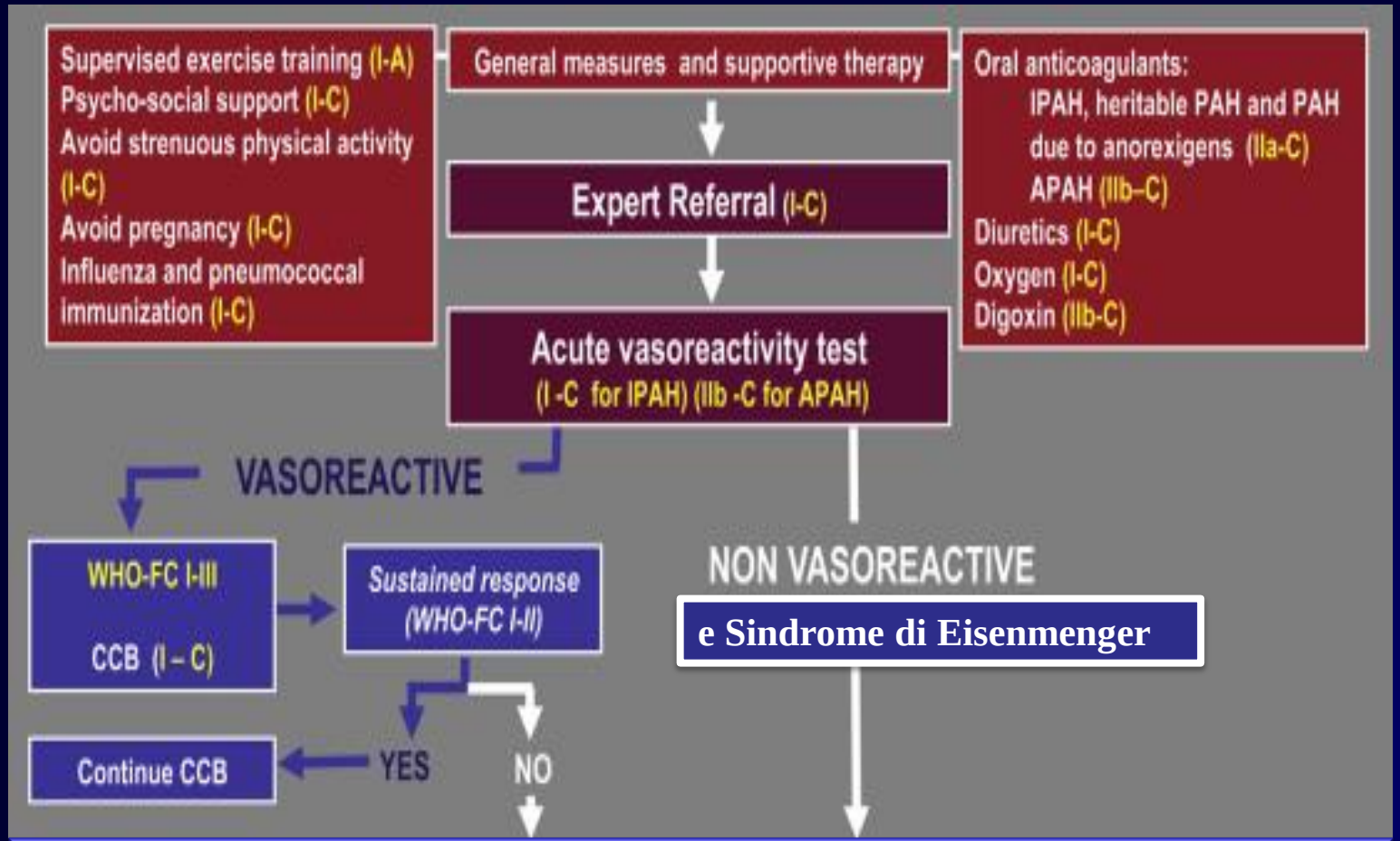
Updated Treatment Algorithm of Pulmonary Arterial Hypertension



Terapia specifica con vasodilatatori polmonari

Farmaci Approvati per IAP

2003

Epoprostenolo
prostaciclina
endovena

Bosentan
antagonista dei recettori dell'endotelina (ERA)
orale

2004-2007

Iloprost
anologo prostaciclina
inalatoria

Treprostinil
prostaciclina sintetica
sottocute 24/24

2005-2008

Sildenafil citrato
inibitore della 5 fosfodiesterasi (5PDE) inibisce il catabolismo del GMP ciclico
orale

2009

Sitaxentan
ERA
(ritirato dal commercio danno epatico mortale)

Ambrisentan
ERA
orale

Tadalafil
inibitore della 5PDE

2013-2014

Imatinib
ibitore della 5PDE

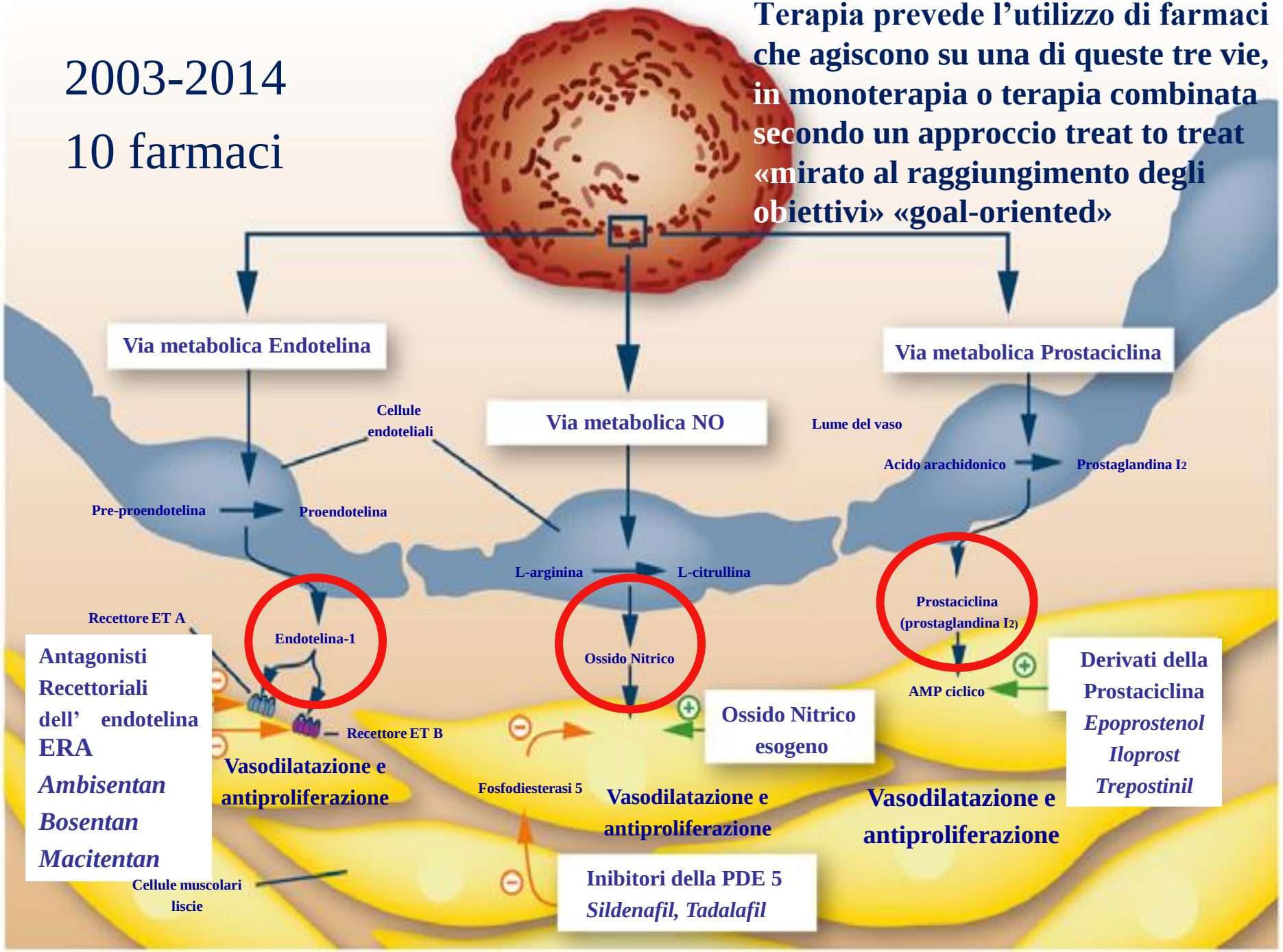
Riociguat
inibitore della 5 PDE
orale

Macitentan
ERA
orale

2003-2014

10 farmaci

Terapia prevede l'utilizzo di farmaci che agiscono su una di queste tre vie, in monoterapia o terapia combinata secondo un approccio treat to treat «mirato al raggiungimento degli obiettivi» «goal-oriented»



Bosentan Antagonista dei Recettori dell'Endotelina (ERA)

strategy. Bosentan is an orally active dual (ET_A and ET_B) endothelin-1 receptor antagonist that is effective in the

Oltre ad una azione vasodilatatoria ha proprietà aggiuntive: antifibrotica, antiproliferativa e antinfiammatoria

Bosentan: studi BREATHE-1-2 EARLY

THE LANCET

ARTICLES

Articles

Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study

Richard N Channick, Gérald Simonneau, Olivier Sitbon, Ivan M Robbins, Adaani Frost, Victor F Tapson, David B Badesch, Sébastien Roux, Maurizio Rainisio, Frédéric Bodin, Lewis J Rubin

INTERPRETATION: Bosentan increases exercise capacity and improves haemodynamics in patients with pulmonary hypertension, suggesting that endothelin has an important role in pulmonary hypertension.

The New England Journal of Medicine

BOSENTAN THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

LEWIS J. RUBIN, M.D., DAVID B. BADESCH, M.D., ROBYN J. BARST, M.D., NAZZARENO GALIÈ, M.D., CAROL M. BLACK, M.D., ANNE KEOGH, M.D., TOMAS PULIDO, M.D., ADAANI FROST, M.D., SÉBASTIEN ROUX, M.D., ISABELLE LECONTE, PH.D., MICHAEL LANDZBERG, M.D., AND GÉRALD SIMONNEAU, M.D., FOR THE BOSENTAN RANDOMIZED TRIAL OF ENDOTHELIN ANTAGONIST THERAPY STUDY GROUP

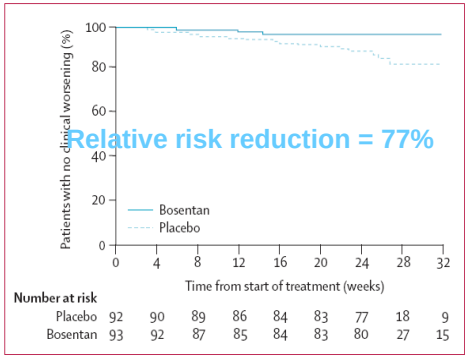
Conclusions The endothelin-receptor antagonist bosentan is beneficial in patients with pulmonary arterial hypertension and is well tolerated at a dose of 125 mg twice daily. Endothelin-receptor antagonism with oral bosentan is an effective approach to therapy for pulmonary arterial hypertension. (N Engl J Med 2002;346:896-903.)

Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial.

Galiè N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G.

INTERPRETATION: Bosentan increases exercise capacity and improves haemodynamics in patients with pulmonary hypertension, suggesting that endothelin has an important role in pulmonary hypertension.

dimostra che i pazienti con IAP lievemente sintomatici presentano, se lasciati non trattati, glruppo placebo, un **progressivo deterioramento clinico ed emodinamico bosentan comparata con placebo (p=0.0114)**



Ambisartan Antagonista dei Recettori dell'Endotelina (ERA)

Ambrisentan is a nonsulfonamide, propanoic acid–based, A-selective endothelin receptor antagonist with a bioavail-

Ambrisentan: studi ARIES-1-2-3 E

Oltre ad una azione vasodilatatoria ha proprietà aggiuntive: antifibrotica, antiproliferativa e antinfiammatoria, non aumenta le amminotrasferasi

ARIES-1: A PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF AMBRISENTAN IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Ronald J. Oudiz MD* Fernando Torres MD Adaani E. Frost MD David B. Badesch MD Horst Olschewski MD Nazzareno Galie MD Michael D. McGoon MD Vallerie McLaughlin MD Lewis J. [illegible]

UCLA Medical Center, Torrance, CA

CHEST

Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2

Nazzareno Galiè, Horst Olschewski, Ronald J. Oudiz, Fernando Torres, Adaani Frost, Hossein A. Ghofrani, David B. Badesch, Michael D. McGoon, Vallerie V. McLaughlin, Ellen B. Roecker, Michael J. Gerber, Christopher Dufton, Brian L. Wiens and Lewis J. Rubin

Conclusions—Ambrisentan improves exercise capacity in patients with pulmonary arterial hypertension. Improvements were observed for several secondary end points in each of the studies, although statistical significance was more variable. Ambrisentan is well tolerated and is associated with a low risk of aminotransferase abnormalities. (***Circulation***. **2008;117:3010-3019.**)

RESEARCH

Cardiovascular Therapeutics

ARIES-3: Ambrisentan Therapy in a Diverse Population of Patients with Pulmonary Hypertension

David B. Badesch,[1] Jeremy Feldman,[2] Anne Keogh,[3] Michael A. Mathier,[4] Ronald J. Oudiz,[5] Shelley Shapiro,[6] Harrison W. Farber,[7] Michael McGoon,[8] Adaani Frost,[9] Martine Allard,[10] Darrin Despain,[10] Christopher Dufton[10] & Lewis J. Rubin[11]; for the ARIES-3 Study Group

dyspnea were the most common adverse events. **Conclusion:** This study reconfirms the results of previous placebo-controlled studies, which demonstrate that ambrisentan is well tolerated and provides benefit in patients with PAH. Definitive conclusions regarding the safety and efficacy of ambrisentan in specific non-Group 1 PH etiologies cannot be determined and larger, controlled studies will be necessary to determine the efficacy and safety of ambrisentan in these populations.

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doi:10.1016/j.jacc.2009.07.033

Pulmonary Hypertension

Long-Term Ambrisentan Therapy for the Treatment of Pulmonary Arterial Hypertension

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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

Table 3 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Endothelin Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Ambrisentan	ARIES-1	No	6MWD	TTCW (NS)	12	202
	ARIES-2	No	6MWD	TTCW	12	192
Bosentan	Study-351	No	6MWD	TTCW	12	32
	BREATHE-1	No	6MWD	TTCW	16	213
	BREATHE-2*	No	PVR	—	12	33
	EARLY	No Sildenafil (16%)	PVR, 6MWD	TTCW	24	185
	BREATHE-5	No	SaO_2, PVR	—	12	54
Macitentan†	SERAPHIN	No, PDE5i or Inhal iloprost	TTCW	Safety	100	742

*Bosentan + epoprostenol versus placebo + epoprostenol. †Approved by the FDA for PAH patients and has obtained at the time of printing the positive opinion of the Committee for Medicinal Products for Human Use of the the EMA for this indication.

6MWD = 6-min walk distance; inhal = inhalation; NS = not statistically significant; PDE5i = phosphodiesterase type-5 inhibitors; PVR = pulmonary vascular resistance; SaO_2 = finger oxygen saturation; TTCW = time to clinical worsening.

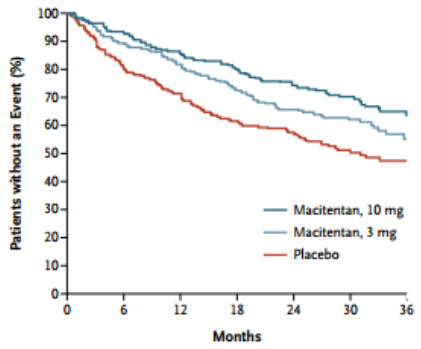
Il macitentan è un potente antagonista dei recettori dell'endotelina attivo per via orale su entrambi i recettori, ET_A e ET_B, , e in vitro risulta approssimativamente 100 volte più selettivo per il recettore ET_A che per il recettore ET_B. Il macitentan presenta elevata affinità e occupazione protratta nel tempo

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 369;9 NEJM.ORG AUGUST 29, 2013

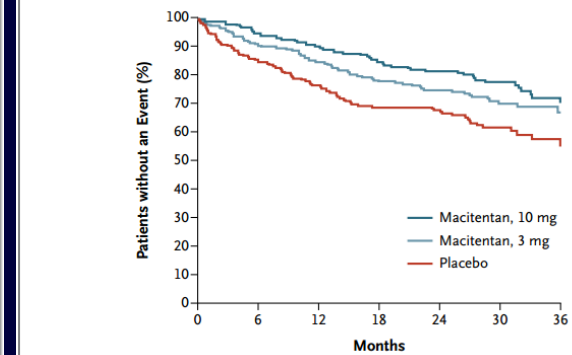
ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Figure 1. Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.



No. at Risk							
Placebo	250	188	155	132	119	62	22
Macitentan, 3 mg	250	208	181	159	144	77	31
Macitentan, 10 mg	242	203	183	166	152	86	39

Figure 2. Effect of Macitentan on the Composite Secondary End Point of Death Due to Pulmonary Arterial Hypertension or Hospitalization for Pulmonary Arterial Hypertension as a First Event.

REPUBBLICA ITALIANA

Regione Siciliana

ASSESSORATO DELLA SALUTE

Dipartimento Regionale per la Pianificazione Strategica

Servizio 7 Farmaceutica

Prot.n. 77443 Palermo, 09.10.2014

Oggetto: Notifica delle decisioni della Commissione Regionale per il Prontuario Terapeutico Ospedaliero/Territoriale della Regione Sicilia del D.A. 1766/2011 e s.m.i.;

ATC C02KX04 – MACITENTAN

La Commissione stabilisce di inserire il farmaco in PTORS.
La prescrivibilità è limitata ai Centri per l'ipertensione polmonare di cui all'allegato 1 del D.A.1766/2011 e s.m.i..
La prescrizione ed erogazione a carico del SSN è vincolata esclusivamente all'acclusione della copia del referto del cateterismo cardiaco effettuato;

4.1 Indicazioni terapeutiche

Opsumit è indicato, sia in monoterapia che in combinazione, per il trattamento a lungo termine dell'ipertensione arteriosa polmonare (PAH) in pazienti adulti in Classe Funzionale (FC) WHO II e III.

L'efficacia è stata dimostrata su una popolazione di pazienti PAH comprendente PAH idiopatica ed ereditabile, PAH associata a malattie del tessuto connettivo e PAH associata a cardiopatie congenite semplici corrette (vedere paragrafo 5.1).

Inibitori delle fosfodiesterasi 5 (5PDE)

Vasodilatatori con effetti antiproliferativi

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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

Table 4 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Nitric Oxide Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
Soluble Guanylate Cyclase Stimulators						
Riociguat*	PATENT	No bosentan or prostanoids	6MWD	TTCW	12	443
Phosphodiesterase Type-5 Inhibitors						
Sildenafil	SUPER-1	No	6MWD	TTCW (NS)	12	277
	Sastry	No	TT	–	12	22
	Singh	No	6MWD	–	6	20
	PACES	Epoprostenol	6MWD	TTCW	16	264
	Iversen	Bosentan	6MWD	–	12	20
Tadalafil	PHIRST	No or bosentan (54%)	6MWD	TTCW	16	405
Vardenafil†	EVALUATION	No	6MWD	TTCW	12	66

*Approved by the FDA for PAH and CTEPH patients and is currently undergoing the regulatory approval process by the EMA for both indications. †Not approved for pulmonary arterial hypertension.
TT = treadmill test; other abbreviations as in Table 3.

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension

Nazzareno Galiè, M.D., Hossein A. Ghofrani, M.D., Adam Torbicki, M.D., Robyn J. Barst, M.D., Lewis J. Rubin, M.D., David Badesch, M.D., Thomas Fleming, Ph.D., Tamiza Parpia, Ph.D., Gary Burgess, M.D., Angelo Branzi, M.D., Friedrich Grimminger, M.D., Marcin Kurzyna, M.D., and Gérald Simonneau, M.D., for the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group

n engl j med 353;20, 17,11, 2005

NCLUSIONS
lenafil improves exercise capacity, WHO functional class, and hemodynamics in pa-
its with symptomatic pulmonary arterial hypertension.

Long-Term Treatment with Sildenafil Citrate in Pulmonary Arterial Hypertension: SUPER-2

EST APERS PRESS
y 5, 2011;

Lewis J. Rubin, David B. Badesch, Thomas R. Fleming, Nazzareno Galiè, Gerald

nclusions: Long-term treatment of PAH initiated as sildenafil monotherapy was
ierally well tolerated. After 3 years, the majority of patients (60%) who entered the
PER-1 trial improved or maintained their functional status, and 46% maintained or
proved 6MWD.

Tadalafil Therapy for Pulmonary Arterial Hypertension

Nazzareno Galiè, Bruce H. Brundage, Hossein A. Ghofrani, Ronald J. Oudiz, Gerald Simonneau, Zeenat Safdar, Shelley Shapiro, R. James White, Melanie Chan, Anthony Beardsworth, Lyn Frumkin and Robyn J. Barst

studio PHIRST

Circulation. 2009;119:2894-2903; originally published online May 26, 2009;
Conclusions—In patients with pulmonary arterial hypertension, tadalafil 40 mg was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening. (*Circulation.* 2009;119:2894-2903.)

Prostaciclina e derivati

Potenti vasodilatatori, prevengono l'aggregazione piastrinica, la crescita cellulare della muscolatura liscia e hanno proprietà antiproliferativa e citoprotettiva

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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

Table 6 Characteristics of Randomized Controlled Trials With Pulmonary Arterial Hypertension Drugs Interfering With the Prostacyclin Pathway (See Text for References)

Drug(s) Tested	Study	Background	Primary Endpoint	Outcome (Secondary Endpoint)	Duration (weeks)	No. of Patients
			Prostanoids			
Beraprost	ALPHABET	No	6MWD	—	12	130
	Barst	No	CW (NS)	—	52	116
Epoprostenol	Rubin	No	6MWD	—	12	23
	Barst	No	6MWD	Survival	12	81
	Badesch	No	6MWD	—	12	111
Iloprost	AIR	No	6MWD and FC	—	12	203
	STEP	Bosentan	6MWD	TTCW	12	67
	COMBI	Bosentan	6MWD (NS)	—	12	40
Treprostinil	SC- Simonneau	No	6MWD	—	12	470
	Inhal TRIUMPH	Bosentan or Sildenafil	6MWD	—	12	235
	PO- Freedom M	No	6MWD	—	16	185
	PO- Freedom C1	Bosentan and/or sildenafil	6MWD (NS)	—	16	354
	PO- Freedom C2	Bosentan and/or sildenafil	6MWD (NS)	—	16	310
			Prostacyclin IP-receptor Agonists			
Selexipag*	Phase 2	Bosentan and/or sildenafil	PVR	6MWD (NS)	17	43

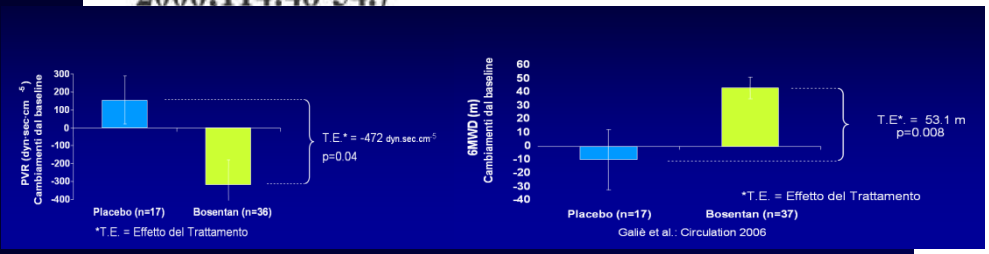
*Not approved for pulmonary artery hypertension.
CW = clinical worsening; FC = Functional Class; inhal = inhalation; PO = oral; SC = subcutaneous; other abbreviations as in Table 3.

Bosentan Therapy in Patients With Eisenmenger Syndrome: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

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

Circulation 2006;114;48-54; originally published online Jun 26, 2006;

Conclusions—In this first placebo-controlled trial in patients with Eisenmenger syndrome, bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation. (*Circulation.* 2006;114:48-54.)



Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Long-term results of treatment with bosentan in adult Eisenmenger's syndrome patients with Down's syndrome related to congenital heart

Int J Cardiol. 2013 Apr 15;164(3):323-6. doi: 10.1016/j.ijcard.2011.07.009. Epub 2011 Jul 28.

Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome.

D'Alto M, Romeo E, Argiento P, D'Andrea A, Sarubbi B, Correra A, Scognamiglio G, Papa S, Bossone E, Calabrò R, Vizza CD, Russo MG.

CONCLUSIONS: Bosentan was safe and well tolerated in adult patients with CHD-related PAH with and without Down's syndrome during 12 months of treatment. Clinical status, exercise tolerance, and pulmonary hemodynamics improved, regardless of the presence of Down's syndrome.

Heart. 2011 Nov;97(22):1876-81. doi: 10.1136/heartjnl-2011-300344. Epub 2011 Sep 21.

Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study.

Zhang ZN, Jiang X, Zhang R, Li XL, Wu BX, Zhao QH, Wang Y, Dai LZ, Pan L, Gomberg-Maitland M, Jing ZC.

Author information

Abstract

BACKGROUND: Although sildenafil has been shown to be safe and effective in idiopathic pulmonary arterial hypertension (PAH) and PAH related t connective tissue disease, its effects in Eisenmenger syndrome are less clear.

ther long-term treatment (12 months) with the phosphodiesterase type 5 inhibitor sildenafil improves clinical and atients with Eisenmenger syndrome.

l, multicentre study.

rtension centres in China.

ndrome functional class II-IV patients.

il 20 mg orally three times a day.

walk distance (6MWD) test, resting systemic arterial blood oxygen saturation (SaO(2)) in room air, haemodynamic eart catheterisation, safety and tolerability.

t effects at 12 months versus baseline (mean changes with 95% CIs) were 56 m increase (42 to 69, p<0.0001) in % to 2.9%, p<0.0001) in resting room air SaO(2). Improvements were also seen in mean pulmonary arterial pressu ice index (-4.7 mm Hg (-7.5 to -1.9), p=0.001; and -474 dyn×s×cm(-5)×m(2) (-634 to -314), p<0.0001, respectively) st adverse events were mild and transient, and occurred in the first 2 weeks of treatment.

s of oral sildenafil treatment was well tolerated and appeared to improve exercise capacity, systemic arterial oxyge arameters in patients with Eisenmenger syndrome.

Am J Cardiol. 2011 May 1;107(9):1381-5. doi: 10.1016/j.amjcard.2010.12.051. Epub 2011 Mar 2.

Ambrisentan for pulmonary arterial hypertension due to congenital heart disease.

Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB.

functional class, and hemoglobin. In conclusion, in this single-center cohort of patients with ES, ambrisentan was safe and was associated with increasing exercise capacity at short-term follow-up, with patients maintaining S(a)O(2), functional class, and hemoglobin, and with no significant evidence of clinical deterioration at longer term follow-up. Additional studies are required to further assess the efficacy of ambrisentan in patients with ES.

Table 24 Recommendations for paediatric PAH

Statement	Class[a]	Level[b]
The PH diagnostic work-up proposed for adults should also be considered in children	IIa	C
The PAH therapeutic algorithm proposed for adults should also be considered in children	IIa	C

[a]Class of recommendation.
[b]Level of evidence.

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Pediatric Pulmonary Hypertension

BJCP British Journal of Clinical Pharmacology

Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study

Maurice Beghetti,[1] Sheila G. Haworth,[2] Damien Bonnet,[3]

More patients with PAH-CHD were female and started bosentan as monotherapy. Congenital heart defects were fully repaired in 19 patients (40%, including 4 patients on pre-existing prostanoid therapy) or partially repaired or unrepaired for 29 patients (60%, including 14 patients on pre-existing prostanoid therapy). A larger percentage of patients on pre-existing prostanoid therapy had partially repaired or unrepaired congenital heart defects compared to repaired defects at bosentan initiation than patients not on prostanoid therapy (78% vs 50%). Hemodynamic parameters were also consistent with more severe disease in the subgroup with pre-existing prostanoid therapy at bosentan initiation (Table 1). Congenital heart defects included (re-

Long-Term Outcomes in Children With Pulmonary Arterial Hypertension Treated With *Bosentan* in Real-World Clinical Settings

Am J Cardiol 2010;106:1332–1338)

D. Dunbar Ivy, MD[a,*], Erika Berman Rosenzweig, MD[b], Jean-Christophe Lemarié[c], Monika Brand[d],

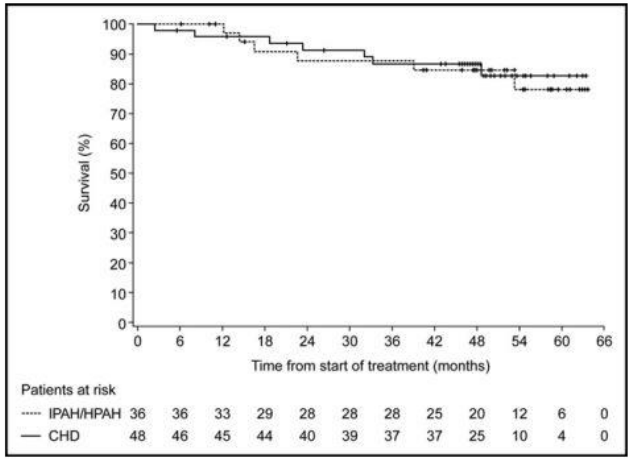

Figure 3. Kaplan-Meier estimates of survival at 1 year and 2, 3, and 4 years for patients with IPAH/HPAH were 100%, 88%, 88%, and 85% and those for patients with PAH-CHD were 96%, 91%, 87%, and 87%, respectively.

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naive Children With Pulmonary Arterial Hypertension

Robyn J. Barst, D. Dunbar Ivy, Guillermo Gaitan, Andras Szatmari, Andrzej Rudzinski, Alberto E. Garcia, B.K.S. Sastry, Tomas Pulido, Gary R. Layton, Marjana Serdarevic-Pehar and David L. Wessel

Circulation. 2012;125:324-334; originally published online November 29, 2011;

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

Update on Pediatric Pulmonary Arterial Hypertension

– Differences and Similarities to Adult Disease –

Tsutomu Saji, MD

Children and adults with pulmonary arterial hypertension (PAH) have similarities and differences in their background characteristics, hemodynamics, and clinical manifestations. Regarding genetic background, mutations in *BMPR2*-related pathways seem to be pivotal; however, it is likely that other modifier genes and bioactive mediators have roles in the various forms of PAH in children and adults. In pediatric PAH, there are no clear sex differences in incidence, age at onset, disease severity, or prognosis but, as compared with adults, syncope incidence, pulmonary vascular resistance, and mean pulmonary artery pressure are higher, and vasoreactivity to acute drug testing is more frequent, among children. Nevertheless, the pharmacokinetic effects of 3 major pulmonary vasodilators appear to be similar in children and adults with PAH. This review focuses on the specific pathophysiologic features of PAH in children. (*Circ J* 2013; **77:** 2639–2650)

Farmaci sicuri ed efficaci nel rallentare la progressione della malattia rispetto al gruppo placebo che peggiora e nei pazienti con S.E.
potenziale possibilità di migliorare la qualità di vita”

Migliorati o invariati parametri clinici

- Classe funzionale WHO
- Tempo di peggioramento
- Test del cammino
- < BNP e NT pro-BNP

Migliorati o invariati parametri emodinamici

- Riduzione della PAP media.
- > Gittata Cardiaca
- < RVP

ACC/AHA 2008 Guidelines; Circulation 2008

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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

INITIAL THERAPY WITH PAH APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.

†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea(beraprost).

‡ Positive opinion for approval of the CHMP of EMA

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

IAPI
Inizio terapia classe NYHA II, in prima battuta con un antagonista recettoriale dell'endotelina o con un inibitore della 5PDE

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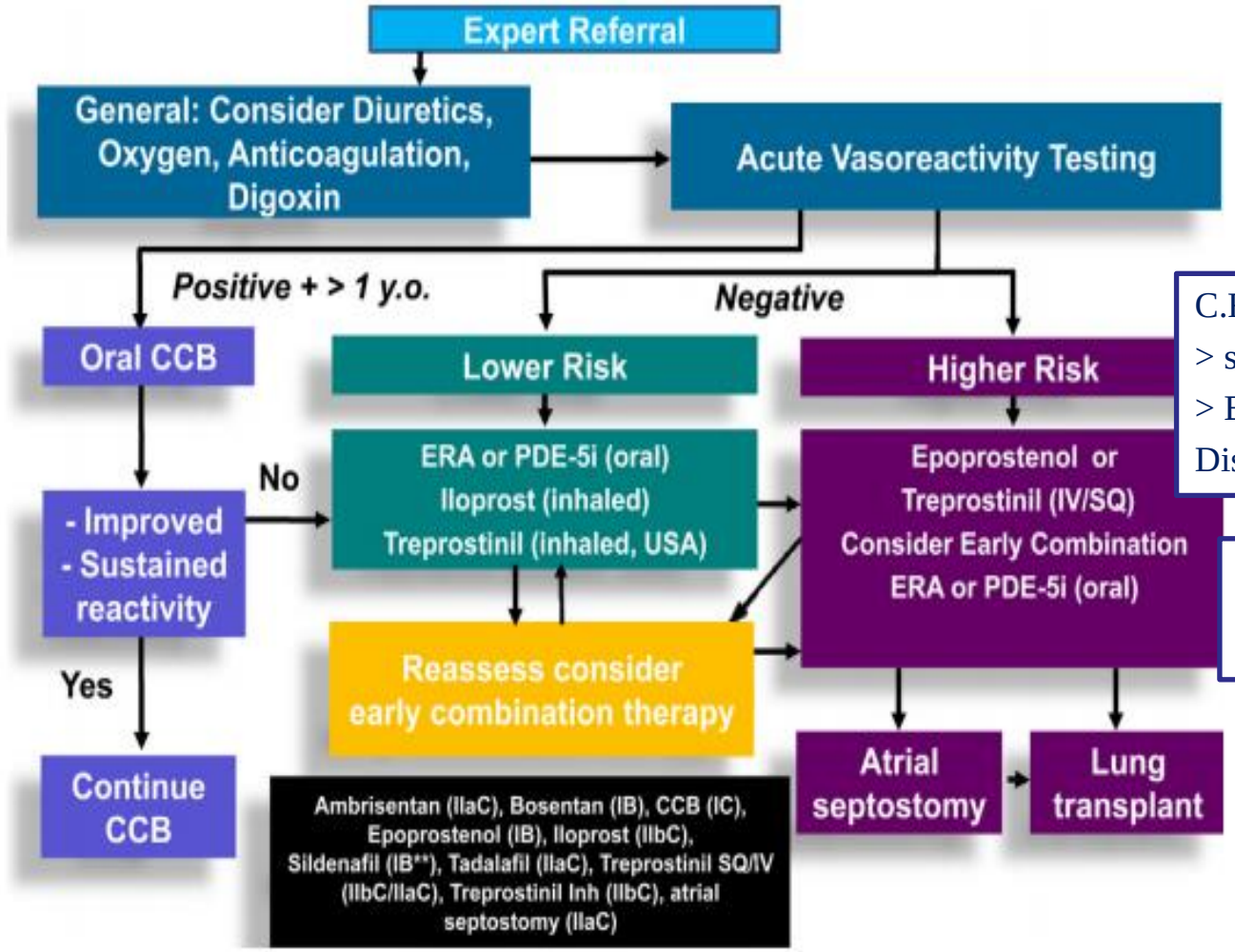
Pediatric Pulmonary Hypertension



C.F WHO
> sintomi
> BNP e NT pro-BNP
Disfunzione Vdx

PAPm/PASm> 0.75
Padx >10 mmHg
RVPI > 20 UW/m2

Algoritmo Eisenmenger

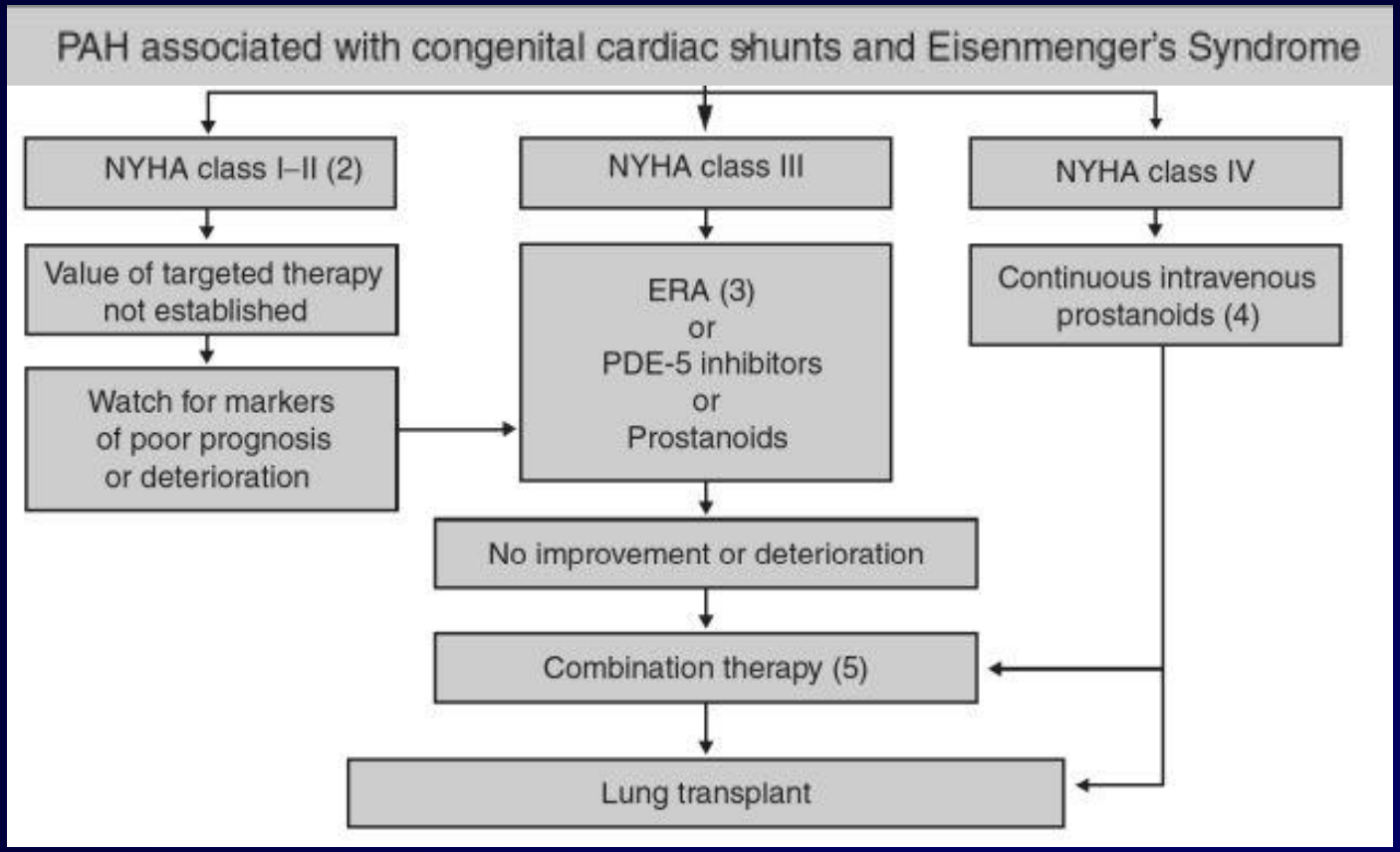
Management of Pulmonary Arterial Hypertension Associated with Congenital Systemic-to-Pulmonary Shunts and Eisenmenger's Syndrome

Nazzareno Galie,[1] Alessandra Manes,[1] Massimiliano Palazzini,[1] Luca Negro,[1]

treatment algorithm based on the one used in the treatment of PAH patients is proposed for patients with PAH associated with corrected and uncorrected congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome.

l'algoritmo si basa su opinioni di esperti, non ci sono prove ne raccomandazioni

1. calcioantagonisti non sono indicati per il maggiore effetto vasodilatatorio nella circolazione sistemica che accentuarebbe lo shunt dx-sn



Possono restare clinicamente stabili, in classe NYHA I-II, per parecchio tempo, il rapporto sicurezza efficacia dell'uso di terapie mirate non è stato stabilito in questa popolazione

Galie N. Drugs 2008

Recommendations for PAH associated with congenital cardiac shunts

Statement	Class[a]	Level[b]
The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger's syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

[a]Class of recommendation.
[b]Level of evidence.

Int J Cardiol. 2012 Mar 22;155(3):378-82. doi: 10.1016/j.ijcard.2010.10.051. Epub 2010 Nov 16.

Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology.

D'Alto M, Romeo E, Argiento P, Sarubbi B, Santoro G, Grimaldi N, Correra A, Scognamiglio G, Russo MG, Calabrò R.

CONCLUSIONS: Addition of sildenafil in adult patients with CHD-related PAH and Eisenmenger syndrome after oral bosentan therapy failure is safe and well tolerated at 6-month follow-up, resulting in a significant improvement in clinical status, effort SpO_2, exercise tolerance and haemodynamics.

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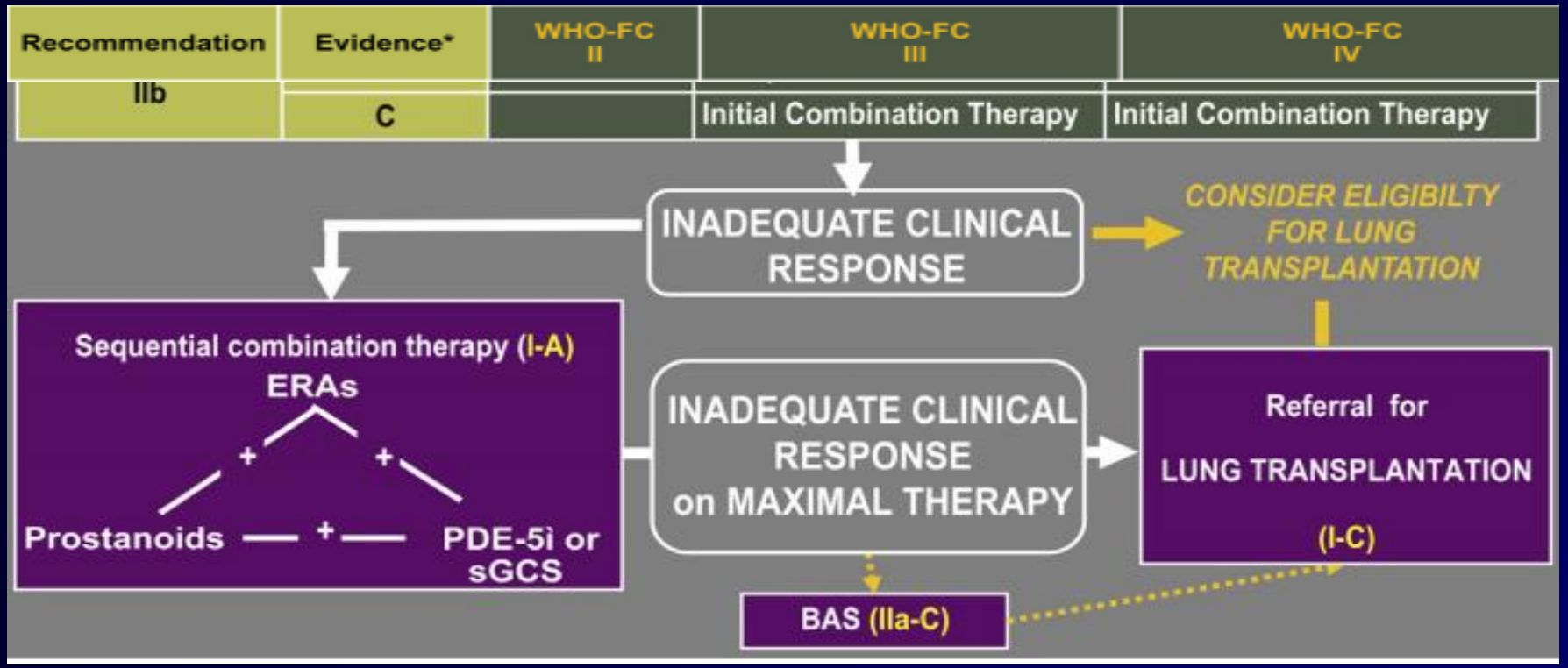
Updated Treatment Algorithm of Pulmonary Arterial Hypertension

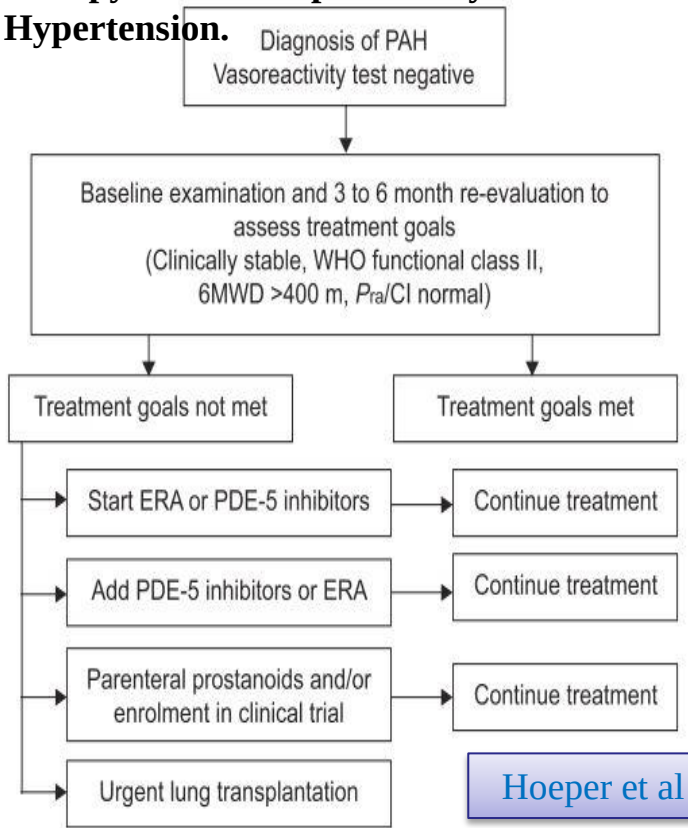
quando il paziente peggiora, o quando in classe NHYA III-IV si passa/inizia terapia di associazione, in modo da colpire tutti i vari aspetti fisiopatologici della malattia e ritardare il più possibile il trapianto



Terapia di Combinazione

Raccomandazione I Evidenza A

Goal-oriented treatment and combination therapy for pulmonary arterial Hypertension.



Hoeper et al Eur Respir J 2005

Eur Respir Rev 2009; 18: 113, 148–153
DOI: 10.1183/09059180.00003809

REVIEW

The use of combination therapy i pulmonary arterial hypertension: new developments

N. Galiè*, L. Negro* and G. Simonneau#

Eur Respir Rev 2010; 19: 118, 272–278
DOI: 10.1183/09059180.00008210

REVIEW

Treat-to-target strategies in pulmona arterial hypertension: the importance using multiple goals

O. Sitbon* and N. Galiè#

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http://dx.doi.org/10.1016/j.jacc.2013.10.034

Treatment Goals of Pulmonary Hypertension

Table 1 Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With PAH

Functional class	I or II
Echocardiography/CMR	Normal/near-normal RV size and function
Hemodynamics	Normalization of RV function (RAP <8 mm Hg and CI >2.5 to 3.0 l/min/m^2)
6-min walk distance	>380 to 440 m; may not be aggressive enough in young individuals
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg and $EqCO_2$ <45 l/min/l/min
B-type natriuretic peptide level	Normal

CI = cardiac index; CMR = cardiac magnetic resonance; $EqCO_2$ = ventilatory equivalent for carbon dioxide; PAH = pulmonary arterial hypertension; RAP = right atrial pressure; RV = right ventricular; VO_2 = peak oxygen consumption.

First-Line Combination of Ambrisentan and Tadalafil Reduces Risk of Clinical Failure Compared to Monotherapy in Pulmonary Arterial Hypertension Outcomes Study

September 8, 2014 8:46 AM ET

-- AMBITION Study of Ambrisentan/Tadalafil Combination Therapy Versus Monotherapy Achieves Primary Endpoint of Time to First Clinical Failure Event --

-- Data Presented at the ERS International Congress 2014 --

Parametri di Sopravvivenza

Journal of the American College of Cardiology
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Treatment Goals of Pulmonary Hypertension

Parameters with established importance for assessing disease severity, stability and prognosis in PAH (adapted from McLaughlin and McGoon[94])

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

EqCO2 <45 l/min /l /min

<1,800 ng/l

[a]Depending on age.
[b]TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients.
BNP = brain natriuretic peptide; CI = cardiac index; 6MWT = 6-minute walking test; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = WHO functional class.

World J Pediatr Congenit Heart Surg. 2013 Jul 1;4(3):286-9. doi: 10.1177/2150135113482739.

Potts shunt in a child with end-stage pulmonary hypertension after late repair of ventricular septal defect.

Petersen C, Helvind M, Jensen T, Andersen HØ.

Author information

Abstract

We report on a 10-year-old boy with medically refractory pulmonary arterial hypertension (PAH) and end-stage right heart failure after closure of a ventricular septal defect. The boy was a candidate for lung transplantation (LTX), but an alternative option was to create an Eisenmenger physiology with right-to-left shunting. The shunt could be created either as an intracardiac or as an extracardiac shunt. We decided to create a Potts shunt, a direct anastomosis between the left pulmonary artery and the descending aorta. The Potts shunt functioned as a right-to-left shunt, thus reducing the afterload on the right ventricle. The boy's clinical condition improved markedly, so he was discharged two weeks after the procedure. The ultimate therapeutic option for medically refractory PAH is LTX or heart-lung transplantation, but because of the short life span after LTX, time was bought by postponing the time of transplantation.

la settostomia atriale è raccomandata nei pazienti con grave ipertensione arteriosa polmonare e insufficienza cardiaca destra intrattabile, nonostante terapia medica massimale (farmaci specifici per IAP e agenti inotropi)

Gli obiettivi della procedura palliativa sono ripristino e mantenimento della stabilità clinica, finché può essere eseguito il trapianto polmonare

Controindicata quando:

- pressione atriale destra >20 mmHg
- SAO2< 85% in aria ambiente

CONGENITAL HEART DISEASE

Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension

A Micheletti, A A Hislop, A Lammers, P Bonhoeffer, G Derrick, P Rees, S G Haworth

DISCUSSION

The present study shows that atrial septostomy is safe and effective in children and young people with IPAH. This is the youngest series of patients yet reported. There were no fatalities and the procedure was successful in 19 of 20 patients, although four patients had a significant morbidity. Syncope was abolished and right heart failure improved. Echocardiographic assessment of right ventricular function improved significantly in seven children and did not deteriorate in the remainder. WHO functional class also improved significantly. Right to left interatrial shunting caused a mean reduction in systemic arterial oxygen saturation of 7.8 percentage points. Closure of one atrial communication led to the introduction of a fenestrated device in subsequent interventions. Seventeen of the 19 children who had an atrial septostomy are alive after a mean follow up of 2.1 years. Two have had a successful bilateral lung transplantation.

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Pediatric Pulmonary Hypertension

The updated Nice classification for PH

1. Eisenmenger syndrome

   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.

2. Left-to-right shunts
   - Correctable†
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease

   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.

4. Post-operative PAH

   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

*Nice 2013.

Gruppo A
la diagnosi è semplice ed esistono raccomandazioni per il trattamento

Gruppo B
il difetto cardiaco non può essere chiuso senza rischi elevati e le opzioni di gestione sono attualmente limitate

Gruppo C
hanno quadro clinico simile a IAPI idiopatica con il vantaggio di uno shunt

Gruppo D
sviluppano IAP in assenza di shunt residui (cambiamenti nella vascolarizzazione polmonare erano in una fase di irreversibilità o hanno avuto andamento progressivo, nonostante correzione)

Trapianto Polmonare

- IAP idiopatica — Bipolmonare
- IAPcch — Cuore-Polmone
  Polmone e Correzione della Cardiopatia

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Updated Treatment Algorithm of Pulmonary Arterial Hypertension

Table 7 Survival After Lung Transplantation in Patients With Pulmonary Arterial Hypertension

	1 year	5 years	10 years
Pittsburgh (Toyoda et al., 2008 [74])	86	75	66
Paris (Fadel et al., 2010 [75])	79	52	43
Toronto (de Perrot et al., 2012 [76])	78	60	45
Vienna (Klepetko, unpublished data, 2011)	73	71	—

BOSENTAN

Nome commerciale:

- **Tracleer 32 mg** compresse rivestite con film.
- **Tracleer 62,5 mg** compresse rivestite con film.
- **Tracleer 125 mg** compresse rivestite con film.

INDICAZIONI:

Trattamento dell'ipertensione arteriosa polmonare (PAH) per migliorare la capacità di fare esercizio fisico nonché i sintomi in pazienti in classe funzionale WHO III. E' stato dimostrato che Tracleer è efficace per:

- ipertensione arteriosa polmonare primitiva (idiopatica ed ereditabile)
- ipertensione arteriosa polmonare secondaria a sclerodermia senza pneumopatia interstiziale significativa
- ipertensione arteriosa polmonare associata a shunt sistemico-polmonari congeniti e Sindrome di Eisenmenger

Tracleer ha dimostrato miglioramenti anche in pazienti con PAH in classe funzionale WHO II. Tracleer è anche indicato per ridurre il numero di nuove ulcere digitali in pazienti con sclerosi sistemica e ulcere digitali attive

Posologia

Età anni	Inizio 4 settimane	mantenimento	Max dose
2-18^ 10-20kg	2 mg/kg x 2	2 mg/kg x2	Plateau per dosi maggiori
< 18 20-40kg	31.25mg x2	62.5mg x 2	
Adulti > 40 kg	62.5 mg x2	125 mg x 2	250 mg x2*

^ esperienza limitata in età inferiore a 2 anni
* Valutare rischi/benefici (tossicità epatica è dose dipendente)
Negli adulti sani, la farmacocinetica del bosentan sono dose-proporzionale fino ad una dose di 500 mg (circa 7 mg/kg per un peso di 70 kg)

Effetti avversi:cefalea, anemia, epatotossicità, flusng, teratonenicità

Monitorare funzionalità epatica, ematocrito ed emoglobina

Posologia
Ambrisentan
5 o 10 mg in una sola somministrazione

Posologia
Macitentan
3 o 10 mg in una sola somministrazione

Sildenafil **Nome commerciale**

- **Revatio 20 mg cp compresse rivestite con film**
- **Revatio 10 mg/ml polvere per sospensione orale**
- **Revatio 0.8 mg/ml soluzione iniettabile**

4.1 Indicazioni terapeutiche

Trattamento di pazienti adulti con ipertensione arteriosa polmonare di classe funzionale II e III dell'OMS, al fine di migliorare la capacità di fare esercizio fisico. L'efficacia è stata dimostrata nell'ipertensione polmonare primaria e nell'ipertensione polmonare associata a malattia del tessuto connettivo.

Popolazione pediatrica

Trattamento di pazienti pediatrici di età compresa tra 1 e 17 anni con ipertensione arteriosa polmonare. L'efficacia in termini di miglioramento della capacità di fare esercizio fisico o di emodinamica polmonare è stata dimostrata nell'ipertensione polmonare primaria e nell'ipertensione polmonare associata a malattia cardiaca congenita (vedere paragrafo 5.1).

Eventi avversi segnalati: cefalea, congestione nasale e disturbi del visus, maggiori dopo 6 settimane di terapia

Posologia	
età	Dose
< 1 anno off-label	0.25-0.5 ogni 4-8 h max 30 mg/die
1-17 anni < 20 kg	10 mg x 3
1-17 anni > 20 kg	20 mg x 3
adulti	20 mg x 3

Posologia
Tadalafil
10 mg in mono somministrazione

Prostacicline e analoghi			
Epoprostenol qualsiasi età		Iloprost > 8 anni	Treprostinil > 18 aa
Dose inizio	2-4 ng/kg/min		1-2ng/kg/min
Dose ottimale	20-40 ng/kg/min	2,5-5 µg in 10-15 min. 6-9 vv/die media 30µg/die	20-80 ng/kg/min
Max dose	Limite effetti collaterali		Limite effetti collaterali

Effetti avversi: cefalea, flushing, dolori articolari ed agli arti, dolore toracico, nausea, vomito, diarrea, ipotensione

Follow-up

Table 16 Suggested assessments and timing for the follow-up of patients with PAH

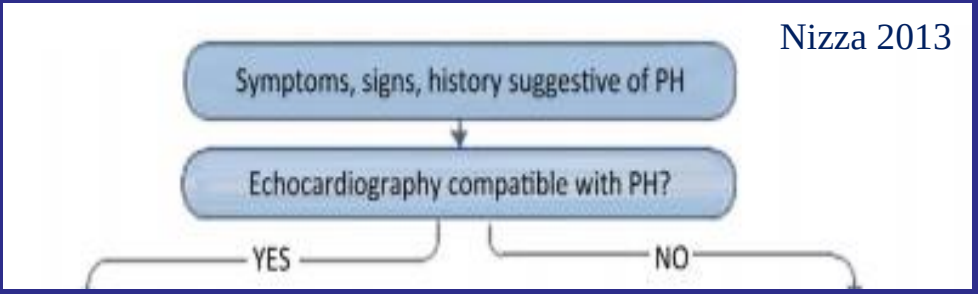
	At baseline (prior to therapy)	Every 3–6 months[a]	3–4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT[b]	✓	✓	✓	✓
Cardio-pulmonary exercise testing[b]	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓[c]		✓[d]	✓[d]

[a]Intervals should to be adjusted to individual patients needs.
[b]Usually one of the two exercise tests is performed.
[c]Is recommended (*Table 11A*).
[d]Should be performed (*Table 11A*).
BNP = brain natriuretic peptide; ECG= electrocardiogram; RHC = right heart catheterization; 6MWT = 6-minute walking test; WHO-FC =WHO functional class.

Ruolo Ecocardiografia Doppler

- esame non invasivo- molto sensibile- valida metodica di screening nella popolazione a rischio, rappresenta il primo step di un iter diagnostico multidisciplinare

Nizza 2013



- Esclude/conferma cardiopatia congenite associate/causa di IAP
- Esclude/conferma cardiopatie congenite e/o acquisite del cuore sn
- Informazioni sulle alterazioni morfo-funzionali Vdx secondari al sovraccarico pressorio e sul vsn sinistro come causa di IP
- Valutazione emodinamica non invasiva
- Prognosi

J Am Soc Echocardiogr. 2010 Jul;23(7):685-713; quiz 786-8. doi: 10.1016/j.echo.2010.05.010.

Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography.

Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB.

frontiers in PEDIATRICS

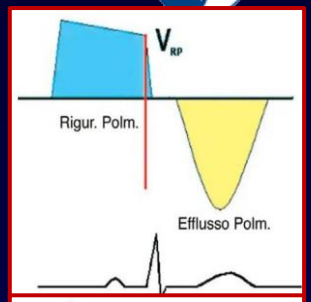
REVIEW ARTICLE
published: 12 November 2014
doi: 10.3389/fped.2014.00124

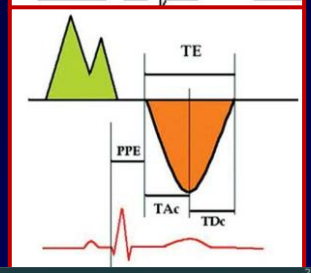
Echocardiography in pediatric pulmonary hypertension

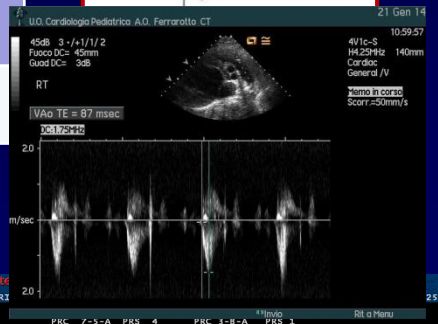
Valutazione Pressione in Arteria Polmonare
Ruolo Ecocardiografia Doppler

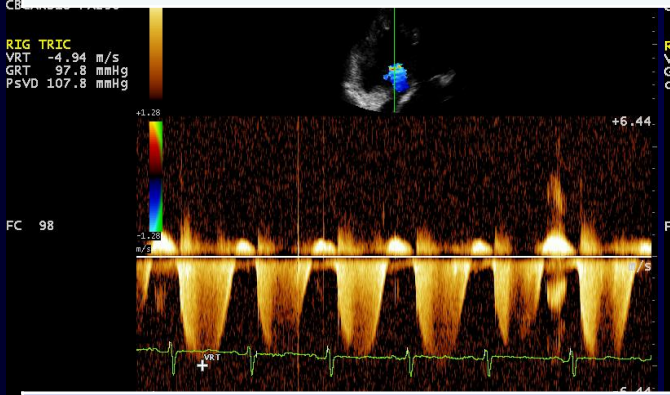
Pressione arteriosa **sistolica** polmonare (PAPs)	Gmax RT (4xV2)+PAD GmaxVsn-Vdx (DIV) Gmax Ao-AP (dotto)
Pressione **telediastolica** polmonare	Gmax telediastolico + PAD
Tempo di accelerazione Arteria polmonare	< 90msec PAPmedia 20-25mmHg
PAPmedia	(0.61 × PAPs) + 2
PAPmedia da insufficienza valvola polmonare	Gmax protodiastolico + PAD
PAPmedia in presenza di dotto arterioso pervio	PA media sistolica-Gmed dotto

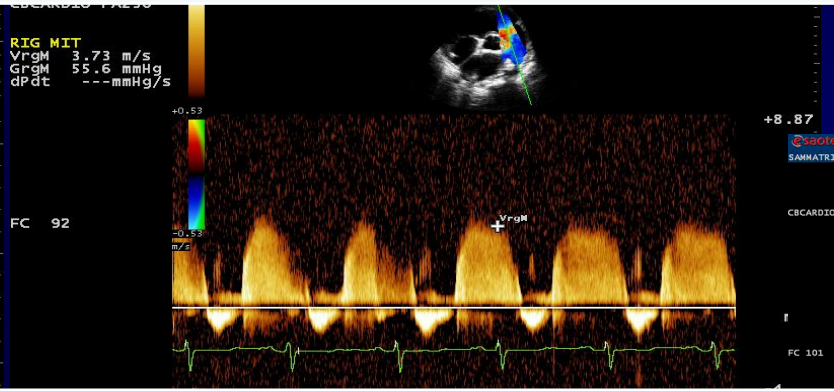
RT rigurgito tricuspidalico, PAD= pressione atrio destro, Tacc= tempo di accelerazione

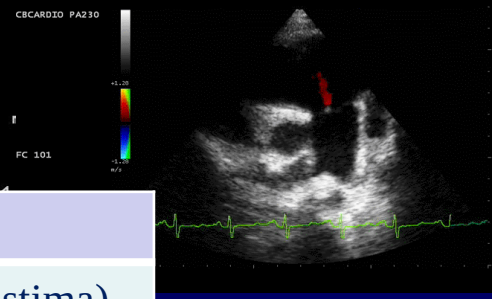












LIMITI metodica

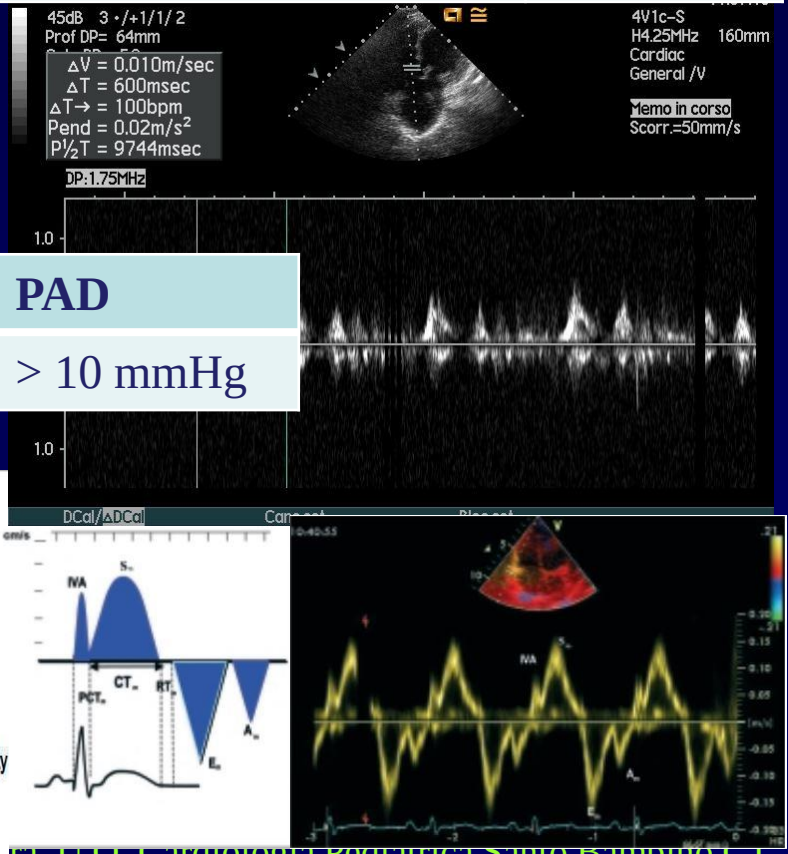
Stima Non Misura, Non sempre fattibile, Non sempre accurata (sottostima/sovrastima)

Ecocardiografia
Stima Pressione atriale destra

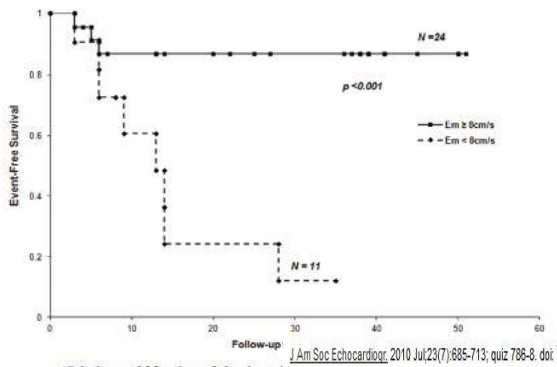
Dimensioni VCI	Collasso Inspiratorio	Stima della PAD mmHg
Piccola <15 mm	> 50%	0-5
Normale 15-25 mm	>50%	5-10
Normale 15-25 mm	< 50%	10-15
Dilatata >25	<50%	15-20
Dilatata	Assente	>20

VCI in età pediatrica % di collasso	Stima PAD
Collasso > 45%	6 mmHg
35% < collasso < 45%	9 mmHg
Collasso < 35%	16 mmHg

Altro Parametro	PAD
E/Em > 6	> 10 mmHg



Tricuspid E' velocity by tissue Doppler imaging at baseline and survival rate



47th Annual Meeting of the Associ

Figure 6. Event-free survival and tricuspid Em velocity on ti
free survival was significantly lower when tricuspid Em was

J Am Soc Echocardiogr. 2010 Jul;23(7):685-713; quiz 786-8. doi: 10.1016/j.echo.2010.05.010.

Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography.

Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB.

Ecocardiografica-Doppler

Anche se esiste una correlazione stastisticamente significativa tra stima ecocardiografica e misura emodinamica di PAPs, gli ampi limiti di confidenza della relazione rendono impreciso il confronto nel singolo paziente, esponendo al rischio di falsi positivi, specie in caso di aumenti di lieve entità in pazienti asintomatici

Int J Cardiol. 2013 Oct 9;168(4):4058-62. doi: 10.1016/j.ijcard.2013.07.005. Epub 2013 Jul 23.

Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension.

D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Calabrò R, Russo MG, Naeije R.

Author information

Abstract

BACKGROUND: Echocardiographic studies have contributed to progress in the understanding of the pathophysiology of the pulmonary circulation and have been shown to be useful for screening for and prognostication of pulmonary hypertension, but are considered unreliable for the diagnosis of pulmonary hypertension. We explored this apparent paradox with rigorous Bland and Altman analysis of the accuracy and the precision of measurements collected in a large patient population.

METHODS: A total of 161 patients referred for a suspicion of pulmonary hypertension were prospectively evaluated by a Doppler echocardiography performed by dedicated cardiologists within 1 h of an indicated right heart catheterization.

RESULTS: Nine of the patients (6%) were excluded due to an insufficient signal quality. Of the remaining 152 patients, 10 (7%) had no pulmonary hypertension and most others had either pulmonary arterial hypertension (36%) or pulmonary venous hypertension (40%) of variable severities. Mean pulmonary artery pressure, left atrial pressure and cardiac output were nearly identical at echocardiography and catheterization, with no bias and tight confidence intervals, respectively ± 3 mm Hg, ± 5 mm Hg and ± 0.3 L/min. However, the ± 2SD limits of agreement were respectively of + 19 and - 18 mm Hg for mean pulmonary artery pressure, + 8 and - 12 mm Hg for left atrial pressure and + 1.8 and - 1.7 L/min for cardiac output.

CONCLUSIONS: Doppler echocardiography allows for accurate measurements of the pulmonary circulation, but with moderate precision, which explains why the procedure is valid for population studies but cannot be used for the individual diagnosis of pulmonary hypertension.

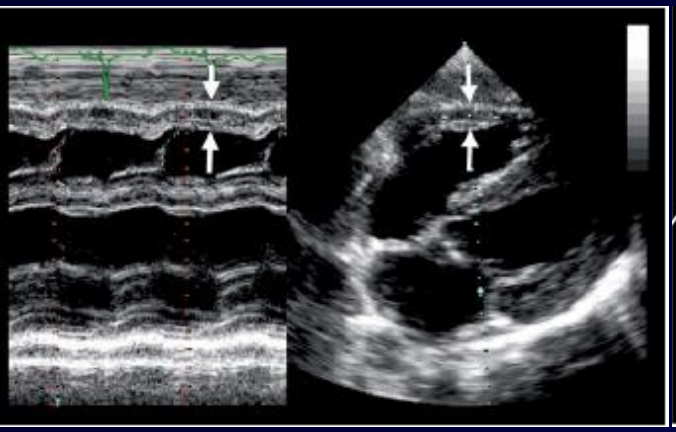
Le linee guida 2009 della Società Europea di Cardiologia e Pneumologia hanno proposto una tabella con dei criteri definiti «arbitrari» per indicare la probabilità di IP

Arbitrary criteria for estimating the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

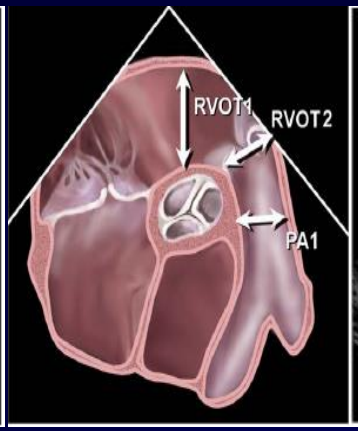
	Class[a]	Level[b]
Echocardiographic diagnosis: PH unlikely		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, and no additional echocardiographic variables suggestive of PH	I	B
Echocardiographic diagnosis: PH possible		
Tricuspid regurgitation velocity ≤2.8 m/s, PA systolic pressure ≤36 mmHg, but presence of additional echocardiographic variables suggestive of PH	IIa	C
Tricuspid regurgitation velocity 2.9–3.4 m/s, PA systolic pressure 37–50 mmHg with/without additional echocardiographic variables suggestive of PH	IIa	C
Echocardiographic diagnosis: PH likely		
Tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure >50 mmHg, with/without additional echocardiographic variables suggestive of PH	I	B
Exercise Doppler echocardiography is not recommended for screening of PH	III	C

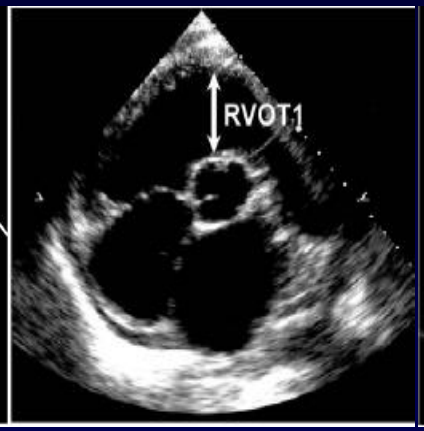
[a]Class of recommendation.
[b]Level of evidence.

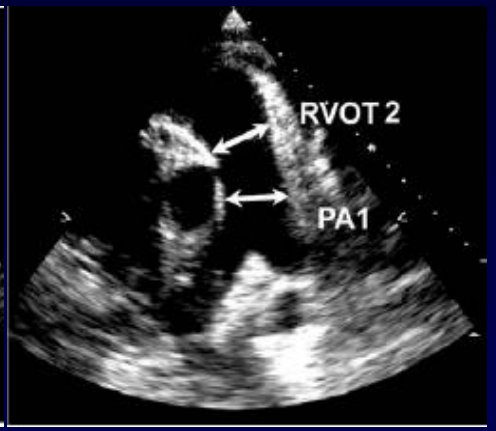
Misure utili



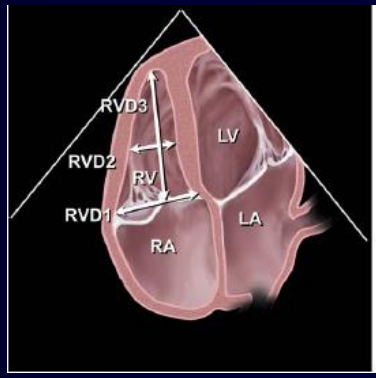
Sottocostale spessore parietale vdx

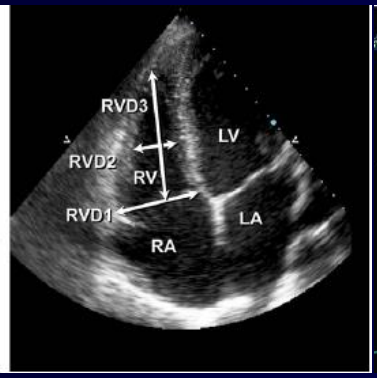




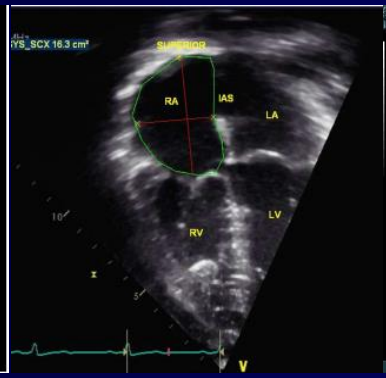


Parasternale asse corto

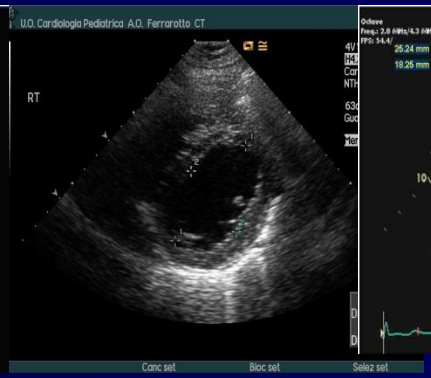




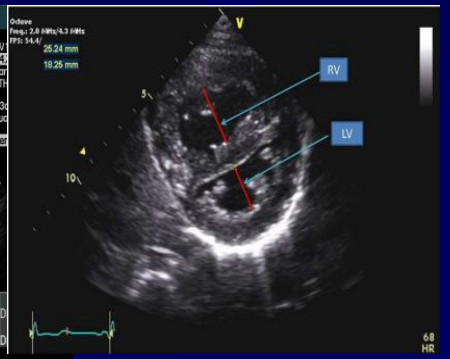
Quattro camere diametro trasverso massimo e medio, diametro longitudinale, area telediastoolica



Area, diametro maggiore e minore fine sistole



D2/D1 >2



RV/LV> 1
(fine sistole)

A.Privitera U.O. Cardiologia Pediatrica Santo Bambino CT

Ipertensione polmonare moderata-severa VDx diventa camera sistemica da cui dipende una adeguata portata

misure	Valori normali	Valori patologici	valore
Area telediastolica VD	19+3.7 cm2	> 25 cm2	Utile
Diametro trasverso massimo VD	35+ 4 mm	> 42 mm	Indispensabile
Diametro trasverso tratto efflusso	26 mm (14 mm/m2)	> 35 mm	
Diametro tronco polmonare	< 30 mm	> 30 mm	Utile
Diametro anulus polmonare	9-22 mm		Utile
Area telesistolica Atrio dx	15 cm2	18 cm2	Indispensabile
Spessore parietale	< 5 mm	> 5 mm	utile
Aspetti Morfologici			
Dilatazione anulus tricuspidalico	> Rigurgito valvolare		
setto interv. mesotelediastole verso sn	D2/D1=1	D2/D1> 2	
Setto interatriale		Convesso a sinistra	
Versamento pericardico predittore di mortalità, indice di scompenso destro avanzato			

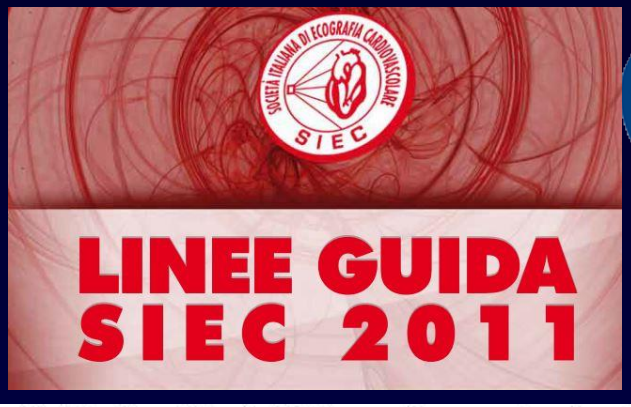


Table 1 Patient demographics

Journal of the American Society of Echocardiography
May 2012

Variable	Controls (n = 44)	Patients with PHT (n = 41)	P
Age (y)	7.7 ± 4.1	7.9 ± 5.6	.82
Height (cm)	126.1 ± 23.7	117.6 ± 34.2	.20
Weight (kg)	31.1 ± 16.5	26 ± 17.5	.14
Heart rate (beats/min)	97 ± 28	105 ± 23	.43

Table 2 Conventional echocardiographic measures

Variable	Controls (n = 44)	Patients with PHT (n = 41)	P
RA area	9.6 ± 2.5	12.4 ± 6.2	.02
LA diameter	9.2 ± 2.8	7.6 ± 3.7	.044
TV diameter	2.15 ± 0.48	2.57 ± 0.75	.005
PV diameter	1.85 ± 0.36	2.06 ± 0.65	.10
Right PA	1.1 ± 0.3	1.3 ± 0.5	.002
Left PA	1.1 ± 0.3	1.4 ± 0.5	.002
RVIDd (cm)	1.83 ± 0.72	2.73 ± 1.29	.0002
RVIDs (cm)	1.5 ± 0.52	3.6 ± 6.5	.002
TR velocity (m/sec)	2 ± 0.4	4.5 ± 1	<.0001
PA acceleration (msec)	119.7 ± 31.8	65.3 ± 22.7	<.0001
MV diameter	2.10 ± 0.45	1.83 ± 0.59	.03
LVEId	1 ± 0	1.6 ± 0.5	<.0001
LVEIs	1.1 ± 0.1	2.1 ± 0.8	<.0001
TAPSE (cm)	1.9 ± 0.2	1.4 ± 0.3	<.0001
EF (%)	58.7 ± 12.6	66.3 ± 16.6	.10

LA, Left atrial; *LVEId*, LVEI in diastole; *LVEIs*, LVEI in systole; *MV*, mitral valve; *PA*, pulmonary artery; *PV*, pulmonary valve; *RA*, right atrial; *RVIDd*, diastolic RV inner diameter; *RVIDs*, systolic RV inner diameter; *TV*, tricuspid valve.
Data are expressed as mean ± SD.

Tabella I. Valori normali indicizzati per BSA calcolati all'ecocardiogramma. Le misure dei diametri ventricolari sinistro destro sono relativi alla sezione parasternale asse lungo in telediastole. I diametri delle valvole aorta e polmonaresono misurati a livello dell'anulus. Tutti i valori sono espressi in millimetri

BSA	Polmonare		Aorta		Ventricolo sn		Ventricolo dx	
	Media	Dev St	Media	Dev St	Media	Dev St	Media	Dev St
25	8.40	1.10	7.20	1.00	20.00	3.60	8.70	4.50
30	9.30	1.15	8.10	1.00	22.90	4.90	8.70	4.50
35	10.10	1.20	8.80	1.00	23.60	4.60	8.80	4.50
40	10.70	1.15	9.50	1.00	26.00	5.00	8.90	4.50
45	11.30	1.15	10.10	1.00	27.10	5.05	9.00	4.50
50	11.90	1.20	10.60	1.00	29.00	5.60	9.30	4.50
60	12.80	1.20	11.40	1.05	31.60	5.60	9.60	4.40
70	13.50	1.15	12.20	1.00	33.90	6.50	10.10	4.40
80	14.20	1.20	12.80	1.00	35.80	6.20	10.50	4.70
90	14.80	1.15	13.40	1.00	37.10	6.10	11.00	4.60
100	15.30	1.15	13.90	1.00	38.50	6.80	11.20	4.80
120	16.20	1.20	14.80	1.00	41.70	6.20	12.4	4.80
140	17.00	1.15	15.60	1.00	43.30	6.00	14.00	5.00
160	17.60	1.15	16.20	1.00	45.8	6.05	16.00	5.05
180	18.20	1.15	16.80	1.00	47.00	8.00	16.70	5.50
200	18.7	1.15	17.30	1.00	53.40	8.00	17.50	6.00

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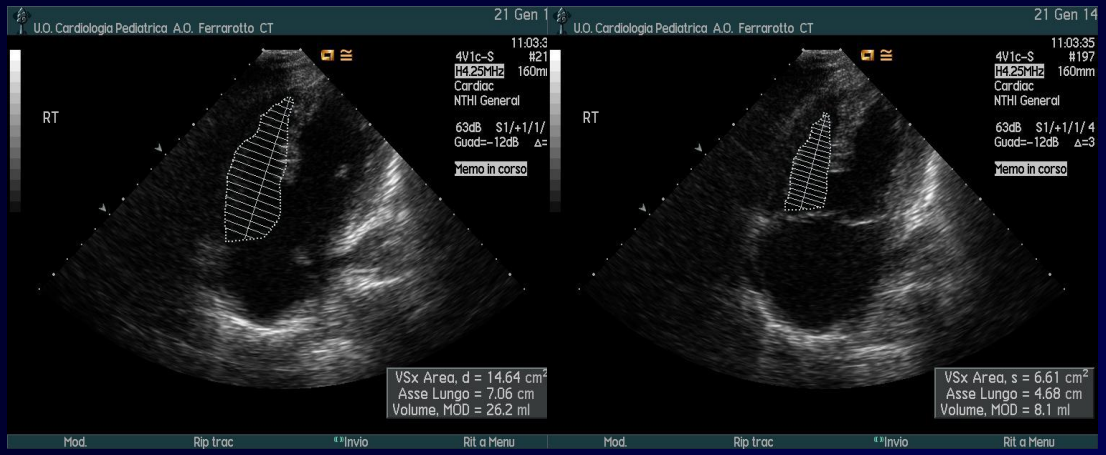
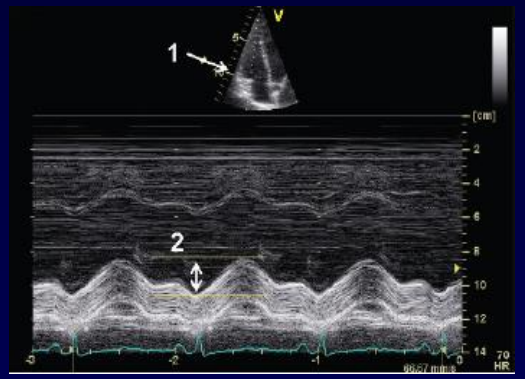
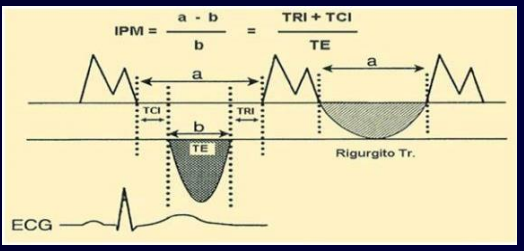
Indici di Funzione



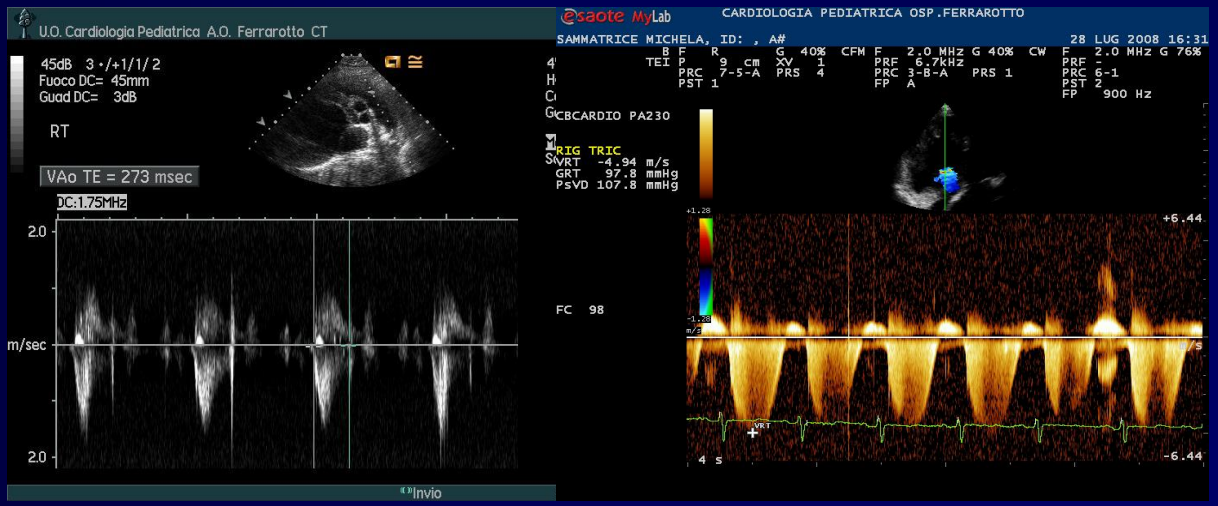
Acc% area Vdx



TAPSE v.n. 22±4



Indice di perfomance cardiaca IPM



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Ecocardiogramma
Indici di funzione sistolica ventricolo dx

Misure di funzione sistolica del Ventricolo destro (VD)			
	Valori normali	Disfunzione VD	
TAPSE	22±0.4	< 15	Indispensabile
Acc.% Area Vdx (Atd-Ats/Atd x100)	41.5±1.2	< 35%	Utile
Acc% TE (Dtd-Dts/Dtd x 100) %	61± 13	<45%	
Tei-index o IPM = TCI-TRI/TE	0.28±0.04	> 0.40	Utile
IPM-TDI	0.39±0.05	> 0.55	Utile
E/Em	< 6	> 6 (PAD > 10 mmHg)	Indispensabile

Tei-index o IPM indice di perfomance miocardica, Atd=area tedelistolia, Ats= area telesistolica, TCI= tempo di contrazione isovolumetrica; TRI =tempo di rilasciamento isovolumetrico; TE= tempo di eiezione

J Am Soc Echocardiogr. 2010 Jul;23(7):685-713; quiz 786-8. doi: 10.1016/j.echo.2010.05.010.

Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography.

Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB.

Table 1 Classification table for TAPSE values

		TAPSE (cm)					BSA (m^2)			
			Bounds for *z*-score ranges							
Age	n	Mean	±2 SD (95%)		±3 SD (99%)		Mean	Minimum	Maximum	Indexed TAPSE mean/BSA mean
0-30 d	41	0.91	0.68	1.15	0.56	1.26	0.22	0.14	0.28	4.13
1-3 mo	45	1.14	0.85	1.42	0.71	1.56	0.29	0.12	0.54	3.93
4-6 mo	20	1.31	1.01	1.65	0.86	1.77	0.34	0.26	0.41	3.85
7-12 mo	22	1.44	1.13	1.77	0.97	1.91	0.40	0.31	0.47	3.6
1 y	25	1.55	1.25	1.88	1.10	2.00	0.47	0.3	0.69	3.29
2 y	39	1.65	1.36	1.94	1.22	2.09	0.53	0.4	0.62	3.11
3 y	27	1.74	1.48	2.02	1.35	2.14	0.63	0.52	0.77	2.76
4 y	47	1.82	1.56	2.07	1.43	2.20	0.70	0.6	0.91	2.6
5 y	29	1.87	1.60	2.13	1.47	2.26	0.77	0.63	0.99	2.42
6 y	41	1.90	1.62	2.18	1.48	2.33	0.82	0.46	1.06	2.31
7 y	32	1.94	1.64	2.25	1.49	2.39	0.94	0.75	1.17	2.06
8 y	23	1.97	1.67	2.28	1.52	2.43	0.97	0.79	1.39	2.03
9 y	20	2.01	1.73	2.30	1.58	2.44	1.00	0.8	1.32	2.01
10 y	27	2.05	1.79	2.31	1.65	2.46	1.15	0.82	1.54	1.78
11 y	25	2.10	1.83	2.36	1.69	2.50	1.28	1.06	1.55	1.64
12 y	18	2.14	1.84	2.43	1.68	2.60	1.39	1.08	1.67	1.53
13 y	20	2.20	1.85	2.54	1.68	2.71	1.48	1.03	1.87	1.48
14 y	35	2.26	1.87	2.65	1.68	2.84	1.55	1.11	1.93	1.45
15 y	25	2.33	1.93	2.75	1.74	2.92	1.59	1.32	1.96	1.46
16 y	34	2.39	1.98	2.78	1.78	3.01	1.66	1.3	2.04	1.43
17 y	27	2.45	2.04	2.88	1.83	3.06	1.77	1.43	2.06	1.38
18 y	21	2.47	2.05	2.91	1.84	3.10	1.79	1.34	2.25	1.37

For each age group, the SD of TAPSE was taken to construct ranges of the mean ± 2 SDs and the mean ± 3 SDs. These ranges represented the expectable normal intervals of deviation for certainty levels of 95% and 99%. Furthermore, the mean, minimum, and maximum of BSA were calculated for the age groups. An index was calculated of mean TAPSE for age divided by mean BSA for each age group.

RVP= rapporto tra pressione polmonare e flusso polmonare

$$PVR = \frac{\text{Mean PAP} - \text{mean LAP (or PCWP)}}{Qp}$$

Utilizzate solo a scopo di ricerca

RVP Cateterismo dx

- RVP= Gradiente transpolmonare/portata cardiaca
- RVP= PAPmedia-PCWP/PC

RVP Ecocardio Doppler

- Pressione polmonare= velocita di rigurgito tricuspidalico= gradiente transpolmonare
- PC=Flusso polmonare= integrale velocità tempo del flusso nel tratto d'efflusso del ventricolo destro
- RVP=10xVRT(m/sec)/IVTTEVD (cm)
- VRT/ IVTTEVD $\geq$ 0.2; RVP $\geq$ 2UW
- PC Doppler= (IVTTEVD x (diametro TEVD)2 x (0.785)] x FC

QP/QS Ecocardio Doppler

- QP/QS= (velocità ne TEVD x area del TEVD/velocità TEVS x area TEVS

Conclusioni

- Le terapie avanzate specifiche per IAP hanno aperto nuovi opzioni terapeutiche per questi pazienti
- Questi farmaci sono efficaci nell'alleviare i sintomi, riducendo le resistenze vascolari polmonari, ma il loro effetto non è curativo, ma palliativo
- Tollerabilità a lungo termine deve essere valutata
- Nella popolazione Eseinmenger, per il benessere e la prognosi di questi pazienti, è essenziale un approccio multidisciplinare per la cura ottimale (gestione dell'eritrocitosi secondaria, abolizione del salasso di routine, supplemento di ferro, adeguato sostegno alla chirurgia non cardiaca


ELSEVIER International Journal of Cardiology 129 (2008) 163–171
www.elsevier.com/locate/ijcard

Review

Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy

Konstantinos Dimopoulos *, Ana Peset, Michael A. Gatzoulis

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Ipertensione Polmonare

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Correzione di Fonten

Uso di vasodilatatori polmonari

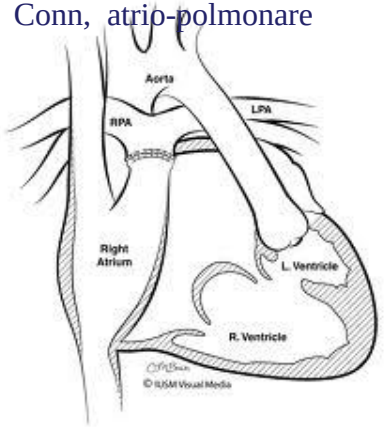
le c.c con ventricolo unico anatomico o funzionale vengono palliate secondo tecnica di Fonten Intervento che ha contribuito notevolmente nella riduzione del tasso di mortalità

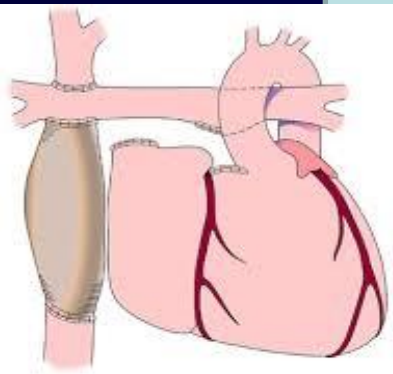
L'unico ventricolo viene utilizzato per la circolazione sistemica

La circolazione polmonare avviene direttamente nelle arterie polmonari sfruttando la pressione negativa intratoracica e la meccanica respiratoria

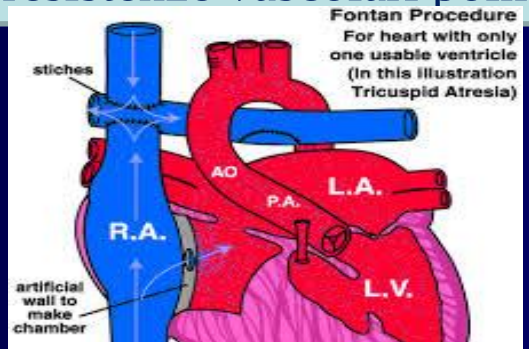
il flusso sanguigno transpolmonare dipende dalla pressione venosa sistemica e dalle resistenze vascolari polmonari

Conn, atrio-polmonare





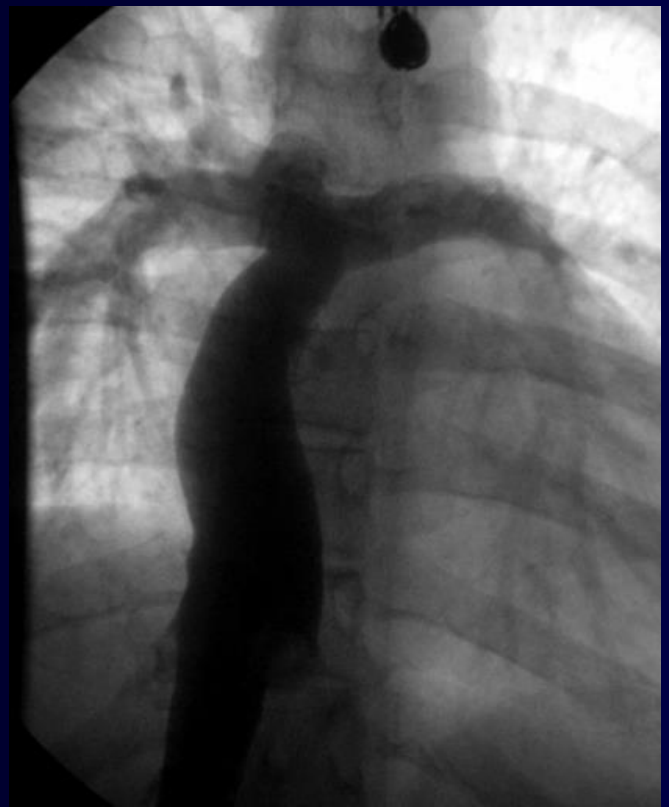
cavo-polmonare tubo extracardiaco



cavo-polmonare tubo intra tracardiaco

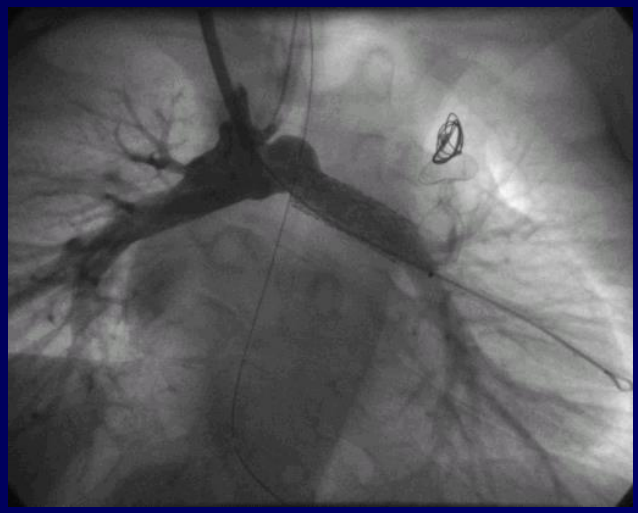
Pediatrica Santo Bambino CT

- Nella circolazione tipo Fontan, la resistenza vascolare polmonare è un fattore determinante nella limitazione della gittata cardiaca: anche un minimo aumento della resistenza vascolare polmonare può sia ostacolare la chirurgia Fontan o fare evolvere a scompenso questo tipo di circolazione



Valori emodinamici favorevoli

- RVPi $\leq$ 2 WU/m^2
- PAPm < 15 mmHg
- PWC < 12 mmHg



Cause di aumento delle resistenze vascolari polmonari

- Il follow -up a lungo termine ha dimostrato che le RVP possono aumentare anche molti anni dopo la procedura di Fontan. Tra le cause possibile:
  - micro-emboli dall'atrio destro dilatato o dal sistema venoso
  - invecchiamento
  - disfunzione linfatica causa ostruzione delle vie aeree
  - assenza di flusso pulsatile polmonare
    - causa un rilascio dall'endotelio di molecole vasoattive
  - prolungata sovraespressione di vasocostrittori (endotelina-1)*

*Livelli plasmatici di endotelina- 1 sono risultati essere significativamente più elevati nei pazienti Fontan rispetto ai controlli sani

Gli antagonisti del recettore dell'endotelina-1 potrebbero contribuire al miglioramento dello stato clinico di questi pazienti

Contemp Clin Trials. 2011 Jul;32(4):586-91. doi: 10.1016/j.cct.2011.04.001. Epub 2011 Apr 17.

Rationale and design of a trial on the role of bosentan in Fontan patients: improvement of exercise capacity?

Schuuring MJ, Vis JC, Bouma BJ, van Dijk AP, van Melle JP, Pieper PG, Vliegen HW, Sieswerda GT, Mulder BJ.

CONCLUSION: We hypothesize that treatment with bosentan, an endothelin-1 receptor antagonist, improves maximum exercise capacity and functional capacity in adult Fontan patients.

Although the results of the TEMPO trial are encouraging, the authors rightly point out that it would be premature to recommend universal therapy with endothelin-1 receptor antagonists for all patients with Fontan physiology. The same is also true for other modulators of PVR. The questions of long-term efficacy and safety are unanswered, and, as such, it would be unjustified to start otherwise asymptomatic patients on untested medications. For those patients with protein-losing enteropathy, plastic bronchitis, or other serious complications of Fontan physiology, the calculus is different, and the benefit of therapy, even without conclusive long-term data, may outweigh the risk. Although medications capable of lowering the dam maintain an allure, it remains the task of the congenital heart disease community to design and execute a trial to definitively answer the question of whether these medications are capable of improving the duration and quality of life of those with Fontan physiology.

Editorial

Circulation December 2, 2014

Fontan Circulation

The Search for Targeted Therapy

David J. Goldberg, MD; Stephen M. Paridon, MD

Impact of Oral Sildenafil on Exercise Performance in Children and Young Adults After the Fontan Operation

A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

David J. Goldberg, MD; Benjamin French, PhD; Michael G. McBride, PhD;

Conclusions—In this cohort, sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise. There was also a suggestion of improved oxygen consumption at the anaerobic threshold in 2 subgroups. These findings suggest that sildenafil may be an important agent for improving exercise performance in children and young adults with single-ventricle physiology after the Fontan operation.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00507819. (***Circulation***. **2011;123:1185-1193.**)

Circ Cardiovasc Imaging. 2014 Mar;7(2):265-73. doi: 10.1161/CIRCIMAGING.113.001243. Epub 2014 Jan 29.

Sildenafil improves exercise hemodynamics in Fontan patients.

Van De Bruaene A[1], La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W.

⊕ **Author information**

Abstract

BACKGROUND: Patients with Fontan circulation have reduced exercise capacity. The absence of a presystemic pump may limit flow through the pulmonary circulation, restricting ventricular filling and cardiac output. We evaluated exercise hemodynamics and the effect of sildenafil on exercise hemodynamics in Fontan patients.

METHODS AND RESULTS: Ten Fontan patients (6 men, 20±4 years) underwent cardiac magnetic resonance imaging at rest and during supine bicycle exercise before and after sildenafil. Systemic ventricular volumes were obtained at rest and during low- (34±15 W), moderate- (69±29 W), and high-intensity (97±36 W) exercise using an ungated, free-breathing cardiac magnetic resonance sequence and analyzed correcting for cardiac phase and respiratory translation. Radial and pulmonary artery pressures and cGMP were measured. Before sildenafil, cardiac index increased throughout exercise (4.0±0.9, 5.9±1.1, 7.0±1.6, 7.4±1.7 L/(min·m(2)); P<0.0001) with 106±49% increase in heart rate. Stroke volume index (P=0.015) and end-diastolic volume index (P=0.001) decreased during exercise. End-systolic volume index remained unchanged (P=0.8). Total pulmonary resistance index (P=0.005) increased, whereas systemic vascular resistance index decreased during exercise (P<0.0001). Sildenafil increased cardiac index (P<0.0001) and stroke volume index (P=0.003), especially at high-intensity exercise (interaction P=0.004 and P=0.003, respectively). Systemic vascular resistance index was reduced (P<0.0001-interaction P=0.1), whereas total pulmonary resistance index was reduced at rest and reduced further during exercise (P=0.008-interaction P=0.029). cGMP remained unchanged before sildenafil (P=0.9), whereas it increased significantly after sildenafil (P=0.019).

CONCLUSIONS: In Fontan patients, sildenafil improved cardiac index during exercise with a decrease in total pulmonary resistance index and an increase in stroke volume index. This implies that pulmonary vasculature represents a physiological limitation, which can be attenuated by sildenafil, the clinical significance of which warrants further study.

- Pochi dati pubblicati sul trattamento di pazienti con insufficienza della circolazione tipo Fontan.

Ossido Nitrico	Riduce le RVP, nessun significativo effetto sull'indice cardiaco
Sildenafil	Aumenta la tolleranza all'esercizio e la risposta emodinamica all'esercizio, dimostrato miglioramento in caso di bronchite plastica e in caso di enteropatia-proteino-disperdente
Prostanoidi	nessuna documentazione
Bosentan	migliorano la capacità di esercizio, classe funzionale WHO, la qualità di vita e i parametri emodinamici (RVP, PAP)
Ambisertan	Non dati disponibili

hanno un potenziale ruolo sia nell'aumentare l'operabilità sia nel trattamento postoperatorio dell'IAP

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Updated Clinical Classification of Pulmonary Hypertension

severity of PAH/PVR in every single patient. Here we make specific reference to patients with the Fontan circulation (atrio- or cavopulmonary connections as palliation for "single ventricle" type hearts), who do not fulfill standard criteria for PH but may have an increased PVR. There are very limited surgical alternatives for this group of patients with complex anatomy/physiology. There has been some recent evidence of potential clinical response to specific PAH therapies in Fontan patients, which needs further exploration before therapeutic recommendations can been made (48,49).

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