CẬP NHẬT VỀ CHẨN ĐOÁN VÀ ĐIỀU TRỊ TĂNG ÁP PHỔI
(Update in the diagnosis and treatment of pulmonary hypertension)

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Định nghĩa

- Tăng áp động mạch phổi tiên phát (TAĐMP – TP): ALĐMP tâm thu > 35 mmHg; ALĐMP trung bình (mPAP) > 25 mmHg lúc nghỉ, > 30 mmHg/gắng sức.
- Tuy nhiên*:

  - ALĐMP tthu > 40mmHg/ 6% người bình thường > 50 tuổi
  - ALĐMP tthu > 40mmHg/ 5% người có BMI > 30kg/m2

TL: Mc Quillan BM et al. Circulation 2001; 104: 2797 - 2802

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Phân loại lâm sàng tăng áp phổi (TAP)

1. Tăng áp động mạch phổi
2. Tăng áp phổi do bệnh tim trái
3. Tăng áp phổi do bệnh lý phổi và/hoặc giảm oxy máu
4. Tăng áp phổi do huyết khối thuyên tắc mạn tính
5. Tăng áp phổi do cơ chế đa yếu tố không rõ ràng

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TL: Simoneau G et al. J. Am Coll Cardiol 62 (25 Suppl): D 34,2013

Phân loại lâm sàng cập nhật TAP (1)

1. Pulmonary arterial hypertension
   - 1.1. Idiopathic PAH
   - 1.2. Heritable PAH
     - 1.2.1. BMPR2
     - 1.2.2. ALK-1, endoglin, 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 venoocclusive disease and/or pulmonary capillary hemangiomatosis

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

TL: Simoneau G et al. J. Am Coll Cardiol 62 (25 Suppl): D 34,2013

Phân loại lâm sàng cập nhật TAP (2)

2. Pulmonary hypertension caused by left-sided heart disease
   - 2.1. Left ventricular systolic dysfunction
   - 2.2. Left ventricular diastolic dysfunction
   - 2.3. Valvular disease
   - 2.4 Congenital/acquired left-sided heart inflow/outflow tract obstruction
3. Pulmonary hypertension caused by lung diseases and/or hypoxia
   - 3.1. COPD
   - 3.2. ILD
   - 3.3. Other pulmonary diseases with a mixed restrictive and obstructive pattern
   - 3.4. Sleep-related disordered breathing
   - 3.5. Alveolar hypoventilation disorders
   - 3.6. Chronic exposure to high altitude
   - 3.7. Developmental lung diseases
     - 3.7.1.Congenital diaphragmatic hernia
     - 3.7.2.Bronchopulmonary dysplasia

TL: Simoneau G et al. J. Am Coll Cardiol 62 (25 Suppl): D 34,2013

Phân loại lâm sàng cập nhật TAP (3)

4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear pulmonary multifactorial mechanisms
   - 5.1. Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
   - 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4. Others: segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure

ALK1 = activin receptor–like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; COPD = chronic obstructive pulmonary disease; ILD, interstitial lung disease.

TL: Simoneau G et al. J. Am Coll Cardiol 62 (25 Suppl): D 34,2013

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So sánh huyết động giữa tuần hoàn phổi và tuần hoàn hệ thống

Parameter	Pulmonary Circulation		Systemic Circulation	
	Range	*Mean*	*Range*	*Mean*
Arterial pressure, mm Hg	25/10	15	120/80	90
Capillary pressure, mm Hg	6-9	7	10-30	17
Venous pressure, mm Hg	1-4	2	0-10	6
Arterial M/D ratio, %*	3-7	5	15-25	20
Venous M/D ratio, %*	2-5	3	3-6	5
Vascular resistance, units	1-4	3	10-25	15
Blood flow, liter/min	4-6	5	4-6	5

*M/D ratio = ratio of the medial thickness to the external diameter of the vessel.

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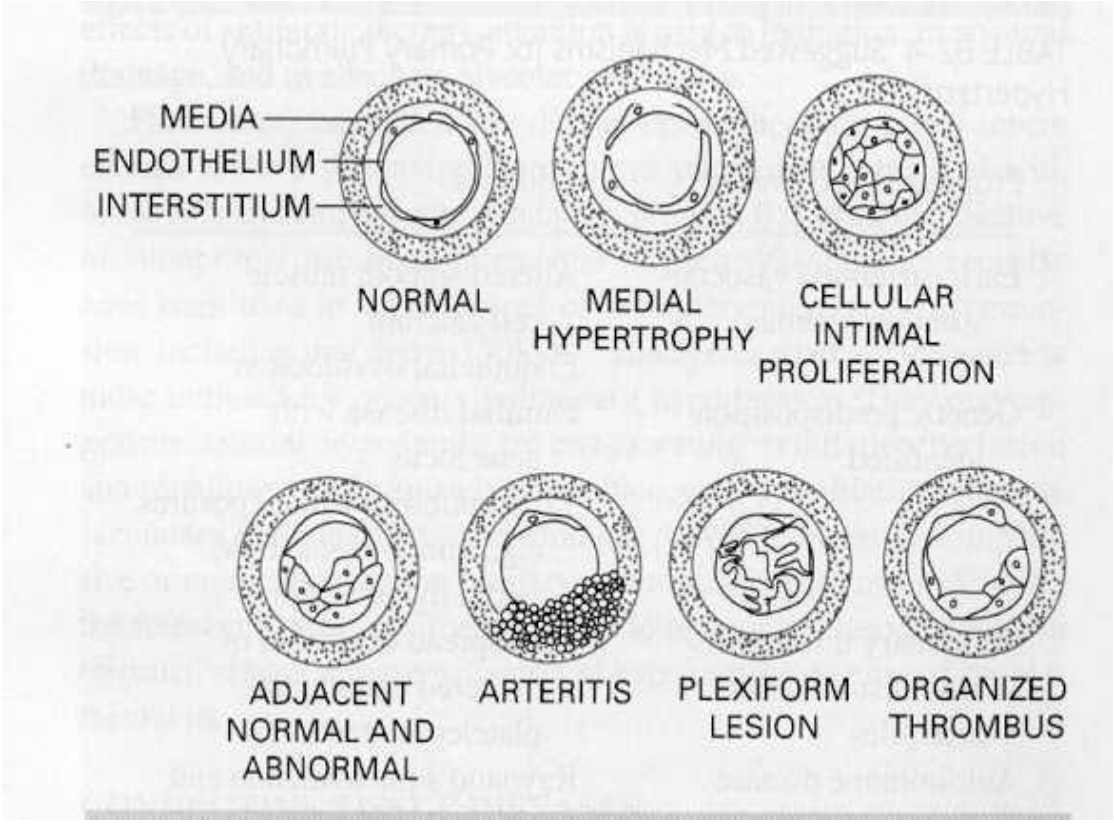
TL: Rich S, McLaughlin VV. In Brauwald's Heart Disease, ed. by Libby, Bonow, Mann, Zipes; Saunders 2008, 8th ed, p.1883 - 1913

Các tổn thương mạch máu trong TAĐMP Tiên phát*



*Tổn thương tương tự ở TAĐMP/ H/c Eisenmenger

Pham Nguyen Vinh

TL: Rubin LJ. The Heart ed by Fuster, Alexander, O'Rourkie. McGraw Hill 2004, 11th ed p.1580

Các điểm chính yếu của cận lâm sàng giúp chẩn đoán TAĐMP (1)

Test	Notable Findings
Chest x-ray	Enlargement of central pulmonary arteries reflects level of PA pressure and duration.
Electrocardiography	Right axis deviation and precordial T wave abnormalities are early signs.
Pulmonary function tests	Elevated pulmonary artery pressure causes restrictive physiology.
Perfusion lung scan	Nonsegmental perfusion abnormalities can occur from severe pulmonary vascular disease.

TL: Rich S, McLaughlin VV. In Brauwald's Heart Disease, ed. by Libby, Bonow, Mann, Zipes; Saunders 2008, 8th ed, p.1883 - 1913

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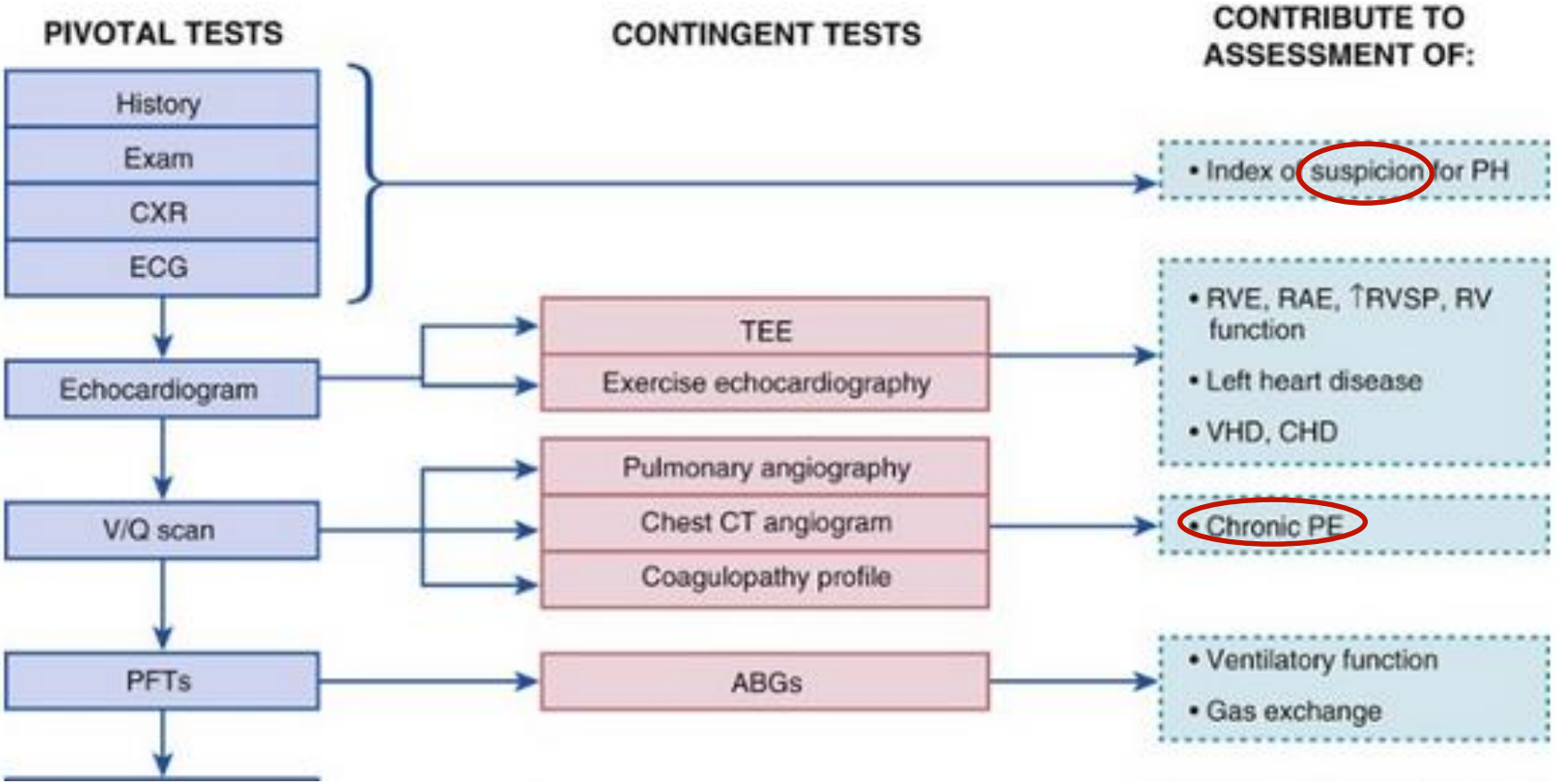
Các điểm chính yếu của cận lâm sàng giúp chẩn đoán TAĐMP (2)

Chest computed tomography scan	Minor interstitial changes may reflect diffuse disease; mosaic perfusion pattern indicates thromboembolism and/or left heart failure.
Echocardiography	Right ventricular enlargement will parallel the severity of the pulmonary hypertension.
Contrast echocardiography	Minor right to left shunting rarely produces hypoxemia.
Doppler echocardiography	This is too unreliable for following serial measurements to monitor therapy.
Exercise testing	This is very helpful to assess the efficacy of therapy. Severe exercise-induced hypoxemia should cause consideration of a right-to-left shunt.

TL: Rich S, McLaughlin VV. In Brauwald's Heart Disease, ed. by Libby, Bonow, Mann, Zipes; Saunders 2008, 8th ed, p.1883 - 1913

Hướng dẫn chung giúp lượng định bệnh nhân tăng áp phổi (1)



TL: McLaughlin VV et al. ACCF/AHA 2009 expert concensus document on pulmonary hypertension J Am Coll Cardio 53: 1573, 2009

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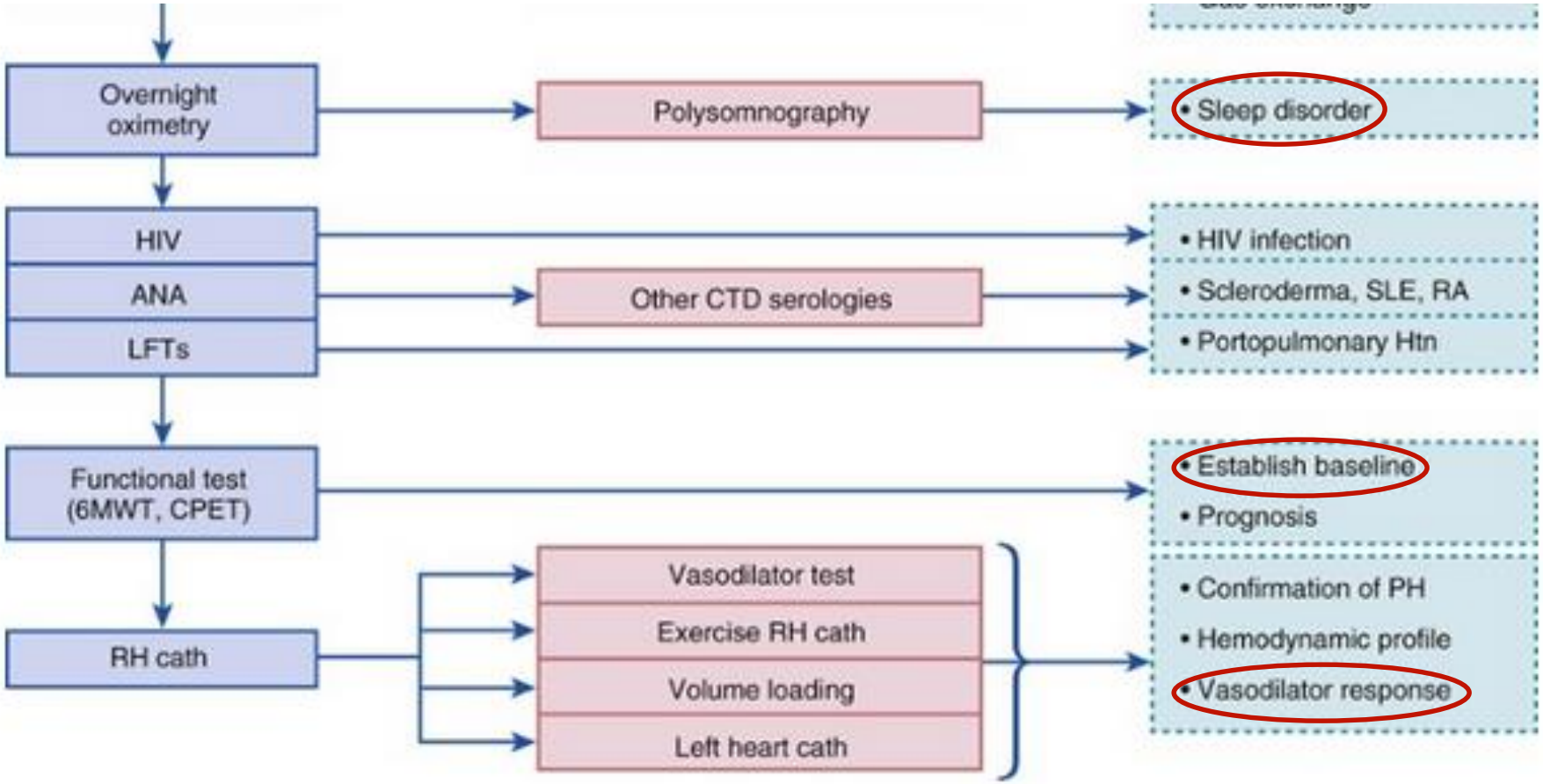
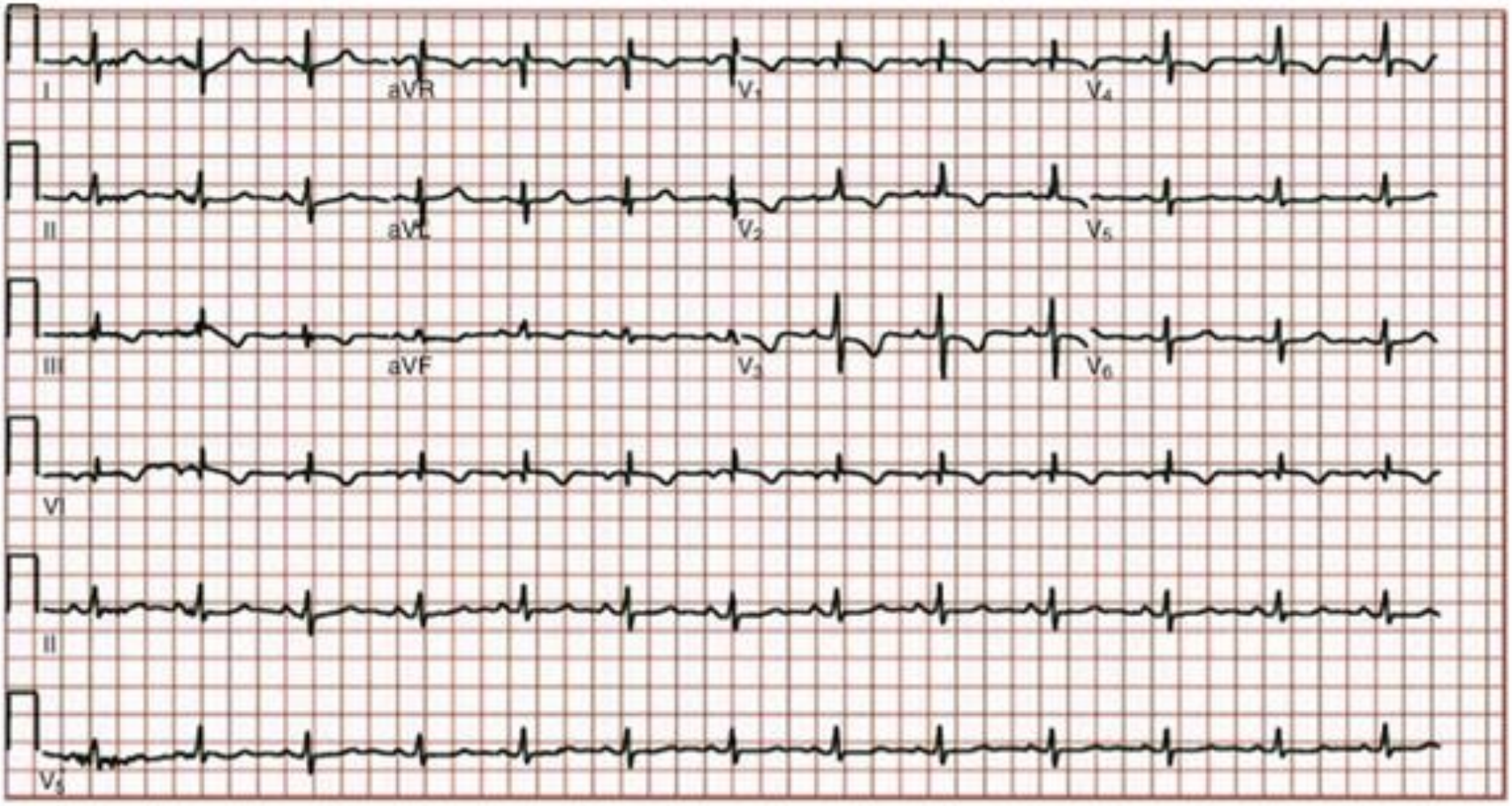
Hướng dẫn chung giúp lượng định bệnh nhân tăng áp phổi (2)



Pham Nguyen Vinh

TL: McLaughlin VV et al. ACCF/AHA 2009 expert concensus document on pulmonary hypertension J Am Coll Cardio 53: 1573, 2009

Điện tâm đồ b/n TAĐMP



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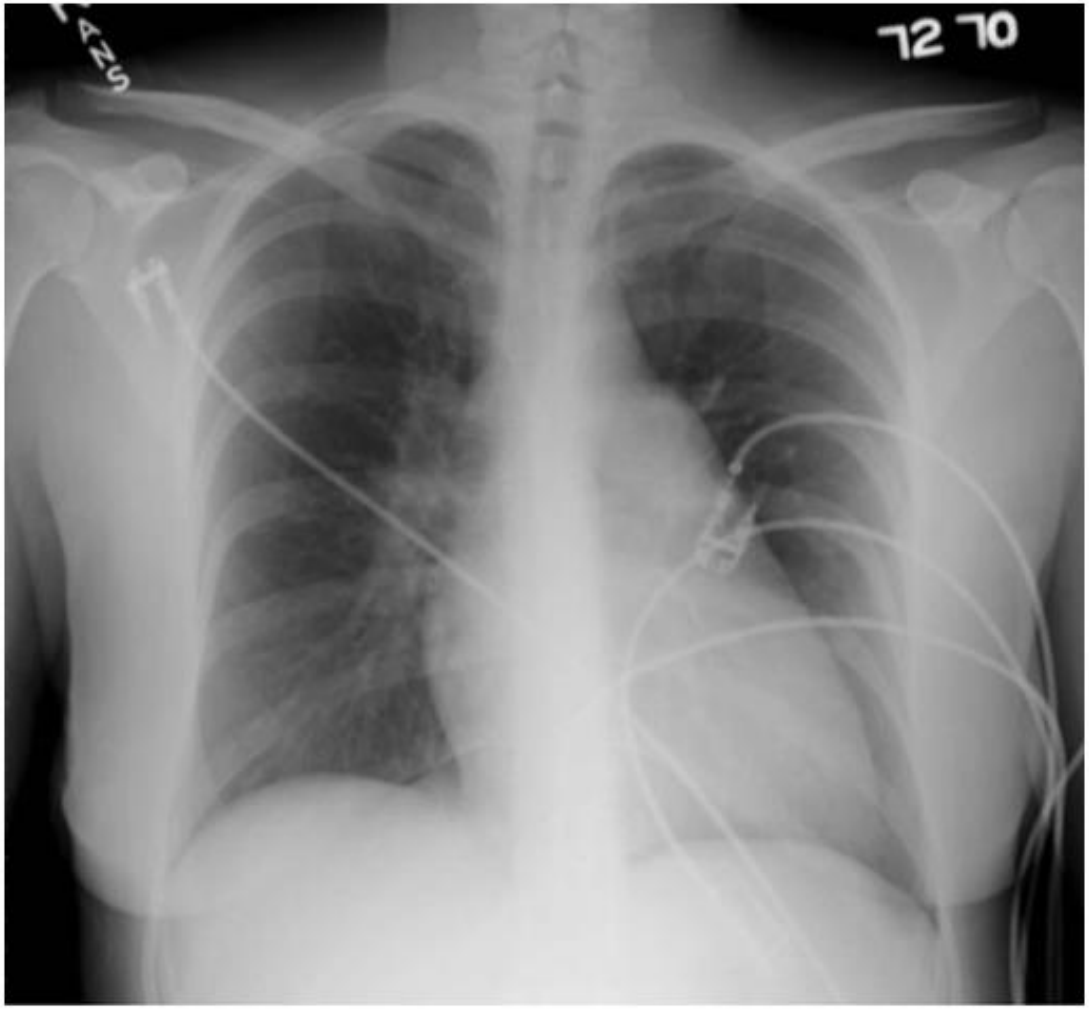
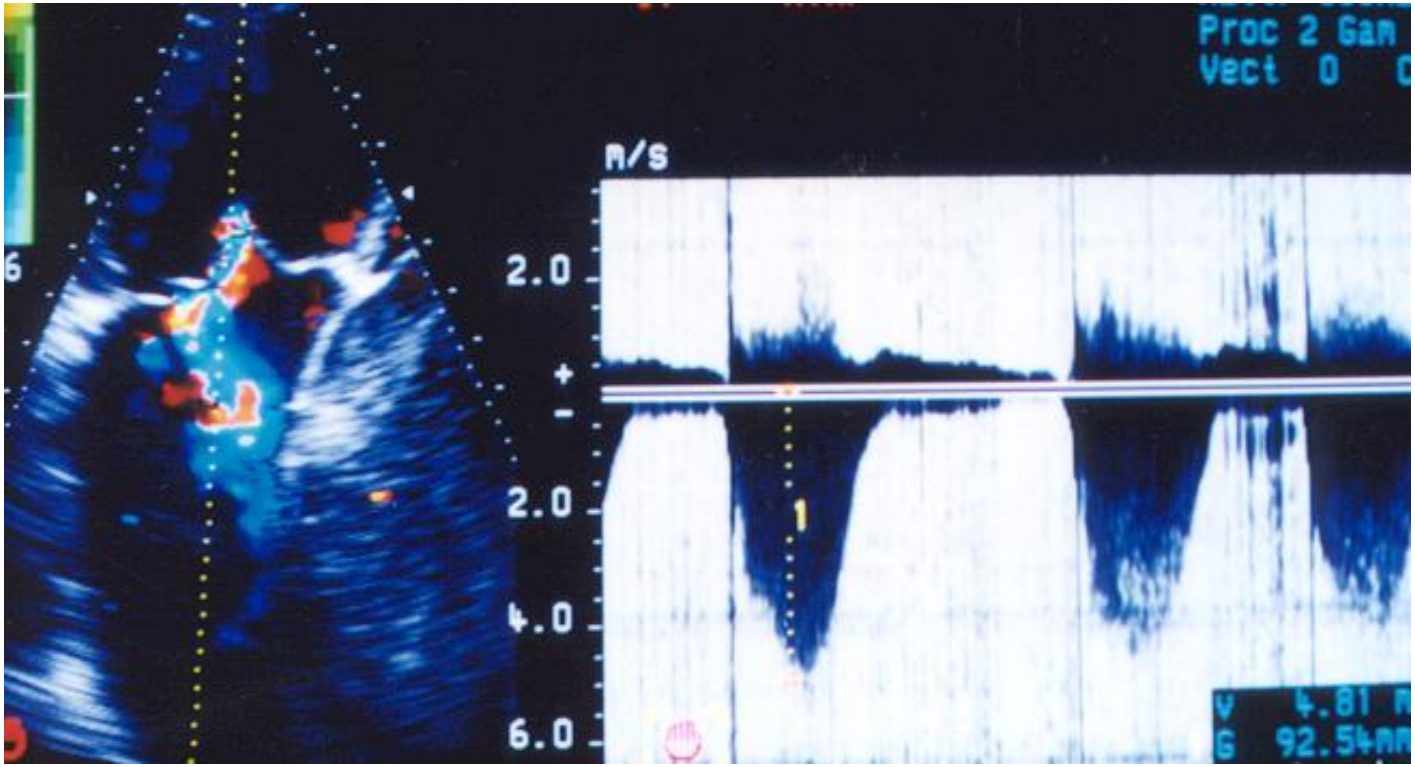
TL: McLaughlin VV, Humbert M. Pulmonary Hypertension. In Braunwald's Heart Disease, Elsevier Saunders, 2015, 10th ed, p. 1682-1700

Phim x-quang ngực b/n TAĐMP



TL: McLaughlin VV, Humbert M. Pulmonary Hypertension. In Braunwald's Heart Disease, Elsevier Saunders, 2015, 10th ed, p. 1682-1700

Siêu âm Doppler giúp đo ALĐMP



Hình ảnh dòng hở van 3 lá – Phổ Doppler liên tục dòng hở van 3 lá- Ap lực Động Mạch Phổi tâm thu là 95 mmHg.

TL: Phạm Nguyễn Vinh. Atlas siêu âm tim 2D & Doppler màu. NXB Y học 2000, p 79

Pham Nguyen Vinh

MSCT phổi có cản quang

- Đường kính ĐMP dãn tại gốc: ý niệm về áp lực ĐMP*
- Tổn thương nhu mô phổi
- Tăng áp phổi do huyết khối thuyên tắc: thay đổi nhiều kích thước mạch máu phổi (có thể thay thế xạ ký tưới máu phổi)**

*TL: * Tan RT et al. Chest 113: 1250 – 1256, 1998*

*** Rich S. In Heart Disease, ed by Braunwald, Zipes, Libby; WB Saunders 2001, 6th ed p. 1921*

Thông tim- chụp mạch máu phổi có cản quang

- Giúp loại trừ TAĐMP thứ phát
- TAĐMP/ TP
  - không tăng áp lực bít mao mạch phổi (ALBMMP)
  - giai đoạn cuối: ALBMMP không quá 16mmHg
- Thông tim: chẩn đoán xác định TAĐMP/TP

Hai điểm chính trong chẩn đoán TAĐMP

- Phát hiện TAĐMP
- Loại trừ các nguyên nhân TAĐMP chú ý:
  - bệnh huyết khối thuyên tắc
  - bệnh chất keo
  - yếu tố gia đình

Các yếu tố tiên lượng b/n TA ĐMP

DETERMINANTS OF RISK	LOWER RISK (GOOD PROGNOSIS)	HIGHER RISK (POOR PROGNOSIS)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class[†]	II, III	IV
6MW distance[‡]	Longer (>400 meters)	Shorter (<300 meters)
CPET	Peak Vo_2 >10.4 mL/kg/min	Peak Vo_2 <10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP <10 mm Hg, CI >2.5 L/min/m^2	RAP >20 mm Hg, CI <2.0 liters/min/m^2
BNP[§]	Minimally elevated	Significantly elevated

BNP = brain natriuretic peptide; CI = cardiac index; CPET = cardiopulmonary exercise testing; RV = right ventricular; peak Vo_2 = average peak oxygen uptake during exercise; RAP = right atrial pressure.

TL: McLaughlin VV et al. ACCF/AHA 2009 expert concensus document on pulmonary hypertension J Am Coll Cardio 53: 1573, 2009

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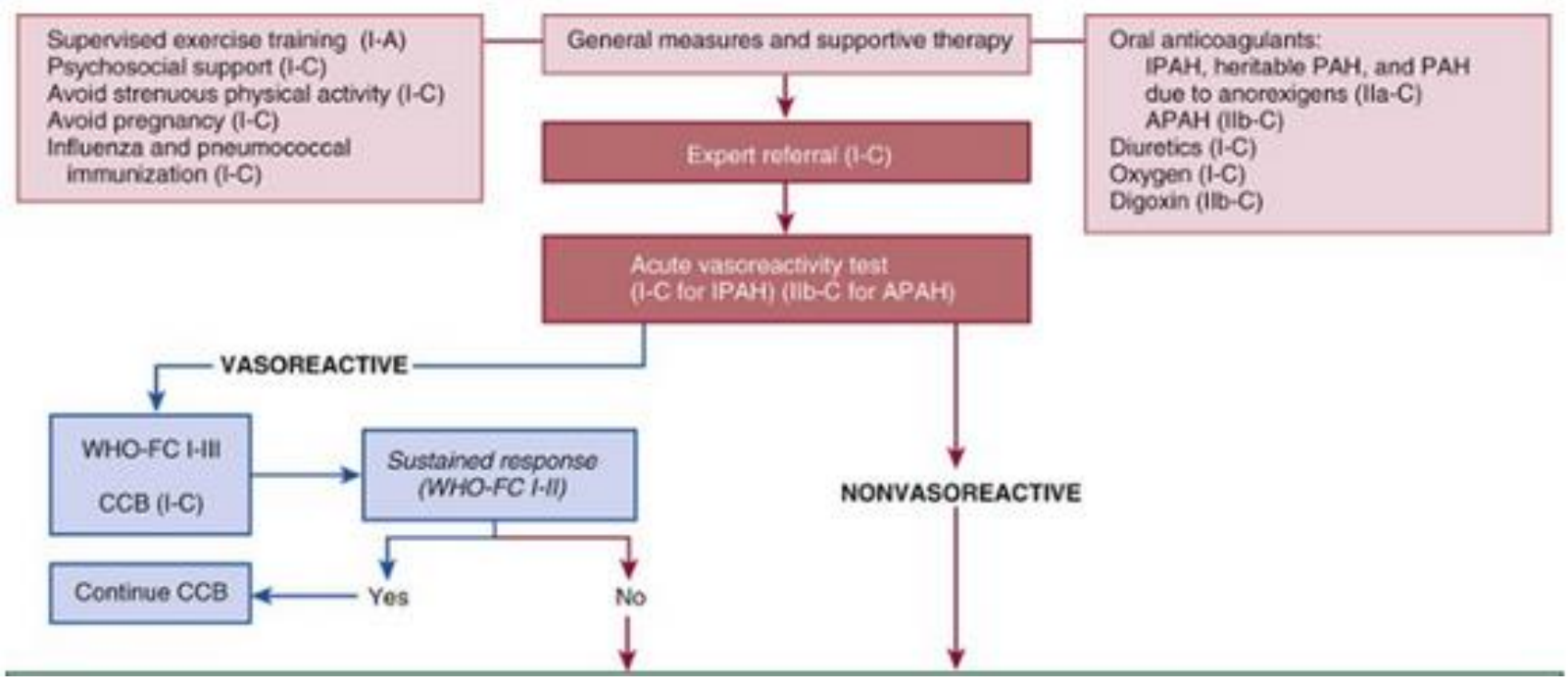
Quy trình điều trị TAĐMP (1)



WHO- FC: a modified of NYHA

Pham Nguyen Vinh

TL: McLaughlin VV, Humbert M. Pulmonary Hypertension. In Braunwald's Heart Disease, Elsevier Saunders, 2015, 10th ed, p. 1682-1700

Quy trình điều trị TAĐMP (2)

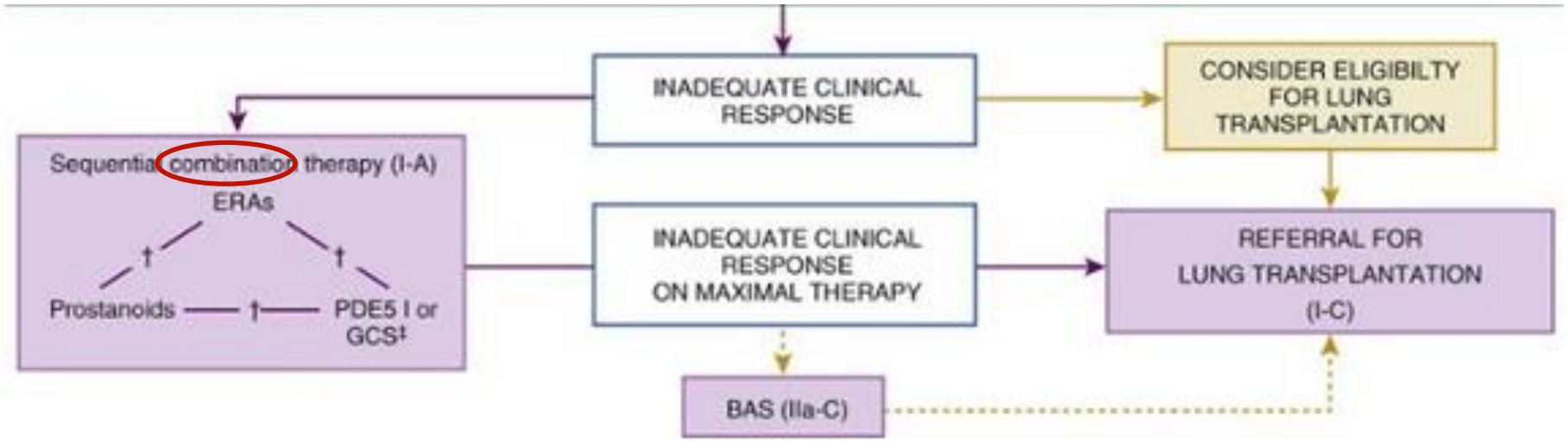
INITIAL THERAPY WITH PAH-APPROVED DRUGS

RED: Morbidity and mortality as primary endpoint in randomized controlled study or reduction in all-cause mortality (prospectively defined)
* Level of evidence is based on the WHO-FC of most of the patients in the studies
† Approved only, in the United States (treprostinil inhaled), in New Zealand (iloprost IV), in Japan and S. Korea (beraprost)
‡ Drugs under regulatory approval

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan, Bosentan Macitentan‡ Riociguat‡ Sildenafil Tadalafil	Ambrisentan, Bosentan, Epoprostenol IV Iloprost inhaled Macitentan‡ Riociguat‡ Sildenafil Tadalafil Treprostinil SC, inhaled†	Epoprostenol IV
IIa	C		Iloprost IV† Treprostinil IN	Ambrisentan, bosentan Iloprost inhaled, and IV† Macitentan‡ Riociguat‡ Sildenafil, tadalafil Treprostinil SC, IV, inhaled†
IIb	B		Beraprost†	
	C		Initial combination therapy	Initial combination therapy

TL: McLaughlin VV, Humbert M. Pulmonary Hypertension. In Braunwald's Heart Disease, Elsevier Saunders, 2015, 10th ed, p. 1682-1700

Quy trình điều trị TAĐMP (3)



BAS= ballon atrial septostomy

Pham Nguyen Vinh

TL: McLaughlin VV, Humbert M. Pulmonary Hypertension. In Braunwald's Heart Disease, Elsevier Saunders, 2015, 10th ed, p. 1682-1700

Điều trị hạ áp ĐMP: ức chế thụ thể endothelin

- Bosentan (kháng thụ thể endothelin kép):
  - Cải thiện phân độ chức năng (57-100%)
  - Giảm kháng lực mạch máu phổi (9%)
  - Cải thiện đi bộ 6 phút (13%)

TL: - Kotlyar E et al. Cardiol Young 2006,16: 268-274
- Chau EM et al. Int J Cardiol 2007; 120: 301-305

Điều trị hạ áp ĐMP: thuốc ức chế phosphodiesterase

- Các thuốc ức chế PDE-5 dùng trong hội chứng Eisenmenger: Sildenafil, Tadalafil.
- Hiệu quả cấp tính và lâu dài, an toàn
- Độ bão hòa oxy cải thiện 10%/lúc 6 tháng, 7%/9 tháng*,**
- Kháng lực mạch máu phổi giảm 50%/6 tháng*, **
- Kháng lực mạch hệ thống không đổi.
- Cung lượng tim tăng (2.9 – 3.7 L/ph/m^2)
- Tăng co bóp thất phải ***

TL: * Garg N et al. Int J Cardiol 2007; 120: 206-313
** Mukhopadhyay S et al. Circulation 2006; 114: 1807-1810
*** Nagendran J et al. Criculatio 2007; 116: 238-248

Tương tác thuốc/ điều trị TAĐMP (1)

PAH Drug	Mechanism of interaction	Interacting drug	Interaction
Ambrisentan	?	Cyclosporine Ketoconazole	Caution is required in the co-administration of ambrisentan with ketoconazole and cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase 4-fold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	Bosentan levels increase 2-fold.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of glibenclamide. Combination contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels considerably increase. Combination potentially contraindicated
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable
Sitaxentan	CYP2C9 inhibitor	Warfarin	Inhibits warfarin metabolism, warfarin dose needs to be reduced by 80% when initiating sitaxentan and INR monitoring intensified.
	? inhibition of OATP transporter	Cyclosporine	Increases sitaxentan levels; combination contraindicated.

TL: Galie N et al. Guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart Journal (2009) 30, 2493-2537

Tương tác thuốc/ điều trị TAĐMP (2)

Sildenafil	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinovir increase sildenafil levels markedly. Sildenafil dose-adjustments are usually required.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fell.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase may not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contraindicated.
Tadalafil	CYP3A4 substrate	Bosentan	Tadalafil plasma levels decreases by 42%, no significant changes in bosentan levels. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contraindicated.

cGMP = cyclic guanosine monophosphate; OATP = organic anion transporter proteins. The table is adapted from National Pulmonary Hypertension Centres of the UK and Ireland. Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland. *Heart* 2008;**94**(Suppl 1):11 14. Since the original publication of these Guidelines, the drug sitaxentan has been withdrawn from the market due to liver toxicity.

Pham Nguyen Vinh

TL: Galie N et al. Guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart Journal (2009) 30, 2493-2537

Các biện pháp điều trị khác

- Mở TLN bằng bóng (Balloon atrial septostomy)
- Ghép phổi

Hiệu quả các biện pháp điều trị b/n TAĐMP (nhóm 1) theo phân độ WHO (WHO-FC)

Measure/treatment		Classes of recommendation–level of evidence		
		WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers		I–C[a]	I–C[a]	–
Endothelin receptor antagonists	Ambrisentan	I–A	I–A	IIa–C
	Bosentan	I–A	I–A	IIa–C
	Sitaxentan	IIa–C	I–A	IIa–C
Phosphodiesterase type 5 inhibitors	Sildenafil	I–A	I–A	IIa–C
	Tadalafil[b]	I–B	I–B	IIa–C
Prostanoids	Beraprost	–	IIb–B	–
	Epoprostenol (intravenous)	–	I–A	I–A
	Iloprost (inhaled)	–	I–A	IIa–C
	Iloprost (intravenous)	–	IIa–C	IIa–C
	Treprostinil (subcutaneous)	–	I–B	IIa–C
	Treprostinil (intravenous)	–	IIa–C	IIa–C
	Treprostinil (inhaled)[b]	–	I–B	IIa–C
Initial drugs combination therapy		–	–	IIa–C
Sequential drugs combination therapy		IIa–C	IIa–B	IIa–B
Balloon atrial septostomy		–	I–C	I–C
Lung transplantation		–	I–C	I–C

[a]Only in responders to acute vasoreactivity tests, I for idiopathic PAH, heritable PAH, and PAH due to anorexigens; IIa for APAH conditions.
[b]Under regulatory review in the European Union.

Pham Nguyen Vinh

TL: Galie N et al. Guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart Journal (2009) 30, 2493-2537

Khuyến cáo điều trị TAĐMP kèm shurt tim bẩm sinh

TL: Galie N et al. Guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart Journal (2009) 30, 2493-2537

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.

Khuyến cáo về chẩn đoán và xử trí TAP do huyết khối thuyên tắc (CTEPH: Chronic thromboembolic pulmonary hypertension)

Statement	Class[a]	Level[b]
The diagnosis of CTEPH is based on the presence of pre capillary PH (mean PAP ≥25 mmHg, PWP ≤15 mmHg, PVR >2 Wood units) in patients with multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental)	I	C
In patients with CTEPH lifelong anticoagulation is indicated	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy	IIa	C
The selection of patients for surgery should be based on the extent and location of the organized thrombi, on the degree of PH, and on the presence of co morbidities	IIa	C
PAH specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after pulmonary endarterectomy	IIb	C

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

TL: Galie N et al. Guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart Journal (2009) 30, 2493-2537

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Lượng định lâu dài bệnh nhân TAĐMP (1)

	LOW RISK	HIGH RISK
Clinical course	Stable; no increase in symptoms and/or decompensation	Unstable; increase in symptoms and/or decompensation
Physical examination	No evidence of right-sided heart failure	Signs of right-sided heart failure
Functional class†	I/II	IV
6MW distance†	>400 meters	<300 meters
Echocardiogram	RV size/function normal	RV enlargement/dysfunction
Hemodynamics	RAP normal CI normal	RAP high CI low
BNP	Nearly normal/remaining stable or decreasing	Elevated/increasing
Treatment	Oral therapy	Intravenous prostacyclin and/or combination treatment

Pham Nguyen Vinh

TL: McLaughlin VV et al. ACCF/AHA 2009 expert concensus document on pulmonary hypertension J Am Coll Cardio 53: 1573, 2009

Lượng định lâu dài bệnh nhân TAĐMP (2)

Frequency of evaluation	Every 3-6 months‡	Every 1-3 months
FC assessment	Every clinic visit	Every clinic visit
6MW distance	Every clinic visit	Every clinic visit
Echocardiogram§	Yearly or center dependent	Every 6-12 months or center dependent
BNP¶	Center dependent	Center dependent
RHC	Clinical deterioration and center dependent	Every 6-12 months or clinical deterioration

CI = cardiac index; FC = functional class; RAP = right atrial pressure; 6MW = 6-minute walk.

RHC: Righ Heart Cathetenization

TL: McLaughlin VV et al. ACCF/AHA 2009 expert concensus document on pulmonary hypertension J Am Coll Cardio 53: 1573, 2009

Kết luận

- Tiên lượng nặng, tiến triển nhanh: cần phát hiện sớm
- Lâm sàng: khó thở chưa rõ nguyên nhân+++
- Tăng áp ĐMP: siêu âm tim Doppler
- TA ĐMP tiên phát: cần loại trừ các nguyên nhân
- Điều trị: Thuốc đối kháng endothelin (Td: Bosentan) ± ức chế phosphodiesterase-5: hiệu quả cao giảm áp lực ĐMP