Non-obstructive hypertrophic cardiomyopathy associated with pulmonary hypertension

Case report from:

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English

Female, 38-year-old patient. She went to the ER of another hospital with symptoms of pain in the right hypochondrium associated to nausea and vomits. She also mentioned dyspnea with minimal efforts. She mentioned that in 2013 she was admitted in the hospital with symptoms of palpitations, syncope, hemiparesis and hemiparesthesia associated to lower limb edema. Former drinker (she stopped smoking 2 years ago). Since then she is using amiodarone, atenolol and marevan.

Physical examination: BP = 100/70 mmHg; regular heart rhythm; HR = 56 bpm, absence of murmurs; clean lungs, abdomen tender to palpitation in the right hypochondrium and the epigastric region; palpable liver 3 cm below the right costal margin; no lower limb edema.

Abdominal echo revealed congestive hepatomegaly.

Echo: LV = 45/27 mm; septal diastolic diameter = 19 mm; posterior wall diastolic diameter = 09 mm; LA 50 mm; EF = 50%; LV mass = 251 gr; asymmetric septal hypertrophy with extension into the apical region; LV diastolic dysfunction, stage II; mild mitral and aortic regurgitation; pulmonary artery systolic pressure = 60 mmHg and accentuated presence of spontaneous echo contrast in the LA (accentuated dilatation)

Conclusions: findings compatible with:

Non-obstructive hypertrophic cardiomyopathy;

Mild systolic dysfunction;

Presence of spontaneous echo contrast (sign of low flow/thrombogenic condition);

Pulmonary hypertension.

Português

Paciente do sexo feminino,38 anos,procurou o serviço de emergência de outro hospital com quadro de dor no hipocôndrio direito associada com náuseas e vômitos.Refere também dispnéia aos mínimos esforços.Relata que em 2013 deu entrada no hospital com quadro de palpitações,síncope,hemiparesia e hemiparestesia associados com edema de membros inferiores .Ex-etilista(parou de fumar há 2 anos).Desde então faz uso de amiodarona,atenolol,marevan.

Exame físico:PA=100/70 mmHg;ritmo cardíaco regular,FC=56 bpm,ausência de sopros;pulmões limpos;abdome doloroso à palpação no hipocôndrio direito e região epigástrica;fígado palpável 3cm abaixo do RCD; sem edema de MMII

Realizou uma US abdominal que revelou hepatomegalia congestiva.

Ecocardiograma :VE=45/27mm;diâmetro diastólico do septo=19 mm;diâmetro diastólico da parede posterior=09 mm;átrio esquerdo 50 mm;FE=50% ; massa VE=251 gramas;Hipetrofia septal assimétrica com extensão para região apical;Disfunção diastólica do VE estágio II;Refluxo mitral e aórtico leves;pressão sistólica da artéria pulmonar=60 mmHg e presença acentuada de ecos de contraste espontâneo no AE(remora acentuada)

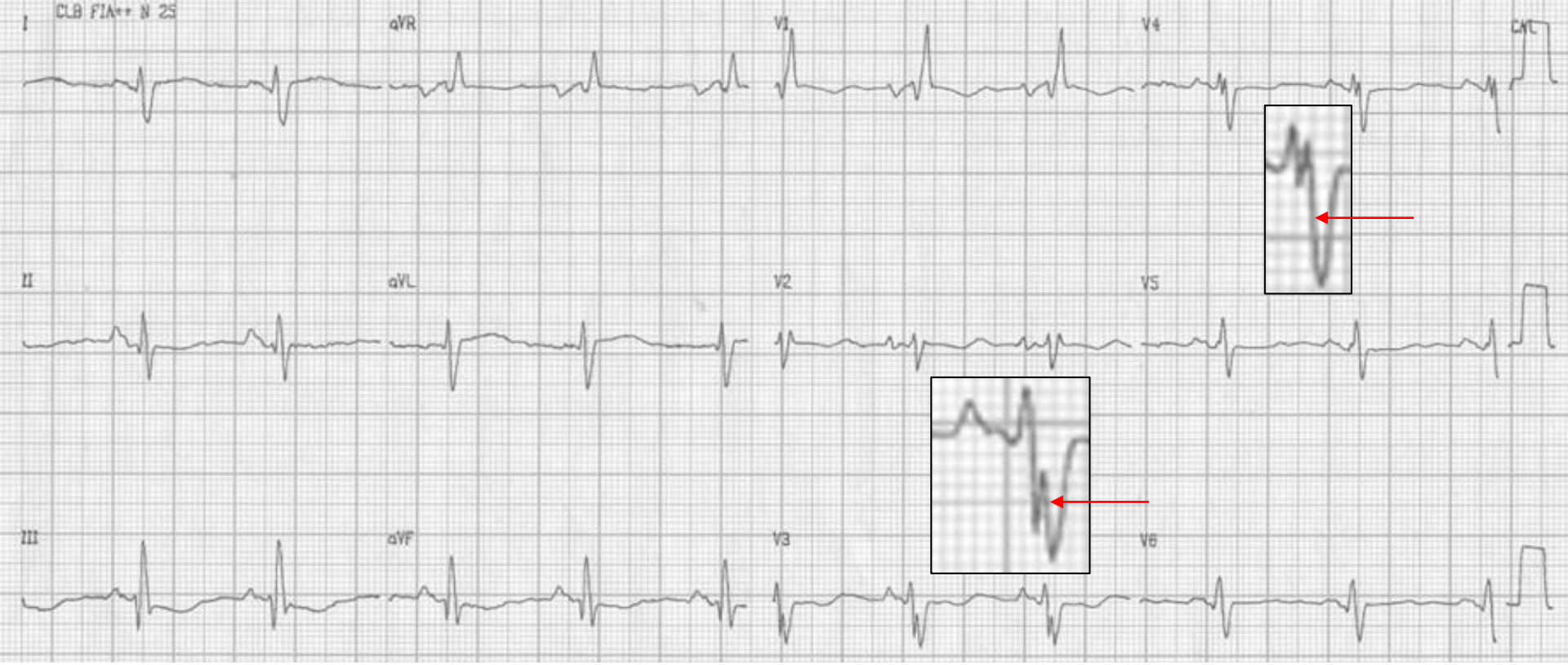
Conclusões:achados compatíveis com:

cardiomiopatia hipertrófica forma não obstrutiva;

disfunção sistólica leve;

presença de ecos de contraste espontâneo(sinal de baixo fluxo /condição trombogênica);

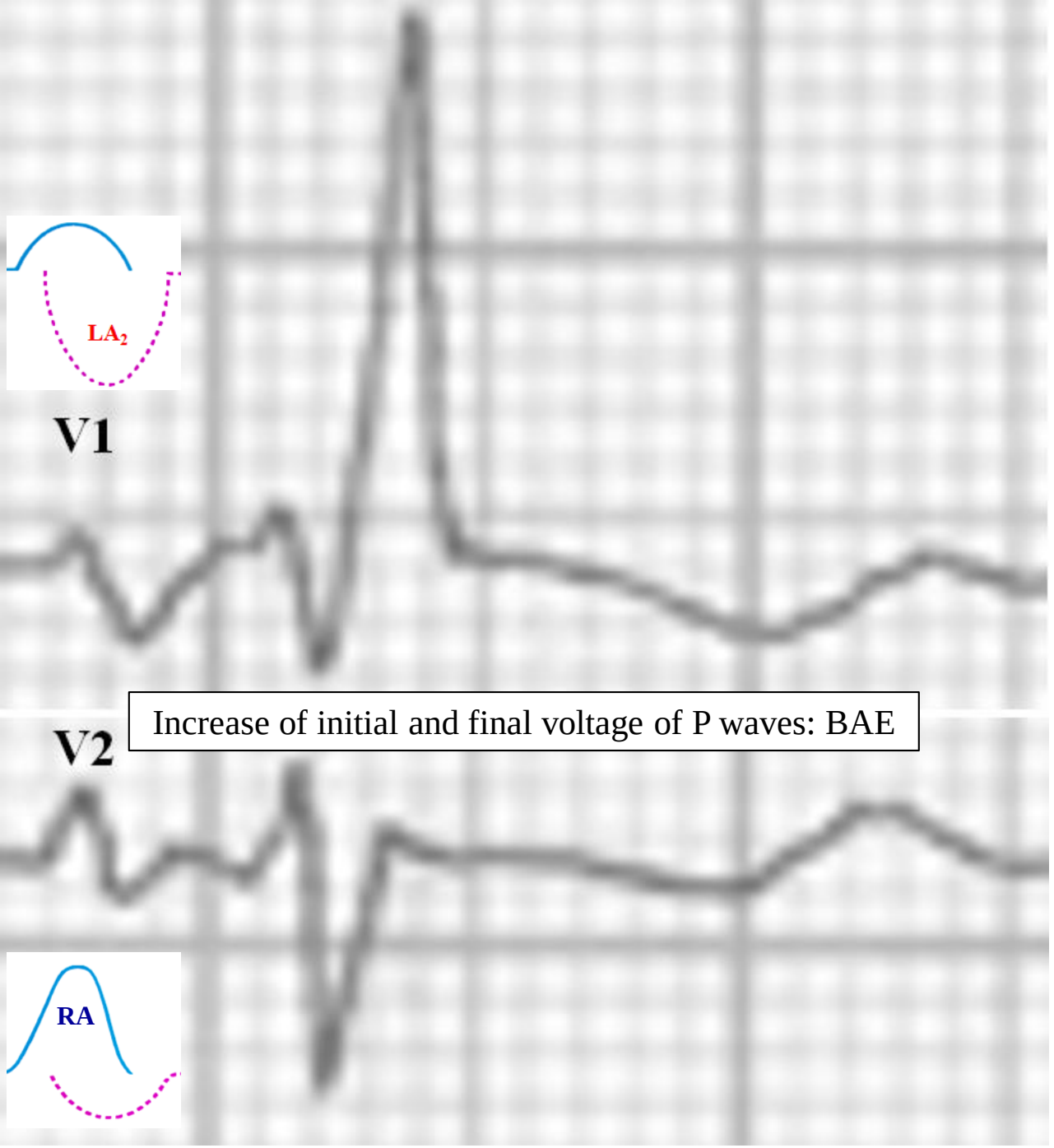
hipertensão pulmonar



ECG diagnosis: Sinus rhythm, HR = 68 bpm, P duration = 135 ms , SÂP = +60º, Initial component of P wave in V2 >1.5 mm and in V1 final slow and deep negative component > 1 mm in depth and 40 ms in duration (biatrial enlargement), PR interval = 160 ms, QRS axis = +140º, QRS duration = 140 ms, triphasic pattern type rsR' in V1, broad final R wave in left lateral leads and prominent final R wave in aVR: complete RBBB. Wide fragmented QRS in V3-V4 (red arrows).

QRS axis in +140º (beyond +110º in adults), prominent final R wave in aVR (R wave of aVR ≥ 5 mm (RV outflow tract), Q/R ratio of aVR ≤ 1: Q ≤ R wave, R < S in V5-V6, regression of R/S ratio in the precordium, RBBB associated to RAE and marked deviation to the right of SÂQRS in the FP = right ventricular hypertrophy.

Conclusion: Biatrial enlargement, right ventricular hypertrophy (RVH), LAE could be an indirect criteria of LVH, complete RBBB and wide fragmented QRS (wf-QRS) (red arrows).

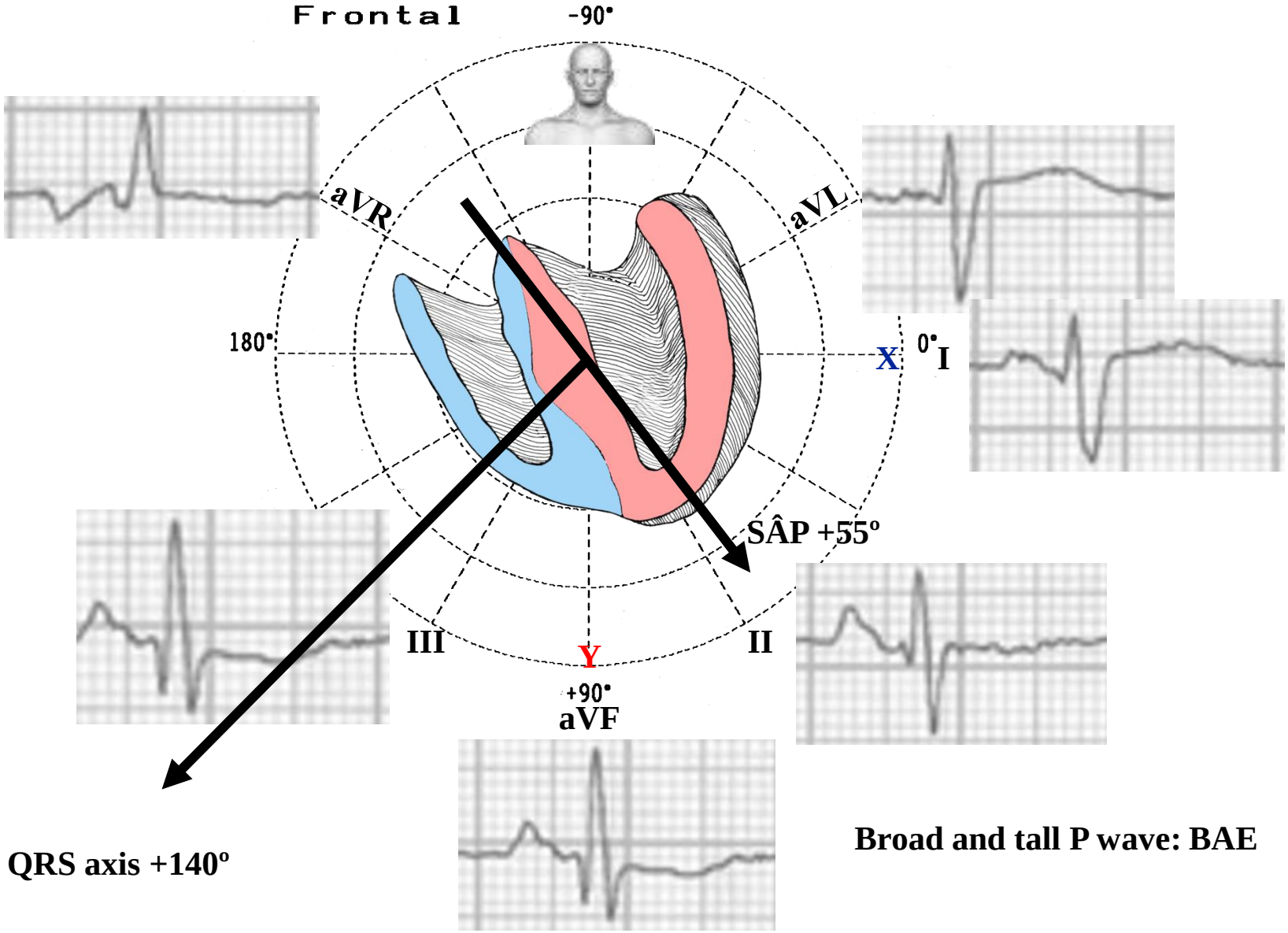


Increase of initial and final voltage of P waves: BAE

$LA_{2/}$: final deep and slow component: LAE

Biatrial enlargement (BAE)

P wave height >1.5 mm in lead V_2: RAE



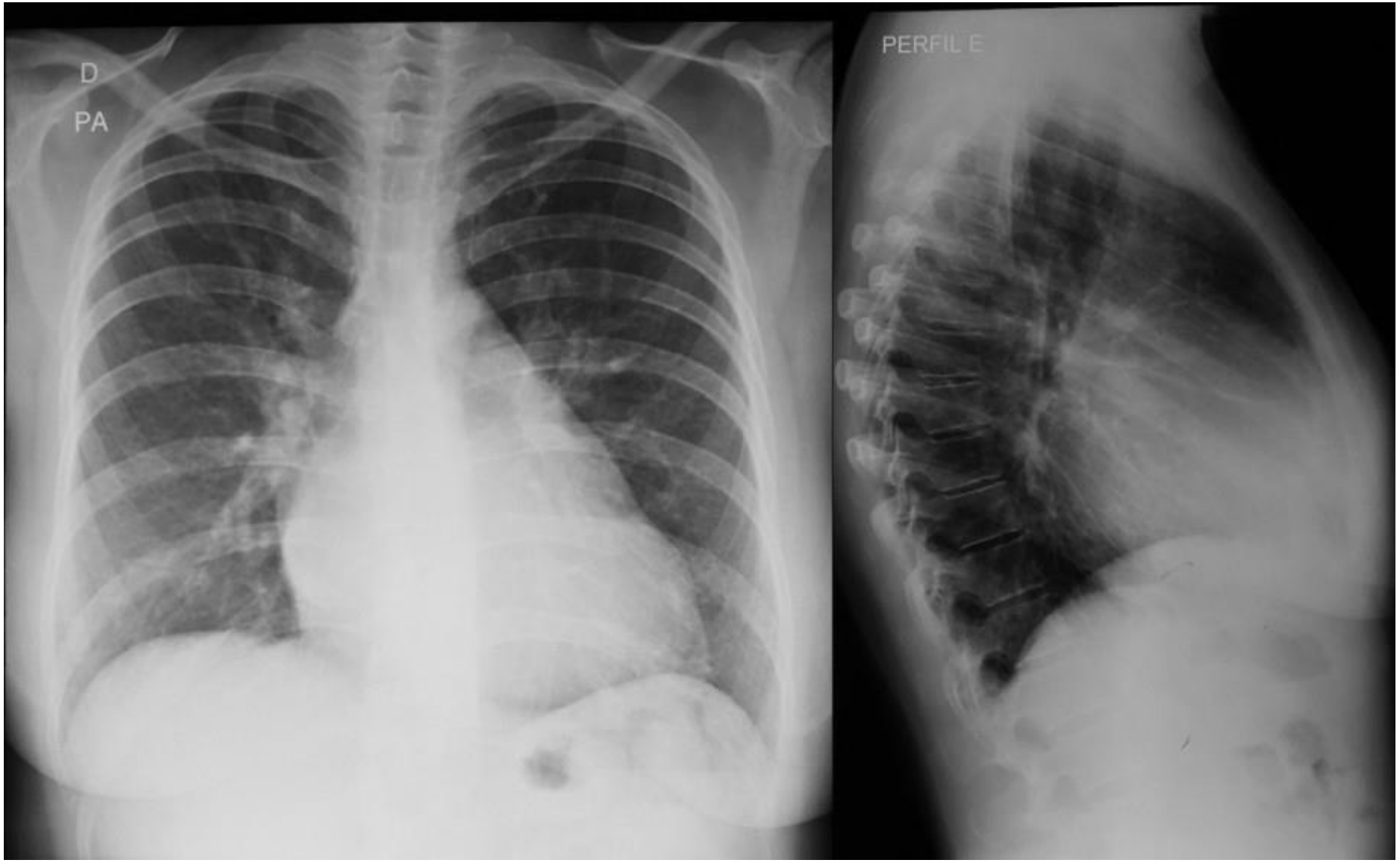
QRS axis +140º

Broad and tall P wave: BAE

Chest X-Ray

Frontal view

Lateral view



I don’t seen typical ECG signs of hypertrophic cardiomyopathy. The ECG shows signs of significant problems in the right side of the heart: P pulmonale, right axis deviation, RV strain. Probably the hypertrophic cardiomyopathy is not the etiology of the problems on the right side. I think there must be some other etiology for the pulmonary hypertension, like primary pulmonary hypertension or pulmonary embolism.

Kind regards

Kjell Nikus
Tampere, Finland

Pulmonary hypertension definition PH has been defined as an increase in mean pulmonary arterial pressure (PAP) 25 mmHg at rest as assessed by right heart catheterization (RHC). This value has been used for selecting patients in all RCTs and registries of PAH. Recent re-evaluation of available data has shown that the normal mean PAP at rest is 14+3 mmHg, with an upper limit of normal of 20 mmHg. The significance of a mean PAP between 21 and 24 mmHg is unclear. Patients presenting with PAP in this range need further evaluation in epidemiological studies. The definition of PH on exercise as a mean PAP .30 mmHg as assessed by RHC is not supported by published data and healthy individuals can reach much higher values. Thus no definition for PH on exercise as assessed by RHC can be provided at the present time. According to various combinations of values of pulmonary wedge pressure (PWP), pulmonary vascular resistance (PVR), and cardiac output (CO), different hemodynamic definitions of PH. Pre-capillary PH includes the clinical groups 1, 3, 4, and 5 while post-capillary PH includes the clinical group 2 the present case

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristic	Clinical group
Pulmonary hypertension (PH)	Mean PAP 25 mmHg	All
Pre-capillary PH	Mean PAP ≥ 25 mmHg PWP ≤ 15 mmHg CO normal or reduced	1. Pulmonary arterial hypertension 2. PH due to lung diseases 3. Chronic thromboembolic PH 4. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥ 25 mmHg PWP > 15 mmHg CO normal or reduced	2. PH due to left heart disease
Passive	TPG 12 mmHg	
Reactive (out of proportion)	TPG .12 mmHg	

a All values measured at rest. High CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, etc. CO ¼ cardiac output; PAP ¼ pulmonary arterial pressure; PH ¼ pulmonary hypertension; PWP ¼ pulmonary wedge pressure; TPG ¼ transpulmonary pressure gradient (mean PAP – mean PWP)

Pulmonary arterial hypertension (PAH) classification system (Dana Point 2008) and is one of five such groups. The groups are divided based on aetiology.

Group 1	Pulmonary arterial hypertension (PAH)
	➢ Idiopathic (IPAH) ➢ Heritable (HPAH) • Bone morphogenetic protein receptor type 2 (BMPR2) • Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia) • Unknown ➢ Drug- and toxin-induced ➢ Associated with (APAH): • Connective tissue diseases • Human immunodeficiency virus (HIV) infection • Portal hypertension • Congenital heart disease (CHD) • Schistosomiasis • Chronic haemolytic anaemia ➢ Persistent pulmonary hypertension of the newborn (PPHN)
Group 1'	Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
Group 2	Pulmonary hypertension due to left heart diseases ➢ Systolic dysfunction ➢ Diastolic dysfunction ➢ Valvular disease **The present case is in this group.**

Group 3.	Pulmonary hypertension due to lung diseases and/or hypoxemia •Chronic obstructive pulmonary disease (COPD) •Interstitial lung disease (ILD) •Other pulmonary diseases with mixed restrictive and obstructive pattern •Sleep-disordered breathing •Alveolar hypoventilation disorders •Chronic exposure to high altitude •Developmental abnormalities
Group 4.	Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5.	PH with unclear multifactorial mechanisms
	•Haematological disorders: myeloproliferative disorders, splenectomy •Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis,vasculitis •Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders •Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH

- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - CTD
  - HIV infection
  - portal hypertension
  - CHD
  - schistosomiasis
  - chronic hemolytic anemia

1'. PVOD and/or PCH

2. PH Owing to Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

The present case

3. PH Owing to Lung Diseases and/or Hypoxia

- COPD
- ILD
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

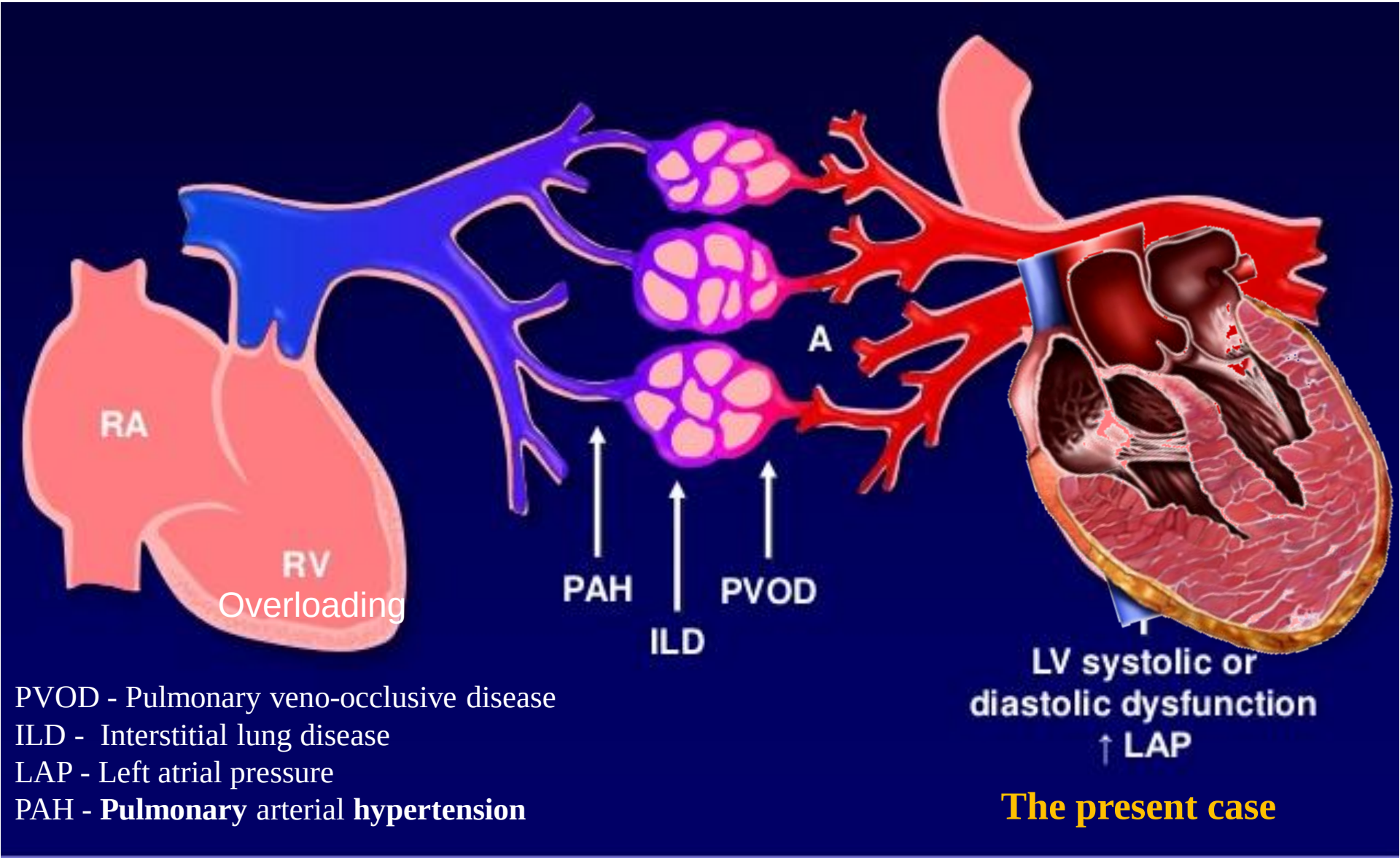
4. CTEPH

5. PH With Unclear Multifactorial Mechanisms

- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

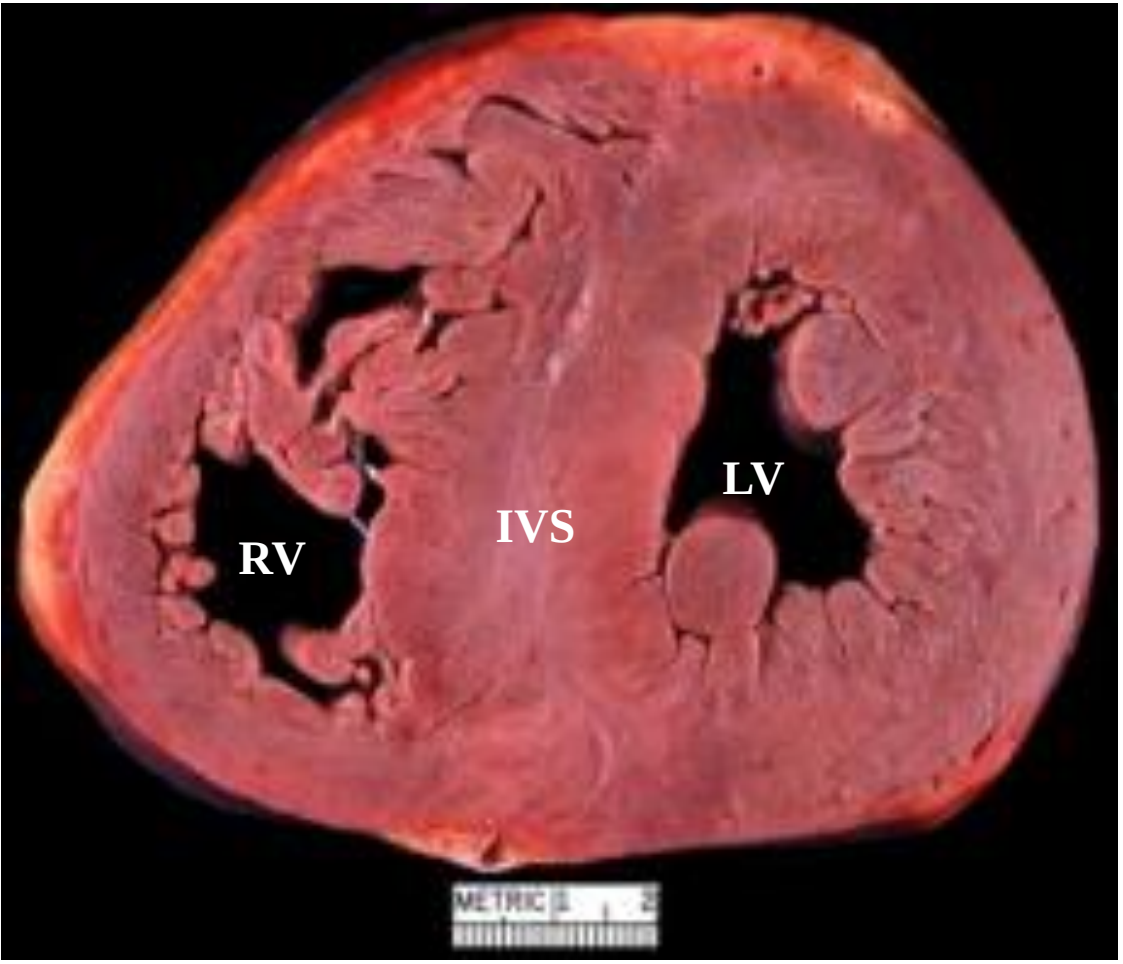
Simonneau G et al. *J Am Coll Cardiol*. 2009;54;S43-S54.

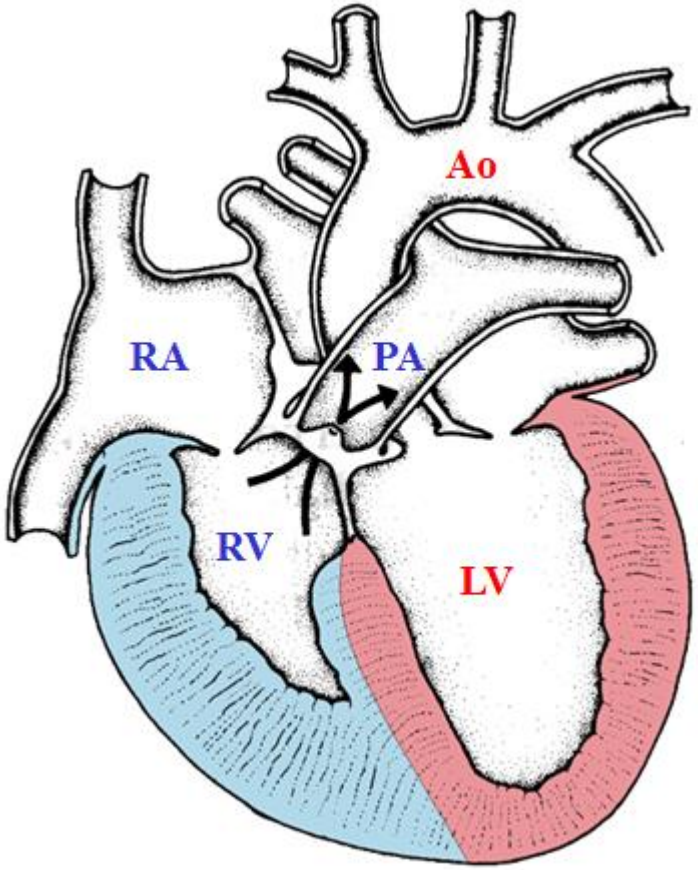
Group 2 - Pulmonary hypertension due to left heart disease physiopathology



PVOD - Pulmonary veno-occlusive disease
ILD - Interstitial lung disease
LAP - Left atrial pressure
PAH - **Pulmonary** arterial **hypertension**

The present case





IVS = very thick interventricular septum

Hypertrophic cardiomyopathy with biventricular hypertrophy and severe diastolic dysfunction. Increased biventricular mass and thick ventricular walls.

Functional classification of pulmonary hypertension modified after the New York Heart Association functional classification according to the WHO 1998 (1)

- **Class I** Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

- **Class II** Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

- **Class III** Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

- **Class IV** Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

1. *Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, Gaine S. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43:S40 –S47.*

The literature review elicits the paucity of information about this condition, despite a frequent involvement of both ventricles in HCM. This pattern of hypertrophy Right ventricular involvement in patients with HCM must be carefully investigated, because it may be more frequent than conventionally deemed.
Although HCM is classically considered a disease of the LV, RV abnormalities have also been reported. However, involvement of the right ventricle in HCM has not been extensively characterized. RV involvement in HCM appears to be as heterogeneous as that of the LV. The spectrum extends from mild concentric hypertrophy to more unusual severe, obstructive disease. While in some cases the extent of RV involvement correlates with LV involvement, predominant RV disease can be seen as well. While the genetics of RV involvement have not been well characterized, histologic findings appear to be similar to those in the LV, suggesting similar pathogenesis. Significant RV involvement may result in RV outflow obstruction and/or reduced RV diastolic filling, with potentially increased incidence of severe dyspnea, supraventricular arrhythmias, and pulmonary thromboembolism. Medical and surgical therapies have been attempted with variable success; experience with newer techniques such as percutaneous catheter ablation has not been reported. Further characterization of RV involvement in HCM is necessary to elucidate more clearly the clinical features and optimal treatments of this manifestation of HCM. HCM patients with RVH on CMR images have a greater incidence of cardiovascular events than non-RVH patients (1). Mass, wall thickness, chamber volume, the EF, and fibrosis were assessed for both ventricles. Maximum RV wall thickness is increased in patients with HCM compared with controls. Extreme RV hypertrophy (≥ 10 mm) is predominantly a diffuse process involving the entire or a significant proportion of the RV wall in most patients. The RV wall mass index is increased in patients with HCM. A significant correlation is found between maximum RV and LV wall thickness and between RV and LV mass. Only 1 (2%) patient with HCM had evidence of RV wall fibrosis. In conclusion, morphologic RV abnormalities are present in a substantial proportion of patients with HCM (2).

1. *Nagata Y, et al. Right Ventricular Hypertrophy Is Associated With Cardiovascular Events in Hypertrophic Cardiomyopathy: Evidence From Study With Magnetic Resonance Imaging. Can J Cardiol. 2015 Jan 24. pii: S0828-282X(15)00039-2.*
2. *Maron MS, et al. Right ventricular involvement in hypertrophic cardiomyopathy. Am J Cardiol. 2007 Oct 15;100(8):1293-8*

Pulmonary hypertension due to left heart disease (group 2)

Most of the advances in the treatment of PH have been made in PAH. At the same time, virtually no progress has been made for the much more common forms of PH as encountered in patients with left heart diseases, lung diseases, or CTEPH. Despite the lack of data, drugs with proven efficacy in PAH are increasingly being used for other forms of PH. This may be clinically justified in some carefully selected patients but may turn out to be useless or even harmful in many others. This development is of concern, and the use of PAH drugs for other forms of PH outside expert centers is discouraged. The pathology, pathophysiology, and epidemiology of PH due to left heart disease have been discussed previously. PH carries a poor prognosis for patients with chronic heart failure (1). In one study the mortality rate after 28 months of follow-up was 57% in patients with moderate PH compared with 17% in patients without PH. In addition, patients who have a PVR exceeding 6 –8 Wood units (480 –640 dynes.s.cm^2) have an increased risk of post-operative RV failure following heart transplantation.

Diagnosis: The diagnostic approach to PH due to left heart disease is similar to that for PAH, Doppler echocardiography being the best tool for screening purposes. LV diastolic dysfunction should be suspected in the presence of a dilated left atrium, AF, characteristic changes in mitral flow profile, pulmonary venous flow profile, mitral annulus tissue Doppler signals and LVH (2).

1. *Grigioni F, Potena L, Galie N, Fallani F, Bigliardi M, Coccolo F, Magnani G, Manes A, Barbieri A, Fucili A, Magelli C, Branzi A. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. J Heart Lung Transplant 2006;25:1241 –1246.*
2. *Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:1451)(Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388 –2442*

Data on tissue Doppler assessment show that the ratio E/E0 of early mitral valve flow velocity (E) divided by the early diastolic (E0) lengthening velocities correlates closely with LV filling pressures: candidates, a persistent increase in PVR .2.5 Wood units and/or TPG .15 mmHg are associated with up to a 3-fold increase in risk of RV failure and early post-transplant mortality (1). When the PVR can be lowered pharmacologically (e.g. with i.v. nitroprusside) this risk may be reduced The absence of consensus on a standardized protocol leads to the use of various agents for testing the responsiveness of the pulmonary circulation, including inotropic agents, vasodilators, prostanoids, NO, and phosphodiesterase type-5 inhibitors. Acute post-operative RV failure may also be observed in patients with normal baseline pulmonary hemodynamics, suggesting that other mechanisms may be involved.

Therapy

Currently, there is no specific therapy for PH due to left heart disease. A number of drugs (including diuretics, nitrates, hydralazine, ACE inhibitors, β-adrenoceptor blockers, nesiritide, and inotropic agents) or interventions (LV assist device implantation, valvular surgery, resynchronization therapy, and heart transplantation) may lower PAP more or less rapidly through a drop in left sided filling pressures. Therefore, management of PH due to left heart disease should be aimed at the optimal treatment of the underlying disease. No heart failure drugs are contraindicated because of PH (2).

1. *Chang PP, Longenecker JC, Wang NY, Baughman KL, Conte JV, Hare JM, Kasper EK. Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. J Heart Lung Transplant 2005;24:998–1007.*
2. *(Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388 –2442*

Few studies have examined the role of drugs currently recommended in PAH. RCTs evaluating the effects of chronic use of epoprostenol (and bosentan (1;2;3) in advanced HF have been terminated early due to an increased rate of events in the investigational drug-treated group compared with conventional therapy. A small sized study recently suggested that sildenafil may improve exercise capacity and quality of life in patients with PH due to left heart disease (4). The history of medical therapy for heart failure is full of examples where drugs had positive effects on surrogate endpoints but eventually turned out to be detrimental, such as the phosphodiesterase type-3 inhibitors. Thus, the use of PAH-specific drugs is not recommended until robust data from long-term studies are available, in particular in 'out of proportion' PH associated with left heart disease. A sustained reduction of PH is expected in weeks to months in most patients successfully operated for mitral valve disease even if PH represents a risk factor for surgery (5;6).

1. *Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, Harrell FE Jr, Wheeler W, Soler-Soler J, Swedberg K. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44 –54.*
2. *Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, Kiowski W, Kostuk W, Krum H, Levine B, Rizzon P, Soler J, Swedberg K, Anderson S, Demets DL. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail 2005;11:12– 20.*
3. *Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? Int J Cardiol 2002;85: 195 –197.*
4. *Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555 – 1562.*
5. *Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230 – 268.*
6. *Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816 –822.*

Recommendations for PH due to left heart disease

Statement	Class	Level
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	**I**	**C**
Patients with ‘out of proportion’ PH due to left heart disease should be enrolled in RCTs targeting PH specific drugs	**IIa**	**C**
Increased left-sided filling pressures may be estimated by Doppler echocardiography	**IIb**	**C**
Invasive measurements of PWP or LV end-diastolic pressure may be required to confirm the diagnosis of PH due to left heart disease	**IIb**	**C**
RHC may be considered in patients with echocardiographic signs suggesting severe PH in patients with left heart disease	**IIb**	**C**
The optimal treatment of the underlying left heart disease is recommended in patients with PH due to left heart disease	**I**	**C**
The use of PAH specific drug therapy is not recommended in patients with PH due to left heart disease	**III**	**C**