Out-of-Proportion Pulmonary Hypertension and Heart Failure with Preserved Ejection Fraction

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Key Words

Heart failure with preserved ejection fraction • Idiopathic pulmonary arterial hypertension • Metabolic syndrome • Pulmonary hypertension • Vascular stiffness

Abstract

Background: A subset of patients with heart failure with preserved ejection fraction (HFpEF) will have a marked increase in pulmonary artery pressure (PAP). **Objective:** To evaluate the clinical and hemodynamic characteristics of these patients in comparison to patients with idiopathic pulmonary arterial hypertension (IPAH). **Methods:** We reviewed the clinical and hemodynamic data of patients with HFpEF with out-of-proportion pulmonary hypertension (HFpEF-PH) and compared it to the corresponding data of age-matched patients with IPAH. **Results:** Twenty consecutive patients with HFpEF-PH and 20 patients with IPAH were included in the study. The mean age ($\pm$ SD) was 71.3 ± 7.8 and 70.2 ± 6.7 years, respectively. The majority of the HFpEF-PH patients were postmenopausal females with at least two features

of the metabolic syndrome and atrial fibrillation. Although HFpEF-PH patients fulfilled the criteria for out-of-proportion PH, with transpulmonary gradient (TPG) >12 mm Hg, the difference between the diastolic PAP and the pulmonary capillary wedge pressure (PCWP) was significantly lower compared to IPAH (6.3 ± 6.2 vs. 27.5 ± 4.8 , $p < 0.00001$). **Conclusions:** Our results suggest that a diagnosis of HFpEF-PH should be suspected when severe PH occurs in an elderly postmenopausal female with one or more features of the metabolic syndrome and atrial fibrillation. Interestingly, these patients had significantly lower differences between diastolic PAP and PCWP, suggesting that the increase in TPG is mainly caused by an elevated systolic PAP, possibly as a result of increased pulmonary vascular stiffness, and not pulmonary vascular remodeling. Copyright © 2012 S. Karger AG, Basel

The study was performed at the Lady Davis Carmel Medical Center, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, and Service de Pneumologie, Hôpital Antoine Bécère and Bicêtre, AP-HP, Clamart and Le Kremlin-Bicêtre, France.

Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest measured during right-sided heart catheterization (RHC) [1–4]. Group 1 of the recently updated PH clinical classification, namely pulmonary arterial hypertension (PAH), is a rare disease causing precapillary PH (mPAP ≥ 25 mm Hg) in the presence of a normal pulmonary capillary wedge pressure (PCWP ≤ 15 mm Hg). A more frequent scenario is a patient presenting with PH in the setting of left heart disease characterized by elevated left-sided cardiac filling pressure as assessed by PCWP or left ventricular end-diastolic pressure (LVEDP). This is commonly termed pulmonary venous hypertension, and these patients fall within group 2 of the PH clinical classification [1–4].

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by the symptoms and signs of heart failure (HF) and preserved ejection fraction (EF), and it is often related to abnormal LV diastolic function [5]. The prevalence of HFpEF increases with age and represents around half of the whole HF population [6, 7]. PH in conjunction with HFpEF is less studied and the optimal treatment of this condition is unknown, although recent studies suggest that PH is highly prevalent [6, 7].

Metabolic syndrome (MS), as defined by the current National Cholesterol Education Program Adult Treatment Panel III, is composed of a cluster of risk factors including impaired fasting glucose levels, elevated blood pressure and triglyceride levels, and increased waist circumference [8]. MS is becoming increasingly common, affecting 22% of the adult population in industrialized countries and over 40% of those aged 50 years and older [9, 10]. Individuals with the MS and normal LV systolic function are frequently found to have LV diastolic dysfunction. Previous studies identified that the components of the MS such as hypertension and obesity are independent predictors of the development of HFpEF [11, 12]. Whether the presence of MS also causes an increased risk of pulmonary vascular disease is unknown, although recent studies suggest that this may be a plausible hypothesis [13, 14].

Severe PH is increasingly recognized in the elderly population [15, 16]. The elevation of pulmonary artery pressure (PAP) which is considered to be out of proportion in relation to that expected from the elevation of left arterial pressure is defined by a transpulmonary gradient (TPG) (mPAP – PCWP) >12 mm Hg and pulmonary vascular

resistance (PVR) above 3.0 Wood units [1–4]. In the present study we aimed to assess the clinical and hemodynamic characteristics of this subgroup of elderly patients with HFpEF and out-of-proportion PH (HFpEF-PH). For that purpose, we retrospectively reviewed the charts of patients with HFpEF-PH and compared their clinical characteristics and hemodynamic data to those of age-matched patients diagnosed with idiopathic PAH (IPAH).

Methods

Subjects

We retrospectively reviewed the charts of patients followed between 2008 and 2010 with a diagnosis of HFpEF and systolic PAP (SPAP) >55 mm Hg on echocardiography. Patients with HFpEF and out-of-proportion PH were included in the study. Out-of-proportion PH was defined by means of RHC as subjects with an mPAP ≥ 25 mm Hg, PCWP >15 mm Hg, PVR >3 Wood units, and TPG >12 mm Hg [1–4]. The clinical characteristic and hemodynamic data of these patients were compared to those of a group of 20 age-matched patients diagnosed with IPAH according to European Respiratory Society/European Society of Cardiology (ERS/ESC) guidelines [1–4]. The study was approved by the Lady Davis Carmel Medical Center IRB committee (approval No. CMC-09-0095) and by the Commission Nationale Informatique et Liberté (approval No. 842063).

HFpEF Diagnosis

The diagnosis of HFpEF was made according to the 2007 consensus statement of the Heart Failure and Echocardiography Association of the ESC and required the following three characteristics: signs and symptoms of HF, normal or mildly abnormal LV systolic function (LVEF $\geq 50\%$), and evidence of LV diastolic dysfunction noninvasively by echocardiography, and it was confirmed by demonstrating high left side filling pressures (PCWP >15 mm Hg) on RHC [17].

Evaluation of PH

All patients were evaluated using ERS/ESC guidelines to determine the presence, severity, and etiology of PH [1–4, 18]. Patients who had any of the following conditions were excluded: congenital heart diseases, connective tissue diseases, HIV infection, portal hypertension, appetite suppressant exposure, chronic hypoxic lung disease, and chronic thromboembolic disease.

RHC was performed using a standard protocol. Inhaled nitric oxide up to 10 ppm for 10 min was used to assess acute vasodilator response. Acute vasodilator responsiveness was defined according to published criteria [2–4, 19].

Statistical Analysis

Data are presented as numbers or means and categorical variables as numbers, percentages, or proportions. The independent-samples *t* test was used to compare continuous variables, and χ^2 tests were used to compare categorical variables. Fisher's exact test was used in cases of small sample sizes. $p < 0.05$ was considered statistically significant. SPSS statistical software was used to perform all statistical analyses.

Table 1. Clinical characteristics of HFpEF-PH and IPAH patients

Clinical characteristics	HFpEF-PH (n = 20)	IPAH (n = 20)	p value
Mean age $\pm$ SD, years	71.3 $\pm$ 7.8	70.2 $\pm$ 6.7	0.63
Male/female ratio	4/16	6/14	0.001
History of smoking, n	2/20 (10)	3/20 (15)	0.63
Mean BMI $\pm$ SD	31 $\pm$ 6.8	28.2 $\pm$ 3.2	0.1
Coronary artery disease, n	6/20 (30)	4/20 (20)	0.28
Diabetes mellitus, n	13/20 (65)	5/20 (25)	0.05
Systemic hypertension, n	16/20 (80)	6/20 (30)	0.0004
Hyperlipidemia, n	16/20 (80)	NA	NA
S/P CABG, n	4/20 (20)	2/20 (10)	0.37
Chronic/paroxysmal atrial fibrillation, n	17/20 (85)	3/20 (15)	<0.00001

Figures in parentheses are percentages. S/P CABG = Status post-coronary artery bypass; NA = not available.

Results

Clinical Characteristics

Twenty consecutive patients with HFpEF-PH and 20 age-matched IPAH patients were included in the study. The mean age was 71.3 $\pm$ 7.8 and 70.2 $\pm$ 6.7 years, respectively. The clinical characteristics of the patients are presented in table 1.

Most HFpEF-PH patients were females (16 out of 20; 80%), as compared to only 6 out of 20 (30%) age-matched elderly IPAH patients.

HFpEF-PH patients were commonly overweight or obese, but there was no statistical difference with age-matched IPAH patients (BMI = 31.0 $\pm$ 6.8 vs. 28.2 $\pm$ 3.2, p = 0.1).

HFpEF-PH patients had a higher prevalence of systemic hypertension and diabetes which were significantly more common in comparison to the IPAH group (p = 0.0004 and p = 0.05, respectively). Hyperlipidemia was also very common in HFpEF-PH patients (data not available in the IPAH group).

Persistent or paroxysmal atrial fibrillation was significantly more common in patients with HFpEF-PH compared to IPAH patients (85 vs. 15%, p < 0.00001).

Hemodynamic Characteristics

The hemodynamic characteristics of the patients are presented in table 2. HFpEF-PH and IPAH patients had severe PH (mPAP = 50.2 $\pm$ 7.1 and 50.2 $\pm$ 9.5, respectively, p = 1.0). The average PCWP was significantly

Table 2. Hemodynamic parameters of HFpEF-PH and IPAH patients

Hemodynamic data (normal values)	HFpEF-PH (n = 20)	IPAH (n = 20)	p value
Mean RAP, mm Hg (0–8)	14.8 $\pm$ 4.9	10.7 $\pm$ 5.6	0.01
SPAP, mm Hg (15–30)	83.6 $\pm$ 9.9	84.2 $\pm$ 16.9	0.81
DPAP, mm Hg (4–12)	29.0 $\pm$ 6.6	31.7 $\pm$ 9.0	0.28
Pulmonary pulse pressure, mm Hg	55.2 $\pm$ 11.3	52.5 $\pm$ 13.5	0.5
mPAP, mm Hg (0–17)	50.2 $\pm$ 7.1	50.2 $\pm$ 9.5	1.0
Mean PCWP, mm Hg (5–15)	22.8 $\pm$ 4.4	9.6 $\pm$ 3.1	<0.0001
CI, l/min/m ² (2.4–4.2)	2.5 $\pm$ 0.5	2.3 $\pm$ 0.3	0.1
SVR, Wood units (14.125 $\pm$ 2.225)	19.2 $\pm$ 3.5	21.9 $\pm$ 6.0	0.12
PVR, Wood units (2.56 $\pm$ 0.6)	6.3 $\pm$ 2.1	9.3 $\pm$ 2.7	0.0005
Mixed venous oxygen saturation, %	58.7 $\pm$ 6.7	57.5 $\pm$ 11.5	0.68
TPG, mm Hg	27.5 $\pm$ 4.8	40.5 $\pm$ 8.8	<0.00001
DPAP – mean PCWP	6.3 $\pm$ 6.2	22.0 $\pm$ 7.8	<0.00001
Acute vasodilator responders, n	2/20 (10)	2/20 (10)	1.0

Values are presented as means $\pm$ SD. Figures in parentheses are percentages. CI = Cardiac index; SVR = systemic vascular resistance.

Table 3. Echocardiographic parameters of HFpEF-PH

Echocardiographic parameters	Mean $\pm$ SD
LV end-diastolic diameter, cm	4.5 $\pm$ 3.7
IVS thickness, cm	1.12 $\pm$ 0.10
LV posterior wall thickness, cm	1.00 $\pm$ 0.05
LV fraction shortening, %	31.8 $\pm$ 4.4
Left atrial diameter, cm	4.48 $\pm$ 0.45
E/A ratio ^a	2.82 $\pm$ 0.86

IVS = Intraventricular septum; E/A ratio = ratio between early and late atrial ventricular filling velocities.

^a The E/A ratio was calculated only in patients with sinus rhythm.

higher in the HFpEF-PH patients compared to the IPAH patients (22.8 $\pm$ 4.4 vs. 9.6 $\pm$ 3.1 mm Hg, respectively, p < 0.00001). Right atrial pressure (RAP) was significantly higher in the HFpEF-PH patients (14.8 $\pm$ 4.9 vs. 10.7 $\pm$ 5.6 mm Hg, p = 0.01). The SPAP and diastolic PAP (DPAP) and the pulmonary pulse pressure were similar in the two groups. By contrast, the TPG was markedly higher in the IPAH patients, as was the difference between the DPAP and the PCWP (40.5 $\pm$ 8.8 and 22.0 $\pm$ 7.8 mm Hg vs. 27.5 $\pm$ 4.8 and 6.3 $\pm$ 6.2 mm Hg, p < 0.00001, respectively). The PVR was significantly higher

in the IPAH patients as compared to the HFpEF-PH patients ($p = 0.0005$). Interestingly, a positive response to inhaled nitric oxide was observed in 10% of patients in both groups.

Echocardiography Data

The echocardiography data is presented in table 3. The typical finding on echocardiography in the HFpEF-PH group was preserved systolic LV function with borderline intraventricular septum hypertrophy and left atrial dilatation, suggesting the diagnosis of HFpEF.

Discussion

The main finding of our study is that in elderly patients with HFpEF and severe PH on echocardiography, out-of-proportion PH is a major differential diagnosis of IPAH and has to be clarified by RHC. Some patient's characteristics are in favor of a diagnosis of HFpEF-PH. In our study, a typical HFpEF-PH patient was a 70-year-old female with chronic atrial fibrillation and features of MS such as morbid obesity, systemic hypertension, diabetes mellitus, and hyperlipidemia. The typical hemodynamic characteristics include markedly elevated SPAP, with high pulmonary pulse pressure similar to that in IPAH patients but with lower TPG and a significantly lower difference between DPAP and PCWP than in IPAH patients.

The prevalence of HFpEF increases with age and, in patients >70 years of age, it may affect around 50% of the population [6, 7]. It is more common among women, and major risk factors include systemic hypertension, ischemic heart disease, diabetes, and obesity [20–22].

Echocardiography is the main diagnostic tool in the evaluation of diastolic dysfunction. However, in patients with chronic atrial fibrillation, assessment of the LV diastolic function is difficult [17, 23, 24]. Tissue Doppler echocardiography is a more reliable tool for further evaluation of diastolic dysfunction. The findings of an enlarged left atrium and borderline hypertrophy of the intraventricular septum and LV posterior wall in our cohort of patients in the presence of preserved LVEF support the diagnosis of HFpEF.

Interestingly, 80% (16 out of 20) of the HFpEF-PH patients were obese postmenopausal women, in contrast to only 30% of the IPAH group. It is well known that in an unselected IPAH population the female/male ratio is 1.7:1 and that the mean age at diagnosis is around 40–50 years [2–4, 15]. However, recent studies suggest that the

age range of affected individuals may be wider than expected, as cases of IPAH, now days, have been reported in many patients older than 70 years [15, 25]. Whether IPAH is more common in males in the older population deserves further investigation but was already reported in the French registry [15]. A recently published study also found a strong association of HFpEF-PH with female gender, similar to a cohort of patients with PAH [26]. However, in contrast to our study, the PAH patient group was significantly younger and not matched by age, suggesting that in elderly patients with IPAH male gender is more predominant.

One of the major findings in our study is the high prevalence of features of MS in the HFpEF-PH patients as opposed to the IPAH patients. Most of the HFpEF-PH patients were obese postmenopausal women with an average BMI of 31, and 80% of the patients had hyperlipidemia and systemic hypertension while 17 out of 20 patients had diabetes mellitus. Interestingly, our age-matched IPAH population was also overweight (BMI 28.2 ± 3.2), which was not significantly different from the HFpEF-PH group.

The relationship of the MS with HFpEF is increasingly recognized [20–22, 27]. The question which arises is whether patients, especially women, with two or more features of the MS are prone to develop not only diastolic dysfunction but also severe and out-of-proportion PH. Robbins et al. [14] also described 17 patients (77% female) with diastolic dysfunction and PH characterized by two or more features of MS. Rifaie et al. [28] showed similar findings – the development of PH in patients with HFpEF was independently associated with obesity (BMI >40), atrial arrhythmias, and age >80 years. A recently published study also found that, compared with PAH, HFpEF-PH is associated with more advanced age, diabetes, obesity, hypertension, and coronary artery disease [26].

Diabetes mellitus and systemic hypertension were significantly more prevalent in the HFpEF-PH group than in IPAH patients.

Systemic hypertension and peripheral vascular stiffness are known as independent risk factors for the development of HFpEF. Furthermore, recent studies demonstrated that MS amplifies the age-associated increases in vascular thickness and stiffness [29, 30]. Interestingly, the HFpEF-PH group was characterized by high SPAP and relatively low DPAP, with a significantly lower difference between the DPAP and PCWP, when compared to the age-matched IPAH patients. A similar phenomenon was reported in a recent study [31] describing

the clinical and hemodynamic characteristics of 239 patients with HFpEF and PH. Although this group of patients fulfilled the definition of disproportionate PH, with a mean TPG of 12.4 mm Hg, their SPAP was relatively higher than the DPAP, which was similar to the LVEDP (22.2 ± 6.8 vs. 22.7 ± 5.8 mm Hg). One explanation for the preferential increase in SPAP might be increased pulmonary vascular stiffness. As in the systemic circulation, the pulmonary vasculature may be affected by age-associated arterial remodeling [32–35], leading to pulmonary vascular stiffness and increases in SPAP. A recent population-based study [36] demonstrated that PAP increases with age. The increase in PAP, estimated by echocardiography, correlated with increases in pulse pressure and estimated left heart filling pressures, suggesting that age-associated blood vessel stiffening and diastolic dysfunction contribute to changes in PAP. Furthermore, elevated SPAP was associated with an increase in all-cause mortality independently of both age and the presence of clinically evident cardiopulmonary disease. It seems that vascular stiffness reflected as increased systemic vascular resistance not only contributes to the development of isolated systolic hypertension and HFpEF but may also affect the pulmonary vasculature, leading to mainly increased SPAP with a higher pulse pressure, a relatively lower DPAP, and a modest increase in PVR as in our HFpEF-PH patients. In contrast, IPAH patients had both a significantly higher difference between the DPAP and PCWP and higher PVR, similar to the findings reported by Thenappan et al. [26]. Furthermore, in our HFpEF-PH patients, the difference between DPAP and PCWP was low, suggesting that pulmonary vascular remodeling and increased PVR was not a major cause of severe PH in these patients, contrasting with our findings in IPAH. It also raises the question of whether the current hemodynamic definition of ‘out-of-proportion’ PH is misleading. The TPG may be augmented by increased PVR or a change in pulmonary vascular compliance. In our HFpEF-PH patients it seems that the main reason for the severely increased SPAP is increased pulmonary vascular stiffness and reduced compliance, which may explain the increased TPG (although lower than the TPG in the IPAH patients), but with only a mild increase in DPAP. Hence, the difference between DPAP and PCWP might better reflect out-of-proportion PH as compared to the TPG and may be considered in future PH hemodynamic guidelines [37–39].

Interestingly, 2 patients with HFpEF-PH had a positive response to inhaled nitric oxide. Although expected, no increase in wedge pressure was observed during nitric

oxide inhalation. Whether these patients have a component of increased vascular reactivity, explaining the observed response, is currently unknown. Of note, RAP was also significantly higher in HFpEF-PH patients. This may reflect volume overload in this patient group and is consistent with the corresponding elevated left heart pressures.

In summary, we suggest that a diagnosis of HFpEF with out-of-proportion PH be considered when elevated PAP is investigated in an elderly female with features of MS, atrial fibrillation, and echocardiography findings of preserved EF, a dilated left atrium, and markers of diastolic dysfunction. Chronic increases in pulmonary venous pressure in combination with individual (possibly genetic) predisposition and combined metabolic and inflammatory changes induced by MS, all acting in concert to increase vascular systemic and pulmonary stiffness, may contribute to the development of clinical out-of-proportion PH. The current definition of out-of-proportion PH might be misleading since the increase in TPG is mainly due to the elevated SPAP and the difference between DPAP and the PCWP is low, suggesting that the increase in TPG is not due to pulmonary vascular remodeling and increased PVR but rather to increased pulmonary vascular stiffness. Therefore, the current definition might be reconsidered and could include an increased difference between DPAP and PCWP. Further studies are needed to investigate the effects of the MS on the pulmonary circulation, and to evaluate the best therapeutic approach in patients with HFpEF, severe PH, and the MS, bearing in mind that currently approved PAH therapies have not been properly tested in this population and should thus not be proposed in that setting before demonstration of their effects in adequately powered randomized placebo-controlled trials.

References

- 1 Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;30:54:S43–S54.
- 2 McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573–1619.
- 3 Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G: Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009;34:1219–1263.
- 4 Galiè N, Hoeper MM, Humbert M, et al: Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
- 5 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM: Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251–259.
- 6 Hogg K, Swedberg K, McMurray J: Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317–327.
- 7 Gabby E, Yeow W, Playford D: Pulmonary arterial hypertension is an uncommon cause of pulmonary hypertension in an unselected population: the Armadale Echocardiography Study. *Am J Respir Crit Care Med* 2007;175:A713.
- 8 Grundy SM, Brewer HB Jr, Cleeman Jr, et al: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–438.
- 9 Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
- 10 Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709–2716.
- 11 Dwyer EM, Asif M, Ippolito T, Gillespie M: Role of hypertension, diabetes, obesity, and race in the development of symptomatic myocardial dysfunction in a predominantly minority population with normal coronary arteries. *Am Heart J* 2000;139:297–304.
- 12 De las Fuentes L, Brown AL, Mathews SJ, Waggoner AD, Soto PF, Gropler RJ, Dávila-Román VG: Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. *Eur Heart J* 2007;28:553–559.
- 13 Zamanian RT, Hansmann G, Snook S, Lillienfeld D, Rappaport KM, Reaven GM, Rabinovitch M and Doyle RL: Insulin resistance in pulmonary arterial hypertension. *Eur Respir J* 2009;33:318–324.
- 14 Robbins IM, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX, Byrne DW: Association of the metabolic syndrome with pulmonary venous hypertension. *Chest* 2009;136:31–36.
- 15 Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G: Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.
- 16 Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong JJ, Billings C, Lawrie A, Sabroe I, Akil M, O'Toole L, Kiely DG: ASPIRE Registry: assessing the spectrum of pulmonary hypertension identified at a referral centre. *Eur Respir J* 2012;39:945–955.
- 17 Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL: How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539–2550.
- 18 Montani D, O'Callaghan S, Jaïs X, Savale L, Natali D, Redzepi A, Hoette S, Parent F, Sitbon O, Simonneau G, Humbert M: Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre. *Eur Respir J* 2009;18:272–290.
- 19 Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau G: Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111:3105–3111.
- 20 McMurray JJ, Carson PE, Komajda M, et al: Heart failure with preserved ejection fraction: clinical characteristics of 4,133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail* 2008;10:149–152.
- 21 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM: Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251–259.
- 22 Hogg K, Swedberg K, McMurray J: Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317–327.
- 23 Wai-Kwok YG, Frenneaux M, Sanderson JE: Heart failure with a normal ejection fraction: new developments. *Heart* 2009;95:1549–1552.
- 24 Maeder MT, Kaye DM: Heart failure with normal left ventricular ejection fraction. *J Am Coll Cardiol* 2009;53:905–918.
- 25 Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD: Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. *Chest* 2010;137:376–387.
- 26 Thenappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P, Rich S: Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2011;4:257–265.
- 27 Berger G, Hardak E, Obaid W, Shaham B, Carasso S, Kerner A, Yigla M, Azzam ZS: Characterization of pulmonary venous hypertension patients with reactive pulmonary hypertension as compared to proportional pulmonary hypertension. *Respiration* 2012;83:494–498.
- 28 Rifaie O, El-Damhory H, Amr M, Namas W: Prevalence and predictors of pulmonary hypertension in elderly patients with isolated diastolic heart failure. *Kardiol Pol* 2010;68:655–661.
- 29 Kawaguchi M, Hay I, Fetis B, et al: Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714–720.
- 30 Saito M, Okayama H, Nishimura K, et al: Possible link between large artery stiffness and coronary flow velocity reserve. *Heart* 2008;94:e20.

- 31 Leung CC, Moondra V, Catherwood E, Andrus BW: Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. *Am J Cardiol* 2010; 106:284–286.
- 32 Hosoda Y, Kawano K, Yamasawa F, Ishii T, Shibata T, Inayama S: Age-dependent changes of collagen and elastin content in human aorta and pulmonary artery. *Angiology* 1984;35:615–621.
- 33 Plank L, James J, Wagenvoort CA: Caliber and elastin content of the pulmonary trunk. *Arch Pathol Lab Med* 1980;104:238–241.
- 34 Harris P, Heath D, Apostolopoulos A: Extensibility of the human pulmonary trunk. *Br Heart J* 1965;27:651–659.
- 35 Mackay EH, Banks J, Sykes B, Lee G: Structural basis for the changing physical properties of human pulmonary vessels with age. *Thorax* 1978;33:335–344.
- 36 Lam CSP, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM: Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 2009;119:2663–2670.
- 37 Sibbald WJ, Paterson NA, Holliday RL, Anderson RA, Lobb TR, Duff JH: Pulmonary hypertension in sepsis: measurement by the pulmonary arterial diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. *Chest* 1978;73: 583–591.
- 38 Cozzi PJ, Hall JB, Schmidt GA: Pulmonary artery diastolic-occlusion pressure gradient is increased in acute pulmonary embolism. *Crit Care Med* 1995;23:1481–1484.
- 39 Kim NHS, Fesler P, Channick RN, Knowlton KU, Ben-Yehuda O, Lee SH, Naeije R, Rubin LJ: Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Circulation* 2004;109:18–22.