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Clinical phenotypes, right ventricular function, exercise pathophysiology and outcomes of pulmonary hypertension due to left heart disease

Role of the precapillary component

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in fulfilment of the requirements of the PhD Degree in Medical Sciences (ULB - "Docteur en Sciences Médicales") and in Public Health ([UNIMIB – "Dottore in Sanità Pubblica"])
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Clinical phenotypes, right ventricular function, exercise pathophysiology and outcomes of pulmonary hypertension due to left heart disease: role of the precapillary component

Standing on the shoulders of Giants

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PREFACE

This doctoral thesis is mainly composed of three articles I published as first author during the last years:

- Caravita S, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. PLoS One. 2018 Jun 19;13(6):e0199164

- Caravita S, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, Parati G, Bondue A, Vachiéry JL. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. Eur Respir J. 2018 Apr 4;51(4). pii: 1702427

- Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, Vachiéry JL. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. J Heart Lung Transplant. 2017 Jul;36(7):754-762

I tried to unify and harmonize them in this single manuscript since they are deeply interrelated. as the main focus of my research has been the clinical significance of the pre-capillary component in patients with pulmonary hypertension due to left heart disease.

Also part of the content of a review article for which I participated as a co-author is obviously embedded in this thesis manuscript:

- Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure. Circ Heart Fail. 2017 Sep;10(9). pii: e004082

All the above cited articles are included in the appendix of this thesis.

ABSTRACT (English)

Background. In pulmonary hypertension (PH), both post-capillary and pre-capillary pulmonary vascular alterations may affect right ventricular (RV) afterload, eventually contributing to exercise intolerance, RV failure and prognosis.

Objectives. To characterize the impact of pulmonary haemodynamics on the RV, exercise pathophysiology, and outcome in patients with PH.

Methods. We firstly conducted a retrospective analysis (2007-2014) at a PH referral Center, comparing patients with PH due to left heart disease (LHD) and treatment-naïve idiopathic/heritable pulmonary arterial hypertension (PAH, n=35). Patients with PH-LHD were further subdivided according to pulmonary haemodynamics in Isolated post-capillary PH (IpcPH: diastolic pressure gradient, DPG<7 mmHg and pulmonary vascular resistance, PVR≤3 WU, n=37), Combined post- and pre-capillary PH (CpcPH: DPG≥7 and PVR>3, n=27), and "indeterminate" PH-LHD (either DPG≥7 or PVR>3, n=29). We then conducted a meta-analysis on studies focusing on the association between pulmonary haemodynamics (PVR, DPG and pulmonary arterial compliance, Ca) and outcome in PH-LHD.

Results. Haemodynamic severity (pulmonary artery pressures, PVR, pulmonary vascular gradients), prevalence of echocardiographic signs of RV failure (RV dilation + dysfunction), and exercise hyperventilation linearly increased from IpcPH, to "indeterminate", CpcPH and PAH ($p<0.001$), while peak oxygen consumption and prevalence of exercise oscillatory ventilation showed an opposite behavior, being higher in IpcPH. Survival did not differ between PH-LHD and PAH; however, CpcPH had worse prognosis than IpcPH and PAH, but similar to "indeterminate" patients. In our retrospective cohort, NT-proBNP and Ca independently predicted survival in PH-LHD. In the meta-analysis, both Ca, PVR and DPG were associated with outcome in PH-LHD.

Conclusions. Haemodynamic characterization of PH-LHD according to DPG and PVR is associated with disease severity, exercise pathophysiology, predisposition to RV failure and prognosis. The CpcPH phenotype appear to have haemodynamic profile closer to PAH but with worse outcome. Ca, PVR and DPG are associated with survival in PH-LHD.

ABSTRACT (Français)

Contexte. Dans l'hypertension pulmonaire (PH), Les altérations vasculaires pulmonaires, qu'elles soient post- ou pré-capillaires, peuvent avoir un effet sur la post-charge du ventricule droit (RV), et contribuer ainsi à la réduction de la capacité d'exercice, à la défaillance du RV et au pronostic du patient.

Objectives. Nous avons voulu caractériser l'impact de l'hémodynamique pulmonaire sur le RV, la physiopathologie de l'exercice, et sur le pronostic des patients avec PH.

Méthodes. Nous avons d'abord effectué une analyse rétrospective (2007-2014) dans un centre de référence pour l'PH, en comparant des patients avec une PH lié à une maladie du cœur gauche (LHD) et des patients avec une hypertension artérielle pulmonaire (PAH, n=35) idiopathique ou héréditaire. Les patients avec une PH-LHD ont été subdivisés en fonction de l'hémodynamique pulmonaire en : PH post-capillaire isolée (IpcPH : gradient diastolique pulmonaire, DPG < 7 mmHg et résistance vasculaire pulmonaire, PVR≤3 UW, n=37), PH combinée post- et pré-capillaire (CpcPH : DPG≥7 et PVR>3, n=27), et PH-LHD « indéterminée » (DPG≥7 ou PVR>3, n=29). Par la suite, nous avons conduit une méta-analyse des études ayant évalué l'association entre l'hémodynamique pulmonaire (PVR, DPG et compliance de l'artère pulmonaire, Ca) et le pronostic des patients PH-LHD.

Résultats. La sévérité hémodynamique (pressions artérielles pulmonaires, PVR, gradients vasculaires pulmonaires), la prévalence des signes échocardiographiques de défaillance du RV (dilatation + dysfonction du RV) et l'hyperventilation à l'effort augmentaient de façon linéaire en passant de IpcPH, aux PH-LHD « indéterminés », jusqu'aux CpcPH et PAH ($p<0.001$), alors que la consommation d'oxygène au pic exercice et la prévalence des oscillations ventilatoires suivaient un comportement opposé, en étant les plus élevées chez les IpcPH. La survie n'était pas différente entre PH-LHD et PAH. Cependant, les patients CpcPH avait un pronostic plus

mauvais que les IpcPH et les PAH, mais similaire aux patients PH-LHD « indéterminés ». Dans notre cohorte rétrospective, NT-proBNP et Ca étaient associés de façon indépendante à la survie. Dans la méta-analyse, Ca, PVR et DPG étaient associés au pronostic chez les patients PH-LHD.

Conclusions. La caractérisation hémodynamique des patients PH-LHD en fonction du DPG et PVR est associée à la sévérité de la maladie, à la physiopathologie de l'exercice, au risque de défaillance du RV et au pronostic. Le phénotype CpcPH présente un profil hémodynamique proche de la PAH mais avec un plus mauvais pronostic. La Ca, la PVR et le DPG sont associés à la survie chez les patients PH-LHD.

ABSTRACT (Italiano)

Razionale. Nell'ipertensione polmonare (PH), alterazioni sia post- sia pre-capillari possono influire sul postcarico del ventricolo destro (RV), contribuendo alla limitazione della capacità di esercizio, alla disfunzione del RV e alla prognosi.

Obiettivi. Caratterizzare l'impatto dell'emodinamica polmonare sul RV, sulla fisiopatologia dell'esercizio e sulla prognosi in pazienti con PH.

Metodi. Abbiamo innanzitutto condotto una analisi retrospettiva (2007-2014) presso un centro di riferimento per PH, confrontando pazienti con PH secondaria a malattia del cuore sinistro (LHD) e pazienti con ipertensione arteriosa polmonare idiopatica/ereditaria (PAH, n=35). I pazienti con PH-LHD sono stati ulteriormente suddivisi in funzione dell'emodinamica polmonare in PH post-capillare isolata (IpcPH: gradiente diastolico polmonare, DPG<7 mmHg e resistenza vascolare polmonare, PVR≤3 UW, n=37), PH combinata post- e pre-capillare (CpcPH: DPG≥7 e PVR>3, n=27) e PH-LHD "indeterminata" (DPG≥7 o PVR>3, n=29). Abbiamo quindi condotto una meta-analisi su studi focalizzati sull'associazione tra l'emodinamica polmonare (PVR, DPG e compliance dell'arteria polmonare, Ca) e la sopravvivenza in PH-LHD.

Risultati. La severità emodinamica (pressioni arteriose polmonari, PVR, gradienti vascolari polmonari), la prevalenza di segni ecocardiografici di disfunzione del RV (dilatazione + disfunzione del RV), e l'iperventilazione da sforzo aumentavano linearmente da IpcPH a PH-LHD "indeterminati", CpcPH e PAH (p<0.001), mentre il consumo di ossigeno di picco e la prevalenza di oscillazioni ventilatorie durante esercizio mostrava un comportamento opposto, risultando più alta nei IpcPH. La sopravvivenza dei pazienti PH-LHD non era diversa da quella dei pazienti PAH; tuttavia, i pazienti CpcPH presentavano una prognosi peggiore dei pazienti IpcPH e dei pazienti PAH, ma simile ai pazienti PH-LHD "indeterminati". Nella nostra coorte retrospettiva, NT-proBNP e Ca risultavano associati in maniera indipendente alla sopravvivenza in PH-LHD.

Conclusioni. La caratterizzazione emodinamica dei pazienti PH-LHD in funzione di DPG e PVR è associata alla gravità di malattia, alla fisiopatologia dell'esercizio, alla predisposizione a disfunzione del RV e alla prognosi. Il fenotipo CpcPH sembra avere un profilo emodinamico simile alla PAH ma con una prognosi peggiore. Ca, PVR e DPG sono associate alla sopravvivenza in PH-LHD.

ABBREVIATIONS

ACE-I=angiotensin converting enzyme inhibitor

ARB=angiotensin receptor blocker

AT=anaerobic threshold

BP=blood pressure

Ca=Pulmonary Artery Compliance

CI=cardiac index

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration

CO=Cardiac Output

COPD=Chronic Obstructive Pulmonary Disease

CpcPH=Combined post- and pre-capillary Pulmonary Hypertension

CPET=cardiopulmonary exercise test

CRT-D=cardiac resynchronization therapy – defibrillator

DBP=diastolic blood pressure

DPG=Diastolic Pressure Gradient

EF=ejection fraction

eGFR=estimated glomerular filtration rate

EOB=Exercise Oscillatory Breathing

GOLD=Global Initiative for Obstructive Lung Disease

Hb=hemoglobin

HFpEF=heart failure with preserved ejection fraction

HFrEF=heart failure with reduced ejection fraction

HR=heart rate

ICD=implanted cardioverter defibrillator

IpcPH=Isolated post-capillary Pulmonary Hypertension

LAP=Left Atrial Pressure

LHD=Left Heart Disease

LV=left ventricle

MVV=maximal voluntary ventilation

NYHA=New York Heart Association

NTproBNP=N-terminal pro brain natriuretic peptide

O2=oxygen

O2p=oxygen pulse

OSAS=obstructive sleep apnea syndrome

PAH=Pulmonary Arterial Hypertension

PAP=Pulmonary Artery Pressure

PAWP=Pulmonary Artery Wedge Pressure

PetCO2=end-tidal pressure for carbon dioxide

PH=pulmonary hypertension

PVR=Pulmonary Vascular Resistance

RAP=right atrial pressure

RC=resistance compliance product

RVOT=right ventricular outflow tract

SaO2=arterial oxygen saturation

SBP=systolic blood pressure

SpO2=peripheral oxygen saturation

SV=stroke volume

SvO2=mixed venous oxygen saturation

TAPSE=Tricuspid Annular Plane Systolic Excursion

TPG=Transpulmonary Pressure Gradient

TR=tricuspid regurgitation

RER=respiratory exchange ratio

RV=Right Ventricle

RVSWI=Right Ventricular Stroke Work Index

VCO2=carbon dioxide production

VE=minute ventilation

VO2=oxygen consumption

INTRODUCTION

Post-capillary pulmonary hypertension (PH) is a frequent complication of left heart disease (LHD). In the majority of cases, the increase in pulmonary artery pressure (PAP) is explained by passive backward transmission of high filling pressure from the left chambers of heart to the pulmonary circulation, defining isolated post-capillary PH (IpcPH). However, in a minority of patients a pre-capillary component is superposed on a post-capillary PH [1-3].

How to define this pre-capillary component, as well as the clinical implications of such definition, have been object of intense debate in recent years [1-4]. In particular, pathophysiological arguments, histological demonstrations and prognostic instances has been advanced to propose, defend or refuse the significance of distinct haemodynamic parameters [2].

This debate grew since 2013, when the diastolic pressure gradient (DPG) was revived and advocated as a suitable candidate to describe the presence and extent of a pre-capillary component, based on physiological arguments [5], further supported by clinical, histopathological and prognostic evidences [6].

As illustrated in figure 1,

DPG = diastolic PAP – PAWP,

where PAWP is pulmonary artery wedge pressure, which approximates left atrial pressure (LAP).

Normally, the DPG should be in the range 0-3 mmHg, with an upper limit of normal at 5 mmHg derived from historical series. Adopting a cautious approach for a small number, it was proposed to consider as “abnormal” a DPG ≥ 7 mmHg [1,2,5,7]. In the context of PH-LHD a high DPG stands for an increase of PAP which is not uniquely due to backward PAWP transmission to the pulmonary circulation (hence the difference between diastolic PAP and PAWP). Interestingly, patients with PH-LHD and a pre-capillary component, defined by a DPG ≥ 7 mmHg were found

to have some degree of pulmonary arteriolar remodeling at histological analysis, resembling pulmonary arterial hypertension (PAH) [6].

From a physiological perspective, the DPG was advanced to present distinct advantages as compared to the transpulmonary pressure gradient (TPG) and to the pulmonary vascular resistance (PVR).

TPG = mean PAP – PAWP

PVR = TPG / CO

where CO is cardiac output.

Indeed, as compared to the TPG, the DPG is less flow- and PAWP- dependent [5], as show in figure 2. This is extremely important, since patients with PH-LHD may often present with low flow (low CO) and high PAWP, leading to high TPG (and potentially high PVR) despite normal DPG.

Nevertheless, the prognostic discrimination offered by the DPG was not uniformly confirmed [6,8-16], and many retrospective patients' series reported a significant proportion (up to 30%) of negative DPGs [2]. This is deemed to be physiologically implausible, but might mainly reflect the lack of standardization in the measure of PAWP (mean PAWP vs mid-A PAWP vs QRS-gated "diastolic" PAWP), that may become extremely important when either mitral regurgitation or left atrial overdistension with loss of atrial compliance occur [17]. Moreover, technical limitations and interpretations drawbacks can occur also for diastolic PAP determination [2,4,17]

These are reasons why other variables, such as the PVR or the pulmonary arterial compliance (Ca) were then proposed as haemodynamic markers of disease severity [2,3,7].

The PVR has the undoubtable advantage to have been widely utilized in clinical practice and since long time, physician in charge of patients with PH or LHD being familial with it. It is a quite robust variable, resisting through decades as a haemodynamic marker of disease severity.

The PVR corrects the TPG for flow; however, it is not uncommon for patients with PH-LHD, low CO and high PVR, to normalize or near normalize haemodynamics when increasing CO by means of inotropes or systemic vasodilators [2]. At the same time, the incorporation in a single variable of a marker of cardiac performance (CO), and of the pulmonary circulation (mean PAP - PAWP), might concur to explain why it has been repeatedly associated with survival in PH-LHD [10,16,18-20].

Ca has been proposed more recently in this specific setting. The simplified formula used to estimate it overestimate the real compliance by 60 to 80% [2]. However, it repeatedly proved to predict outcome in LHD [16,18-20], and even in the absence of PH [21].

Given these uncertainties and ongoing debates on the definition and the clinical and prognostic implications of the presence of a pre-capillary component in PH-LHD, we decided to perform the research that constitute my PhD thesis, and whose results have been published within 3 articles [4,22-23].

In particular, we retrospectively analyzed the clinical characteristics of patients with PH-LHD according to the presence or absence of a pre-capillary component, using patients with idiopathic or heritable pulmonary arterial hypertension (PAH, i.e. patients with a pre-capillary PH due to a “true” pulmonary vascular disease) as a comparator. In doing this, we focused on the relationship between pulmonary haemodynamics and right ventricular (RV) function, the cardiorespiratory adaptation to exercise, and survival.

Then, to substantiate and complete our results, we conducted a meta-analysis of available studies on the prognostic role of haemodynamics in PH-LHD, restricting our field to those where

DPG or PVR or Ca were rigorously considered to be or not to be associated with survival in univariate and/or multivariate analysis.

METHODS

1) Retrospective data analysis, Erasme cohort

The study had been approved by the Ethics Committee of the Erasme Hospital (ref. n. P2015/359). In agreement with Belgian laws and with local Ethics committee, informed consent was not required according to the retrospective nature of the study. None of the patients had denied the use for research purposes of anonymized data collected in routine clinical practice at an academic hospital.

We retrospectively compared patients with PH undergoing a first elective assessment in stable clinical conditions at the Pulmonary Hypertension and Heart Failure Clinic of the Erasme Hospital between January 2007 and October 2014. Clinical indication for right heart catheterization was given according to international guidelines [7,24]. PH was defined and classified according to ESC/ERS guidelines [7]. In particular, PH was defined by a mean PAP ≥ 25 mmHg. Distinction between pre-capillary and post-capillary PH was made based on a PAWP ≤ or > 15 mmHg, respectively [7]. We first compared patients with PH-LHD versus patients with idiopathic or heritable PAH naïf of specific therapy. Then, we subdivided PH-LHD in:

- IpcPH, if DPG < 7 mmHg and PVR ≤ 3 WU
- CpcPH, if DPG ≥ 7 mmHg and PVR > 3 WU
- "intermediate" PH-LHD, if either DPG < 7 mmHg or PVR < 3 WU

We kept for the analysis only patients with complete haemodynamic data and not presenting severe lung disease as a comorbid condition, such as chronic obstructive pulmonary disease (COPD) in Global Initiative for Chronic Obstructive Lung Disease (GOLD) class 4, severe interstitial lung disease. Glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Chronic thromboembolic PH was ruled out in all patients by a combination of clinical history, lung scintigraphy, computed tomography of the chest, pulmonary haemodynamics.

Haemodynamics

All right heart catheterizations were performed and reviewed by a cardiologist expert in PH. The transducer was zeroed at the midthoracic line in a supine patient, halfway between the anterior sternum and the bed surface [7]. Pulmonary artery pressures were measured at end-expiration and averaged over several cardiac cycles (5 to 8). PAWP was measured by a single expert reader at mid-A wave, as it more closely approximates left ventricular end-diastolic pressure [17]. Cardiac output was measured by thermodilution in triplicate (using an average of three measurements within 10% of agreement). DPG was calculated as the difference between diastolic PAP and PAWP [1,2,7]. PVR was calculated as (mean PAP – PAWP) / cardiac output [2,7]. Ca was estimated as the ratio between stroke volume and pulmonary arterial pulse pressure, and the resistance-compliance product (RC-time) as the product of Ca and PVR, and expressed in seconds [2].

The right ventricle and right ventricular function

Right ventricular (RV) enlargement was defined as a ratio between right ventricle and left ventricle >1 [7]. Reduced RV systolic function was qualified as a fractional area change ≤ 35% [25,26] by an experienced cardiologist blinded to invasive haemodynamics. Validation was then performed on a sample of 74 subjects by an independent observer who recalculated fractional

area change. RV dysfunction was defined as a combination of reduced RV systolic function and RV enlargement, i.e. as a failing of the homeometric adaptation of the RV faced to an increased afterload [27]. Tricuspid annular plane systolic excursion (TAPSE) was measured according to current recommendations [25,26]. Also, the ratio between TAPSE and systolic PAP was calculated, as a possible surrogate index of RV to pulmonary artery coupling [8]. We kept in the analysis only the echocardiographic examinations which had been performed between 90 days before and one week after right heart catheterization, given that there were no significant changes in treatment between echocardiography and invasive haemodynamic assessment.

RV stroke work index (RVSWI), an index of RV workload, was calculated as (mean PAP – right atrial pressure) * (cardiac index / heart rate) * 0.0136.

The ratio between right atrial pressure and PAWP was used as a haemodynamic surrogate of RV dysfunction [28].

Cardiopulmonary exercise test

All cardiopulmonary exercise tests (CPET) has been performed on an electromagnetically braked cycle ergometer, with the patient connected to the VMAX Metabolic Cart (SensorMedics, Yorba Linda, CA, USA) through a mask. After a 3-minutes warm-up period (unloaded pedaling), a 1-minute step-increase protocol (5 to 10 W/min) had been performed in order to achieve exhaustion in about 10 minutes [29]. An average of the last 30-second period of exercise was taken as peak value for the variables of interest. Ventilatory threshold was calculated by the V-slope method and confirmed by the analysis of the end-tidal pressures plot and the ventilatory equivalents plot by two independent operators. The regression slope of minute ventilation over carbon dioxide production (VE/VCO2 slope) was calculated over the linear component of VE versus VCO2 [29]. Exercise oscillatory breathing (EOB) was defined as cyclic fluctuations in VE at

rest that persist during effort lasting > or = 60% of the exercise duration, with an amplitude > or = 15% of the average resting value [30].

We kept for CPET analysis only patients with complete haemodynamic data, who had a CPET within 7 days from right heart catheterization. Patients with a respiratory exchange ratio at peak exercise < 1.00 were discarded.

Statistics

Descriptive data are reported as mean±standard deviation for continuous variable and as absolute numbers and percentages for categorical variables. Distribution of variables in terms of proximity to normal curve and the homogeneity of variances were detected by Shapiro-Wilk test and Bartlett test, respectively. When needed, either a logarithmic or box-cox transformation was performed to achieve normal distribution. ANOVA with “a posteriori contrasts” was used for variables normally distributed and homoscedastic; otherwise ANOVA “on ranks” was performed. For multiple comparisons, the algorithm which controls the expected rate of false-positive results for all positive results (false discovery rate) was used [31]. Linear dependence between prevalence of RV dysfunction and TAPSE/systolic PAP on one side, and PVR, DPG and Ca on the other side, was evaluated with Pearson correlation coefficient. Pearson's Chi-squared contingency table test or Fisher Exact test for count data has been used to analyze categorical variables, as necessary.

Estimates of the survival probability were calculated using the Kaplan-Meier method, and the log rank test was employed to test the null hypothesis of equality in overall survival among groups. Univariate and multivariate Cox regression models were calculated to examine factors associated with adverse outcomes. Predictors in the multiple Cox model were selected from the set of variables that reached statistical significance in univariate analysis, by a stepwise procedure with the significance limit set to 0.05, taking care to avoid the simultaneous inclusion

of collinear variables. The proportional-hazards assumption was tested using Schoelfeld residuals, with $p<0.05$ evidence for non-proportionality. Results were expressed as hazard ratios with 95% confidence intervals.

The regression analysis between both diastolic pressure gradient and PVR vs end-tidal pressure for carbon dioxide (PetCO2) at the anaerobic threshold was performed using the ordinary least-squares method, while vs VE/VCO2 slope and VE/VCO2 at the anaerobic threshold was performed using a robust regression with MM-type estimator [32,33]. Pearson's Chi-squared contingency table test has been used to analyze categorical variables; the p-value was computed for a Monte Carlo test [34] with 2000 replicates when needed.

An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using R Core Team (2016), Vienna, Austria.

2) Meta-analysis

Identification of articles

We conducted a Medline literature research according to PRISMA recommendations [35] on articles published between 2013, when the diastolic pressure gradient (DPG) was introduced as a possible marker of the pre-capillary component in PH-LHD [5], and November 2017. We used the following combinations of search terms (“pulmonary hypertension” OR “heart failure” OR “left heart disease”) AND (“prognosis” OR “outcome” OR “outcomes” OR “survival”) AND (“pulmonary vascular resistance” OR “diastolic pressure gradient” OR “diastolic pressure difference” OR “diastolic pulmonary gradient” OR “diastolic pulmonary vascular pressure gradient” OR “pulmonary artery compliance” OR “hemodynamics”). We only considered papers in which DPG and/or PVR and/or Ca were analysed for their capability to predict survival in PH-

LHD. We excluded articles reporting composite outcome, those focusing only on outcome after heart transplantation, evaluating short-term follow-up, or including unstable patients.

Statistics

We pooled the original estimates by using both the fixed-effects model and the random-effects model. Heterogeneity between study-specific estimates was tested using the Q statistic and I2 index. When a significant heterogeneity was found (Q statistic p-value <0.05), the results from the random-effects model were presented. To evaluate publication bias, the "trim and fill" method was used [36]. This is an extension of the funnel plot technique, where "missing studies" are identified and estimated based on the symmetry of the funnel plot [37].

RESULTS

1) Retrospective data analysis, Erasme Hospital cohort

From January 2007 to October 2014, 548 patients underwent right heart catheterization. Patients with group 3-5 PH, associated PAH, congenital heart disease, veno-occlusive disease, patients with mean PAP < 25 mmHg as well as patients undergoing right heart catheterization in unstable clinical conditions were discarded from analysis. Thus, one hundred and twenty-eight patients met the inclusion criteria, consisting in 93 patients with PH-LHD and 35 idiopathic/heritable PAH (figure 3).

The subdivision of PH-LHD according to the haemodynamic classification is depicted in table 1.

General characteristics

Table 2 summarizes the general characteristics of the study population. Pooled together, PH-LHD were heavier than PAH patients, and presented with slightly lower glomerular filtration

rate. New York Heart Association (NYHA) class and N-terminal pro brain natriuretic peptide (NTproBNP) levels did not differ between the two groups.

When further subdividing PH-LHD in IpcPH, intermediate and CpcPH, general characteristics were similar in the three groups, although CpcPH presented with slightly higher weight and body mass index than intermediate patients ($p<0.05$).

The underlying causes of PH-LHD were similar between the three groups, with heart failure with preserved ejection fraction being the leading etiology, followed by heart failure with reduced ejection fraction and a small number of patients with valvular heart disease (table 3). Patients with heart failure and a reduced ejection fraction were more likely treated with drugs acting on the renin-angiotensin-aldosterone system and with beta-blockers as compared with patients with a preserved ejection fraction ($p<0.01$), while diuretics prescription was similar among subgroups. Known obstructive sleep apnea was not represented in the "intermediate" group. The remaining spectrum of comorbidities, as well as background treatment, did not differ between the three subgroups (table 3). COPD GOLD 2 was diagnosed in 3 PAH, 3 CpcPH, 1 "intermediate", 1 IpcPH patients, while COPD GOLD 3 only in 2 IpcPH patients.

Haemodynamics

The haemodynamic profile was more disturbed in PAH patients (higher pulmonary pressures, gradients and PVR, and lower Ca and cardiac index) as compared with PH-LHD (table 4).

When further subdividing PH-LHD, we found that the severity of the haemodynamic profile (pulmonary pressures, pulmonary gradients and PVR) stepwisely increased from IpcPH to intermediate to CpcPH to PAH (table 4). However, diastolic and mean pulmonary pressure did not significantly differ when comparing CpcPH and PAH ($p=0.308$ and $p=0.052$, respectively), and Ca was similar between CpcPH and intermediate patients ($p=0.169$). There was no significant

difference in PAWP and cardiac index across the three subgroups of PH-LHD, although PAWP was slightly higher and stroke volume slightly lower in intermediate patients compared with IpcPH (p=0.053 and p=0.063, respectively). All patients but one in the intermediate group had PVR > 3 WU and DPG < 7 mmHg. When subdividing patients according to left ventricular ejection fraction, we could not find any difference in the principal haemodynamic variables except in cardiac index, which resulted lower in patients with a reduced than in those with a normal left ventricular ejection fraction (1.9±0.4 vs 2.5±0.6, p<0.01).

Effect of the DPG on the PVR-Ca relationship

Figure 4A depicts the Log(PVR) – Log(Ca) as a function of PAWP and DPG. PH-LHD with low DPG, PH-LHD with high DPG and PAH all presented with a similar slope of the Log(PVR)-Log(Ca) regression relationship, but with different intercepts, so that the slope of PH-LHD with high DPG lied in between PH-LHD with low DPG and PAH. The relation between RC-time and PAWP across the three different conditions was not linear as it would have been expected, with PH-LHD with high DPG presenting with higher RC-time than PH-LHD with a low DPG for a nearly identical PAWP (Figure 4B).

RV afterload and RV dysfunction

Eighty-three percent of echocardiography had been performed within 72 hours from right heart catheterization, 91% within 1 week and 97% between 1 month and a few days after right heart catheterization. Mean and median time span between right heart catheterization and echocardiography was -4 ±12 days and -1 (-78 to +6) days, respectively. Thus, a minimal data set from echocardiography was available in 119 over 128 patients.

RV enlargement was more prevalent in PAH than in PH-LHD patients. Moreover, RV enlargement became progressively more frequent passing from IpcPH to “intermediate” PH-LHD to CpcPH to PAH (table 5).

Echocardiographic signs of reduced RV systolic function were more represented in PAH as compared with PH-LHD (table 5). However, the prevalence RV dysfunction showed a crescendo from IpcPH to “intermediate” to CpcPH to PAH patients ($p<0.001$). Mean PVR and mean DPG of each haemodynamic subgroup resulted highly correlated with the prevalence of RV dysfunction (figure 5), while the relation between RV dysfunction and Ca was not linear.

A similar pattern of correlation was found between the same haemodynamic variables on one side and the ratio between right atrial pressure and PAWP (figure 6).

TAPSE, which was available in 80% of cases, did not significantly differ between groups, while the ratio between TAPSE and systolic PAP progressively decreased from IpcPH to “intermediate” PH-LHD to CpcPH to PAH (table 5). TAPSE/systolic PAP resulted highly correlated with Ca but not with DPG and PVR (figure 7).

Cardiopulmonary exercise test

Seventy patients (55% of the whole cohort; 20 IpcPH, 10 “intermediate” PH, 11 CpcPH and 29 PAH) had a CPET was performed on average 1.3 ± 0.8 days before or after right heart catheterization. CPET results are reported in table 6.

Oxygen consumption (VO2) at peak exercise was lower in PAH than in patients with IpcPH both when expressed as a percentage of predicted values and as absolute values, but not when weight- normalized ($p<0.05$).

At rest, peripheral oxygen saturation (SpO2) was lower in CpcPH and in PAH than in IpcPH ($p<0.05$), but only PAH patients developed a real exercise-induced desaturation, with lower

SpO2 values than all the PH-LHD subgroups both at the anaerobic threshold ($p<0.05$) and at peak exercise ($p<0.01$).

At rest, patients with CpcPH presented with intermediate values of PetCO2 when compared with the other two PH-LHD subgroups and PAH ($p<0.05$). Such difference persisted also at the anaerobic threshold (figure 8) but not at peak exercise, where IpcPH and CpcPH had similar PetCO2 values, which were overall higher ($p<0.001$) than in PAH patients.

At rest, the VE/VCO2 was higher in PAH than in IpcPH ($p=0.001$) and in "intermediate" PH-LHD ($p=0.06$) but not different between CpcPH and PAH ($p=0.183$). VE/VCO2 ratio at the anaerobic threshold, as well as the VE/VCO2 slope, were lower in IpcPH and in "intermediate" PH-LHD, intermediate in CpcPH and higher in PAH patients (figure 3). At peak exercise, the VE/VCO2 was higher ($p<0.01$) in PAH than in patients with PH-LHD.

The prevalence of EOB increased ($P<0.001$) from PAH (absence of EOB) to CpcPH (18%) and "intermediate" PH-LHD (20%) to IpcPH (50%).

Correlations between ventilatory response to exercise and resting haemodynamics

Across the whole population, both DPG and PVR directly correlated to the VE/VCO2 slope ($R2=0.48$ and $R2=0.43$ respectively, $p<0.001$), to the VE/VCO2 at anaerobic threshold ($R2=0.42$ and $R2=0.44$ respectively, $p<0.001$, figure 9), and inversely correlated to PetCO2 at anaerobic threshold ($R2=0.48$ and $R2=0.49$ respectively, $p<0.001$).

Outcome predictors in PH-LHD

Follow-up data were available for 115 patients (90%). There were 36 deaths (31%) over a median follow up of 26 months (25th and 75th percentile: 11 and 46 months).

At univariate analysis, glomerular filtration rate, NTproBNP, echocardiographic signs of RV dysfunction, diastolic, mean and systolic pulmonary pressures, as well as PVR and Ca were independent predictors of mortality (table 7). However, at multivariate analysis, only NTproBNP and Ca maintained their prognostic power (table 7).

Survival was similar in PH-LHD and PAH (figure 10A). However, subgrouping PH-LHD according to DPG and PVR revealed a worse prognosis in CpcPH as compared both with IpcPH and PAH. Survival was similar in CpcPH and in "intermediate" patients (figure 10B). There were 14 events (56%) in the CpcPH population, 11 events (31%) in the PAH population, 7 events (30%) in the "intermediate" population, and 4 events (13%) in the IpcPH population.

When testing the capability of DPG, TPG, PVR and Ca to predict mortality by ROC curves analysis, we did not find significant differences between the four haemodynamic variables, with area under the curve in between 69 and 75% (figure 11a). Compared with the optimal cut-off value of ≥3 mmHg, a DPG of ≥7 mmHg was associated with increased (79%) specificity at the expenses of lower (47%) sensitivity (figure 11b).

Meta-analysis

PRISMA flow diagram is shown in figure 12a.

Out of 32 articles, 10 responded to the pre-specified criteria [6,8,10,15,16,18-20,38,39]. Analysis of the different populations revealed heterogeneity in terms of age, gender and aetiology of PH-LHD, as detailed in table 8.

These articles considered DPG, PVR and Ca as continuous or dichotomous variables. For purpose of consistency, and to better individuate the risk associated with each variable, independently of arbitrary cut-offs, we only included those that reported the prognostic power of variables intended in a continuous way. The final analysis was thus conducted on six articles [6,10,16,18-

20], including 2513 patients with LHD overall, followed up for 9−15 years. In four studies, all patients had PH [6,10,16,18], while in the remaining two articles at least two-thirds of patients had PH [19,20]. In the majority of the studies, a multivariate analysis was performed, adjusting the hazard ratios associated with PVR, DPG and Ca for covariates such as age and sex [6,10,18,19], body mass index [10,19], ethnicity [18,10], and also for comorbidities [6,20] and other haemodynamic parameters [18,19].

Mean age was 60 years old, with mean values varying between 49 and 69 years old across the studies. Younger ages were more represented in heart failure with reduced ejection fraction (HFrEF) cohorts while older ages were found in cohorts of heart failure with preserved ejection fraction (HFpEF) or valvular heart disease. Male sex prevalence varied between 25 and 79%. HFpEF was the leading aetiology in 3 studies [6,16,18], while valvular heart disease was the leading aetiology or a significant comorbidity (present in up to 30% of patients) in three studies [6,16,20]. In these latter studies, it is possible that right heart catheterisation has been performed in some patients as a pre-therapeutic assessment, although this has not been systematically reported by the authors. Neither symptoms (e.g. New York Heart Association functional class) nor concomitant relevant pathological conditions were consistently reported in all studies.

Mean pulmonary artery pressure was on average 35 mmHg, mean PVR 3.0 WU, mean DPG was 1.2 mmHg (this latter derived from five studies [6,10,16,18,19]) and mean Ca 2.5 mL/mmHg (derived from four studies [16,18-20]). Mean PVR was >3 WU in three studies [16,18,20], mean DPG was <7 mmHg in all studies, while mean Ca was <2.3 mL/mmHg in two studies [16,18]. Based on mean±sd values, there is a high suspicion of a significant proportion of negative DPGs, at least in five out of six studies [6,10,16,18-19].

Forest plots analysis for survival according to DPG, PVR and Ca are depicted in figure 12b. Increasing values of PVR and DPG were associated with higher risk of death in PH-LHD, while increasing values of Ca were associated with lower risk. Results did not change when performing a sensitivity analysis including only the four studies in which all patients had PH [6,10,16,18]. Some suggestions of presence of publication bias come from the results obtained from the "trim and fill" method. The summary estimates coming from this method are very similar to the summary original estimates for each outcome, even if the summary estimates of DPG and Ca were not statistically significant. Nevertheless, the paucity of included studies puts caution in interpreting the results obtained by the "trim and fill" method [37].

DISCUSSION

Our studies, taken together, highlight several aspects of PH-LHD. In particular, haemodynamic phenotyping of PH-LHD adds to the clinical characterization of this cohort. It provides markers of disease severity with distinct pathophysiological correlates, both in terms of right heart function and ventilatory adaptation to exercise, as well as prognostic implications.

Haemodynamic severity, right heart remodeling and ventilator adaptation to exercise in PH-LHD

Our population reflects current knowledge: PH, whichever its cause, is associated with poor functional status (high NYHA class), significant neurohumoral activation (high NT-proBNP levels) and poor outcomes [7,40]. Importantly, the haemodynamic impact of PH seemed to be largely independent of LHD etiology and of background treatment, with few differences in haemodynamic parameters between heart failure with preserved and heart failure with reduced ejection fraction. Moreover, survival of PH-LHD was not different from PAH.

However, further subdividing PH-LHD according to DPG and PVR allowed the discrimination of a subgroup of patients that may present a milder form of PH (namely IpcPH) as opposed to “intermediate” patients and to CpcPH. Indeed, in spite of minimal differences in general patients' characteristics, the haemodynamic profile of the three PH-LHD subgroups diverged significantly: haemodynamic severity increased stepwisely from IpcPH to “intermediate” to CpcPH, so that this latter resulted closer to PAH. Such haemodynamic differences were somehow paralleled by a stepwise increase in RV dimensions and RV workload, suggesting that they could be maladaptive, negatively impacting on the RV.

Additionally, haemodynamics severity was mirrored on the ventilatory adaptation to exercise. In particular, in the subgroup of patients undergone CPET within a week from right heart catheterization, we could observe two main findings. Firstly, the degree of exercise hyperventilation was quite fairly and directly correlated with haemodynamic markers of a pre-capillary component, increasing in a stepwise fashion from IpcPH and “intermediate” PH-LHD, to CpcPH, to PAH. Secondly, EOB displayed an opposite behavior, with an exceptionally high prevalence in IpcPH, being absent in PAH, and with an in-between prevalence in “intermediate” PH-LHD and CpcPH patients. All this occurred with minimal differences in exercise capacity, which was on average slightly better in IpcPH and slightly worse in PAH.

Many factors have been proposed to explain excessive exercise-induced hyperventilation in heart failure and in pulmonary hypertension [41-50], with a plausibly prominent role of neural reflex pathways [50,51].

Stimulation of stretch receptors in the right heart chambers (Bainbridge reflex) [52], might be called into question to contribute to our results, either directly or via interaction with the chemoreflex. This may be supported in our population by echocardiographic findings (RV dilation) as well as by the ratio between right and left filling pressures, which was higher in PAH,

intermediate in CpcPH and lower in IpcPH, somehow mirroring the afterload imposed by the different conditions on the right heart. Despite a progressive increase of right ventricular afterload from IpcPH, to "intermediate" PH-LHD, to CpcPH, to PAH, exercise capacity was not strikingly different between the different groups: only PAH patients showed a pattern consistent with a more impaired stroke volume (O2 pulse) rise than PH-LHD [29,53], which was somehow partly counterbalanced by a less decreased heart rate reserve. But a similar stroke volume response to exercise in conditions characterized by progressively increasing afterload at rest may imply that Starling's heterometric adaptation [27] might become more prominent when passing from IpcPH to CpcPH to PAH, further supporting of a role for right heart chambers stretch in driving the ventilatory response to exercise in these subpopulations [45].

Interestingly, EOB decreased its prevalence in PH-LHD patients with high PVR and/or high DPG. As recently reported, EOB is generally not found in PAH [54], reinforcing the concept that increased pulmonary wedge pressure should play a major role in the development of Cheyne-Stokes and oscillatory respiration [55,56], over sympathetic dysregulation and peripheral reflexes [57]. In our population as well as in other studies [8], however, pulmonary wedge pressure was similar in the subgroup of patients with PH-LHD at rest, and there is no reason to suspect that it may behave differently during exercise [58]. We may thus speculate that the pre-capillary component in PH-LHD might exert a sort of upstream "protective" barrier limiting the afferent input implicated in the genesis of oscillatory ventilation (J-receptors) [59]. Alternatively, the same reflex mechanism underlying exercise-induced hyperventilation might centrally interact with chemoreflex in such a way to leftward shift the CO2 threshold [57], thus overriding and stabilizing oscillations.

Haemodynamic phenotyping and the effect of DPG on PVR-Ca relationship

Noteworthy, the degree of PAP, pulmonary vascular gradients and PVR elevation resulted largely independent of PAWP when comparing IpcPH and CpcPH, reinforcing the idea that there might be an additional mechanism at pulmonary arterial level that may explain the precapillary component in CpcPH [6,15,60]. Interestingly, "intermediate" patients, i.e. predominantly those patients with an isolated elevation of PVR, presented with a slightly higher PAWP and a slightly lower stroke volume than IpcPH, suggesting that in this specific case the increase in PAP and transpulmonary gradient might be partly explained by low flow and by the exaggerated amplification of left-sided filling pressures [5].

In this perspective, our data seem to support the pathophysiological reasoning suggesting that the DPG may be a marker of the pre-capillary component [6,15,60]. Increasing the DPG in PH-LHD led to a rightward and upward shift of the PVR-Ca relationship, so that patients with PH-LHD and high DPG lied in between PAH and patients with PH-LHD with low DPG, consistently with a previous report [8], and supporting a distinct pulmonary vascular phenotype in CpcPH [15]. Moreover, patients with high DPG presented also with higher PVR than "intermediate" PH-LHD patients.

Haemodynamics and prognosis

Haemodynamic predictors of prognosis in LHD may be influenced by the study characteristics (single center vs multicentric), the methodology (univocally standardized haemodynamic assessment with review of single traces vs utilization of protocol data), the characteristics of the referral center (mainly heart failure vs mainly PH center) as well as of the population (heart failure pre-transplant, reduced or preserved left ventricular ejection fraction, valvular heart disease, cardiomyopathies, PH). All these factors may explain at least in part the different and sometimes contrasting results obtained in recent years by several groups [6,8,10,15,16,18, 20,39,61-64]. In this context, our own data seem to confirm that the milder haemodynamic

profile of IpcPH (low DPG, low PVR) is mirrored by an overall lower prevalence of RV dysfunction, and a clearly overall better prognosis than the other PH-LHD patients [8]. As such, despite several differences in haemodynamics, we may be tempted to pool CpcPH and "intermediate" all together in saying that when patients with PH-LHD have high PVR, their prognosis is dismal [7,10,20] (acknowledging that high DPG with low PVR in PH-LHD appears to be extremely uncommon [65]). In this perspective, the current guidelines subdivision of PH-LHD in two rather than three groups might be sufficient [16]. Anyway, it is also interesting to point out that in a contemporary PH population, newly diagnosed PAH had overall better survival than patients with PH-LHD and a pre-capillary component. This on one side may confirm that approved and currently prescribed treatment in PAH referral centers had impacted the outcome of this condition [7], at the same time reinforcing the need for further research efforts in order to better understand and possibly improve prognosis of the subgroups of PH-LHD at higher risk [66].

Our meta-analysis may reconcile contrasting theories and evidences on which parameter(s) to define a pre-capillary component and/or to predict prognosis in PH-LHD. In particular, pooling together data from more than 2500 PH-LHD patients, heterogeneous in terms of age, aetiology, proportion of negative DPGs and haemodynamic presentation, our meta-analysis shows that both DPG, PVR and Ca are associated with prognosis. The DPG is a small number, whose unitary increase carries a small increase in risk, in the order of 2%. The unitary increase in PVR is associated with 9% increase in risk of adverse outcome. At variance, a unitary increase in Ca is associated with better outcome and 27% risk reduction.

We may speculate that these variables should be viewed as complementary and may be used in combination as an intrinsic control. Which combination of variables would best be used to predict outcome remains a matter of debate.

CONCLUSIONS

PH-LHD embodies a broad spectrum of haemodynamic presentations. The presence of a precapillary component, defined by a DPG >= 7 mmHg and/or PVR > 3 WU is associated with adverse right heart remodeling, distinct ventilatory adaptation to exercise and a worse prognosis as compared with patients with low DPG and low PVR. Ca and NT-proBNP may better predict outcome than other clinical and haemodynamic variables suggesting that characterization of patients with PH-LHD should probably incorporate further elements, probably in combination, including RV function. Collaborative study should be encouraged in order to provide a more precise characterization of patients with PH-LHD at high risk, that may help improving the current haemodynamic definition.

REFERENCES

1. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D100-8
2. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure. Circ Heart Fail. 2017 Sep;10(9). pii: e004082
3. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J. 2018 Dec 13. pii: 1801897
4. Caravita S, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, Parati G, Bondue A, Vachiéry JL. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. Eur Respir J. 2018 Apr 4;51(4). pii: 1702427
5. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J. 2013 Jan;41(1):217-23
6. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013 Mar;143(3):758-766
7. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119

8. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM. Pulmonary Hypertension in Heart Failure. Epidemiology, Right Ventricular Function, and Survival. Am J Respir Crit Care Med. 2015 Nov 15;192(10):1234-46
9. Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, Leary PJ, Kass DA, Shah AS. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. J Heart Lung Transplant. 2014 Mar;33(3):289-97
10. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, Russell SD, Kasper EK, Tedford RJ. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Heart Fail. 2015 Jan;3(1):9-16
11. Naeije R. Measurement to predict survival: the case of diastolic pulmonary gradient. JACC Heart Fail. 2015 May;3(5):425.
12. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, Bonderman D. Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2016 Jul 12;68(2):189-99
13. Zotter-Tufaro C, Duca F, Kammerlander AA, Koell B, Aschauer S, Dalos D, Mascherbauer J, Bonderman D. Diastolic Pressure Gradient Predicts Outcome in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2015 Sep 15;66(11):1308-1310

14. Nagy AI, Venkateshvaran A, Merkely B, Lund LH, Manouras A. Determinants and prognostic implications of the negative diastolic pulmonary pressure gradient in patients with pulmonary hypertension due to left heart disease. Eur J Heart Fail. 2017 Jan;19(1):88-97
15. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension. J Am Coll Cardiol. 2016 Dec 13;68(23):2525-2536
16. Palazzini M, Dardi F, Manes A, Bacchi Reggiani ML, Gotti E, Rinaldi A, Albini A, Monti E, Galiè N. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes. Eur J Heart Fail. 2018 Feb;20(2):248-255
17. Houston BA, Tedford RJ. What We Talk About When We Talk About the Wedge Pressure. Circ Heart Fail. 2017 Sep;10(9). pii: e004450
18. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015 Jun;3(6):467-474
19. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N, Aronson D. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. Eur J Heart Fail. 2015 Jan;17(1):74-80
20. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail. 2013 Aug;1(4):290-299

21. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, Dini FL, Temporelli PL, Vassanelli C, Vanderpool R, Naeije R, Ghio S. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. Chest. 2014 May;145(5):1064-1070
22. Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, Vachiéry JL. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. J Heart Lung Transplant. 2017 Jul;36(7):754-762
23. Caravita S, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. PLoS One. 2018 Jun 19;13(6):e0199164
24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-2200
25. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. 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. J Am Soc Echocardiogr. 2010 Jul;23(7):685-713

26. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39.e14
27. Sagawa K, Maughan L, Suga H, Sunagawa K. Cardiac Contraction and the Pressure-Volume Relationship. New York: Oxford University Press, 1988
28. Drazner MH, Velez-Martinez M, Ayers C, Reimold SC, Thibodeau JT, Mishkin JD, Mammen PP, Markham DW, Patel CB. Relationship of Right- to Left-Ventricular Filling Pressures in Advanced Heart Failure: Insights from the ESCAPE Trial. Circulation Circ Heart Fail. 2013;6(2):264–70
29. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005
30. Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest 2002;121:1572-80
31. Benjamini Y and Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Statist Soc B 1995;57:289-300
32. Yohai VJ. High Breakdown-Point and High Efficiency Robust Estimates for Regression. Ann Statist 1987;15:642-56
33. Koller M, Stahel WA. Sharpening wald-type inference in robust regression for small samples. Computational Statistics & Data Analysis 2011;55:2504-15
34. Hope AC. A Simplified Monte Carlo Test Procedure. J R Statist Soc B 1968;30:582-8

35. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097
36. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000 Jun;56(2):455-63
37. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis: techniques and a guide for the academic surgeon. Ann Cardiothorac Surg. 2015 Mar;4(2):112-22
38. Brunner NW, Yue SF, Stub D, Ye J, Cheung A, Leipsic J, Lauck S, Dvir D, Perlman G, Htun N, Fahmy P, Prakash R, Eng L, Ong K, Tsang M, Cairns JA, Webb JG, Wood DA. et al. The prognostic importance of the diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance in patients undergoing transcatheter aortic valve replacement. Cath Cardiovasc Interv 2017; 90: 1185–1191
39. O'Sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, Spitzer E, Zanchin T, Praz F, Tüller D, Huber C, Pilgrim T, Nietlispach F, Khattab AA, Carrel T, Meier B, Windecker S, Buellesfeld L. Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification. Circ Cardiovasc Interv. 2015;8(7):e002358
40. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942–54
41. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilator efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail 2008;1:227-33

42. Guazzi M, Cahalin LP, Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. J Card Fail 2013;19:461-7
43. Taylor BJ, Smetana MR, Frantz RP, Johnson BD. Submaximal exercise pulmonary gas exchange in left heart disease patients with different forms of pulmonary hypertension. J Card Fail 2015;21:647-55
44. Chua TP, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity and the ventilator response to exercise in chronic heart failure. J Am Coll Cardiol. 1996;27:650-7
45. Jones PW, Huszczuk A, Wasserman K. Cardiac output as a controller of ventilation through changes in right ventricular load. J Appl Physiol Respir Environ Exerc Physiol 1982;53:218-24
46. Theodore J, Robin ED, Morris AJ, Burke CM, Jamieson SW, Van Kessel A, Stinson EB, Shumway NE. Augmented ventilatory response to exercise in pulmonary hypertension. Chest 1986;89:39-44
47. Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE, Wasserman K. A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension. Chest 2001;119:824-32
48. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. Circulation 1997;96:2221–7
49. Otulana B, Higenbottam T. The role of physiological deadspace and shunt in the gas exchange of patients with pulmonary hypertension: a study of exercise and prostacyclin infusion. Eur Respir J 1988;1:732-7

50. Weatherald J, Sattler C, Garcia G, Laveneziana P. Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. Eur Respir J. 2018 Feb 7;51(2). pii: 1700860
51. Farina S, Bruno N, Agalbato C, Contini M, Cassandro R, Elia D, Harari S, Agostoni P. Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. Int J Cardiol. 2018 May 15;259:178-182
52. Ciarka A, Vachièry JL, Houssière A, et al. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. Chest 2007;131:1831-7
53. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A, Bogaard HJ. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. Am J Respir Crit Care Med 2015;191:1050-7
54. Vicenzi M, Deboeck G, Faoro V, Loison J, Vachiéry JL, Naeije R. Exercise Oscillatory Ventilation In Pulmonary Arterial Hypertension Versus Heart Failure. Int J Cardiol 2016;202;736-40
55. Murphy RM, Shah RV, Malhotra R, Pappagianopoulos PP, Hough SS, Systrom DM, Semigran MJ, Lewis GD. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. Circulation 2011;124:1442-51
56. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999;99:1574-9
57. Caravita S, Faini A, Lombardi C, Valentini M, Gregorini F, Rossi J, Meriggi P, Di Rienzo M, Bilo G, Agostoni P, Parati G. Sex and acetazolamide effects on chemoreflex and periodic breathing during sleep at altitude. Chest 2015;147:120-31

58. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3(5):588-95
59. Roberts AM, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JC. Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. Circ Res. 1986;58:512-22
60. Gerges C, Gerges M, Fesler P, Pistritto AM, Konowitz NP, Jakowitsch J, Celermajer DS, Lang IM. In-depth haemodynamic phenotyping of pulmonary hypertension due to left heart disease. Eur Respir J. 2018 May 24;51(5). pii: 1800067
61. Chatterjee NA, Lewis GD. Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: limitations of a solitary measurement. JACC Heart Fail. 2015;3(1):17–21
62. Brittain EL, Assad TR, Hemnes AR, Newman JH. The Diastolic Pressure Gradient Does Not-and Should Not-Predict Outcomes. JACC Heart Fail. 2015;3(10):845
63. Tampakakis E, Tedford RJ. Reply: characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: the conundrum of high and low diastolic pulmonary gradient. JACC Heart Fail. 2015;3(5):426–7
64. Tampakakis E, Tedford RJ. Balancing the positives and negatives of the diastolic pulmonary gradient. Eur J Heart Fail. 2017;19(1):98–100
65. Gerges M, Gerges C, Lang IM. How to define pulmonary hypertension due to left heart disease. Eur Respir J 2016; 48(2):553–5
66. Hoeper MM, Lam CS, Vachiery JL, Bauersachs J, Gerges C, Lang IM, Bonderman D, Olsson KM, Gibbs JSR, Dorfmuller P, Guazzi M, Galiè N, Manes A, Handoko ML, Vonk-Noordegraaf A, Lankeit M, Konstantinides S, Wachter R, Opitz C, Rosenkranz S. Pulmonary hypertension in heart failure with preserved ejection fraction: a plea for proper phenotyping and further research†. Eur Heart J. 2017;38:2869–2873

TABLES

PH-LHD N=93		*DPG (mmHg)*	
		< 7	≥ 7
PVR (WU)	≤ 3	*IpcPH N=37*	*Intermediate N=1*
	> 3	*Intermediate N=28*	*CpcPH N=27*

Table 1. Patients' subdivision according to the haemodynamic classification of pulmonary hypertension due to left heart disease. CpcPH=combined post- and pre-capillary pulmonary hypertension; DPG=diastolic pressure gradient; IpcPH=isolated post-capillary pulmonary hypertension; PH-LHD=pulmonary hypertension due to left heart disease; PVR=pulmonary vascular resistance.

	PAH n=35	PH-LHD N=93	CpcPH n=27	Interm n=29	IpcPH n=37	P value, overall
Demographics & anthropometrics						
Females, n (%)	19 (54%)	51 (55%)	14 (52%)	16 (55%)	21 (57%)	0.984
Age (years)	57±16	64±13	64±14	67±13	62±13	0.075
Height (cm)	165±10	166±10	168±10	166±10	165±9	0.560
Weight (Kg)	71±14	79±17	85±16	75±17	79±17	**0.005**
BMI (Kg/m^2)	26±5	29±5	30±5	27±4	29±6	**0.010**
NYHA class						0.372
I-II	7 (20%)	29 (31%)	8 (30%)	7 (24%)	14 (38%)	
III-IV	28 (80%)	64 (69%)	19 (70%)	22 (76%)	23 (62%)	
Blood tests						
Creatinine (mg/dL)	1.1±0.4	1.4±0.7	1.4±0.6	1.5±0.9	1.3±0.6	0.148
eGFR (mL/min/1.73m^2)	70±24	59±25	58±25	55±26	63±25	0.056
Sodium (mmoL/L)	141±3	141±4	141±3	140±4	141±4	0.829
NT-proBNP (pg/mL)	2930±3002	3685±6936	4136±3845	5034±11573	2214±2126	0.211

Table 2. Patients' general characteristics. BMI=body mass index; CpcPH=combined post- and pre-capillary pulmonary hypertension; eGFR=estimated glomerular filtration rate; Interm=intermediate; IpcPH=Isolated post-capillary pulmonary hypertension; NYHA=New York Heart Association; NT-proBNP=N-terminal pro Brain Natriuretic Peptide; PAH=pulmonary arterial hypertension; RV=right ventricle.

	IpcPH n=37	Interm n=29	CpcPH n=27	p-value
Etiology of left heart failure				0.210
HFpEF, n (%)	19 (51%)	13 (45%)	17 (63%)	
Valvular heart disease, n (%)	0 (0%)	3 (10%)	2 (7%)	
HFrEF, n (%)	18 (49%)	13 (45%)	8 (30%)	
Comorbidities				
Ischemic heart disease, n (%)	13 (35%)	14 (48%)	5 (19%)	0.064
Diabetes Mellitus, n (%)	14 (41%)	10 (35%)	10 (37%)	0.956
Arterial Hypertension, n (%)	19 (51%)	17 (59%)	18 (67%)	0.470
Dyslipidemia, n (%)	17 (46%)	19 (66%)	11 (41%)	0.139
Obesity, n (%)	15 (41%)	8 (28%)	12 (44%)	0.384
Permanent atrial fibrillation, n (%)	4 (11%)	6 (21%)	4 (15%)	0.538
Smoking habits, n (%)	16 (43%)	13 (45%)	11 (41%)	0.953
Chronic obstructive pulmonary disease, n (%)	3 (8%)	1 (3%)	3 (11%)	0.380
Known and treated OSAS, n (%)	7 (19%)	0 (0%)	6 (22%)	0.024
Treatment				
Diuretics	28 (76%)	26 (90%)	22 (82%)	0.360
ACE-I or ARBs	27 (73%)	24 (83%)	19 (70%)	0.515
Beta-blockers	26 (70%)	24 (83%)	19 (70%)	0.446
Spironolactone	18 (49%)	12 (41%)	7 (26%)	0.182
Digoxin	5 (14%)	3 (10%)	4 (15%)	0.857
Amiodaron	7 (19%)	7 (24%)	6 (22%)	0.872
Anticoagulant	12 (32%)	13 (45%)	9 (33%)	0.536
Antiplatelet	19 (51%)	12 (41%)	10 (37%)	0.491
Insulin	6 (22%)	7 (24%)	7 (19%)	0.872
O2 therapy	4 (15%)	0 (0%)	2 (5%)	0.081
CRT-D	7 (19%)	5 (17%)	0 (0%)	0.363
ICD	5 (13%)	2 (7%)	1 (4%)	0.371

Table 3. Clinical characteristics of patients with pulmonary hypertension secondary to left heart disease. ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; CpcPH=combined post- and pre-capillary pulmonary hypertension; CRT-D=cardiac resynchronization therapy – defibrillator; HFpEF=heart

failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; Interm=intermediate; IpcPH=isolated post-capillary pulmonary hypertension; ICD=implanted cardioverter defibrillator; O2=oxygen; OSAS=obstructive sleep apnea syndrome.

	PAH n=35	PH-LHD n=93	CpcPH n=27	Interm n=29	IpcPH n=37	ANOVA
HR (bpm)	79±15	71±13	74±13	71±14	69±13	**0.017**
BP (mmHg)						
Systolic	126±18	130±30	131±31	137±31	123±28	0.183
Diastolic	79±12	72±14	74±16	74±13	67±11	**0.002**
Mean	95±12	91±17	94±18	95±17	86±14	**0.037**
PAP (mmHg)						
Systolic	86±17	61±18	76±16	63±16	48±8	**<0.001**
Diastolic	37±8	28±8	35±7	28±6	23±4	**<0.001**
Mean	53±11	39±10	49±9	39±8	31±5	**<0.001**
PAWP (mmHg)	10±4	23±5	24±6	25±6	22±4	**<0.001**
RAP (mmHg)	8±5	13±6	14±6	13±6	11±5	**<0.001**
RAP/PAWP	0.88±0.46	0.54±0.21	0.60±0.22	0.54±0.21	0.50±0.21	**<0.001**
SaO2 (%)	92±4	96±3	94±5	97±3	97±3	**<0.001**
SvO2 (%)	59±10	63±8	60±7	64±8	64±8	**0.005**
SV (mL)	45±14	59±19	58±21	54±14	64±20	**<0.001**
CI (L/min/m^2)	1.9±0.4	2.2±0.6	2.3±0.5	2.1±0.6	2.2±0.7	**0.041**
TPG (mmHg)	44±11	16±8	25±8	15±5	10±3	**<0.001**
DPG (mmHg)	27±9	5±5	11±5	3±2	1±2	**<0.001**
PVR (WU)	13±4	4±3	7±4	4±1	2±1	**<0.001**
Ca (mL/mmHg)	0.9±0.3	2.1±1.1	1.5±0.6	1.8±1.3	2.7±0.9	**<0.001**
RC-time (s)	0.69±0.13	0.41±0.13	0.51±0.08	0.40±0.16	0.35±0.07	**<0.001**

Table 4. Patients' invasive haemodynamic profile. BP=systemic blood pressure; CI=cardiac index; CpcPH=combined post- and pre-capillary pulmonary hypertension; DPG=diastolic pressure gradient; Interm=intermediate; IpcPH=isolated post-capillary pulmonary hypertension; PAH=pulmonary arterial hypertension; PAP=pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure; RC-time=resistance-compliance product; SV=stroke volume; TPG=transpulmonary pressure gradient; SaO2=arterial oxygen saturation; SvO2=mixed venous oxygen saturation.

	PAH	PH-LHD	CpcPH	Interm	IpcPH	p value, overall
RVOT, proximal (mm)	37±6	32±6	36±7	30±6	31±6	**<0.001**
RV/LV≥1	82%	51%	69%	39%	46%	**0.001**
Reduced RV systolic function	79%	47%	52%	45%	38%	**0.005**
TAPSE (mm)	15±4	18±6	18±5	17±5	19±7	0.083
TAPSE/sPAP (mm/mmHg)	0.18±0.07	0.32±0.14	0.25±0.08	0.29±0.11	0.40±0.16	**<0.001**
TR > than moderate, n (%)	9 (30)	14 (21)	5 (24)	7 (30)	4 (17)	0.703
RVSWI (g/m^2/beat)	15.6±5.3	11.3±5.1	14.1±5.8	10.7±4.8	9.8±4.1	**<0.001**

Table 5. Right ventricular function in the different haemodynamic subgroups. CpcPH=combined post- and pre-capillary pulmonary hypertension; Intem="intermediate PH-LHD"; IpcPH=isolated post-capillary pulmonary hypertension; LV=left ventricle; PAH=pulmonary arterial hypertension; PH-LHD=pulmonary hypertension due to left heart disease; sPAP=systolic pulmonary artery pressure; RV=right ventricle; RVOT=right ventricular outflow tract; RVSWI=right ventricular stroke work index; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation.

		PAH n=29	CpcPH n=11	Interm n=10	IpcPH n=20	Overall
REST	*VE (L/min)*	16 ± 5	14 ± 3	13 ± 4	12 ± 3	**0.012**
	SpO2 (%)	93 ± 5	95 ± 4	97 ± 3	98 ± 1	**<0.001**
	PetCO2 (mmHg)	25 ± 5	29 ± 5	33 ± 3	33 ± 4	**<0.001**
	VE/VCO2	54 ± 13	48 ± 8	45 ± 5	42 ± 7	**0.001**
	VE/VO2	47 ± 12	43 ± 9	40 ± 5	38 ± 8	**0.017**
	HR (bpm)	84 ± 17	77 ± 12	69 ± 12	72 ± 14	**0.009**
	SBP (mmHg)	117 ± 23	131 ± 37	129 ± 36	125 ± 27	0.466
	DBP (mmHg)	85 ± 13	72 ± 11	70 ± 16	76 ± 18	**0.020**
AT	*Identifiable, n (%)*	29 (100)	9 (82)	8 (80)	17 (85)	1.000
	VE (L/min)	26 ± 8	25 ± 4	22 ± 8	24 ± 4	0.631
	SpO2 (%)	91 ± 5	95 ± 3	96 ± 4	97 ± 1	**<0.001**
	PetCO2	24 ± 5	29 ± 5	33 ± 3	35 ± 5	**<0.001**
	VE/VCO2	52 ± 12	43 ± 8	38 ± 4	35 ± 5	**<0.001**
	VE/VO2	49 ± 11	40 ± 9	37 ± 5	33 ± 6	**<0.001**
	HR (bpm)	98 ± 18	94 ± 11	85 ± 18	91 ± 14	0.216
	O2 p (mL/beat)	5.6 ± 1.8	7.1 ± 1.8	7.4 ± 3.7	8.5 ± 2.7	**0.002**
	VO2 (L/min)	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.3	0.8 ± 0.2	**0.017**
	VO2 (mL/Kg/min)	7.7 ± 2.6	8.2 ± 1.9	8.3 ± 5.5	10.1 ± 2.5	**0.013**
PEAK	*VE (L/min)*	61 ± 19	47 ± 12	40 ± 11	53 ± 14	**0.002**
	SpO2 (%)	88 ± 7	94 ± 4	95 ± 3	96 ± 3	**<0.001**
	PetCO2	20 ± 6	27 ± 5	30 ± 5	30 ± 5	**<0.001**
	VE/VCO2	64 ± 21	45 ± 12	40 ± 7	38 ± 7	**<0.001**
	VE/MVV, %	68 ± 17	63 ± 15	59 ± 11	58 ± 12	0.111
	MVV - VE	33 ± 23	28 ± 17	30 ± 17	39 ± 16	0.550
	HR (bpm)	130 ± 28	115 ± 18	97 ± 21	113 ± 24	**0.004**
	HR (% max pred)	79 ± 13	75 ± 10	74 ± 16	71 ± 15	**0.018**
	O2 p (mL/beat)	6.9 ± 2.2	8.6 ± 2.8	9.4 ± 3.8	11.0 ± 4.2	**<0.001**
	Workload (W)	51 ± 25	51 ± 22	46 ± 26	73 ± 30	**0.015**
	VO2 (L/min)	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.4	1.2 ± 0.5	**0.029**
	VO2 (mL/min)	12.5 ± 4.5	11.7 ± 2.7	12.3 ± 1.8	15.7 ± 5.5	0.063
	VO2 (% pred)	48 ± 16	61 ± 27	52 ± 15	70 ± 31	**0.019**
	RER	1.16 ± 0.06	1.12 ± 0.09	1.15 ± 0.08	1.19 ± 0.08	0.108
	SBP (mmHg)	147 ± 26	150 ± 43	141 ± 35	149 ± 37	0.917
	DBP (mmHg)	96 ± 13	85 ± 11	79 ± 17	85 ± 16	**0.007**
	VE/VCO2 slope	53 ± 16	41 ± 11	31 ± 5	33 ± 5	**<0.001**
	EOB, %	0	18	20	50	**<0.001**

Table 6. Cardiopulmonary exercise test in the three groups of patients. AT=anaerobic threshold; CpcPH=combined post- and pre-capillary pulmonary hypertension; DBP=diastolic blood pressure; EOB=exercise oscillatory breathing; HR=heart rate; IpcPH=isolated post-capillary pulmonary hypertension; MVV=maximal voluntary ventilation; O2p=oxygen pulse; PAH=pulmonary arterial hypertension; PetCO2=end tidal partial pressure for carbon dioxide; RER=respiratory exchange ratio; RR=respiratory rate; SBP=systolic blood pressure; SpO2=peripheral oxygen saturation; VE=minute ventilation; VO2=oxygen consumption; VCO2=carbon dioxide production; Vt=tidal volume.

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Clinical parameters				
Age, years	1.016 (0.986-1.046)	0.302		
Male sex	1.501 (0.740-3.047)	0.260		
BMI, Kg/m^2	0.959 (0.894-1.028)	0.236		
NYHA III-IV	0.772 (0.356-1.672)	0.511		
Ischemic aetiology	0.982 (0.479-2.014)	0.960		
Atrial fibrillation	1.137 (0.437-2.960)	0.793		
Diabetes mellitus	1.504 (0.720-3.139)	0.277		
Smoking history	0.954 (0.474-1.919)	0.895		
Heart rate, beats/min	1.021 (0.994-1.048)	0.134		
Laboratory parameters				
Hb, g/dL	0.937 (0.805-1.091)	0.403		
GFR, mL/min/1.73 m^2	**0.979 (0.964-0.993)**	**0.004**		
proBNP > 1400 pg/mL	**4.768 (1.662-13.678)**	**0.004**	**5.066 (1.751-14.660)**	**0.003**
Echocardiographic variables				
Reduced LV EF	0.915 (0.435-1.927)	0.816		
RV dysfunction	**2.242 (1.095-4.592)**	**0.027**		
TAPSE/sPAP ≤ 0.35	**1.565 (0.514-4.767)**	**0.430**		
Haemodynamic variables				
mPAP, mmHg	**1.034 (1.003-1.066)**	**0.030**		
sPAP, mmHg	**1.018 (1.000-1.037)**	**0.050**		
dPAP, mmHg	**1.044 (1.003-1.088)**	**0.036**		
PAWP, mmHg	1.051 (0.984-1.123)	0.136		
RAP, mmHg	1.011 (0.955-1.070)	0.709		
RAP/PAWP	0.706 (0.146-3.399)	0.664		
DPG, mmHg	1.049 (0.993-1.108)	0.088		
TPG, mmHg	1.037 (0.999-1.077)	0.058		
CI, L/min/m^2	0.941 (0.526-1.686)	0.839		
RVSWI, g/m^2/beat	1.037 (0.975-1.103)	0.246		
PVR, WU	**1.130 (1.016-1.256)**	**0.024**		
Ca, mL/mmHg	**0.602 (0.391-0.926)**	**0.021**	**0.509 (0.298-0.872)**	**0.014**

Table 7. Univariate and multivariate predictors of survival in pulmonary hypertension due to left heart disease. BMI=body mass index; Ca=pulmonary arterial compliance; CI=cardiac index; DPG=diastolic pressure gradient; GFR=estimated glomerular filtration rate; Hb=haemoglobin; LV EF=left ventricular ejection fraction; NTproBNP=N terminal pro Brain Natriuretic Peptide;

NYHA=New York Heart Association; dPAP=diastolic pulmonary artery pressure; mPAP=mean pulmonary artery pressure; sPAP=systolic pulmonary artery pressure; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure; RV=right ventricle; TPG=transpulmonary pressure gradient.

Author	Year	Country	Lenght of study, years	PH-LHD, n	Age, years	Males	pEF	rEF	VHD	Variables, univariate	Variables, multivariate	Covariates in multivariate analysis
Miller[20]	2013	USA	8.5	337	57±13	79%	0%	100%	Significant VHD ≥ 1/3 of patient (comorbidity)	Ca bin	PVR bin Ca cont	Risk factors different among the groups at baseline and clinically important factors
Gerges[6]	2013	Austria	15	1094	63±13	61%	≈55%	≈45%	Significant VHD ≥ 1/3 of patient (comorbidity)		DPG cont	Sex, age, GFR <60, CAD
Al-Naamani[18]	2015	USA	9.8	73	69±12	26%	100%	0%		DPG cont DPG bin PVR cont	Ca cont	Age, sex, ethnicity, BMI, haemodynamic parameters
Tampakakis[10]	2015	USA	11	469	49	74%					DPG cont PVR cont	Age, gender, race, BMI
O'Sullivan[39]	2015	Switz.	6.3	269	83±5	42%			100%		DPG bin	Age, sex, BMI, DM, previous CABG, PVD, previous MI, CAD, LVEF ≤30%, COPD
Dragu[19]	2015	Israel	>9	264	66±12	45%	76%	24%		PVR cont		
Gerges[8]	2015	Austria	17	668	63±12	67%	38%	62%			DPG bin	Sex, age, GFR <60, CAD
Assad[15]	2016	USA	18	1361	60±14	56%			Significant VHD ≥ 8% of patient (comorbidity)	DPG bin	DPG cont	Age, sex, BMI, COPD, ILD, OSA, CAD, AF, VHD, lupus, scleroderma
Palazzini[16]	2017	Italy	18	276	69 (60-75)	25%	41%	9%	50%	DPG cont DPG bin PVR cont PVR bin Ca cont Ca bin.		
Brunner[38]	2017	Canada	10	133	80±8	53%			100%		DPG bin PVR bin	Age, sex, BMI, PASP at echo

Table 8. Studies meeting inclusion criteria for meta-analysis. AF=atrial fibrillation; bin.=binary; BMI= body mass index; Ca=pulmonary arterial compliance; CABG=coronary artery by-pass grafting; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; cont.=continuous; DPG=diastolic pressure gradient; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; ILD=interstitial lung disease; LHD=left heart disease; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NTproBNP=N-terminal pro brain natriuretic peptide; pEF=preserved ejection fraction; OSA=obstructive sleep apnea; rEF=reduced ejection fraction; PASP=pulmonary artery systolic pressure; PH=pulmonary hypertension; PVD=pulmonary vascular disease; PVR=pulmonary vascular resistance; RV=right ventricle; VHD=valvular heart disease

FIGURES

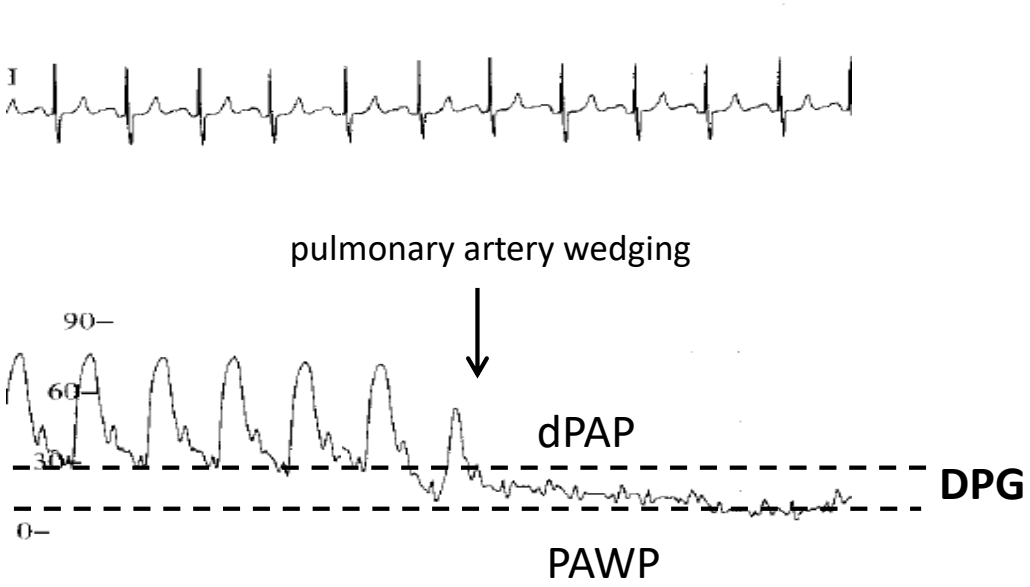

Figure 1. Graphical representation of the diastolic pressure gradient (DPG), i.e. the difference between diastolic pulmonary artery pressure (dPAP) and pulmonary artery wedge pressure (PAWP).

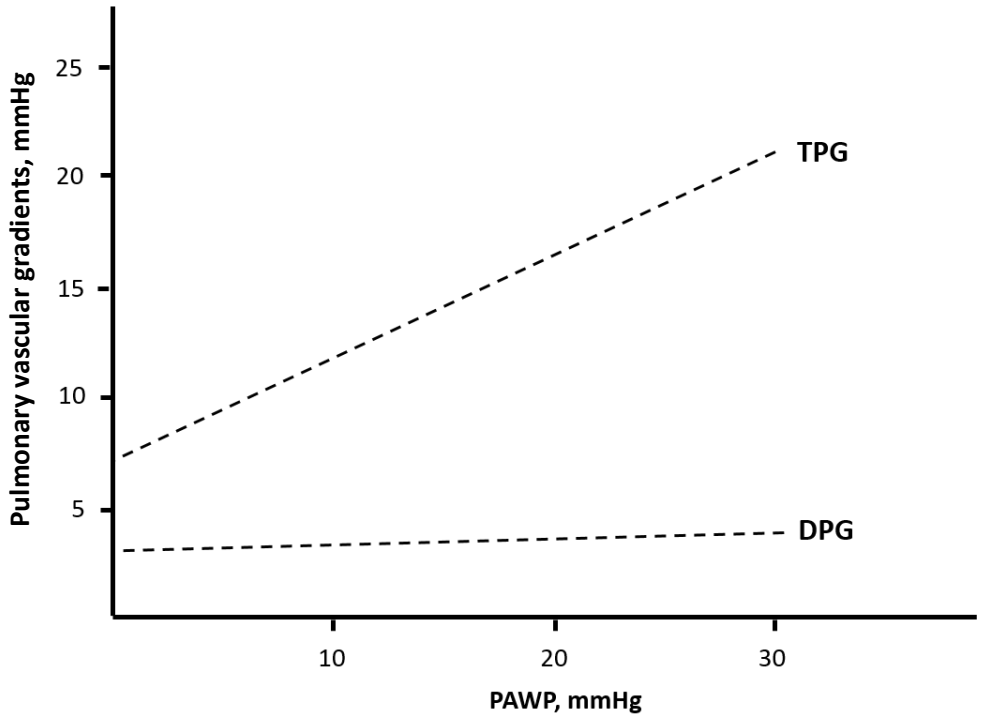

Figure 2. Exemplificative relationship between pulmonary vascular gradients (the transpulmonary gradient, TPG, and the diastolic pressure gradient, DPG) and the pulmonary artery wedge pressure (PAWP). The DPG is more stable than the TPG when PAWP increases.

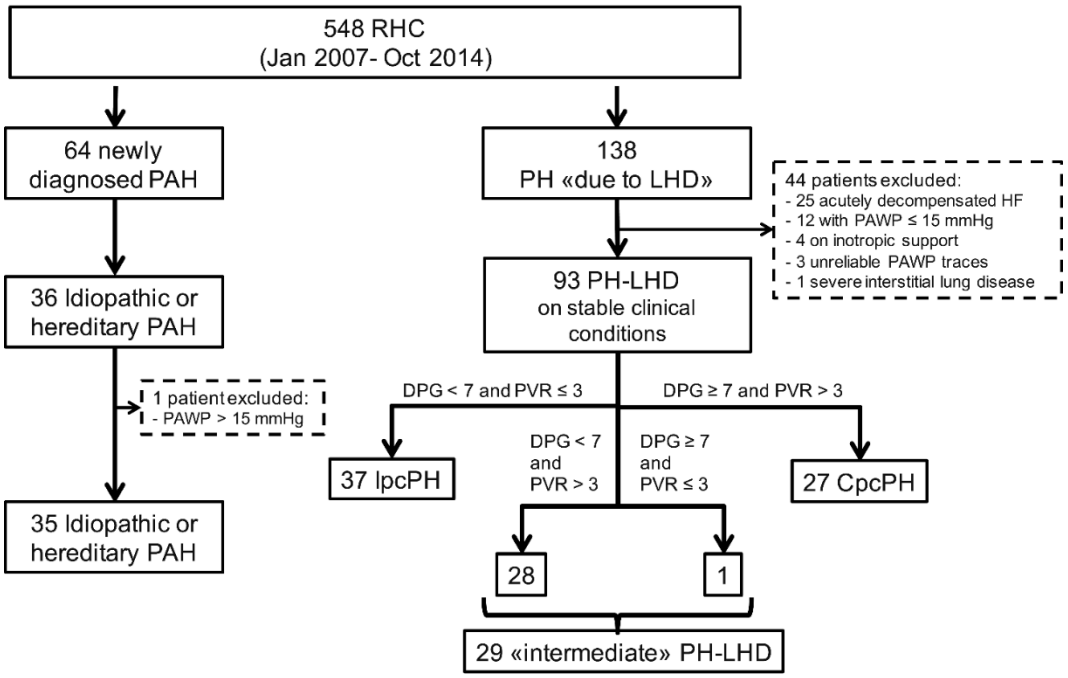

Figure 3. Patients disposition according to the study protocol and haemodynamic definitions. CpcPH=Combined post- and pre-capillary Pulmonary Hypertension; DPG=diastolic pressure gradient; HF=heart failure; IpcPH=Isolated post-capillary Pulmonary Hypertension; LHD=left heart disease; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; RHC=right heart catheterization.

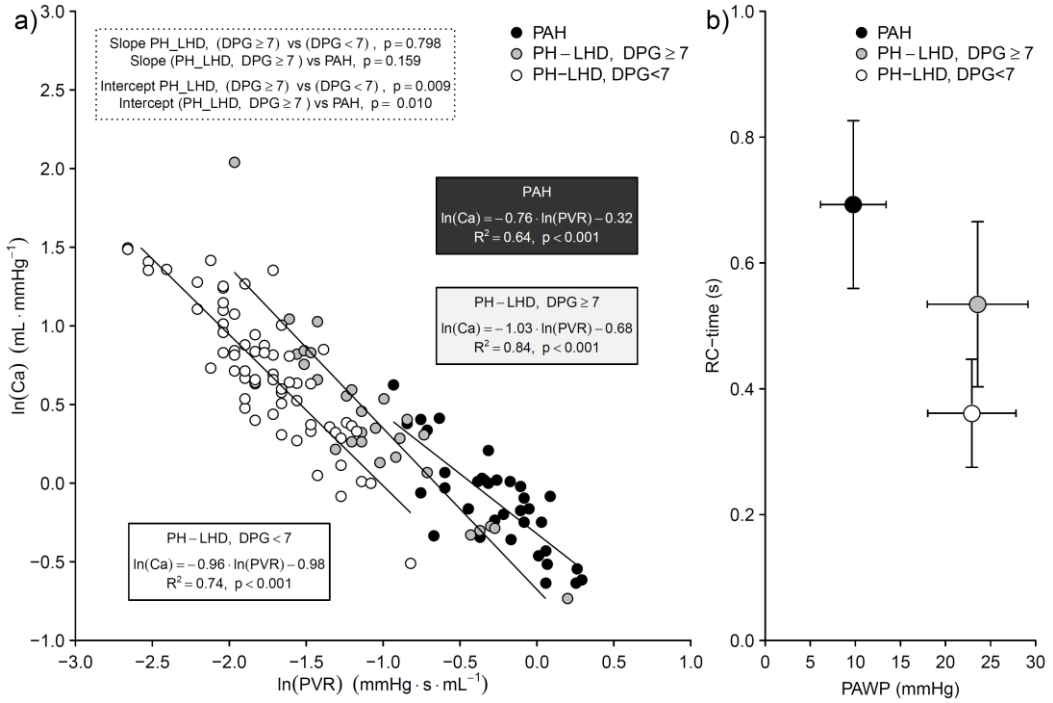

Figure 4. Effects of varying the diastolic pressure gradient and pulmonary artery wedge pressure on the compliance-resistance relationship in patients with pulmonary hypertension. Panel a): pulmonary arterial compliance as a function of pulmonary vascular resistance, both logarithmically transformed. Panel b): resistance-compliance product as a function of pulmonary artery wedge pressure. Ca=pulmonary arterial compliance; DPG=diastolic pressure gradient; PAH=pulmonary arterial hypertension; PH-LHD=pulmonary hypertension due to left heart disease; PVR=pulmonary vascular resistance; RC-time=pulmonary vascular resistance-compliance product.

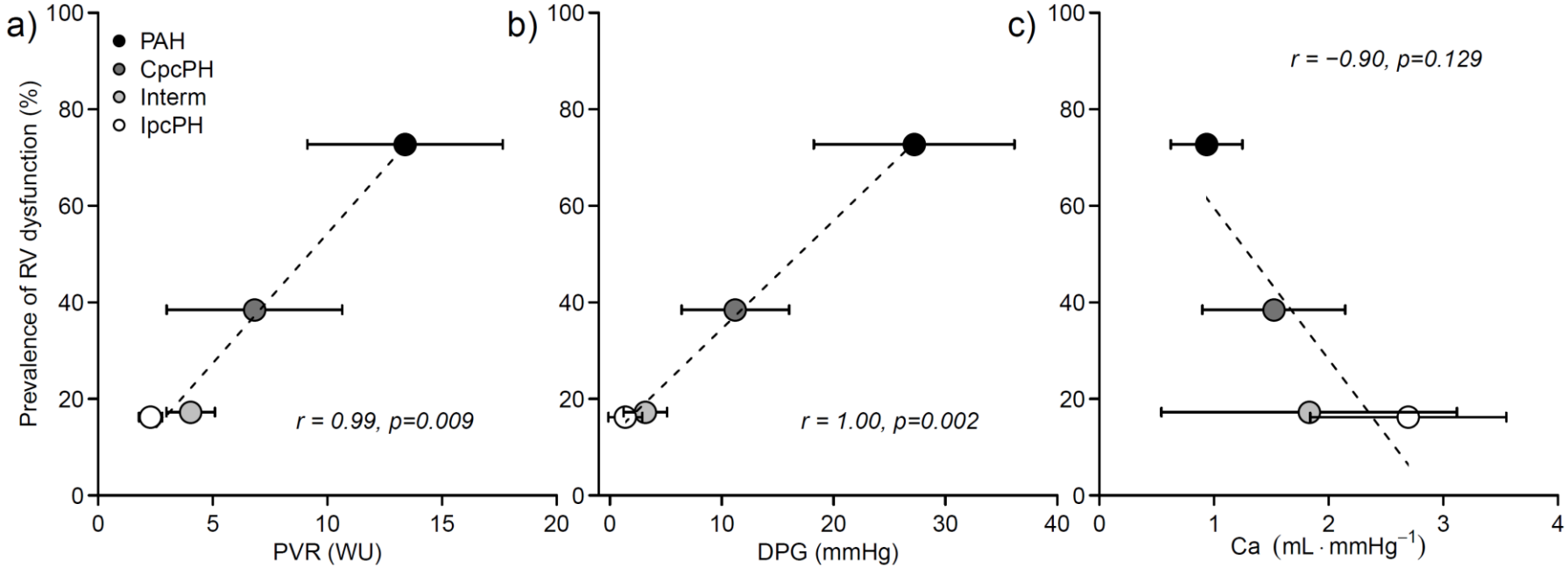

Figure 5. Prevalence of echocardiographic signs of right ventricular dysfunction in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca=pulmonary arterial compliance; CpcPH=combined post- and pre-capillary pulmonary hypertension; DPG=diastolic pressure gradient; Interm=intermediate; IpcPH=isolated post-capillary pulmonary hypertension; PAH=pulmonary arterial hypertension; PVR=pulmonary vascular resistance; RV=right ventricle.

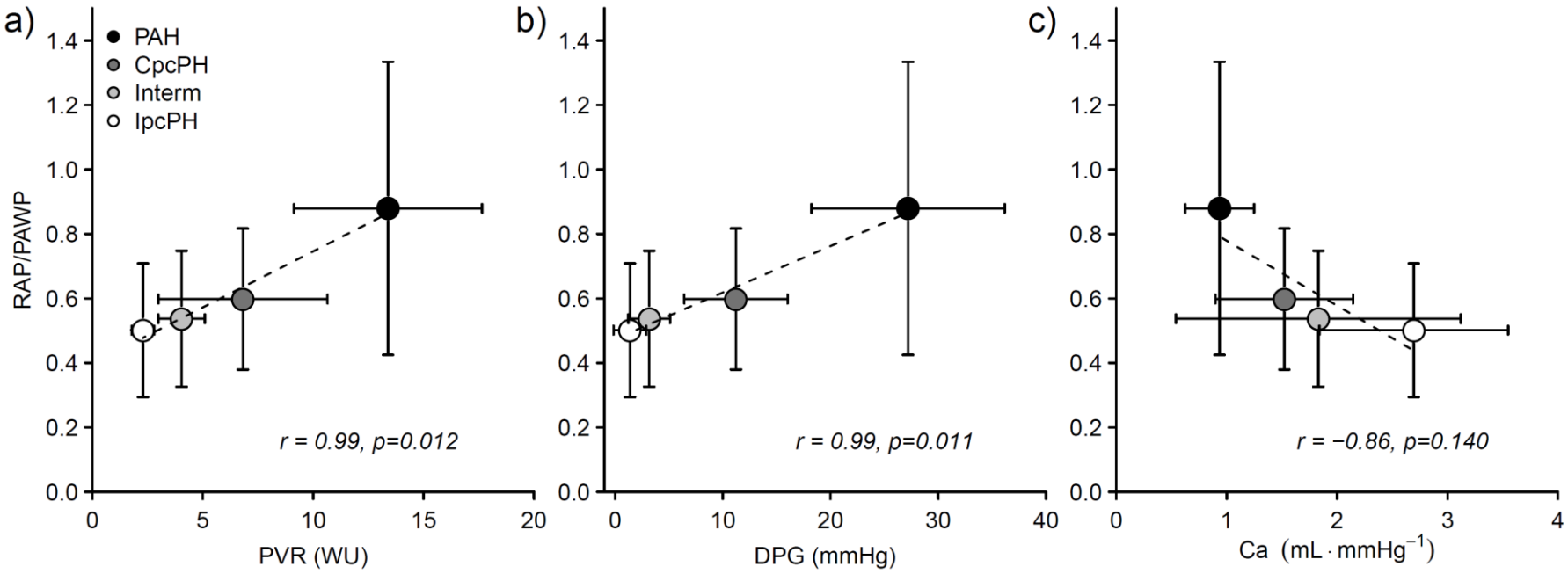

Figure 6. The ratio of right atrial pressure and pulmonary artery wedge pressure in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca=pulmonary arterial compliance; CpcPH=combined post- and pre-capillary pulmonary hypertension; DPG=diastolic pressure gradient; Interm=intermediate; IpcPH=isolated post-capillary pulmonary hypertension; PAH=pulmonary arterial hypertension; PAWP=pulmonary artery wedge pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure.

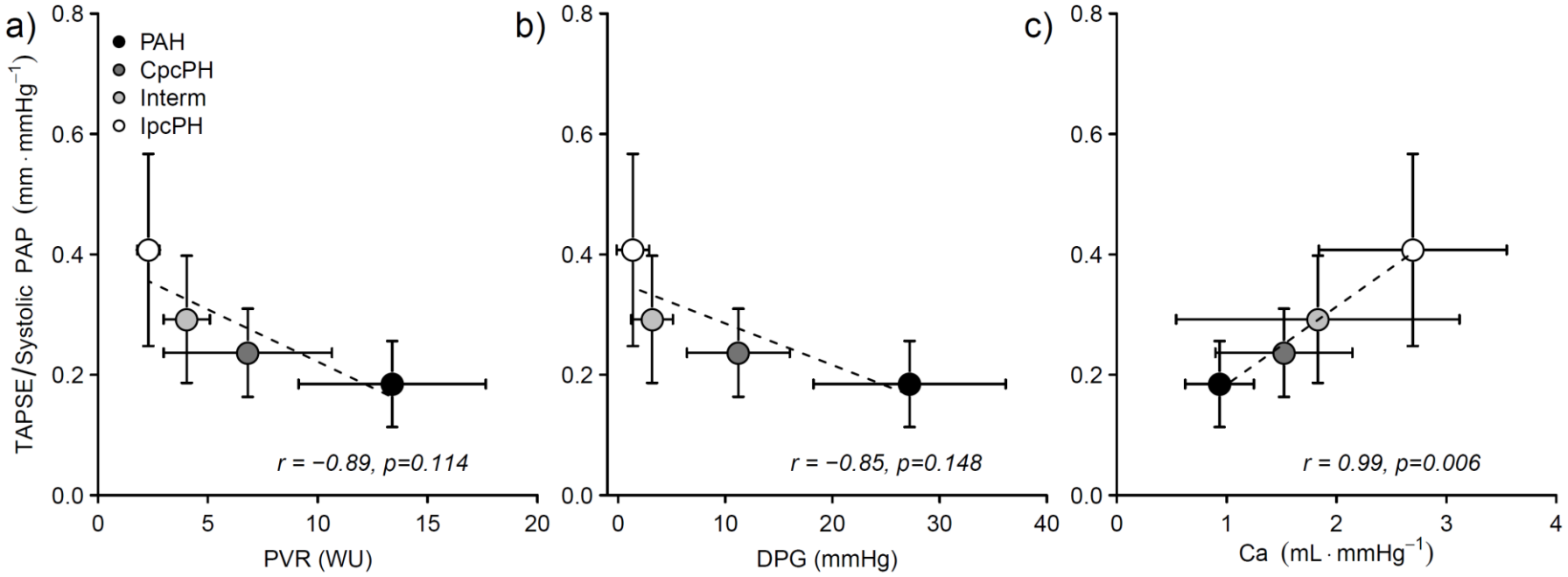

Figure 7. The ratio of tricuspid annular plane systolic excursion and systolic pulmonary artery pressure in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca=pulmonary arterial compliance; CpcPH=combined post- and pre-capillary pulmonary hypertension; DPG=diastolic pressure gradient; Interm=intermediate; IpcPH=isolated post-capillary pulmonary hypertension; PAH=pulmonary arterial hypertension; PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TAPSE=tricuspid annular plane systolic excursion.

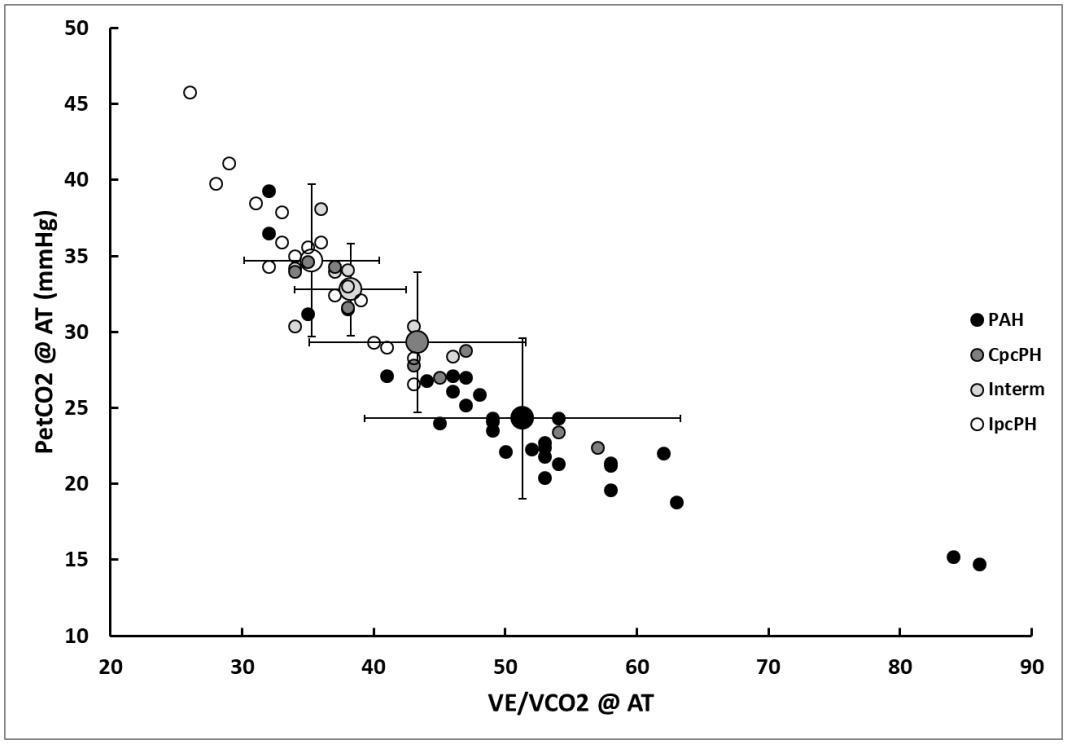

Figure 8. The hyperbolic relationship between end-tidal pressure of carbon dioxide and ventilatory equivalents for carbon dioxide at the anaerobic threshold. AT = anaerobic threshold; CpcPH = Combined pre- and post-capillary Pulmonary Hypertension; IpcPH = Isolated post-capillary Pulmonary Hypertension; PAH = pulmonary arterial hypertension; PetCO2 = end-tidal pressure of carbon dioxide; VE = minute ventilation; VCO2 = carbon dioxide production.

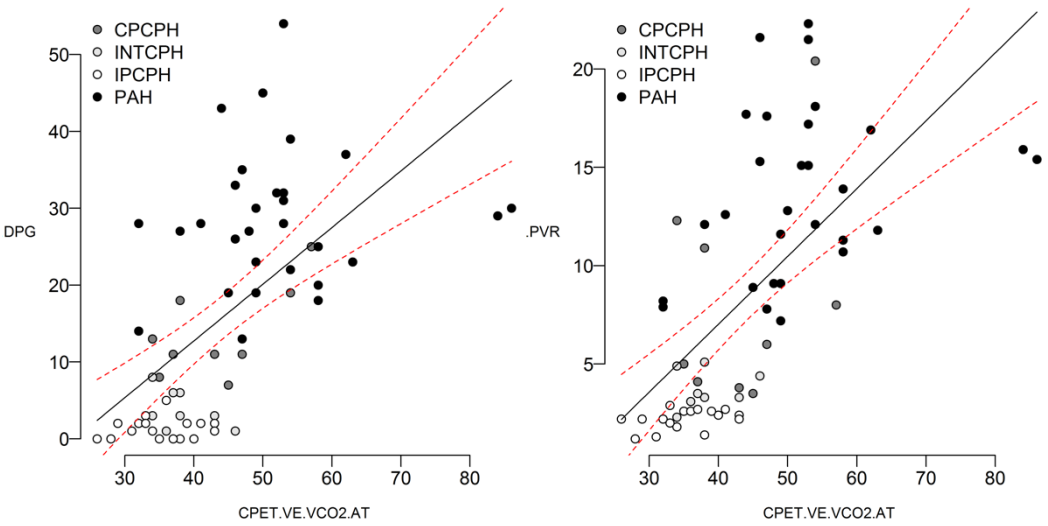

Figure 9. Regression analysis between the ventilatory equivalents at the anaerobic threshold and haemodynamics markers of pulmonary vascular disease. AT=anaerobic threshold; CpcPH=combined post- and pre-capillary pulmonary hypertension. DPG=diastolic pressure gradient; IntcPH=”intermediate” PH; IpcPH=isolated post-capillary pulmonary hypertension; PAH=pulmonary arterial hypertension; PVR=pulmonary vascular resistance; VCO2=carbon dioxide production; VE=minute ventilation.

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to their side, taught

me a great deal by example

APPENDIX

List of published articles:

1. **Caravita S**, Faini A, Carolino D'Araujo S, Dewachter C, Chomette L, Bondue A, Naeije R, Parati G, Vachiéry JL. Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component. PLoS One. 2018 Jun 19;13(6):e0199164
2. **Caravita S**, Dewachter C, Soranna D, D'Araujo SC, Khaldi A, Zambon A, Parati G, Bondue A, Vachiéry JL. Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis. Eur Respir J. 2018 Apr 4;51(4). pii: 1702427
3. **Caravita S**, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, Vachiéry JL. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. J Heart Lung Transplant. 2017 Jul;36(7):754-762
4. Naeije R, Gerges M, Vachiery JL, **Caravita S**, Gerges C, Lang IM. Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure. Circ Heart Fail. 2017 Sep;10(9). pii: e004082

In the following pages the whole text of the articles is reported.

PLOS ONE

RESEARCH ARTICLE

Clinical phenotypes and outcomes of pulmonary hypertension due to left heart disease: Role of the pre-capillary component

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Abstract

Background

In pulmonary hypertension (PH), both wedge pressure elevation (PAWP) and a precapillary component may affect right ventricular (RV) afterload. These changes may contribute to RV failure and prognosis. We aimed at describing the different haemodynamic phenotypes of patients with PH due to left heart disease (LHD) and at characterizing the impact of pulmonary haemodynamics on RV function and outcome PH-LHD.

Methods

Patients with PH-LHD were compared with treatment-naïve idiopathic/heritable pulmonary arterial hypertension (PAH, n = 35). PH-LHD patients were subdivided in Isolated post-capillary PH (IpcPH: diastolic pressure gradient, DPG<7 mmHg and pulmonary vascular resistance, PVR≤3 WU, n = 37), Combined post- and pre-capillary PH (CpcPH: DPG≥7 mmHg and PVR>3 WU, n = 27), and "intermediate" PH-LHD (either DPG <7 mmHg or PVR ≤3 WU, n = 29).

Results

Despite similar PAWP and cardiac index, haemodynamic severity and prevalence of RV dysfunction increased from IpcPH, to "intermediate" and CpcPH. PVR and DPG (but not compliance, Ca) were linearly correlated with RV dysfunction. CpcPH had worse prognosis (p<0.05) than IpcPH and PAH, but similar to "intermediate" patients. Only NTproBNP and Ca independently predicted survival in PH-LHD.

Conclusions

In PH-LHD, haemodynamic characterization according to DPG and PVR provides important information on disease severity, predisposition to RV failure and prognosis. Patients

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presenting the CpcPH phenotype appear to have haemodynamic profile closer to PAH but with worse prognosis. In PH-LHD, Ca and NTproBNP were independent predictors of survival.

Introduction

Post-capillary pulmonary hypertension (PH) is a frequent complication of left heart disease (LHD) [1,2]. However, a small number of PH-LHD patients may present an increase in pulmonary artery pressures (PAP) that cannot be explained by an increase in pulmonary artery wedge pressure (PAWP). In these cases, a cascade of events involving complex interplay of endothelial dysfunction, vasoconstriction and possibly remodeling, may contribute to the development of a pre-capillary component superimposed to post-capillary PH [1–4].

How to define a pre-capillary component in PH-LHD has been debated in recent years. Current ESC/ERS PH guidelines have proposed a haemodynamic definition that subdivides post-capillary PH based on the diastolic pressure gradient (DPG) and on pulmonary vascular resistance (PVR): Isolated post-capillary PH (IpcPH, with PVR $\leq$3 WU *and/or* DPG <7 mmHg), and Combined post- and pre-capillary PH (CpcPH, with PVR >3 WU *and/or* DPG $\geq$7 mmHg) [1].

However, this definition has also been recently challenged [5–7]. Firstly, its literal application may result in an ambiguous classification of a proportion of patients (i.e. those with PVR >3 WU *or* DPG $\geq$7 mmHg, that may fall in both in the IpcPH and in the CpcPH group) [5]. Moreover, each of the two variables (DPG and PVR) presents with certain advantages and disadvantages: the DPG was initially introduced based on solid physiological background as a potential marker of the pre-capillary component [2,3] but its prognostic role is controversial [4, 8–17], while PVR was proposed mainly due to its solid prognostic significance [1,11,18] although it may be highly sensitive to PAWP and cardiac output changes [3]. Finally, pulmonary arterial compliance (Ca) has been suggested to carry additional insights in particular in patients' description and outcome [17,19–21]. More specifically, Ca has been shown to be sensitive to changes in PAWP in the presence of PH [22]. It has been also suggested to have prognostic significance even in the absence of PH [23].

With the present work, we aimed at describing the clinical and haemodynamic profile of a PH-LHD population assessed in a PH referral center, as compared with patients with pulmonary arterial hypertension (PAH). Secondly, we aimed at evaluating the predictors of prognosis in PH-LHD and determine whether the current classification of IpcPH vs CpcPH provides additional risk stratification.

Methods

The study had been approved by the Ethics Committee of the Erasme Hospital (ref. n. P2015/359). In agreement with Belgian laws and with local Ethics committee, informed consent was not required according to the retrospective nature of the study. None of the patients had denied the use for research purposes of anonymized data collected in routine clinical practice at an academic hospital.

We retrospectively compared patients with PH undergoing a first elective assessment in stable clinical conditions at the Pulmonary Hypertension and Heart Failure Clinic of the Erasme Hospital between January 2007 and October 2014. Clinical indication for right heart catheterization was given according to international guidelines [1,24]. PH was defined and classified

according to recent ESC/ERS guidelines [1]. In particular, PH was defined by a mean PAP $\geq$ 25 mmHg. Distinction between pre-capillary and post-capillary PH was made based on a PAWP $\leq$ or $>$ 15 mmHg, respectively [1]. We first compared patients with PH-LHD versus patients with idiopathic or heritable PAH naïf of specific therapy. Then, we subdivided PH-LHD in:

- IpcPH, if DPG $<$ 7 mmHg and PVR $\leq$ 3 WU
- CpcPH, if DPG $\geq$ 7 mmHg and PVR $>$ 3 WU
- "intermediate" PH-LHD, if either DPG $<$ 7 mmHg or PVR $<$ 3 WU

We kept for the analysis only patients with complete hemodynamic data and not presenting severe lung disease as a comorbid condition, such as chronic obstructive pulmonary disease (COPD) in Global Initiative for Chronic Obstructive Lung Disease (GOLD) class 4, severe interstitial lung disease. Sleep apnea was not an exclusion criterion. Glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [25]. Chronic thromboembolic PH was ruled out in all patients by a combination of clinical history, lung scintigraphy, computed tomography of the chest, pulmonary haemodynamics.

Haemodynamics

All right heart catheterizations were performed and reviewed by a cardiologist expert in PH. The transducer was zeroed at the midthoracic line in a supine patient, halfway between the anterior sternum and the bed surface [1]. Pulmonary artery pressures were measured at end-expiration and averaged over several cardiac cycles (5 to 8). PAWP was measured by a single expert reader at mid-A wave, as it more closely approximates left ventricular end-diastolic pressure [26]. Cardiac output was measured by thermodilution in triplicate (using an average of three measurements within 10% of agreement). DPG was calculated as the difference between diastolic PAP and PAWP [1–3]. PVR was calculated as (mean PAP–PAWP) / cardiac output [1]. Ca was estimated as the ratio between stroke volume and pulmonary arterial pulse pressure, and the resistance-compliance product (RC-time) as the product of Ca and PVR, and expressed in seconds [22].

The right ventricle and right ventricular function

RV enlargement was defined as a ratio between right ventricle and left ventricle $>$1 [1]. Reduced RV systolic function was qualified as a fractional area change $\leq$ 35% by an experienced cardiologist blinded to invasive haemodynamics. Validation was then performed on a sample of 74 subjects by an independent observer who recalculated fractional area change. RV dysfunction was defined as a combination of reduced RV systolic function and RV enlargement, i.e. as a failing of the homeometric adaptation of the RV faced to an increased afterload [27].

Tricuspid annular plane systolic excursion (TAPSE) was measured according to current recommendations [28,29]. Also, the ratio between TAPSE and systolic PAP was calculated, as a possible surrogate index of RV to pulmonary artery coupling [8].

RV stroke work index (RVSWI), an index of RV workload, was calculated as (mean PAP–right atrial pressure) * (cardiac index / heart rate) * 0.0136.

The ratio between right atrial pressure and PAWP was used as a haemodynamic surrogate of RV dysfunction [30].

Statistics

Descriptive data are reported as means±standard deviations for continuous variable and as absolute numbers and percentages for categorical variables. Distribution of variables in terms of proximity to normal curve and the homogeneity of variances were detected by Shapiro-Wilk test and Bartlett test, respectively. When needed, either a logarithmic or box-cox transformation was performed to achieve normal distribution. ANOVA with contrasts *a posteriori* was used for variables normally distributed and homoscedastic; otherwise ANOVA on ranks was performed. For multiple comparisons, the algorithm which controls the expected rate of false-positive results for all positive results (false discovery rate) was used. Linear dependence between prevalence of RV dysfunction and TAPSE/systolic PAP on one side, and PVR, DPG and Ca on the other side, was evaluated with Pearson correlation coefficient. Pearson's Chi-squared contingency table test or Fisher Exact test for count data has been used to analyze categorical variables, as necessary.

Estimates of the survival probability were calculated using the Kaplan-Meier method, and the log rank test was employed to test the null hypothesis of equality in overall survival among groups. Univariate and multivariate Cox regression models were calculated to examine factors associated with adverse outcomes. Predictors in the multiple Cox model were selected from the set of variables that reached statistical significance in univariate analysis, by a stepwise procedure with the significance limit set to 0.05, taking care to avoid the simultaneous inclusion of collinear variables. The proportional-hazards assumption was tested using Schoelfeld residuals, with $p<0.05$ evidence for non-proportionality. Results were expressed as hazard ratios with 95% confidence intervals.

An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using R Core Team (2016), Vienna, Austria.

Results

From January 2007 to October 2014, 548 patients underwent right heart catheterization. Patients with group 3–5 PH, associated PAH, congenital heart disease, veno-occlusive disease, patients with mean PAP < 25 mmHg as well as patients undergoing right heart catheterization in unstable clinical conditions were discarded from analysis. Thus, one hundred and twenty-eight patients met the inclusion criteria, consisting in 93 patients with PH-LHD and 35 idiopathic/heritable PAH (S1 Fig). The subdivision of PH-LHD according to the haemodynamic classification is depicted in Table 1.

General characteristics

Table 2 summarizes the general characteristics of the study population. Pooled together, PH-LHD were heavier than PAH patients, and presented with slightly lower glomerular filtration rate. NYHA class and NTproBNP levels did not differ between the two groups.

Table 1. Patients' subdivision according to the haemodynamic classification of pulmonary hypertension due to left heart disease.

PH-LHD ***N = 93***		***DPG (mmHg)***	
		< 7	**≥ 7**
PVR (WU)	≤ 3	*IpcPH* *N = 37*	*Intermediate* *N = 1*
	> 3	*Intermediate* *N = 28*	*CpcPH* *N = 27*

CpcPH = combined post- and pre-capillary pulmonary hypertension; DPG = diastolic pressure gradient; IpcPH = isolated post-capillary pulmonary hypertension; PH-LHD = pulmonary hypertension due to left heart disease; PVR = pulmonary vascular resistance.

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Table 2. Patients' general characteristics.

	PAH n = 35	PH-LHD N = 93	CpcPH n = 27	Interm n = 29	IpcPH n = 37	p overall
Demographics & anthropometrics						
Females, n (%)	19 (54%)	51 (55%)	14 (52%)	16 (55%)	21 (57%)	0.984
Age (years)	57±16	64±13	64±14	67±13	62±13	0.075
Height (cm)	165±10	166±10	168±10	166±10	165±9	0.560
Weight (Kg)	71±14	79±17	85±16	75±17	79±17	**0.005**
BMI (Kg/m^2)	26±5	29±5	30±5	27±4	29±6	**0.010**
NYHA class						0.372
I-II	7 (20%)	29 (31%)	8 (30%)	7 (24%)	14 (38%)	
III-IV	28 (80%)	64 (69%)	19 (70%)	22 (76%)	23 (62%)	
Blood tests						
Creatinine (mg/dL)	1.1±0.4	1.4±0.7	1.4±0.6	1.5±0.9	1.3±0.6	0.148
eGFR (mL/min/1.73m^2)	70±24	59±25	58±25	55±26	63±25	0.056
Sodium (mmoL/L)	141±3	141±4	141±3	140±4	141±4	0.829
NT-proBNP (pg/mL)	2930±3002	3685±6936	4136±3845	5034±11573	2214±2126	0.211

BMI = body mass index; CpcPH = combined post- and pre-capillary pulmonary hypertension; eGFR = estimated glomerular filtration rate; Interm = intermediate; IpcPH = Isolated post-capillary pulmonary hypertension; NYHA = New York Heart Association; NT-proBNP = N-terminal pro Brain Natriuretic Peptide; PAH = pulmonary arterial hypertension; RV = right ventricle.

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When further subdividing PH-LHD in IpcPH, intermediate and CpcPH, general characteristics were similar in the three groups, although CpcPH presented with slightly higher weight and body mass index than intermediate patients ($p<0.05$).

The underlying causes of PH-LHD were similar between the three groups, with heart failure with preserved ejection fraction being the leading etiology, followed by heart failure with reduced ejection fraction and a small number of patients with valvular heart disease (S1 Table). Patients with heart failure and a reduced ejection fraction were more likely treated with drugs acting on the renin-angiotensin-aldosterone system and with beta-blockers as compared with patients with a preserved ejection fraction ($p<0.01$), while diuretics prescription was similar among subgroups. Known obstructive sleep apnea was not represented in the "intermediate" group. The remaining spectrum of comorbidities, as well as background treatment, did not differ between the three subgroups (S1 Table). COPD GOLD 2 was diagnosed in 3 PAH, 3 CpcPH, 1 "intermediate", 1 IpcPH patients, while COPD GOLD 3 only in 2 IpcPH patients.

Haemodynamics

The hemodynamic profile was more disturbed in PAH patients (higher pulmonary pressures, gradients and PVR, and lower Ca and cardiac index) as compared with PH-LHD (Table 3).

When further subdividing PH-LHD, we found that the severity of the hemodynamic profile (pulmonary pressures, pulmonary gradients and PVR) stepwisely increased from IpcPH to intermediate to CpcPH to PAH (Table 3). However, diastolic and mean pulmonary pressure did not significantly differ when comparing CpcPH and PAH ($p = 0.308$ and $p = 0.052$, respectively), and Ca was similar between CpcPH and intermediate patients ($p = 0.169$). There was no significant difference in PAWP and cardiac index across the three subgroups of PH-LHD, although PAWP was slightly higher and stroke volume slightly lower in intermediate patients compared with IpcPH ($p = 0.053$ and $p = 0.063$, respectively). All patients but one in the

Table 3. Patients' invasive hemodynamic profile.

	PAH n = 35	PH-LHD n = 93	CpcPH n = 27	Interm n = 29	IpcPH n = 37	ANOVA
HR (bpm)	79±15	71±13	74±13	71±14	69±13	**0.017**
Systolic BP	126±18	130±30	131±31	137±31	123±28	0.183
Diastolic BP	79±12	72±14	74±16	74±13	67±11	**0.002**
Mean BP	95±12	91±17	94±18	95±17	86±14	**0.037**
Systolic PAP (mmHg)	86±17	61±18	76±16	63±16	48±8	**<0.001**
Diastolic PAP (mmHg)	37±8	28±8	35±7	28±6	23±4	**<0.001**
Mean PAP (mmHg)	53±11	39±10	49±9	39±8	31±5	**<0.001**
PAWP (mmHg)	10±4	23±5	24±6	25±6	22±4	**<0.001**
RAP (mmHg)	8±5	13±6	14±6	13±6	11±5	**<0.001**
RAP/PAWP	0.88±0.46	0.54±0.21	0.60±0.22	0.54±0.21	0.50±0.21	**<0.001**
SaO2 (%)	92±4	96±3	94±5	97±3	97±3	**<0.001**
SvO2 (%)	59±10	63±8	60±7	64±8	64±8	**0.005**
Stroke volume (mL)	45±14	59±19	58±21	54±14	64±20	**<0.001**
CI (L/min/m^2)	1.9±0.4	2.2±0.6	2.3±0.5	2.1±0.6	2.2±0.7	**0.041**
TPG (mmHg)	44±11	16±8	25±8	15±5	10±3	**<0.001**
DPG (mmHg)	27±9	5±5	11±5	3±2	1±2	**<0.001**
PVR (WU)	13±4	4±3	7±4	4±1	2±1	**<0.001**
Ca (mL/mmHg)	0.9±0.3	2.1±1.1	1.5±0.6	1.8±1.3	2.7±0.9	**<0.001**
RC-time (s)	0.69±0.13	0.41±0.13	0.51±0.08	0.40±0.16	0.35±0.07	**<0.001**

BP = systemic blood pressure; CI = cardiac index; CpcPH = combined post- and pre-capillary pulmonary hypertension; DPG = diastolic pressure gradient; Interm = intermediate; IpcPH = isolated post-capillary pulmonary hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RC-time = resistance-compliance product; TPG = transpulmonary pressure gradient; SaO2 = arterial oxygen saturation; SvO2 = mixed venous oxygen saturation.

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intermediate group had PVR > 3 WU and DPG < 7 mmHg. When subdividing patients according to left ventricular ejection fraction, we could not find any difference in the principal haemodynamic variables except in cardiac index, which resulted lower in patients with a reduced than in those with a normal left ventricular ejection fraction (1.9±0.4 vs 2.5±0.6, $p<0.01$).

Effect of the DPG on the PVR-Ca relationship

Fig 1A depicts the Log(PVR)–Log(Ca) as a function of PAWP and DPG. PH-LHD with low DPG, PH-LHD with high DPG and PAH all presented with a similar slope of the Log(PVR)-Log(Ca) regression relationship, but with different intercepts, so that the slope of PH-LHD with high DPG lied in between PH-LHD with low DPG and PAH. The relation between RC-time and PAWP across the three different conditions was not linear as it would have been expected, with PH-LHD with high DPG presenting with higher RC-time than PH-LHD with a low DPG for a nearly identical PAWP (Fig 1B).

RV afterload and RV dysfunction

We kept in the analysis only the echocardiographic examinations which had been performed between 90 days before and one week after right heart catheterization, given that there were no significant changes in treatment between echocardiography and invasive haemodynamic assessment. Eighty-three percent of echocardiography had been performed within 72 hours

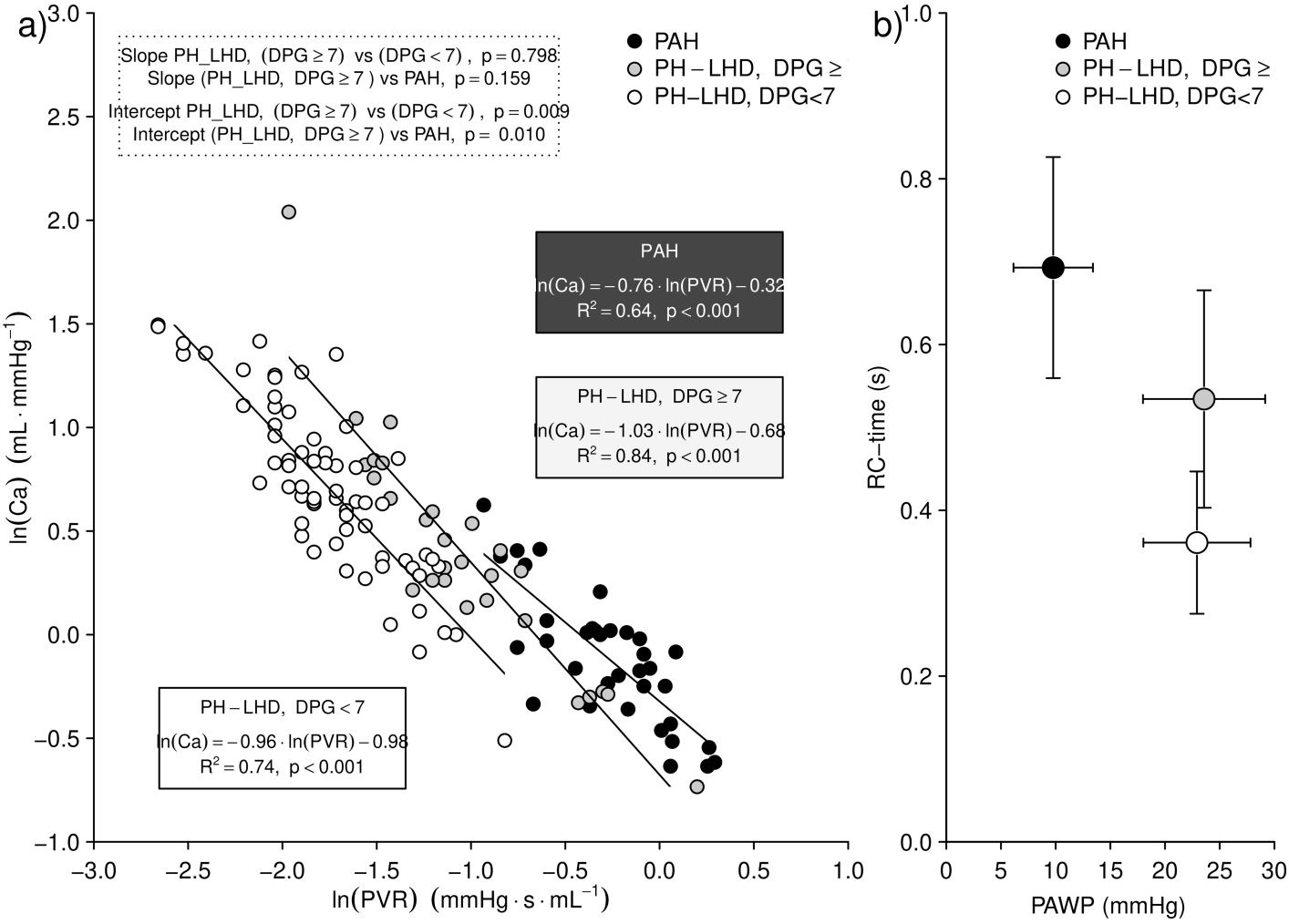

Fig 1. Effects of varying the diastolic pressure gradient and pulmonary artery wedge pressure on the compliance-resistance relationship in patients with pulmonary hypertension. Panel a): pulmonary arterial compliance as a function of pulmonary vascular resistance, both logarithmically transformed. Panel b): resistance-compliance product as a function of pulmonary artery wedge pressure. Ca = pulmonary arterial compliance; DPG = diastolic pressure gradient; PAH = pulmonary arterial hypertension; PH-LHD = pulmonary hypertension due to left heart disease; PVR = pulmonary vascular resistance; RC-time = pulmonary vascular resistance-compliance product.

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from right heart catheterization, 91% within 1 week and 97% between 1 month and a few days after right heart catheterization. Mean and median time span between right heart catheterization and echocardiography was -4 ±12 days and -1 (-78 to +6) days, respectively. Thus, a minimal data set from echocardiography was available in 119 over 128 patients.

RV enlargement was more prevalent in PAH than in PH-LHD patients. Moreover, RV enlargement became progressively more frequent passing from IpcPH to "intermediate" PH-LHD to CpcPH to PAH (Table 4).

Echocardiographic signs of reduced RV systolic function were more represented in PAH as compared with PH-LHD (Table 4). However, the prevalence RV dysfunction showed a crescendo from IpcPH to "intermediate" to CpcPH to PAH patients ($p<0.001$). Mean PVR and mean DPG of each hemodynamic subgroup resulted highly correlated with the prevalence of RV dysfunction (Fig 2), while the relation between RV dysfunction and Ca was not linear. A similar pattern of correlation was found between the same haemodynamic variables on one side and the ratio between right atrial pressure and PAWP (S2 Fig).

Table 4. Right ventricular function in the different haemodynamic subgroups.

	PAH	PH-LHD	CpcPH	Interm	IpcPH	p overall
RVOT, proximal (mm)	37±6	32±6	36±7	30±6	31±6	**<0.001**
RV/LV≥1	82%	51%	69%	39%	46%	**0.001**
Reduced RV systolic function	79%	47%	52%	45%	38%	**0.005**
TAPSE (mm)	15±4	18±6	18±5	17±5	19±7	0.083
TAPSE/sPAP (mm/mmHg)	0.18±0.07	0.32±0.14	0.25±0.08	0.29±0.11	0.40±0.16	**<0.001**
RVSWI (g/m²/beat)	15.6±5.3	11.3±5.1	14.1±5.8	10.7±4.8	9.8±4.1	**<0.001**

CpcPH = combined post- and pre-capillary pulmonary hypertension; Intem = "intermediate PH-LHD"; IpcPH = isolated post-capillary pulmonary hypertension; LV = left ventricle; PAH = pulmonary arterial hypertension; PH-LHD = pulmonary hypertension due to left heart disease; sPAP = systolic pulmonary artery pressure; RV = right ventricle; RVOT = right ventricular outflow tract; RVSWI = right ventricular stroke work index; TAPSE = tricuspid annular plane systolic excursion.

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TAPSE, which was available in 80% of cases, did not significantly differ between groups, while the ratio between TAPSE and systolic PAP progressively decreased from IpcPH to "intermediate" PH-LHD to CpcPH to PAH (Table 4). TAPSE/systolic PAP resulted highly correlated with Ca but not with DPG and PVR (S3 Fig).

Outcome predictors in PH-LHD

Follow-up data were available for 115 patients (90%). There were 36 deaths (31%) over a median follow up of 26 months (25th and 75th percentile: 11 and 46 months).

At univariate analysis, glomerular filtration rate, NTproBNP, echocardiographic signs of RV dysfunction, diastolic, mean and systolic pulmonary pressures, as well as PVR and Ca were independent predictors of mortality (Table 5). However, at multivariate analysis, only NTproBNP and Ca maintained their prognostic power (Table 5). Survival was similar in PH-LHD and PAH (Fig 3A). However, subgrouping PH-LHD according to DPG and PVR

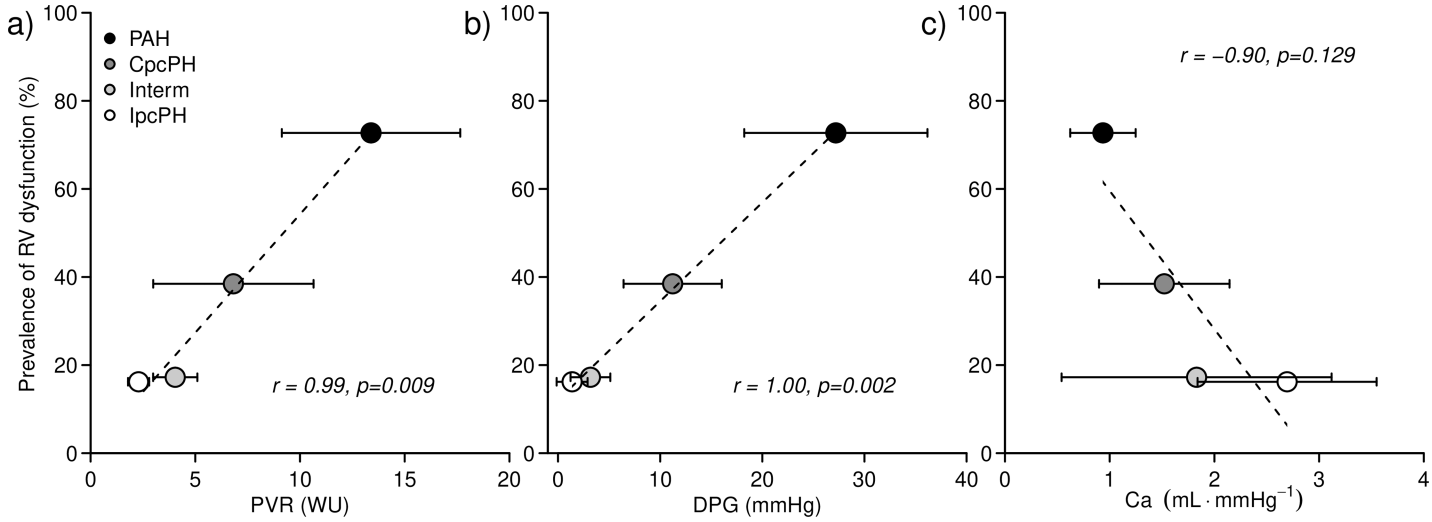

Fig 2. Prevalence of echocardiographic signs of right ventricular dysfunction in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca = pulmonary arterial compliance; CpcPH = combined post- and pre-capillary pulmonary hypertension; DPG = diastolic pressure gradient; Interm = intermediate; IpcPH = isolated post-capillary pulmonary hypertension; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RV = right ventricle.

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Table 5. Univariate and multivariate predictors of survival in pulmonary hypertension due to left heart disease.

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Clinical parameters				
Age, years	1.016 (0.986–1.046)	0.302		
Male sex	1.501 (0.740–3.047)	0.260		
BMI, Kg/m^2	0.959 (0.894–1.028)	0.236		
NYHA III-IV	0.772 (0.356–1.672)	0.511		
Ischemic aetiology	0.982 (0.479–2.014)	0.960		
Atrial fibrillation	1.137 (0.437–2.960)	0.793		
Diabetes mellitus	1.504 (0.720–3.139)	0.277		
Smoking history	0.954 (0.474–1.919)	0.895		
Heart rate, beats/min	1.021 (0.994–1.048)	0.134		
Laboratory parameters				
Hb, g/dL	0.937 (0.805–1.091)	0.403		
eGFR, mL/min/1.73 m^2	**0.979 (0.964–0.993)**	**0.004**		
NTproBNP > 1400 pg/mL	**4.768 (1.662–13.678)**	**0.004**	**5.066 (1.751–14.660)**	**0.003**
Echocardiographic variables				
Reduced LV EF	0.915 (0.435–1.927)	0.816		
RV dysfunction	**2.242 (1.095–4.592)**	**0.027**		
TAPSE/systolic PAP ≤ 0.35	**1.565 (0.514–4.767)**	**0.430**		
Haemodynamic variables				
Mean PAP, mmHg	**1.034 (1.003–1.066)**	**0.030**		
Systolic PAP, mmHg	**1.018 (1.000–1.037)**	**0.050**		
Diastolic PAP, mmHg	**1.044 (1.003–1.088)**	**0.036**		
PAWP, mmHg	1.051 (0.984–1.123)	0.136		
RAP, mmHg	1.011 (0.955–1.070)	0.709		
RAP/PAWP	0.706 (0.146–3.399)	0.664		
DPG, mmHg	1.049 (0.993–1.108)	0.088		
TPG, mmHg	1.037 (0.999–1.077)	0.058		
Cardiac Index, L/min/m^2	0.941 (0.526–1.686)	0.839		
RVSWI, g/m^2/beat	1.037 (0.975–1.103)	0.246		
PVR, WU	**1.130 (1.016–1.256)**	**0.024**		
Ca, mL/mmHg	**0.602 (0.391–0.926)**	**0.021**	**0.509 (0.298–0.872)**	**0.014**

BMI = body mass index; Ca = pulmonary arterial compliance; DPG = diastolic pressure gradient; eGFR = estimated glomerular filtration rate; Hb = haemoglobin; LV EF = left ventricular ejection fraction; NTproBNP = N terminal pro Brain Natriuretic Peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricle; TPG = transpulmonary pressure gradient.

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revealed a worse prognosis in CpcPH as compared both with IpcPH and PAH. Survival was similar in CpcPH and in "intermediate" patients (Fig 3B). There were 14 events (56%) in the CpcPH population, 11 events (31%) in the PAH population, 7 events (30%) in the "intermediate" population, and 4 events (13%) in the IpcPH population.

When testing the capability of DPG, TPG, PVR and Ca to predict mortality by ROC curves analysis, we did not find significant differences between the four hemodynamic variables, with area under the curve in between 69 and 75% (S4A Fig). Compared with the optimal cut-off value of ≥3 mmHg, a DPG of ≥7 mmHg was associated with increased (79%) specificity at the expenses of lower (47%) sensitivity (S4B Fig).

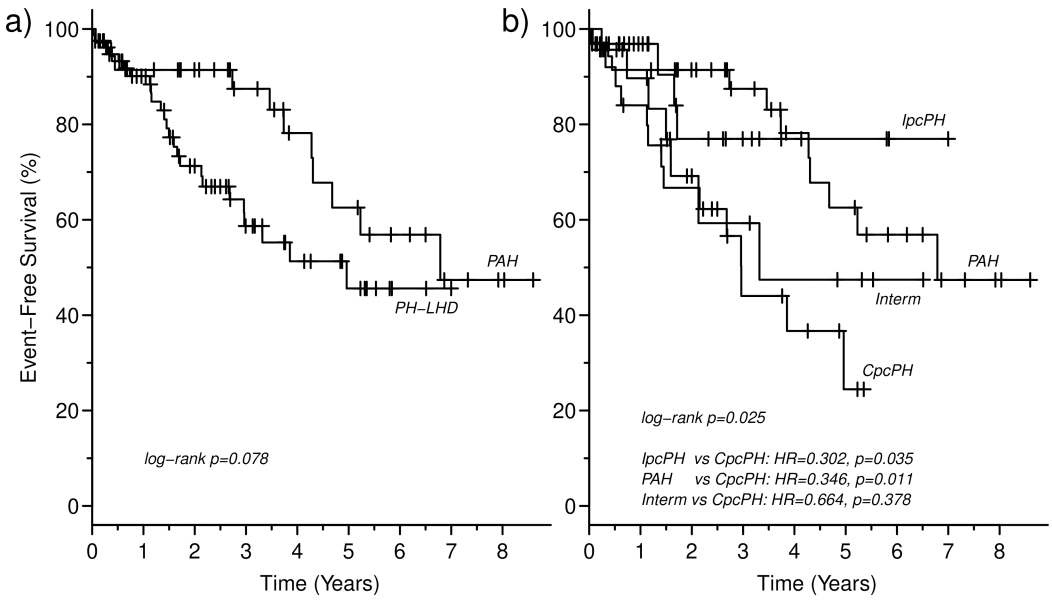

Fig 3. Kaplan-Meier curves of survival for patients with pulmonary arterial hypertension and patients with pulmonary hypertension due to left heart disease. In the panel a) patients with pulmonary hypertension due to left heart disease are all pooled together, while in the panel b) they are subdivided in three groups according to the diastolic pressure gradient and pulmonary vascular resistance. CpcPH = combined post- and pre-capillary pulmonary hypertension; Interm = intermediate PH-LHD; IpcPH = isolated post-capillary pulmonary hypertension; PAH = pulmonary arterial hypertension; PH-LHD = pulmonary hypertension due to left heart disease.

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Discussion

In our population of PH, we could confirm that deranged pulmonary haemodynamics is associated with poor survival. However, subdivision of PH-LHD according to DPG and PVR allowed the discrimination of different profiles of disease severity, so that the prevalence of RV dysfunction increased with increasing DPG and PVR. Moreover, we could show the effect of high/low PAWP and high/low DPG on the PVR-Ca relationship in our PH population, demonstrating that patients with PH-LHD and high DPG may display some characteristics of the pulmonary circulation in between IpcPH and PAH. Finally, despite several differences in pulmonary haemodynamics between patients with high DPG and high PVR as compared with patients with high DPG and/or high PVR, prognosis was similar in these two groups, and only Ca and NTproBNP independently predicted outcome in our PH-LHD population.

Our population reflects current knowledge: PH, whichever its cause, is associated with poor functional status (high NYHA class), significant neurohumoral activation (high NT-proBNP levels) and poor outcomes [1,31]. Importantly, the haemodynamic impact of PH seemed to be largely independent of LHD etiology and of background treatment, with few differences in haemodynamic parameters between heart failure with preserved and heart failure with reduced ejection fraction. Moreover, survival of PH-LHD was not different from PAH.

However, further subdividing PH-LHD according to DPG and PVR allowed the discrimination of a subgroup of patients that may present a milder form of PH (namely IpcPH) as opposed to "intermediate" patients and to CpcPH. Indeed, in spite of minimal differences in general patients' characteristics, the haemodynamic profile of the three PH-LHD subgroups diverged significantly: haemodynamic severity increased stepwisely from IpcPH to "intermediate" to CpcPH, so that this latter resulted closer to PAH. Such haemodynamic differences were

somehow paralleled by a stepwise increase in RV dimensions and RV workload, suggesting that they could be maladaptive, negatively impacting on the RV.

Noteworthy, the degree of PAP, pulmonary vascular gradients and PVR elevation resulted largely independent of PAWP when comparing IpcPH and CpcPH, reinforcing the idea that there might be an additional mechanism at pulmonary arterial level that may explain the pre-capillary component in CpcPH [4,16,32]. Interestingly, "intermediate" patients, i.e. predominantly those patients with an isolated elevation of PVR, presented with a slightly higher PAWP and a slightly lower stroke volume than IpcPH, suggesting that in this specific case the increase in PAP and transpulmonary gradient might be partly explained by low flow and by the exaggerated amplification of left-sided filling pressures [3].

In this perspective, our data seem to support the pathophysiological reasoning suggesting that the DPG may be a marker of the pre-capillary component [4,16]. Increasing the DPG in PH-LHD led to a rightward and upward shift of the PVR-Ca relationship, so that patients with PH-LHD and high DPG lied in between PAH and patients with PH-LHD with low DPG, consistently with a previous report [8], and supporting a distinct pulmonary vascular phenotype in CpcPH [16].

Despite this, DPG taken in isolation did not discriminate survival. Haemodynamic predictors of prognosis in LHD may be influenced by the study characteristics (single center vs multicentric), the methodology (univocally standardized haemodynamic assessment with review of single traces vs utilization of protocol data), the characteristics of the referral center (mainly heart failure vs mainly PH center) as well as of the population (heart failure pre-transplant, reduced or preserved left ventricular ejection fraction, valvular heart disease, cardiomyopathies, PH). All these factors may explain at least in part the different and sometimes contrasting results obtained in recent years by several groups [4,8,11,16–18,20,33–37]. In this context, our data seem to confirm that the milder haemodynamic profile of IpcPH (low DPG, low PVR) is mirrored by an overall lower prevalence of RV dysfunction and a clearly overall better prognosis than the other PH-LHD patients [8]. As such, despite several differences in haemodynamics, we may be tempted to pool CpcPH and "intermediate" all together in saying that when patients with PH-LHD have high PVR, their prognosis is dismal [1,11,18] (acknowledging that high DPG with low PVR in PH-LHD appears to be extremely uncommon [5]). In this perspective, the current guidelines subdivision of PH-LHD in two rather than three groups might be sufficient [17]. However, this would neglect that neither PVR nor DPG seem to be independent predictors of outcome in our cohort of PH-LHD. In this perspective, our data suggest that other parameters (both haemodynamic and non-haemodynamic) may better (independently) discriminate prognosis in PH-LHD, in agreement with previous reports [17–20]. In particular, estimates of Ca may be more sensitive to early vascular changes, and accordingly to right heart dysfunction, because of their nonlinear relation with PVR [38], thus confirming its supposed better discriminative potential across patients without PH or with relatively low PVR [10]. Keeping in mind that PVR increased from PH-LHD with low DPG to PH-LHD with high DPG to PAH [31], our data also show that, at a given PVR, Ca would be higher with high than with low DPG, thus linking these three variables and possibly contributing to explain why even some patients with low DPG may present with RV failure and poor outcomes. As such, PVR and DPG should be probably viewed as complementary rather than mutually exclusive, as previously suggested [6,7]. In addition to a hemodynamic phenotype based on these pressure variables, outcome prediction appears reinforced by the integration of Ca [17], parameters of RV function [31] and biomarkers. In other words, a combined approach of a set of variables appears to have more clinical relevance than any one taken in isolation.

Finally, it is also interesting to point out that in a contemporary PH population, newly diagnosed PAH had overall better survival than patients with PH-LHD and a pre-capillary component. This on one side may confirm that approved and currently prescribed treatment in PAH referral centers had impacted the outcome of this condition [1], at the same time reinforcing the need for further research efforts in order to better understand and possibly improve prognosis of the subgroups of PH-LHD at higher risk [39].

Study limitations

This is a retrospective study done on a relatively small number of patients evaluated at a PH referral center. This selection bias may partly explain differences of our population and of our results with those normally evaluated at mainly heart transplant or heart failure centers. Despite our small sample size, high mortality rates and adequate follow-up time allowed meaningful subgroup analysis.

Ca was not directly measured, but rather estimated by the simplified formula using parameters obtainable from right heart catheterization, acknowledging that this practice, albeit accurate, may result in a significant overestimation of its real value [40]. RV function was evaluated only by means of standard echocardiography and invasive haemodynamics rather than relying on magnetic resonance imaging or 3D echo, both of which allow for better characterization of the complex geometry of the RV.

Finally, we acknowledge that Cheyne-Stokes respiration and central sleep apnea were not routinely assessed, albeit they can be highly prevalent and related both to pulmonary haemodynamics and to prognosis in LHD [41].

Conclusions

PH-LHD represents a broad spectrum of haemodynamic presentations. The presence of a pre-capillary component, defined by a DPG $\geq$ 7 mmHg and/or PVR $>$ 3 WU is associated with a worse prognosis as compared with patients with low DPG and low PVR. Ca and NTproBNP may better predict outcome than other clinical and haemodynamic variables suggesting that characterization of patients with PH-LHD should probably incorporate further elements, including RV function. Collaborative study should be encouraged in order to provide a more precise characterization of patients with PH-LHD at high risk, that may help improving the current haemodynamic definition.

Supporting information

S1 Table. Clinical characteristics of patients with pulmonary hypertension secondary to left heart disease. ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CpcPH = combined post- and pre-capillary pulmonary hypertension; CRT-D = cardiac resynchronization therapy–defibrillator; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; Interm = intermediate; IpcPH = isolated post-capillary pulmonary hypertension; ICD = implanted cardioverter defibrillator; O2 = oxygen; OSAS = obstructive sleep apnea syndrome.
(DOCX)

S1 Fig. Patients disposition according to the study protocol and haemodynamic definitions. CpcPH = Combined post- and pre-capillary Pulmonary Hypertension; DPG = diastolic pressure gradient; HF = heart failure; IpcPH = Isolated post-capillary Pulmonary Hypertension; LHD = left heart disease; PAH = pulmonary arterial hypertension; PH = pulmonary

hypertension; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RHC = right heart catheterization.
(TIF)

S2 Fig. The ratio of right atrial pressure and pulmonary artery wedge pressure in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca = pulmonary arterial compliance; CpcPH = combined post- and pre-capillary pulmonary hypertension; DPG = diastolic pressure gradient; Interm = intermediate; IpcPH = isolated post-capillary pulmonary hypertension; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.
(PDF)

S3 Fig. The ratio of tricuspid annular plane systolic excursion and systolic pulmonary artery pressure in the four groups of patients as a function of pulmonary haemodynamics: pulmonary vascular resistance (panel a), diastolic pressure gradient (panel b), and pulmonary arterial compliance (panel c). Ca = pulmonary arterial compliance; CpcPH = combined post- and pre-capillary pulmonary hypertension; DPG = diastolic pressure gradient; Interm = intermediate; IpcPH = isolated post-capillary pulmonary hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; TAPSE = tricuspid annular plane systolic excursion.
(PDF)

S4 Fig. Panel a) Receiver operating characteristic curves of haemodynamic predictors of survival in pulmonary hypertension due to left heart disease, with their respective optimal cut-off point, specificity, sensitivity and area under the curve. Panel b) Sensitivity and specificity of different threshold DPG values for predicting outcome. AUC = area under the curve; Ca = pulmonary arterial compliance; DPG = diastolic pressure gradient; PVR = pulmonary vascular compliance; Sens = sensitivity; Spec = specificity; TPG = transpulmonary pressure gradient.
(PDF)

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JLV had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SC and JLV designed the study, interpreted data and drafted the manuscript. SC collected and analyzed data. AF performed statistical analysis. AF, SCDA, CD, LC, AB, RN, GP have made substantial contributions to conception and design and interpretation of data, and revised the article critically for important intellectual content. All authors have provided final approval of the version to be published.

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References

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46:903–75 https://doi.org/10.1183/13993003.01032-2015 PMID: 26318161
2. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013; 62:D100–8 https://doi.org/10.1016/j.jacc.2013.10.033 PMID: 24355634
3. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013; 41:217–23 https://doi.org/10.1183/09031936.00074312 PMID: 22936712
4. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013; 143:758–66. https://doi.org/10.1378/chest.12-1653 PMID: 23580984
5. Gerges M, Gerges C, Lang IM. How to define pulmonary hypertension due to left heart disease. Eur Respir J 2016; 48(2):553–5 https://doi.org/10.1183/13993003.00432-2016 PMID: 27174881
6. Galiè N, Manes A, Palazzini M. The difficult diagnosis of pulmonary vascular disease in heart failure. Eur Respir J. 2016; 48(2):311–4 https://doi.org/10.1183/13993003.00854-2016 PMID: 27478188
7. Naeije R, Hemnes AR. The difficult diagnosis of pulmonary vascular disease in heart failure. Eur Respir J. 2016; 48(2):308–10 https://doi.org/10.1183/13993003.00789-2016 PMID: 27478187
8. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, et al. Pulmonary Hypertension in Heart Failure: Epidemiology, Right Ventricular Function and Survival. Am J Respir Crit Care Med 2015; 192:1234–46 https://doi.org/10.1164/rccm.201503-0529OC PMID: 26181215
9. Gerges C, Gerges M, Lang IM. Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: the conundrum of high and low diastolic pulmonary gradient. JACC Heart Fail. 2015; 3(5):424–5. https://doi.org/10.1016/j.jchf.2014.12.015 PMID: 25951764
10. Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, et al. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. J Heart Lung Transplant. 2014; 33(3):289–97 https://doi.org/10.1016/j.healun.2013.11.008 PMID: 24462554
11. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Heart Fail. 2015; 3(1):9–16 https://doi.org/10.1016/j.jchf.2014.07.010 PMID: 25453535
12. Naeije R. Measurement to predict survival: the case of diastolic pulmonary gradient. JACC Heart Fail. 2015; 3:425. https://doi.org/10.1016/j.jchf.2014.12.014 PMID: 25951765
13. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, et al. Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2016; 68(2):189–99 https://doi.org/10.1016/j.jacc.2016.04.052 PMID: 27386773

14. Zotter-Tufaro C, Duca F, Kammerlander AA, Koell B, Aschauer S, Dalos D, et al. Diastolic Pressure Gradient Predicts Outcome in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2015; 66(11):1308–10 https://doi.org/10.1016/j.jacc.2015.07.011 PMID: 26361165

15. Nagy AI, Venkateshvaran A, Merkely B, Lund LH, Manouras A. Determinants and prognostic implications of the negative diastolic pulmonary pressure gradient in patients with pulmonary hypertension due to left heart disease. Eur J Heart Fail. 2017; 19(1):88–97 https://doi.org/10.1002/ejhf.675 PMID: 27748008

16. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, et al. Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension. J Am Coll Cardiol. 2016; 68:2525–2536 https://doi.org/10.1016/j.jacc.2016.09.942 PMID: 27931609

17. Palazzini M, Dardi F, Manes A, Bacchi Reggiani ML, Gotti E, Rinaldi A, et al. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes. Eur J Heart Fail. 2018; 20(2):248–255 https://doi.org/10.1002/ejhf.860 PMID: 28464427

18. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail. 2013; 1(4):290–9 https://doi.org/10.1016/j.jchf.2013.05.001 PMID: 24621932

19. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. Circ Heart Fail. 2012; 5(6):778–85 https://doi.org/10.1161/CIRCHEARTFAILURE.112.968511 PMID: 23087402

20. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015; 3(6):467–74 https://doi.org/10.1016/j.jchf.2015.01.013 PMID: 26046840

21. Lankhaar JW, Westerhof N, Faes TJ, Marques KM, Marcus JT, Postmus PE, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol. 2006; 291(4):H1731–7 https://doi.org/10.1152/ajpheart.00336.2006 PMID: 16699074

22. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation. 2012; 125(2):289–97 https://doi.org/10.1161/CIRCULATIONAHA.111.051540 PMID: 22131357

23. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. Chest. 2014; 145(5):1064–70 https://doi.org/10.1378/chest.13-1510 PMID: 24356904

24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14; 37(27):2129–200. https://doi.org/10.1093/eurheartj/ehw128 PMID: 27206819

25. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 2010; 55(4):622–627 https://doi.org/10.1053/j.ajkd.2010.02.337 PMID: 20338463

26. Houston BA, Tedford RJ. What We Talk About When We Talk About the Wedge Pressure. Circ Heart Fail. 2017 Sep; 10(9). pii: e004450

27. Sagawa K, Maughan L, Suga H, Sunagawa K. Cardiac Contraction and the Pressure-Volume Relationship. New York: Oxford University Press, 1988

28. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. 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. J Am Soc Echocardiogr. 2010; 23(7):685–713 https://doi.org/10.1016/j.echo.2010.05.010 PMID: 20620859

29. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1):1–39.e14 https://doi.org/10.1016/j.echo.2014.10.003 PMID: 25559473

30. Drazner MH, Velez-Martinez M, Ayers C, Reimold SC, Thibodeau JT, Mishkin JD, et al. Relationship of Right- to Left-Ventricular Filling Pressures in Advanced Heart Failure: Insights from the ESCAPE Trial. Circulation Circ Heart Fail. 2013; 6(2):264–70

31. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016; 37:942–54 https://doi.org/10.1093/eurheartj/ehv512 PMID: 26508169

32. Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, et al. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. J Heart Lung Transplant 2017; 36:754–762 https://doi.org/10.1016/j.healun.2016.12.011 PMID: 28131663

33. O'Sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, et al. Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification. Circ Cardiovasc Interv. 2015; 8(7):e002358 https://doi.org/10.1161/CIRCINTERVENTIONS.114.002358 PMID: 26156149

34. Chatterjee NA, Lewis GD, Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: limitations of a solitary measurement. JACC Heart Fail. 2015; 3(1):17–21. https://doi.org/10.1016/j.jchf.2014.09.002 PMID: 25453537

35. Brittain EL, Assad TR, Hemnes AR, Newman JH. The Diastolic Pressure Gradient Does Not-and Should Not-Predict Outcomes. JACC Heart Fail. 2015; 3(10):845. https://doi.org/10.1016/j.jchf.2015.06.008 PMID: 26450004

36. Tampakakis E, Tedford RJ. Reply: characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: the conundrum of high and low diastolic pulmonary gradient. JACC Heart Fail. 2015; 3(5):426–7 https://doi.org/10.1016/j.jchf.2015.02.002 PMID: 25951766

37. Tampakakis E, Tedford RJ. Balancing the positives and negatives of the diastolic pulmonary gradient. Eur J Heart Fail. 2017; 19(1):98–100 https://doi.org/10.1002/ejhf.704 PMID: 28052546

38. Stevens GR, Garcia-Alvarez A, Sahni S, Garcia MJ, Fuster V, Sanz J. RV dysfunction in pulmonary hypertension is independently related to pulmonary artery stiffness. JACC Cardiovasc Imaging. 2012; 5(4):378–87 https://doi.org/10.1016/j.jcmg.2011.11.020 PMID: 22498327

39. Hoeper MM, Lam CS, Vachiery JL, Bauersachs J, Gerges C, Lang IM, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a plea for proper phenotyping and further research†. Eur Heart J. 2017; 38:2869–2873 https://doi.org/10.1093/eurheartj/ehw597 PMID: 28011705

40. Segers P, Brimioulle S, Stergiopulos N, Westerhof N, Naeije R, Maggiorini M, et al. Pulmonary arterial compliance in dogs and pigs: the three-element windkessel model revisited. Am J Physiol. 1999; 277:H725–31 PMID: 10444499

41. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999; 99(12):1574–9. PMID: 10096933

Haemodynamics to predict outcome in pulmonary hypertension due to left heart disease: a meta-analysis

To the Editor:

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), as the result of a "passive" increase of left atrial pressure (LAP), leading to isolated post-capillary PH [1–3]. Several haemodynamic parameters have been proposed to identify a more severe phenotype of PH-LHD, for which the increase in pulmonary artery pressure cannot be accounted for by the increase in LAP, and described as combined post-capillary PH with a pre-capillary component, or CpcPH [1–3]. The latter haemodynamic phenotype may potentially expose patients to a higher risk of right ventricular failure and a poorer outcome [4, 5]. However, since the last World Symposium in 2013, how to define the pre-capillary component in PH-LHD has been a matter of debate, as pathophysiological arguments have been suggested to potentially contrast with clinical and prognostic evidences [1].

Given current controversies and uncertainties on this topic, we sought to perform a meta-analysis in order to determine which variable would be associated with mortality in PH-LHD.

We conducted a Medline literature research according to PRISMA recommendations [6] on articles published since 2013, when the diastolic pressure gradient (DPG) was introduced as a possible marker of the pre-capillary component in PH-LHD [2]. We used the following combinations of search terms ("pulmonary hypertension" OR "heart failure" OR "left heart disease") AND ("prognosis" OR "outcome" OR "outcomes" OR "survival") AND ("pulmonary vascular resistance" OR "diastolic pressure gradient" OR "diastolic pressure difference" OR "diastolic pulmonary gradient" OR "diastolic pulmonary vascular pressure gradient" OR "pulmonary artery compliance" OR "hemodynamics"). We only considered papers in which DPG and/or pulmonary vascular resistance (PVR) and/or pulmonary artery compliance (PAC) were analysed for their capability to predict survival in PH-LHD. We excluded articles reporting composite outcome, those focusing only on outcome after heart transplantation, evaluating short-term follow-up, or including unstable patients. PRISMA flow diagram is shown in figure 1a.

Out of 32 articles, 10 responded to the above-mentioned criteria [4, 5, 7–14]. These articles considered DPG, PVR and PAC as continuous or dichotomous variables. For purpose of consistency, and to better individuate the risk associated with each variable, independently of arbitrary cut-offs, we only included those that reported the prognostic power of variables intended in a continuous way. The final analysis was thus conducted on six articles [4, 7–11], including 2513 patients with LHD overall, followed up for 9−15 years. In four studies, all patients had PH [4, 8, 9, 11], while in the remaining two articles at least two-thirds of patients had PH [7, 10]. In the majority of the studies, a multivariate analysis was performed, adjusting the hazard ratios associated with PVR, DPG and PAC for covariates such as age and sex [4, 8, 10, 11], body mass index [10, 11], ethnicity [8, 11], and also for comorbidities [4, 7] and other haemodynamic parameters [8, 10].

Analysis of the different populations revealed heterogeneity in terms of age, gender and aetiology of PH-LHD. Mean age was 60 years old, with mean values varying between 49 and 69 years old across the studies. Younger ages were more represented in heart failure with reduced ejection fraction (HFrEF) cohorts while older ages were found in cohorts of heart failure with preserved ejection fraction (HFpEF) or valvular heart disease. Male sex prevalence varied between 25 and 79%. HFpEF was the leading aetiology

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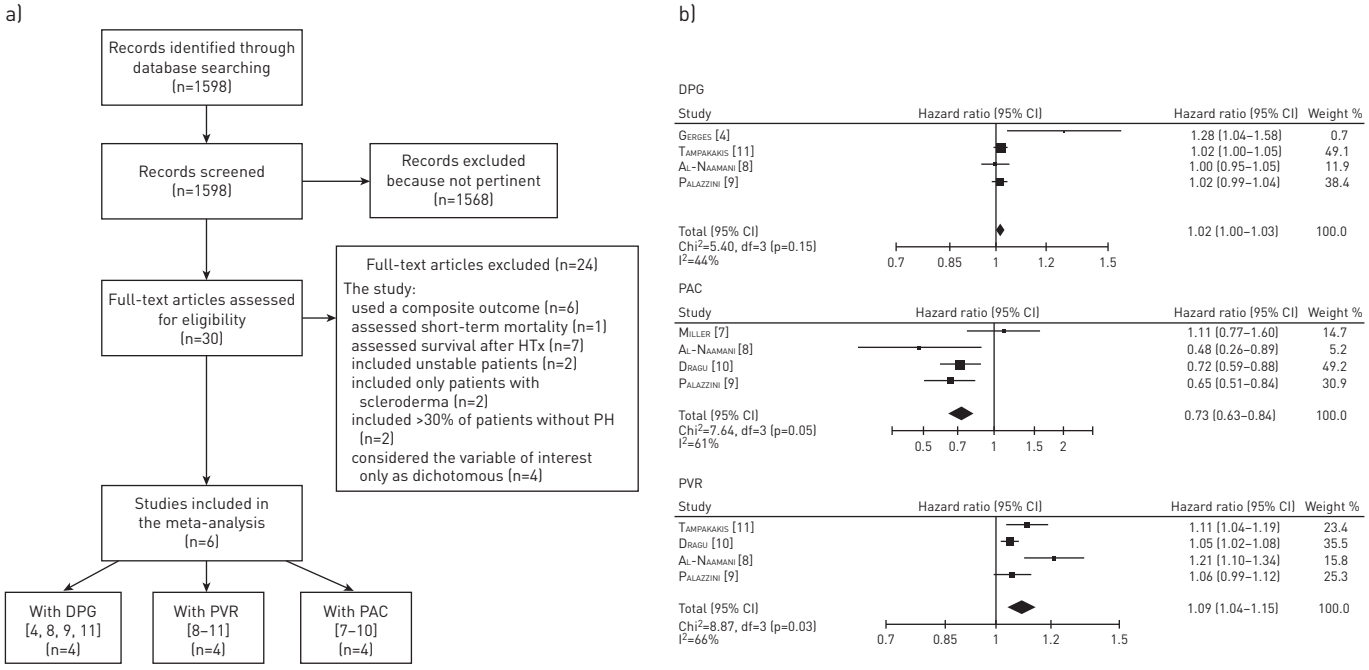

FIGURE 1 a) Flow diagram of study selection. b) Forest plot analysis for survival according to pulmonary vascular resistance (PVR), diastolic pressure gradient (DPG) and pulmonary arterial compliance (PAC). HTx: heart transplant; PH: pulmonary hypertension.

in 3 studies [4, 8, 10], while valvular heart disease was the leading aetiology or a significant comorbidity (present in up to 30% of patients) in three studies [4, 7, 9]. In these latter studies, it is possible that right heart catheterisation has been performed in some patients as a pre-therapeutic assessment, although this has not been systematically reported by the authors. Neither symptoms (*e.g.* New York Heart Association functional class) nor concomitant relevant pathological conditions were consistently reported in all studies.

Mean pulmonary artery pressure was on average 35 mmHg, mean PVR 3.0 WU, mean DPG was 1.2 mmHg (this latter derived from five studies [4, 8–11]) and mean PAC 2.5 mL·mmHg^{-1}(derived from four studies [7–10]). Mean PVR was >3 WU in three studies [7–9], mean DPG was <7 mmHg in all studies, while mean PAC was <2.3 mL·mmHg^{-1} in two studies [8, 9]. Based on mean±SD values, there is a high suspicion of a significant proportion of negative DPGs, at least in five out of six studies [4, 8–11].

We pooled the original estimates by using both the fixed-effects model and the random-effects model. Heterogeneity between study-specific estimates was tested using the Q statistic and I^2 index. When a significant heterogeneity was found (Q statistic p-value <0.05), the results from the random-effects model were presented. To evaluate publication bias, the "trim and fill" method was used [15]. This is an extension of the funnel plot technique, where "missing studies" are identified and estimated based on the symmetry of the funnel plot [16].

Forest plots analysis for survival according to DPG, PVR and PAC are depicted in figure 1b. Increasing values of PVR and DPG were associated with higher risk of death in PH-LHD, while increasing values of PAC were associated with lower risk. Results did not change when performing a sensitivity analysis including only the four studies in which all patients had PH [4, 8, 9, 11]. Some suggestions of presence of publication bias come from the results obtained from the "trim and fill" method. The summary estimates coming from this method are very similar to the summary original estimates for each outcome, even if the summary estimates of DPG and PAC were not statistically significant. Nevertheless, the paucity of included studies puts caution in interpreting the results obtained by the "trim and fill" method [16].

This meta-analysis may thus reconcile contrasting theories and evidences on which parameter(s) to define a pre-capillary component and/or to predict prognosis in PH-LHD.

Indeed, the DPG was re-introduced as a marker of disease in 2013 based on solid physiological background, histological demonstration of association with pulmonary arterial remodelling, and possible prognostic potential [2, 4]. However, the DPG is a small number highly subjected to background noise, partly related to problems in the measurement of diastolic pulmonary artery pressure and pulmonary artery wedge pressure (PAWP) [1, 17], so that over 30% of patients in the published series may present

with negative DPG, which is deemed to be physiologically impossible [1]. This may be due to technical limitations and interpretations drawbacks in the accuracy of PAWP and/or diastolic pulmonary artery pressure determination [1–3, 17], that may also affect, to some extent, PAC and PVR [1]. It is also interesting to note that only a minority of patients with PH-LHD may present with high DPGs, which is confirmed by low mean DPGs values (about 1 mmHg) in the whole cohort that was subjected to meta-analysis. However, at variance from some individual reports, DPG was found to be associated with outcome, with a 2% increase in risk for a unitary increase in DPG.

Based on contrasting evidences on DPG, PVR was reintroduced because it may have additional value as an indirect reflection of right ventricular function [3] since, in patients with PH-LHD, it may normalise when improving cardiac output by means of systemic vasodilators or inotropes. It should be underscored that PVR is a well-consolidated and longstanding used variable in clinical practice, despite physiological limitations due to its flow and filling pressure dependency [1]. Our meta-analysis confirms available data on the prognostic discriminative potential of PVR. A unitary increase in PVR was associated with 9% increase in risk of adverse outcome.

Recently, PAC has been increasingly investigated in PH-LHD, and it was proposed as a predictor of outcome [1, 7–10]. However, PAC is an even smaller number than DPG, it may be highly dependent on PAWP [18], and the formula utilised to calculate it in clinical practice may overestimate the true PAC by 60 to 80% [1]. Despite these limitations, PAC is also associated with outcome, with higher values being related with lower risk.

Some other limitations of this analysis should be underlined. In particular, only few retrospective studies (or retrospective analysis of a prospective registry) were available for this analysis, without prospective validation of haemodynamic measurements. This should encourage confirmation of our results in *ad hoc* designed prospective studies.

In summary, the present analysis confirms that the population of PH-LHD is heterogeneous in terms of age, aetiology, proportion of negative DPGs and haemodynamic presentation. However, despite the differences in cohorts and the intrinsic limitations of each variable [1], PVR, DPG and PAC appear to be associated with survival in PH-LHD. Importantly, we may speculate that these variables should be viewed as complementary and may be used in combination as an intrinsic control. Which combination of variables would best be used to predict outcome remains a matter of debate.

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References

1 Naeije R, Gerges M, Vachiéry JL, *et al.* Hemodynamic phenotyping of pulmonary hypertension in left heart failure. *Circ Heart Fail* 2017; 10: e004082.
2 Vachiéry JL, Adir Y, Barberà JA, *et al.* Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol* 2013; 62: D100–D108.
3 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.

4 Gerges C, Gerges M, Lang MB, *et al.* Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest* 2013; 143: 758–766.
5 Gerges M, Gerges C, Pistritto AM, *et al.* Pulmonary hypertension in heart failure: epidemiology, right ventricular function and survival. *Am J Respir Crit Care Med* 2015; 192: 1234–1246.
6 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; 6: e1000097.
7 Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail* 2013; 1: 290–299.
8 Al-Naamani N, Preston IR, Paulus JK, *et al.* Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail* 2015; 3: 467–474.
9 Palazzini M, Dardi F, Manes A, *et al.* Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes. *Eur J Heart Fail* 2017; in press [https://doi.org/10.1002/ejhf.860].
10 Dragu R, Rispler S, Habib M, *et al.* Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail* 2015; 17: 74–80.
11 Tampakakis E, Leary PJ, Selby VN, *et al.* The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail* 2015; 3: 9–16.
12 O'Sullivan CJ, Wenaweser P, Ceylan O, *et al.* Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: insights from the new proposed pulmonary hypertension classification. *Circ Cardiovasc Interv* 2015; 8: e002358.
13 Assad TR, Hemnes AR, Larkin EK, *et al.* Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. *J Am Coll Cardiol* 2016; 68: 2525–2536.
14 Brunner NW, Yue SF, Stub D, *et al.* The prognostic importance of the diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance in patients undergoing transcatheter aortic valve replacement. *Cath Cardiovasc Interv* 2017; 90: 1185–1191.
15 Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56: 455–463.
16 Phan K, Tian DH, Cao C, *et al.* Systematic review and meta-analysis: techniques and a guide for the academic surgeon. *Ann Cardiothorac Surg* 2015; 4: 112–122.
17 Houston BA, Tedford RJ. What we talk about when we talk about the wedge pressure. *Circ Heart Fail* 2017; 10: e004450.
18 Tedford RJ, Hassoun PM, Mathai SC, *et al.* Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation* 2012; 125: 289–297.

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ORIGINAL CLINICAL SCIENCE

Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component

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KEYWORDS:
pulmonary hypertension;
cardiopulmonary exercise test;
ventilation;
oscillatory breathing;
diastolic pressure gradient

BACKGROUND: Excessive exercise-induced hyperventilation and high prevalence of exercise oscillatory breathing (EOB) are present in patients with post-capillary pulmonary hypertension (PH) complicating left heart disease (LHD). Patients with pre-capillary PH have even higher hyperventilation but no EOB. We sought to determine the impact of a pre-capillary component of PH on ventilatory response to exercise in patients with PH and left heart disease.

METHODS: We retrospectively compared patients with idiopathic or heritable pulmonary arterial hypertension (PAH, $n = 29$), isolated post-capillary PH (IpcPH, $n = 29$), and combined post- and pre-capillary PH (CpcPH, $n = 12$). Diastolic pressure gradient (DPG = diastolic pulmonary artery pressure − pulmonary wedge pressure) was used to distinguish IpcPH (DPG <7 mm Hg) from CpcPH (DPG ≥ 7 mm Hg).

RESULTS: Pulmonary vascular resistance (PVR) was higher in PAH, intermediate in CpcPH, and low in IpcPH. All patients with CpcPH but 1 had PVR >3 Wood unit. Exercise-induced hyperventilation (high minute ventilation over carbon dioxide production, low end-tidal carbon dioxide) was marked in PAH, intermediate in CpcPH, and low in IpcPH ($p < 0.001$) and correlated with DPG and PVR. Prevalence of EOB decreased from IpcPH to CpcPH to PAH ($p < 0.001$).

CONCLUSIONS: Patients with CpcPH may have worse hemodynamics than patients with IpcPH and distinct alterations of ventilatory control, consistent with more exercise-induced hyperventilation and less EOB. This might be explained at least in part by the presence and extent of pulmonary vascular disease.

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One characteristic of pre-capillary pulmonary hypertension (PH) is the exaggerated ventilatory response to exercise, as expressed by an increased ratio between minute ventilation (V_E) and carbon dioxide production (VCO_2).[1–3] An increased V_E/VCO_2 ratio can also be found, although to a lesser extent, in patients with left heart disease (LHD).[1] In the latter patients, the development of post-capillary pulmonary hypertension (PH) may have an additional impact on the control of ventilation during exercise,[4–6] which might be even more pronounced in the presence of a pre-capillary component.[7,8] Exercise oscillatory breathing

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(EOB), another manifestation of ventilatory control derangement, has been related to the presence of post-capillary PH in patients with LHD,[6] but it is generally not found in patients with pre-capillary PH.[9]

How to identify a pre-capillary component in patients with PH-LHD has been revised in recent years.[10–12] Based on physiologic reasoning, the diastolic pressure gradient (DPG) has been proposed as 1 of the hemodynamic parameters serving this purpose.[10,12,13] In addition, pathologic specimens from patients with PH-LHD and an elevated DPG present with some degree of arterial remodeling evoking a real pulmonary vasculopathy, in contrast to the general sparing of the arterial side of the pulmonary circulation in cases of isolated post-capillary PH (IpcPH).[14] Therefore, combined post- and pre-capillary PH (CpcPH) appears to represent a distinct phenotype of PH-LHD.[10,12,14,15] We hypothesized that the presence of exercise hyperpnea, as reflected by a high V_E/VCO_2 ratio and low end-tidal pressure for carbon dioxide ($PETCO_2$), would be linked to the degree of pulmonary vasculopathy. In addition, as EOB is virtually absent in purely pre-capillary PH but extremely frequent in post-capillary PH, we hypothesized that in PH-LHD a pre-capillary component might be associated with less EOB. Therefore, the aim of our study was to determine whether patients with CpcPH would have an exercise profile closer to patients with PAH compared with patients with IpcPH.

Methods

The study was approved by the Ethics Committee of the Erasme Hospital (reference number P2015/359). We retrospectively compared patients with PH undergoing an elective assessment at the Pulmonary Hypertension and Heart Failure Clinic of the Erasme Hospital between January 2007 and October 2014. PH was defined according to European Society of Cardiology and European Respiratory Society guidelines.[12] Three groups of patients were studied: patients with idiopathic or heritable PAH naïve of specific therapy and patients with PH-LHD, further subdivided into patients with IpcPH, with DPG $<$ 7 mm Hg, and patients with CpcPH, with DPG $\geq$ 7 mm Hg. Only patients with complete hemodynamic data, who had a cardiopulmonary exercise test within 7 days from right heart catheterization, were included. Patients with a respiratory exchange ratio at peak exercise <1.00 were excluded.

Hemodynamics

All right heart catheterizations were performed and reviewed by a cardiologist expert in PH. Pulmonary artery pressures (PAPs) were measured at end expiration and averaged over several cardiac cycles (5–8 cycles). Cardiac output was measured by thermodilution in triplicate (using an average of 3 measurements within 10% of agreement). DPG was calculated as the difference between diastolic PAP and pulmonary wedge pressure.[10–12] Transpulmonary pressure gradient (TPG) was calculated as the difference between mean PAP and pulmonary wedge pressure.[10] Pulmonary vascular resistance (PVR) was calculated as the ratio between TPG and cardiac output.

Cardiopulmonary exercise test

All cardiopulmonary exercise tests were performed on an electromagnetically braked cycle ergometer with the patient connected to the Vmax Metabolic Cart (SensorMedics Corp., Yorba Linda, CA) through a mask. After a 3-minute warm-up period (unloaded pedaling), a 1-minute step-increase protocol (5–10 W/min) was performed to achieve exhaustion in approximately 10 minutes.[16] An average of the last 30-second period of exercise was taken as peak value for the variables of interest. Ventilatory threshold was calculated by the V-slope method and confirmed by analysis of the end-tidal pressures plot and the ventilatory equivalents plot by 2 independent operators. The V_E/VCO_2 slope was calculated over the linear component of V_E vs VCO_2.[16] EOB was defined as cyclic fluctuations in V_E at rest that persist during effort lasting $\geq$60% of the exercise duration, with an amplitude $\geq$15% of the average resting value.[17]

Statistics

Descriptive data are reported as mean $\pm$ SD for continuous variables and absolute number with percentage for categorical variable. Distribution of the variables in terms of proximity to normal was detected by the Shapiro-Wilk test; the homogeneity of variances was performed with the Bartlett test. When needed, a logarithmic transformation was performed to achieve normal distribution. For the variables normally distributed and homoscedastic, analysis of variance with contrasts a posteriori was used. A Kruskal-Wallis rank sum test was used with pairwise Wilcoxon rank sum test as post-hoc when necessary. For multiple comparisons, the algorithm that controls the expected rate of false-positive results for all positive results (false discovery rate) was used.[18] The regression analysis between both DPG and PVR vs $PETCO_2$ at the anaerobic threshold was performed using the ordinary least-squares method. The regression analysis between both DPG and PVR vs V_E/VCO_2 slope and vs V_E/VCO_2 at the anaerobic threshold was performed using a robust regression with MM-type estimator.[19,20] Pearson's chi-square contingency table test was used to analyze categorical variables; the p-value was computed for a Monte Carlo test[21] with 2,000 replicates when needed. An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using R (R Foundation, Vienna, Austria).

Results

From 2007 to 2014, 548 patients with PH were assessed. Inclusion criteria were met by 70 patients, including 41 patients with PH-LHD (12 CpcPH, 29 IpcPH) and 29 with PAH.

General characteristics

The general characteristics of the 3 groups of patients are reported in Table 1. The New York Heart Association class and NT-proBNP values did not differ between the 3 groups. There were no significant differences in the etiology of LHD, comorbidities, and background therapy between IpcPH and CpcPH (Table 2). Of patients with PH-LHD, 49% presented with preserved left ventricular ejection fraction. Chronic thromboembolic PH was ruled out by ventilation/perfusion scan and computed tomography (CT)

Table 1 General Characteristics of the 3 Groups of Patients

	IpcPH ($n = 29$)	CpcPH ($n = 12$)	PAH ($n = 29$)	*p*-value			
				Overall	CpcPH vs IpcPH	CpcPH vs PAH	IpcPH vs PAH
Demographics and anthropometrics							
Female patients, *n* (%)	13 (45)	6 (50)	14 (48)	0.943			
Age, years	63 ± 11	66 ± 12	57 ± 16	0.081			
Height, cm	166 ± 9	170 ± 13	167 ± 10	0.406			
Weight, kg	75 ± 17	87 ± 21	72 ± 14	0.033	0.050	0.030	0.496
BMI, kg/m^2	27 ± 6	30 ± 4	26 ± 5	0.080			
NYHA class	2.6 ± 0.6	2.7 ± 0.5	2.9 ± 0.3	0.076			
NT-proBNP, pg/ml	2,713 ± 2,819	2,636 ± 2,421	2,946 ± 3,149	0.972			
Lung function tests							
Spirometry, *n*	26	11	28				
FEV_1, liter	2.0 ± 0.6	1.9 ± 0.5	2.4 ± 0.8	0.091			
FEV_1, % of predicted	78 ± 19	71 ± 13	83 ± 17	0.146			
FVC (L)	2.4 ± 0.7	2.6 ± 0.8	3.0 ± 1.0	0.065			
FVC, % of predicted	77 ± 20	75 ± 13	86 ± 18	0.118			
FEV_1/FVC	81 ± 8	75 ± 9	79 ± 9	0.118			
Diffusion capacity, *n*	20	10	27				
D_{LCO}, % of predicted	62 ± 16	58 ± 24	51 ± 26	0.237			
K_{CO}, % of predicted	66 ± 14	53 ± 21	49 ± 25	0.026	0.176	0.593	0.023

BMI, body mass index; CpcPH, combined pre- and post-capillary pulmonary hypertension; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expired volume in one second; FVC, forced vital capacity; IpcPH, isolated post-capillary pulmonary hypertension; K_{CO}, diffusing capacity for carbon monoxide normalized for alveolar volume; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PAH, pulmonary arterial hypertension.

angiography of the lungs. Results of lung spirometry (Table 1) were available for all patients except 3 in the IpcPH group, 1 in the CpcPH group, and 1 in the PAH group. However, 4 patients (2 in the IpcPH group) underwent high-resolution CT scan of the chest, excluding parenchymal lung disease. The prevalence of chronic

Table 2 Clinical Characteristics of Patients With Pulmonary Hypertension Secondary to Left Heart Disease

	IpcPH	CpcPH	*p*-value
Etiology of left heart failure			
HFpEF, *n* (%)	13 (45)	7 (58)	
Valvular heart disease, *n* (%)	3 (10)	2 (17)	0.558
HFrEF, *n* (%)	13 (45)	3 (25)	
Comorbidities			
Diabetes mellitus, *n* (%)	11 (38)	3 (25)	0.504
Arterial hypertension, *n* (%)	15 (52)	7 (58)	0.967
Dyslipidemia, *n* (%)	16 (55)	6 (50)	1.000
Obesity, *n* (%)	8 (28)	4 (33)	1.000
Permanent atrial fibrillation, *n* (%)	5 (17)	2 (17)	1.000
Smoking, *n* (%)	14 (48)	7 (58)	0.733
History of pulmonary embolism, *n* (%)	5 (17)	3 (25)	0.688
Known and treated OSAS, *n* (%)	6 (21)	2 (17)	1.000
Treatment			
Diuretics, *n* (%)	22 (76)	9 (75)	1.000
ACEI or ARB, *n* (%)	22 (76)	8 (67)	0.545
Beta blockers, *n* (%)	22 (76)	6 (50)	0.140
Spironolactone, *n* (%)	13 (45)	4 (33)	0.732
Digoxin, *n* (%)	3 (10)	3 (25)	0.339
Amiodarone, *n* (%)	7 (24)	1 (8)	0.394
CRT-D, *n* (%)	6 (21)	1 (8)	0.339
ICD, *n* (%)	3 (10)	0 (0)	0.247
Pacemaker, *n* (%)	0 (0)	1 (8)	0.116

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CpcPH, combined post- and pre-capillary pulmonary hypertension; CRT-D, cardiac resynchronization therapy–defibrillator; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IpcPH, isolated post-capillary pulmonary hypertension; ICD, implanted cardioverter defibrillator; OSAS, obstructive sleep apnea syndrome.

Table 3 Invasive Hemodynamics at Rest in the 3 Groups of Patients

				p-value			
	IpcPH	CpcPH	PAH	Overall	CpcPH vs IpcPH	CpcPH vs PAH	IpcPH vs PAH
HR, beats/min	70 ± 13	74 ± 12	77 ± 12	0.083			
BP, mm Hg							
Systolic	124 ± 26	131 ± 27	131 ± 27	0.675			
Diastolic	69 ± 11	74 ± 13	74 ± 13	0.003	0.254	0.168	0.002
Mean	88 ± 14	93 ± 14	93 ± 14	0.117			
PAP, mm Hg							
Systolic	51 ± 12	73 ± 21	89 ± 17	<0.001	<0.001	0.004	<0.001
Diastolic	24 ± 4	34 ± 6	38 ± 9	<0.001	<0.001	0.147	<0.001
Mean	33 ± 6	47 ± 10	55 ± 11	<0.001	<0.001	0.020	<0.001
PAWP, mm Hg	22 ± 4	22 ± 4	10 ± 4	<0.001	0.967	<0.001	<0.001
RAP, mm Hg	11 ± 6	13 ± 3	9 ± 5	0.012	0.102	0.014	0.102
RAP/PAWP	0.5 ± 0.2	0.6 ± 0.2	0.9 ± 0.5	<0.001	0.105	0.051	<0.001
Sa_{O_2}, %	97 ± 2	93 ± 5	91 ± 4	<0.001	0.021	0.238	<0.001
Sv_{O_2}, %	65 ± 8	60 ± 7	59 ± 10	0.038	0.093	0.844	0.066
CI, liters/min/m^2	2.3 ± 0.5	2.3 ± 0.6	1.9 ± 0.4	0.021	0.921	0.060	0.034
TPG, mm Hg	11 ± 4	25 ± 10	46 ± 11	<0.001	<0.001	<0.001	<0.001
DPG, mm Hg	2 ± 2	13 ± 5	29 ± 9	<0.001	<0.001	<0.001	<0.001
PVR, Wood unit	3 ± 1	7 ± 5	14 ± 4	<0.001	<0.001	<0.001	<0.001

BP, systemic blood pressure; CI, cardiac index; CpcPH, combined post- and pre-capillary pulmonary hypertension; DPG, diastolic pressure gradient; HR, heart rate; IpcPH, isolated post-capillary pulmonary hypertension; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TPG, transpulmonary pressure gradient; Sa_{O_2}, arterial oxygen saturation; Sv_{O_2}, mixed venous oxygen saturation.

obstructive pulmonary disease was similar ($p = 0.713$) in the 3 groups (2 in the IpcPH group, 2 in the CpcPH group, and 2 in the PAH group). The contribution of chronic obstructive pulmonary disease in PH was considered highly unlikely, based on pulmonary function tests, CT scan of the chest, and blood gas analysis. In addition, no patient had ventilatory limitation to exercise. Lung diffusion capacity for carbon monoxide (Table 1) was available in a subgroup of patients. Diffusion capacity for carbon monoxide corrected for alveolar volume was lower in patients with PAH than in patients with IpcPH.

Hemodynamics

Patients with CpcPH presented with values of systolic, mean, and diastolic PAP; PVR; DPG; and TPG in between IpcPH (lower extreme) and PAH (higher extreme), as shown in Table 3 and Figure 1. Pulmonary wedge pressure values did not differ between IpcPH and CpcPH and were as expected higher in PH-LHD than in PAH. Right atrial pressure was higher in patients with CpcPH than in patients with PAH. The ratio between filling pressures (right atrial pressure/pulmonary artery wedge pressure) was higher in PAH than in IpcPH. Cardiac output was not different between CpcPH and PAH but was lower in PAH compared with IpcPH. Arterial oxygen saturation was lower in PAH and CpcPH than in IpcPH, without significant differences in mixed venous saturation between the 3 groups. Among patients with PH-LHD, all patients with CpcPH but 1 had a TPG >12 mm Hg, but 30% of patients with IpcPH had a

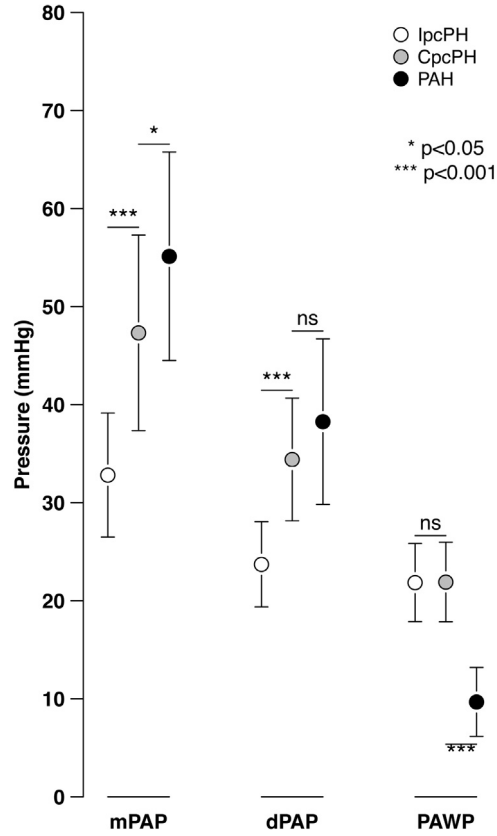

Figure 1 Mean pulmonary artery pressure (mPAP), diastolic pulmonary pressure (dPAP), and pulmonary artery wedge pressure (PAWP) in the 3 groups of patients.

Table 4 Cardiopulmonary Exercise Test in the 3 Groups of Patients

				p-value			
	IpcPH	CpcPH	PAH	Overall	CpcPH vs IpcPH	CpcPH vs PAH	IpcPH vs PAH
Rest							
V_E, liters/min	12 ± 3	14 ± 3	16 ± 5	0.001	0.080	0.365	0.001
V_T, liters	0.6 ± 0.1	0.7 ± 0.2	0.8 ± 0.2	<0.001	0.189	0.146	<0.001
RR, minute^{-1}	21 ± 5	22 ± 5	21 ± 6	0.764			
HR, beats/min	71 ± 13	76 ± 11	84 ± 17	0.004	0.287	0.169	0.003
SBP, mm Hg	127 ± 30	129 ± 36	117 ± 23	0.398			
DBP, mm Hg	74 ± 17	74 ± 12	85 ± 13	0.013	0.991	0.055	0.019
AT							
Identifiable, *n* (%)	24 (83)	10 (83)	29 (100)	0.063			
V_E, liters/min	23 ± 5	27 ± 6	26 ± 8	0.202			
V_T, liters	0.9 ± 0.3	1.0 ± 0.2	1.1 ± 0.4	0.200			
RR, minute^{-1}	25 ± 8	28 ± 6	25 ± 7	0.467			
HR, beats/min	90 ± 16	93 ± 11	98 ± 18	0.171			
O_2 pulse, ml/beat	7.9 ± 2.8	7.7 ± 2.6	5.6 ± 1.8	0.002	0.804	0.026	0.002
V_{O_2}, liters/min	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.021	0.757	0.049	0.047
V_{O_2}, ml/kg/min	9.5 ± 2.4	8.2 ± 1.8	7.7 ± 2.6	0.029	0.260	0.529	0.026
VCO_2, liters/min	0.6 ± 0.2	0.7 ± 0.2	0.5 ± 0.2	0.032	0.773	0.066	0.066
Peak							
V_E, liters/min	48 ± 15	48 ± 12	61 ± 19	0.006	0.962	0.035	0.008
V_T, liters	1.3 ± 0.5	1.3 ± 0.4	1.7 ± 0.5	0.017	0.855	0.046	0.030
RR, minute^{-1}	38 ± 9	39 ± 10	38 ± 7	0.872			
V_E/MVV, %	58 ± 12	63 ± 14	68 ± 17	0.051			
MVV − V_E	35 ± 17	29 ± 17	33 ± 23	0.719			
HR, beats/min	108 ± 25	113 ± 18	130 ± 28	0.006	0.534	0.095	0.005
HR, % maximum predicted	69 ± 16	74 ± 11	79 ± 13	0.024	0.315	0.315	0.020
O_2 pulse, mL/beat	10.3 ± 3.9	9.3 ± 3.7	6.9 ± 2.2	<0.001	0.439	0.030	<0.001
Workload, W	62 ± 31	55 ± 26	51 ± 25	0.271			
V_{O_2}, liters/min	1.1 ± 0.5	1.0 ± 0.4	0.9 ± 0.3	0.119			
V_{O_2}, ml/min	14.6 ± 4.9	11.9 ± 2.6	12.5 ± 4.5	0.103			
V_{O_2}, % of predicted	64 ± 28	62 ± 26	48 ± 16	0.035	0.867	0.125	0.043
VCO_2, liters/min	1.3 ± 0.5	1.2 ± 0.4	1.0 ± 0.4	0.085			
RER	1.18 ± 0.08	1.12 ± 0.08	1.16 ± 0.06	0.073			
SBP, mm Hg	145 ± 39	148 ± 41	147 ± 26	0.989			
DBP, mm Hg	83 ± 16	86 ± 11	96 ± 13	0.003	0.474	0.084	0.003
V_E/VCO_2 slope	32 ± 5	40 ± 11	53 ± 16	<0.001	0.029	0.010	<0.001

AT, anaerobic threshold; CpcPH, combined post- and pre-capillary pulmonary hypertension; DBP, diastolic blood pressure; HR, heart rate; IpcPH, isolated post-capillary pulmonary hypertension; MVV, maximal voluntary ventilation; PAH, pulmonary arterial hypertension; $PETCO_2$, end-tidal partial pressure for carbon dioxide; RER, respiratory exchange ratio; RR, respiratory rate; SBP, systolic blood pressure; V_E, minute ventilation; V_{O_2}, oxygen consumption; VCO_2, carbon dioxide production; V_T, tidal volume.

TPG >12 mm Hg. PVR was >3 Wood units in 11 of 12 patients with CpcPH compared with 9 of 29 patients with IpcPH.

Cardiopulmonary exercise test

Cardiopulmonary exercise testing was performed on average 1.3 days ± 0.8 before or after right heart catheterization. Cardiopulmonary exercise test results are reported in Table 4. Oxygen consumption (V_{O_2}) at peak exercise was lower in patients with PAH than in patients with IpcPH as a percentage of predicted values but not when expressed as absolute or weight-normalized values. At rest, peripheral oxygen saturation (Spo_2) was lower in patients with CpcPH and patients with PAH than in patients with IpcPH, but only patients with PAH developed a real exercise-induced desaturation, with lower Spo_2 values than PH-LHD both at the anaerobic threshold and at peak exercise (Figure 2). At rest, patients with CpcPH had intermediate values of $PETCO_2$ (30 mm Hg ± 5) compared with IpcPH and PAH (33 mm Hg ± 4 and 25 mm Hg ± 5, respectively, $p < 0.05$). This difference persisted also at the anaerobic threshold (Figure 3) but not at peak exercise, where patients with IpcPH and patients with CpcPH had similar $PETCO_2$ values (30 mm Hg ± 5 vs 28 mm Hg ± 5, $p = 0.275$), which were overall higher ($p < 0.001$) than in patients with PAH (20 mm Hg ± 6). At rest, the V_E/VCO_2 ratio was higher ($p = 0.001$) in patients with PAH (54 ± 13) than in patients with IpcPH (43 ± 6) but was not different between patients with CpcPH (47 ± 8) and patients with PAH ($p = 0.136$) or between patients with CpcPH and patients with IpcPH ($p = 0.222$). The V_E/VCO_2 ratio at the anaerobic threshold and the V_E/VCO_2 slope were lower in

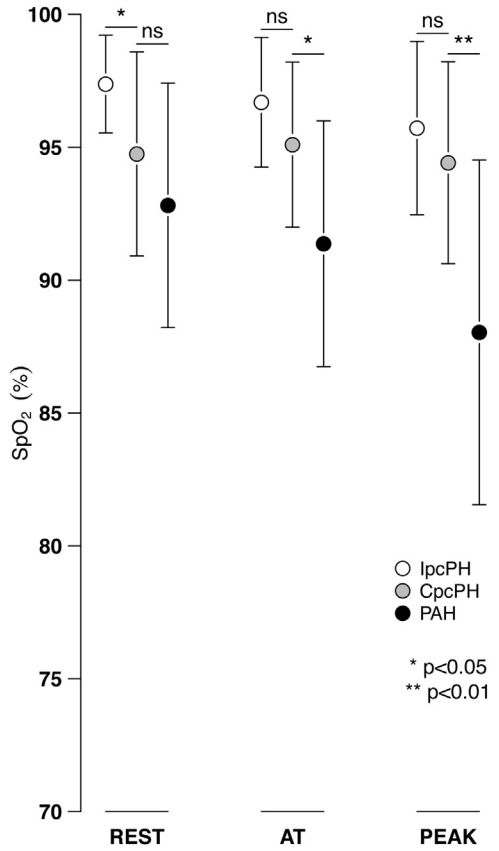

Figure 2 Evolution of peripheral oxygen saturation from rest to peak exercise in the 3 groups of patients. AT, anaerobic threshold.

patients with IpcPH, intermediate in patients with CpcPH, and higher in patients with PAH (Figure 3). At peak exercise, the V_E/VCO_2 ratio was higher ($p < 0.001$) in patients with PAH (64 ± 21) than in patients with CpcPH (44 ± 12) and patients with IpcPH (39 ± 7) but was not different between CpcPH and IpcPH ($p = 0.243$). The prevalence of EOB increased ($p < 0.001$) from PAH (absence of EOB) to CpcPH (17%) to IpcPH (40%).

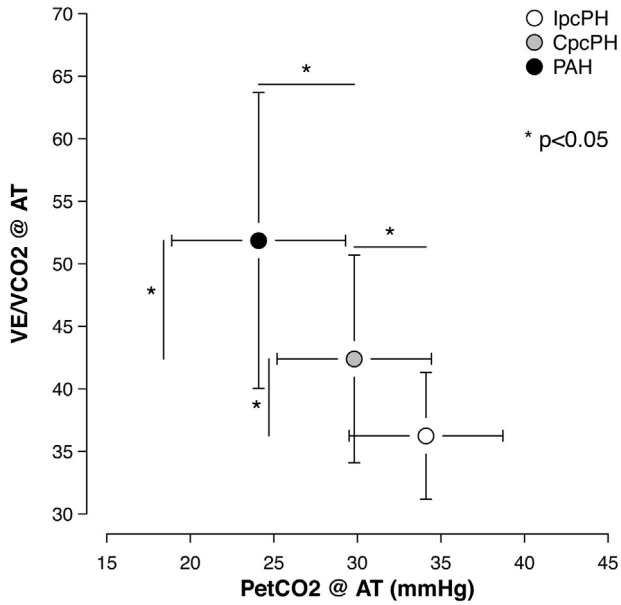

Figure 3 Hyperbolic relationship between $PETCO_2$ and ventilatory equivalents for CO_2 at the anaerobic threshold (AT).

Correlations between ventilatory response to exercise and resting hemodynamics

Across the whole population, both DPG and PVR were directly correlated to the V_E/VCO_2 slope ($R^2 = 0.48$ and $R^2 = 0.43$, respectively; $p < 0.001$), were directly correlated to the V_E/VCO_2 ratio at anaerobic threshold (Figure 4), and were inversely correlated to $PETCO_2$ at anaerobic threshold ($R^2 = 0.48$ and $R^2 = 0.49$, respectively; $p < 0.001$).

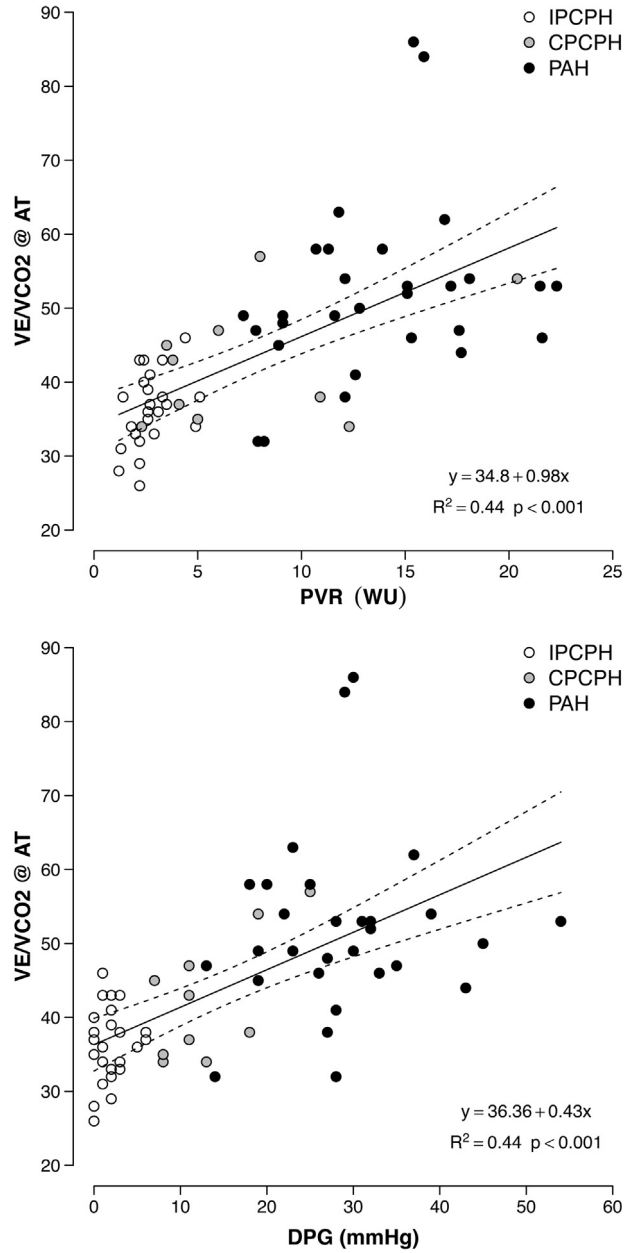

Figure 4 Regression analysis between the ventilatory equivalents at the anaerobic threshold (AT) and hemodynamics markers of pulmonary vascular disease.

Discussion

In this retrospective study, we investigated the cardiorespiratory profile during exercise in patients with IpcPH, CpcPH, and idiopathic/heritable PAH. We found a stepwise increase of exercise-induced hyperventilation as well as a reduction of the occurrence of EOB passing from IpcPH to CpcPH to PAH, consistent with our hypothesis. In our cohort, 25% of the patients who underwent right heart catheterization had PH-LHD, with CpcPH representing only 5% of the whole cohort. Therefore, CpcPH appears to be a relatively uncommon condition, which is in keeping with previous findings.[14,15,22,23] With a female predominance and the inclusion of a significant number of patients with preserved left ventricular ejection fraction, our population contrasts with previous reports coming from heart failure centers,[7,8,22] but it is consistent with the large cohort of Gerges et al,[15] reflecting current practice in PH referral centers.

DPG alone was used as a marker of disease to discriminate CpcPH from IpcPH, according to previous work.[10,13–15] The addition of PVR to DPG as a marker of pulmonary vasculopathy has been proposed by recent guidelines,[12] and a "strict" combination of the 2 parameters (DPG and PVR instead of DPG and/or PVR) appears to be supported by more recent observations.[15,24] Given the severity of our CpcPH population (mean DPG of 13 mm Hg and mean PVR of 7 Wood units), such refinement of the definition would not have changed the interpretation of our results: All patients with CpcPH but 1 had PVR >3 Wood units, whereas 70% of patients with IpcPH had PVR <3 Wood units; PVR was >3.5 Wood units in only 14% of patients with IpcPH. In other words, most patients with PH-LHD with a high DPG presented also with higher TPG and PVR than patients with a low DPG,[24] whereas neither cardiac output nor wedge pressure differed between the 2 groups. Taken together, these findings may reinforce the hypothesis that CpcPH could represent a subpopulation of PH-LHD with a distinct or more severe pulmonary vascular phenotype[14,15]; this supports the pathobiologic hypothesis of an additional mechanism beyond the increase of pulmonary artery wedge pressure leading to an elevation of diastolic PAP in CpcPH.[10,25]

The pattern of exercise response found in our patients with PAH is consistent with previous findings.[1–3,9] It is characterized by clear exercise-induced desaturation and exercise hyperventilation, with very low $PETCO_2$ values and very high ventilatory equivalent for carbon dioxide. Similarly, our IpcPH population behaved as expected, with a high prevalence of EOB and a modest increase in exercise-induced hyperventilation.[5,6,9,26] Our CpcPH population behaved as in between IpcPH and PAH, with an intermediate pattern of ventilatory control derangement, eventually supporting the hypothesis that CpcPH may represent a different or more severe phenotype than IpcPH.[10,13–15]

A possible link between the presence and extent of a pre-capillary pulmonary vascular component and the degree of exercise-induced hyperventilation may be suggested by the fair correlations we found between markers of pulmonary vascular disease (e.g., DPG and PVR) and V_E/VCO_2 slope, V_E/VCO_2 ratio at the anaerobic threshold, and $PETCO_2$ at the anaerobic threshold.

Many factors have been proposed to explain excessive exercise-induced hyperventilation, including neural reflex pathways,[27–29] right ventricular function,[5] pulmonary vascular function, and ventilation/perfusion mismatch with increased dead space ventilation.[6,8,30–32] Neural reflex pathways contributing to sympathetic activation and hyperventilation, and in particular stimulation of stretch receptors in the right heart chambers (Bainbridge reflex),[33] might be plausibly called into question to contribute to our results. This may be supported by the ratio between right and left filling pressures, which was higher in PAH, intermediate in CpcPH, and lower in IpcPH, mirroring the afterload imposed by the 3 different conditions on the right heart. Despite a progressive increase of right ventricular afterload from IpcPH to CpcPH to PAH, exercise capacity was not strikingly different between the 3 groups; only patients with PAH showed a pattern consistent with a more impaired stroke volume (oxygen pulse) increase than PH-LHD,[16,34] which was partly counterbalanced by a less decreased heart rate reserve. However, a similar stroke volume response to exercise in conditions characterized by progressively increasing afterload at rest may imply that Starling's heterometric adaptation[35] might become more prominent when passing from IpcPH to CpcPH to PAH, further supporting a role for right heart chamber stretch in driving the ventilatory response to exercise in the 3 study populations.[28]

Chemoreflex also could play a role[9,27] in justifying the different pattern of hyperventilation. Patients with CpcPH presented with modestly but significantly lower Sao_2 at rest, possibly secondary to low mixed venous oxygen content[36,37] and eventually suggesting chronic chemoreflex stimulation; however, hypoxemia is generally unrelated to increased V_E/VCO_2 slope in patients with pulmonary vascular disease.[29,36] Finally, ventilation/perfusion matching[30,36,37] is less likely to explain exercise hyperpnea in our study. Ventilation/perfusion inequality may be effectively present in patients with PAH,[30] but it is thought to be generally mild,[36,37] which contrasts with patients with LHD, where high dead space ventilation may significantly account for exercise-induced hyperventilation.[31]

The different and opposite behavior of EOB in the 3 conditions (higher prevalence in IpcPH, intermediate prevalence in CpcPH, and lower prevalence in PAH) warrants attention. As recently reported, EOB is generally not found in patients with PAH,[9] reinforcing the concept that increased pulmonary wedge pressure should play a major role in the development of Cheyne-Stokes and oscillatory respiration[26,38] over sympathetic dysregulation and peripheral reflexes.[39] However, in our population as well as in other studies,[15] pulmonary wedge pressure was nearly identical in patients with IpcPH and CpcPH at rest, and there is no reason to suspect that it may behave differently during exercise.[40] Thus, we may speculate that the pre-capillary component in PH-LHD might exert a sort

of upstream "protective" barrier limiting the afferent input implicated in the genesis of oscillatory ventilation.[41] Alternatively, the same reflex mechanism underlying exercise-induced hyperventilation (e.g., Bainbridge reflex) might centrally interact with chemoreflex in such a way to shift the carbon dioxide threshold leftward,[39] overriding and stabilizing oscillations.

Limitations

This is a single-center, retrospective study including a relatively small number of stable patients with PH, which may limit generalization of the results and requires further confirmation in larger, independent, and possibly multicentric cohorts. Among patients with PH-LHD, we included both patients with preserved and patients with reduced ejection fraction as well as a small number of patients with significant valvular heart disease. Albeit at a first glance these patients may appear as heterogeneous, they all were unified by being stable patients with an advanced form of LHD complicated by PH, receiving a background treatment that was considered optimized based on clinical information available before right heart catheterization. Moreover, the relative distribution of these subgroups as well as comorbidities and long-term therapy was similar when comparing IpcPH and CpcPH. Hemodynamic measurements were available only at rest. However, exercise hemodynamics are not routine practice, and many investigators have reported baseline hemodynamics in association with exercise variables. We relied on non-invasive end-tidal values to indirectly characterize the ventilatory control, in keeping with clinical practice. Finally, despite significant intergroup differences, consistent with what we interpreted as a different exercise pathophysiology in the 3 conditions, several variables of interest showed some overlap between IpcPH and CpcPH and between CpcPH and PAH, preventing clear implications for everyday clinical practice.

Conclusions

Our results suggest that in patients with PH-LHD, a high DPG may discriminate a subpopulation with a worst hemodynamic profile and distinct alterations of ventilatory control, consistent with more exercise-induced hyperventilation and less EOB. These characteristic alterations of ventilatory control might be explained, at least in part, by the presence and extent of pulmonary vascular disease.

Disclosure statement

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References

1. Deboeck G, Niset G, Lamotte M, Vachiéry JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. Eur Respir J 2004;23:747-51.
2. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001;104:429-35.
3. Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. Chest 2005;127:1637-46.
4. Reindl I, Wernecke KD, Opitz C, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. Am Heart J 1998;136:778-85.
5. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail 2008;1:227-33.
6. Guazzi M, Cahalin LP, Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. J Card Fail 2013;19:461-7.
7. Lim HS, Theodosiou M. Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure. J Card Fail 2014;20:650-7.
8. Taylor BJ, Smetana MR, Frantz RP, Johnson BD. Submaximal exercise pulmonary gas exchange in left heart disease patients with different forms of pulmonary hypertension. J Card Fail 2015;21:647-655.
9. Vicenzi M, Deboeck G, Faoro V, Loison J, Vachiéry JL, Naeije R. Exercise oscillatory ventilation in pulmonary arterial hypertension versus heart failure. Int J Cardiol 2016;202:736-40.
10. Vachiéry JL, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 2013;62:D100-8.
11. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34-D42.
12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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 Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-975.
13. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013;41:217-23.
14. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013;143:758-66.
15. Gerges M, Gerges C, Pistritto AM, et al. Pulmonary hypertension in heart failure: epidemiology, right ventricular function and survival. Am J Respir Crit Care Med 2015;192:1234-46.
16. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
17. Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest 2002;121:1572-80.

18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289-300.
19. Yohai VJ. High breakdown-point and high efficiency robust estimates for regression. Ann Stat 1987;15:642-56.
20. Koller M, Stahel WA. Sharpening wald-type inference in robust regression for small samples. Comput Stat Data Anal 2011;55:2504-15.
21. Hope AC. A simplified Monte Carlo test procedure. J R Stat Soc Series B Stat Methodol 1968;30:582-8.
22. Tampakakis E, Leary PJ, Selby VN, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Heart Fail 2015 9-16.
23. Tedford RJ, Beaty CA, Mathai SC, et al. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. J Heart Lung Transplant 2014;33:289-97.
24. Gerges M, Gerges C, Lang IM. How to define pulmonary hypertension due to left heart disease. Eur Respir J 2016;48:553-5.
25. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942-54.
26. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. Circulation 2011;124:1442-51.
27. Chua TP, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1996;27:650-7.
28. Jones PW, Huszczuk A, Wasserman K. Cardiac output as a controller of ventilation through changes in right ventricular load. J Appl Physiol Respir Environ Exerc Physiol 1982;53:218-24.
29. Theodore J, Robin ED, Morris AJ, et al. Augmented ventilatory response to exercise in pulmonary hypertension. Chest 1986;89:39-44.
30. Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE, Wasserman K. A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension. Chest 2001;119: 824-32.
31. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. Circulation 1997;96:2221-7.
32. Otulana B, Higenbottam T. The role of physiological deadspace and shunt in the gas exchange of patients with pulmonary hypertension: a study of exercise and prostacyclin infusion. Eur Respir J 1988;1: 732-737.
33. Ciarka A, Vachièry JL, Houssière A, et al. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. Chest 2007;131:1831-7.
34. Spruijt OA, de Man FS, Groepenhoff H, et al. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. Am J Respir Crit Care Med 2015;191: 1050-1057.
35. Sagawa K, Maughan L, Suga H, Sunagawa K. Cardiac Contraction and the Pressure-Volume Relationship. New York, NY: Oxford University Press; 1988.
36. Mélot C, Naeije R. Pulmonary vascular diseases. Compr Physiol 2011;1: 593-619.
37. Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. J Clin Invest 1979;64:1050-5.
38. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999;99:1574-9.
39. Caravita S, Faini A, Lombardi C, et al. Sex and acetazolamide effects on chemoreflex and periodic breathing during sleep at altitude. Chest 2015;147:120-31.
40. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.
41. Roberts AM, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JC. Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. Circ Res 1986;58:512-22.

Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure

See Editorial by Houston and Tedford

ABSTRACT: Increased pulmonary venous pressure secondary to left heart disease is the most common cause of pulmonary hypertension (PH). The diagnosis of PH due to left heart disease relies on a clinical probability assessment followed by the invasive measurements of a mean pulmonary artery pressure (PAP) ≥25 mm Hg and mean wedged PAP (PAWP) >15 mm Hg. A combination of mean PAP and mean PAWP defines postcapillary PH. Postcapillary PH is generally associated with a diastolic pulmonary pressure gradient (diastolic PAP minus mean PAWP) <7 mm Hg, a transpulmonary pressure gradient (mean PAP minus mean PAWP) <12 mm Hg, and pulmonary vascular resistance ≤3 Wood units (WU). This combination of criteria defines isolated postcapillary PH. Postcapillary PH with elevated vascular gradients and pulmonary vascular resistance defines combined post- and precapillary PH (Cpc-PH). Postcapillary PH is associated with a decreased survival in proportion to increased pulmonary vascular gradients, decreased pulmonary arterial compliance, and reduced right ventricular function. The Cpc-PH subcategory occurs in 12% to 13% of patients with PH due to left heart disease. Patients with Cpc-PH have severe PH, with higher diastolic pulmonary pressure gradient, transpulmonary pressure gradient, and pulmonary vascular resistance and more pronounced ventilatory responses to exercise, lower pulmonary arterial compliance, depressed right ventricular ejection fraction, and shorter life expectancy than isolated postcapillary PH. Cpc-PH bears similarities to pulmonary arterial hypertension. Whether Cpc-PH is amenable to therapies targeting the pulmonary circulation remains to be tested by properly designed randomized controlled trials.

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Heart failure (HF) has long been known to affect the pulmonary circulation by upstream transmission of increased pulmonary venous pressures as a cause of pulmonary congestion and pulmonary vascular remodeling. The histopathologic profile of pulmonary vascular disease was established before the introduction of cardiac catheterization in clinical practice,[1] and hemodynamic correlates of high pulmonary vascular gradients and increased pulmonary vascular resistance (PVR) soon followed.[2,3] Thus, pulmonary hypertension due to left heart disease (PH-LHD) was characterized by various combinations of arteriolar medial hypertrophy, intimal proliferation, adventitial thickening and microthrombi, rarely fibrinoid necrosis (identified in exceptionally severe mitral stenosis), capillary congestion with hemosiderosis, thickened alveolocapillary membranes and sometimes interstitial fibrotic changes, venules undergoing medial hypertrophy and intimal fibrosis, dilated/muscularized lymphatics, but no plexiform lesions.[1,3] Some of these aspects are illustrated in Figure 1.

PH-LHD is currently defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg with a wedged PAP (PAWP) >15 mm Hg[4–6] and is also called postcapillary PH. A passive increase in mPAP in proportion to increased PAWP defines isolated postcapillary PH (Ipc-PH). An out-of-proportion increase in mPAP with respect to increased PAWP suggestive of pulmonary vascular remodeling and constriction defines combined post- and precapillary PH (Cpc-PH).[2,4–6]

PULMONARY ARTERIAL COMPLIANCE

The PVR equation rests on the assumptions that the pulmonary vascular pressure difference–flow relationship is linear and crosses the origin and that left atrial pressure is transmitted upstream to mPAP in a 1:1 ratio.[7] While PAWP is a reasonable estimate of left atrial pressure,[8] the assumption of a linear proportional upstream transmission of left atrial pressure to mPAP is not correct because of the natural compliance of pulmonary vessels. Furthermore, PVR calculations do not take into account the pulsatility of the pulmonary circulation, that is, the difference between systolic PAP (sPAP) and diastolic PAP (dPAP) or pulse pressure (PP), which increases with pulmonary arterial stiffening. Thus, there is interest in estimating pulmonary arterial compliance (C_{PA}). For this purpose, several methods have been proposed. The most accurate is the PP method, which uses a 2-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures.[9] However, most clinical studies use the ratio of stroke volume (SV) to pulmonary artery PP, or difference between sPAP and dPAP, which is simpler to calculate from standard right heart catheterization measurements. The SV/PP ratio assumes that the complete SV is buffered in the large elastic arteries in systole, without any peripheral outflow. In such a hypothetical closed system, SV is the volume increase and PP is the associated pressure increase. However, there is a continuous flow toward the periphery, and the volume increase during ejection is only a fraction of SV. Therefore, SV/PP is a theoretical maximum possible pulmonary vascular compliance and overestimates the true C_{PA} by 60% to 80%.[10] However, whether this is

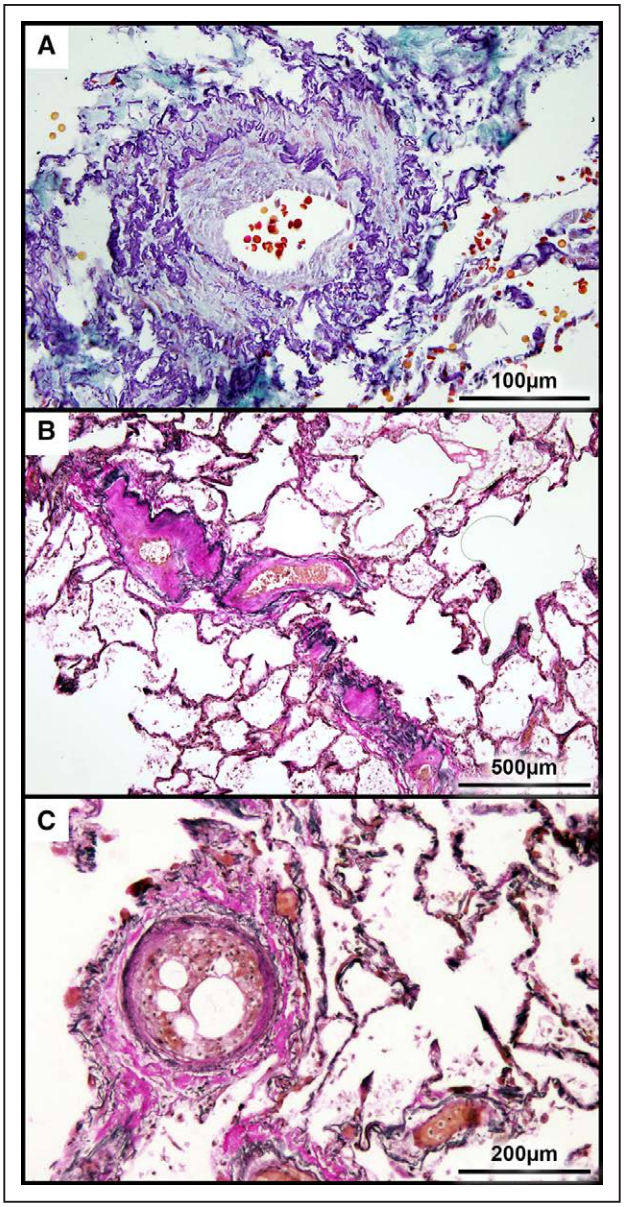

Figure 1. Histopathology of pulmonary vessels in pulmonary hypertension due to left heart disease (PH-LHD).
A, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary artery. **B**, Medial hypertrophy with intimal and adventitial proliferation of a small pulmonary vein. **C**, Recanalyzed fibrotic thrombus in arterioles. Scale bars are shown for individual panels.

clinically relevant has not been tested in patients with PH. Right ventricular (RV) afterload is determined by a dynamic interplay between PVR, C_{PA}, and wave reflections.[11] An increase in PAWP decreases C_{PA}[12,13] and may, therefore, be an important cause of RV dysfunction. On the other hand, the product of PVR and C_{PA} is fairly constant over a wide range of severities of PH in HF[13] and other types of PH,[14] suggesting a negligible contribution of wave reflection on RV afterload.

C_{PA} integrates the volume change per pressure change in the entire arterial segment of the pulmonary circulation. Large artery compliance by magnetic resonance imaging of instantaneous volume changes per pressure changes amounts to no more than 20% of C_{PA}.[14] Therefore, proximal pulmonary arterial stiffness is then an only minor component of RV afterload.

A decrease in C_{PA} has been shown to be an independent predictor of outcome in HF over a wide range of PVR.[15–18] This may be explained by the fact that decreased C_{PA} increases RV afterload and may, thus, determine a predominantly right HF phenotype of poor prognosis. The exquisite sensitivity of C_{PA} to increased PAWP[12,13] makes it also a marker of the severity of left ventricular (LV) failure, which in itself is an additional risk factor of decreased survival.

THE TRANSPULMONARY PRESSURE GRADIENT

Chronically increased pulmonary venous pressure is a cause of endothelial dysfunction related to perturbation of a series of signaling pathways with increased endothelin-1 and decreased nitric oxide and prostacyclin.[6,19-21] This is associated with pulmonary vasoconstriction and remodeling identified at hemodynamic measurements by a >1:1 upstream transmission of PAWP and, thus, an increased PVR.[4–7,20,22] When cardiac output (CO) is normal or low-normal, the difference between mPAP and PAWP, or transpulmonary pressure gradient (TPG), becomes a major determinant of increased PVR. The limits of normal TPG are not exactly known. The upper limit of normal of TPG was thought to be 10 mm Hg until the 1970s,[23] but has since drifted upwards to 12 mm Hg[24] or even most recently to 15 mm Hg.[25] The differential diagnosis between pulmonary vascular tone versus remodeling versus decreased C_{PA} as causes of disproportional increase of mPAP may be difficult. The definitive test is repetition of measurements after a therapeutic decrease in PAWP, such as with diuretics, acute vasodilator testing in pretransplantation evaluation of HF,[26–29] mechanical left ventricular assist,[29] and of course cardiac transplantation.[28] A persistently high PVR in spite of normalized PAWP can only but be explained by irreversible pulmonary vascular remodeling.

THE DIASTOLIC PULMONARY PRESSURE GRADIENT

Another more straightforward approach for the diagnosis of pulmonary vascular disease in PH-LHD relies on the measurement of the gradient between dPAP and mean PAWP (mPAWP) or diastolic pulmonary pressure gradient (DPG). A progressive increase in PAWP in Ipc-PH or in healthy subjects inevitably increases sPAP, mPAP, and dPAP.[12,13] The increase in dPAP is proportionally less than the increase in mPAP. With increased PAWP, the TPG increases, but DPG on average does not change.[7,12]

The DPG was used in the 1970s in combination with PAWP, CO (or arteriovenous oxygen content difference), and systemic blood pressure measurements for the differential diagnosis of cardiac and pulmonary causes of acute respiratory failure.[30] The upper limit of normal of DPG was assumed to be 5 mm Hg,[12] derived from measurements in healthy athletic young adults. The true upper limit of normal over the entire age range and levels of fitness and ages is probably a few mm Hg higher.

Soon after its revival,[7] DPG was evaluated for the differential diagnosis of PH-LHD in a large patient database.[31] Pulmonary vascular gradients were assessed in 3107 patients referred to the catheterization laboratory of the General Hospital of Vienna (AKH-Wien), Medical University of Vienna. PH-LHD defined by mPAP ≥25 mm Hg and mPAWP >15 mm Hg was diagnosed in 1094 of these patients, TPG >12 mm Hg in 490 of them, and DPG was in addition increased ≥7 mm Hg in 179, accounting for 16% of PH-LHD patients. Survival of patients with both high TPG and DPG was poor, like untreated pulmonary arterial hypertension (PAH). In multivariate analysis, DPG emerged as an independent predictor of survival with a cutoff value of 7 mm Hg rigorously derived from the best combination of sensitivity and specificity.

This data inspired a revision of definitions and terminology of PH-LHD at the 5th World PH Symposium held in Nice in 2013, with introduction of the new acronyms Ipc-PH and Cpc-PH.[4] It is of interest that Cpc-PH was initially defined solely by a DPG ≥7 mm Hg,[4] but an element of increased PVR was added in the European guidelines definitions of the European Society of Cardiology/European Respiratory Society.[5] Adding a PVR makes sense, as the DPG is much smaller than PAP but exposed to the same magnitude of errors on the measurement. Therefore, a combination of increased DPG and PVR (or TPG) may indeed be preferable for more robust Cpc-PH phenotyping. However, increased DPG with or instead of and increased PVR as written in the guidelines[5] doubles the prevalence of Cpc-PH from some 12%–14% to 24% in patients with PH-LHD.[32] Accordingly, defining Cpc-PH by the combination of increased DPG and PVR seems preferable.[32,33]

Histopathologic correlates of DPG are scarce. Some sections of pulmonary vessels of patients with both increased TPG and DPG showed pulmonary vascular remodeling with medial hypertrophy, intimal thickening, and adventitial proliferation,[31] as previously reported in severe PH secondary to HF.[1,3]

Support for the clinical relevance of DPG for the definition of Cpc-PH was given by a small study in which the ventilatory equivalents for carbon dioxide (V_E/V_{CO_2}) slope during a cardiopulmonary exercise test was found to be high in PAH, intermediate in Cpc-PH, and mild in Ipc-PH, while exercise oscillatory ventilation occurred in 40% of Ipc-PH and 17% of Cpc-PH and was absent in PAH patients[34] (Figure 2). Patients with PAH present with markedly increased ventilation but no oscillatory ventilation during exercise, while patients with advanced Ipc-PH may present with exercise oscillatory ventilation known as a marker of poor prognosis.[35] In another larger scale study, fluid challenge did not affect the time constant of the pulmonary circulation, or PVR×C_{PA}, in Cpc-PH or in PAH, while it decreased it significantly in Ipc-PH, suggesting fixed pulmonary vascular remodeling in Cpc-PH.[36] Biological support for a Cpc-PH phenotype was recently provided by an analysis of a large database of 2817 PH patients from Vanderbilt University in Nashville.[37] In that study, patients with Cpc-PH were younger but with more severe pulmonary vascular disease than patients with Ipc-PH, despite similar comorbidities and prevalence, severity, and chronicity of LHD, and presented with 75 exonic single-nucleotide polymorphisms enriched in pathways involving cell structure, extracellular matrix, and immune function that were shared with PAH and not with Ipc-PH patients.

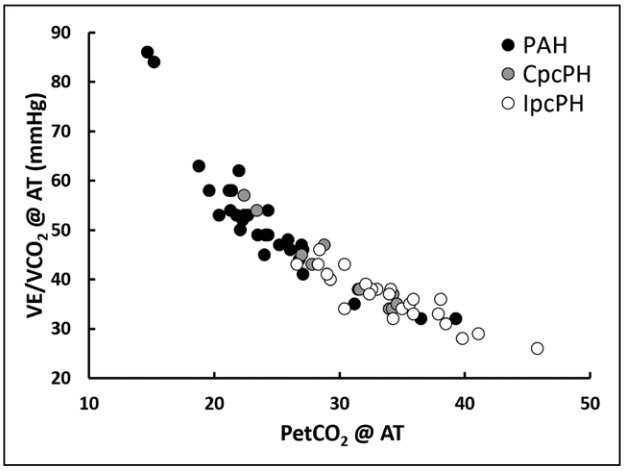

Figure 2. Ventilatory equivalents for CO2 (V_E/V_{CO_2}) as a function of end-tidal partial pressure of CO_2 ($PetCO_2$) in patients with pulmonary arterial hypertension (PAH), combined pre- and postcapillary pulmonary hypertension (Cpc-PH), and isolated postcapillary pulmonary hypertension (Ipc-PH) showing ventilatory responses to exercise measured at the anaerobic threshold (AT) of Cpc-PH being intermediate to those of PAH and Ipc-PH.
Data derived from Caravita et al.[34]

The prevalence of Cpc-PH in PH-LHD is not exactly known, but may be around 12% to 14% in patients with HF referred to the catheterization laboratory.[37,38] In the database of the Medical University of Vienna, independent predictive capability of DPG by multivariate analysis was significant in both diastolic HF (DHF)/HF with preserved ejection fraction (EF) and systolic HF (SHF)/HF with reduced EF, even when the definition included a PVR >3 WU. However, PVR alone was a predictor of outcome in HF with reduced EF but not in HF with preserved EF (Figure 3). By contrast, in the database of the Vanderbilt University, DPG did not predict outcome, while PVR only predicted outcome in patients with Cpc-PH. Furthermore, prognosis of Cpc-PH and Ipc-PH was not found to be different.

Previous studies have generally found PVR to be a strong predictor of outcome in PH-LHD,[39,40] raising discussion about the added predictive value of DPG in PH-LHD. At present, an almost equal number of studies have confirmed[41–43] or refuted[44–46] the prognostic relevance of DPG. These discrepancies are explained by the fact that the DPG represents a small number, is exposed to instability, as shown in studies where high DPGs were sometimes found in patients with a normal PVR[44] or where DPG was reported as negative in a proportion of patients,[47] conditions which are both physiologically impossible. TPG or PVR have to increase in proportion of the DPG,[7] while reported negative DPG values may be because of improper incorporation of V waves in the reading of PAWP tracings or simply because of a lack of precision of the measurement.[48] On the other hand, the severity of PH and degree of RV dysfunction may be predominant in the impact on outcome.[49]

THE RIGHT VENTRICLE IN LEFT HEART FAILURE

PH is associated with decreased exercise capacity and shorter life expectancy in HF.[4–6,25] This could be explained by more advanced HF causing more upstream transmission of increased PAWP to PAP and, thus, by afterload-induced RV failure. Preserved RV EF as measured with radionuclide technology had been shown to predict exercise capacity and survival in advanced HF.[50] The first study combining pulmonary vascular function and RV function measurements was reported in 2001.[51] The authors measured pulmonary vascular pressures, CO, and thermodilution-derived RVEF in 377 consecutive patients with HF. Mean PAP and RVEF were inversely correlated, but were shown to be independent predictors of death or urgent transplantation in multivariate analysis. The prognosis of patients with PH but a preserved RVEF was similar to that of patients without PH.

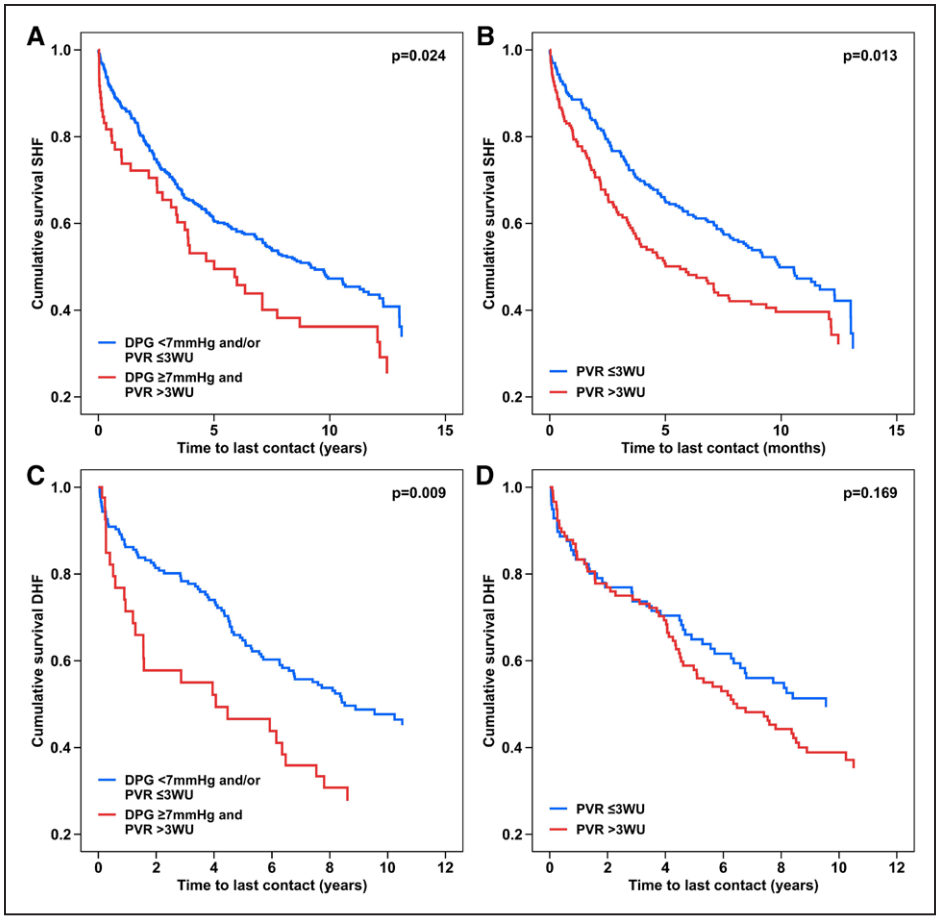

Figure 3. Survival curves illustrating a population of 636 patients with heart failure with reduced ejection fraction/systolic heart failure (SHF) pulmonary hypertension (A and B) and 286 patients with heart failure with preserved ejection fraction/diastolic heart failure (DHF) pulmonary hypertension (C and D) with diastolic pulmonary pressure gradient (DPG) <7 mm Hg and pulmonary vascular resistance (PVR) ≤3 WU, versus DPG of ≥7 mm Hg and PVR >3 WU (A and C) and PVR ≤3 WU alone versus PVR >3 WU alone (B and D).
Data derived from Gerges et al.[38]

These results have been confirmed,[52] and emphasize that RV function is a major determinant of outcome in severe PH.[53]

The RV in PH-LHD is exquisitely sensitive to afterload. As already discussed, increased PAWP increases RV afterload out of proportion to increased PVR because of associated decrease in C_{PA}. Furthermore, cardiomyopathies of course involve the RV, which may fail to adapt to minimally increased PAP. This has been demonstrated by rigorously defined coupling of RV function to the pulmonary circulation by the measurement of the ratio of end-systolic to arterial elastances in an animal model of overpacing-induced HF with reduced EF and "borderline PH."[54] On the other hand, 20% to 40% of RV systolic pressure results from LV contraction[55]; thus, decreased LV contractility and associated systemic hypotension alters ventricular systolic interdependence and, thereby, impairs coupling of RV function to the pulmonary circulation. As patients with Cpc-PH have higher pulmonary vascular pressure gradients and PVR than Ipc-PH, they are more likely to have RV failure and shorter life expectancy, even though this may vary depending on the underlying cause of HF.

In the large PH-LHD database of the Medical University of Vienna,[38] standard echocardiography was not able to discriminate between Ipc-PH and Cpc-PH, except when tricuspid annular plane systolic excursion to sPAP ratio was calculated. The tricuspid annular plane systolic excursion/sPAP ratio was initially introduced as an estimate of RV length–tension relationship,[56] but also considered as an indirect estimate of RV–arterial coupling.[57–60] The tricuspid annular plane systolic excursion/sPAP ratio has been shown to be a potent predictor of survival in HF, alone,[56] combined with cardiopulmonary exercise testing,[57] or measured at rest and during exercise to assess RV contractile reserve.[58] However, the exact functional significance of tricuspid annular plane systolic excursion/sPAP is not yet entirely understood.[59]

Accordingly, RV pressure curves of the large cohort of patients with PH-LHD of the Medical University of Vienna were analyzed to derive end-systolic and arterial elastances[38] as gold standard measures of contractility

and afterload.[53] End-systolic elastance increased from Ipc-PH to idiopathic PAH, with Cpc-PH in between, but the ratio of end-systolic to arterial elastance was decreased in Cpc-PH only as a function of increased DPG.[38] RV contractility increases in the presence of increased afterload to preserve RV–arterial coupling.[53] This is observed in PAH at rest,[60–62] if not during exercise.[61,62] Altered RV–arterial coupling in severe PH results in increased RV dimensions, systemic congestion, and decreased survival.[53]

The observation that Cpc-PH is more likely associated with worse RV function is further underscored by the DPG-dependent clustering of PAH, Cpc-PH, and Ipc-PH in relation to RV and LV volumes and a filling pressures-dependent prediction score for precapillary PH developed from invasive and noninvasive measurements in 240 patients referred with PH[63,64] (Figure 4).

PROVOCATIVE TESTING

Provocative testing of the pulmonary circulation relies mainly on exercise test or fluid challenge. Both approaches have been part of standard clinical practice for decades, but have only been recently standardized.

The upper limit of normal of mPAP during an incremental dynamic exercise challenge is now well established at 30 mm Hg at a CO <10 L/min, which corresponds to a total pulmonary vascular resistance (TPR, or mPAP/CO). (or mPAP/CO) of 3 WU.[65–67] Meaningful accurate but less precise noninvasive measurements of PAP and CO during exercise are being reported by dedicated groups.[65,66] The cause of higher than normal mPAP during "exercise or exercise-induced PH" is either an upstream transmission of increased PAWP, such as in HF, or an increase of PVR, such as in pulmonary vascular disease, disturbed lung mechanics, or hypoxia.[65,66] This differential diagnosis is most often clinically straightforward but has to be established by precise measurement and interpretation of PAWP or LV end-diastolic pressure. The upper limit of normal of PAWP during exercise is generally thought to be between 15 and 20 mm Hg, but higher values can be recorded in athletes and in elderly subjects.[68] A cutoff value of 25 mm Hg has been proposed for the diagnosis of HF.[69,70] Likewise, for mPAP, a flow-corrected measure may be more appropriate for PAWP, but there has been no study specifically addressing this.

A fluid challenge is probably easier to standardize than an exercise stress test. Any condition associated with altered LV diastolic compliance or valvular heart disease will be associated with a rapid increase in PAWP when challenged with an increased systemic venous return.[2,71] There is an emerging consensus to infuse 500 mL or 7 mL/kg of saline in 5 to 10 minutes as best compromise between safety and stress efficacy, and 18 mm Hg seems to be the optimal cutoff to separate abnormal from normal.[71–76]

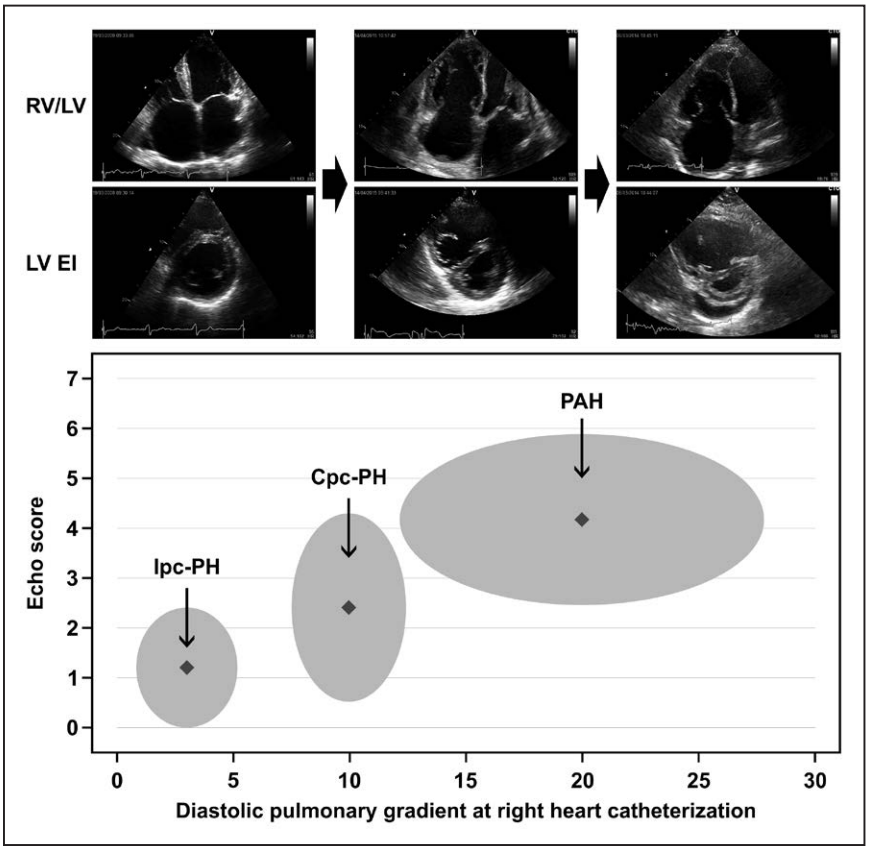

Figure 4. Clustering of isolated postcapillary pulmonary hypertension (Ipc-PH), combined pre- and postcapillary pulmonary hypertension (Cpc-PH), and pulmonary arterial hypertension (PAH) as a function of diastolic pulmonary pressure gradient (DPG).
A high DPG is closely associated with an increased ratio of right ventricular (RV) to left ventricular (LV) surface areas (RV/LV) and decreased LV eccentricity index (EI). A scoring system from 1 to 6 facilitates the diagnosis of precapillary pulmonary hypertension (PH) in patients referred for PH. Adapted from D'Alto et al[64] with permission. Copyright ©2017, Wolters Kluwer Health, Inc.

CONCLUSIONS

PH as a complication of left heart conditions with increased pulmonary venous pressure can be differentiated in Cpc-PH and Ipc-PH phenotypes based on clinical features, pulmonary vascular pressure gradients, and RV function. The prognosis of Cpc-PH is poor. Whether therapies targeting the pulmonary circulation and efficacious in PAH improve the outcome of Cpc-PH remains to be tested in properly designed multicenter randomized controlled trials.

DISCLOSURES

Dr Naeije has relationships with drug companies, including AOPOrphan Pharmaceuticals, Actelion, Bayer, Reata, Lung Biotechnology Corporation, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Drs M. Gerges and C. Gerges have received compensation for scientific symposia from AOPOrphan Pharmaceuticals AG, Actelion, and GlaxoSmithKline. Dr M. Gerges received in the past an educational grant from United Therapeutics Corporation (Grant No. REG-NC-002). Dr C. Gerges received in the past an educational grant from Bayer (Grant No. 15662). Dr Vachiery has relationships with drug companies, including Actelion, Bayer, Glaxo, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Dr Caravita has received an ERS PAH Short-Term Research Training Fellowship (STRTF 2014–5264), was supported by an unrestricted grant from GSK, and received payment of expenses related to congress participations by Bayer, Actelion, and Pfizer. Dr Lang has relationships with drug companies, including AOPOrphan Pharmaceuticals, Actelion, Bayer-Schering, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

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FOOTNOTES

Circ Heart Fail is available at http://circheartfailure.ahajournals.org.

REFERENCES

1. Parker F, Weiss S. The nature and significance of the structural changes in the lungs in mitral stenosis. *Am J Pathol*. 1936;12:573–598.15.
2. Wood P. Pulmonary hypertension with special reference to the vasoconstrictive factor. *Br Heart J*. 1958;20:557–570.
3. Heath D, Edwards JE. Histological changes in the lung in diseases associated with pulmonary venous hypertension. *Br J Dis Chest*. 1959;53:8–18.
4. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol*. 2013;62(25 suppl):D100–D108. doi: 10.1016/j.jacc.2013.10.033.
5. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119. doi: 10.1093/eurheartj/ehv317.
6. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J*. 2016;37:942–954. doi: 10.1093/eurheartj/ehv512.
7. Naeije R, Vachiery JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J*. 2013;41:217–223. doi: 10.1183/09031936.00074312.
8. Connolly DC, Kirklin JW, Wood EH. The relationship between pulmonary artery wedge pressure and left atrial pressure in man. *Circ Res*. 1954;2:434–440.
9. Stergiopulos N, Segers P, Westerhof N. Use of pulse pressure method for estimating total arterial compliance in vivo. *Am J Physiol*. 1999;276(2 pt 2):H424–H428.
10. Segers P, Brimioulle S, Stergiopulos N, Westerhof N, Naeije R, Maggiorini M, Verdonck P. Pulmonary arterial compliance in dogs and pigs: the three-element windkessel model revisited. *Am J Physiol*. 1999;277(2 pt 2):H725–H731.
11. Sniderman AD, Fitchett DH. Vasodilators and pulmonary arterial hypertension: the paradox of therapeutic success and clinical failure. *Int J Cardiol*. 1988;20:173–181.
12. Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. *Chest*. 1971;59:82–94.
13. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, Cingolani OH, Mudd JO, Borlaug BA, Redfield MM, Lederer DJ, Kass DA. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012;125:289–297. doi: 10.1161/CIRCULATIONAHA.111.051540.
14. Saouti N, Westerhof N, Helderman F, Marcus JT, Stergiopulos N, Westerhof BE, Boonstra A, Postmus PE, Vonk-Noordegraaf A. RC time constant of single lung equals that of both lungs together: a study in chronic thromboembolic pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2009;297:H2154–H2160. doi: 10.1152/ajpheart.00694.2009.
15. Malhotra R, Dhakal BP, Eisman AS, Pappagianopoulos PP, Dress A, Weiner RB, Baggish AL, Semigran MJ, Lewis GD. Pulmonary vascular distensibility predicts pulmonary hypertension severity, exercise capacity, and survival in heart failure. *Circ Heart Fail*. 2016;9:e003011. doi: 10.1161/CIRCHEARTFAILURE.115.003011.
16. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, Starling RC, Tang WH. Prognostic role of pulmonary arterial capacitance in advanced heart failure. *Circ Heart Fail*. 2012;5:778–785. doi: 10.1161/CIRCHEARTFAILURE.112.968511.
17. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013;1:290–299. doi: 10.1016/j.jchf.2013.05.001.

18. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, Dini FL, Temporelli PL, Vassanelli C, Vanderpool R, Naeije R, Ghio S. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest*. 2014;145:1064–1070. doi: 10.1378/chest.13-1510.
19. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail*. 2015;3:467–474. doi: 10.1016/j.jchf.2015.01.013.
20. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. *Circulation*. 2000;102:1718–1723.
21. Breitling S, Ravindran K, Goldenberg NM, Kuebler WM. The pathophysiology of pulmonary hypertension in left heart disease. *Am J Physiol Lung Cell Mol Physiol*. 2015;309:L924–L941. doi: 10.1152/ajplung.00146.2015.
22. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D42–D50. doi: 10.1016/j.jacc.2013.10.032.
23. Dalen JE, Dexter L, Ockene IS, Carlson J. Precapillary pulmonary hypertension; its relationship to pulmonary venous hypertension. *Trans Am Clin Climatol Assoc*. 1975;86:207–218.
24. 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, Harrington RA, Anderson JL, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Grines CL, Hlatky MA, Jacobs AK, Kaul S, Lichtenberg RC, Lindner JR, Moliterno DJ, Mukherjee D, Pohost GM, Rosenson RS, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Weitz HH, Wesley DJ; ACCF/AHA. 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. *Circulation*. 2009;119:2250–2294. doi: 10.1161/CIRCULATIONAHA.109.192230.
25. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation*. 2012;126:975–990. doi: 10.1161/CIRCULATIONAHA.111.085761.
26. Murali S, Uretsky BF, Reddy PS, Tokarczyk TR, Betschart AR. Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: comparative effects of various pharmacologic agents. *Am Heart J*. 1991;122:1375–1381.
27. Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol*. 1992;19:48–54.
28. Naeije R, Lipski A, Abramowicz M, Lejeune P, Mélot C, Antoine M, De Smet JM, Leclerc JL, Primo G. Nature of pulmonary hypertension in congestive heart failure. Effects of cardiac transplantation. *Am J Respir Crit Care Med*. 1994;149(4 pt 1):881–887. doi: 10.1164/ajrccm.149.4.8143050.
29. Fang JC, DeMarco T, Givertz MM, Borlaug BA, Lewis GD, Rame JE, Gomberg-Maitland M, Murali S, Frantz RP, McGlothlin D, Horn EM, Benza RL. World Health Organization Pulmonary Hypertension group 2: pulmonary hypertension due to left heart disease in the adult–a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2012;31:913–933. doi: 10.1016/j.healun.2012.06.002.
30. Stevens PM. Assessment of acute respiratory failure: cardiac versus pulmonary causes. *Chest*. 1975;67:1–2.
31. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest*. 2013;143:758–766. doi: 10.1378/chest.12-1653.
32. Gerges M, Gerges C, Lang IM. How to define pulmonary hypertension due to left heart disease. *Eur Respir J*. 2016;48:553–555. doi: 10.1183/13993003.00432-2016.
33. Naeije R, Hemnes AR. The difficult diagnosis of pulmonary vascular disease in heart failure. *Eur Respir J*. 2016;48:308–310. doi: 10.1183/13993003.00789-2016.
34. Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G, Vachiéry JL. Pulmonary hypertension and ventilation during exercise: Role of the pre-capillary component. *J Heart Lung Transplant*. 2017;36:754–762. doi: 10.1016/j.healun.2016.12.011.
35. Vicenzi M, Deboeck G, Faoro V, Loison J, Vachiery JL, Naeije R. Exercise oscillatory ventilation in heart failure and in pulmonary arterial hypertension. *Int J Cardiol*. 2016;202:736–740. doi: 10.1016/j.ijcard.2015.09.087.
36. Assad TR, Brittain EL, Wells QS, Farber-Eger EH, Halliday SJ, Doss LN, Xu M, Wang L, Harrell FE, Yu C, Robbins IM, Newman JH, Hemnes AR. Hemodynamic evidence of vascular remodeling in combined post- and precapillary pulmonary hypertension. *Pulm Circ*. 2016;6:313–321. doi: 10.1086/688516.
37. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. *J Am Coll Cardiol*. 2016;68:2525–2536. doi: 10.1016/j.jacc.2016.09.942.
38. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM. Pulmonary hypertension in heart failure. Epidemiology, right ventricular function, and survival. *Am J Respir Crit Care Med*. 2015;192:1234–1246. doi: 10.1164/rccm.201503-0529OC.
39. Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T; ESCAPE Investigators. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. *Am Heart J*. 2009;157:1026–1034. doi: 10.1016/j.ahj.2009.02.022.
40. Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. *Circ Heart Fail*. 2011;4:644–650. doi: 10.1161/CIRCHEARTFAILURE.110.960864.
41. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N, Aronson D. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail*. 2015;17:74–80. doi: 10.1002/ejhf.192.
42. Ibe T, Wada H, Sakakura K, Ikeda N, Yamada Y, Sugawara Y, Mitsuhashi T, Ako J, Fujita H, Momomura S. Pulmonary hypertension due to left heart disease: The prognostic implications of diastolic pulmonary vascular pressure gradient. *J Cardiol*. 2016;67:555–559. doi: 10.1016/j.jjcc.2015.07.015.
43. Rezaee ME, Nichols EL, Sidhu M, Brown JR. Combined post- and precapillary pulmonary hypertension in patients with heart failure. *Clin Cardiol*. 2016;39:658–664. doi: 10.1002/clc.22579.
44. Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, Leary PJ, Kass DA, Shah AS. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. *J Heart Lung Transplant*. 2014;33:289–297. doi: 10.1016/j.healun.2013.11.008.
45. Palazzini M, Dardi F, Manes A, Bacchi Reggiani ML, Gotti E, Rinaldi A, Albini A, Monti E, Galiè N. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes. *Eur J Heart Fail* 2017. doi: 10.1002/ejhf.860.
46. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, Russell SD, Kasper EK, Tedford RJ. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail*. 2015;3:9–16. doi: 10.1016/j.jchf.2014.07.010.
47. Nagy AI, Venkateshvaran A, Merkely B, Lund LH, Manouras A. Determinants and prognostic implications of the negative diastolic pulmonary pressure gradient in patients with pulmonary hypertension due to left heart disease. *Eur J Heart Fail*. 2017;19:88–97. doi: 10.1002/ejhf.675.
48. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest*. 2009;136:37–43. doi: 10.1378/chest.08-2784.
49. Chatterjee NA, Lewis GD. Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: limitations of a solitary measurement. *JACC Heart Fail*. 2015;3:17–21. doi: 10.1016/j.jchf.2014.09.002.
50. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol*. 1995;25:1143–1153.
51. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37:183–188.
52. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, Roger VL, Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation*. 2014;130:2310–2320. doi: 10.1161/CIRCULATIONAHA.113.008461.

53. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. *J Am Coll Cardiol*. 2017;69:236–243. doi: 10.1016/j.jacc.2016.10.047.
54. Pagnamenta A, Dewachter C, McEntee K, Fesler P, Brimioulle S, Naeije R. Early right ventriculo-arterial uncoupling in borderline pulmonary hypertension on experimental heart failure. *J Appl Physiol (1985)*. 2010;109:1080–1085. doi: 10.1152/japplphysiol.00467.2010.
55. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. *Prog Cardiovasc Dis*. 1998;40:289–308.
56. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, Temporelli PL, Arena R. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol*. 2013;305:H1373–H1381. doi: 10.1152/ajpheart.00157.2013.
57. Guazzi M, Naeije R, Arena R, Corrà U, Ghio S, Forfia P, Rossi A, Cahalin LP, Bandera F, Temporelli P. Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. *Chest*. 2015;148:226–234. doi: 10.1378/chest.14-2065.
58. Guazzi M, Villani S, Generati G, Ferraro OE, Pellegrino M, Alfonzetti E, Labate V, Gaeta M, Sugimoto T, Bandera F. Right ventricular contractile reserve and pulmonary circulation uncoupling during exercise challenge in heart failure: pathophysiology and clinical phenotypes. *JACC Heart Fail*. 2016;4:625–635. doi: 10.1016/j.jchf.2016.03.007.
59. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol*. 2017;69:1718–1734. doi: 10.1016/j.jacc.2017.01.051.
60. Vanderpool RR, Pinsky MR, Naeije R, Deible C, Kosaraju V, Bunner C, Mathier MA, Lacomis J, Champion HC, Simon MA. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. *Heart*. 2015;101:37–43. doi: 10.1136/heartjnl-2014-306142.
61. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A, Bogaard HJ. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. *Am J Respir Crit Care Med*. 2015;191:1050–1057. doi: 10.1164/rccm.201412-2271OC.
62. Hsu S, Houston BA, Tampakakis E, Bacher AC, Rhodes PS, Mathai SC, Damico RL, Kolb TM, Hummers LK, Shah AA, McMahan Z, Corona-Villalobos CP, Zimmerman SL, Wigley FM, Hassoun PM, Kass DA, Tedford RJ. Right ventricular functional reserve in pulmonary arterial hypertension. *Circulation*. 2016;133:2413–2422. doi: 10.1161/CIRCULATIONAHA.116.022082.
63. D'Alto M, Romeo E, Argiento P, Pavelescu A, Mélot C, D'Andrea A, Correra A, Bossone E, Calabrò R, Russo MG, Naeije R. Echocardiographic prediction of pre- versus postcapillary pulmonary hypertension. *J Am Soc Echocardiogr*. 2015;28:108–115. doi: 10.1016/j.echo.2014.09.004.
64. D'Alto M, Romeo E, Argiento P, Pavelescu A, D'Andrea A, Di Marco GM, Mattera Iacono A, Sarubbi B, Rea G, Bossone E, Russo MG, Naeije R. A simple echocardiographic score for the diagnosis of pulmonary vascular disease in heart failure. *J Cardiovasc Med (Hagerstown)*. 2017;18:237–243. doi: 10.2459/JCM.0000000000000485.
65. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med*. 2013;187:576–583. doi: 10.1164/rccm.201211-2090CI.
66. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128:1470–1479. doi: 10.1161/CIRCULATIONAHA.112.000667.
67. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J*. 2015;46:728–737. doi: 10.1183/09031936.00021915.
68. Oliveira RK, Agarwal M, Tracy JA, Karin AL, Opotowsky AR, Waxman AB, Systrom DM. Age-related upper limits of normal for maximum upright exercise pulmonary haemodynamics. *Eur Respir J*. 2016;47:1179–1188. doi: 10.1183/13993003.01307-2015.
69. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588–595. doi: 10.1161/CIRCHEARTFAILURE.109.930701.
70. Andersen MJ, Ersbøll M, Bro-Jeppesen J, Gustafsson F, Hassager C, Køber L, Borlaug BA, Boesgaard S, Kjærgaard J, Møller JE. Exercise hemodynamics in patients with and without diastolic dysfunction and preserved ejection fraction after myocardial infarction. *Circ Heart Fail*. 2012;5:444–451. doi: 10.1161/CIRCHEARTFAILURE.112.967919.
71. Borlaug BA. Invasive assessment of pulmonary hypertension: time for a more fluid approach? *Circ Heart Fail*. 2014;7:2–4. doi: 10.1161/CIRCHEARTFAILURE.113.000983.
72. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G, Levine BD. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. *Circulation*. 2013;127:55–62. doi: 10.1161/CIRCULATIONAHA.112.111302.
73. Fox BD, Shimony A, Langleben D, Hirsch A, Rudski L, Schlesinger R, Eisenberg MJ, Joyal D, Hudson M, Boutet K, Serban A, Masetto A, Baron M. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J*. 2013;42:1083–1091. doi: 10.1183/09031936.00091212.
74. Robbins IM, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, Fong PP, Newman JH. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail*. 2014;7:116–122. doi: 10.1161/CIRCHEARTFAILURE.113.000468.
75. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail*. 2015;8:41–48. doi: 10.1161/CIRCHEARTFAILURE.114.001731.
76. D'Alto M, Romeo E, Argiento P, Motoji Y, Correra A, Di Marco GM, Iacono AM, Barracano R, D'Andrea A, Rea G, Sarubbi B, Russo MG, Naeije R. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest*. 2017;151:119–126. doi: 10.1016/j.chest.2016.08.1439.