



Impaired right ventricular lusitropy is associated with ventilatory inefficiency in pulmonary arterial hypertension

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Right ventricular diastolic stiffness and afterload (pressure–volume loop measurement) are associated with ventilatory inefficiency during exercise and may contribute to dyspnoea via increased chemosensitivity in pulmonary arterial hypertension <http://bit.ly/30Ly9t>

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ABSTRACT Cardiopulmonary exercise testing (CPET) is an important tool for assessing functional capacity and prognosis in pulmonary arterial hypertension (PAH). However, the associations of CPET parameters with the adaptation of right ventricular (RV) function to afterload remain incompletely understood.

In this study, 37 patients with PAH (idiopathic in 31 cases) underwent single-beat pressure–volume loop measurements of RV end-systolic elastance (Ees), arterial elastance (Ea) and diastolic elastance (Eed). Pulmonary arterial stiffness was assessed by magnetic resonance imaging. The results were correlated to CPET variables. The predictive relevance of RV function parameters for clinically relevant ventilatory inefficiency, defined as minute ventilation/carbon dioxide production (V_E/V'_{CO_2}) slope >48, was evaluated using logistic regression analysis.

The median (interquartile range) of the V_E/V'_{CO_2} slope was 42 (32–52) and the V_E/V'_{CO_2} nadir was 40 (31–44). The mean±SD of peak end-tidal carbon dioxide tension (P_{ETCO_2}) was 23±8 mmHg. Ea, Eed and parameters reflecting pulmonary arterial stiffness (capacitance and distensibility) correlated with the V_E/V'_{CO_2} slope, V_E/V'_{CO_2} nadir, P_{ETCO_2} and peak oxygen pulse. RV Ees and RV–arterial coupling as assessed by the Ees/Ea ratio showed no correlations with CPET parameters. Ea (univariate OR 7.28, 95% CI 1.20–44.04) and Eed (univariate OR 2.21, 95% CI 0.93–5.26) were significantly associated with ventilatory inefficiency ($p<0.10$).

Our data suggest that impaired RV lusitropy and increased afterload are associated with ventilatory inefficiency in PAH.

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Individual participant data that underlie the results reported in this article, after de-identification, may be shared upon reasonable request, subject to approval from the Right Heart I study committee.

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Introduction

Shortness of breath dominates the symptomatology of pulmonary arterial hypertension (PAH). Much of it is related to an excess of ventilation (V'_E) at any level of metabolic rate, as defined by an elevated V'_E /carbon dioxide output (V'_{CO_2}) slope during a cardiopulmonary exercise test (CPET) [1, 2]. An increase in V'_E/V'_{CO_2} slope is an important predictor of outcome in patients with PAH [3, 4] and evaluating the V'_E/V'_{CO_2} slope has therefore been recommended as part of the risk assessment in these patients [5]. However, the pathophysiology of PAH is currently understood to depend on the adaptation of right ventricular (RV) function to afterload [6–8]. Thus, symptomatology and survival in these patients is critically dependent on the adequacy of RV–pulmonary arterial (PA) coupling, as defined by a preserved ratio of end-systolic elastance (E_{es}) to arterial elastance (E_a) at a normally low end-diastolic elastance (E_{ed}) [6–8]. Although the V'_E/V'_{CO_2} slope has previously shown associations with other parameters reflecting RV afterload and function in heart failure [9, 10], the relationship of wasted ventilation to E_{es}/E_a and E_{ed} in PAH remains incompletely understood.

We therefore investigated RV function by invasive determination of RV pressure–volume loops to calculate E_{es} , E_a and E_{ed} and related the results to V'_E/V'_{CO_2} slope or nadir and other CPET parameters previously reported to be of relevance, such as peak oxygen uptake (V'_{O_2}) and O_2 pulse [11]. We also measured PA compliance as an important determinant of RV afterload by magnetic resonance imaging (MRI) [12].

Methods

Study design and patients

For the current analysis, we included consecutive patients with PAH who were prospectively enrolled into the Right Heart I study (NCT03403868) and the Giessen Pulmonary Hypertension Registry [13] between January 2016 and April 2019. A subset of the patients had also been included in previously published analyses from the Right Heart I study [14–17]. The patients were diagnosed according to current recommendations [5], and each diagnosis was assessed by a multidisciplinary board (including pulmonary physicians and radiologists) before enrolment. All patients underwent CPET, MRI and pressure–volume/Swan-Ganz catheterisation. PAH therapies were administered based on clinical grounds and best standard of care. B-type natriuretic peptide (BNP) was measured with a fully automated, two-site sandwich immunoassay (ADVIA Centaur BNP Test; Siemens Healthineers, Erlangen, Germany). Diffusion capacity of the lung for carbon monoxide (D_{LCO}) was measured by the single-breath technique [18]. All participating patients gave written informed consent for enrolment into the Right Heart I study. The investigation conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine at the University of Giessen (approval no. 108/15).

Cardiopulmonary exercise testing

All patients underwent symptom-limited incremental CPET (Vmax 229[®] system; Carefusion[®], now part of Vyair[™] Medical, Yorba Linda, CA, USA) using a cycle ergometer in a semi-supine position and wearing a face mask. After an initial baseline measurement without exercise for 2 min, exercise was initiated at a work rate of 10–30 W, which was increased by 10–30 W every 1–2 min using a stepwise protocol as published previously [19]. Blood gases were analysed at rest and maximal exercise (from the hyperaemic ear lobe); heart rate was continuously monitored and a noninvasive blood pressure measurement was performed every 2 min. Peak oxygen uptake (V'_{O_2}) was defined as the V'_{O_2} measured during the last 30 s of peak exercise. The respiratory exchange ratio (RER) was calculated as V'_{CO_2}/V'_{O_2} , and O_2 pulse as V'_{O_2} /heart rate. The ventilatory equivalents for carbon dioxide were calculated by dividing V'_E (corrected for equipment external dead space) by V'_{CO_2} . V'_E/V'_{CO_2} slopes were measured between warm up and anaerobic threshold. The nadir of V'_E/V'_{CO_2} was assessed as described previously [20]. Arterial carbon dioxide tension (P_{aCO_2}) to end-tidal carbon dioxide tension (P_{ETCO_2}) carbon dioxide gradient ($P_{(a-ET)CO_2}$) was measured at rest and during exercise [19].

Magnetic resonance imaging

Imaging was performed with the Avanto 1.5 Tesla scanner system (Siemens Healthineers; gradient strength and slew rate: SQ-Engine (45 mT·m⁻¹ at 200 T·m⁻¹·s⁻¹)). Stiffness, distensibility and capacitance of the pulmonary arteries were measured as described in detail previously [12].

Right heart catheterisation

Resting right heart catheterisation was performed as described previously [21]. Pressure values were continuously assessed. Cardiac index was measured using the direct or indirect Fick method as available. Pulmonary vascular resistance (PVR) was calculated as (mean pulmonary arterial pressure (mPAP)–pulmonary arterial wedge pressure)/cardiac output [5].

Pressure–volume catheterisation

Pressure–volume catheterisation was performed and pressure–volume loops were generated as described previously [14]. Ees was calculated using the single-beat method for the right ventricle, and Ea was calculated as end-systolic pressure/stroke volume [22]. RV–PA coupling was calculated as Ees/Ea. A diastolic stiffness factor β was calculated as described previously by a nonlinear fit of diastolic pressure–volume coordinates as $p = \alpha(e^{\beta V} - 1)$ (where p is pressure, V is volume and α is a curve-fitting parameter) through the diastolic portion of the pressure–volume loops using a custom MATLAB program [23–25]. Three points (origin (0,0), beginning diastolic point and end-diastolic point) were used for the exponential fit. Eed was obtained from the relationship $dP/dV = \alpha\beta \times e^{\beta \times \text{end-diastolic volume}}$ at calculated end-diastolic volumes [23, 25, 26]. Volume measurements were calibrated with MRI data.

Statistical analyses

Histograms were visually assessed and the Kolmogorov–Smirnov test was used to determine adherence to a Gaussian distribution. Associations of functional parameters (derived from CPET) with pressure–volume variables and PA parameters were measured with Spearman’s rank correlation coefficient; lines show least-squares fits of straight-line models. In addition, Ea and Eed were stratified according to the categories of V'_E/V'_{CO_2} slope proposed for risk assessment of patients with PAH in current guidelines [5]. Between-group differences were analysed with the Kruskal–Wallis test or unpaired t-tests as appropriate. For these analyses, $p < 0.05$ was considered statistically significant.

TABLE 1 Clinical characteristics

	Patients with PAH
Subjects n	37
Sex	
Male	17
Female	20
Age years	50±14
PAH subtype	
Idiopathic PAH	31 (84)
Heritable PAH	2 (5)
PAH associated with	4 (11)
HIV infection	1
Connective tissue disease	3
Treatment	
PDE5i	16 (43)
ERA	22 (59)
sGC stimulator	14 (38)
Prostanoid	8 (22)
Selexipag	3 (8)
Combination therapy	
Dual therapy	10 (27)
Triple therapy	9 (24)
WHO functional class[#]	
I	2 (6)
II	17 (47)
III	17 (47)
BNP[¶] pg·mL⁻¹	66 [26–177]
D_{LCO}[#] % predicted	61 [48–71]
Right heart catheterisation	
mPAP mmHg	38 [34–54]
RAP mmHg	6±3
PVR Wood units	6.6 (4.3–10.4)
Cardiac index L·min ⁻¹ ·m ⁻²	2.8±0.7
PAWP mmHg	9±3

Data are presented as n (%), mean±SD and median (interquartile range), unless otherwise indicated. PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase type 5 inhibitor; ERA: endothelin receptor antagonist; sGC: soluble guanylate cyclase; WHO: World Health Organization; BNP: B-type natriuretic peptide; D_{LCO} : diffusion capacity of the lung for carbon monoxide; mPAP: mean pulmonary artery pressure; RAP: right atrial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure. [#]: n=36; [¶]: n=35.

To determine which pressure–volume loop parameter is most strongly related to ventilatory inefficiency based on the previously recommended prognostically relevant cut-off value of >48 for V_E/V_{CO_2} slope [4, 27], Ea, Ees, Ees/Ea and Eed were included in a univariate logistic binary regression analysis as continuous variables. We then built a multivariate model including BNP, sex, Ea and Eed; multicollinearity was assessed using the variance inflation factor. For the regression analysis, $p < 0.10$ was considered statistically significant.

SPSS version 23.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

Patients

In total, 37 patients with PAH were included in the analysis; the majority of the patients (84%) presented with idiopathic PAH (table 1). A substantial proportion of the patients were already receiving double or

TABLE 2 Right ventricular pressure–volume loop measurements and CPET and MRI-derived parameters

	Patients with PAH
Subjects n	37
Pressure–volume loop measurements	
Ea mmHg·mL ⁻¹	0.69 [0.46–1.04]
Ees mmHg·mL ⁻¹	0.61 [0.45–0.78]
Ees/Ea ratio	0.88 [0.50–1.24]
Eed mmHg·mL ⁻¹	0.12 [0.05–0.22]
Tau ms	32 [28–40]
EDP mmHg	6 [4–11]
ESP mmHg	54 [44–81]
MRI measurements	
Stiffness index $\beta^{\#}$	4.2 [3.0–6.0]
Capacitance [¶] mL·mmHg ⁻¹	2.2 [1.5–3.1]
Distensibility [*] %·mmHg ⁻¹	0.5 [0.3–0.7]
CPET	
V_{O_2} rest L·min ⁻¹	0.3±0.1
V_{O_2} peak L·min ⁻¹	1.1±0.4
V_{O_2} peak mL·kg ⁻¹ ·min ⁻¹	13 [11–17]
V_{O_2} peak % pred	56 [39–87]
V_E rest L·min ⁻¹	13 [10–16]
V_E peak L·min ⁻¹	46 [38–56]
O ₂ pulse rest mL·beat ⁻¹	4 [3–5]
O ₂ pulse peak mL·beat ⁻¹	8 [6–10]
V_E/V_{CO_2} rest [§]	42 [38–50]
V_E/V_{CO_2} peak [§]	41 [34–54]
V_E/V_{CO_2} nadir [§]	40 [31–44]
V_E/V_{CO_2} slope	42 [32–52]
P_{ETCO_2} rest mmHg	25±6
P_{ETCO_2} peak mmHg	23±8
P_{aCO_2} rest mmHg	32±6
P_{aCO_2} peak mmHg	33±6
P_{O_2} rest mmHg	67±13
P_{O_2} peak mmHg	69±18
$P_{[a-ET]CO_2}$ rest mmHg	7.7±5.1
$P_{[a-ET]CO_2}$ peak mmHg	9.8±4.5
RER rest	0.84 [0.74–0.93]
RER peak	1.01 [0.89–1.13]
Endurance time s	623±165
Work rate watts	60 [45–85]

Values represent mean±SD or median (interquartile range). PAH: pulmonary arterial hypertension; Ea: arterial elastance; Ees: end-systolic elastance; Eed: end-diastolic elastance; EDP: end-diastolic pressure; ESP: end-systolic pressure; MRI: magnetic resonance imaging; CPET: cardiopulmonary exercise testing; V_{O_2} : oxygen uptake; V_E : minute ventilation; V_E/V_{CO_2} : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide); P_{ETCO_2} : end-tidal carbon dioxide tension; P_{aCO_2} : arterial carbon dioxide tension; P_{O_2} : oxygen tension; $P_{[a-ET]CO_2}$: arterial to end-tidal carbon dioxide tension gradient; RER: respiratory exchange ratio. [#]: n=33; [¶]: n=36; ^{*}: n=32; [§]: n=35.

triple combinations of drugs targeting the pulmonary circulation, and the majority presented in World Health Organization (WHO) functional classes II or III. Right heart catheterisation measurements showed that the patients had severe, chronic pressure overload. Mean D_{LCO} was 61% of predicted. Pressure–volume loop measurements (table 2) showed that the Ees/Ea ratio was lower than the optimal value for RV–PA coupling (1.5–2.0) [15]. MRI measurements revealed a high stiffness index β and low capacitance and distensibility in the pulmonary artery. CPET measurements showed an impaired peak work rate with low peak $V'O_2$ (in $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ and % predicted) and peak O_2 pulse, a high V'_E/V'_{CO_2} slope and a low P_{ETCO_2} at peak exercise. The $P_{(a-ET)CO_2}$ gradient was moderately elevated. Maximum RER slightly exceeded 1.

Association of CPET parameters with pressure–volume loop-derived measurements of RV function and afterload and MRI-derived measurements of PA stiffness

The pressure–volume loop-derived parameters Ea and Eed correlated with V'_E/V'_{CO_2} slope and peak P_{ETCO_2} (figure 1). In addition, Ea correlated with peak O_2 pulse. V'_E/V'_{CO_2} slope and peak P_{ETCO_2} also correlated with PVR (supplementary figure E1). Of note, Eed strongly correlated with resting cardiac index (supplementary figure E2). BNP levels correlated with Ea and Eed as well as V'_E/V'_{CO_2} slope and peak P_{ETCO_2} (supplementary figure E3). There were no correlations between Ees/Ea or Ees and CPET parameters (data not shown). There was no correlation between pressure–volume loop-derived measurements and peak $V'O_2$. MRI-derived measurements of the stiffness of the pulmonary arteries correlated with V'_E/V'_{CO_2} slope, peak P_{ETCO_2} and peak O_2 pulse (figure 2). V'_E/V'_{CO_2} nadir showed even more significant correlations with Ea, Eed, stiffness of the pulmonary arteries, PVR and BNP than V'_E/V'_{CO_2} slope (figure 3).

Eed and Ea were related to V'_E/V'_{CO_2} slope cut-offs proposed for risk assessment of patients with PAH in current guidelines (figure 4) [5].

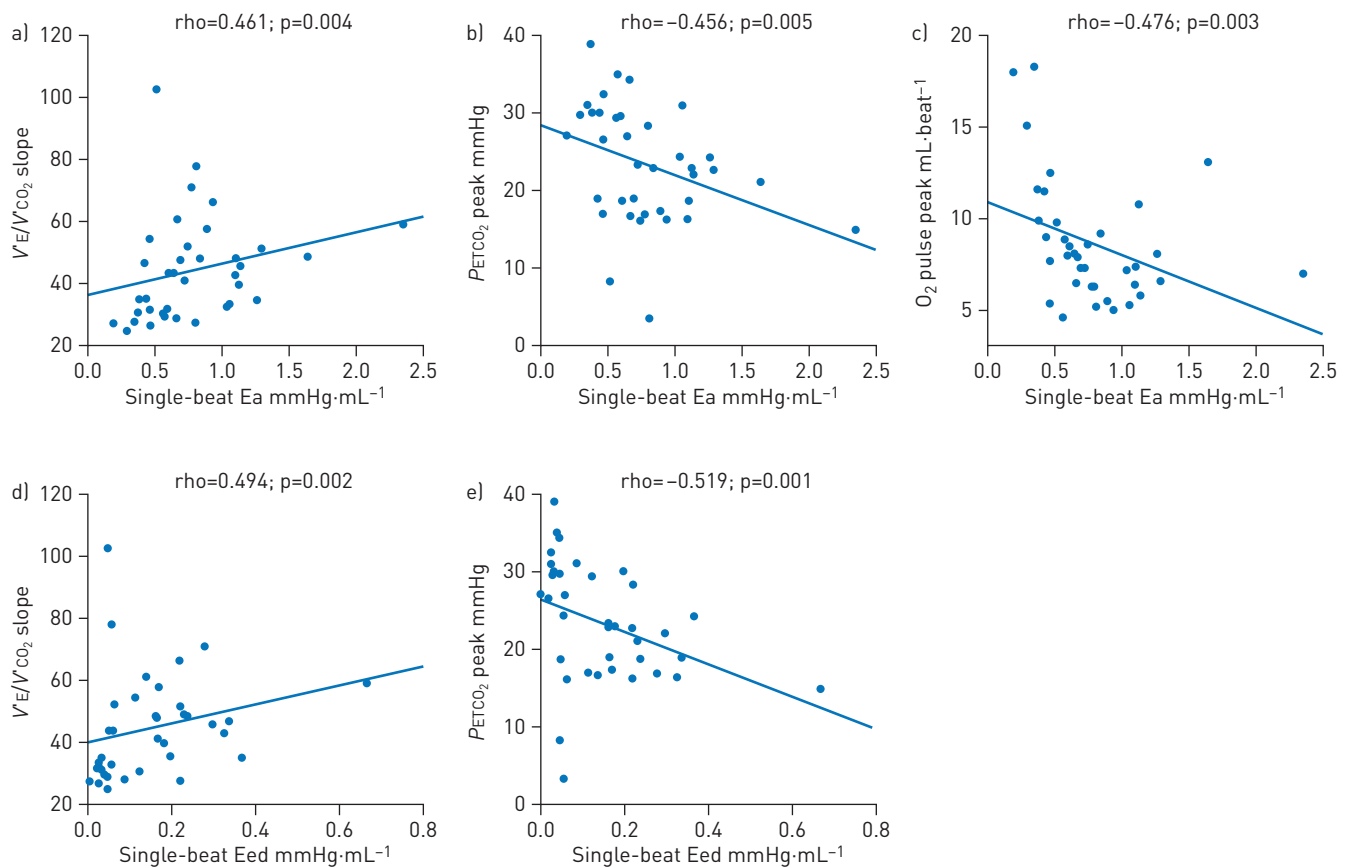


FIGURE 1 Association of cardiopulmonary exercise test parameters with single-beat pressure–volume loop-derived measurements of right ventricular a–c) afterload and d, e) diastolic stiffness. V'_E/V'_{CO_2} : minute ventilation/carbon dioxide production [ventilatory equivalent for carbon dioxide]; Ea: arterial elastance; P_{ETCO_2} : end-tidal carbon dioxide tension; Eed: end-diastolic elastance.

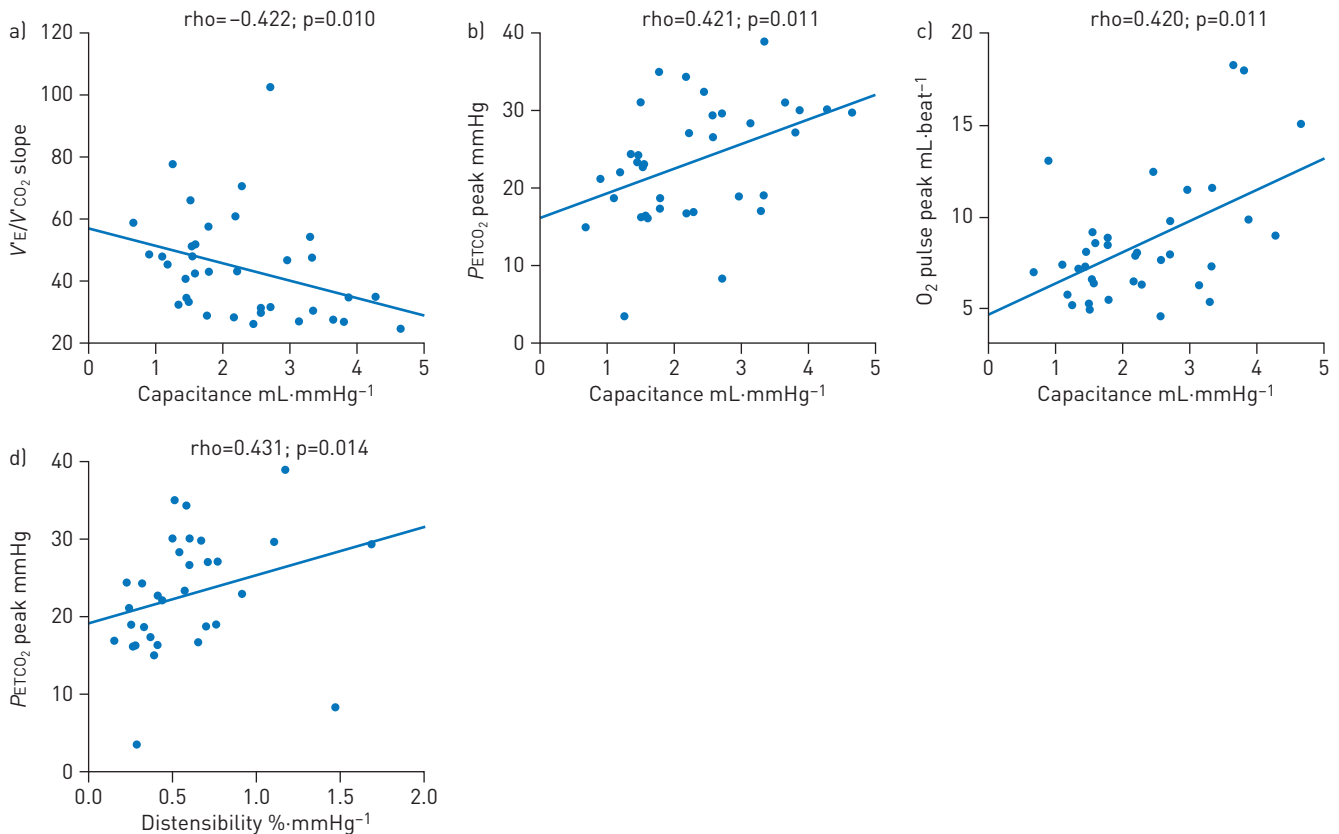


FIGURE 2 Association of cardiopulmonary exercise test parameters with magnetic resonance imaging-derived pulmonary arterial a–c) capacitance and d) distensibility. V_E/V'_{CO_2} : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide); P_{ETCO_2} : end-tidal carbon dioxide tension.

Predictive relevance of E_a and E_{ed} for ventilatory inefficiency

In univariate logistic regression analysis, E_a (univariate OR 7.28, 95% CI 1.20–44.04, $p=0.031$) and E_{ed} (univariate OR 2.21, 95% CI 0.93–5.26, $p=0.073$), but not E_{es} (univariate OR 1.04, $p=0.955$) or E_{es}/E_a (univariate OR 2.30, $p=0.129$), were significantly associated with ventilatory inefficiency (V_E/V'_{CO_2} slope >48). A model including BNP, sex, E_{ed} and E_a as predictor variables indicated superiority of E_a over E_{ed} (Wald values 3.111 and 0.468, respectively). Multivariate odds ratios for the association of E_a and E_{ed} with ventilatory inefficiency were 13.16 (95% CI 0.75–230.53, $p=0.078$) and 1.71 (95% CI 0.37–7.87, $p=0.494$), respectively.

Discussion

In the present study, both diastolic stiffness and increased afterload of the right ventricle were associated with exercise hyperventilation in patients with PAH, while RV contractility (E_{es}) in isolation or coupled to afterload (E_{es}/E_a) was not.

Hyperventilation in PAH is caused by a combination of increased dead space ventilation and increased chemosensitivity [1, 2]. In the present study, the $P_{(a-ET)CO_2}$ gradients were only moderately elevated, on average by 2–3 mmHg above the upper limit of normal of 5 mmHg [28], and both P_{ETCO_2} and P_{aCO_2} were low, arguing in favour of a dominant role of increased chemosensitivity [29]. Increased ventilatory responses to both hypercapnia and hypoxia have been reported in patients with severe pulmonary hypertension [30]. Consistent with those observations, increased sympathetic nervous system activity has been demonstrated by microneurography in patients with PAH [31]. Increased sympathetic nervous system activity predicts a poor prognosis in PAH [32], and an increased V_E/V'_{CO_2} slope has also been identified as a predictor of poor prognosis in PAH, albeit with some variability between PAH subtypes [3, 4]. The mechanisms of increased chemosensitivity in PAH remain incompletely understood. Atrial septostomy has been reported to decrease sympathetic nervous system tone in PAH, in spite of right-to-left atrial shunt-induced hypoxaemia, which the authors explained by a reverse Bainbridge reflex [33]. Thus, right atrial (and RV) stretch or stiffness could be an important trigger of chemosensitivity and sympathetic nervous system tone in PAH. The increased BNP levels correlating with

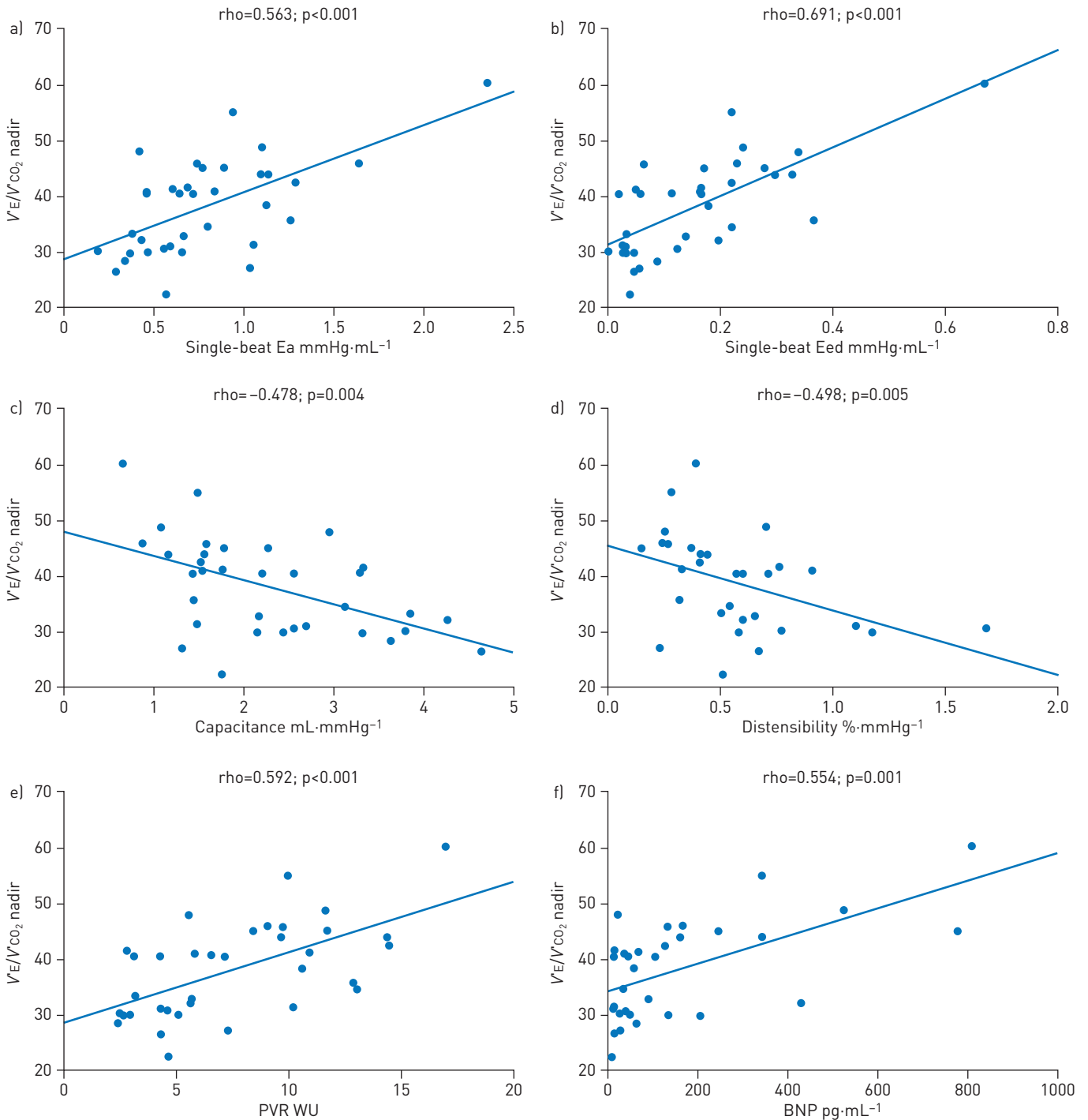


FIGURE 3 Association of V_E/V'_{CO_2} nadir with a) single-beat arterial elastance (Ea), b) single-beat end-diastolic elastance (Eed), c) capacitance, d) distensibility, e) pulmonary vascular resistance (PVR) and f) B-type natriuretic peptide (BNP). V_E/V'_{CO_2} : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide); WU: Wood units.

increased V_E/V'_{CO_2} in the present study support this mechanism, as does the observed prediction of ventilatory inefficiency by increased RV diastolic stiffness (Eed) in the presence of increased afterload (Ea). As illustrated in figure 5, plotting of V_E/V'_{CO_2} as a function of P_{aCO_2} revealed a characteristic leftward shift of the curve (indicative of increased chemosensitivity [34]) in the patients with PAH who also had maladaptive high Eed (based on a previously described cut-off [17]). In addition, V_E/V'_{CO_2} was substantially increased at rest and during exercise in patients with high *versus* low Eed (figure 5b).

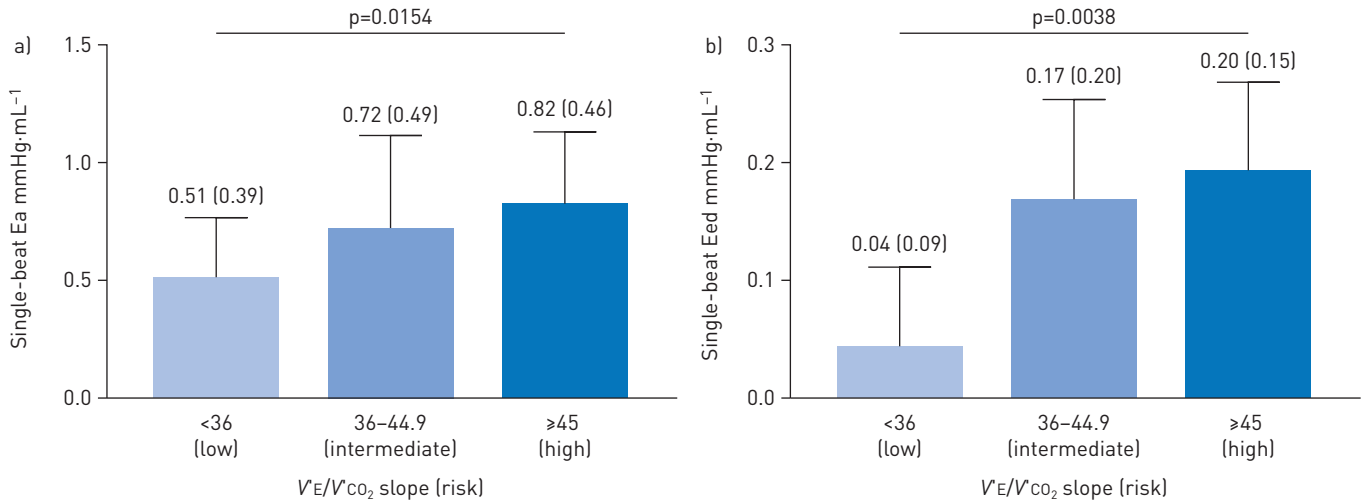


FIGURE 4 a) Afterload and b) right ventricular diastolic stiffness stratified according to the V'_E/V'_{CO_2} slope proposed for risk assessment of patients with pulmonary arterial hypertension in current guidelines [5]. Bar graphs show median and interquartile range. Statistical significance was assessed using the Kruskal–Wallis test. Ea: arterial elastance; V'_E/V'_{CO_2} : minute ventilation/carbon dioxide production [ventilatory equivalent for carbon dioxide]; Eed: end-diastolic elastance.

Another possible reflex mechanism would be triggered by PA distension, but this is less convincingly supported by the available evidence. Nevertheless, we found a significant correlation between MRI-derived parameters of PA stiffness and exercise hyperventilation; this might be mediated *via* the association of these parameters with afterload [12] rather than a direct relationship.

The right ventricle in severe pulmonary hypertension initially adapts by increasing contractility to match the increased afterload [6, 7]. This “homeometric adaptation” is assessed by an Ees/Ea ratio determined from pressure–volume loops. When RV–PA coupling deteriorates, reflected by a progressive decrease in Ees/Ea, a “heterometric adaptation” (dimension-dependent) is turned on to preserve cardiac output responses to peripheral demand. This eventually occurs at the price of excessive RV dilatation and systemic congestion. We previously showed that RV–PA coupling in severe PAH has a lot of reserve, because the Ees/Ea ratio needs to decrease from normal values of 1.5–2 to <0.8 before excessive RV dilatation occurs [15]. While RV dilatation is an obvious cause of increased atrial and RV stretch and stiffness, diastolic elastance may also increase out of proportion to systolic elastance in the presence of increased afterload [23]. The present data indirectly support the occurrence of this dissociation because V'_E/V'_{CO_2} increased in association with Eed and Ea. Of note, a further differentiation of Ea and Eed according to the risk stratification cut-offs proposed for the V'_E/V'_{CO_2} slope in current guidelines [5] showed a distinctive pattern. This sub-differentiation revealed that even patients with an intermediate elevation of V'_E/V'_{CO_2} slope [5], and thus ventilatory inefficiency, had a substantial increase in Ea and Eed.

In the present study, RV Ees, Ea and Eed were determined using the single-beat method, which was experimentally validated in animals [22] and thereafter applied to patients with PAH [15, 35, 36]. The alternative would be to derive these measurements using a multiple-beat approach with families of RV pressure–volume loops obtained at decreasing venous return, as was initially reported in isolated heart preparations [37] and later applied to patients with PAH [38, 39]. A decrease in venous return can be obtained by inflating a balloon in the inferior vena cava [16] (although this additional invasive procedure may carry some risk and cause ethical concern) or by a Valsalva manoeuvre [38, 39]. However, it is not known how positive intrathoracic pressures affect RV–PA coupling. Furthermore, decreasing venous return may decrease Ees/Ea because of sympathetic nervous system activation leading to an increase in Ea [22]. On the other hand, the single-beat analysis depends on a maximum RV pressure calculation based on extrapolation of RV pressure curves, which may be technically challenging. Further studies are needed to validate single- and multiple-beat methods against each other. In the meantime, it is conceivable that Ees or Ees/Ea determined by different methods, while being consistent and tending to agree [40], may still differ in terms of correlation to V'_E/V'_{CO_2} . RV Ees and V'_E/V'_{CO_2} showed a borderline significant correlation ($p=0.049$) in a multiple-beat study of RV function in a mixed population of patients with systemic sclerosis-associated and idiopathic PAH [38], whereas this correlation did not achieve significance in the present single-beat study of patients with predominantly idiopathic PAH.

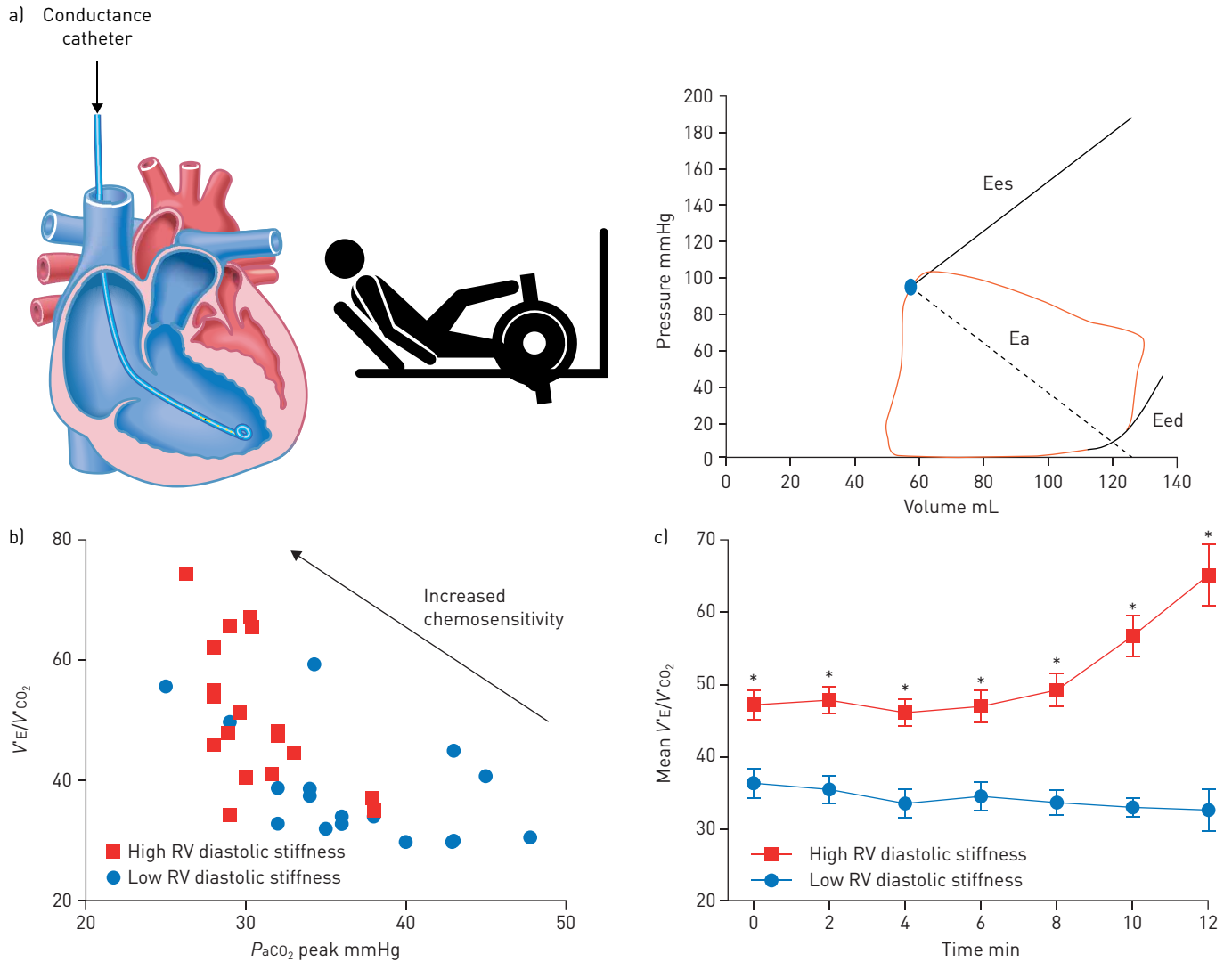


FIGURE 5 Pathophysiological concept of the association of increased diastolic stiffness with increased chemosensitivity in pulmonary arterial hypertension. a) Conductance catheterisation and cardiopulmonary exercise testing allow assessment of right ventricular (RV) diastolic stiffness (end-diastolic elastance (Eed)) and its relationship with chemosensitivity. b) A leftward shift of V_E/V_{CO_2} versus arterial carbon dioxide tension (P_{aCO_2}) plots to lower P_{aCO_2} and higher V_E/V_{CO_2} indicates increased chemosensitivity [34], which was found to be present in patients with high RV diastolic stiffness in the current study. c) V_E/V_{CO_2} at rest (0 min) and during symptom-limited incremental cycle exercise (2–12 min) was increased in patients with high versus low RV diastolic stiffness. High RV diastolic stiffness was defined as $E_{ed} > 0.124 \text{ mmHg} \cdot \text{mL}^{-1}$ as previously described [17]. Error bars show standard error of the mean. *: $p < 0.01$ (between-group differences analysed with unpaired t-test). Ea: arterial elastance; V_E/V_{CO_2} : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

The ventilatory response to exercise is usually assessed by the slope of V_E as a function of V'_{CO_2} . Although studies of the prognostic role of the V_E/V'_{CO_2} slope have produced variable results in PAH [3, 4, 41, 42], the V_E/V'_{CO_2} slope has been identified as an important and potent predictor of outcome in left-sided heart failure [43, 44] and PAH [3, 4, 27], and has been reported to be associated with afterload (assessed as PVR) in heart failure with preserved ejection fraction [9]. It has been argued that the slope of V_E/V'_{CO_2} would be better replaced by its nadir as being a less effort-dependent and more stable measurement [20]. In the present study, the nadir of V_E/V'_{CO_2} actually showed a better correlation with RV diastolic stiffness and afterload than did the slope of V_E/V'_{CO_2} . However, V_E/V'_{CO_2} to predict outcome in PAH or left-sided heart failure is usually reported as slope instead of nadir.

In addition, echocardiographic measurements of RV dimensions and systolic function have been shown to be related to ventilatory inefficiency in patients with severe left heart failure [10], in keeping with the notion of increased chemosensitivity secondary to increased RV stretch and stiffness. Whether a right heart phenotype might worsen wasted ventilation and associated dyspnoea in heart failure remains to be clarified.

There is more to shortness of breath in PAH than wasted ventilation. Recent studies have suggested a significant contribution of dynamic hyperinflation during exercise in these patients [45, 46]. Even though this mechanism is not a cause of ventilatory limitation to aerobic exercise and is not related to respiratory muscle weakness in PAH [47], it contributes to exercise intolerance by worsening dyspnoea at any level of workload. However, the extent to which hyperventilation, dead space ventilation, chemosensitivity and/or the abnormal response of the pulmonary circulation during exercise contribute to excessive dynamic hyperinflation is currently unknown.

The patients with PAH included in the present study were severely ill, with about half in WHO functional class III and most of the others in WHO functional class II (the remaining two patients were in WHO functional class I). However, they are representative of patients with PAH admitted and followed in pulmonary hypertension referral centres. In a review of 11 PAH registries, McGOON *et al.* [48] reported that 54%–80% of the patients were in WHO functional classes III/IV; previous PAH registry populations were thus even more severely ill than our cohort. The peak \dot{V}_{O_2} and workload values in the present study were typical for patients with PAH [4, 27, 42, 49], and similar to those reported in multiple-beat RV function studies [38]. It cannot be excluded that clustering of Ees at a very low range of values prevented the uncovering of significant correlations with \dot{V}_E/\dot{V}_{CO_2} .

Limitations

We compared pressure–volume parameters at rest with parameters assessed under exercise (CPET). The analysis is thus limited by the fact that pressure–volume loops were not generated during exercise. We performed a single-beat analysis of pressure–volume loops, and it is unclear if the multiple-beat approach would produce similar results. The prognostic \dot{V}_E/\dot{V}_{CO_2} cut-off value of 48 relied mainly on the study by GROEPENHOFF and co-workers [4, 27] and may thus not be sufficiently robust [3]. The small size, the relatively low RER and the advanced functional status of our study population may also have biased our results. Nevertheless, we believe the sample size is reasonable for a study of invasive pressure–volume catheterisation in patients with PAH, and submaximal exercise testing yielding a RER <0.9 in PAH did not affect key ventilatory parameters [50]. The small sample size limited the univariate and multivariate logistic regression analyses and prevented further in-depth or receiver operating characteristic analysis. In addition, data-driven cut-offs, especially in small sample sizes, should be interpreted with caution and need external validation. Finally, it has to be underscored that showing independent prediction of \dot{V}_E/\dot{V}_{CO_2} by RV Eed and Ea does not prove causation, which needs to be further investigated by dedicated studies.

Conclusion

Our data suggest that both impaired RV lusitropy and increased RV afterload are associated with ventilatory inefficiency in PAH. The potential implications of this finding for PAH treatment warrant further study.

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References

- 1 Weatherald J, Sattler C, Garcia G, *et al.* Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur Respir J* 2018; 51: 1700860.
- 2 Dumitrescu D, Sitbon O, Weatherald J, *et al.* Exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir Rev* 2017; 26: 170039.
- 3 Deboeck G, Scoditti C, Huez S, *et al.* Exercise testing to predict outcome in idiopathic versus associated pulmonary arterial hypertension. *Eur Respir J* 2012; 40: 1410–1419.
- 4 Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, *et al.* Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008; 40: 1725–1732.
- 5 Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
- 6 Vonk Noordegraaf A, Chin KM, Haddad F, *et al.* Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J* 2019; 53: 1801900.
- 7 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.
- 8 Naeije R, Manes A. The right ventricle in pulmonary arterial hypertension. *Eur Respir Rev* 2014; 23: 476–487.
- 9 Klaassen SHC, Liu LCY, Hummel YM, *et al.* Clinical and hemodynamic correlates and prognostic value of VE/VCO₂ slope in patients with heart failure with preserved ejection fraction and pulmonary hypertension. *J Card Fail* 2017; 23: 777–782.
- 10 Methvin AB, Owens AT, Emmi AG, *et al.* Ventilatory inefficiency reflects right ventricular dysfunction in systolic heart failure. *Chest* 2011; 139: 617–625.
- 11 Farina S, Correale M, Bruno N, *et al.* “Right and Left Heart Failure Study Group” of the Italian Society of Cardiology. The role of cardiopulmonary exercise tests in pulmonary arterial hypertension. *Eur Respir Rev* 2018; 27: 170134.
- 12 Sanz J, Kariisa M, Dellegrattaglia S, *et al.* Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2009; 2: 286–295.
- 13 Gall H, Felix JF, Schneck FK, *et al.* The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups. *J Heart Lung Transplant* 2017; 36: 957–967.
- 14 Tello K, Richter MJ, Axmann J, *et al.* More on single-beat estimation of right ventriculoarterial coupling in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2018; 198: 816–818.
- 15 Tello K, Dalmer A, Axmann J, *et al.* Reserve of right ventricular-arterial coupling in the setting of chronic overload. *Circ Heart Fail* 2019; 12: e005512.
- 16 Tello K, Dalmer A, Husain-Syed F, *et al.* Multi-beat right ventricular-arterial coupling during a positive acute vaso-reactivity test. *Am J Respir Crit Care Med* 2019; 199: e41–e42.
- 17 Tello K, Dalmer A, Vanderpool R, *et al.* Cardiac magnetic resonance imaging-based right ventricular strain analysis for assessment of coupling and diastolic function in pulmonary hypertension. *JACC Cardiovasc Imaging* 2019; 12: 2155–2164.
- 18 Macintyre N, Crapo RO, Viegi G, *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720–735.
- 19 Scheidl SJ, Englisch C, Kovacs G, *et al.* Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. *Eur Respir J* 2012; 39: 119–124.
- 20 Wasserman K, Hansen JE, Sue DY, *et al.* Principles of Exercise Testing and Interpretation. 5th Edn. Philadelphia, Lippincott Williams & Wilkins, 2011.
- 21 Tello K, Axmann J, Ghofrani HA, *et al.* Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. *Int J Cardiol* 2018; 266: 229–235.
- 22 Brimiouille S, Wauthy P, Ewalenko P, *et al.* Single-beat estimation of right ventricular end-systolic pressure-volume relationship. *Am J Physiol Heart Circ Physiol* 2003; 284: H1625–H1630.
- 23 Rain S, Handoko ML, Trip P, *et al.* Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. *Circulation* 2013; 128: 2016–2025.
- 24 Vanderpool RR, Pinsky MR, Naeije R, *et al.* RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. *Heart* 2015; 101: 37–43.
- 25 Vanderpool RR, Puri R, Osorio A, *et al.* EXPRESS: surfing the right ventricular pressure waveform: methods to assess global, systolic and diastolic RV function from a clinical right heart catheterization. *Pulm Circ* 2019; in press [<https://doi.org/10.1177/2045894019850993>].
- 26 Trip P, Rain S, Handoko ML, *et al.* Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension. *Eur Respir J* 2015; 45: 1603–1612.
- 27 Groepenhoff H, Vonk-Noordegraaf A, van de Veerdonk MC, *et al.* Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. *PLoS One* 2013; 8: e72013.
- 28 Robin ED, Forkner CE Jr., Bromberg PA, *et al.* Alveolar gas exchange in clinical pulmonary embolism. *N Engl J Med* 1960; 262: 283–287.
- 29 Naeije R, Faoro V. The breathlessness of pulmonary hypertension. *Int J Cardiol* 2018; 259: 183–184.

- 30 Farina S, Bruno N, Agalbato C, *et al.* Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2018; 259: 178–182.
- 31 Velez-Roa S, Ciarka A, Najem B, *et al.* Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* 2004; 110: 1308–1312.
- 32 Ciarka A, Doan V, Velez-Roa S, *et al.* Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010; 181: 1269–1275.
- 33 Ciarka A, Vachiery JL, Houssiere A, *et al.* Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. *Chest* 2007; 131: 1831–1837.
- 34 Naeije R, Faoro V. The great breathlessness of cardiopulmonary diseases. *Eur Respir J* 2018; 51: 1702517.
- 35 Kuehne T, Yilmaz S, Steendijk P, *et al.* Magnetic resonance imaging analysis of right ventricular pressure-volume loops: *in vivo* validation and clinical application in patients with pulmonary hypertension. *Circulation* 2004; 110: 2010–2016.
- 36 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.
- 37 Maughan WL, Shoukas AA, Sagawa K, *et al.* Instantaneous pressure-volume relationship of the canine right ventricle. *Circ Res* 1979; 44: 309–315.
- 38 Hsu S, Houston BA, Tampakakis E, *et al.* Right ventricular functional reserve in pulmonary arterial hypertension. *Circulation* 2016; 133: 2413–2422.
- 39 Tedford RJ, Mudd JO, Girgis RE, *et al.* Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circ Heart Fail* 2013; 6: 953–963.
- 40 Inuzuka R, Hsu S, Tedford RJ, *et al.* Single-beat estimation of right ventricular contractility and its coupling to pulmonary arterial load in patients with pulmonary hypertension. *J Am Heart Assoc* 2018; 7: e007929.
- 41 Wensel R, Francis DP, Meyer FJ, *et al.* Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. *Int J Cardiol* 2013; 167: 1193–1198.
- 42 Wensel R, Opitz CF, Anker SD, *et al.* Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324.
- 43 Francis DP, Shamim W, Davies LC, *et al.* Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO₂ slope and peak VO₂. *Eur Heart J* 2000; 21: 154–161.
- 44 Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *Am J Respir Crit Care Med* 2011; 183: 1302–1310.
- 45 Richter MJ, Voswinckel R, Tiede H, *et al.* Dynamic hyperinflation during exercise in patients with precapillary pulmonary hypertension. *Respir Med* 2012; 106: 308–313.
- 46 Laveneziana P, Garcia G, Joureau B, *et al.* Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2013; 41: 578–587.
- 47 Laveneziana P, Humbert M, Godinas L, *et al.* Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2015; 45: 1495–1498.
- 48 McGoon MD, Benza RL, Escribano-Subias P, *et al.* Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol* 2013; 62: D51–D59.
- 49 Deboeck G, Niset G, Lamotte M, *et al.* Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J* 2004; 23: 747–751.
- 50 Woods PR, Frantz RP, Taylor BJ, *et al.* The usefulness of submaximal exercise gas exchange to define pulmonary arterial hypertension. *J Heart Lung Transplant* 2011; 30: 1133–1142.