



Early View

Original article

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Impaired right ventricular lusitropy is associated with ventilatory inefficiency in PAH

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Keywords: functional capacity, pressure-volume loop, single-beat analysis, contractility, pulmonary hypertension, cardiopulmonary exercise testing, afterload, diastolic elastance, right ventriculo-arterial coupling

Take-home message: 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.

Abstract

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

Thirty-seven 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). They also underwent magnetic resonance imaging of pulmonary arterial stiffness. The results were correlated to CPET variables. 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.

Median [interquartile range] of V_E/V_{CO_2} slope was 42 [32–52], of V_E/V_{CO_2} nadir was 40 [31–44], and mean \pm SD of peak end-tidal CO₂ tension ($P_{ET}CO_2$) was 23 \pm 8 mmHg. Ea, Eed and parameters reflecting pulmonary arterial stiffness (capacitance and distensibility) were correlated to V_E/V_{CO_2} slope, V_E/V_{CO_2} nadir, $P_{ET}CO_2$ 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 odds ratio: 7.28; 95% confidence interval: 1.20–44.04) and Eed (univariate odds ratio: 2.21; 95% confidence interval: 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.

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 (VCO_2) slope during a cardiopulmonary exercise test (CPET) [1, 2]. An increase in V_E/VCO_2 slope has been shown to be an important predictor of outcome in patients with PAH [3, 4] and evaluation of V_E/VCO_2 slope has therefore been recommended as part of risk assessment in these patients [5]. On the other hand, 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 to arterial elastances (E_{es}/E_a) at a normally low end-diastolic elastance (E_{ed}) [6-8]. Although the V_E/VCO_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/VCO_2 slope or nadir and other CPET parameters previously reported to be of relevance such as peak oxygen uptake (VO_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 (DLCO) 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).

CPET

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 non-invasive blood pressure

measurement was performed every 2 min. Peak VO_2 was defined as the VO_2 measured during the last 30 s of peak exercise. The respiratory exchange ratio (RER) was calculated as VCO_2/VO_2 , and O_2 pulse as $\text{VO}_2/\text{heart rate}$. The ventilatory equivalents for CO_2 were calculated by dividing V_E (corrected for equipment external dead space) by VCO_2 . V_E/VCO_2 slopes were measured between warm up and anaerobic threshold. The nadir of V_E/VCO_2 was assessed as described previously [20]. Capillary (PaCO_2) to end-tidal ($\text{P}_{\text{ET}}\text{CO}_2$) carbon dioxide gradient ($\text{P}_{(\text{a-ET})}\text{CO}_2$) was measured at rest and during exercise [19].

MRI

Imaging was performed with the Avanto 1.5 Tesla scanner system (Siemens Healthineers, Erlangen, Germany; gradient strength and slew rate: SQ-Engine (45mT/m @ 200 T/m/s)). 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 (PAWP))/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 (ESP)/stroke volume [22]. RV-PA coupling was calculated as Ees/Ea. A diastolic stiffness factor β was calculated as described previously by a non-linear 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/VCO_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.

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/VCO_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

Thirty-seven 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 triple combinations of drugs targeting the pulmonary circulation, and the majority presented in World Health Organization (WHO) functional class II and III. Right heart catheterisation measurements showed that the patients had severe, chronic pressure overload. Mean DLCO was 61% 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 VO_2 (in $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ and % predicted) and peak O_2 pulse, a high V_E/VCO_2 slope and a low P_{ETCO_2} at peak exercise. The $\text{P}_{(\text{a-ET})\text{CO}_2}$ 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 were correlated to V_E/VCO_2 slope and peak P_{ETCO_2} (figure 1). In addition, Ea was correlated to peak O_2 pulse. V_E/VCO_2 slope and peak P_{ETCO_2} were also correlated to PVR (supplementary figure E1). Of note, Eed was strongly correlated to resting cardiac index (supplementary figure E2). BNP levels were correlated to Ea and Eed as well as V_E/VCO_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 VO_2 . MRI-derived measurements of the stiffness of the pulmonary arteries were correlated to V_E/VCO_2 slope, peak P_{ETCO_2} and peak O_2 pulse (figure 2). V_E/VCO_2 nadir

showed even more significant correlations with Ea, Eed, stiffness of the pulmonary arteries, PVR and BNP than V_E/VCO_2 slope (figure 3).

Eed and Ea were well related to V_E/VCO_2 slope cut-offs proposed for risk assessment of patients with PAH in current guidelines (figure 4) [5].

Predictive relevance of Ea and Eed for ventilatory inefficiency

In univariate logistic regression analysis, Ea (univariate odds ratio: 7.28; 95% confidence interval: 1.20–44.04; $p=0.031$) and Eed (univariate odds ratio: 2.21; 95% confidence interval: 0.93–5.26; $p=0.073$) (but not Ees (univariate odds ratio: 1.04; $p=0.955$) or Ees/Ea (univariate odds ratio: 2.30; $p=0.129$)) were significantly associated with ventilatory inefficiency (V_E/VCO_2 slope >48). A model including BNP, sex, Eed and Ea as predictor variables indicated superiority of Ea over Eed (Wald values: 3.111 and 0.468, respectively).

Multivariate odds ratios for the association of Ea and Eed with ventilatory inefficiency were 13.16 (95% confidence interval: 0.75–230.53; $p=0.078$) and 1.71 (95% confidence interval: 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 (Ees) in isolation or coupled to afterload (Ees/Ea) 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 $P_{ET}CO_2$ and $PaCO_2$ were low, arguing in favour of a dominant role of increased chemosensitivity [29]. Increased ventilatory responses to both hypercapnia and hypoxia have been recently 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 hypoxemia, 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 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 (E_{ed}) in the presence of increased afterload (E_a). As illustrated in figure 5, plotting of V_E/V_{CO_2} as a function of $PaCO_2$ revealed a characteristic leftward shift of the curve (indicative of increased chemosensitivity [34]) in the patients with PAH who also had maladaptive high E_{ed} (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 vs low E_{ed} (figure 5b).

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 E_{es}/E_a ratio determined from pressure-volume loops. When RV-PA coupling

deteriorates, reflected by a progressive decrease in E_{es}/E_a , 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, as the E_{es}/E_a ratio needs to decrease from normal values of 1.5–2 to less than 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/VCO_2 increased in association with E_{ed} and E_a . Of note, a further differentiation of E_a and E_{ed} according to the risk stratification cut-offs proposed for the V_E/VCO_2 slope in current guidelines [5] showed a distinctive pattern. This subdifferentiation revealed that even patients with an intermediate elevation of V_E/VCO_2 slope [5] and thus ventilatory inefficiency had a substantial increase in E_a and E_{ed} .

In the present study, RV E_{es} , E_a and E_{ed} 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 inflation of 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 intra-thoracic pressures may affect RV-PA coupling. Furthermore, decreasing venous return may decrease E_{es}/E_a because of sympathetic nervous system activation leading to an increase in E_a [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/VCO_2 . RV Ees and V_E/VCO_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.

The ventilatory response to exercise is usually assessed by the slope of V_E as a function of VCO_2 . Although studies of the prognostic role of the V_E/VCO_2 slope have produced variable results in PAH [3, 4, 44, 45], the V_E/VCO_2 slope has been identified as an important and potent predictor of outcome in left-sided heart failure [46, 47], 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/VCO_2 should be better replaced by its nadir as being a less effort-dependent and more stable measurement [20]. Accordingly, in the present study, the nadir of V_E/VCO_2 was actually even better correlated to RV diastolic stiffness and afterload than the slope of V_E/VCO_2 . However, V_E/VCO_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 [41, 42]. Even though this mechanism is not a cause of ventilatory limitation to aerobic exercise and is not related to respiratory muscle weakness in PAH [43], 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. reported that 54–80% of the patients were in WHO functional classes III/IV [48]; 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, 45, 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 coworkers [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 below 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 V_E/VCO_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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Conflict of interest

Dr Tello has received speaking fees from Actelion and Bayer. Ms Dalmer and Dr Vanderpool have nothing to disclose. Dr Ghofrani has received consultancy fees from Bayer, Actelion, Pfizer, Merck, GSK, and Novartis; fees for participation in advisory boards from Bayer, Pfizer, GSK, Actelion, and Takeda; lecture fees from Bayer HealthCare, GSK, Actelion, and Encysive/Pfizer; industry-sponsored grants from Bayer HealthCare, Aires, Encysive/Pfizer,

and Novartis; and sponsored grants from the German Research Foundation, Excellence Cluster Cardiopulmonary Research, and the German Ministry for Education and Research. Dr Naeije has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer, Reata, Lung Biotechnology Corporation, and United Therapeutics. In addition to being an investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards. Dr Roller has nothing to disclose. Dr Seeger has received speaker/consultancy fees from Pfizer and Bayer Pharma AG. Dr Dumitrescu has received fees for participation in advisory boards from Actelion and Novartis; and lecture fees from Bayer HealthCare, GSK, Actelion, MSD, and Servier. Dr Sommer has received fees from Actelion. Dr Brunst has nothing to disclose. Dr Gall has received fees from Actelion, AstraZeneca, Bayer, BMS, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer, and United Therapeutics. Dr Richter has received support from United Therapeutics and Bayer; speaker fees from Bayer, Actelion, Mundipharma, Roche, and OMT; and consultancy fees from Bayer.

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Figure legends

FIGURE 1 Association of cardiopulmonary exercise test parameters with single-beat pressure-volume loop-derived measurements of right ventricular a) afterload (Ea) and b) diastolic stiffness (Eed). Ea: arterial elastance; Eed: end-diastolic elastance; O₂: oxygen; P_{ET}CO₂: end-tidal carbon dioxide; V_E/VCO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

FIGURE 2 Association of cardiopulmonary exercise test parameters with magnetic resonance imaging-derived pulmonary arterial a) capacitance and b) distensibility. O₂: oxygen; P_{ET}CO₂: end-tidal carbon dioxide; V_E/VCO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

FIGURE 3 Association of V_E/VCO₂ nadir with a) single-beat Ea and Eed, b) capacitance and distensibility, c) PVR and d) BNP. BNP: B-type natriuretic peptide; Ea: arterial elastance; Eed: end-diastolic elastance; P_{ET}CO₂: end-tidal carbon dioxide; PVR: pulmonary vascular resistance; V_E/VCO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

FIGURE 4 a) Afterload (Ea) and b) right ventricular diastolic stiffness (Eed) stratified according to the categories of V_E/VCO₂ 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; Eed: end-diastolic elastance; V_E/VCO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

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 RV diastolic stiffness (Eed) and its relationship with chemosensitivity. b) A leftward shift of V_E/V_{CO_2} versus $PaCO_2$ plots to lower $PaCO_2$ 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 vs 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; Eed: end-diastolic elastance; Ees: end-systolic elastance; $PaCO_2$: capillary carbon dioxide tension; RV: right ventricular; V_E/V_{CO_2} : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).

Tables

TABLE 1 Clinical characteristics

	Patients with PAH (n=37)
Male/female	17/20
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]
DLCO % 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

Values represent n, n/n, n (%), mean ± standard deviation or median [interquartile range].

BNP: B-type natriuretic peptide; DLCO: diffusion capacity of the lung for carbon monoxide;

ERA: endothelin receptor antagonist; HIV: human immunodeficiency virus; mPAP: mean

pulmonary artery pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery

wedge pressure; PDE5i: phosphodiesterase type 5 inhibitor; PAH: pulmonary arterial

hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; sGC: soluble

guanylate cyclase; WHO: World Health Organization. [#]n=36; [¶]n=35.

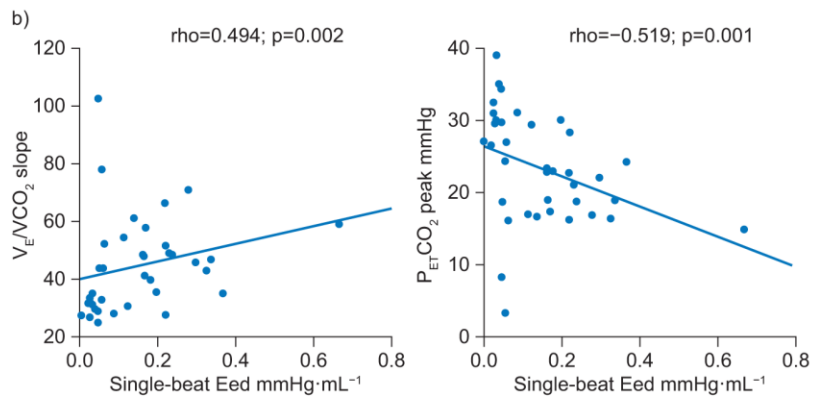
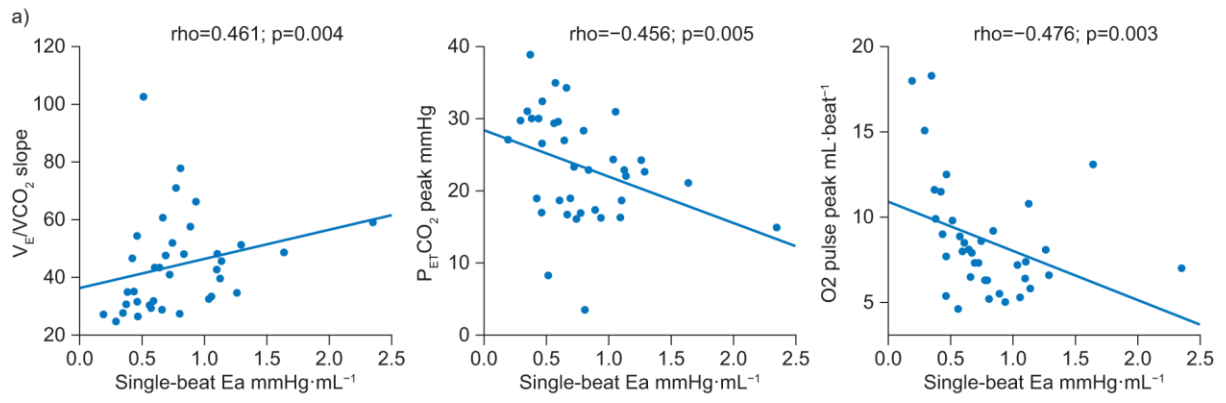
TABLE 2 Right ventricular pressure-volume loop measurements and CPET and MRI-derived parameters

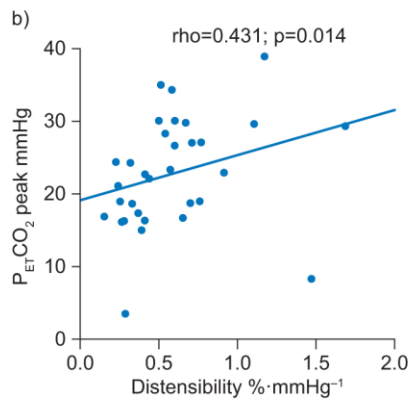
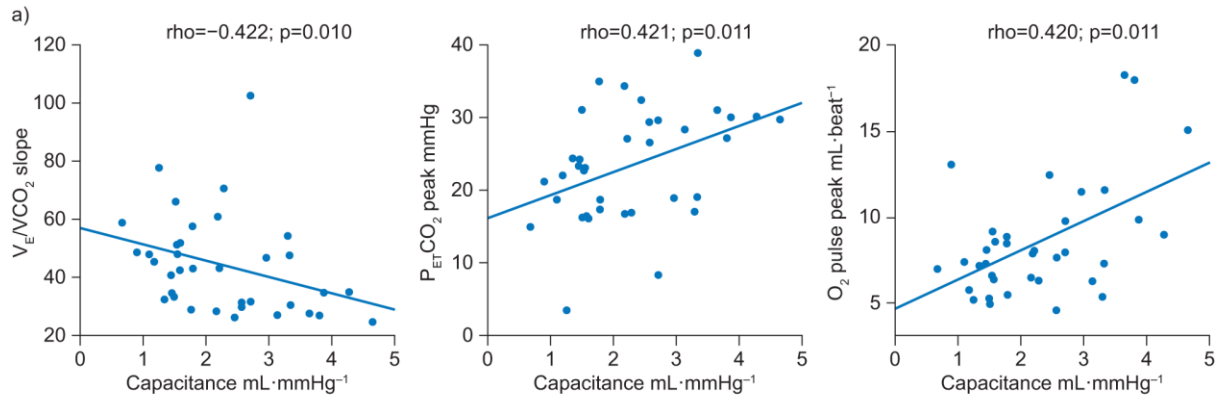
	Patients with PAH (n=37)
Pressure-volume loop measurements	
Ea mmHg·mL ⁻¹	0.69 [0.46–1.04]
Ees mmHg·mL ⁻¹	0.61 [0.45–0.78]
Ees/Ea ratio	0.88 [0.50–1.24]
Eed mmHg·mL ⁻¹	0.12 [0.05–0.22]
Tau ms	32 [28–40]
EDP mmHg	6 [4–11]
ESP mmHg	54 [44–81]
MRI measurements	
Stiffness index β [#]	4.2 [3.0–6.0]
Capacitance mL·mmHg ^{-1¶}	2.2 [1.5–3.1]
Distensibility %·mmHg ⁻¹⁺	0.5 [0.3–0.7]
CPET	
VO ₂ rest L·min ⁻¹	0.3±0.1
VO ₂ peak L·min ⁻¹	1.1±0.4
VO ₂ peak mL·kg ⁻¹ ·min ⁻¹	13 [11–17]

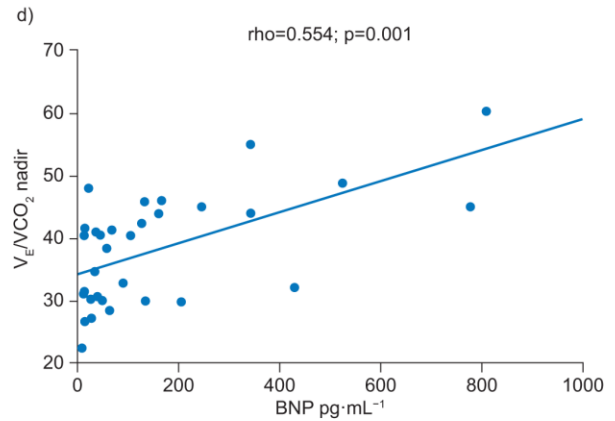
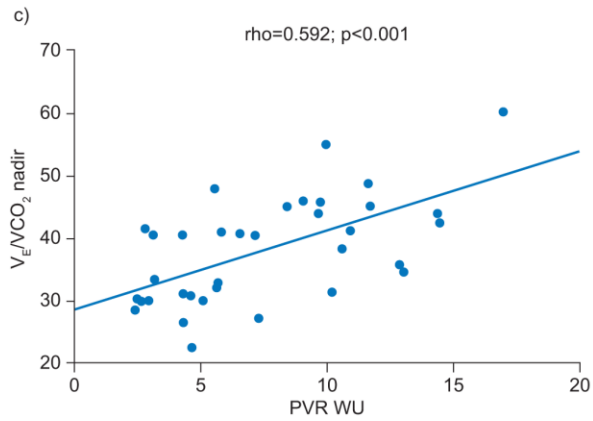
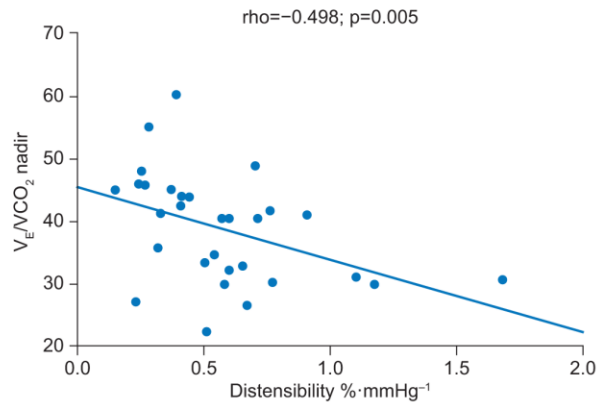
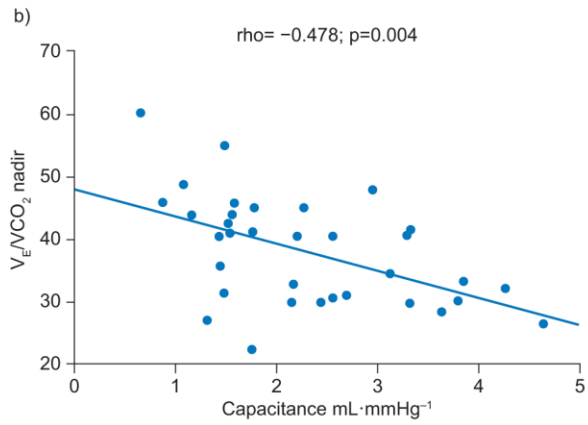
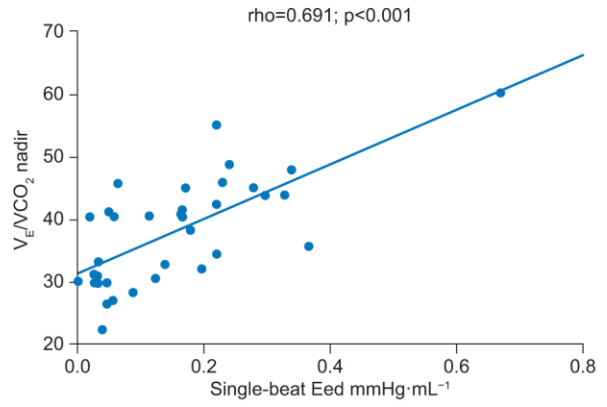
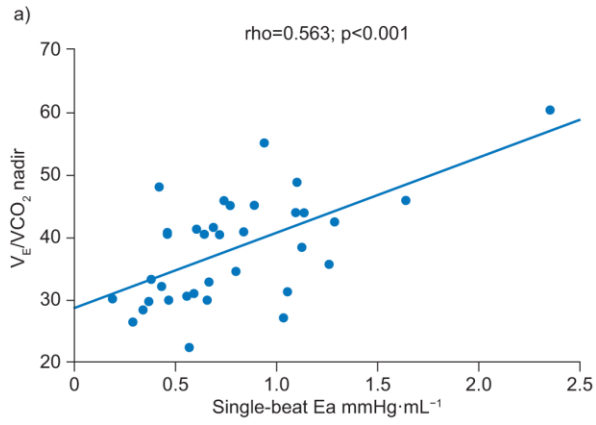
VO ₂ peak % predicted	56 [39–87]
V _E rest L·min ⁻¹	13 [10–16]
V _E peak L·min ⁻¹	46 [38–56]
O ₂ pulse rest mL·beat ⁻¹	4 [3–5]
O ₂ pulse peak mL·beat ⁻¹	8 [6–10]
V _E /VCO ₂ rest ^{##}	42 [38–50]
V _E /VCO ₂ peak ^{##}	41 [34–54]
V _E /VCO ₂ nadir ^{##}	40 [31–44]
V _E /VCO ₂ slope	42 [32–52]
P _{ET} CO ₂ rest mmHg	25±6
P _{ET} CO ₂ peak mmHg	23±8
PaCO ₂ rest mmHg	32±6
PaCO ₂ peak mmHg	33±6
pO ₂ rest mmHg	67±13
pO 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

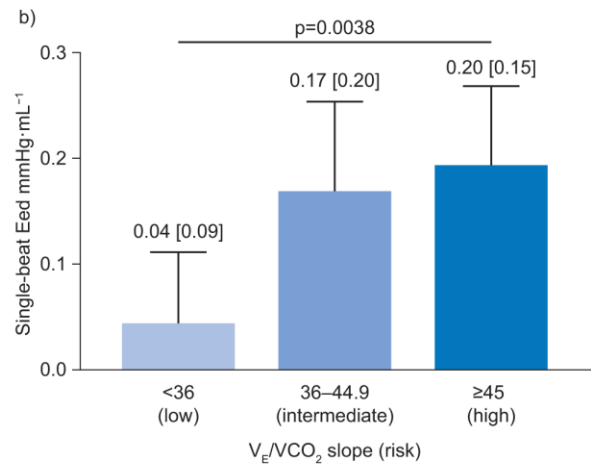
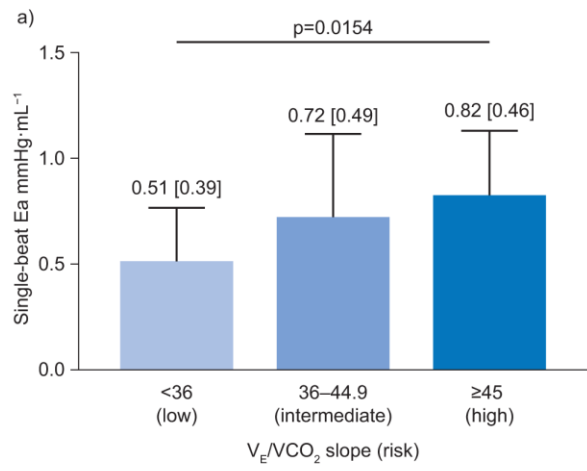
Work rate watts	60 [45–85]
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Values represent mean \pm standard deviation or median [interquartile range]. CPET: cardiopulmonary exercise testing; Ea: arterial elastance; EDP: end-diastolic pressure; Eed: end-diastolic elastance; Ees: end-systolic elastance; ESP: end-systolic pressure; MRI: magnetic resonance imaging; O₂ pulse: oxygen pulse; PaCO₂: capillary carbon dioxide tension; P_(a-ET)CO₂: capillary to end-tidal carbon dioxide gradient; PAH: pulmonary arterial hypertension; P_{ET}CO₂: end-tidal carbon dioxide tension; RER: respiratory exchange ratio; V_E/VCO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide); V_E: minute ventilation; VO₂: oxygen uptake. [#]n=33; [¶]n=36; ⁺n=32; ^{##}n=35.

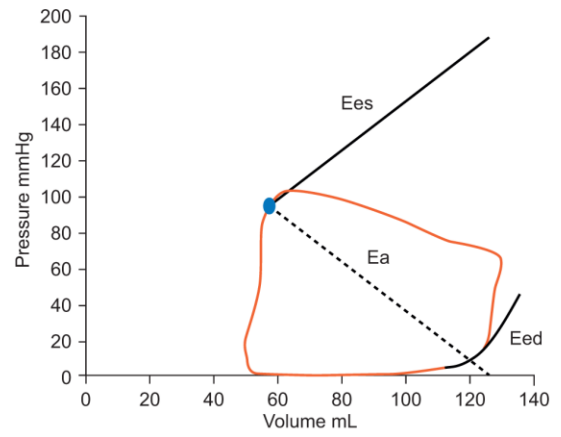
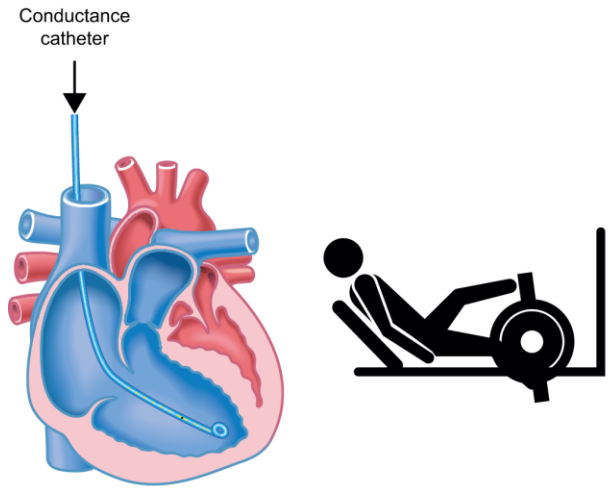




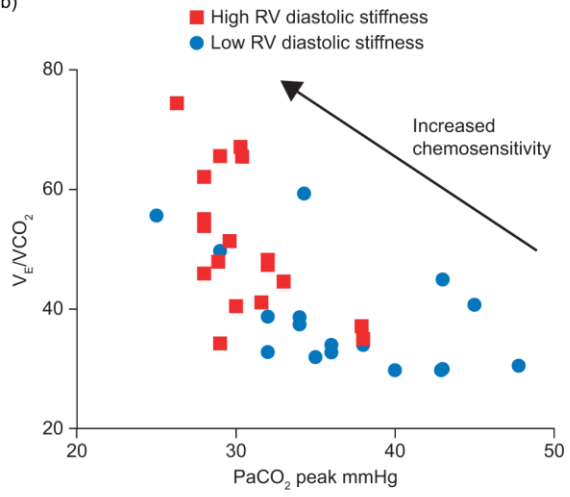




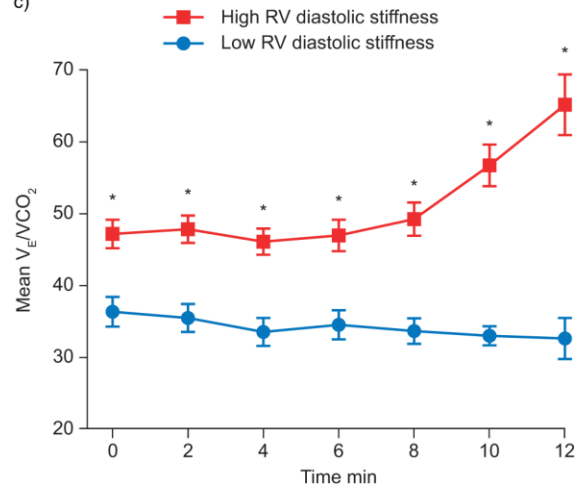
a)



b)



c)



Supplementary material

Impaired right ventricular lusitropy is associated with ventilatory inefficiency in PAH

Khodr Tello, Antonia Dalmer, Rebecca Vanderpool, Hossein A. Ghofrani, Robert Naeije, Fritz Roller, Werner Seeger, Daniel Dumitrescu, Natascha Sommer, Anne Brunst, Henning Gall and Manuel J. Richter

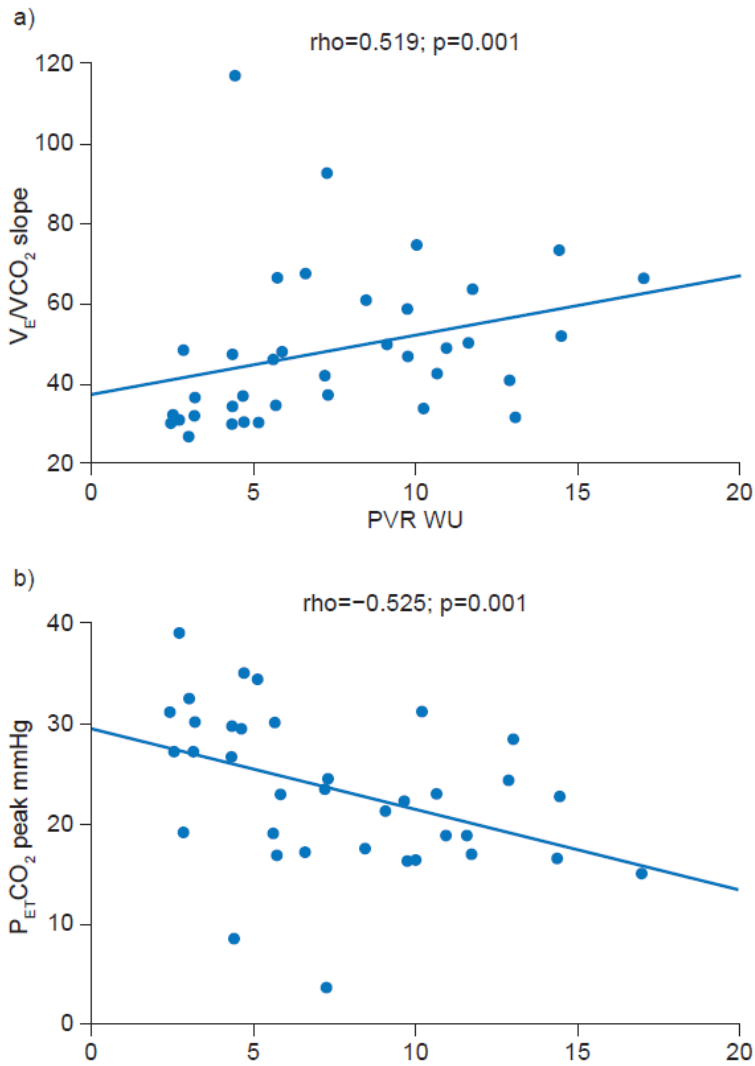


FIGURE E1 Correlation of PVR with a) V_E/VCO_2 slope and b) peak $P_{ET}CO_2$. $P_{ET}CO_2$: end-tidal carbon dioxide; PVR: pulmonary vascular resistance; V_E/VCO_2 : minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide); WU: Wood Units.

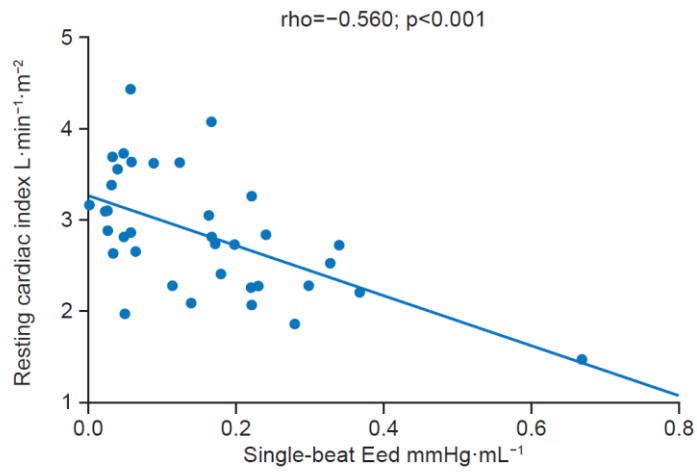


FIGURE E2 Correlation of single-beat Eed with cardiac index at rest. Eed: end-diastolic elastance.

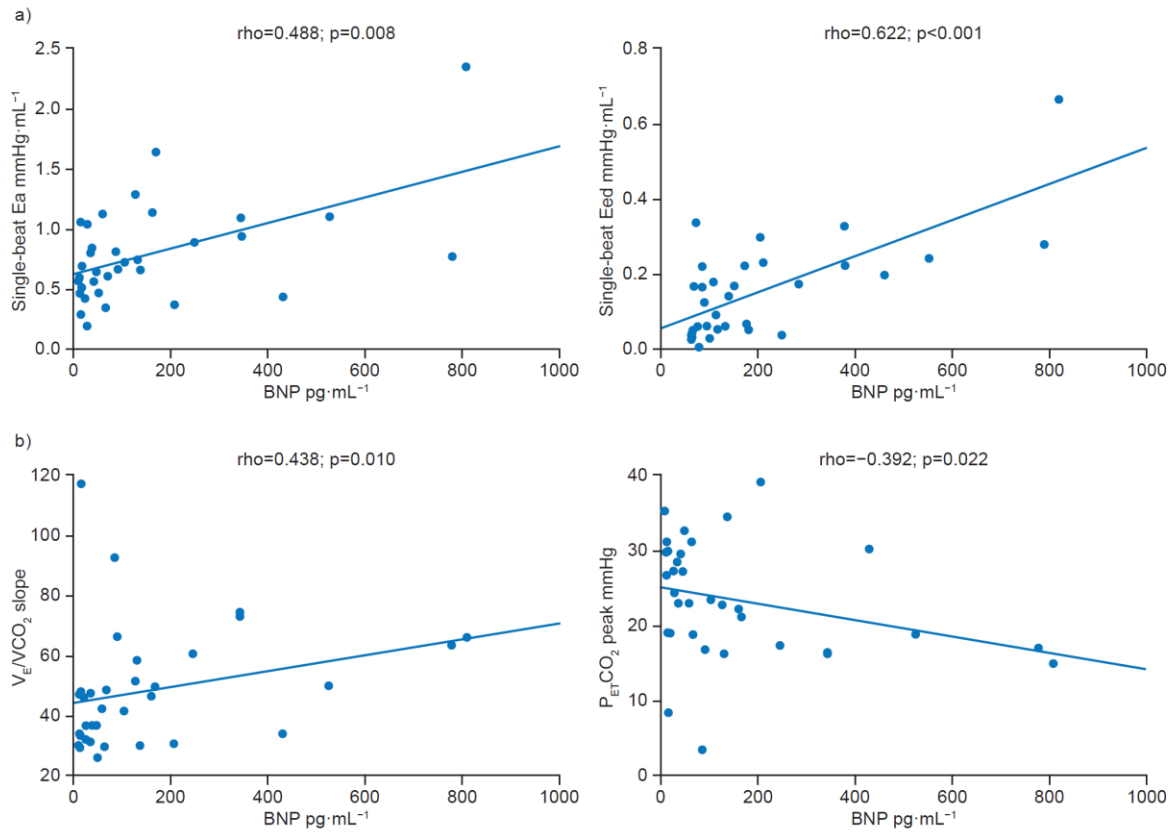


FIGURE E3 Correlation of BNP with a) single-beat Ea and Eed, and b) V_E/V_{CO₂ slope and peak P_{ET}CO₂. BNP: B-type natriuretic peptide; Ea: arterial elastance; Eed: end-diastolic elastance; P_{ET}CO₂: end-tidal carbon dioxide; V_E/V_{CO₂: minute ventilation/carbon dioxide production (ventilatory equivalent for carbon dioxide).}}