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Neural respiratory drive in chronic thromboembolic pulmonary hypertension: effect of balloon pulmonary angioplasty

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1. Introduction

Hyperventilation and ventilatory inefficiency during exercise are hallmarks of chronic thromboembolic pulmonary hypertension (CTEPH) [1]. Ventilatory efficiency can be assessed by the steepness with which ventilation (\dot{V}_E) rises during exercise with respect to CO_2 output (\dot{V}_{CO_2}), *i.e.*, the $\dot{V}_E/\dot{V}_{\text{CO}_2}$ ratio. The determinants of the $\dot{V}_E/\dot{V}_{\text{CO}_2}$ ratio have been summarized according to the Enghoff modification to the Bohr equation in the Equation 1:

$$\dot{V}_E/\dot{V}_{\text{CO}_2} = 863/[\text{PaCO}_2 \times (1-\text{VD}/\text{VT})]$$

where PaCO_2 is the arterial CO_2 partial pressure and VD/VT is the physiological dead space fraction of tidal volume [2]. In patients with CTEPH, these 2 determinants are altered during exercise: PaCO_2 is decreased (hypocapnia) and physiological VD/VT is increased [3, 4]. Hypocapnia is considered to be due, at least in part, to heightened neural ventilatory drive secondary to increased chemosensitivity to CO_2 in the context of altered heart function with sympathetic nervous system overactivity [3]. The classical explanation for the increase in physiological VD/VT is increased “wasted” ventilation, *i.e.*, hypoperfusion of well-ventilated alveoli [4]. Although physiological VD/VT is easily calculated according to the Enghoff simplification, the demonstration of an increased neural ventilatory drive during exercise is challenging. Recently, Neder *et al.* proposed an original method to determine the contribution of increased neural ventilatory drive to hyperventilation during exercise in CTEPH patients [5]. These authors considered that from exercise to recovery during a cardiopulmonary exercise test (CPET), the abrupt transition in terms of metabolic demand “provides a window to understand the complexities linking tissue gas exchange to pulmonary ventilation” [5]. During CPET in CTEPH patients, end-tidal CO_2 (PETCO_2) paradoxically increases (instead of further decreasing as

in normal subjects) as soon as patients enter the recovery phase. Neder *et al.* measured PaCO₂ and PETCO₂ (and calculated P_{(a-ET)CO₂}) across the exercise-to-recovery transition during CPET. They found a narrower P_{(a-ET)CO₂} that developed as a consequence of a PaCO₂ that increased less than PETCO₂, and interpreted this finding as a heightened V_D/V_T plus a heightened neural drive during exercise [5]. To further study neural ventilatory drive, the same authors also measured the decline in \dot{V}_E and in \dot{V}_{CO_2} across the exercise-to-recovery transition [5]. Their finding that \dot{V}_E decreased faster than \dot{V}_{CO_2} in the recovery phase was interpreted as an abrupt reduction in neural ventilatory drive, suggesting that neural drive was abnormally elevated during exercise [5].

Balloon pulmonary angioplasty (BPA) allows near-normalization of resting haemodynamic parameters in eligible patients with CTEPH [6]. After BPA, patients also experience an improvement of ventilatory efficiency (*i.e.*, a decrease of \dot{V}_E/\dot{V}_{CO_2} ratio) together with a decrease in physiological V_D/V_T [6]. Nevertheless, although less severe than before BPA, excess exercise hyperventilation persists after BPA [6]. Whether or not this remaining excess exercise hyperventilation is due at least in part to heightened neural ventilatory drive remains unknown. We therefore aimed to use the approach described by Neder *et al.* [5] in order to study the effects of BPA on neural ventilatory drive in CTEPH patients.

2. Methods

Patients referred for BPA at our institution between March and December 2019 were considered for inclusion. Eligibility criteria and techniques used to perform BPA were similar to those described elsewhere [7]. We included in our analysis patients who had two evaluations (one at baseline [pre-BPA] and one at a subsequent visit after at least 2 BPA sessions [post-BPA]) that comprised clinical evaluation, right heart catheterization and CPET, all performed within 24 h. To avoid confounding factors (such as exercise training) that could interfere with the direct

effects of BPA on neural ventilatory drive, we excluded patients who had “post-BPA” evaluation performed more than 3 months after the last BPA session. Patients who had any change in PH-targeted therapy between the two evaluations were excluded from the analysis. Patients with an obstructive ventilatory disorder and/or interstitial lung disease, and/or pulmonary arterial wedge pressure (PAWP) > 15 mmHg were also excluded. The study protocol was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Est V, 2013-AO1036-39). All the patients provided written informed consent.

Symptom-limited incremental cardio-pulmonary exercise tests (CPET) were performed on an electronically braked cycle ergometer (Ergometrics 900; Ergoline; Bitz, Germany), as previously described [8]. CPET were performed without adjunction of oxygen, even in patients with arterial oxygen desaturation. Oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$) and PETCO₂ were obtained breath by breath (Ergocard CPX, Medisoft, Belgium). Blood samples were drawn from the arterialized earlobe to measure CO₂ and oxygen (O₂) partial pressures at peak and during recovery (at 2.5-min and 5-min of unloaded cycling). PaCO₂ and arterialized CO₂ were considered as equivalent, and appropriate corrections were made to estimate arterial O₂ (PaO₂) from arterialized O₂ [9]. The physiological VD/VT ratio was calculated according to the Enghoff modification of the Bohr dead-space equation [10].

Neural ventilatory drive was estimated indirectly according to methods proposed by Neder *et al.* [5]. During CPET in CTEPH patients, the $\dot{V}E/\dot{V}CO_2$ ratio decreases (instead of further increasing as in normal subjects) from peak throughout 5-6 minutes of recovery, thereby contributing to an increase in PETCO₂ as patients enter the recovery phase. To decipher this phenomenon, PaCO₂ and PETCO₂ were measured during CPET (and P_{(a-ET)CO₂} was calculated) across the exercise-to-recovery transition. 3 scenarios were proposed *a priori*: (i) if PaCO₂ remained stable or further decreased during recovery despite increasing PETCO₂, a narrower P_{(a-ET)CO₂} was interpreted as an

improvement in V_D/V_T during recovery (thus suggesting that heightened V_D/V_T was the primary cause of hyperventilation during exercise); (ii) if P_aCO_2 and $P_{ET}CO_2$ increased proportionally leading to stable $P_{(a-ET)}CO_2$, decreasing neural drive was retained to explain increasing $P_{ET}CO_2$ (thus suggesting that heightened neural drive was the primary cause of hyperventilation during exercise); (iii) if a narrower $P_{(a-ET)}CO_2$ developed as a consequence of a P_aCO_2 that increased less than $P_{ET}CO_2$, improved V_D/V_T plus lower neural drive were considered to explain increasing $P_{ET}CO_2$ during recovery (thus suggesting that heightened V_D/V_T plus heightened neural drive both caused of hyperventilation during exercise).

To further study neural ventilatory drive, the decline in \dot{V}_E was compared with the decline in $\dot{V}CO_2$ during recovery [5]. A “normal” behaviour was characterized by a \dot{V}_E that “waits” for $\dot{V}CO_2$ during the recovery phase (considering that \dot{V}_E normally lags behind $\dot{V}CO_2$). Conversely, when \dot{V}_E decreased faster than $\dot{V}CO_2$ in the recovery phase, an abrupt reduction in neural ventilatory drive and thus an “abnormally” elevated neural drive during exercise was retained [5]. Results were presented as mean \pm standard deviation (SD) and n (%) for continuous and categorical data, respectively. The Shapiro-Wilk test was used to test distribution normality. Comparisons of pre- and post-BPA continuous parameters were performed using the t-test for paired data, or the Wilcoxon signed-rank test for paired data when data were not normally distributed. Categorical parameters were compared using the McNemar test. All analyses were performed using R software (version 3.6) and a *P*-value below 0.05 was considered as significant.

3. Results

The selection of patients is summarized on Figure 1. For the 22 patients included in the analysis, the mean interval between the 2 evaluations was 3.3 ± 2.3 months and the mean number of BPA

sessions was 4.4 ± 1.7 . After BPA, patients had near-normalization of mean pulmonary artery pressure and pulmonary vascular resistance (Table 1). Peak $\dot{V}O_2$ and peak workload increased significantly by $25 \pm 31\%$ and $22 \pm 29\%$, respectively (Table 1). At peak exercise, $\dot{V}E/\dot{V}CO_2$ ratio and physiological VD/VT ratio were lower (*i.e.*, improved) after BPA than before, $PETCO_2$ and $PaCO_2$ were both higher, but $P(a-ET)CO_2$ was similar (Table 1). Of note, $\dot{V}E$ and breathing reserve were similar at peak exercise before and after BPA (Table 1). At peak exercise, alveolar-arterial oxygen gradient ($P(A-a)O_2$) decreased by 30% after BPA, from 61 ± 10 mmHg to 50 ± 11 mmHg ($P < 0.001$).

During recovery, $\dot{V}E/\dot{V}CO_2$ ratio and physiological VD/VT ratio were lower after BPA than before (Table 2). From peak throughout the 5-min recovery period, $PETCO_2$ increased pre-BPA but decreased post-BPA (Figure 2 and Table 2). In addition, $P(a-ET)CO_2$ decreased during the recovery period before BPA but remained stable after BPA (Figure 2 and Table 2).

From the maximum value reached during CPET before and after BPA, an identical drop in $\dot{V}E$ was observed at 2.5-min and 5-min post exercise. On the contrary, the drop in $\dot{V}CO_2$ (expressed as the percentage of maximal $\dot{V}CO_2$) was significantly faster after BPA than before BPA. Before BPA, $\dot{V}E$ decreased at a faster rate than $\dot{V}CO_2$ from peak to end of recovery period. After BPA, $\dot{V}E$ and $\dot{V}CO_2$ recovered at a similar rate (Figure 3 and Table 2).

4. Discussion

In line with results observed by others in well-selected inoperable CTEPH patients [7, 11], BPA had a beneficial effect of on functional class, exercise capacity and hemodynamics as well as on ventilatory efficacy and on “wasted” ventilation in our series of 22 CTEPH patients. Nevertheless, after BPA, the 22 patients still had high values of $\dot{V}E/\dot{V}CO_2$ ratio and of VD/VT

ratio (46 ± 11 and 33 ± 10 , respectively, at peak exercise). Before BPA, our analyses across the exercise-to-recovery transition of PaCO_2 , PETCO_2 and P(a-ET)CO_2 , \dot{V}_E and in $\dot{V}\text{CO}_2$ are consistent with both increased “wasted” ventilation and heightened neural ventilatory drive to explain excess exercise ventilation. After BPA, these analyses suggest that heightened neural ventilatory drive was no longer present. Nevertheless, the high value of the VD/VT ratio, and the fact that PETCO_2 remained below PaCO_2 throughout recovery suggests that an abnormally high “wasted” ventilation persisted.

We estimated neural ventilatory drive indirectly according to methods proposed by Neder *et al.* [5]. Before BPA, in our group of 22 CTEPH patients, we confirmed that PETCO_2 increased from peak throughout the 5-min recovery period. We also found that in the meantime, PaCO_2 remained stable. These findings differ from that reported by Neder *et al.* in 10 CTEPH patients. Taking into account the above 3 scenarios proposed by Neder *et al.*, our data (*i.e.*, a narrower P(a-ET)CO_2 together with a stable PaCO_2) suggest improved VD/VT during recovery before BPA, an interpretation that is in accordance with the decrease in physiological VD/VT measured during recovery. Nevertheless, contrary to the findings of Neder *et al.*, our measurements of PaCO_2 , PETCO_2 , P(a-ET)CO_2 in CTEPH patients before BPA was not suggestive of excess neural ventilatory drive. After BPA, we found that PETCO_2 was stable from peak throughout the 5-min recovery period and that PaCO_2 tended to decrease in the meantime, a finding that does not suggest heightened ventilatory neural drive. Nevertheless, PETCO_2 remained lower than PaCO_2 , suggesting that abnormalities of alveolar ventilation/perfusion (\dot{V}_A/Q) ratio with overrepresentation of under-perfused pulmonary zones persisted after BPA. In other words, our data suggest that increased “wasted” ventilation persisted after BPA and could explain, at least in part, persistence of excess exercise hyperventilation.

In line with the findings of Neder *et al.*, we found that \dot{V}_E decreased faster than \dot{V}_{CO_2} from peak to end of the 5-min recovery period in CTEPH patients before BPA, suggesting excess in neural ventilatory drive during exercise [5]. After BPA, we found that \dot{V}_E and \dot{V}_{CO_2} recovered at similar rates, suggesting that neural drive was reduced post-BPA compared to pre-BPA. This could be due, at least in part, to improvement in blood oxygenation. Indeed, although mild for PaO_2 levels that are above 60 mmHg, it has been shown that hypoxia has an effect in increasing exercise hyperventilation even in normal humans [12].

With effective reduction in right ventricular afterload by BPA, the increase in $PaCO_2$ found at peak exercise and during recovery post-BPA vs. pre-BPA in our patients was expected. It is well documented that patients with CTEPH develop hypocapnia as a result of hyperventilation and that this correlates with impairment of cardiac function [3, 6, 13]. By analogy with left heart failure, it has therefore been accepted that increased CO_2 chemosensitivity secondary to impaired right ventricular performance contributes significantly to excessive exercise ventilation in CTEPH [14]. Nevertheless, to our knowledge, this assertion is based on indirect arguments and not on a direct exploration of the ventilatory response to CO_2 [3, 5].

According to the Equation 1 (which is a rearranging of the Enghoff simplification of the Bohr equation), the \dot{V}_E/\dot{V}_{CO_2} ratio is believed to depend on two parameters regarded as independent, that is, $PaCO_2$ and V_D/V_T . This is not the case, as discussed in details elsewhere [6, 10, 15]. It has been demonstrated in a computer model [16] as well as in an inert gas exchange model [17] that for a given CO_2 output, the sole increase in ventilation (that directly leads to a decrease in $PaCO_2$) will contribute to increase the physiological V_D/V_T calculated with the Enghoff simplification of the Bohr equation [10]. Reciprocally, the decrease in physiological V_D/V_T observed for a given metabolic rate after BPA is likely to be explained, at least in part, by a decrease in ventilation (keeping in mind that any decrease in ventilation for a given metabolic rate also induces an

increase in PaCO₂). Thus, because they assume that ventilatory neural drive and VD/VT are independent, the *a priori* scenarios used to decipher the mechanisms of excessive hyperventilation in CTEPH should be considered with caution.

To determine the causes of excessive hyperventilation in patients with CTEPH is important because although they have near-normalization of mean pulmonary arterial pressure and pulmonary vascular resistance after BPA, these patients still exhibit excessive hyperventilation during exercise. Determining whether this excess hyperventilation during exercise is due, at least in part, to excess neural drive is clinically relevant when designing evidence-based strategies, such as rehabilitation, to improve symptoms and quality of life. In particular, breathing techniques that are used to reduce respiratory frequency and depth of breathing (tidal volume) to match alveolar ventilation to metabolic demand in patients with dysfunctional breathing/hyperventilation syndrome would be worth to be tested in CTEPH patients with excess ventilatory neural drive.

5. Conclusion

To summarize, the current analyses suggest that after BPA, CTEPH patients do not have abnormally heightened ventilatory neural drive. Nevertheless, the method used here to determine the causes of excessive hyperventilation in patients with CTEPH is indirect. A more direct approach to studying neural ventilatory control in patients with CTEPH, such as measuring the ventilatory response to CO₂, may be useful to confirm our findings.

Author contributions

B.D. conceived and designed the study, and drafted the manuscript; B.D., N.P., M.S., F.T., C.A. and H.B. performed the experiments; B.D., M.B.N. and A.G. analysed data; B.D. and M.B.N.

interpreted the results of experiments; A.G. prepared figures; all authors revised the manuscript and approved final version of manuscript.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest for the submitted work.

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Table 1. Comparison of clinical characteristics, hemodynamic parameters and CPET parameters measured at peak exercise before and after balloon pulmonary angioplasty (BPA)

| | Pre-BPA | Post-BPA | <i>P</i> -value |
|---|----------------|-----------------|-----------------|
| NYHA FC, % (I-II/III-IV) | 50/50 | 91/9 | 0.02 |
| NT-proBNP, pg·mL ⁻¹ | 2011 ± 2885 | 554 ± 947 | <0.001* |
| Hemodynamic variables, at rest | | | |
| Mean RAP, mmHg | 7 ± 3 | 5 ± 2 | 0.02* |
| Mean PAP, mmHg | 42 ± 9 | 29 ± 9 | <0.001* |
| Cardiac index, L·min ⁻¹ ·m ⁻² | 2.6 ± 0.6 | 3.0 ± 0.5 | <0.001 |
| PVR, Wood Units | 6.9 ± 2.8 | 3.5 ± 1.4 | < 0.001 |
| SvO ₂ , % | 61 ± 6 | 69 ± 5 | 0.06* |
| CPET variables, at peak | | | |
| Work load, W | 81 ± 27 | 95 ± 29 | < 0.001 |
| $\dot{V}O_2$, mL·min ⁻¹ | 1189 ± 372 | 1427 ± 354 | < 0.001 |
| $\dot{V}O_2$, mL·kg ⁻¹ ·min ⁻¹ | 15.3 ± 3.9 | 18.5 ± 4.1 | < 0.001 |
| $\dot{V}CO_2$, mL·min ⁻¹ | 1330 ± 456 | 1523 ± 415 | 0.01 |
| $\dot{V}E/\dot{V}CO_2$ | 58 ± 18 | 46 ± 11 | < 0.001* |
| Physiological VD/VT, % | 39 ± 12 | 33 ± 10 | 0.01 |
| $\dot{V}E$, L·min ⁻¹ | 72 ± 19 | 69 ± 18 | 0.20 |
| <i>f</i> B, min ⁻¹ | 40 ± 9 | 37 ± 7 | 0.11 |
| V _T , L | 1.8 ± 0.6 | 1.9 ± 0.5 | 0.43 |
| Breathing reserve, % | 15 ± 14 | 19 ± 16 | 0.30 |
| PaO ₂ , mmHg | 61 ± 11 | 68 ± 11 | 0.001 |
| PETCO ₂ , mmHg | 22 ± 5 | 28 ± 4 | 0.004 |
| PaCO ₂ , mmHg | 30 ± 4 | 34 ± 4 | 0.001 |
| P _{(a-ET)CO₂} | 8 ± 3 | 6 ± 4 | 0.22 |

Data are presented as mean ± standard deviation or n (%). Continuous parameters were compared using the paired t-test and categorical parameters were compared using the McNemar test, unless otherwise stated.

*Use of the non-parametric Wilcoxon signed-rank test for paired data

BPA: balloon pulmonary angioplasty; NYHA FC: New York Heart Association functional class; NT-proBNP: N-terminal pro-brain natriuretic peptide; RAP: right atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation. $\dot{V}O_2$: oxygen consumption; $\dot{V}CO_2$: carbon dioxide output; VD/VT: dead space fraction of tidal volume; $\dot{V}E$: minute ventilation; *f*B: breathing frequency; PaO₂: partial oxygen arterial pressure; PETCO₂: end-tidal carbon dioxide pressure; PaCO₂: partial carbon dioxide arterial pressure.

Table 2. Comparison of selected CPET variables after 2.5-min and 5-min of unloaded cycle, before and after balloon pulmonary angioplasty (BPA)

| | Recovery @ 2.5-min | | | Recovery @ 5-min | | |
|--------------------------------------|--------------------|-----------|-----------------|------------------|-----------|-----------------|
| | Pre-BPA | Post-BPA | <i>P</i> -value | Pre-BPA | Post-BPA | <i>P</i> -value |
| $\dot{V}O_2$, mL·min ⁻¹ | 774 ± 143 | 842 ± 178 | 0.01 | 689 ± 150 | 730 ± 176 | 0.27 |
| $\dot{V}CO_2$, mL·min ⁻¹ | 820 ± 171 | 889 ± 164 | 0.03 | 656 ± 152 | 695 ± 143 | 0.30* |
| $\dot{V}E/\dot{V}CO_2$ | 55 ± 14 | 47 ± 10 | <0.001* | 53 ± 9 | 49 ± 10 | <0.001* |
| Physiological VD/VT, % | 36 ± 11 | 30 ± 11 | 0.046 | 31 ± 11 | 30 ± 11 | 0.67 |
| $\dot{V}E$, L·min ⁻¹ | 44 ± 9 | 41 ± 9 | 0.01 | 34 ± 7 | 34 ± 9 | 0.40 |
| <i>f</i> B, min ⁻¹ | 31 ± 7 | 29 ± 6 | <0.001 | 29 ± 7 | 29 ± 7 | 0.87* |
| VT, L | 1.5 ± 0.4 | 1.5 ± 0.4 | 0.93 | 1.3 ± 0.4 | 1.2 ± 0.4 | 0.41 |
| PaO ₂ , mmHg | 71 ± 12 | 81 ± 15 | <0.001 | 74 ± 10 | 83 ± 10 | <0.001 |
| PaCO ₂ , mmHg | 30 ± 3 | 32 ± 4 | 0.01 | 29 ± 3 | 31 ± 4 | 0.03* |
| PETCO ₂ , mmHg | 24 ± 4 | 28 ± 4 | <0.001* | 25 ± 3 | 27 ± 4 | 0.002* |

Data are presented as mean ± standard deviation or n (%). Continuous parameters were compared using the paired t-test and categorical parameters were compared using the McNemar test, unless otherwise stated.

*Use of the non-parametric Wilcoxon signed-rank test for paired data

BPA: balloon pulmonary angioplasty; $\dot{V}O_2$: oxygen consumption; $\dot{V}CO_2$: carbon dioxide output; $\dot{V}E$: minute ventilation; VD/VT: dead space fraction of tidal volume; *f*B: frequency of breathing; VT: tidal volume; PaO₂: partial oxygen arterial pressure; PaCO₂: partial carbon dioxide arterial; PETCO₂: end-tidal carbon dioxide pressure.

Legends of the figures

Figure 1. Flowchart of the study. BPA: balloon pulmonary angioplasty; CTEPH: chronic thromboembolic pulmonary hypertension; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; LHF: left heart failure.

Figure 2. Arterial carbon dioxide (CO_2) tension (PaCO_2) and end-tidal CO_2 tension (PETCO_2) at peak exercise and during recovery in patients with chronic thromboembolic pulmonary hypertension (CTEPH), before and after balloon pulmonary angioplasty (BPA). Data are presented as mean \pm SE. *: $p < 0.05$ for comparisons pre- versus post-BPA at a given time-point.

Figure 3. (A) Minute ventilation (\dot{V}_E) and (B) carbon dioxide output (\dot{V}_{CO_2}) at peak exercise and during recovery in patients with chronic thromboembolic pulmonary hypertension (CTEPH), before and after balloon pulmonary angioplasty (BPA). Data are presented as mean \pm SE. *: $p < 0.05$ for comparison between \dot{V}_E and \dot{V}_{CO_2} at a given time-point.

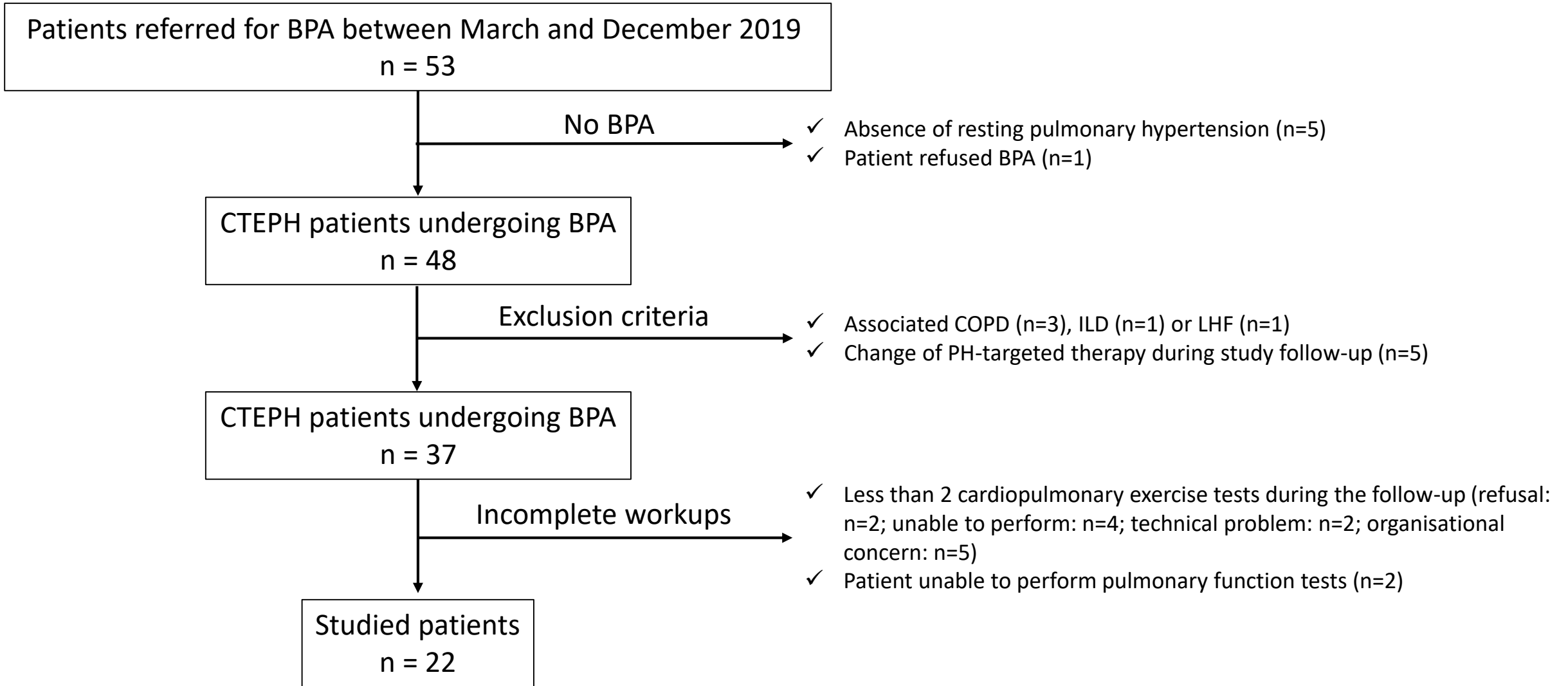


Figure 1

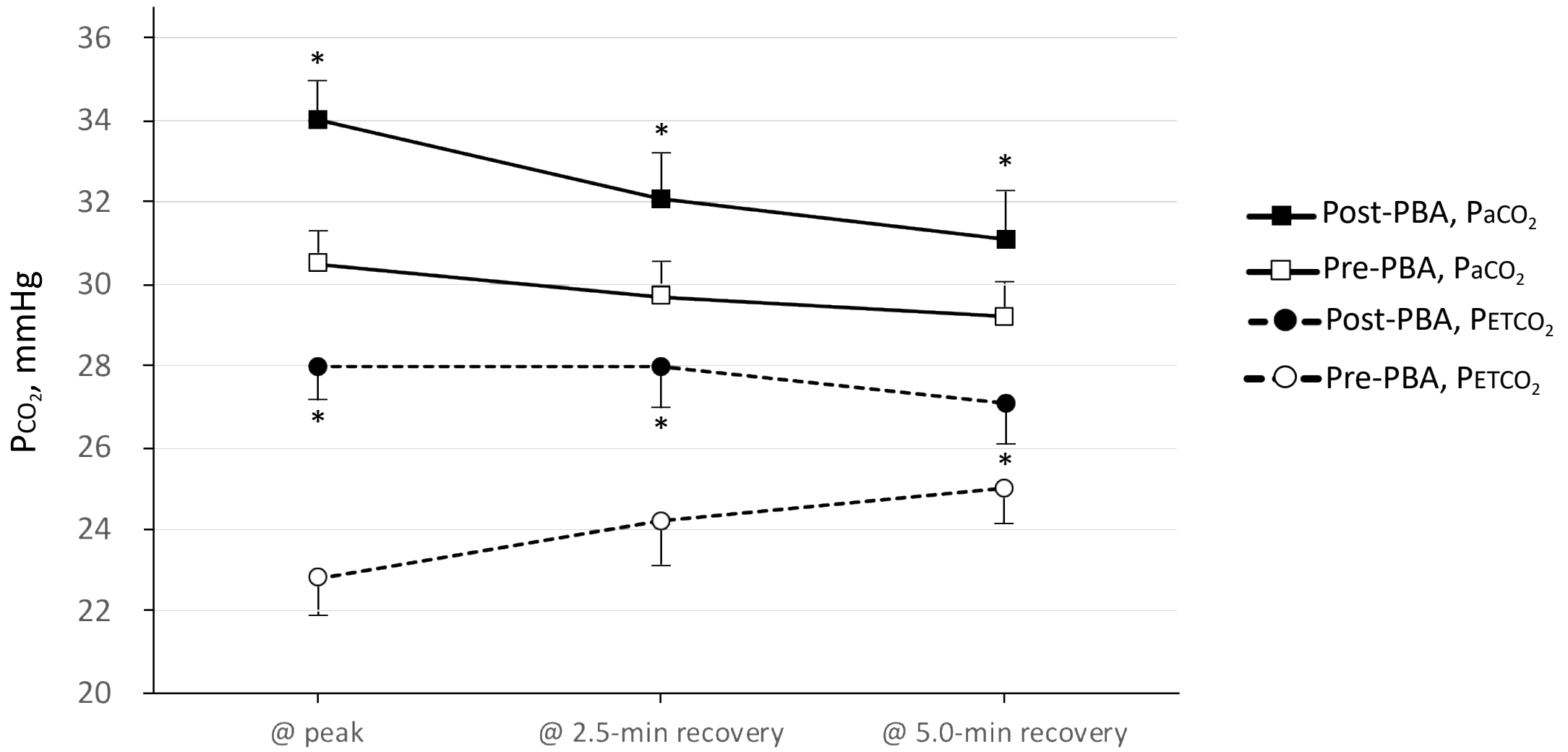


Figure 3

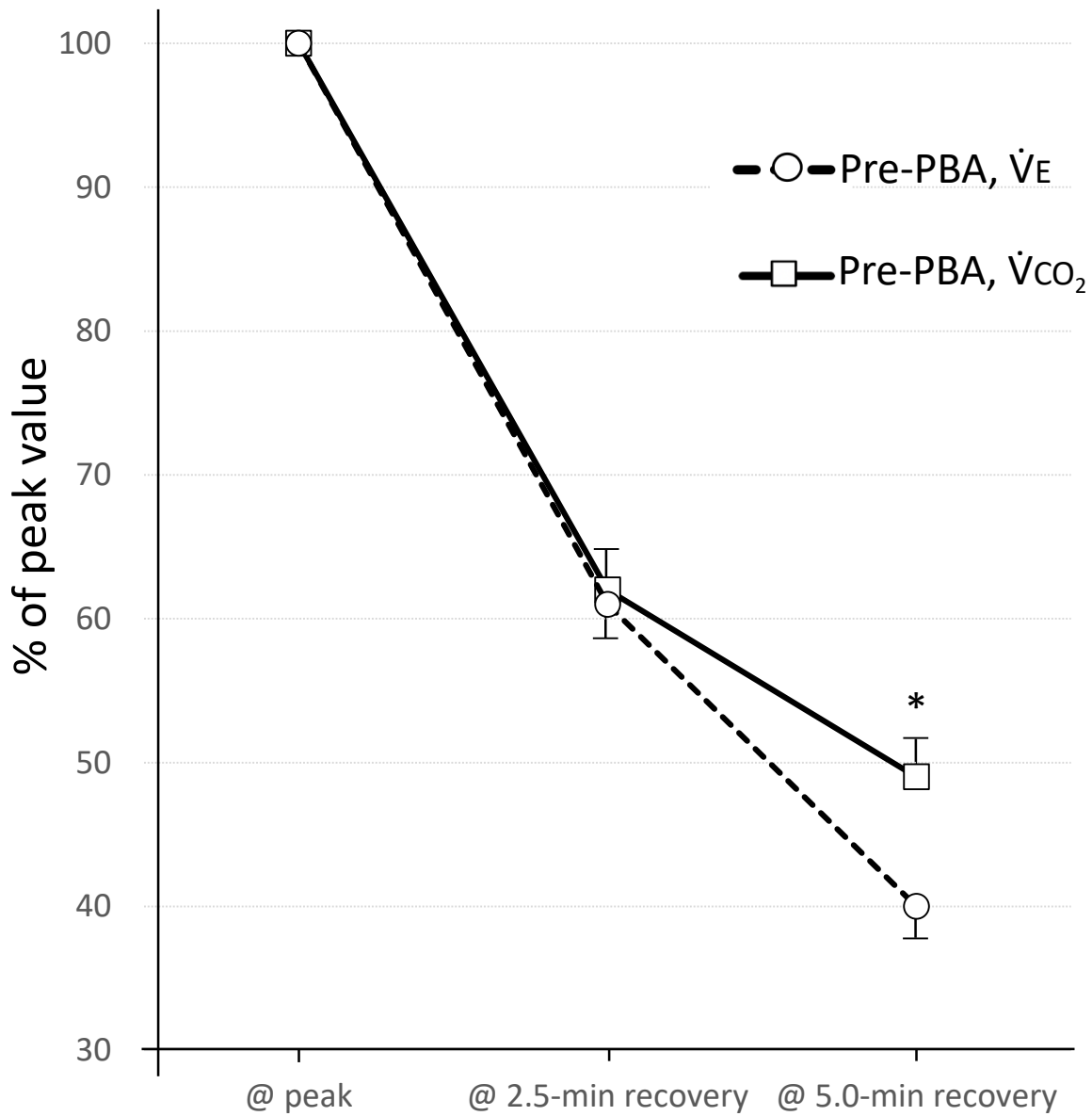


Figure 2A

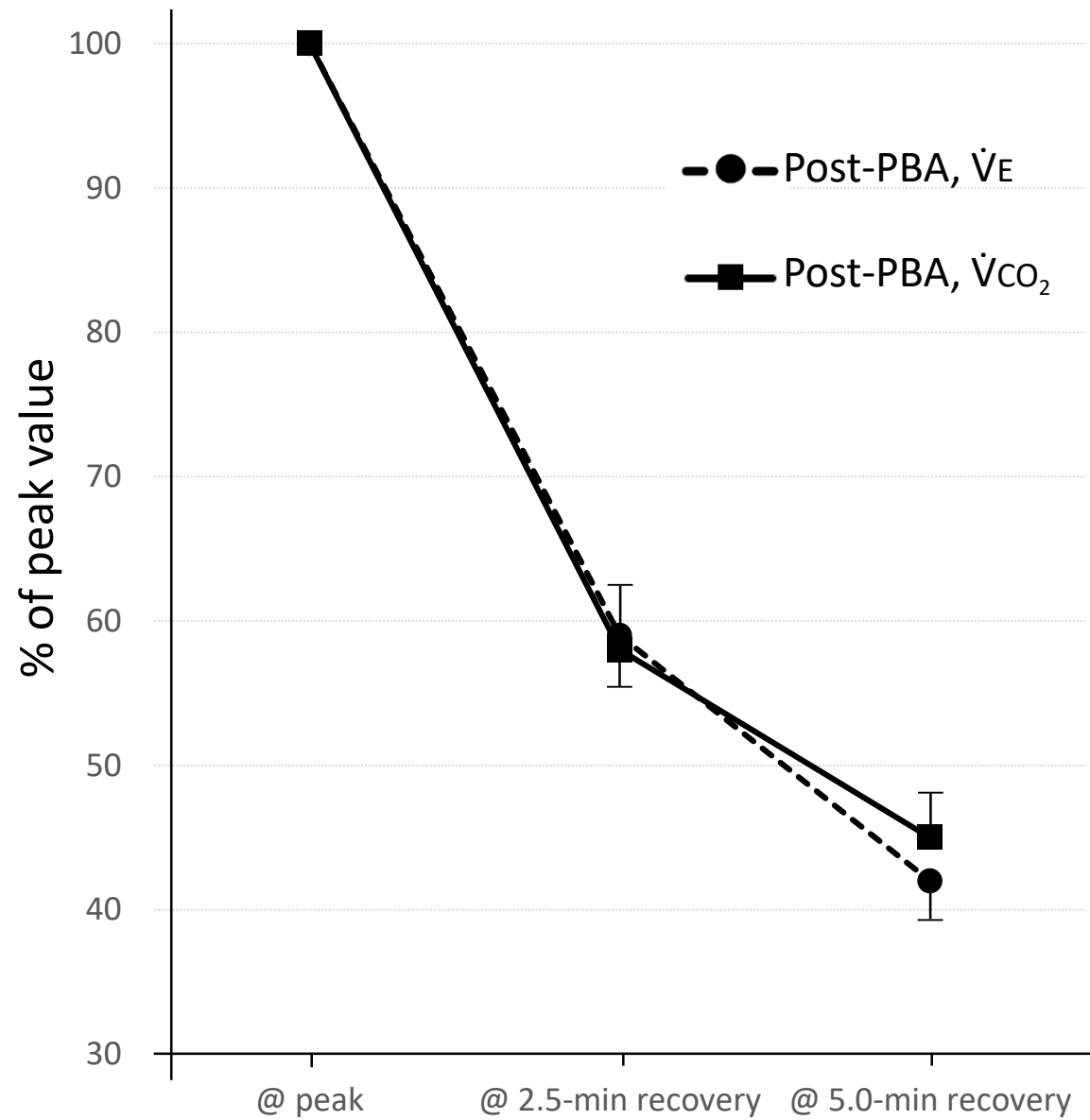


Figure 2B