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## **Exercise hyperventilation and pulmonary gas exchange in chronic thromboembolic pulmonary hypertension: effects of balloon pulmonary angioplasty**

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**Running Title:** *Ventilation and gas exchange in CTEPH: effects of BPA*

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**ABBREVIATION:** 6MWD = 6-min walk distance; BPA = balloon pulmonary angioplasty; COPD = chronic obstructive pulmonary disease; CPET = cardio-pulmonary exercise test; CTEPH = chronic thromboembolic pulmonary hypertension; CO<sub>2</sub> = carbon dioxide; DLCO = carbon monoxide lung diffusion; *f*B = breathing frequency; FEV<sub>1</sub> = forced expiratory volume in 1 s; FVC = forced vital capacity; ILD = interstitial lung disease; KCO = rate of uptake of CO from alveolar gas; LHF = left heart failure; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA FC = New York Heart Association functional class; PaCO<sub>2</sub> = partial carbon dioxide arterial pressure; PaO<sub>2</sub> = partial oxygen arterial pressure; P(Ai-a)O<sub>2</sub> = ideal alveolar-arterial oxygen gradient; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PEA = pulmonary endarterectomy; PETCO<sub>2</sub> = end-tidal carbon dioxide; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RER = respiratory exchange ratio; SD: standard deviation; SvO<sub>2</sub> = mixed venous oxygen saturation; V<sub>A</sub> = alveolar volume;  $\dot{V}_A/Q$  = alveolar ventilation/perfusion ratio;  $\dot{V}_{CO_2}$  = carbon dioxide output; V<sub>D</sub>/V<sub>T</sub> = dead space fraction of tidal volume;  $\dot{V}_E$  = minute ventilation;  $\dot{V}_{O_2}$  = oxygen consumption.

## ABSTRACT

**Background:** Excessive ventilation ( $\dot{V}_E$ ) and abnormal gas exchange during exercise are features of chronic thromboembolic pulmonary hypertension (CTEPH). In selected CTEPH patients, balloon pulmonary angioplasty (BPA) improves symptoms and exercise capacity. How BPA affects exercise hyperventilation and gas exchange is poorly understood.

**Methods:** In this longitudinal observational study, symptom-limited cardio-pulmonary exercise tests and carbon monoxide lung diffusion (DLCO) were performed before and after BPA (interval, mean (SD): 3.1 (2.4) months) in 36 CTEPH patients without significant cardiac and/or pulmonary comorbidities.

**Results:** Peak work rate improved by 20% after BPA whilst  $\dot{V}_E$  at peak did not change despite improved ventilatory efficiency (lower  $\dot{V}_E$  with respect to  $\dot{V}_{CO_2}$ ). At the highest identical work rate pre- and post-BPA (75 (30) watts),  $\dot{V}_E$  and ~~the ideal~~ alveolar-arterial oxygen gradient ( $P_{(A_i-a)O_2}$ ) decreased by 17% and 19% after BPA, respectively. The physiological dead space fraction of tidal volume ( $V_D/V_T$ ), calculated from measurements of arterial and mixed expired  $CO_2$ , decreased by 20%. In the meantime, DLCO did not change. The best correlates of  $P_{(A_i-a)O_2}$  measured at peak exercise were physiological  $V_D/V_T$  before BPA and DLCO after BPA.

**Conclusions:** Ventilatory efficiency, physiological  $V_D/V_T$  and pulmonary gas exchange improved after BPA. The fact that DLCO did not change suggests that the pulmonary capillary blood volume and probably the true alveolar dead space were unaffected by BPA. The correlation between DLCO measured before BPA and  $P_{(A_i-a)O_2}$  measured after BPA suggests that DLCO may provide an easily accessible marker to predict the response to BPA in terms of pulmonary gas exchange.

**Keywords:** chronic thromboembolic pulmonary hypertension; balloon pulmonary angioplasty; cardiopulmonary exercise test.

## INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease that results from occlusion of large pulmonary arteries by persistent thrombi and from distal small-vessel vasculopathy.<sup>1</sup> During exercise, excessive ventilation ( $\dot{V}_E$ ) with respect to  $\text{CO}_2$  output ( $\dot{V}_{\text{CO}_2}$ ) and abnormal pulmonary gas exchange (increased ideal alveolar-arterial gradient for oxygen [ $P_{(\text{Ai-a})\text{O}_2}$ ]) are hallmarks of CTEPH.<sup>2</sup> Several pathophysiological mechanisms have been proposed to explain the increased  $\dot{V}_E/\dot{V}_{\text{CO}_2}$  ratio in CTEPH, including a reduction in capillary blood volume leading to greater true alveolar dead space (ventilated but non-perfused pulmonary zones) and increased heterogeneity of the alveolar ventilation/perfusion ( $\dot{V}_A/Q$ ) ratio (across under-perfused and over-perfused pulmonary zones). Abnormal pulmonary oxygen exchange has been ascribed to a broadened  $\dot{V}_A/Q$  distribution with increased pulmonary zones of low  $\dot{V}_A/Q$  and to a lowered mixed venous oxygen saturation ( $\text{SvO}_2$ ), as demonstrated using the multiple inert gas elimination technique (MIGET).<sup>3-5</sup>

Three options are now available to treat CTEPH patients, alone or in combination, with the aim to decrease pulmonary vascular resistance (PVR) and to improve symptoms, exercise capacity and survival.<sup>6</sup> Pulmonary endarterectomy (PEA) is the option of choice for eligible patients with proximal occlusion of large vessels. PEA improves ventilatory efficiency and pulmonary gas exchange (*i.e.*, decreases  $\dot{V}_E/\dot{V}_{\text{CO}_2}$  and  $P_{(\text{Ai-a})\text{O}_2}$ ) measured during cardiopulmonary exercise testing (CPET) and also decreases the physiological dead space fraction of tidal volume ( $\text{VD}/\text{VT}$  ratio) calculated from measurements of arterial  $\text{CO}_2$  and mixed expired  $\text{CO}_2$ .<sup>7</sup> These improvements have been interpreted as the consequence of both a lower heterogeneity in  $\dot{V}_A/Q$  and an increased cardiac output.<sup>8,9</sup> A second therapeutic option is to administer pulmonary hypertension (PH)-targeted drugs, preferentially to CTEPH patients with significant small-vessel vasculopathy. These drugs improve ventilatory efficiency and pulmonary gas exchange, but contrary to PEA, they lead to an increase in the physiological  $\text{VD}/\text{VT}$  ratio.<sup>10</sup>

Although mechanisms have not been formally demonstrated, the improvement in  $\dot{V}_E/\dot{V}_{CO_2}$  has been attributed to a decrease in chemosensitivity to  $CO_2$ , while the increase in  $V_D/V_T$  ratio has been attributed to further  $\dot{V}_A/Q$  heterogeneity following PH-targeted drugs.<sup>10</sup> Balloon pulmonary angioplasty (BPA) is an endovascular procedure that has recently emerged as a third treatment option for patients with inoperable CTEPH.<sup>6,11</sup> Improvements in ventilatory efficiency and pulmonary gas exchange have been reported after BPA,<sup>12,13</sup> but the mechanisms involved are still unknown. We therefore aimed to analyze the effects of BPA on exercise ventilation and pulmonary gas exchange parameters measured during CPET in CTEPH patients.

## **METHODS**

### **Study population**

All patients referred for BPA at our institution between March 2019 and November 2020 were considered for inclusion. Eligibility criteria and techniques used to perform BPA were similar to those described elsewhere.<sup>11</sup> We included in our analysis patients who had one complete workup at baseline (pre-BPA) and at least one complete workup at a subsequent visit after at least 2 BPA sessions (post-BPA). A complete workup comprised clinical evaluation, right heart catheterization, CPET, pulmonary function tests, 6-min walk test and blood tests, all performed within 24 h. The last available “post-BPA” complete workup was retained for the current analysis. To avoid confounding factors (such as the plausible effects on cardiopulmonary responses to rehabilitation and/or of long-term pulmonary vascular remodeling) that could interfere with the direct effects of BPA on ventilation and pulmonary gas exchange, we excluded workups performed more than 3 months after the last BPA session. Patients who had any change in PH-targeted therapy between the two workups were excluded from the analysis. Patients with an obstructive ventilatory disorder according to the latest ERS definition<sup>14</sup> 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), and all the patients were informed about the potential risks and benefits of BPA and provided written informed consent.

### **Study procedures**

Routine spirometry, constant-volume body plethysmography and single breath lung diffusion of carbon monoxide [DLCO] tests were performed in accordance with recommendations. DLCO and KCO (rate of uptake of CO from alveolar gas) were corrected according to hemoglobin concentration. Reference values for spirometry and for DLCO, KCO and alveolar volume (VA) were those proposed by the Global Lung Initiative.<sup>14,15</sup> Results were expressed as percentage of predicted value and as z-scores. Z-scores indicate how many standard deviations measured values are from predicted. Predicted value and z-scores were calculated according to the lambda-mu-sigma method from tables at <http://gli-calculator.ersnet.org/index.html>.

Symptom-limited incremental CPET were performed on an electronically braked cycle ergometer (Ergometrics 900; Ergoline; Bitz, Germany), as previously described.<sup>16</sup> 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 end-tidal carbon dioxide (PETCO<sub>2</sub>) were obtained breath by breath (Ergocard CPX, Medisoft, Belgium). Predicted maximum  $\dot{V}E$  was based on  $35 \times FEV_1$ . Subjects rated the perceived magnitude of their breathing and leg discomfort on a 10-point Borg scale.<sup>17</sup> Blood samples were drawn from the arterialized earlobe to measure carbon dioxide and oxygen at peak. During the second CPET (post-BPA), a blood sample was also taken at the CPET peak power pre-BPA (iso-work, *i.e.*, highest same work rate available in both tests). Arterial carbon dioxide (PaCO<sub>2</sub>)

and arterialized CO<sub>2</sub> were considered as equivalent, and appropriate corrections were made to estimate arterial O<sub>2</sub> (PaO<sub>2</sub>) from arterialized O<sub>2</sub>.<sup>18</sup> The ideal alveolar-arterial gradient for oxygen [P(Ai-a)O<sub>2</sub>] and the arterial to end-tidal carbon dioxide gradient [P(a-ET)CO<sub>2</sub>] were calculated. The physiological dead space fraction of tidal volume (VD/VT ratio) was calculated according to the Enghoff modification of the Bohr dead-space equation.<sup>7</sup>

### **Study design and statistical analysis**

In this longitudinal observational study, exercise ventilation, ventilatory efficiency and pulmonary gas exchange were compared at the highest same work rate available pre- and post-BPA (iso-work) and at peak exercise (pre- vs. post-BPA). To study the effects of BPA on pulmonary gas exchange, we reasoned that in CTEPH, arterial oxygenation abnormalities (leading to elevated P(Ai-a)O<sub>2</sub>) result mainly from pulmonary zones of low  $\dot{V}A/Q$  (leading to  $\dot{V}A/Q$  heterogeneity and a high physiological VD/VT ratio), poor cardiac function (leading to low SvO<sub>2</sub>) and small-vessel vasculopathy (leading to low DLCO).<sup>19</sup> We therefore studied the relationship between P(Ai-a)O<sub>2</sub> (measured at peak exercise) on the one hand, and the physiological VD/VT ratio (measured at peak exercise), SvO<sub>2</sub> and DLCO (both measured at rest) on the other hand, pre- and post-BPA.

Results are presented as mean (standard deviation) and n (%) for continuous and categorical data, respectively. Comparisons of pre- and post-BPA continuous parameters were performed using the t-test for paired data. Categorical parameters were compared using the McNemar test. To identify factors associated with P(Ai-a)O<sub>2</sub>, the selected continuous variables were analyzed using univariable and multivariable linear regression. All variables associated with P(Ai-a)O<sub>2</sub> in univariable analysis with a *P*-value < 0.20 were included in the multivariable analysis.

All analyses were performed using R software (version 3.6) and a *P*-value below 0.05 was considered as significant.



## RESULTS

The selection of patients is summarized on Figure 1. For the 36 patients included in the analysis, the mean (standard deviation) interval between the 2 evaluations was 3.1 (2.4) months and the mean number of BPA sessions was 4.7 (1.7). After BPA, improvements in NYHA functional class, 6-min walk distance, NT-proBNP and hemodynamic parameters (in particular, mean pulmonary artery pressure, cardiac index and PVR) were all significant (Table 1). Resting pulmonary function test values did not change after BPA (Table 2).

### Exercise ventilation and pulmonary gas exchange at iso-work rate

At the highest identical work rate available in the pre- and post-BPA tests (iso-work) of 75 (30) watts,  $\dot{V}CO_2$  was identical pre- and post-BPA, while  $\dot{V}E$  was lower by about 17% after BPA, mainly due to a significantly lower breathing frequency (Table 3). In line with lower  $\dot{V}E/\dot{V}CO_2$ ,  $PETCO_2$  and  $PaCO_2$  were higher post-BPA than pre-BPA. We also observed a significant increase in  $\dot{V}O_2$  (at identical mechanical workload) as well as an increase in the  $\dot{V}O_2$ /Watts slope (data not shown) (Table 3). Of note, Borg scores for dyspnea and leg fatigue were much lower post-BPA than pre-BPA (Table 3).

At iso-work rate,  $P(Ai-a)O_2$  and physiological  $VD/VT$  were lower (*i.e.*, improved) by about 20% after BPA.

### Exercise ventilation and pulmonary gas exchange at peak exercise

After BPA, peak  $\dot{V}O_2$  and peak workload increased significantly by 20 (25) % and 20 (26) %, respectively (Table 3). In line with the trend observed at iso-work,  $\dot{V}E/\dot{V}CO_2$  ratio, physiological  $VD/VT$  ratio,  $P(Ai-a)O_2$ ,  $P(a-ET)CO_2$  and Borg dyspnea score at peak exercise were all lower (*i.e.*, improved) after BPA (Table 3). In contrast, Borg leg fatigue score,  $\dot{V}E$  and breathing reserve were similar at peak exercise before and after BPA (Table 3).

Of note, ventilatory thresholds (expressed as percentage of predicted peak  $\dot{V}O_2$ ) were remarkably stable (56 (17) % vs. 57 (14) % pre- and post-BPA, respectively;  $P = 0.63$ ).

### **Correlations with pulmonary gas exchange**

Before BPA, maximal values of  $P(Ai-a)O_2$  strongly correlated with the maximal values of physiological  $V_D/V_T$  in univariate analysis, while a weaker correlation was observed with resting  $SvO_2$  and DLCO (Table 4). The multivariate regression analysis showed that only physiological  $V_D/V_T$  was independently associated with  $P(Ai-a)O_2$  before BPA (Table 4).

After BPA, all strong correlations observed before BPA disappeared, and a significant strong correlation between  $P(Ai-a)O_2$  and DLCO was found.

## **DISCUSSION**

The beneficial effects of BPA on symptoms, exercise capacity and hemodynamics in well-selected inoperable CTEPH patients are now clearly demonstrated<sup>6,11</sup> and were also found in our patients. Our analyses confirm clinically meaningful improvements in ventilatory efficiency and pulmonary gas exchange after BPA and suggest, for the first time, that these improvements are mainly a consequence of reduced  $\dot{V}A/Q$  heterogeneity and are not secondary to an effect of BPA on pulmonary zones that are ventilated but non-perfused (true alveolar dead space).

### *Effects of BPA on $V_D/V_T$ ratio*

Although high physiological  $V_D/V_T$  ratio in CTEPH patients is widely interpreted as the consequence of ventilation of non-perfused zones, and although improvements in physiological  $V_D/V_T$  after de-occlusion of large pulmonary arteries is ascribed by many authors to improvements in the true alveolar dead space, *i.e.*, to restoration of capillary perfusion within normally-ventilated alveoli,<sup>20,21</sup> our data in patients undergoing BPA are compatible with

another hypothesis, for the following reasons. First, huge differences exist between the  $V_D/V_T$  ratio calculated with the Bohr equation and the physiological  $V_D/V_T$  ratio calculated with the Enghoff simplification, for reasons described by others.<sup>7</sup> Briefly, although true  $V_D$  is by definition a pulmonary zone that is ventilated but not perfused, the substitution of  $P_aCO_2$  in the Enghoff simplification for the original  $PACO_2$  of the Bohr equation adds a new component to the estimation of  $V_D$  that is the gas exchange abnormality.<sup>7</sup> Indeed, while the difference between mean  $PACO_2$  and  $P_aCO_2$  is quite small in normal lungs, any gas exchange abnormality that increases the alveolar-arterial  $O_2$  difference will also increase the arterial-alveolar  $CO_2$  difference. Specifically, in contrast to the original calculation of  $V_D$  with the Bohr equation, the calculation of the physiological  $V_D$  with the Enghoff simplification will be sensitive to intrapulmonary shunt and will have a greater sensitivity to  $\dot{V}_A/Q$  heterogeneity.<sup>7</sup> Thus, in CTEPH patients, improvement (*i.e.*, a decrease) in the physiological  $V_D/V_T$  ratio does not necessarily mean that true  $V_D$  is improved (*i.e.*, decreased): lower physiological  $V_D/V_T$  ratio is likely to be secondary, at least in part, to improvement in  $\dot{V}_A/Q$  heterogeneity with fewer zones of low  $\dot{V}_A/Q$  (zones that are less perfused after BPA due to pulmonary blood flow redistribution towards reopened zones) and less zones of high  $\dot{V}_A/Q$  (zones that are better perfused after BPA due to de-occlusion and/or zones that are less ventilated because of an overall decrease in ventilation after BPA), as summarized in Figure 2. Secondly, it has been demonstrated in a computer model<sup>22</sup> as well as in an inert gas exchange model<sup>23</sup> that the sole shift of a given  $\dot{V}_A/Q$  distribution to a higher mean  $\dot{V}_A/Q$  ratio increases the physiological  $V_D/V_T$ .<sup>24</sup> In other words, any stimulus that markedly increases ventilation and hence overall  $\dot{V}_A/Q$  ratio will contribute to increase the physiological  $V_D/V_T$ .<sup>24</sup> Reciprocally, the decrease in physiological  $V_D/V_T$  observed for a given work rate after BPA is likely to be explained, at least in part, by a decrease in ventilation. Thirdly, studies using MIGET reported that true alveolar  $V_D$  was similar in normal subjects and in CTEPH patients, and that the higher-than-normal physiological  $V_D/V_T$

ratio found in CTEPH was explained by a combination of high  $\dot{V}A/Q$ ,  $\dot{V}A/Q$  heterogeneity and shunt.<sup>3-5</sup> A plausible explanation for the normal true alveolar  $V_D$  found in CTEPH is that capillary alveoli that are not perfused by pulmonary arteries (due to their occlusion) are in fact perfused by systemic arteries coming from the bronchial circulation.<sup>1,5,25</sup> Fourthly, evidence that argues against a change in true alveolar  $V_D$  after BPA comes from the finding that KCO and DLCO were remarkably stable pre- vs. post-BPA in our patients. Patients with CTEPH have moderately altered or even near-normal DLCO because of the back-perfusion of the capillary bed in occluded areas by the extensive bronchial arterial collateral flow.<sup>1,5,25,26</sup> Before pulmonary artery de-occlusion, this perfusion plays a role in carbon monoxide uptake, although it does not improve the oxygen exchange,<sup>9,26</sup> as summarized on Figure 2.

#### *Effects of BPA on DLCO*

A stability of DLCO at the end of follow-up has already been reported in patients undergoing either PEA<sup>9,26-28</sup> or BPA.<sup>29</sup> After de-occlusion, perfusion of the capillary bed comes from pulmonary arteries, although persistence of some perfusion by bronchial arterial collateral flow cannot be excluded (Figure 2). As MIGET studies have clearly established that there is no diffusion impairment of pulmonary gas exchange in CTEPH,<sup>5</sup> the stability of KCO and DLCO between two tests performed only 3.3 (2.3) months apart suggests stability in pulmonary capillary blood volume.<sup>30</sup> The persistence of a significant impairment of DLCO in some patients after BPA may be attributed to the remodeling of distal small vessels that was present before de-occlusion.<sup>26</sup>

It has been reported in a single study that changes in DLCO might be different depending on the lung regions targeted by BPA.<sup>31</sup> Nevertheless, we consider that these findings cannot be applied to most CTEPH patients, for at least two reasons: firstly, patients included in this study had significant airflow limitation, a condition that may differently influence DLCO measurement

depending on the etiology of airflow limitation (*e.g.*, lower DLCO if airflow limitation is due to emphysema and higher DLCO if it is due to asthma<sup>32</sup>); secondly, patients included in this study who improved DLCO after BPA had intriguing findings at CPET: before BPA, their end-tidal CO<sub>2</sub> fraction was 4.83% (corresponding to a PETCO<sub>2</sub> of around 34.5 mmHg, a value that is much higher compared with values reported in the literature for CTEPH patients eligible for BPA) and their  $\dot{V}_E/\dot{V}_{CO_2}$  slope was 35, a value that is much lower than values reported in CTEPH patients undergoing BPA.<sup>8,10,12,20,33–35</sup>

### *Effects of BPA on pulmonary gas exchange*

Our results suggest hypothesis regarding the mechanisms by which BPA improves pulmonary gas exchange. The regression analyses made with P(Ai-a)O<sub>2</sub> as the dependent variable shows that before BPA, physiological VD/VT ratio was the most important determinant of gas exchange abnormalities. Among the components used to estimate VD/VT with the Enghoff simplification, it is likely that intrapulmonary shunt (low  $\dot{V}_A/Q$  in over-perfused, non-occluded pulmonary zones) rather than small-vessel vasculopathy (causing low DLCO) explain high P(Ai-a)O<sub>2</sub> before BPA because the association between P(Ai-a)O<sub>2</sub> and DLCO, although significant, was weak. In contrast, after BPA, only DLCO was significantly associated with P(Ai-a)O<sub>2</sub>, with a  $\beta$  coefficient in multivariable analysis as high as 0.50. This suggests that once pulmonary perfusion becomes less heterogeneous (lower physiological VD/VT ratio) and hemodynamics are improved after BPA, small-vessel vasculopathy is a major determinant of gas exchange abnormalities (Figure 2). This observation can be paralleled with recent data showing that in CTEPH patients undergoing PEA, a low preoperative DLCO was a strong predictor of persistent exercise intolerance after surgery.<sup>34</sup>

### *Effects of BPA on ventilatory limitation during exercise*

An increased  $\dot{V}_E/\dot{V}_{CO_2}$  ratio, reflecting impaired ventilatory efficiency, contributes to higher perceived dyspnea during exercise.<sup>21</sup> In line with this, we report that after BPA, the improvement in ventilatory efficiency was accompanied by a decrease in the dyspnea Borg score measured at iso-work. Of note, iso-work was greater by more than 20 watts (i.e., more than one third) than the work-load found at the ventilatory threshold (data not shown). In contrast, at peak exercise, dyspnea did not improve significantly after BPA although the  $\dot{V}_E/\dot{V}_{CO_2}$  ratio was about 25% lower. In other words, an improvement in ventilatory efficiency as high as 25% was not associated with less dyspnea. At peak exercise,  $\dot{V}_E$  were similar pre- and post-BPA, and mean breathing reserve was as low as ~15%. Although variance is wide, breathing reserve in normal non-athletic subjects is on average 38 L.min<sup>-1</sup> and/or 20%, and values <15% suggest ventilatory limitation.<sup>36</sup> Our data therefore suggest that despite improvements in ventilatory efficiency after BPA and despite normal FEV<sub>1</sub> (z-scores > -1.64), patients had a breathing reserve that remained near-exhaustion at peak exercise, potentially contributing to persistent dyspnea.

### *Comparisons between our analyses and those made in CTEPH patients receiving either PEA or PH-targeted drugs*

There is an increasing body of evidence that in CTEPH, DLCO reflects the microvasculopathy that persists even after interventional treatments.<sup>37</sup> Although highly stable values of DLCO have been largely reported after PEA,<sup>9,26-28</sup> to the best of our knowledge, the effects of PH-targeted drugs on DLCO have not been reported. After PH-targeted therapies, exercise ventilatory efficiency has been reported to not significantly improve, either in patients deemed to have inoperable CTEPH or in those deemed to have an operable form.<sup>10</sup> In contrast, ventilatory efficiency improved after PEA<sup>10,34</sup> – as was the case in our patients after BPA. Nevertheless, in

line with our results, ventilatory reserve did not improve after PEA despite improved ventilatory efficiency,<sup>10,34</sup> for reasons discussed above. Regarding physiological  $VD/VT$ , the effects are also different between PEA and PH-targeted drugs:  $VD/VT$  ratio was shown to increase after PH-targeted drugs (this increase being attributed to further  $\dot{V}A/Q$  heterogeneity)<sup>10</sup> while decreased physiological  $VD/VT$  was reported after PEA.<sup>10</sup> The main difference between previous papers reporting decreased physiological  $VD/VT$  after interventional CTEPH treatments and our analyses concerns the interpretation of data, as discussed above.

### *Limitations of the study*

We recognize some limitations to our study. First, post-BPA data were not measured after the complete BPA treatment course. This choice was made in order (i) to avoid a supplementary complete workup immediately after the last BPA session (complete workups are currently scheduled 3-6 months after the last BPA session) and (ii) to minimize confounding factors that might interfere with the effects of BPA on ventilation and gas exchange. Nevertheless, the clinical and hemodynamic characteristics of our patients post-BPA were identical to those of patients in another cohort on completion of all BPA sessions.<sup>11</sup> Second, we did not measure inspiratory capacity during exercise due to difficulty in obtaining reliable data both on gas exchange and on inspiratory capacity in CTEPH patients, especially before BPA. We were therefore unable to determine the potential effect of BPA on dynamic hyperinflation, a condition found in two thirds of CTEPH patients despite normal spirometry.<sup>38</sup> Third, because patients with CTEPH have been shown not to have altered pulmonary gas diffusion, a stable DLCO was interpreted in our study as a stable capillary blood volume, although we did not measure either membrane or blood gas resistances in our patients. Indeed, a growing body of evidence suggests that the calculation of capillary blood volume and membrane conductance by the Roughton and Forster equation, which postulates a separation between independent

membrane and blood resistances, is a mathematical conjecture that can lead to incorrect physiological interpretations of DLCO.<sup>39</sup> Fourth, as we did not perform hemodynamic measurements during exercise, we were unable to determine whether or not lower DLCO was associated with more severe pulmonary hypertension at exercise.

### *Conclusion*

Our observations and analyses suggest that the lower physiological VD/VT ratio found after BPA is a consequence of reduced  $\dot{V}A/Q$  heterogeneity rather than an improvement of true alveolar VD/VT. Our results also suggest that DLCO measured at CTEPH diagnosis, before BPA, may provide an easily accessible marker to predict the response to BPA in terms of pulmonary gas exchange, at least in patients without significant cardiac and/or pulmonary comorbidities. In addition, we found that despite improvements in ventilatory efficiency after BPA, breathing reserve remains at near-exhaustion at peak exercise, potentially contributing to persistent dyspnea.

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### **CONFLICT OF INTEREST STATEMENT**

MBN, NP, AG, SD, MS, FT, CA, HB report no disclosures. CP reports personal fees from Boehringer Ingelheim, Glaxo Smith Kline, Astra Zeneca and Sanofi outside submitted work. BA reports honoraria and consulting fees grant funding from Boehringer Ingelheim, Glaxo Smith Kline, Menarini, Chiesi, Astra Zeneca and Sanofi unrelated to the submitted work. BD



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## **AUTHOR CONTRIBUTIONS**

BD & BA contributed to the design of the study, interpretation of the analysis, drafting of the manuscript, and final approval. AG contributed statistical advice and final approval. MBN, NP, AG, SD, MS, FT, CA, HB and CP contributed to the interpretation of the data, revisions for important intellectual content, and final approval.

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**Table 1.** Comparison of clinical characteristics and hemodynamic parameters before and after balloon pulmonary angioplasty (BPA)

	<b>Pre-BPA</b>	<b>Post-BPA</b>	<i>P</i> -value
<b>PH-targeted treatments</b>			
sGCs, n (%)	22 (61%)	22 (61%)	1
ERA, n (%)	9 (25%)	9 (25%)	1
PDE5i, n (%)	0	0	1
None/single/double/triple (%)	28/55/17/0	28/55/17/0	1
NYHA FC, % (I-II/III-IV)	39/61	94/6	<0.001
6MWD, m	391 (116)	434 (99)	<0.001
NT-proBNP, pg·mL <sup>-1</sup>	1739 (2672)	404 (458)	0.003
Systolic PAP, mmHg	73 (18)	50 (15)	<0.001
Diastolic PAP, mmHg	24 (7)	17 (7)	<0.001
Mean PAP, mmHg	41 (9)	29 (9)	<0.001
Mean RAP, mmHg	7 (3)	5 (3)	0.03
PAWP, mmHg	10 (3)	10 (4)	0.80
Cardiac output, L·min <sup>-1</sup>	4.9 (1.4)	5.6 (1.2)	<0.001
Cardiac index, L·min <sup>-1</sup> ·m <sup>-2</sup>	2.7 (0.7)	3.0 (0.6)	0.008
PVR, Wood Units	6.8 (3.3)	3.5 (1.4)	< 0.001
SvO <sub>2</sub> , %	63 (7)	68 (4)	<0.001

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.

BPA: balloon pulmonary angioplasty; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor; sGCs: synthetic guanylate cyclase stimulator; NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: pulmonary artery pressure; RAP: right atrial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO<sub>2</sub>: mixed venous oxygen saturation.

**Table 2.** Pulmonary function tests measured before and after balloon pulmonary angioplasty (BPA)

	<b>Pre-BPA</b>	<b>Post-BPA</b>	<i>P</i> -value	<b>Post- minus pre-BPA</b>
<b>FEV<sub>1</sub></b>				
% predicted	85 (16)	86 (16)	0.53	0.6 (-0.2;1.5)
z-score	-0.90 (1.02)	-0.88 (1.03)	0.51	0.03 (-0.02;0.09)
<b>FVC, % predicted</b>				
% predicted	89 (15)	89 (16)	0.67	-0.4 (-2.0;1.3)
z-score	-0.69 (0.99)	-0.73 (0.99)	0.62	-0.03 (-0.14;0.07)
<b>DLCO</b>				
% predicted	80 (13)	80 (13)	0.58	-0.5 (-2.2;1.3)
z-score	-1.29 (0.87)	-1.30 (0.87)	0.34	-0.02 (-0.07;0.06)
<b>KCO</b>				
% predicted	85 (15)	85 (14)	0.54	1.0 (-4.1;2.2)
z-score	-1.02 (0.99)	-1.00 (0.95)	0.52	-0.03 (-0.17;0.14)
<b>VA</b>				
% predicted	95 (12)	96 (14)	0.23	1.3 (-0.9;3.5)
z-score	-0.41 (1.02)	-0.36 (1.13)	0.26	0.06 (-0.11;0.18)

Data are presented as mean (standard deviation) or n (%) excepted for the differences between pre- and post-BPA values (mean (95% confidence interval)). Continuous parameters were compared using the paired t-test. BPA: balloon pulmonary angioplasty; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: single breath lung diffusion of carbon monoxide (corrected for hemoglobin concentration); KCO: rate of uptake of CO from alveolar gas (corrected for hemoglobin concentration); VA: alveolar volume.

**Table 3.** Cardiopulmonary exercise variables obtained at peak exercise before and after balloon pulmonary angioplasty (BPA), and at the identical maximal work rate achieved before and after BPA (iso-work). Comparisons are made between post-BPA values (at peak and at iso-work) and peak pre-BPA values.

	Pre-BPA		Post-BPA				
	At peak	At peak			At iso-work		
		<i>P</i> -value <sup>1</sup>	Post- <i>minus</i> pre-BPA	<i>P</i> -value <sup>1</sup>	Post- <i>minus</i> pre-BPA	<i>P</i> -value <sup>1</sup>	Post- <i>minus</i> pre-BPA
Work load, W	75 (30)	88 (34)	< 0.001	13 (9;17)	75 (30)	1.00	0 (0;0)
Work load, %	64 (26)	76 (30)	< 0.001	12 (8;16)	64 (26)	1.00	0 (0;0)
$\dot{V}O_2$ , mL·min <sup>-1</sup>	1143 (408)	1319 (386)	< 0.001	176 (109;243)	1220 (347)	0.04	67 (1;132)
$\dot{V}O_2$ , mL·kg <sup>-1</sup> ·min <sup>-1</sup>	15.0 (4.6)	17.4 (4.6)	< 0.001	2.5 (1.6;3.4)	16.0 (4.1)	0.03	1.0 (0.1;1.8)
$\dot{V}CO_2$ , mL·min <sup>-1</sup>	1229 (463)	1432 (475)	<0.001	203 (108;298)	1249 (424)	0.83	19 (-64;79)
RER	1.07 (0.14)	1.08 (0.13)	0.76	0.01 (-0.05;0.07)	1.02 (0.13)	0.08	-0.05 (-0.11;0.01)
Dyspnea (Borg, 0-10)	7.5 (2.0)	5.8 (2.1)	0.004	-1.6 (-2.2;-0.5)	4.5 (2.2)	<0.001	-2.9 (-3.2;-2.5)
Leg fatigue (Borg, 0-10)	6.3 (2.9)	5.9 (2.5)	0.24	-0.5 (-1.3;0.2)	4.3 (2.8)	0.01	-1.9 (-2.9;-0.9)
Lactate, mmol·L <sup>-1</sup>	4.9 (1.9)	5.2 (1.8)	0.18	0.3 (-0.1;0.8)	4.5 (2.3)	0.09	-0.4 (-0.9;0.1)
Heart rate, beat·min <sup>-1</sup>	133 (17)	137 (16)	0.02	4 (1;8)	126 (21)	0.009	-7 (-12;-2)
O <sub>2</sub> pulse, mL·beat <sup>-1</sup>	8.6 (2.9)	9.6 (3.1)	<0.001	1.1 (0.6;1.7)	9.7 (2.8)	<0.001	1.1 (0.5;1.8)
$\dot{V}E/\dot{V}CO_2$	57 (17)	47 (11)	< 0.001	-10 (-14;-7)	45 (10)	< 0.001	-12 (-16;-8)
Physiological VD/VT, %	39 (11)	33 (10)	<0.001	-7 (-10;-3)	30 (10)	<0.001	-8 (-12;-6)
$\dot{V}E$ , L·min <sup>-1</sup>	66 (21)	65 (22)	0.73	-1 (-4;3)	54 (15)	<0.001	-13 (-16;-9)
<i>f</i> <sub>B</sub> , min <sup>-1</sup>	41 (8)	40 (7)	0.24	-1 (-3;1)	33 (6)	< 0.001	-8 (-10;-6)



VT, L	1.7 (0.6)	1.7 (0.5)	0.23	0.1 (0.0;0.1)	1.7 (0.5)	0.88	0.0 (-0.1;0.1)
Breathing reserve, %	15 (17)	16 (16)	0.53	2 (-4;7)	30 (14)	<0.001	15 (12;19)
PaO <sub>2</sub> , mmHg	61 (10)	69 (14)	<0.001	8 (4;11)	69 (11)	<0.001	8 (5;10)
P(Ai-a)O <sub>2</sub> , mmHg	59 (11)	50 (12)	<0.001	-9 (-13;-5)	47 (10)	<0.001	-13 (-21;-8)
PETCO <sub>2</sub> , mmHg	24 (6)	28 (5)	<0.001	4 (3;5)	29 (5)	<0.001	5 (6;4)
PaCO <sub>2</sub> , mmHg	32 (5)	34 (4)	0.003	2 (1;4)	35 (4)	<0.001	3 (1;5)
P(a-ET)CO <sub>2</sub>	7 (3)	6 (4)	0.005	-1 (-3;-1)	5 (4)	<0.001	-2 (-3;-1)

Data are presented as mean (standard deviation) or n (%) excepted for the differences between pre- and post-BPA values (mean (95% confidence interval)). Continuous parameters were compared using the paired t-test and categorical parameters were compared using the McNemar test.

<sup>1</sup>Comparisons are made versus Pre-BPA

BPA: balloon pulmonary angioplasty;  $\dot{V}O_2$ : oxygen consumption;  $\dot{V}CO_2$ : carbon dioxide output; RER: respiratory exchange ratio;  $\dot{V}E$ : minute ventilation;  $V_D/V_T$ : dead space fraction of tidal volume;  $f_B$ : breathing frequency; PaO<sub>2</sub>: partial oxygen arterial pressure; P(Ai-a)O<sub>2</sub>: ideal alveolar-arterial gradient for oxygen; PETCO<sub>2</sub>: end-tidal carbon dioxide pressure; PaCO<sub>2</sub>: partial carbon dioxide arterial pressure.

**Table 4.** Univariable and multivariable linear regression with ideal alveolar-arterial oxygen gradient ( $P_{(A_i-a)O_2}$ ) as the dependent variable.

	Pre-BPA				Post-BPA			
	Univariable analysis		Multivariable analysis <sup>§</sup>		Univariable analysis		Multivariable analysis <sup>§</sup>	
	$\beta$ (95% CI)	<i>P</i> -value	$\beta$ (95% CI)	<i>P</i> -value	$\beta$ (95% CI)	<i>P</i> -value	$\beta$ (95% CI)	<i>P</i> -value
Physiological $V_D/V_T$ , %*	56.00 (25.91;48.83)	<0.001	40.54 (3.93;77.15)	0.03	34.75 (-6.13;75.64)	0.09	6.15 (-38.48;50.78)	0.78
$S_{vO_2}$ , %*	-0.62 (-1.12;-0.11)	0.02	-0.36 (-0.86;0.15)	0.16	-0.62 (-1.63;0.39)	0.22	-	-
DLCO, % pred <sup>#</sup>	-0.31 (-0.58;-0.04)	0.03	-0.23 (-0.49;0.03)	0.08	-0.52 (-0.85;-0.19)	0.003	-0.50 (-0.86;-0.14)	0.009

$\beta$ : coefficient that compares the strength of the effect of each individual independent variable (*i.e.*, “physiological”  $V_D/V_T$ , DLCO and PVR) to the dependent variable (*i.e.*,  $P_{(A_i-a)O_2}$ ); 95% CI: 95% confidence interval for the  $\beta$  coefficient.

BPA: balloon pulmonary angioplasty;  $V_D/V_T$ : dead space fraction of tidal volume; DLCO: single breath lung diffusion of carbon monoxide (corrected for hemoglobin concentration); % pred: percentage of the predicted value;  $S_{vO_2}$ : mixed venous oxygen saturation.

\*Physiological  $V_D/V_T$  and  $S_{vO_2}$  were measured pre- and post-BPA for the corresponding analyzes; physiological  $V_D/V_T$  was measured at peak exercise while  $S_{vO_2}$  was measured at rest, pre- and post-BPA.

<sup>#</sup>DLCO was measured before BPA.

<sup>§</sup>All variables associated with  $P_{(A_i-a)O_2}$  in univariable analysis with a *P*-value < 0.20 were included in the multivariable analysis

## 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.** Schematic view of ventilation/perfusion relationships in chronic thromboembolic pulmonary hypertension and effects of balloon pulmonary angioplasty. In CTEPH, a subset of large pulmonary arteries is occluded by persistent organized thrombi (1). In addition, arterioles, venules and capillaries are remodeled (2), both downstream the occlusion of large arteries (occluded areas) and in non-occluded areas. Interpretation of our measurements are the following. **(A)** Before BPA, the cardiac output (3) is directed in totality towards non-occluded areas (right panel) while in occluded areas (left panel), perfusion of alveolar capillaries comes from systemic bronchial arteries (4). As ventilation is homogeneous (5), this results in low  $\dot{V}_A/Q$  in non-occluded areas (contributing to high  $P_{(A_i-a)}O_2$ ) and in high  $\dot{V}_A/Q$  in occluded areas. The overall  $\dot{V}_A/Q$  heterogeneity largely contributes to high “physiological”  $V_D/V_T$ . In occluded as well as in non-occluded areas, the zones with remodeling of small vessels (2) also contributes to high  $P_{(A_i-a)}O_2$  and high “physiological”  $V_D/V_T$ , and are the major contributors of alteration of KCO and DLCO (6). Expired  $CO_2$  ( $\dot{V}_{CO_2}$ ) comes in large majority from the non-occluded zones (dark grey points). **(B)** BPA restores homogeneous distribution of cardiac output (3) in all pulmonary arteries, leading to decreased  $\dot{V}_A/Q$  heterogeneity and thus decreased “physiological”  $V_D/V_T$ . KCO and DLCO are however unaffected by BPA, suggesting that alterations of CO transfer are secondary to persistent alteration of remodeled small vessels (2) rather than to a change of lung capillary blood volume after BPA. For a given  $\dot{V}_{CO_2}$  (iso-work), ventilation ( $\dot{V}_E$ ) is lower after BPA, presumably at least in part because expired  $CO_2$

comes from all ventilated alveoli. How perfusion of alveolar capillaries by systemic bronchial arteries is affected by BPA remains essentially unknown.

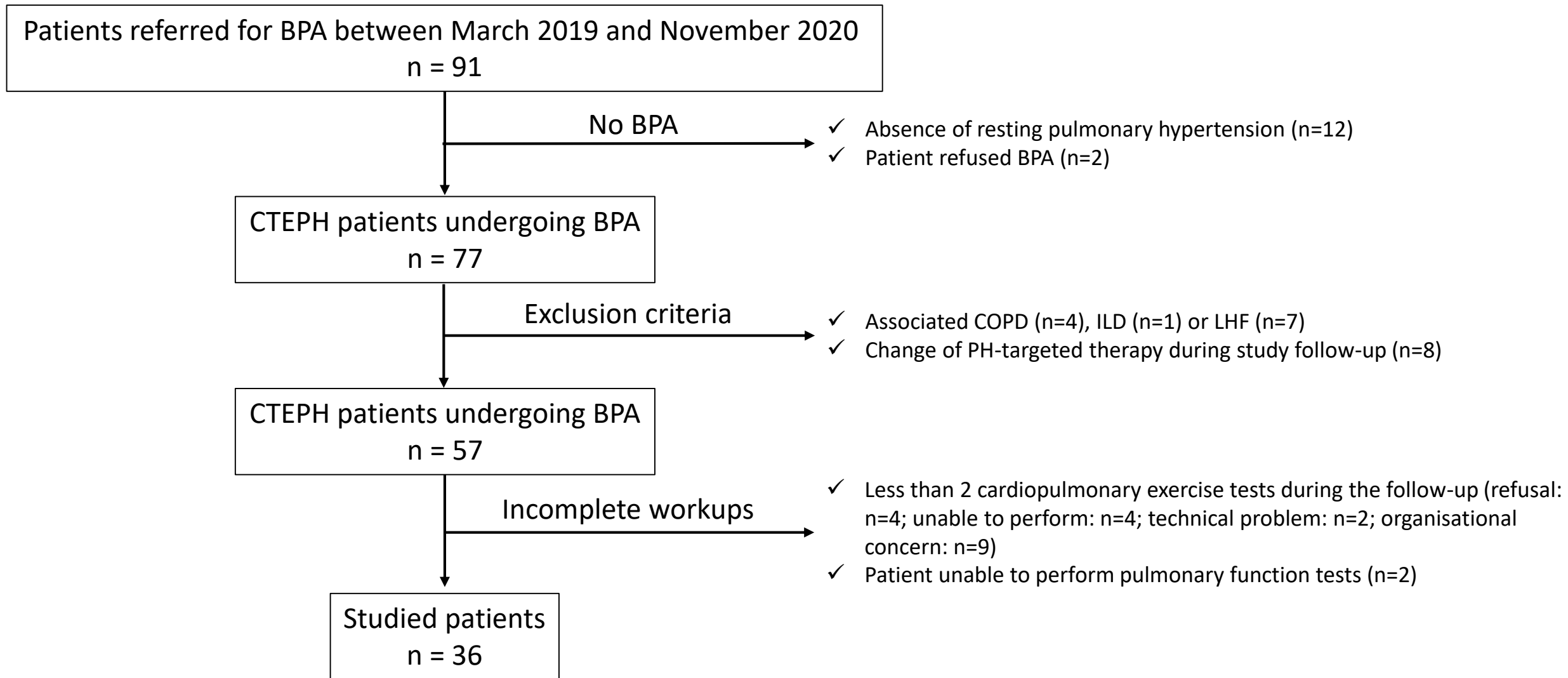
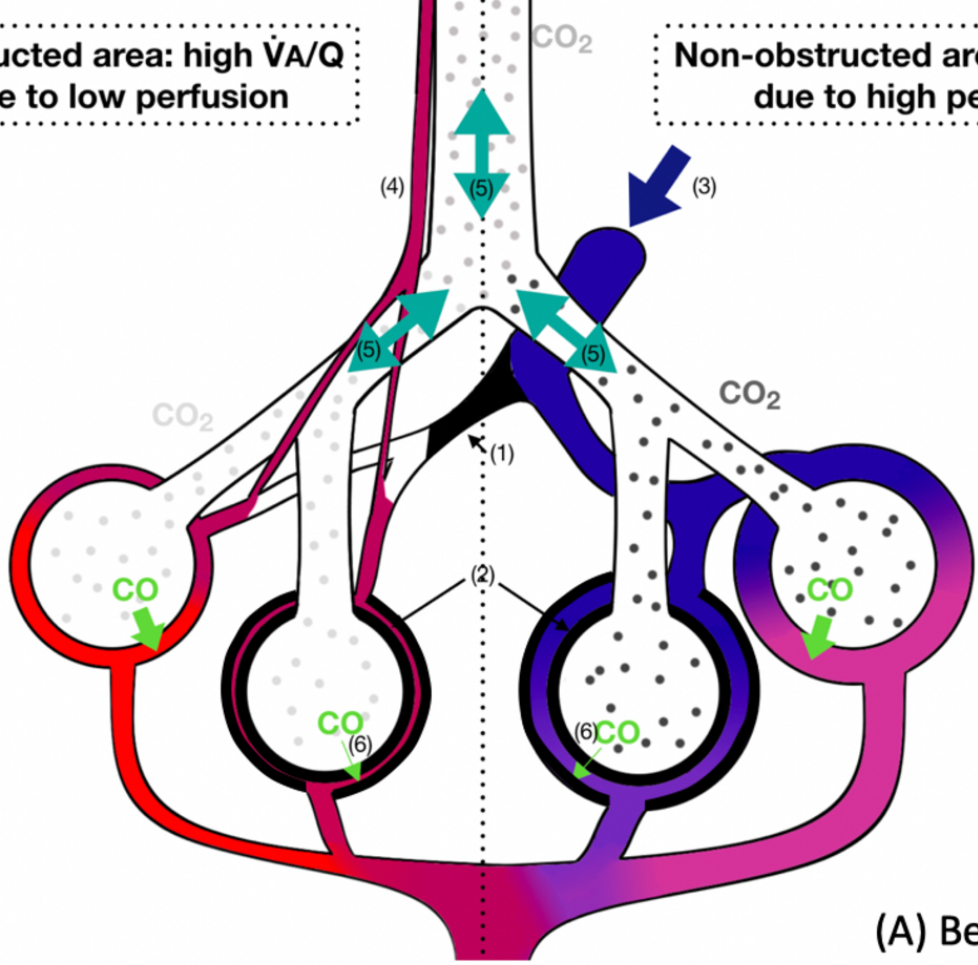


Figure 1

Obstructed area: high  $\dot{V}_A/Q$  due to low perfusion

Non-obstructed area: low  $\dot{V}_A/Q$  due to high perfusion

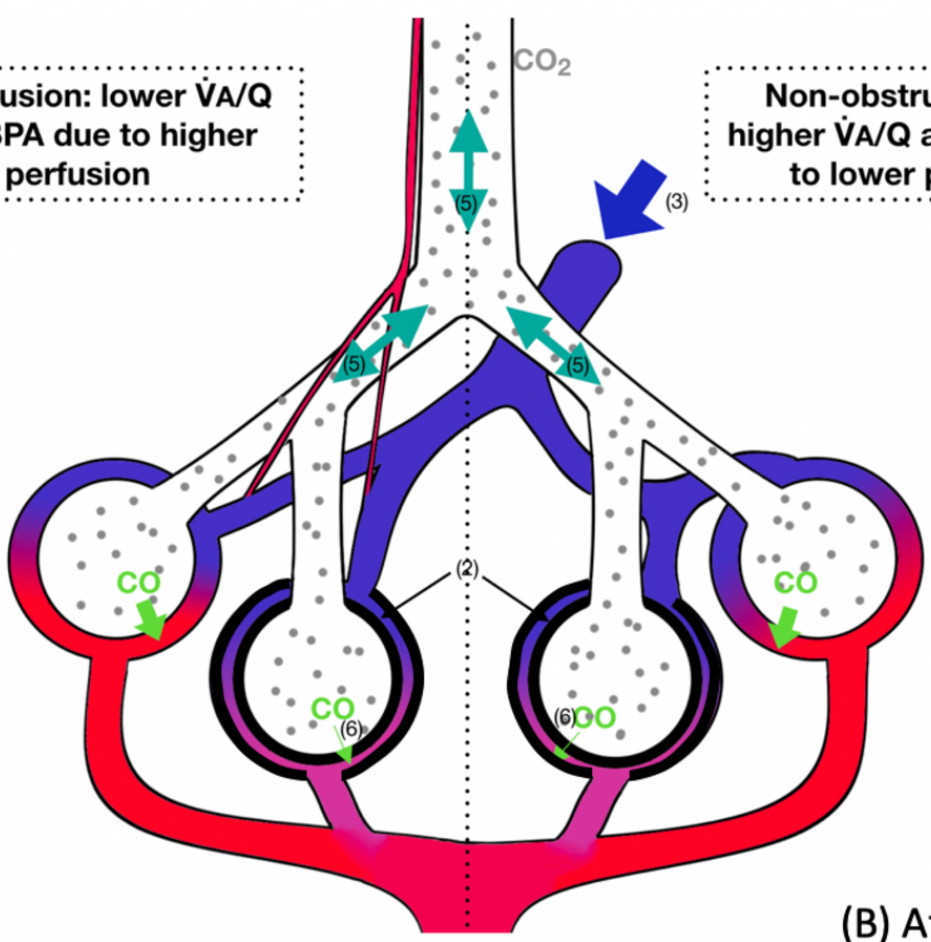


(A) Before BPA

Heterogeneity of  $\dot{V}_A/Q$

De-obstruction: lower  $\dot{V}_A/Q$  after BPA due to higher perfusion

Non-obstructed area: higher  $\dot{V}_A/Q$  after BPA due to lower perfusion



(B) After BPA

Less heterogeneity of  $\dot{V}_A/Q$