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Series "CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION"
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Number 1 in this Series

Vascular and right ventricular remodelling in chronic thromboembolic pulmonary hypertension

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ABSTRACT: In chronic thromboembolic pulmonary hypertension (CTEPH) increased pulmonary vascular resistance is caused by fibrotic organisation of unresolved thromboemboli. CTEPH mainly differs from pulmonary arterial hypertension (PAH) by the proximal location of pulmonary artery obliteration, although distal arteriopathy can be observed as a consequence of non-occluded area over-perfusion. Accordingly, there is proportionally more wave reflection in CTEPH, impacting on pressure and flow wave morphology. However, the time constant, *i.e.* resistance × compliance, is not different in CTEPH and PAH, indicating only trivial effects of proximal wave reflection on hydraulic right ventricular load. More discriminative is the analysis of the pressure decay after pulmonary arterial occlusion, which is more rapid in the absence of significant distal arteriopathy.

Structure and function of the right ventricle show a similar pattern to right ventricular hypertrophy, namely dilatation and wall thickening, as well as loss of function in CTEPH and PAH. This is probably related to similar loading conditions. Hyperventilation with hypocapnia is characteristic of both PAH and CTEPH. Ventilatory equivalents for carbon dioxide, as a function of arterial carbon dioxide tension, conform to the alveolar ventilation equation in both conditions, indicating a predominant role of increased chemosensitivity. However, a slight increase in the arterial to end-tidal carbon dioxide tension gradient in CTEPH shows a contribution of increased dead space ventilation.

KEYWORDS: Chronic thromboembolic pulmonary hypertension, gas exchange, pulmonary arterial hypertension, pulmonary circulation, remodelling, right ventricular function

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by the presence of unresolved thromboemboli undergoing fibrotic organisation. This results in obstruction of proximal pulmonary arteries, increased pulmonary vascular resistance (PVR), pulmonary hypertension (PH) and progressive right ventricle remodelling and failure. Pulmonary embolism, either as single or recurrent episodes, is thought to be the initiating event followed by progressive pulmonary vascular remodelling. CTEPH mainly differs from pulmonary arterial hypertension (PAH) by the proximal location of pulmonary artery obliteration, although distal arteriopathy can be observed as a consequence of non-occluded area over-perfusion [1]. Also characteristic for CTEPH is the extensive collateral blood supply to the ischemic lung, developed from the systemic circulation.

Diagnosis is based on the presence of pre-capillary PH, defined by a mean pulmonary arterial pressure (PAP) $\geqslant$25 mmHg and a wedge pressure $\leqslant$15 mmHg, in combination with a lung scan showing segmental perfusion defects after a prolonged period of anticoagulation [2]. Further

For editorial comments see page 8.

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evaluation is performed by helical computed tomography and pulmonary angiography in order to localise vascular obstructions precisely.

Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH [3]. Under optimal conditions, including experienced centres and selected patients, PEA can be performed with low perioperative mortality, with improvements in haemodynamics, symptoms and survival [4]. However, only part of the patients fulfil the criteria for surgical intervention and some operated patients may experience a gradual haemodynamic and symptomatic decline related to secondary hypertensive arteriopathy in the small pre-capillary pulmonary vessels [3]. Therefore, techniques to discriminate between proximal and distal increases in PVR would be useful.

ANIMAL MODELS OF CTEPH

In order to better understand the pathophysiology of the disease, efforts have been taken to develop an animal model of CTEPH. Acute pulmonary embolism can be reproduced in different animal species, either with glass beads or autologous blood clots. The development of a chronic model of CTEPH is more challenging because of the very efficient endogenous fibrinolytic system [5]. The systemic vascular response to chronic pulmonary vascular obstruction also varies from species to species, with proliferation of bronchial arteries into the intraparenchymal airways in large animals or of intercostal arteries into the pleural space in mice [6].

MOSER *et al*. [7] described a chronic model of CTEPH in dogs by combining embolisation of autologous blood thrombi with the injection of tranexamic acid, a strong inhibitor of the fibrinolytic system, or with addition of plasminogen activator inhibitor type-1 [8]. Despite these attempts to stabilise thrombus, rapid resolution occurred. More recently, FADEL *et al.* [9] used unilateral pulmonary artery banding to mimic CTEPH in pigs. However, this model could only answer questions on chronic lung ischaemia, post-obstructive vasculopathy and reperfusion injury, because it did not reproduce distal vascular remodelling in the non-obstructed pulmonary arterial bed. Ligation of the right or left pulmonary artery is not sufficient to cause PH, and more extended ligation is lethal. Therefore, the same authors later combined the ligation of the left pulmonary artery, *via* sternotomy, with a weekly embolisation, under fluoroscopic control, of tissue adhesive enbucrilate (Histoacryl®; Aesculap AG, Tüttlingen, Germany) into the right lower lobe for 5 weeks [10]. Thus, the right upper lobe arteries remained patent reproducing the non-obstructed territories in CTEPH. This progressive obstruction of the pulmonary arterial tree was associated with sustained increase in mean PAP reaching or exceeding 20 mmHg at 5 weeks. This piglet model of CTEPH reproduced all aspects of the disease: increased PVR; increased media thickness of distal pulmonary arteries in both obstructed and non-obstructed lung areas; right ventricular hypertrophy; increased tricuspid annular plane systolic excursion; and paradoxical septal motion. The authors even observed increased systemic blood supply through the bronchial arteries in the obstructed areas. Interestingly, although the embolisations were stopped after 5 weeks, the increase in PVR persisted for up to 1 month later. An over-expression of endothelin-1 and angiopoietin-1 was shown to occur in remodelled distal arterioles of the unobstructed over-perfused lung areas, which is in keeping with previous observations in piglets with high-flow PH induced by chronic aorto-pulmonary shunting [11, 12].

PULMONARY VASCULAR REMODELLING

Studies that describe the composition of the material removed during PEA observed similarities with atherosclerotic lesions. ARBUSTINI *et al*. [13] described two types of intimal lesions in PEA material: 1) fibrous plaques with angiogenesis, and 2) atherosclerotic plaques that consist of cholesterol clefts, macrophages, T-lymphocytes and calcification. A clinicopathological study performed on 200 endarterectomised cases evidenced various stages of thrombus remodelling, associated with variable degrees of inflammation and cellularity within the specimen [14]. BLAUWET *et al*. [15] described organised thrombus formation and intimal thickening consisting of collagen, inflammation, calcification and atherosclerosis. The basic mechanisms responsible for this remodelling of proximal vessels will be described in the next article in the series by LANG *et al*. [16].

Distal pulmonary vascular remodelling is also involved in the development of CTEPH. This is supported by the fact that: 1) there is a lack of correlation between elevated PAP and the degree of angiographic pulmonary vascular bed obstruction; 2) PH progresses in the absence of recurrent embolism; and 3) PVR is still significantly higher in CTEPH patients than in acute pulmonary embolism patients with a similar percentage of vascular bed obstruction (fig. 1) [17–19].

In patients with concomitant small vessel arteriopathy, PH can persist after PEA despite removal of proximal material, and is associated with increased morbidity and mortality. More than one-third of perioperative deaths and nearly half of long-term deaths have been attributed to persistent PH [18, 20]. More recently, persistent PH has been shown in 17% of a registry population of 384 operated patients [4]. The current standard

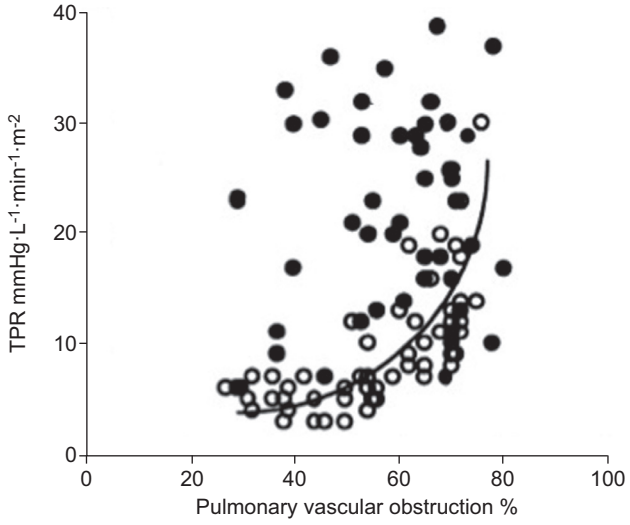

FIGURE 1. Relationship between pulmonary vascular obstruction score, assessed by perfusion lung scan, and total pulmonary resistance (TPR) in acute pulmonary embolism (open circles) and chronic thromboembolic pulmonary hypertension (closed circles; CTEPH). For a given degree of obstruction, patients with CTEPH had higher TPR values than patients with acute pulmonary embolism. Reproduced from [17] with permission from the publisher.

pre-operative evaluation does not accurately detect the presence or assess the degree of small vessel involvement in patients with CTEPH, nor does it reliably predict post-operative haemodynamic outcome. The analysis of pressure decay curves after pulmonary arterial occlusion (by the Swan Ganz catheter balloon) was developed to estimate true pulmonary capillary pressure and most probably approximates pre-capillary pressure [21, 22]. Such curves consist of a first, fast component that corresponds to the stop of flow through arterial resistance, and a second, slower component, which corresponds to the emptying of compliant capillaries through a venous resistance. From the intersection of these two components, one calculates an upstream resistance, essentially determined by the resistive properties of the large pulmonary arteries, and the other a downstream resistance, determined by the cumulated resistances of small arterioles, venules and capillaries [23]. KIM *et al.* [24] showed a higher upstream resistance in patients with CTEPH who had predominantly proximal (large-vessel) disease, whereas CTEPH patients with lower upstream resistance had significant concomitant small-vessel disease and more frequently persistent PH and death after PEA (fig. 2) [24]. These patients, if identified pre-operatively, could benefit from medical therapy. However, PVR partitioning is technically challenging requiring a perfect position of the Swan Ganz catheter with regular pressure decay after occlusion, and has, for a long time, not been further implemented and validated. A recent study on a large number of patients seems to confirm previous findings but also shows that discrimination on an individual basis is insufficient for clinical decision [25].

The bronchial vasculature is the systemic arterial blood supply to the lung. Although small in relation to the pulmonary blood flow, the bronchial vasculature serves important functions in pulmonary vascular and airway diseases. Experimental lung transplantation suggests that a loss of the bronchial artery supply of airways may be a trigger of obliterative bronchiolitis [26]. However, systematic re-implantation of the bronchial arteries (*i.e.* bronchial artery revascularisation) [27] has not resulted in the prevention of bronchiolitis obliterans, or in an improved clinical evolution including gas exchange or ventilatory responses. However, recurrent haemoptysis has been successfully managed by bronchial artery embolisation in PAH [28] and in CTEPH.

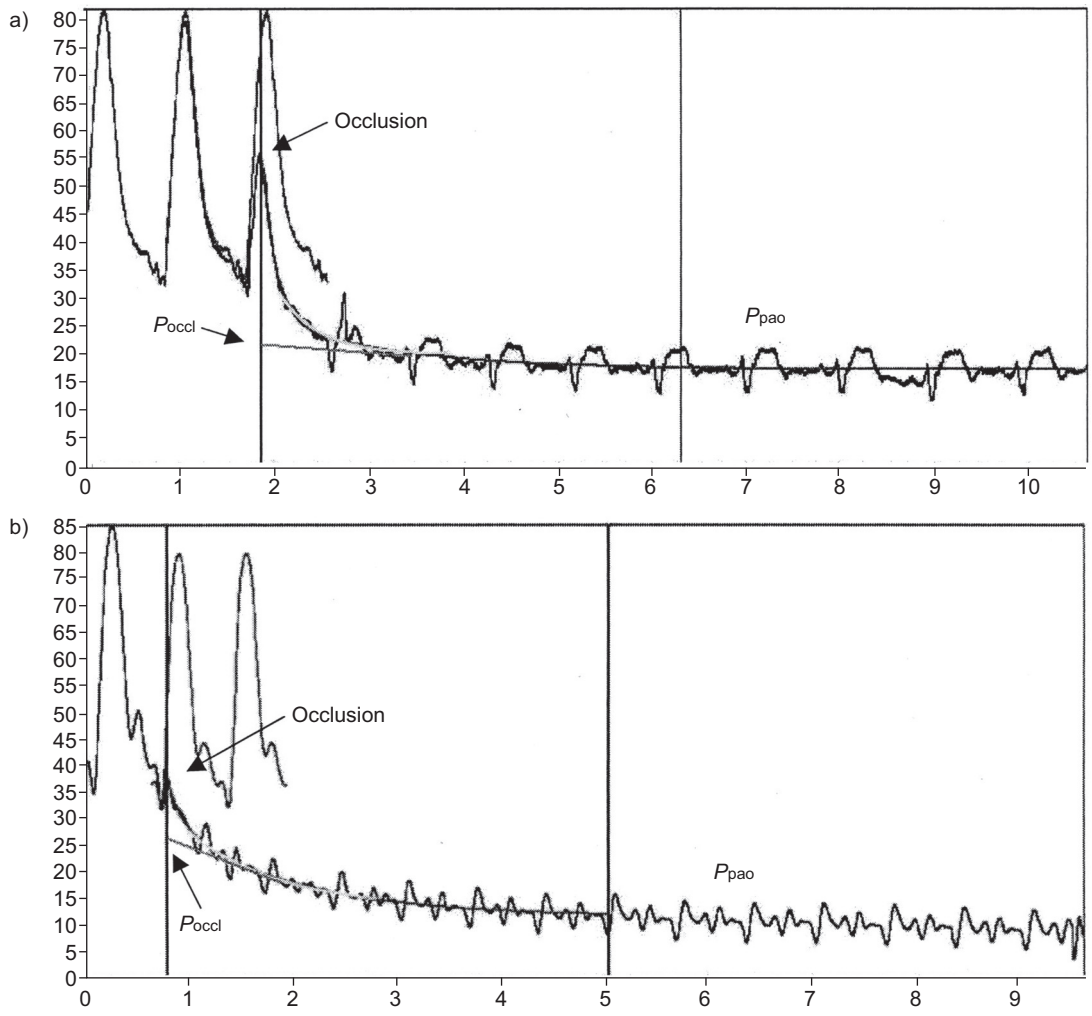

FIGURE 2. Pulmonary artery occlusion in two patients with a) primarily upstream resistance with a rapid drop in pressure to pulmonary arterial occlusion pressure (P_{pao}) or ''wedge'', and b) significant downstream resistance with a longer time needed for the pressure to reach P_{pao}. P_{occl}: pulmonary capillary pressure after occlusion. Reproduced from [24] with permission from the publisher.

Normally, two-thirds of bronchial flow drains into the pulmonary arteries and one-third into the pulmonary veins. In contrast to patients with PAH, CTEPH patients may display significant bronchopulmonary collateral blood flow, accounting for up to 30% of systemic blood flow draining directly into the pulmonary veins [29, 30]. The presence of bronchial collaterals has been used as a ''biomarker'' for the diagnosis of CTEPH [31]. A linear correlation exists between the magnitude of bronchosystemic shunt and dilatation of the bronchial arteries in patients with CTEPH [32]. There is little evidence that acute bronchial vascular congestion contributes significantly to airway narrowing. Post-operative PVR is lower in patients with dilated bronchial arteries, and dilated bronchial arteries have been positively correlated with a lower mortality rate after PEA [33]. A probable explanation for these observations is that a large bronchial collateral circulation is commonly associated with proximal occlusion (*i.e.* type 1 CTEPH, Jamieson classification [34]) and operable disease. Current evidence is not sufficient to support invasive bronchial artery angiography as a routine method for the diagnosis and prognostic assessment of CTEPH [35], but evaluation of the bronchial circulation on the helical computed tomography images should be considered.

In contrast to the pulmonary circulation, the bronchial circulation has a remarkable ability to proliferate [36]. Numerous reports have documented hypertrophy and angiogenesis of the bronchial circulation in response to a variety of stimuli, including chronic lung infections, pulmonary artery occlusion, lung tumours and lung transplantation. Occlusion of one main pulmonary artery stimulates angiogenesis in the bronchial circulatory system of the ipsilateral lung [37]. Bronchial arteries begin to enlarge as soon as 2–3 days after ligation of the pulmonary artery and 50–200 μm pre-capillary anastomoses form between the bronchial circulation and the pulmonary artery. These anastomoses may maintain oxygenation of airway epithelium and prevent epithelial–mesenchymal transition and fibrosis [38], and may salvage the blood supply distal to the complete occlusion of a pulmonary artery. Consequently, it has been speculated that the ipsilateral bronchial artery blood supply must be interrupted to maintain pulmonary artery functional patency after unilateral surgical pulmonary endarterectomy. However, because bronchial walls do not allow sufficient diffusion of carbon dioxide and oxygen, the role of the bronchial circulation in maintaining gas exchange within the lung distal to obstructed pulmonary arteries is doubtful. Whether major vessel thrombus represents a stimulus for the formation of bronchopulmonary anastomoses remains to be determined. Few in-depth studies exist on the vascular biology of the bronchial circulation. An increase in endothelial-1-like immunoreactivity in newly formed bronchial arteries within the ligated lung has been shown and suggests that endothelial-1, among other angiogenic factors, for example hypoxia-inducible factors-1 [39], may play a role in bronchial arterial angiogenesis [19] and the integrity of airway microvasculature. Taken together, much uncertainty still exists regarding the molecular stimuli of collateral bronchial artery growth, and the precise role of the bronchial circulation in CTEPH.

PRESSURE AND FLOW WAVE MORPHOLOGY

It was believed that loading conditions in CTEPH are different from other types of PH, based on the fact that CTEPH causes partial or complete occlusion of the proximal vessels leading to pressure wave reflections. In addition, it was thought that the involvement of the large vessels in the disease might decrease compliance, out of proportion of increased resistance in these patients.

Increased wave reflection affects pulmonary pressure waves by an increased pulse pressure, which is the difference between systolic and diastolic pressure, and late systolic peaking of pressure, because backward and forward waves add up to the measured signal. For the flow, the backward wave is inversed with respect to the forward wave, resulting in a late or mid-systolic deceleration of the flow wave [40]. NAKAYAMA *et al.* [41] measured pulse pressure relative to mean PAP (pulse pressure/meanPAP = fractional pulse pressure) in 22 patients with CTEPH and in 12 patients with idiopathic PAH. In patients with CTEPH, fractional pulse pressure was 1.41 ± 0.2 compared to 0.80 ± 0.18 in patients with idiopathic PAH [41]. This difference was highly significant, and there was no overlap. The same authors repeated the study in 19 patients with CTEPH and in 19 patients with idiopathic PAH measuring systolic PAP (PAP_{sys}) from the maximum velocity of tricuspid regurgitation, and diastolic PAP (PAP_{dias}) from the maximum velocity of pulmonary regurgitation [42]. While PAP_{sys} was not different, fractional pulse pressure was 1.65 ± 0.30 in the CTEPH patients and 0.94 ± 0.25 in the idiopathic PAH patients. Receiver operating characteristics analysis revealed that fractional pulse pressure separated CTEPH from idiopathic PAH with a sensitivity of 0.95 and a specificity of 1.0. NAKAYAMA *et al.* [43] went on to show the relatively more important impact of wave reflection on PAP wave morphology in CTEPH compared to idiopathic PAH. CTEPH pressure waves presented with shorter time to inflection, and increased difference between PAP_{sys} and inflection pressure, leading to an increased augmentation index calculated as (PAPsys–inflection pressure)/pulse pressure. The authors found that the augmentation index and the time to inflection discriminated 32 patients with CTEPH from 31 patients with idiopathic PAH. However, this result was not confirmed by CASTELAIN *et al.*

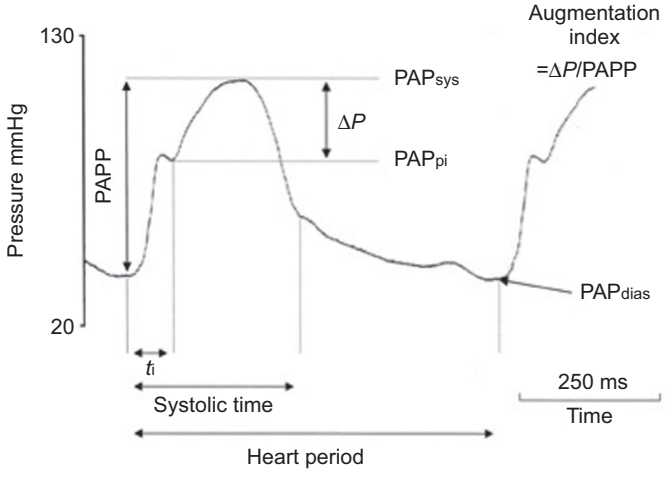

FIGURE 3. Typical pulmonary artery pressure (PAP) tracings. Chronic thromboembolic pulmonary hypertension patients have an increased time to inflection (*ti*) and augmentation index. PAPP: pulmonary artery pulse pressure; Δ*P*: change in pressure; PAP_{pi}: PAP at the inflexion point; PAP_{sys}: systolic PAP; PAP_{dias}: diastolic PAP. Reproduced from [44] with permission from the publisher.

[44] who performed PAP wave analysis with high-fidelity micromanometer-tipped catheters in 14 patients with CTEPH and seven patients with idiopathic PAH. Both groups had comparable cardiac index, mean PAP, pulse pressure and fractional pulse pressure. The time to inflection and the augmentation index were increased in CTEPH patients (fig. 3), but the measurements did not allow for sufficient discrimination.

PAP_{sys} and PAP_{dias} in CTEPH are proportional to the mean in a similar way as in idiopathic PAH [45]. Proportionality of the PAP_{sys} and PAP_{dias} can only be explained if the time constant, which is the product of resistance and compliance, is constant at the same value in CTEPH and idiopathic PAH [46]. Indeed, several studies have confirmed that the load of the right ventricle, described by resistance × compliance product, is similar for CTEPH and idiopathic PAH [47–49]. For example, LANKHAAR *et al.* [46] showed that in patients with CTEPH (n=10), idiopathic PAH (n=9) and controls without PH (n=10), the time constant was always equal to 0.72 s. The explanation for this is that compliance and resistance are equally distributed over the pulmonary vascular bed. Indeed, SAOUTI *et al.* [50] showed that only 30% of compliance is localised in the large pulmonary artery vessels. Another strong supporting argument is that the time constant remains unaffected by endarterectomy

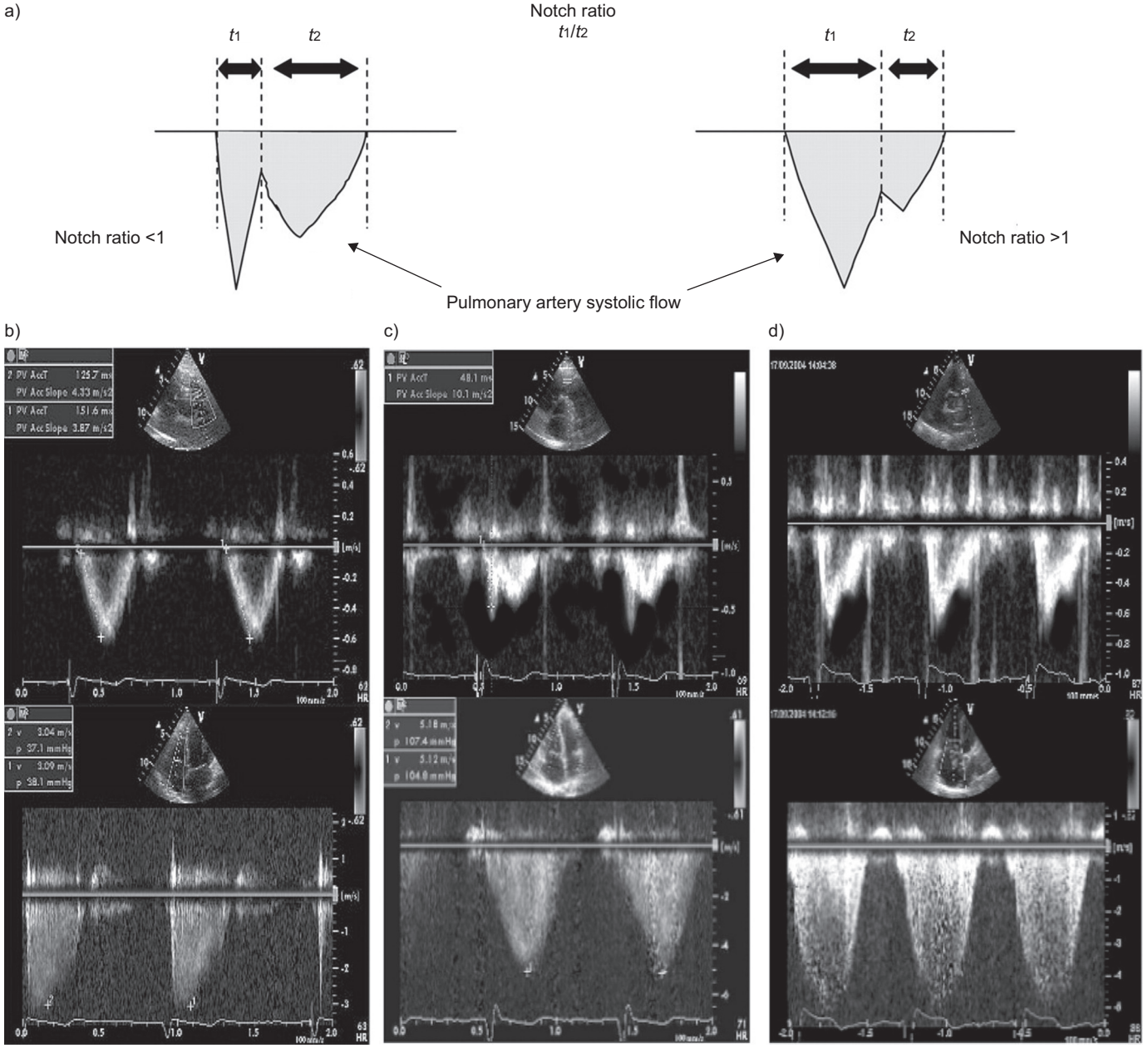

FIGURE 4. a) Notch ratio calculated on Doppler pulmonary flow waves. b–d) Pulmonary flow waves (top tracings) and tricuspid regurgitant jets (bottom tracings) in different patients with chronic thromboembolic pulmonary hypertension. b) Exercise-induced pulmonary hypertension, and c, d) with similar severity of pulmonary hypertension but a notch ration <1 and >1, respectively. t_1: time interval from the onset of pulmonary artery systolic flow to the maximal systolic flow deceleration; t_2: time interval from the maximal systolic flow deceleration to the end of pulmonary artery systolic flow. Reproduced from [52] with permission from the publisher.

[49]. This similar relationship in CTEPH and PAH predicts that, for a similar PVR, right ventricular load must be similar [50, 51]. A disproportionate increase in pulse pressure because of haemodynamically significant wave reflection would have decreased the time constant of the pulmonary circulation because of a decreased compliance at any given PVR. These results suggest that increased wave reflection in CTEPH does not affect monotonous response of the pulmonary circulation to vascular disease.

HARDZIYENKA *et al.* [52] reasoned that increased wave reflection in CTEPH should affect Doppler pulmonary flow wave morphology by an increased late or mid-systolic deceleration (notching) of flow. They defined a time to notching expressed as a notch ratio, or the ratio of time from onset of flow to maximum flow deceleration to time from maximum flow deceleration to end of flow (fig. 4). A notch ratio >1 in 18 out of 58 consecutive patients with CTEPH undergoing PEA was found to be associated with in-hospital mortality and persistent post-operative PH. Thus an increased notch ratio would allow for the identification of peripheral small vessel disease that is not amenable to surgery, as an early notch would indicate a proximal obstruction site while a late notch maps the obstruction to a more distal location. However, while this result is in keeping with predicted increased effects of reflections on proximal obstruction in CTEPH [53], the method has not been evaluated prospectively in larger patient populations. It would be interesting to combine pressure- and flow-wave analysis, which has not yet been attempted. A recent study revisited simple visual assessment of pulmonary flow wave morphology for the diagnosis of PH [54]. In 88 patients referred for PH and 32 patients with systolic heart failure, mid-systolic or late-systolic notching was highly associated with an increased PVR >3 Wood Units, whereas a normal shape of the pulmonary flow wave predicted a PVR <3 Wood Units. Because of increased wave speed along with severity of PH, pressure and wave morphology changes may also occur in pulmonary vascular disease with a purely distal site of increased PVR [53].

RIGHT VENTRICULAR REMODELLING

Right heart failure is caused by exposure to pressure overload of the right ventricle. Similar loading conditions in CTEPH and other types of PH have been discussed previously. Patient outcome is predominantly determined by the response of the right ventricle to this increased load [55]. Initially, the increase in pressure leads to an increase in wall stress causing an augmentation of wall thickness by increasing the muscle mass resulting in right ventricle hypertrophy. This increase in ventricular mass is predominantly the result of protein synthesis and an increase in cell size through the addition of sarcomeres. However, the right ventricle is not capable of sustaining a long-term pressure overload. Eventually, cardiac contractile force decreases resulting in right ventricular dilation. This dilation increases the wall tension which requires a higher oxygen demand and decreases the perfusion leading to a vicious circle of further compromised contractility and dilation [56]. Maladaptive neurohumoral signalling, oxidative stress and inflammatory responses may further accelerate the development of right heart failure, characterised by increasing filling pressures, diastolic dysfunction and diminished cardiac output. Pressure overload and right ventricular hypertrophy might also result in diastolic dysfunction of the left ventricle through ventricular interdependence and leftward septal displacement. The specific mechanisms underlying the transition from hypertrophy to dilation in right ventricular failure secondary to PH remain unclear [55].

The period between the episode of acute embolism, if known by the patient, and symptoms of CTEPH varies considerably from patient to patient [1]. Since the right ventricle needs time to adapt to the increased load, this variable time-course might explain the differences in right heart function seen between CTEPH patients. Some CTEPH patients only have mild symptoms and a preserved right ventricular function at the time of presentation despite having a high PVR, whereas others present with overt right ventricular failure despite a low PVR. This variation between patients in right ventricular adaptation might be more prominent in the CTEPH patient group than in PAH. Whether the right ventricular remodelling in CTEPH is, on average, different from other types of PH is unknown. The age of CTEPH patients at the time of presentation is, on average, higher than in most PAH subgroups, which might limit the right ventricle in its ability to remodel. Comparing magnetic resonance imaging data of the right ventricle of 17 CTEPH patients with operable disease showed identical data for PAP, stroke volume, right ventricular ejection fraction and mass than a cohort of 64 patients with idiopathic PAH reported by the same group [57, 58]. Another way to look for possible differences between right ventricular adaptation in CTEPH *versus* other types of PAH is to compare haemodynamics. If PAP is lower for a given PVR in CTEPH this provides evidence that right ventricular function is more impaired in CTEPH. To date, no studies have been specifically designed to investigate this question. Reported haemodynamic data from a study by QUARCK *et al.* [59] showed that PAP was, on average, lower in the CTEPH group than PAH (table 1). However, PVR was also lower in CTEPH in this study, although not significant. Comparing the haemodynamic data of randomised controlled trials performed exclusively in CTEPH, the BENEFIT trial [60], or solely in PAH, the BREATHE-1 study [61], a similar pattern was observed although PVR was, on average, different between both studies (table 1). However, there was a significant age difference between both studies. Thus, although reported haemodynamic data might suggest that right

TABLE 1 Demographic and pulmonary haemodynamic parameters in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

	PAH [59]	CTEPH [59]	BREATHE-1 [61]	BENEFIT [60]
Subjects n	104	79	213	157
Age yrs	58±15	62±14*	48±16	63±11
Females	66	62	79	65
PAP mmHg	50±13	45±11*	54±16	46±11
PVR dyn·s·cm^{-5}	850±397	804±381	970±630	702±328
CI L·min^{-1}·m^{-2}	2.42±0.81	2.19±0.53*	2.4±0.8	2.29±0.55

Data are presented as mean± SD or %, unless otherwise stated. PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance, CI: cardiac index. *: p<0.05 *versus* PAH, only available for [59].

ventricular adaptation is less in CTEPH than PAH, it is unknown whether these differences are explained by disease specific factors or age. Pump function graphs (right ventricle pressure *versus* stroke volume at steady state) or ventriculo-arterial coupling measurements (right ventricle pressure *versus* volume measurements over time) [62] in age-matched patients with both forms of PH, would help to solve this question but require invasive right ventricle pressure and volume tracings which are currently unavailable.

After PEA the right ventricle function improves, together with a reduction of right ventricular mass, size and strain [63]. PEA normalises interventricular asynchrony and right ventricular systolic wall stress. It has, however, been observed that this recovery is not complete [57, 64, 65]. Right ventricular mass measured by magnetic resonance imaging decreases significantly but does not completely normalise [57]. Moreover, the tricuspid annular plane systolic excursion initially deteriorates after PEA with an incomplete restoration after 1 yr of follow-up [64], although this acute post-operative deterioration could be explained by post-operative changes in global heart motion [66]. One explanation for these observations is recent evidence that right ventricle loading conditions are not normalised in CTEPH patients although PAP nearly normalised [48, 49]. After successful PEA with persistent exertional dyspnoea, patients display an abnormal pulmonary haemodynamic response to exercise, characterised by increased PVR and decreased compliance, which is an independent predictor of limited exercise capacity [48]. Thus, although intrinsic damage of the right ventricle cannot be excluded, the most likely explanation for persisting minimal structural and functional abnormalities of the right ventricle is increased load.

VESSEL OBSTRUCTION AND DEAD SPACE VENTILATION

Pulmonary gas exchange is determined by ventilation, perfusion and diffusion. Large vessel and cardiac remodelling are, therefore, expected to influence gas exchange in CTEPH. However, in spite of extensive vascular obstruction and obliteration, pulmonary gas exchange is generally well preserved in both PAH and CTEPH [67–72]. Patients with both idiopathic PAH and CTEPH usually present with only mild-to-moderate hypoxaemia, most often with hypocapnia, and cannot actually be differentiated on the basis of arterial blood gas analysis [67]. Measurements of ventilation/perfusion (V'/Q') distributions using the multiple inert gas elimination technique in both conditions generally show: preserved matching of V'/Q'modes; a mild to moderately increased perfusion to lung units with lower than normal V'/Q'; no or minimal pulmonary shunting; and no diffusion limitation [68–72]. The mean V'/Q'in both CTEPH and PAH is shifted to higher V'/Q'in relation to hyperventilation, which decreases the efficiency of gas exchange and increases physiologic dead space [73]. Anatomic dead space, or inert gas dead space defined by a $V'/Q' > 100$, remains normal or near-normal, and V'/Q'distributions do not usually exhibit higher than normal V'/Q'modes. When hypoxaemia occurs, it is mostly due to a low mixed venous oxygen tension as a result of low cardiac output at rest as well as at exercise, in the context of right ventricular failure. In some patients, hypoxaemia is caused by right-to-left shunting through a patent foramen ovale [70]. Arterial hypocapnia is typically present in both PAH and CTEPH. Hypocapnia in PAH has been shown to be associated with a decreased survival [74].

Patients with either PAH or CTEPH hyperventilate at rest and during exercise. Hyperventilation in both conditions cannot be explained by arterial hypoxaemia. Hyperventilation causes the Bohr physiological dead space calculation to increase, because of disproportionate effects on arterial and mixed expired carbon dioxide tension. Therefore, it is difficult to evaluate the respective contributions of wasted ventilation and chemosensitivity to increased ventilation in patients with idiopathic PAH and CTEPH. This problem can be explored by plotting ventilatory equivalents for carbon dioxide (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2})) at exercise as a function of arterial carbon dioxide tension (P_{a,CO_2}) or end-tidal carbon dioxide tension (P_{ET,CO_2}) during exercise [75]. ZHAI *et al.* [76] recently reported on these measurements in 50 patients with CTEPH and 77 patients with PAH. Physiological dead space at maximal exercise and V'_E/V'_{CO_2} as a function of P_{a,CO_2} were increased in CTEPH compared to PAH (fig. 5), but the difference disappeared when V'_E/V'_{CO_2} was expressed as a function of P_{ET,CO_2}; thus, it is strongly suggestive of a contribution of increased dead space ventilation in CTEPH. It is of interest that V'_E/V'_{CO_2} *versus* P_{ET,CO_2} or P_{a,CO_2} in PAH patients conformed to the alveolar ventilation equation, which, together with hypocapnia, shows the major contribution of increased chemosensitivity in this condition. However, figure 5 shows a considerable overlap, so that individual discrimination between CTEPH and PAH on the basis of gas exchange and ventilatory measurements is not possible.

CONCLUSION

In CTEPH, vascular obstruction is originally proximal with some distal remodelling as a consequence of prolonged overperfusion. Accordingly, there is proportionally more wave reflection in CTEPH than in PAH, impacting on pressure and

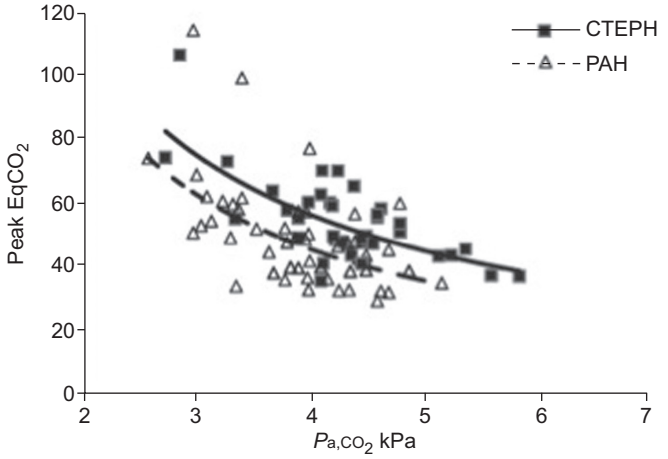

FIGURE 5. Ventilatory equivalent for CO_2 ($EqCO_2$) as a function of arterial carbon dioxide tension (P_{a,CO_2}) during exercise in patients with either chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH). Increased minute ventilation/carbon dioxide production at lower P_{a,CO_2} reflects increased chemosensitivity but P_{a,CO_2} is higher in CTEPH, indicating a contribution of dead space to increased ventilation. Reproduced from [76] with permission from the publisher.

flow wave morphology. However, the arterial load in CTEPH and PAH is not different. Whether right ventricular function adaptation to afterload is different in PAH *versus* CTEPH is currently unknown and should be explored using pump function graphs and ventriculo-arterial coupling measurements. Finally it seems that large vessel obstruction in CTEPH could cause more dead space ventilation than in PAH.

STATEMENT OF INTEREST

Statements of interest for M. Delcroix, A. Vonk-Noordegraaf, I. Lang, G. Simonneau and R. Naeije can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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