

## Chronic Thromboembolic and Pulmonary Arterial Hypertension Share Acute Vasoreactivity Properties

a report by

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Structural and functional changes in the vascular wall and thrombus formation are the main factors responsible for increased pulmonary vascular resistance in patients with pulmonary hypertension (PH).<sup>1,2</sup> The contribution of each of these factors is thought to be different among the variable underlying causes of PH, thereby accounting for varying response to vasodilative and antiproliferative agents in PH of different aetiology.<sup>3</sup> Accordingly, pulmonary vasodilators have been used primarily for patients with pulmonary arterial hypertension (PAH) and less for those with chronic thromboembolic pulmonary hypertension (CTEPH) because of the notion that the fibrous organisation of thrombotic material in the proximal vessel wall would block the vasodilator effect.

Nakayama and co-workers suggested the use of pulsatility indices to distinguish between proximal and distal pulmonary arterial involvement.<sup>4</sup> They showed that patients with CTEPH have higher pulmonary artery pulse pressures (PP = systolic minus diastolic pressure) and lower mean pulmonary artery pressures (MPAP) compared with patients with PAH, suggesting decreased proximal pulmonary arterial compliance and a less pronounced distal vessel involvement.<sup>4</sup> However, these haemodynamic differences could not be confirmed in a recent cohort.<sup>5</sup> Castelain et al. explained their results by a secondary increase in vascular resistance at the level of small pulmonary arteries in end-stage CTEPH, and suggested a common pathophysiological mechanism between end-stage CTEPH and end-stage PAH. This new theory is supported by histological examination of small pulmonary vessels of CTEPH patients,<sup>6</sup> which indicates that the morphology of the vessels not affected by thrombotic occlusion is similar to that of PAH, as well as by recent clinical trials that show a favourable effect of vasodilator treatment not only in patients with PAH but also in those with CTEPH.<sup>7-9</sup>

To test this new concept, the authors conducted acute vasoreactivity testing using inhaled nitric oxide (iNO) and inhaled iloprost (iILO) in 35 patients with PAH and 25 patients CTEPH (World Health

Organization (WHO) class III-IV) during their initial diagnostic right heart catheterisation.<sup>10</sup>

The authors found that inhalation of iNO and/or iILO during initial diagnostic right heart catheterisation decreases MPAP and increases cardiac index (CI) in patients with CTEPH and PAH in WHO functional classes III-IV, the magnitude of the response as well as the number of responders being not different between CTEPH and PAH. Patients with PAH and CTEPH also had similar indices of proximal pulmonary arterial compliance. These results suggest that CTEPH and PAH may share some pathophysiological characteristics, which probably involve both the proximal and the distal pre-capillary pulmonary arteries.

Previous studies in patients with PAH have shown that iNO and iILO decrease MPAP on average by 9%, increase cardiac output by 5-8% and decrease PVR by 18%.<sup>11-14</sup> The authors found a similar extent of vasodilator effect of these agents in their patients. However, despite a similar effect on MPAP and CI, in the authors' study more patients tested with iILO could be identified as responders than using iNO, this independently of the criterion used to distinguish between vasoreactivity testing responder and non-responder. Inhalation with iILO predicted a positive response to iNO in 75% of patients; conversely, inhalation with iNO identified only 25% of the iILO responders. Whether this difference between iNO and iILO is of clinical relevance for the small number of responders in this and other studies<sup>11,15-17</sup> remains to be established. Until then, vasoreactivity testing with either single agent is considered sufficient in the baseline evaluation of patients with PH.<sup>18</sup>

It is remarkable that in our cohort, the acute vasodilator response between patients with major vessel CTEPH and PAH was not different. Acute response to various vasodilators has been widely investigated in patients with PAH,<sup>1,11,13,17-22</sup> but not in patients with CTEPH. Comparable acute haemodynamic responses have been reported for different PAH subclasses,<sup>23</sup> and were attributed to qualitatively similar histopathological vascular

characteristics between subclasses<sup>24</sup> mainly located in the distal pulmonary vascular bed with a higher capacity to vasodilate. In recent years, a better understanding of the mechanisms responsible for elevated pulmonary arterial pressure and vascular resistance in the different types of PH has led to the suggestion that the thromboembolic and non-thromboembolic types of PH may share common pathophysiological features.<sup>25</sup> This concept is supported by data indicating that the mechanisms leading to pulmonary hypertension in patients with repeated pulmonary thromboembolic events are not only mechanistic (non-recanalised thrombotic vessel occlusion),<sup>26,27</sup> but possibly also related to vascular remodelling located distal to the occluded artery<sup>28</sup> and in non-involved adjacent pulmonary vessels<sup>6</sup> may lead to endothelial dysfunction. The vascular lesions in this non-involved vessel segment were histologically indistinguishable from those in PAH.<sup>6</sup> In line with this concept are observations that almost half of patients with CTEPH do not have a history suggestive of acute pulmonary thromboembolism, and that only 45% have findings suggestive of previous venous thrombosis on lower extremity duplex ultrasound.<sup>29</sup> In addition, the incidence of hereditary thrombophilia seems not to be increased in patients with CTEPH.<sup>30,31</sup> Central pulmonary artery thrombi have been shown to occur also in patients with PAH.<sup>32</sup> In line with an active vascular remodelling process in CTEPH are studies reporting the successful use of oral and inhaled vasodilators in patients with CTEPH.<sup>7-9</sup> Thus, our results indicating a similar acute vasodilator response in patients with CTEPH and PAH support this new concept and encourage future vasodilator trials also in selected patients with CTEPH who are waiting for thrombendarterectomy, or who are not operable or have major contraindication for surgery, many of whom suffering from a very restricted quality of life with dismal prognosis.

The primary objective of acute vasodilator testing in patients with PAH is to identify the subset of patients who might be treated effectively with oral calcium-channel blockers. However, this drug class will probably never be a valuable therapeutic option

in patients with CTEPH due to its capacity to increase ventilation perfusion mismatch and thus intrapulmonary shunting.<sup>14,33-36</sup> In patients with PAH, a pronounced response to short-acting pulmonary vasodilators has been shown to be associated with a better prognosis at least in some patients.<sup>37,38</sup> However, vasoreactivity testing has not been recommended for the assessment of long-term prognosis because of great inter-individual variability. This view might be strengthened by the authors' study results, which fail to show an association between acute vasodilatation response and change in functional class or six-minute walk distance (6MWD) three and twelve months after initiation of long-term vasodilator therapy in both CTEPH and PAH patients. The authors' findings also indicate that neither a structural difference between CTEPH and PAH nor the baseline vasodilator reserve are indicators of long-term treatment response. Thus, there is no rationale to perform vasoreactivity testing at baseline evaluation in CTEPH patients as well. But these findings have to be interpreted with caution, as the present study was not designed to answer questions concerning the relationship between acute vasoreactivity and long-term response to vasodilative treatment, as individual treatment strategies after the acute assessment differed considerably, not allowing a formal correlation study. Further, the results of the present study have to be interpreted with caution as, for logistical reasons, the design was not randomised and placebo controlled and investigators were not blinded concerning the patients' medical records and history. This study, however, provides a rationale for future studies sufficiently powered and designed to answer these clinically important questions.

In summary, in the present study it was shown that, despite obvious differences between CTEPH and PAH, both entities share similar acute vasoreactivity properties and vessel compliance indicating some common pathogenetic pathways and thus giving a rationale for long-term vasodilator and antiproliferative strategies, also in patients with inoperable CTEPH. ■

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