Low diffusing capacity for carbon monoxide in chronic thromboembolic pulmonary hypertension: a biomarker for microvascular disease?

Christian Gerges,[1] Hiromi Matsubara,[2] Irene Lang [1]

Chronic thromboembolic pulmonary hypertension (CTEPH) is a complex pulmonary vascular disorder that involves major vessel and microvascular disease components. Fibrotic obstructions resulting from unresolved pulmonary emboli constitute the major vessel disease component. Major vessel disease is subject to mechanical treatments such as surgical pulmonary endarterectomy (PEA) and balloon pulmonary angioplasty (BPA). Secondary microvascular disease in CTEPH is characterised by remodelling of small arteries resembling pulmonary arterial hypertension (PAH), predominantly in non-occluded vascular territories.[1 2] Moreover, venous remodelling in occluded vascular territories due to bronchopulmonary venous shunting has been documented at the microvascular level.[1 2] Secondary microvasculopathy of CTEPH forms the pathophysiological basis for pulmonary hypertension-targeted medical therapies given for CTEPH. Microvascular disease plays a crucial role in the development of persistent pulmonary hypertension and confers a worse prognosis.[2]

Different techniques have been proposed to assess microvascular disease in CTEPH: (1) Imaging of poor subpleural perfusion during pulmonary angiography has been suggested as a sign of thrombotic microvascular obstruction.[3] However, poor subpleural perfusion may also be due to proximally located chronic thromboembolic lesions that restrict flow to distal vessels. Moreover, poor subpleural perfusion may be caused by competitive flow through arterial collaterals to distal pulmonary arteries or veins. (2) Acute vasoreactivity testing with inhaled nitric oxide has been suggested as a functional test to assess microvascular function in patients with CTEPH.[4] However, its correlation with the degree of histologically confirmed microvascular disease has not been demonstrated. (3) The pulmonary artery occlusion technique has been developed to partition pulmonary vascular resistance into a major vessel upstream component and a microvascular downstream component. A lower upstream and increased downstream resistance have been demonstrated to correlate with the extent of microvascular disease on histology[2] and to predict haemodynamic outcome and prognosis after PEA.[2]

Minatsuki and colleagues[5] introduce the diffusing capacity of the lung for carbon monoxide (DLCO) as a potential new biomarker of microvascular disease in CTEPH. The study investigated the influence of DLCO on treatment response to BPA in 75 patients with CTEPH. Authors hypothesised that patients with low DLCO should benefit less from BPA because the diameter of the smallest balloon is at least 10 times larger than an average microvessel. In support of this concept is that DLCO inversely correlated with the need to start pulmonary vasodilator therapy after PEA in the Papworth series.[6]

The single-breath technique for assessing DLCO was pioneered over a century ago by Marie and August Krogh.[7] Physiologically, their method elucidated the passive diffusion of oxygen from the gas phase to blood by extrapolating from their observation with carbon monoxide (CO). In 1957, Ogilvie and colleagues[8] standardised the clinical application of the Krogh single-breath method using a tracer gas to determine both the alveolar volume and the alveolar concentration of CO at the onset of breath-holding. The capacity of the lungs to exchange gas across the alveolar–capillary interface is determined by its structural and functional attributes. Pulmonary vascular diseases characterised by significant involvement of capillaries and venules are known to cause a marked decrease in DLCO. For instance, in pulmonary veno-occlusive disease (PVOD), which is characterised by extensive remodelling of pulmonary venules and capillaries, DLCO is typically reduced below 55% of the predicted value. In contrast, DLCO tends to remain normal or only mildly reduced in the majority of patients with idiopathic PAH, which primarily affects the pre-capillary small arterial compartment.[9] However, a DLCO ≤45% may be observed in ~30% of patients with idiopathic PAH and has been linked with a higher age at diagnosis, history of smoking and worse survival.[9] A severe reduction in DLCO in the presence of otherwise normal pulmonary function tests can be found in PAH with systemic sclerosis, which is often accompanied by PVOD.

Similar to idiopathic PAH, DLCO is either normal or only mildly reduced in the majority of patients with CTEPH. However, CTEPH involves various vascular compartments such as major pulmonary arteries that are obstructed by fresh red and organised thrombus, microvasculopathy resembling PAH, microvascular thrombus and microvascular venous remodelling resembling PVOD.[1 2] Venous remodelling in CTEPH is believed to be uncommon and may result from high shear stress induced by bronchopulmonary venous shunting.[1] A histological study by Dorfmüller and colleagues revealed that patients with persistent PH after PEA (labelled as 'ineffective PEA'; n=9) exhibited intimal fibrosis of small pre-septal venules and larger septal veins, as well as pulmonary capillary hemangiomatosis-like foci, representing a CTEPH phenotype with PVOD characteristics. These patients demonstrated a low DLCO of 61±5% predicted. For comparison, the mean DLCO in the French BPA registry was 61.2±13.6% for the entire cohort.[10] Previous series testing the predictive value of DLCO for outcomes in CTEPH have indicated thresholds of 67%[6] or 54% (own series).

Minatsuki and colleagues propose a significantly higher cut-off value for identifying patients with microvascular disease in CTEPH. They categorised patients into low and normal DLCO groups based on a DLCO ≤80% predicted, corresponding to the lower limit of normal. Consequently, approximately half of their patient cohort (36/75, 48%) was classified as having a low DLCO, and thus, a significant microvascular disease component. Both groups showed a significant improvement in haemodynamics and exercise capacity after BPA, although the impact on mean pulmonary artery pressure and pulmonary vascular resistance was less pronounced in the low DLCO group.

[1]Department of Internal Medicine II, Division of Cardiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria
[2]Department of Cardiology and Department of Clinical Science, National Hospital Organization, Okayama Medical Centre, Okayama, Japan

Correspondence to Dr Irene Lang, Cardiology, University Hospital Vienna, Austria, Vienna, Austria; irene.lang@meduniwien.ac.at

In summary, the authors' hypothesis is supported by their observation that in patients with low DLCO the effect of BPA on mPAP and PVR was reduced; however, numbers are small, DLCO thresholds are high and no further technique was employed to substantiate the presence of microvascular disease in patients with low DLCO. Authors should consider the opposite hypothesis that BPA may exert a reverse remodelling effect on secondary microvasculopathy by effectuating a substantial decrease of mPAP and increases in arterial oxygen saturation. Whether successful mechanical treatments may reverse microvascular disease needs to be rigorously studied using upstream resistance measurements.[2] Today, mechanical treatments of CTEPH have become extremely successful, alone or in combination, leading to superior 3-year survival rates well above 90%, and suggesting that in the majority of cases, microvascular disease is overcome.

Contributors IL, HM and CG discussed the planning, conduct, reporting, conception and design, acquisition of data and analysis of the manuscript under discussion and decided together the interpretation of data. The editorial was written over several rounds by IL and CG and reviewed and commented by HM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

OPEN ACCESS

To cite Gerges C, Matsubara H, Lang I. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2024-324237

► http://dx.doi.org/10.1136/heartjnl-2024-323883

Heart 2024;**0**:1–2. doi:10.1136/heartjnl-2024-324237

ORCID iD
Irene Lang http://orcid.org/0000-0003-0485-2692

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