Pulmonary hypertension associated with left heart disease: efforts to improve the meaning of haemodynamic phenotypes

To the Editor:

We read with great interest the recent article by Gerges et al. [1] on partitioning pulmonary vascular resistance (PVR) at baseline and after inhaled nitric oxide (iNO) in patients with pulmonary hypertension associated with left heart disease (PH-LHD). The study highlighted that the increase of right ventricular (RV) afterload in isolated post-capillary PH (Ipc-PH) primarily depended on a passive backward transmission of left ventricular filling pressure and left atrial (LA) function, explaining the very high upstream resistance ($R_{up}$). Further afterload increase secondary to an elevated vessel resistance in combined post- and pre-capillary pulmonary hypertension (Cpc-PH), was associated with a lower $R_{up}$ similar to that seen in idiopathic pulmonary arterial hypertension (iPAH) patients.

Pulmonary vascular disease (PVD) in PH-LHD in patients with heart failure is associated with a prevalence of pulmonary veins, capillaries and distal muscular pulmonary arteries (PAs) remodelling [2, 3]. Current dogma suggests that decreased pulmonary arterial capacitance (PAC) in pulmonary hypertension (PH) is a consequence of distal proliferative PVD. We have shown that Ipc-PH patients with PVR and diastolic pulmonary gradient (DPG) within normal limits have a significant increase in area wall thickness and stiffening of proximal PA, and impairment of RV-to-pulmonary arterial coupling, suggesting the presence of early PVD and questioning the definition of “passive” PH-LHD [4]. We speculate that the presence of proximal PA wall disease in addition to the passive upstream transmission of elevated LA pressure may explain the significant lower PAC in Ipc-PH patients. The elevation of PVR and DPG would occur later with further reductions in PAC associated with distal PVD, as seen in Cpc-PH patients [4].

The definition of PH-LHD haemodynamic phenotypes is a matter of debate. The Ipc-PH and Cpc-PH phenotypes defined in the most recent 2015 ESC/ERS guidelines [5] have been challenged due to their controversial prognostic role and the ambiguous classification of a significant proportion of patients [6]. Both the stationary (PVR) and the pulsatile (PAC) components of afterload exhibit an inverse hyperbolic relationship. The product of resistance and compliance (RC-time) is mostly constant in both healthy and diseased states, with the exception of a few clinical scenarios like elevated left-sided filling pressures, proximal chronic thromboembolic PH (CTEPH) and heart rate (HR) increase. In all these cases, PAC decreases proportionally more than the increase in PVR, RC-time decreases and the R-C curve shifts downwards left [7, 8].

We have previously proposed an original dimensionless haemodynamic index, upstream impedance ($Z_{up}$) ($(TPG-DPG)/TPG$) (where TPG is transpulmonary gradient), that enables the characterisation of the broad spectrum of dynamic afterload and predicts early outcome after pulmonary endarterectomy for CTEPH [9]. Replacing mean pulmonary arterial pressure (mPAP) with $(sPAP+2dPAP)/3$ (where sPAP and dPAP are systolic and diastolic PAP, respectively) in the numerator and with $PVR \times SV \times HR + PAOP$ (where SV is systolic volume and PAOP is pulmonary arterial occlusion pressure, end-expiratory automated digital mean measurements across the cardiac cycle) in the denominator, $Z_{up}$ is inversely

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Upstream impedance could characterise the RV afterload and the relative contribution of large and small vessel disease in PH, regardless of the PAOP, including the inverse relationship with HR as an indirect RV functional response http://ow.ly/fqvN30nbNFo

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In PH states, the greater increase of pulsatile to the stationary component of RV afterload determines elevated PA pressures with a large pulse pressure or “ventricularisation” and higher Zup values [10]. We hypothesised that Zup could characterise the relative contribution of large and small vessels disease through its differential impact on the afterload components in PH states, regardless of the PAOP. We compare Zup values in patients with PH-LHD (post-capillary PH), and operable CTEPH and iPAH (pre-capillary PH).

We can see that Zup values are higher in post-capillary PH than pre-capillary PH, which is probably due to the greater pulsatile afterload associated with higher PAOP and lower HR. In pre-capillary PH, the more proximal occlusive site causes a higher PA stiffness and an earlier and greater wave reflection, increasing total PVR but with a lower dPAP and PAC and a higher Zup in operable CTEPH than in iPAH. Similarly, among post-capillary PH, the presence of proximal PVD determines the Pac decrease and the highest Zup in Ip-PH patients. The elevation of PVR and DPG with more reductions in PAC associated with distal PVD, would explain the lower Zup of Cpc-PH than Ip-PH. Despite the fact that the PA wall stiffness and the haemodynamic profile of Cpc-PH patients are very similar compared to historical patients with PAH, Zup is significantly higher, which is likely to be due to lower HR and the post-capillary condition (figure 1) [4, 11].

We observed substantial haemodynamic improvements in Cpc-PH patients after iNO administration [4] according to GERGES et al. [1]. The improved RV afterload with a concomitant 8% of Rup increase, indicates a decrease of distal PVR [1, 4].

GERGES et al. [1] proposed DPG as a surrogate of Rup, which is debatable, since while Rup corresponds to small PAs and arterioles resistances, DPG (>7 mmHg) defines the presence of PVD associated with the increase of pulsatile and/or stationary components of RV afterload.

In conclusion, GERGES et al. [1] have made an “in-depth” effort to link haemodynamics to PVD by partitioning the stationary component of the RV afterload in PH-LHD patients. We can speculate that Zup could provide a simple haemodynamic tool to characterise the different spectrum of RV afterload and the relative contribution of large and small vessel disease in PH states regardless of the PAOP, including the inverse relationship with HR as an indirect RV functional response.

Subjects n | Ipc-PH | Cpc-PH | CTEPH | iPAH
---|---|---|---|---
mPAP mmHg | 32±4 | 44±12# | 48±14# | 47±10#
PAP mmHg | 22±4 | 19±2 | 9±3# | 8±3#
CI L·min⁻¹·m⁻² | 2.3±0.5 | 2.0±0.5 | 2.5±0.5# | 2.3±0.6
HR bpm | 60±14 | 60±11 | 80±10# | 75±11#\+
DPG mmHg | -1.8±3.0 | 7.9±5# | 18±11# | 22±9#\+
TPG mmHg | 10±2 | 26±10# | 40±15# | 39±10#\+
PVR Wood unit | 2.5±0.6 | 8.5±3.4# | 8.8±4.9# | 10.6±4.7#\+
PAC mL·mmHg⁻¹ | 2.0±0.4 | 1.1±0.6# | 0.9±0.5# | 1.1±0.5#\+
RC-time s | 0.3±0.06 | 0.55±0.22# | 0.52±0.16# | 0.73±0.22#\+
Zup % | 113±30 | 70±25# | 55±16# | 40±13#\±
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the subgroup of 30 patients with available invasive haemodynamic data, thus resembling the haemodynamic phenotype of Ipc-PH. Application of these data are therefore limited to Ipc-PH and cannot be applied to Cpc-PH.

Our recent manuscript in the *European Respiratory Journal* demonstrates that in Cpc-PH effective capillary pressure ($Pc'$), which reflects the pressure in pre-capillary small pulmonary arteries and pulmonary capillaries, is significantly higher than mean pulmonary arterial wedge pressure (mPAWP), resulting in a decrease in upstream resistance ($R_{up}$) [1]. In contrast, $Pc'$ and mPAWP are at the same level in Ipc-PH, leading to a high $R_{up}$, close to 100%. These results are in line with our previous observations from histomorphometric analyses of lung samples from PH-LHD patients, where arteriolar changes were most pronounced in patients with Cpc-PH [3]. $R_{up}$ may therefore be used to provide haemodynamic proof of pre-capillary pulmonary vascular disease. However, this needs to be tested in further studies.

J.C. Grignola and colleagues propose upstream impedance ($Z_{up}$), a composite haemodynamic index, which is thought to assess pulsatile and steady components of right ventricular (RV) afterload simultaneously. The clinical metric most often used to assess RV afterload is PVR. However, even when measured from multiple points derived from pressure–flow curves during exercise, PVR provides only information on peripheral arterial function, but not on proximal arterial function, and gives an incomplete description of all the forces that oppose RV flow output [4]. Pulmonary vascular impedance spectra (PVZ) capture the impact of proximal and peripheral arterial structure and function on RV function. PVZ is a complex, frequency-dependent function of pulsatile pulmonary pressure and flow that is sensitive to changes in proximal, intermediate and peripheral pulmonary arterial resistance and compliance. Typically, Fourier series analyses are performed to calculate PVZ from pressure and flow waves measured at a single location in the pulmonary circulation. J.C. Grignola and colleagues propose that $Z_{up}$ may be a simple alternative to complex and cumbersome PVZ calculations potentially applicable in clinical routine. However, there is a lack of studies that have confirmed that $Z_{up}$ is indeed related to impedance of the pulmonary circulation via simultaneous assessment. Furthermore, it has not been demonstrated that $Z_{up}$ truly correlates with the pulmonary vascular changes to which J.C. Grignola and colleagues refer.

Interestingly, the proposed formula for the calculation of $Z_{up}$ is strikingly similar to the $R_{up}$ formula:

$$Z_{up} = \frac{mPAP - dPAP}{mPAP - mPAWP}$$

$$R_{up} = \frac{mPAP - Pc'}{mPAP - mPAWP}$$

where mPAP is mean pulmonary artery pressure and dPAP is diastolic pulmonary artery pressure.

As can be seen above, the only difference between the two formulae is that $Pc'$ is substituted by dPAP. Indeed, as already hypothesised by CHEMLA *et al.* [5], $Pc'$ is within the limits of dPAP and mPAWP. In healthy subjects or patients with Ipc-PH, where the dPAP–mPAWP gradient is small [1], $Pc'$ may be theoretically substituted by dPAP. However, pre-capillary pulmonary vascular disease may alter the validity of this assumption, with dPAP and $Pc'$ being significantly above mPAWP [1]. We found that in patients with idiopathic pulmonary arterial hypertension, estimation of $Pc'$ using dPAP lacked precision and accuracy (bias 8.7 mmHg, limits of agreement from −4.3 to 21.7 mmHg). Hence, despite similar formulae, $Z_{up}$ cannot replace $R_{up}$ for the assessment of upstream and downstream resistance.

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