Will we be singing a different tune on combined post- and pre-capillary pulmonary hypertension?

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There have been many well-intended pursuits in medicine that should have panned out, but did not. Case in point: premature ventricular complexes (PVC) post-myocardial infarction were noted to be associated with increased risk of death, and thus the Cardiac Arrhythmia Suppression Trial (CAST) Study investigated if pharmacological PVC suppression with class I anti-arrhythmics would reduce the rate of arrhythmic death [1]. Surprisingly, the study showed that although PVCs were successfully suppressed, there were excess deaths due to arrhythmia and shock in such patients treated with encainide or flecainide [1].

Perhaps along similar lines, there is on-going controversy regarding the treatment of group II pulmonary hypertension (PH), or PH due to left heart disease (PH-LHD). Group II PH is defined by a mean pulmonary artery pressure (mPAP) of ⩾25 mmHg with a pulmonary artery wedge pressure (PAWP) of >15 mmHg. However, a subset of these patients also have a pre-capillary component, defined by a diastolic pulmonary gradient (DPG) ⩾7 mmHg and/or pulmonary vascular resistance (PVR) >3 Wood units (WU) [2]. Combined post- and pre-capillary PH (CpcPH) is not only common in group II PH [2], but numerous studies have shown it confers increased risk of mortality in the LHD population beyond isolated post-capillary PH (IpcPH) [3, 4]. Enticingly, multiple pulmonary vasodilator therapies exist for the treatment of pre-capillary PH associated with group I pulmonary arterial hypertension (PAH). Whether such therapies should be used to treat the pre-capillary component of PH-LHD remains the topic of much debate [5].

There exists a strong pathobiologic rationale for therapeutically targeting CpcPH with PAH-specific drugs. In the setting of passive increases in pulmonary pressure in PH-LHD, endothelial dysfunction leads to reduced nitric oxide, enhanced endothelin-1, pulmonary arterial vasoconstriction [6], and even pulmonary arterial remodelling [7, 8]. Recently, Assad *et al.* [9, 10] found patients with CpcPH had a genetic profile that more closely resembled that of PAH than of IpcPH. In support of treatment, some relatively small studies using prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE5) inhibitors have shown acute improvement in symptoms, haemodynamics, and exercise capacity [5]. The PDE5 inhibitor sildenafil has the most supportive data, with several single-centre, randomised controlled

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trials showing an improvement in exercise haemodynamics and functional capacity in LHD populations with and without PH [11–13], alongside other studies demonstrating reductions in PVR in patients awaiting heart transplant or after mechanical circulatory support [14, 15].

Data also exist to the contrary. The aforementioned sildenafil trials should be interpreted with caution, as all were single-centre trials. The multicentred PhosphodiesteRasE-5 Inhibition to Improve CLinical Status and EXericse Capacity in Diastolic Heart Failure (RELAX) trial did not find improvement in peak oxygen consumption after 12 weeks of sildenafil treatment in patients with heart failure with preserved ejection fraction (HFpEF) [16], many of whom had PH. Other PAH drugs including epoprostenol and bosentan have been studied in LHD with disappointing or adverse results [17, 18], with bosentan notable for causing increased oedema [18].

However, although results are mixed for the use of PAH-specific therapies in PH-LHD, it would be hard to discount their use in CpcPH altogether. It has been difficult to interpret PAH-specific treatment studies in LHD and PH-LHD since many have studied heterogeneous populations or lacked a haemodynamic diagnosis of PH-LHD upon enrolment [5]. If the totality of these studies to date have taught us anything, it is that CpcPH and IpcPH are very different entities, as are heart failure with preserved and reduced ejection fraction (HFrEF), and that the successful study of these entities requires invasive haemodynamic confirmation.

The Macitentan in subjects with combined prE- and post-capiLlary pulmonary hypertension due to left ventricular DYsfunction (MELODY-1) trial, a phase II study reported in this issue of the *European Respiratory Journal*, is thus immensely important in the field [19]. It is the first study to look at the use of an ERA specifically in patients with CpcPH, and one of the few PH-LHD trials to require invasive diagnostic confirmation. With these characteristics alone, MELODY-1 defines its study cohort better than the vast majority of existing PH trials in PH-LHD. In this study, Vachiery and colleagues enrolled 63 patients across multiple sites and continents into a randomised, double-blind, placebo-controlled trial of macitentan *versus* placebo for the treatment of CpcPH in LHD. Patients were formally defined with CpcPH using right heart catheterisation to document mPAP $\geqslant$25 mmHg, PAWP >15 mmHg, and PVR $\geqslant$3 WU and DPG $\geqslant$7 mmHg. Although it was a phase II study primarily focused on safety end-points (namely, fluid retention or change in functional capacity), the authors also looked at exploratory secondary end-points of efficacy, most notably change in PVR. Overall, they find a non-statistically significant increase in fluid retention in the macitentan arm, as well as a higher number of patients who discontinued study treatment in the macitentan arm. Perhaps most notably, they did not find a significant different in PVR after 12 weeks of treatment, with a similar decrease noted in both arms.

Several important strengths of this study merit highlighting. First, the authors required an invasive haemodynamic diagnosis of CpcPH as well as post-treatment haemodynamic measures, which in itself is a significant undertaking. How to define CpcPH haemodynamically remains debated [20], yet impressively, the carefully designed inclusion and exclusion criteria led to enrolment of a cohort that clearly had significant CpcPH, with an average PVR of 5.8 WU, TPG of 27 mmHg, and DPG of 10 mmHg. As such, the conclusions we can glean from MELODY-1 surpass those that can be made from similar prior studies. In this context, it is important to note, and perhaps disappointingly so, that PVR did not decrease in the macitentan arm, and actually decreased similarly in both arms. Although a phase II study would be underpowered to detect differences, it is striking that macitentan failed to show even a trend of lowering PVR. Perhaps its mechanism of action is not optimal for lowering PVR in a CpcPH cohort, yet we also recall that in the RELAX study, sildenafil also failed to lower total right ventricular afterload [21]. The reason for PVR decrease in the control arm is also unclear, but vascular decongestion from heart failure therapy alone can reduce PVR [22], and perhaps trial enrolment led to more rigorous heart failure assessment and treatment in the placebo group. Any PVR conclusions are made with the phase II caveat, but the rigorous definition of CpcPH and the near absence of signal would argue this is still worth noting.

The other important item to note is the increased fluid retention and functional decline in the macitentan arm. Although macitentan theoretically has less propensity for fluid retention than bosentan [23], the fact that a signal was noted in a small study are relevant in light of the ENABLE study, which noted, in a much larger cohort, significantly greater fluid retention in the first 2 to 4 weeks of bosentan [18]. In MELODY-1 study there was a 10% greater rate of fluid retention or worsening functional capacity in the macitentan arm, coupled with a significantly greater rate of treatment discontinuation for any reason. Such data will be important to bear in mind with future ERA studies in PH-LHD. These results also remind us that the use of PAH-specific therapies in PH-LHD should only be in the context of clinical trials, as duly noted by the authors.

The odds were perhaps stacked against finding benefit for macitentan, as it was not powered for such. Macitentan was also studied here in a primarily older HFpEF cohort, with concomitant high proportions

of obesity, hypertension, and atrial fibrillation, which are comorbidities that can worsen right ventricular-pulmonary vascular coupling and make the search for treatment benefit difficult. Macitentan may still prove more useful in a larger cohort of CpcPH, or in specific CpcPH or LHD sub-populations. For instance, patients with scleroderma and LHD may also suffer from concomitant group I PAH pathology, and it remains to be seen if they could benefit from PAH specific therapy [24].

Thus, the present study raises some important caution to the notion of using ERAs for the treatment of CpcPH in PH-LHD. The lack of therapeutic benefit (no PVR decline) coupled with potential harm (increase in fluid retention) sounds similar to the failed experiments of anti-arrhythmics in post-myocardial infarction arrhythmia. That said, while the current results may be disheartening, not all hope is lost for the use of PAH-specific therapies in PH-LHD. More work remains to be done in the study of macitentan as well as other PAH-specific therapies in PH-LHD. The most important aspect of MELODY-1 is that by rigorously defining CpcPH using right heart catheterisation, the authors set a new standard in the design and interpretation of pulmonary vasodilator studies in PH-LHD. This standard will hopefully inform the design of future studies to come.

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