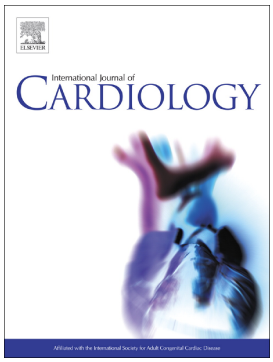

Pulmonary hypertension in left heart disease: The need to continue to explore

Stefano Ghio, Michele D'Alto, Roberto Badagliacca, Carmine Dario Vizza

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Pulmonary hypertension in left heart disease: the need to continue to explore.

Ghio Stefano [a], D'Alto Michele [b], Badagliacca Roberto [c], Vizza Carmine Dario [c].

a Dept. of Cardiology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

b Dept. of Cardiology, University "L. Vanvitelli" – Monaldi Hospital, Naples, Italy

c Pulmonary Hypertension Unit, Dept. of Cardiovascular and Respiratory Science, "Sapienza" University of Rome, Italy

Corresponding author:

Stefano Ghio

Divisione di Cardiologia

Fondazione IRCCS Policlinico S Matteo

27100 Pavia, Italy

Mail address: s.ghio@smatteo.pv.it

Pulmonary hypertension (PH) in left heart disease (LHD) is a challenge for cardiologists: in a setting of left ventricular dysfunction, the coexistence of PH and right ventricular dysfunction is known to be associated with very poor prognosis and limited efficacy of conventional medical treatments. This might explain why the off-label use of drugs specific for pulmonary arterial hypertension is quite diffuse in clinical practice in PH-LHD, despite randomized clinical trials do not provide evidence of their efficacy in such patients (1).

This topic has been addressed by two manuscripts published in the present issue of the IJC, which are seemingly in sharp contrast with each other.

The first one, by Cao et al, is a meta-analysis (2) including ten randomized, placebo controlled trials comprising 777 patients. Overall, right heart hemodynamics showed a trend towards improvement; however, clinical events such as all-cause mortality, cardiovascular mortality and worsening heart failure were higher in treated patients as compared to control groups (albeit not statistically significant). The conclusion was that PAH active drugs have an unfavourable effect in this setting.

What arises from this meta-analysis is the heterogeneity of the populations included in the different studies, in terms of different aetiologies of LHD (systolic dysfunction, diastolic dysfunction, valve disease), different severity and type of PH (including both patients with isolated post-capillary PH (Ipc-PH) and combined pre-post capillary PH (Cpc-PH)) and poor characterization of right ventricular (RV) function. The latter point is of particular interest, since RV dysfunction is the most important independent prognostic factor in advanced LHD, and the main objective of a pulmonary vasodilator drug should be the reduction of RV afterload to improve RV function (3). In other words, we may not expect a huge clinical benefit treating patients with mild PH and trivial RV dysfunction.

The second manuscript, by Rosenkranz et al, is a retrospective evaluation of 40 pts with heart failure associated with preserved ejection fraction (HFpEF) and Cpc-PH treated with a phosphodiesterase-5 inhibitor (PDE5i) for at least 12 months (4). Even though the correct methodology to evaluate drug efficacy is based on randomized, double blind, placebo-controlled trials, this retrospective evaluation adds useful information to the literature. The results support the importance of proper hemodynamic phenotyping in Group 2 PH. In particular the results suggest that the specific subgroup of HFpEF patients having Cpc-PH and RV dysfunction may benefit from PAH targeted therapy. Noticeably, this is the first suggestion that the sub-classification of PH-LHD in Cpc-PH and Ipc-PH, as recommended in the 2016 ESC/ERS Guidelines, may help to identify treatable patients with pulmonary vascular disease (1).

The authors of the present editorial believe that, despite the seemingly different conclusions, both manuscripts move toward the same objectives: i.e. the necessity to avoid off-label treatments in Group 2 PH and the need of continuing research in Group 2 patients, testing the most appropriate class of drugs and focusing on specific sub-populations which might potentially benefit of it.

Before discussing this therapeutic gap of evidence in Group 2 PH, it is necessary to acknowledge that it is the obvious clinical consequence of two other gaps of knowledge: one pathobiological and one pathophysiological.

As a matter of fact, the pathogenesis of PH occurring as a complication of LHD and the timing of the development of irreversible vascular remodelling are still largely unknown. Unfortunately, few studies have analysed pulmonary histopathology in Group 2 PH patients (5,6).

In the absence of strong histopathologic data, the experts have relied on hemodynamic parameters to identify patients with pulmonary vascular remodelling. The definitions of PH-LHD have been repeatedly modified over the years with the aim to better approach the characteristics required to define the presence of pulmonary vascular disease (7). However, the clinical implication of these different right heart hemodynamic profiles remains largely controversial (8-10). On the contrary, the criteria used by heart surgeons to assess reversibility of PH and thus to define eligibility for heart transplantation, have not been changed over the past 25 years (11,12). Nonetheless, whichever the definition, we have learnt that even in patients with the most advanced forms of PH-LHD, the long-term mechanical unloading of the left ventricle obtainable with heart transplantation or implantation of a pulsatile or axial-flow left ventricular assist device may normalize pulmonary hypertension (13-15).

Interestingly, the only hemodynamic parameter that does not normalize at 1 year after heart transplantation in Cpc-PH patients is pulmonary arterial compliance (16). Pulmonary arterial compliance is also the only hemodynamic parameter that improves less in Cpc-PH as compared to Ipc-PH patients in response to an acute vasodilator challenge (17).

In summary, we have to accept the idea that the link between right heart hemodynamics and pulmonary vascular disease remains elusive.

The questions that have to be answered are the following:

1) Which patients should be enrolled in future trials?

Data in the literature support the concept that RV dysfunction due to PH is an important independent prognostic factor in LHD, regardless of the extent of left ventricular dysfunction (18). Thus, future trials to test the efficacy of PAH drugs should include PH-LHD patients with significant

RV dysfunction. Concerning the aetiology of LHD, it is critical to include patients with a similar pathophysiology, avoiding to pool together patients with valve diseases, patients with severe left ventricular systolic dysfunction (HFrEF) and patients with HFpEF.

To this aim, the paper by Rosenkranz et al. identifies HFpEF-PH patients with Cpc-PH as a subset of patients who are likely responders to PAH-specific therapies. There might be several reasons for this finding. First, PH is the main determinant of right ventricular dysfunction in HFpEF patients, unlike what is observed in HFrEF patients in whom several factors, but not PH, seem to correlate with RV dysfunction (18). Furthermore, significant mitral regurgitation is often present in HFrEF patients and acts as a determinant of persistent left atrial pressure increase that cannot be treated with PAH specific drugs. Second, the pathogenesis of PH in HFpEF is different from that in patients with HFrEF, even though the primum movens for the development of PH in LHD is the elevation in pulmonary artery wedge pressure. For similar levels of wedge pressure, the pulmonary circulation is in fact stiffer in patients with HFpEF-PH compared to HFrEF-PH, leading to higher pulmonary resistances and gradients (19). The hypothesis is therefore that the constellation of comorbidities encountered in HFpEF may induce a systemic pro-inflammatory state that at the myocardial level has been shown to directly damage cardiomyocytes, which become hypertrophic and stiff, and may also affect the pulmonary microvasculature leading to increased stiffness and vascular remodelling (20). Whether the different pathogenesis is associated with a different response to drugs is yet to be demonstrated.

2) Which PAH drug should be tested in future trials?

Theoretically, all three pathways involved in the development of PAH (nitric oxide, endothelin and prostacycline pathways) may contribute to the pathogenesis of heart failure and PH due to LHD, providing a rationale for investigating the role of their modulation in this setting (21). A list of the

trials in whom there was a precise characterization of the right heart hemodynamic profile of the heart failure patients enrolled is provided in Table 1. Notably, all trials proved negative. However, the Table also clarifies that there was a substantial heterogeneity among patients enrolled in terms of aetiology of heart failure and type and severity of PH.

Epoprostenol was the first drug to be tested and proved ineffective (22). Interestingly, a multicenter randomized double blind study to evaluate safety and efficacy of oral treprostinil in PH-HFpEF patients is currently ongoing (23). Studies with bosentan initially performed in HFrEF patients and more recently in PH-HFpEF patients, led to disappointing results (24). Adverse effects were also observed with macitentan in the MELODY-1 study, which specifically included patients with Cpc-PH, in most cases due to HFpEF (25). In this trial a significantly increased risk of fluid retention and serious adverse effects versus placebo, particularly during the first month, occurred in the treated arm.

Riociguat, a guanylate cyclase stimulator, significantly decreased pulmonary vascular resistances but did not improve mean pulmonary artery pressure (which was the primary end-point of the trial) after 12 weeks in patients with PH due to HFrEF (26).

Sildenafil efficacy was initially suggested in single-centre studies (27,28). Positive results were not confirmed subsequently. The effects of 60 mg sildenafil 3 times daily were compared with placebo in 52 patients with PH due to HFpEF at 12 weeks; no effect was observed in the primary end-point (mean pulmonary artery pressure), although pulmonary vascular resistance (PVR) significantly decreased and exercise capacity improved (29). The SIOVAC trial enrolled 200 patients with persistent PH after successful correction of valvular heart disease (30). Patients were randomized to receive sildenafil 40 mg three times daily or placebo for 6 months. The primary endpoint was the composite clinical score combining death, hospital admission for heart failure, change in

functional class, and patient global self-assessment. Treatment with sildenafil was associated with worse clinical outcomes than placebo.

Finally, it is likely that protocol design in PH-LHD patients should also consider a strict management of fluid retention, as the CHAMPION study demonstrated the impact of aggressive diuretic therapy in reducing hospitalization in advanced HF patients (31)

3) Which end-point?

We need proof-of-concept studies to demonstrate the efficacy of a PAH drug on hemodynamics (reduction in PVR, increase in CI, no change in PAWP) and functional capacity, associated with a favourable safety profile (absence of fluid retention, weight increase, impairment of gas exchange) in the short-term (16-24 weeks). After this demonstration, the next step would be a large morbidity trial.

In conclusion, the therapeutic dilemma of PH-LHD has yet to be solved.

Meta-analysis of published studies are negative, but the huge variability of patients enrolled in previous trials and the variability of the classes of drugs tested, make these pooled results not conclusive. Future studies should address HFpEF patients, with a Cpc-PH hemodynamic profile, using a drug with a potentially favourable efficacy profile.

The take home message for clinicians is not to use off-label therapies, but randomize patients in trials; the take-home message for researchers is to better focus trials on specific subsets of PH-LHD patients and to test only the most promising classes of drugs.

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Table 1. Summary of studies with PAH specific drugs in PH-LHD patients reporting the right heart hemodynamic profile of patients.

	Name	Drug	N° pts	LHD	PH type*	RAP (mmHg)		mPAP (mmHg)		PAWP (mmHg)		PVR (WU)		Morbi-mortality	Exercise Capacity
						Treat	Control	Treat	Control	Treat	Control	Control	Treat		
Califf (22)	FIRST	Epo	471	HFrEF	Ipc	10	12	38	40	25	16	-	-	↑	NA
Koller (24)	BADDHY	Bos	20	HFpEF	Cpc	11	13	36	41	21	21	3.7	4.6	NA	↓
Vachiery (25)	MELODY	Maci	63	HFpEF	Cpc	13	13	44	49	20	20	5.6	6	↑	↓
Bonderman (26)	LEPHT	Rio	191	HFrEF	Cpc	9	10	37	40	3.4	3.8	9	10	=	=
Lewis (27)	-	Sild	34	HFrEF	Cpc	6	8	30	33	18	19	4.3	4.5	↓	↑
Guazzi (28)	-	Sild	44	HFrEF	Cpc	23	23	39	37	22	22	3.9	3.3	NA	↑
Hoendermis (29)	-	Sild	52	HFpEF	Ipc	9	10	35	35	20	21	2.6	2.5	↑	=
Bermejo (30)	SIOVAC	Sild	200	VHD	Ipc	12	12	39	37	23	22	3.4	3.1	↑	↓

* = Most represented hemodynamic type of PH.

HFrEF = heart failure reduced ejection fraction; HFpEF = heart failure preserved ejection fraction; Ipc = isolated post-capillary PH; Cpc = combined pre-post capillary PH; Epo = epoprostenol; Sild = sildenafil; Bos = bosentan; Maci = macitentan; Rio = riociguat; mPAP = mean pulmonary artery pressure; sPAP = systolic pulmonary artery pressure; PAWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; WU = Wood units; RAP = right atrial pressure; ↑ = increase; ↓ = decrease; NA = not assesse