Pulmonary hypertension-specific therapy in patients with chronic respiratory insufficiency

To the Editor:

We read with much interest the article by HELD *et al.* [1] regarding pulmonary hypertension (PH) due to hypoventilation. In this retrospective study, the authors reported 18 patients with alveolar hypoventilation (due to obesity or chronic obstructive pulmonary disease (COPD)) and daytime PH associated with reduced exercise capacity. They showed that noninvasive positive-pressure ventilation (NIPPV) was followed by significant improvement in haemodynamics and exercise capacity; thus, strongly supporting the use of NIPPV in patients with hypoventilation and PH, and suggesting a major role for hypoxia and hypercapnia in PH [2].

As it is unknown whether PH-specific therapy targeting vasculopathy and remodelling of the pulmonary arteries may also have an impact in this setting, we retrospectively studied patients with chronic respiratory insufficiency and hypoventilation treated with long-term NIPPV who received off-label specific therapy for severe PH.

We extracted from the French registry, in which all consecutive adult patients with PH are prospectively included with written consent [3], incident cases from our centre seen between 2006 and 2013 with the following criteria. 1) Chronic respiratory insufficiency with alveolar hypoventilation (daytime arterial carbon dioxide tension >45 mmHg and hypoxaemia before NIPPV), receiving long-term NIPPV for at least 6 months. 2) Precapillary PH: defined by mean pulmonary artery pressure (PAP) $\geqslant$25 mmHg and pulmonary artery wedge pressure $\leqslant$15 mmHg at right heart catheterisation. 3) Severe PH: defined by mean PAP $\geqslant$35 mmHg and/or cardiac index <2 $L \cdot min^{-1} \cdot m^{-2}$. 4) Off-label PH-specific therapy. 5) Available follow-up for at least 6 months. 6) Absence of associated conditions: chronic thromboembolic PH, post-capillary PH or severe left heart conditions. 18 out of 626 patients with precapillary PH were identified with chronic respiratory insufficiency, of whom 11 had severe PH, including two treated with NIPPV for at least 6 months prior to initiation of PH-specific therapy and followed for at least 6 months (table 1).

Both patients (one female and one male) had COPD with a forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio of 49% and 43%, respectively, FEV_1 of 45% predicted and 36% pred, respectively, and a diffusing capacity of the lung for carbon monoxide of 27% pred and 41% pred, respectively. Body mass index was 24 $kg \cdot m^{-2}$ and 35 $kg \cdot m^{-2}$, respectively. Neither patient had associated sleep apnoea syndrome or obesity hypoventilation syndrome. Both patients were efficiently treated with NIPPV (with an inspiratory pressure of 15 mmHg and 20 mmHg, respectively) and 1.5 $L \cdot min^{-1}$ supplemental oxygen overnight for 6 months before PH was diagnosed, with adequate correction of night-time and daytime hypoxaemia and hypercapnia (44 mmHg and 45 mmHg, respectively). The patients received a further 5 $L \cdot min^{-1}$ and 3 $L \cdot min^{-1}$, respectively, of oxygen continuously during the daytime. Routine echocardiography suggested presence of PH in both patients, and right heart catheterisation demonstrated severe precapillary PH with preserved cardiac index. After discussion, it was considered that severe PH may contribute to their functional limitation. Patients' consent was obtained and off-label sildenafil therapy was initiated, with later combination with bosentan in one case and diuretics in both cases. In patient 1, no clinical or haemodynamic improvement was observed. Patient 2 had no clinical or functional improvement, despite long-term haemodynamic improvement with increase in cardiac index and decrease in mean PAP. Inhaled bronchodilators, NIPPV and supplemental oxygen were unchanged. No significant change was observed in arterial oxygen tension, or oxygen saturation at rest or during 6-min walking test over more than 1 year of follow-up. However, hypoxaemia worsened in patient 1 after 38 months of sildenafil treatment, with an increase in alveolar–arterial partial pressure of oxygen gradient, which partially corrected after sildenafil had been discontinued.

These observations of COPD hypoventilation with severe PH differ from the study of HELD *et al.* [1], which predominantly included patients with obesity hypoventilation syndrome. This report emphasises that severe precapillary PH is rare in the setting of chronic respiratory insufficiency, even in a large Dept of Respiratory Medicine and referral centre for PH, further suggesting that PH-specific drug therapy is unlikely to be

TABLE 1 Main characteristics of patients at baseline and during follow-up

	Patient 1				Patient 2			
	Baseline	**3 months**	**12 months**	**24 months**	**Baseline**	**3 months**	**12 months**	**45 months**
NYHA class	III	II	III	IV	III	III	III	III
FEV1								
L	1.46	1.21	1.33	1.22	0.56	0.64	0.58	0.71
%	45	40	44	41	36	40	37	50
PH therapy	None	Sildenafil	Sildenafil	Sildenafil	None	Sildenafil	Sildenafil and bosentan	Sildenafil and bosentan
Oxygen supplementation at rest L·min^{-1}	5	5	5	12	3	3	4	4
***P*aO_2 on oxygen mmHg**	66	79	61	51[#]	88	63	82	76
6-MWD m	300	330	270	120	180	180	186	243
Saturation at end of 6-MWT								
%	78	82	79	70	86	76	80	96
Oxygen supplementation L·min^{-1}	6	5	6	12	4	4	6	6
PAP systolic/diastolic/mean mmHg	51/18/36	50/24/37	51/18/35	57/39/45	55/16/35	41/16/24	33/19/24	33/18/23
Cardiac index L·min^{-1}·m^{-2}	3.24	3.62	3.30	5.52	3.24	2.73	4.73	3.60
PVR dyn·s·cm^{-5}	360	355	340	265	372	332	147	148
NT-proBNP serum level pg·mL^{-1}	130	160	110	150	159	137	201	154
Right ventricular ejection fraction %	31	N/A	33	28	32	33	37	35
Change in therapy	Initiation of sildenafil	No change	No change	Discontinuation of sildenafil	Initiation of sildenafil	Initiation of bosentan	No change	No change

Patient 1 was a 54-year-old male, patient 2 was a 71-year-old female. NYHA: New York Heart Association; FEV1: forced expiratory volume in 1 s; PH: pulmonary hypertension; *P*aO_2: arterial oxygen tension; 6-MWD: 6-min walk distance; 6-MWT: 6-min walking test; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; NT-proBNP: N-terminal pro-brain natriuretic peptide. [#]: *P*aO_2 increased from 51 mmHg with 12 L·min^{-1} of nasal oxygen to 69 mmHg with 15 L·min^{-1}, after sildenafil was discontinued.

beneficial in this setting. As stated at a recent international conference on PH, PH-specific drugs are not recommended in patients with PH associated with chronic respiratory diseases (group 3), and treatment should focus on managing the underlying disease [4]. Oxygen supplementation may stabilise PH in patients with COPD [5], and NIPPV may improve haemodynamics in patients with alveolar hypoventilation [1]. Although off-label treatment is sometimes considered in individuals with severe PH when functional limitation is considered to be related to pulmonary vascular disease, there is currently little if any evidence that PH therapy may be beneficial in this setting, with further anecdotal evidence that treatment may increase hypoxaemia through ventilation/perfusion mismatch.

We therefore strongly agree with HELD *et al.* [1] that correction of hypoventilation should be the main objective of management in chronic respiratory insufficiency, even in the presence of severe PH.

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Correction of hypoventilation should be the main objective in chronic respiratory insufficiency, even with severe PH http://ow.ly/wxvcN

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From the author:

I would like to thank V. Cottin and co-workers for their interest in our recently published study [1]. Their comments emphasise our conclusion that the treatment of the underlying disease should be the favoured strategy.

Since both patients did not have a reduced cardiac index, when treatment with sildenafil and bosentan was started the lack of a significant improvement was not really surprising. The two patients reported by V. Cottin and co-workers showed different reactions. Patient one deteriorated dramatically in World Health Organization (WHO) functional class and 6-min walk distance (6MWD) "despite" (or due to!) a decrease of pulmonary vascular resistance. This patient showed an excessive increase of cardiac index and a worsening of oxygenation, probably the consequence of increasing shunt perfusion resulting from reversing of vasoconstriction.

Patient two showed an early decrease of pulmonary artery pressure, no change in WHO functional class, and stable oxygenation and cardiac index, but a late improvement in 6MWD. It is questionable whether a short-term follow-up period is appropriate for patients with pulmonary hypertension due to obstructive lung disease. Patients with pulmonary hypertension and chronic obstructive pulmonary disease showed a maximum improvement of 6MWD after 8–9 months, thus, it is probable that these patients need a longer period in order to improve their functional capacity rather than decrease their pulmonary artery pressure [2].

As MEYER *et al.* [3] reported on respiratory muscle dysfunction and respiratory insufficiency in patients with idiopathic pulmonary arterial hypertension, in our daily practice we have to differentiate whether a patient presenting with severe pulmonary hypertension and hypoventilation is a patient with pulmonary