

# Kidney pulmonary hypertension: another road on the map?

## Iperensione reno-polmonare: un'altra meta sulla via?

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Pulmonary hypertension (PH) is a serious disorder that worsens the course of chronic heart, lung or systemic diseases. However the need to discriminate PH, a pathophysiological condition, from pulmonary arterial hypertension (PAH), which is a rare clinical condition, has been recently stressed [1]. PH is defined as an increase in mean pulmonary arterial pressure (P $\bar{A}P$ ) > 25 mm Hg at rest, as assessed by right heart catheterisation. According to various combinations of values of pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR) and cardiac output, different hemodynamic types of PH can be identified. In the updated clinical classification of PH, 37 clinical conditions with PH are classified into six groups according to pathological, pathophysiological and therapeutic characteristics: PAH (group 1), pulmonary veno-occlusive disease (group 1'), PH due to left heart disease (group 2), PH due to lung disease (group 3), chronic thromboembolic PH (CTEPH, group 4) and PH with unclear and/or multifactorial mechanisms (group 5) [4].

In this issue of MRM, Bozbas et al. [2] report that pulmonary hypertension is not uncommon in patients with end stage renal disease (ESRD). They detected an increase of systolic pulmonary arterial pressure (sPAP) in 85 of the 500 (17%) patients undergoing pre-transplant evaluation. Moreover, a significant decrease was observed in mean sPAP values in an average of 53 months of postoperative follow up on 42 patients who had undergone both pre- and post-transplant echocardiographic examination compared to pre-transplant values [3]. As the authors acknowledge, their retrospective data have

the important limitation of lacking direct hemodynamic assessment which would have readily diagnosed and classified PH occurring in ESRD. Accordingly, the correlation between echocardiographic estimate of sPAP and right heart catheterization is not absolute. Thus if we apply the PH echo probability criteria of ESC/ERS guidelines [4], we could find only 6 patients fulfilling PH high probability criteria. Nevertheless the potential role of PH as a cardiovascular complication of ESRD should be acknowledged.

The death rate among U.S patients undergoing dialysis continues to exceed 20% per year during the first 2 years after maintenance dialysis has begun. Moreover, hospitalization rates have remained nearly constant, averaging almost 13 hospital days and two admissions per patient/year [5]. It has been suggested that dialysis-focused quality measures should also include an assessment of risk factors for cardiovascular disease which constitutes the major cause of hospitalization and death in the population receiving dialysis. Indeed while it is well known that cardiovascular diseases including ischemic heart disease, heart failure and arrhythmias are very common and are the most frequent causes of mortality in patients with ESRD, data on PH in patients with ESRD are limited.

PH is a strong independent predictor of mortality in hemodialysis (HD) patients [6]. In a recent review, the prevalence of PH in ESRD patients was reported to be around 40-50% [7]. Its frequency has been reported to be higher in HD than in peritoneal dialysis (PD) patients due to the presence of arterio-venous fistula (AVF) [8]. The mechanisms involved in

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PH development are still under investigation, but it has been reported that HD patients with PH show a significantly higher cardiac output than HD patients with normal sPAP [9]. It has been suggested that some factors such as the size or the location of AVF are involved in the mechanism that increases PAP, as an AVF with a high flow may have a flow of 1.0–1.5 L/min with a cardiopulmonary recirculation up to 20% [10,11].

It has been reported that PH improves after successful kidney transplantation, as well as after short AVF compression, indicating that both ESRD and AVF contribute to its pathogenesis [12]. Issa et al. reported that time on dialysis was the strongest correlation to elevated right ventricular systolic pressure. The same authors stated that right ventricular systolic pressure greater than 50 mm Hg was associated with significant reduced post-transplant survival [12]. Interestingly, data from the REVEAL Registry [13], which has collected a large number of PAH patients, show that 10% of these patients demonstrate PCWP between 15 and 18 mm Hg depicting a grey zone of unclear clinical significance. Remarkably, obesity, sleep apnea and renal failure were among the factors responsible for PCWP increase while left heart echo data did not differ in comparison to patients with PAH and PCWP < 15 mm Hg, suggesting that chronic renal disease could potentially represent an aggravating factor also in PAH.

There is much debate on the occurrence of severe PH, with clinical characteristics resembling idiopathic PH, in groups other than PAH. Actually in both groups 2 and 3 (e.g. left heart disease and lung disease, respectively) patients with severe out-of-proportion PH have been identified, raising the question of a possible targeted therapy for these patients [4]. From this point of view there is evidence that endothelial dysfunction may play a role in ESRD patients interfering with a possible target of the drugs used in PAP. Patients with chronic renal failure (CRF) show an endothelial dysfunction related to defective nitric oxide activity, which is not corrected by hemodialysis (HD). Nakhoul et al. [11] demonstrated that reduced nitric oxide production could increase PAP; furthermore, PH among HD patients who underwent successful kidney transplantation reversed, even if their AVF remained

patent. Moreover, HD induces a detectable extracorporeal increase of thromboxane(TX)B<sub>2</sub>, through blood membrane interaction causing degranulation of neutrophils with the increase of TXB<sub>2</sub> in HD patients. The increased synthesis of these vasoactive agents may lead to pulmonary venous constriction, as pulmonary veins are the primary sites of action of thromboxane, with increased microvascular pressures and abnormalities in gas exchange leading to hypoxia and consequent pulmonary vasoconstriction (14). Other risk factors for PH associated to ESRD have been identified such as age and hormonal disturbances. Hyperparathyroidism, by causing precipitation of calcium in many tissues, could play a role in the development of PH secondary to pulmonary artery, but other studies did not confirm this finding in ESRD on regular HD [15,16]. Finally diastolic dysfunction may contribute to the development of PH by causing an elevated left atrial pressure. Accordingly, patients with brachial AVF have a more than double risk of developing PH, while patients with left ventricular diastolic dysfunction (LVDD) have a very high risk compared to those without LVDD [17,18]. To summarize the occurrence of pulmonary hypertension is likely to be multifactorial (see Table I).

In conclusion, the data of Bozbas et al. are welcome because they unmask the clinical problem of PH in ESRD, which may represent a challenge for many medical specialties in the future. It is likely that the application of current guidelines and diagnostic algorithms in this patient population will increase our knowledge concerning the true relevance of kidney pulmonary hypertension.

**TABLE I: CONFIRMED AND SUSPECTED FACTORS LEADING TO INCREASED SYSTOLIC PULMONARY ARTERIAL PRESSURE IN END STAGE RENAL DISEASE (ESRD)**

Factors of PH in ESRD	Consequences
High flow arteriovenous fistula	High cardiac output
Endothelium dysfunction	↓NO; ↑TXB; ↑ET-1
Left heart dysfunction	↑pulmonary wedge pressure
Hormonal disturbances	Hyperparathyroidism
Abnormal gas exchange	Hypoxia, pulmonary vasoconstriction

*Definition of abbreviations:* ET, endothelin; PH, pulmonary hypertension; TXB, thromboxane.

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