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REVIEW

Pulmonary hypertension: a neglected risk condition in renal patients?

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Pulmonary hypertension (PH), an acknowledged risk condition at the community level and in patients with heart or lung diseases, is now getting growing attention as a new, potentially modifiable cardiovascular (CV) risk factor also in individuals affected by kidney diseases. PH is highly prevalent in this setting, being about 3 to 6 times more frequent that in the general population and portends a risk excess for mortality, adverse CV outcomes and also worsen graft function in kidney transplant recipients. Several factors might be involved to explain PH in renal patients, including but not limited to volume overload, breath disorders, left heart dysfunction and the presence of high-flow artero-venous fistulas. Targeting PH might lead to improved outcomes in renal patients but the lack of specific interventional studies and the need for more accurate evidence adopting standardized ways to assess PH leave the issue open for future research.

Keywords

Pulmonary hypertension; chronic kidney disease; end-stage kidney disease; mortality; cardiovascular disease

1. Introduction

It has been estimated that over 50 million people are affected by chronic kidney disease (CKD) and over 2 million persons need chronic renal replacement therapy for end-stage kidney disease (ESKD) (Eggers et al., 2011). The incidence of CKD is steadily on the rise and this condition is now acknowledged as one of the main risk factors for cardiovascular (CV) mortality and morbidity with a dramatic impact on health expenditures (Honeycutt et al., 2013). Although the majority of renal patients may have concomitant CV risk factors like hypertension, diabetes and hyperlipidemia, large trials targeting these conditions have failed to improve CV survival and reduce morbidity. Pulmonary hypertension (PH) is nowadays considered an acknowledged risk condition for worsen CV outcomes in the general population, as well as in individuals affected by heart, connective or lung diseases. In a large 20-year surveillance at the community level (Hyduk et al., 2005), there were stable death rates ranging from 5.2 to 5.4 per 100.000 persons and increasing rates of hospitalization associated with PH. In another epidemiological survey, an increasing trend in mortality was documented from 2003 to 2013 with an estimated age-adjusted death rate of 4.5 to 12.3 per 100.000 (George et al., 2014).

Recently, evidence has accumulated indicating that pauci- or non-symptomatic PH is remarkably prevalent also in CKD persons, particularly in ESKD patients on chronic dialysis (Bolignano et al., 2013). This may have relevant clinical value as the presence of PH in CKD is generally associated with increased mortality, CV events and even delayed graft function in renal transplanted patients (Bolignano et al., 2015, 2018). Screening of pulmonary pressure might therefore represent an additional, helpful tool for risk stratification of renal patients and targeting overt PH, whenever present, may translate into additional benefits also in the CKD setting. In this manuscript, we will briefly review the key-concepts of the (still) neglected clinical relationship between pulmonary hypertension and renal disease.

2. Epidemiological significance of PH in the general and renal populations

In the general population, PH is much more prevalent than initially supposed (Simonneau et al., 2009). Unfortunately, this condition often remain invisible due to the absence of symptoms in the early phases, being suspected only in the presence of clinical evidence of heart dysfunction (e.g. dyspnea, fatigue, non-productive cough or peripheral edema) (Badesch et al., 2009). In a large community study focusing on a random sample of the Olmsted county (Lam et al., 2009), the prevalence of PH was about 5% in indi-

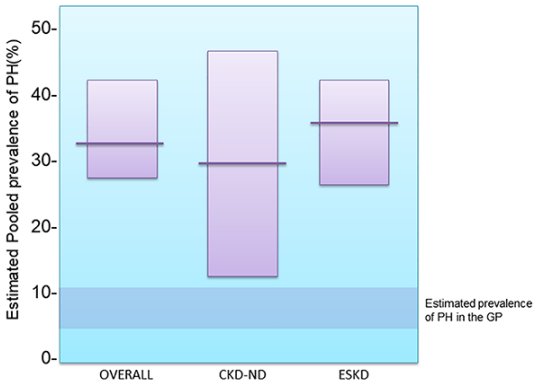

Figure 1. Pooled prevalence of PH in CKD and ESKD cohorts as compared to estimates in the general population

viduals older than 45 year. The majority of cases of PH in this population was associated to the presence of left heart disorders or severe systemic hypertension. In another, large survey on 4579 patients undergoing echocardiography (Strange et al., 2012), the prevalence of PH was 10.5% and among individuals showing this condition, 78.7% had left heart disease, 9.7% had lung diseases, 4.2% had primary pulmonary artery hypertension and 0.6% had pulmonary thromboembolism.

As briefly alluded to before, PH is exceedingly prevalent also in renal patients (Fig. 1). In a recent meta-analysis of observational studies (Bolignano et al., 2018) PH had an overall pooled prevalence of 33% (95% CI 28-42) that resulted lower in CKD (30%; 95% CI 13-47) than in dialysis (35%; 95% CI 28-42) populations. Hence, the overall estimated frequency of this condition was about 3-times higher than that reported in the general population. With respect to dialysis modality, the prevalence of PH was reported to be lower in patients treated with peritoneal dialysis (from 0% to 42%) than in those receiving chronic hemodialysis (from 18.8% to 68.8%) (Bolignano et al., 2013). Unfortunately, poor consistency exists among studies with respect to the estimated pulmonary artery pressure (ePAP) thresholds considered as "pathologic", which ranged from 25 to ≥ 45 mmHg.

Another important point when looking at the significance of PH in renal patients is related to the type of PH that these individuals may have.

Indeed, according to a joint ESC-ERS guideline (Galie et al., 2009), which has subsequently been endorsed by a WHO document (Ryan et al., 2012), different types of PH exist, based on the pathogenesis and the anatomic alteration underlying the increase in pulmonary pressure (Table. 1). In fact, the pulmonary circulation consists of an arterial side which compliance and sectional structure recalls that of systemic veins and a venous side bringing back the oxygenated blood to left heart. The capillary barrier, which ideally divides the two sides, is used to distinguish forms of PH characterized by a primary increase in pulmonary artery resistances ("pre-capillary") from those secondary to a passive venous congestion ("post-capillary"). Pre-capillary PH is mostly identified with the so-called "Pulmonary arterial hypertension" (PAH) that may be idiopathic (IPAH), familial (FPAH) or associated (APAH) to other conditions like connective tissue diseases, drugs and toxins, HIV or portal hypertension. Another pre-capillary form of PH is that secondary to chronic thromboembolism. Conversely post-capillary forms, which are the most frequent ones, are usually associated to left heart disorders or valve diseases. Differential diagnosis among different types of PH is crucial as the clinical management, treatment approach and long-term outcomes are considerably different. Yet, the only way to perform such a clear distinction is by performing right heart catheterization (RHC) to measure the pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistances (PVR). Giving the invasiveness of the procedure and the potential risks related, this approach cannot be considered in daily practice as the first line. Hence, individuals are usually first screened by echocardiography to estimate the pulmonary pressure (ePAP) and then referred to RHC for diagnosis confirming and disease characterization, whenever abnormally high ePAP are found. In one study of RHC in renal patients with unexplained dyspnea and various degree of renal function impairment (Pabst et al., 2012), PH was present in 81% of hemodialysis (HD) and in 71% of CKD patients. Of note, PH was post-capillary in most cases (71% and 65% of HD and CKD patients, respectively) while the prevalence of pre-capillary PH was as low as 6% in CKD and 13% in HD patients, respectively. These observations indicate that, similarly to the general population, PH in renal patients is likely to depend mostly from heart dysfunction or fluid overload. Left heart dysfunction is a common report in renal patients and its severity goes along with the entity of kidney function impairment. This condition elicits volume overload but can be worsened itself by fluid excess, which is at the basis of a vicious circle eventually contributing to pulmonary venous congestion. Despite heart dysfunction plays a key-role, however, a large bunch of parallel evidence suggest that the pathogenesis of PH in CKD may involve several other co-protagonists in a more complex multifactorial scenario (Fig. 2).

3. Factors potentially involved in the pathogenesis of PH in renal patients

In the general population endothelial dysfunction is a major cause of PH (Giaid et al., 1998) and this condition is now recognized to be largely prevalent also in renal patients (Zoccali et al., 2007). Interestingly, circulating levels of nitric oxide (NO), a powerful endothelial-derived vasodilator, are more reduced in chronic hemodialysis patients with higher ePAP as compared to those with normal pulmonary pressure (Yigla et al., 2004). Asymmetric dimethyl-arginine (ADMA), an endogenous inhibitor of NO synthase which is mostly released by the lung (Arrigoni et al., 2003), is a key-trigger of experimental forms of PH (Sasaki et al., 2007). ADMA is notably increased in patients with sleep breathing disorders (Barceló et al., 2009), but also in subjects with renal function impairment (Zoccali et al., 2001) due to an increased systemic production and a reduced renal clearance. Sleep apnea is frequently reported in CKD populations (Sakaguchi et al., 2011) and nocturnal hypoxemia caused by this sleep breathing disorder is a strong trigger of PH as it promotes sympathetic activation (Ward et al., 2009; Sica et al., 2000). In addition, hypoxia can be further aggravated by severe anaemia, another hallmark of advanced CKD, with indirect effects also on PH (Buemi et al., 2007). In the general population, stiffening of the pulmonary artery is significantly corre-

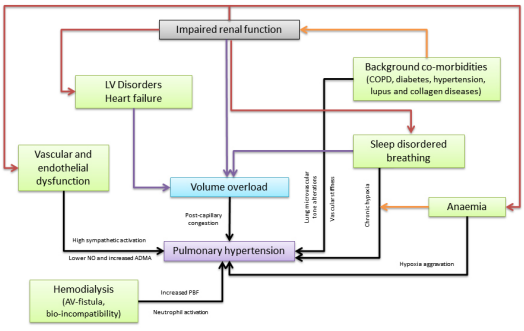

Figure 2. Multifactorial pathogenesis of PH in renal patients (see section 3 in the main text for details)

Table 1. Different types of PH according to WHO and anatomic classification

WHO type	Definition	Anatomic location	Characteristics	Examples
PH type I	Pulmonary arterial hypertension (PAH)	Pre-Capillary	PAWP low PVR high	Idiopathic, familiar or associated to connective diseases, HIV, drug or toxins, portal hypertension, pulmonary veno-occlusive disease
PH type 2	PH associated to left ventricular disorders	Post-Capillary	PAWP high PVR low	Left heart systolic dysfunction, left heart diastolic dysfunction, left-sided valve disease (mitral and/or aortic)
PH type 3	PH associated to lung diseases	Mixed	Variable	COPD, ILS, sleep-apnea, fibrosis
PH type 4	PH associated to chronic thromboembolism	Pre-Capillary	Variable	Obstruction of pulmonary arterial vessels by emboli, tumors or foreign bodies
PH type 5	PH of unclear or multifactorial etiology	Mixed	Variable	Various or unknown etiology

PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistances, COPD: chronic obstructive pulmonary disease, ILS: interstitial lung disease, WHO: world health organization

lated to high pulmonary pressures (Lam et al., 2009). In CKD patients, arterial rigidity is even more pronounced as the result of the overall dysfunction in mineral metabolism, with abundant calcium deposits that have been found even in the distal branches of the pulmonary artery (Nitta et al., 2003). Artero-venous fistula (AVF) access for chronic hemodialysis treatment might increase pulmonary blood flow and, therefore, pulmonary pressure, by decreasing systemic vascular resistances and increasing venous return and cardiac output, a compensatory mechanism aiming at maintaining adequate blood flow to peripheral tissues. Indeed, PH is notoriously more prevalent in individuals undergoing chronic hemodialysis by AVF than in patients on chronic peritoneal dialysis or in early CKD stages (Bolignano et al., 2013). Temporary AVF compression by a sphygmomanometer or surgical AVF closure induces a rapid and stable decline in ePAP (Nakhoul et al., 2005). ePAP rises in parallel with AVF creation (Abassi et al., 2006), is correlated to AVF flow and duration and worsens overtime in chronic hemodialysis populations (Fabbian et al., 2010). This is also due to chronic exposure of blood to dialysis membranes which leads to neutrophil activation in the lung with following micro-vascular pulmonary disease (Kiykim et al., 2010). Finally, other concomitant conditions frequently associated to CKD like diabetes, connective, liver, infectious and hematologic diseases may significantly affect also the control of micro-vascular tone in the lung, therefore contributing to aggravating PH.

4. Prognostic significance of PH in the general population and in renal patients

As briefly alluded to before, PH is an acknowledged risk factor for worsen outcomes at the community level, with documented increased trends in age-adjusted death rate (George et al., 2014) and hospitalizations (Hyduk et al., 2005) over an ample observation window. Interestingly, this association was found to be independent from background CV disease and, particularly, severity of impaired LV function either in cohorts of patients with heart (Kjaergaard et al., 2007) and lung diseases (Lau et al., 2015), therefore suggesting that the prognostic impact of PH is not influenced by traditional risk factors but conveys an excess risk per se.

There is now a large bunch of accumulating evidence indicating that PH may hold the same prognostic power also in renal patients. This starts from various observations on high risk chronic hemodialysis cohorts (Yigla et al., 2003, 2009; Agarwal, 2012; Ramasubbu et al., 2010) that have subsequently been extended also to pre-dialysis CKD populations (Bolignano et al., 2015). A very recent meta-analysis (Bolignano et al., 2018) collected data from 18 outcome studies (10740 participants) focusing on individuals with various degree of renal function impairment who were stratified according to the presence or absence of PH. Overall, PH conveyed a significantly higher risk of all-cause mortality (RR 2.08; 95% CI 1.06-4.08), a finding that was more evident in individuals on ESKD in chronic renal replacement therapy than in those with early renal impairment (RR 1.90; 95% CI 1.61-2.25). PH resulted also a significant predictor of cardiovascular mortality (RR 3.77; 95% CI 2.46-5.78) and non-fatal cardiovascular events (RR 1.60; 95% CI 1.28-1.99), particularly in patients with non-advanced CKD (RR 1.90; 95% CI 1.50-2.40). Unfortunately, the studies retrieved were highly heterogeneous with respect to renal disease severity, baseline PH prevalence, sample size, follow-up length and, above all, with respect to the diagnostic criterion (ePAP cutoff) adopted for identifying PH. No less important, in almost all the studies "true" PH remained only suspected as high ePAP values obtained by echocardiography were not confirmed by RHC. This, of course, also hampered the possibility to further characterize the pre- or post-capillary nature of PH across the different study cohorts.

PH could be useful for outcome prediction also in kidney transplant recipients. This concept firstly relies on isolate observational reports showing that, in a large percentage of dialysis patients, renal transplantation is able to normalize ePAP, despite the mortality risk associated to PH may persists (Nakhoul et al., 2005). In a retrospective study (Zlotnick et al., 2010), 55 patients underwent successful kidney transplantation were followed for 3 year to assess

the occurrence of early graft dysfunction (EGD). The incidence of EGD was higher among individuals with PH (ePAP > 35 mmHg) prior to transplantation with a OR of 15.0 (95% CI 1.1-118.0) fully adjusted for a series of other risk factors like age of recipient, pre-transplant dialysis vintage, presence of functional AVF, age of donor and cold ischaemia time, history of coronary artery disease and left ventricular ejection fraction. In another retrospective study (Issa et al., 2008) 215 transplant candidates were stratified into three different groups according to their pre-surgical ePAP value (< 35, 35-59 and > 60 mmHg). ePAP directly correlated to dialysis vintage and individuals falling within the higher pre-transplant ePAP category had a significantly higher risk of death after transplantation (HR 3.5; 95% CI 1.17-11.97) which persisted after adjustment for age, reduced left ventricular ejection fraction, serum albumin and delayed graft function.

5. Treatment approach of PH in renal patients

The lack of specific studies of PH treatment in individuals with CKD or ESKD makes extremely difficult to ascertain whether PH should be targeted as a modifiable factor or considered a mere risk variable. This also hampers the possibility to tailor proper therapeutic approaches in this particular clinical setting. In the absence of such evidence, it might be wise to refer to a stepped treatment approach proposed for the general population (Galie et al., 2009). In this model, the first step remains a correct diagnosis, severity assessment and type classification of PH by performing RHC in the presence of suggestively high ePAP values at screening test. A following vasoreactivity test would help tailoring the best treatment to the patient according to the individual response to drugs, if these are needed.

Moving to the renal setting, the ideal solution to treat PH would be to encourage kidney transplantation, given the preliminary evidence that pulmonary pressure may revert to normal after this procedure. In real world, considering that almost all forms of PH in this population are post-capillary in nature and/or associated with sleep breathing disorders, concrete efforts should be put to maximize volume overload correction by ultrafiltration intensification or peritoneal dialysis to improve LV dysfunction and venous congestion. The identification and surgical correction of very high flow AVF would probably be helpful, as well as the treatment of other systemic abnormalities that usually develop over the course of renal disease that may trigger high pulmonary pressure (e.g. anaemia, inflammation or mineral bone disease). Finally, when a pharmacological approach is needed, this should always be carefully considered taking into account the likelihood of response and the overall risks, considering that most drugs for PH treatment can be dangerous in patients with reduced renal clearance.

6. Conclusions

Evaluation of pulmonary pressure might represent an important missing piece for risk stratification of renal patients. In fact, abnormally high ePAP values have been found in a substantial percentage of individuals with impaired renal function, also showing a significant capacity to predict worsen outcomes independently from a series of traditional or kidney-disease related risk factors. Nevertheless, new larger prospective studies adopting well standardized criteria of PAP assessment, such as right heart catheterization, appear mandatory to clarify the exact role of PH in the renal setting. Such an evidence would be also desirable to define the exact clinical form(s) of PH in CKD and to set the stage for interventional trials aiming at evaluating whether improving PH may effectively translate into better patient outcomes also in this particular population.

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Conflict of interest

The authors declare no competing interest.

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