

# Pulmonary Hypertension in Patients with Chronic Kidney Disease

Alessandro Domenici, Remo Luciani, Francesco Principe,  
Francesco Paneni, Giuseppino Massimo Ciavarella and Luciano De Biase  
*Department of Cardiovascular, Renal and Pulmonary Diseases,  
Sant'Andrea Hospital, Sapienza University of Rome,  
Italy*

## 1. Introduction

An unexpectedly high prevalence of pulmonary hypertension (PH) has been detected by Doppler echocardiography in chronic kidney disease (CKD) patients and found to be associated with overall poor outcome. A number of pathogenetic mechanisms appears to act synergistically in producing such a condition, the relative importance of which is a matter of ongoing investigation. This chapter will review the literature on the topic and summarizes what can be drawn from published studies. Our work and experience at Sant'Andrea University Hospital is also extensively reported and area for future research addressed.

## 2. The facts

### 2.1 Pulmonary hypertension in CKD patients on maintenance hemodialysis

Quite surprisingly, PH remained an overlooked issue in CKD patients until very recent years. Moving from an analysis of the background diseases in their series of patients with PH, Yigla and co-workers were the first to report, in a seminal paper (Yigla et al., 2003), a PH prevalence as high as 39.7% in patients receiving haemodialysis (HD) through a surgically created arteriovenous fistula (AVF). These authors found PH to be associated with cardiac output (CO) and anemia. They were also the first to report that temporary occlusion of the AVF by compression results in a reduction of both CO and systolic pulmonary artery pressure (PAP<sub>s</sub>), that PH may actually increase in pre-dialysis patients after renal replacement therapy (RRT) initiation, and that it might reduce after successful renal transplantation (Tx). This findings prompted other studies from the same group, focusing on the possible role of pulmonary calcifications (Yigla et al., 2004) and endothelin-1 (ET-1) and nitric oxide (NO) (Nakhoul et al., 2005) in the pathogenesis of PH in HD patients. In the first study, in a group of HD patients, 57% of whom with PH, no correlation was found with pulmonary calcification detected by technetium-99m diphosphonate scanning. In the second study they found ET-1 level to be higher in HD patients, both with and without PH, than in controls; no correlation with PAP<sub>s</sub> could be demonstrated, however. Indeed, lower NO metabolites were detected in HD patients with PH than in those without and in controls, as well as a blunted increase during the HD session. Two years later, another group reported on PH in chronic renal failure (CRF) patients

(Havlucu et al., 2007). Despite severe exclusion criteria, they found a echocardiographically estimated  $PAP_s \geq 35$  mmHg in 14 out of 25 (56%) patients already on HD and in 9 out of 23 (39%) patients not yet on dialysis. Patients with PH showed significantly higher CO, higher serum levels of parathyroid hormone (PTH), higher calcium-phosphate product and a longer CRF duration. They also found that the presence of an AVF was associated with a higher risk of PH, and that Doppler estimated AVF flow correlated with  $PAP_s$ . Patients were reevaluated at least 6 months later: quite interestingly, while patients still in pre-dialysis had deteriorated, in those who had started HD in the meanwhile  $PAP_s$ , blood pressure (BP) and serum PTH had overall decreased and ejection fraction increased. In a very similar study (Abdelwhab & Elshinnawy, 2008), PH was detected in 20 out of 45 (44%) patients on HD and in 10 out of 31 (32%) pre-dialysis patients on conservative treatment. Dialysis patients with PH had higher AVF blood flow, higher prevalence of left ventricular diastolic dysfunction and higher NT-proBNP and  $TXB_2$  levels. A role for inflammation in the pathogenesis of PH in HD was addressed by researchers from Taiwan (Yu et al., 2009). In this study high sensitivity-C reactive protein (hs-CRP) and a number of cytokines were measured in 39 patients on long standing maintenance HD and correlated with the presence of PH. The prevalence of PH was remarkably high (61%), and patients with PH exhibited higher CO, higher AVF blood flow rate and, intriguingly, poorer residual renal function (RRF) and dialytic solute clearances. Serum levels of hs-CRP, IL-1 $\beta$ , TNF- $\alpha$ , IL-6 were significantly higher in patients with PH than in those without.

In all these studies, echocardiography was performed within one hour from the completion of the HD procedure, in order to possibly avoid the effect of volume overload, almost always present immediately before the haemodialysis treatment in the most commonly used thrice weekly in-centre schedule.  $PAP_s$  was measured according to the modified Bernoulli equation:  $PAP = 4 \times (\text{peak tricuspid regurgitant jet velocity})^2 + 10$  mmHg (estimated right atrial pressure, RAP). Patients with cardiac, pulmonary or systemic diseases known to associate with PH were *a priori* excluded in these earlier studies. A somewhat different approach was used in a prospective study from Texas, USA (Ramasubbu et al, 2010), including 90 HD patients (64% afro-american, 18% Hispanic and 18% Caucasian), dialyzed trough arterio-venous graft (44%), AVF (40%) or catheters (16%). Patients underwent comprehensive echocardiographic examination before the haemodialysis session, because it was felt that the pre-dialysis status of the patients more closely reflects the chronic volume status than the immediate post dialysis “dry weight” state. Furthermore, PH was defined as a peak tricuspid regurgitant (TR) jet velocity  $\geq 2,5$  m/sec, and as “more severe PH” when TR jet velocity was  $\geq 3$  m/sec. Forty-two patients (42%) met the definition of PH, 18 of whom (20%) of more severe grade. Quite surprisingly, patients with PH did have a significantly lower BMI. As expected, on the other hand, patients with PH were found to have larger right atrial (RA) and right ventricular (RV) sizes, higher RAP, and a trend towards decreased RV function and more left ventricular (LV) hypertrophy. Mean LVEF tended to be lower with increasing  $PAP_s$ , but was still overall preserved. There was a trend to larger left atrial (LA) size with increasing  $PAP_s$ , consistent with significantly higher estimates of left sided filling pressures. After 12 months, 14 patients (15,6%) had died. Mortality was significantly higher in patients who had PH (26%), particularly in those with a TR jet velocity  $\geq 3$  m/sec. Patients who died had been longer on HD, and they had larger RA and RV sizes, worse RV function, more severe TR, significantly higher RAP,  $PAP_s$  and pulmonary capillary wedge pressure (PCWP). This study provides evidence that development of PH in HD patients may well reflect the consequence of chronic volume overload and

chronically elevated left heart filling pressures, suggesting that elevated PCWP may play a major role in PAP increase. Of note, in this study population 77% of the patients exhibited abnormal LV diastolic function, possibly the result of LVH and myocardial stiffness.

Three studies attempt to explore specifically the role of the AVF in determining PH in CKD patients. The first published study (Acarturk et al, 2008) used mean PAP calculated from the right ventricular outflow tract acceleration time according to the Mahan's equation ( $mPAP$  in mmHg =  $79 - 0.45 \times$  acceleration time in ms); AVF blood flow rate was estimated by Doppler sonography. Thirty-two patients were included, 24 with a radial and 8 with a brachial AVF created  $32 \pm 34$  months before evaluation. PH (defined as  $mPAP > 25$  mmHg) was detected in 14 patients (43%). Results confirmed the already reported relationship between PAP and cardiac index (CO normalized to body surface area) and disclosed a higher cardiac index in patients with PH. No direct relationship between AVF blood flow rate and  $mPAP$  could be demonstrated, however. The second study (Beigi et al, 2009), did find a statistically significant positive correlation between AVF flow and PAP in 34 patients studied before AVF creation and at least 6 months apart. The mean AVF flow was 1322 ml/min in patients without PH and 2750 ml/min in patients with PH, the latter being clearly higher than currently regarded as necessary and safe, even more when considering that the authors reported a negative correlation between PAP and ejection fraction (EF) before as well as after the creation of AVF. The third study (Ünal et al, 2010) included 20 patients evaluated before AVF creation and  $23 \pm 2$  months later, failed to find an effect of AVF creation on PAP, which indeed tend to decrease after AVF creation and initiation of RRT, and a correlation between PAP and AVF blood flow rate (truly not given). A further study with an original design has been recently published (Kiykim et al, 2010). Seventy-four HD patients dialyzed through permanent tunnelled jugular central venous catheter (CVC) were studied echocardiographically immediately before and at the end of a HD session with two different dialysis membrane - cellulose acetate and high-flux polysulfone - in a cross-over design. Pre-HD PH prevalence was remarkably high (68,8%, moderate in 40,5%). A significant PAP reduction and a significant correlation with UF volume was observed only when patients were dialyzed with the more biocompatible polysulfone membrane, suggesting a role for biocompatibility on short-term PAPs.

## 2.2 Pulmonary hypertension in patients on Peritoneal Dialysis

Apart from the data on 5 patients on peritoneal dialysis (PD) included in the control group of the first study from Yigla and co-workers (Yigla et al, 2003), none of whom found to have PH, the first study of PH in PD patients was published in 2007 (Kumbar et al, 2007). In this retrospective study including 36 patients undergoing echocardiographic evaluation on clinical indication, a PH prevalence of 42% was found. Due to the selection bias, however, patients with congestive heart failure and/or coronary artery disease were probably overrepresented in the study; indeed, patients with PH exhibited more dilated left ventricular chamber and their mean EF ( $46 \pm 19$  %) would have represented a reason for exclusion in most of the previously published studies. An unexplained higher PH prevalence in patients on continuous cycling PD (CCPD) as compared to continuous ambulatory PD (CAPD) was noted. Duration of PD was not reported, but overall residual renal function was marginal. Two years later, to date the largest study on PH in PD patients was published (Ünal et al, 2009). One hundred and thirty five, quite young ( $47 \pm 13$  years old)

patients on CAPD (64 females) were studied and, notably, this is the first study which included a bioelectrical impedance analysis to estimate the ratio of extracellular water (ECW) to total body water (TBW) and thus stratified patients according to volume status. PH was found in 17 patients (12,6%), who showed also significantly higher ECW/TBW ratio and lower serum albumin, triglyceride and ejection fraction. No differences were found between patients with PH and patients without in terms of age, gender, smoking, diabetes or hypertension, use of erythropoietin (EPO), duration of dialysis, systolic and diastolic blood pressure, body mass index (BMI), white blood cell count, haemoglobin (Hb), serum creatinine, solute clearances, residual glomerular filtration rate (GFR), alkaline phosphatase, intact parathyroid hormone (iPTH), hs-CRP, LDL and total cholesterol, calcium-phosphate product, amount of ultrafiltration (UF), left ventricular mass (LVM), and hypertrophy (LVH) and plasma level of asymmetric dimethylarginine (ADMA). Echocardiographically estimated PAP<sub>s</sub> correlated with ECW/TBW ratio, LVM and LVMI, and, inversely, with serum albumin, triglyceride, Hb and EF. In multivariate analysis, serum albumin, ECW/TBW and LVMI were found to be independent risk factors for PH. According to bioelectrical impedance analysis no patient was hypovolemic, 51 (37,8%) of the 135 patients were hypervolemic and 84 (62,2%) were normovolemic. Hypervolemic patients had lower Hb levels, higher mean systolic PAP and a significantly higher prevalence of PH (27,5% vs 3,6%,  $p=0.001$ ). These findings are highly suggestive of a major role for fluid overload in determining PH in PD patients and the same should hold true for all CKD disease patients, regardless of dialysis modality, and even for those on conservative pre-dialysis treatment. An Italian study (Fabbian et al, 2011) including 29 patients on HD and 27 patients on PD found PH in 22 patients (39%), and confirmed a higher prevalence in patient on HD (58,6% versus 18,5%,  $p=0.002$ ). Patients with PH had been longer on RRT, had higher inter-dialytic weight gain, lower diastolic pressure and ejection fraction than those without. PH positively correlated with diastolic left ventricular volume ( $r = 0.32$ ,  $p=0.013$ ) and negatively with EF ( $r = -0.54$ ,  $p< 0.0001$ ).

### 2.3 Pulmonary hypertension and mortality

The impact of PH on mortality of patients undergoing chronic HD was investigated by Yigla and co-workers (Yigla et al, 2009) in a retrospective study including 127 HD patients representative of the national cohort of patients on HD in Israel. Including also patients with already known cardiac disease, but using a higher threshold cut-off value ( $\geq 45$  mmHg) for PH definition, the prevalence of PH in the whole cohort was found to be 29,1%, and it was present before dialysis initiation in 13,4%, while developed after HD initiation in 15,7%. In latter group, the time interval to the first echocardiographic study showing PH was less than 1 year in 75% of the cases. No differences in baseline cardiac status could be demonstrated between patients without PH at any time and patients developing PH after the initiation of HD, that instead was significantly worse in patients with pre-existing PH. The overall 1-, 3-, and 5-year survival was 90.6, 66.9 and 52.8 %, respectively. Survival of patients with PH was significantly shorter than that of those without (78.6, 42.9 and 25.2 %, log-rank test  $p=0.0001$ ), regardless PH was present before dialysis initiation or developed thereafter. The age of non survivors at HD initiation was meaningfully higher, however, yet a survival advantage was found in 20 patients without PH matched to the group with PH developed after dialysis initiation for age, gender, aetiology of kidney disease, location of vascular access and comorbidity.

Very interestingly, when PAP<sub>s</sub> was analyzed as a continuous variable, as it is, the authors were able to demonstrate an adjusted hazard ratio (HR) for mortality of 1.5 for each 10 mmHg increase in PAP<sub>s</sub> (95% CI 1.2-1.9,  $p=0.0007$ ). One pitfall of this study is that patients who have had only one echocardiographic evaluation while on HD, showing no PH, were assumed and analyzed as having normal pre-HD PAP<sub>s</sub>, which is not necessarily true, as suggested by several papers reporting the possibility of actual modification of PAP in a substantial proportion of patients on RRT, which holds true in our experience.

## 2.4 Pulmonary hypertension and renal transplantation

The association between PH before transplantation and subsequent outcome was first addressed by a study from the Mayo Clinic College of Medicine, Rochester, MN, USA (Issa et al., 2008). In this retrospective analysis of 215 dialysis patients who have had an echocardiographic evaluation before renal transplantation, mean PAP<sub>s</sub> was found to be  $34\pm 10$  mmHg (range 21-71) in the whole cohort; 146 patients (68%) have PAP<sub>s</sub> < 35 mmHg (regarded as normal), 47 (22%) have moderately high PAP<sub>s</sub> (36-50 mm Hg) and 22 (10%) markedly elevated PAP<sub>s</sub> (> 50 mm Hg), suggestive of severe PH. Longer time on dialysis was the strongest correlate of higher PAP<sub>s</sub> pre-transplant ( $r= 0.252$ ,  $p < 0.001$ ), PH being detected in 25% of patients who had never been on RRT (pre-emptive Tx) or had received dialysis for less than 1 year, in 38% of those who had been on dialysis longer than 1 but less 2 years, and in 58% of those who have been on dialysis for more than 2 years before transplantation. Patients with severe PH had a significantly higher risk of death (HR 3.75, 1.17-11.97,  $p=0.025$ ) early after Tx than patients with lower PAP<sub>s</sub>. Age was associated with both PAP<sub>s</sub> and mortality in this study. A significantly lower prevalence of PH (17%) was found in a cohort of 500 younger patients studied as a part of pre-transplant evaluation (Bozbas et al, 2009), and again PH was associated with longer duration of dialysis and HD as the RRT modality versus PD. Amongst echocardiographic data, LVEF was significantly lower and right and left atria diameters greater in patients with PH than in those without. The prevalence of LVH was higher in patients with PH, while the percentage of patient with diastolic dysfunction was not significantly different. Another recently published study (Zlotnick et al, 2010) investigated the possible relationship between pre-transplant echocardiographically detected PH and early graft function. In 55 patients, 21 of whom (38%) with pH, the incidence of the composite outcome of delayed or slow graft function was found to be significantly higher in patients with pre-transplant PH (43 vs 6%,  $p=0.002$ ), supporting the hypothesis that pre-transplant pulmonary hypertension could represent an independent predictor of early graft dysfunction.

## 3. What we have done

Sant' Andrea Hospital is a tertiary 450-bed University Hospital which began its activity in 2003. At that time the burden of cardio-renal syndromes was increasingly recognized as an emerging epidemic and prompted a strict and motivated cooperation between Cardiologists and Nephrologists. In that context all patients with kidney disease underwent first a comprehensive cardiovascular evaluation by one experienced Cardiologist (L.D.B.), who acts as the referring physician responsible for individually tailored work up, treatment and follow up of patients with renal diseases. The first patients with CKD at our Institution were those referred to the nephrology outpatient clinic, the nephrology ward and the outpatients

dialysis facility. At the same time many patients with cardiac diseases were referred for a nephrological consultation due to evidence of renal dysfunction. This interplay helped to disclose a number of interesting and quite novel findings. Among these, the unexpected, and at that time largely underrecognized, high prevalence of elevated pulmonary artery pressure as detected by Doppler echocardiography was one of the main framework. At the beginning most CKD patients on maintenance RRT at our hospital had started dialysis elsewhere, with quite large differences of previous duration of RRT and co-morbidities burden. Pivotal to the evaluation of their cardiac status was conventional and tissue Doppler imaging (TDI) trans-thoracic echocardiography, performed by two sonographer-experienced Cardiologists (F.P. & G.M.C.). In more detail, patients with stage 5 CKD on RRT underwent two-dimensional and M-mode study using an Acuson Sequoia® C 256 ultrasound machine. Left ventricular diameters and wall thickness were measured according to the American Society of Echocardiography, left ventricular volumes were estimated using the z-derived method. LVEF was calculated using the Teicholz formula and further confirmed with Simpson's technique in the 4-chamber view. Pulsed-wave Doppler of mitral inflow velocity was performed. The maximal tricuspid regurgitation velocity was measured by continuous wave Doppler echocardiography from the apical 4-chamber view. The highest peak velocity was recorded and the average peak velocity from 3 beats were calculated and used to calculate systolic pulmonary pressure according to the modified Bernoulli equation. Pulmonary hypertension was defined as a value of systolic pulmonary pressure > 35 mmHg at rest. Right ventricular diameters were measured in the long axis view. EF of the right ventricle was calculated by using the Simpson's formula from the apical 4-chamber view. Early (E) and late (A) right ventricular inflow velocity were measured with pulse-wave Doppler by placing the sample volume in between the tips of the tricuspid valve in the apical 4-chamber window. TDI spectral signal was acquired from the apical 4-chamber view, with the sample volume placed along the lateral and septal tricuspid annulus. The systolic myocardial velocity (Sm), protodiastolic myocardial velocity (Em), and late peak diastolic myocardial velocity (Am) were measured. The E/Em ratio, an index of ventricular filling pressure, was calculated. Ejection time, isovolumic relaxation and contraction time were also measured. Regional TDI myocardial performance index (MPI) was calculated. Average regional TDI MPI of the right ventricle was calculated as follow:  $(MPI_{lateral} + MPI_{septal}) / 2$ . Right ventricular dysfunction (RVD) was defined by an average regional MPI value > 2 SD from the mean of the values derived from 100 healthy subjects ( $MPI > 0.53$ ). An early analysis included 68 patients on RRT, 54 (79%) on thrice weekly HD and 14 (21%) on PD, who did not differ in age, gender, height, weight, BMI, BSA, blood pressure, heart rate, serum calcium, phosphate, Ca x P product, uric acid, Hb, total cholesterol, triglyceride and total protein. Patients on PD had however significantly higher HDL cholesterol, lower serum albumin, shorter duration of RRT and more preserved residual renal function (RRF) than their HD counterpart. Patients on HD showed a significantly higher left and right ventricular wall thickness, higher  $PAP_s$  ( $35 \pm 8$  versus  $28 \pm 9$  mmHg) and higher left ventricular mass index ( $p < 0.01$ ). A significant correlation was found between  $PAP_s$  and some measures of diastolic and systolic function of the right ventricle, such as isovolumic relaxation time (IVRT) ( $r = 0.414$ ,  $p = 0.003$ ) and Sm ( $r = -0.454$ ,  $p = 0.001$ ). Both these measures were significantly more compromised in the HD cohort. As long as CKD patients new to dialysis entered our RRT program, we were able to extend our observation in a larger study (Paneni et al, 2010), including 94 patients on HD, 62 dialyzed

through a radial AVF and 32 through a brachial AVF, and 26 on PD, most of whom on nightly automated PD (APD), compared with 100 healthy controls matched for age, gender and BMI. Patients on RRT did not differ with regards to the prevalence of hypertension and diabetes and type of medications used. Duration of dialysis tended to be longer in HD patients ( $45 \pm 3$  months versus  $37 \pm 3$  in patients on PD) but this difference was no longer statistically significant. LV diameters and volumes were higher in dialysis patients than in controls. LVEF was significantly lower in HD patients than in PD patients and controls. No significant differences in the indices of systolic and diastolic function were found between HD patients with radial or brachial AVF.  $PAP_s$  was significantly higher in HD patients than in PD patients and controls ( $38.9 \pm 6.8$ ,  $29.7 \pm 6.7$  and  $21.7 \pm 6.8$  mmHg, respectively,  $p < 0.001$ ). Patients on HD presented larger right ventricular diameters than PD patients and controls; RVEF was significantly reduced in dialysis patients as compared to controls, but to a different extent in the HD and PD group. TDI indices of diastolic and systolic function were significantly lower in patients undergoing HD, and the impairment was more pronounced in those with a brachial AVF. Compared to PD patients, patients on HD showed a prolonged IVRT and higher E/EM ratio. Lateral and septal Sm velocities were reduced among HD patients, the greatest reduction being observed in patients with a brachial AVF. When right ventricular dysfunction was defined by a TDI MPI  $> 2$  SD from the mean value derived from healthy controls, RVD was identified in 79 (65.8%) dialysis patients, the prevalence being significantly higher in HD as compared to PD patients (71.3 versus 34.6%,  $p < 0.001$ ). RVD was significantly more prevalent in HD patients with a brachial versus radial AVF (90.6 versus 61.3%,  $p < 0.001$ ). TDI MPI of the right ventricle showed significant correlation with systolic PAP ( $r = 0.45$ ,  $p < 0.01$ ), Sm velocity measured at both lateral and septal tricuspid annulus, Em velocity, Am velocity, right and left ventricular EF. Linear regression analysis adjusted for age, gender, heart rate, duration of dialysis, dialysis adequacy and  $PAP_s$ , showed that HD treatment was independently associated with average TDI MPI of the right ventricle ( $\beta = 0.34$ ,  $p < 0.001$ ). Logistic regression analysis adjusted for the same confounding showed that patients on HD have an increased risk of RVD as compared to patient on PD (OR 6.3 95% CI 2-19.5,  $p < 0.001$ ). Our preliminary data deriving from longitudinal follow up examinations show that "aggressive" correction of over hydration, as addressed by bio-impedance spectroscopy, may result in significant reduction of  $PAP_s$  and improvement of most indices of diastolic and systolic function of both ventricle, thus supporting a major role for chronic volume overload in determining overall cardiac compromise in our CKD patients.

## 4. Summary

### 4.1 Diagnosis

The gold standard for the diagnosis of PH is right heart catheterization (RHC), usually performed as a pre-operative tool in cardiac surgery, for hemodynamic evaluation of the critically ill patient, or in the suspicion of severe PH. To the best of our knowledge, no study has been published to date systematically performing RHC in patients with kidney diseases. The whole literature on PH in CKD patients employed rather uniform echocardiographic criteria to detect  $PAP_s$ . Reliance on echocardiography to diagnose PH has recently been mitigated, especially when pre-load is not controlled. The most recent consensus conference on PH, held in Dana Point in 2008, do not mention anymore echocardiographic parameters

for the diagnosis of PH, while citing for the first time dialysis-dependent CKD as a self-standing entity among group 5, PH with unclear multifactorial mechanisms. It appears however unlikely that RHC will be largely used in this subset of patients, as long as the less invasive ultrasound study will refine to provide clinically adequate informations. To date, unfortunately, only the study from Ünal and co-workers on PD patients (Ünal et al, 2009) included an imperfect yet objective measure of the hydration status, which should be included in future studies on PH in CKD patients.

#### **4.2 The role of the AV haemodialysis access**

When PH was first detected in a high percentage of patients on maintenance HD, the possibility that AV access could play a major role in the development of PH was greatly emphasized. Subsequent studies, yet including relatively small numbers of patients, fail to demonstrate a major impact of AVF creation on PH in the short-medium term, with the possible exception of very high flow fistulas, in most cases brachial. It is our opinion that caution should be paid not to get excessively high, yet unnecessary, flow when creating arterio-venous access for RRT.

#### **4.3 PH and dialysis modality**

That the AV access cannot tell the whole story is clearly indicated by the absence of PH in about 50% of HD patients carrying an AVF and, on the other side, by the occurrence of PH in CKD patients without. PH prevalence and severity has been consistently reported to be lower in PD patients than in their HD counterpart (Domenici et al, 2010). One possible and little investigated explanation could well be the usually higher RRF of patients on PD, at least in the first years of RRT. A role for the differences in biocompatibility and intermittency schedules of different dialysis modalities seems likely, but has not been adequately explored.

#### **4.4 PH, inflammation and endothelial dysfunction**

A correlation between inflammation markers and PAP<sub>s</sub> has been suggested, but this link has not been investigated in a longitudinal perspective. The pathogenetic relevance of endothelial dysfunction in CKD appears likely, as suggested by the increasing evidence of a common pathway in sleep disordered breathing, PH, early renal Tx outcome and markers of endothelial dysfunction.

#### **4.5 PH and renal Tx**

Current limited evidence suggests that echocardiographically-estimated PAP<sub>s</sub> and RV function should be part of the pre-transplant evaluation, because of their prognostic relevance. Successful renal Tx is associated with normalization of PAP<sub>s</sub> and improvement of cardiac function in most, but not all, transplanted patients.

### **5. Area for future research**

The prevalence and the clinical correlates of PH in CKD needs to be better defined in larger prospective studies, which should take into account volume status and RRF. Patients with

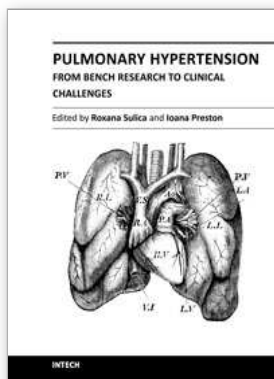


lower degree of renal impairment should be included, as well as patients with renal diseases but preserved glomerular filtration rate (GFR), such as nephrotics. PH has been recently detected in conjunction with sleep disordered breathing, a common co-morbidity in CKD patients that independently portends an unfavourable outcome. The prevalence and clinical relevance of PH in critically ill patients, its role as a risk factor for acute kidney injury (AKI) and its relevance to outcome warrants to be investigated. Studies focusing on the impact of different dialytic strategies and/or pharmacologic tools to efficaciously treat this condition in patients with CKD are urgently needed.

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## **Pulmonary Hypertension - From Bench Research to Clinical Challenges**

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The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; dysregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe dysregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

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University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821



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