Renal Replacement Therapy in Patients with Severe Precapillary Pulmonary Hypertension with Acute Right Heart Failure

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Key Words

Acute • Critical care • Pulmonary hypertension • Renal replacement therapy • Right ventricular failure

Abstract

Background: Renal replacement therapy has been suggested as a therapeutic option in the setting of acute right ventricular failure in patients with severe precapillary pulmonary hypertension. However, there are few data supporting this strategy. **Objectives:** To describe the clinical course and the prognosis of pulmonary hypertensive patients undergoing renal replacement therapy in the setting of acute right heart failure. **Methods:** This was a single-center retrospective study over an 11-year period. Data were collected from all patients with chronic precapillary pulmonary hypertension requiring catecholamine infusions for clinical worsening and acute kidney injury that necessitated renal replacement therapy. **Results:** Fourteen patients were included. At admission, patients had a blood urea of 28.2 mmol/l (22.3–41.2), a creatinine level of 496 μ mol/l (304–590), and a mean urine output in the 24 h preceding hospitalization of 200 ml (0–650). Sixty-eight renal replacement therapy sessions were performed, 36 of which were continuous and 32 of

which were intermittent. Systemic hypotension occurred in 16/32 intermittent and 16/36 continuous sessions ($p = 0.9$). Two patients died during a continuous session. The intensive care unit-related, 1-, and 3-month mortality was 46.7, 66.7, and 73.3%, respectively. **Conclusion:** Renal replacement therapy is feasible in the setting of acute right ventricular failure in patients with severe precapillary pulmonary hypertension but is associated with a poor prognosis. The best modality and timing in this population remain to be defined.

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Introduction

Severe precapillary pulmonary hypertension (PH) leads to chronically elevated pulmonary vascular resistance and right ventricular (RV) failure [1]. PH patients may experience severe acute RV failure that may be related to disease progression itself or to an acute intercurrent illness during the course of their disease [2]. There are very limited evidence-based data regarding the management of acute RV failure in PH patients, with, to our knowledge, only four cohort studies to date [3–6, 7]. Acute kidney injury (AKI) is frequently observed as a complication during such episodes and its prognostic significance has recently

been highlighted [4, 6, 7]. The precise pathophysiological pathways leading to decreased kidney function in PH remain unclear. Proposed mechanisms include venous congestion, decreased cardiac output and subsequent regional blood flow, and neurohormonal modifications [8]. Renal replacement therapy (RRT) may be considered as a therapeutic adjunct when AKI or severe volume overload develop as complications of acute right heart failure [9, 10]. However, there is no evidence-based data to support this strategy. Furthermore, it is not known whether the potential benefits of administration of RRT in this challenging patient population outweigh the risks, which may include hemodynamic instability or relate to venous access. Furthermore, the optimal timing for introduction of RRT is unclear, as is whether continuous or intermittent RRT is preferable. In an attempt to address these questions, we conducted a single-center retrospective study at the French National Reference Center for Pulmonary Hypertension, evaluating all PH patients with acute right-sided heart failure treated with RRT over an 11-year period.

Methods

Design

This was a retrospective single-center study.

Patients

All patients with chronic precapillary PH corresponding to pulmonary arterial hypertension (PAH) or inoperable chronic thromboembolic pulmonary hypertension (CTEPH) hospitalized at our center for acute (<7 days) clinical worsening of PH treated with catecholamines for severe right heart failure and/or low cardiac output, as previously described [4], were eligible for inclusion if they had AKI. They were included if RRT was initiated. The RIFLE criteria were used to define and classify AKI [11]. The diagnosis of precapillary PH was established according to current international guidelines (mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary artery wedge pressure ≤ 15 mm Hg measured during right heart catheterization). The study period began in May 2000 and ended in August 2011. This retrospective study had no consequence on patient management. All patients and families were informed on the admission leaflet that anonymous data could be used for academic research. According to French legislation, neither ethics committee approval nor informed patient consent is required for retrospective data collection. However, the database was anonymized and complied in compliance with the requirements of the Commission Nationale Informatique et Liberté, the organization dedicated to privacy, information technology, and civil rights in France. For the present study, this latter committee approved our data collection and their analysis on May 24, 2003. The approval number furnished by this committee was 842063. No patient included in our previous prospective analysis [4] was included in the present work.

Data

Baseline demographic data, serum level of creatinine and estimated glomerular filtration rate (eGFR), modified New York Heart Association (NYHA) functional class, and baseline pulmonary hemodynamic values corresponding to the most recent data obtained during a period of clinical stability (i.e. prior to an episode of acute clinical worsening) and information relating to the cause of clinical deterioration and usual therapies were collected. In addition, values for systemic arterial pressure, total diuresis for the 24 h preceding admission, serum creatinine, blood urea level, sodium, brain natriuretic peptide (BNP), and C-reactive protein (CRP) on the day of admission were recorded.

Patient status following intensive care unit (ICU) admission, and at 28 days, 3 months, and 6 months was determined. Finally, information relating to the type of RRT used, the settings relevant for each RRT session, and any treatment-related side effects were documented.

Renal Replacement Therapy

For both techniques, a 12-French Arrow® dialysis catheter (Teleflex, Durham, N.C., USA) was inserted in the right jugular vein.

AK 100® (prior to 2008) and AK 200 Ultra S® series monitors (from 2008 onwards) (Gambro, Stockholm, Sweden) were used in the IRRT procedures. Circuits were primed with 2 liters of 0.9% saline solution to which 20,000 units of heparin were added. The conductivity and temperature of the dialysate were set on an individual basis. Blood flow was progressively increased to achieve the desired value. Dialysate flow was set at 500 ml/min. APS-21U polysulfone membranes (Asahi Kasei Corporation®, Tokyo, Japan) were used.

Continuous veno-venous hemodiafiltrations were performed on Prisma® (Hospal France, Meyzieu, France) until 2007 and Multifiltrate® (Fresenius France, Fresnes, France) monitors after 2008. Ultraflux AV600S polysulfone membranes (Fresenius France, Fresnes, France) were used. Circuits were primed with 2 liters of 0.9% saline solution to which 20,000 units of heparin were added.

Statistical Analysis

Statistical analysis was performed using Statview 4.5 software (SAS Institute, Cary, N.C., USA). Results are expressed as medians (25th to 75th percentiles). Percentages and categorical variables were compared using the χ^2 test. Continuous variables were compared using the Mann-Whitney test. Survival was studied with Kaplan-Meier analysis followed by a log-rank test when appropriate. $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Fourteen patients were included (table 1) (as an idea of the denominator, the medical and respiratory ICUs in our institution admitted about 400 and 300 patients, respectively, per year during the study period). The median age at admission was 62.5 years (53.2–72.9), with a fe-

Table 1. Baseline population characteristics

Age, years	64.5 (53.7–73.4)
Female/male ratio	9/5
Body mass index	26.4 (22.3–28.0)
Serum level of creatinine, $\mu\text{mol/l}$	118 (87.5–125)
eGFR, ml/min/1.73 m^2	55 (41.4–61.5)
Type of PAH, n	
Idiopathic PAH	4
Inoperable CTEPH	4
Systemic sclerosis-associated PAH	2
Anorexigen-induced PAH	1
Microscopic polyangiitis-related PAH	1
Portal cavernoma-related PAH	1
Patent ductus arteriosus-related PAH	1
NYHA functional class when last stable, n	
II	2
III	12
Pulmonary hemodynamic when last stable	
mPAP, mm Hg	59.0 (57.3–62)
PVR, Wood units $\cdot \text{m}^2$	14.3 (8.8–23.9)
RAP, mm Hg	12 (9.3–15.8)
CI, l/min/m^2	2.47 (2.3–3.1)
PCWP, mm Hg	12 (8–15)

Values are presented as medians (25th to 75th percentiles) unless otherwise stated. mPAP = Mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure.

Table 2. Clinical and biological characteristics of the patients at admission

Systemic systolic arterial pressure, mm Hg	126 (108–154)
Systemic diastolic arterial pressure, mm Hg	59 (45–72)
Systemic mean arterial pressure, mm Hg	84 (64–88)
UO during 24 h prior to admission, ml	200 (0–650)
Sodium serum level, mmol/l	127 (124–133)
Potassium serum level, mmol/l	4.4 (3.9–5.2)
CRP, mg/l	46 (27–188)
BNP, ng/l	3,580 (924–4,635)
Urea serum level, mmol/l	28.2 (22.3–41.2)
Creatinine serum level, $\mu\text{mol/l}$	496 (304–590)

Values are presented as medians (25th to 75th percentiles) unless otherwise stated. BNP = Brain natriuretic peptide; UO = urine output.

male/male ratio of 1.5/1. The median body mass index was 26.7 (22.6–27.3). Thirteen patients were transferred to the medical ICU after a stay in the respiratory ICU (hemodialysis is available only in the medical ICU at our center) and one patient was transferred directly from the

respiratory ward. The mean interval between the first diagnosis of PH and ICU admission was 1.6 years (0.8–5.7). The patients were classified as having idiopathic PAH (n = 4), inoperable chronic thromboembolic hypertension (CTEPH, n = 4), systemic sclerosis-associated PAH (n = 2), anorexigen-induced PAH (n = 1), microscopic polyangiitis-related PAH (n = 1), porto-pulmonary hypertension (n = 1), and PAH associated with patent ductus arteriosus (n = 1). PH therapy at admission included intravenous prostacyclin alone (n = 4), intravenous prostacyclin combined with sildenafil (n = 1), intravenous prostacyclin combined with both bosentan and sildenafil (n = 1), bosentan alone (n = 2), bosentan in combination with sildenafil (n = 2), or no specific treatment (n = 5). The previous hemodynamic evaluation when last stable was available for 12 patients, had been performed 3.5 years (0.1–8.1) prior to admission, and showed severe hemodynamic impairment. The median baseline serum creatinine when last stable was 118 $\mu\text{mol/l}$ (87.5–125), with an eGFR of 55 ml/min/1.73 m^2 (41.4–61.5). Two patients had known chronic kidney failure prior to the episode of clinical worsening.

Characteristics at Admission in the ICU

The clinical and biological characteristics at admission are summarized in table 2. Patients had severe renal impairment as evidenced by a median blood urea level of 28.2 mmol/l (22.3–41.2) and a serum creatinine level of 496 $\mu\text{mol/l}$ (304–590). The total urine output during the 24 h before admission was available for all but 1 patient [200 ml (0–650)]. A cause for acute worsening was identified in 8 cases (53%), corresponding to sepsis (no urinary tract infections) (n = 6), pericarditis (n = 1), and gastrointestinal bleeding (n = 1). None of the two patients with porto-pulmonary hypertension met the hepato-renal syndrome criteria.

At admission, 13 patients were treated with dobutamine at a median infusion rate of 10 $\mu\text{g/kg/min}$ (5–12.5), 9 patients received norepinephrine at a median infusion rate of 2.0 mg/h (0.5–3.7), 12 patients received continuous inhaled nitric oxide, and 12 patients received intravenous furosemide at a median dose of 500 mg/day (375–1,000). Patients continued their specific PH therapy while in the ICU. No patients underwent mechanical ventilation during the study period.

Renal Replacement Therapy

Precise indications for RRT are listed as follows: 13 patients had oligoanuria, with subsequent life-threatening hyperkalemia in 4 cases and serum urea above 35

Fig. 1. Comparison of survival of patients from the current study treated with RRT (continuous line) and the previously described cohort of patients with acute right heart failure without need for RRT (dotted line) [4]. Log-rank test, $p = 0.02$.

mmol/l in 3 of these patients. All patients also exhibited clinical features of volume overload, the most common sign being lower limb edema. Sixty-eight RRT sessions were performed in total, corresponding to 32 IRRT and 36 CRRT sessions. Patients had a median of 3 sessions (1–4). This number was not defined according to the number of days spent with RRT but rather by the number of new sessions applied to the patients. Because of the retrospective nature of the study, no predefined RRT pacing or dose was determined. The RRT settings are summarized in table 3. Episodes of systemic hypotension occurred in 16 of 32 intermittent hemodialysis sessions (50%), which were complicated by a generalized convulsive episode in one patient and a syncopal episode in another. These hypotensive episodes were managed by increasing the rate of catecholamine infusion ($n = 8$), increasing the dose of inhaled nitric oxide rate ($n = 2$), or modification of the ultrafiltration rate ($n = 2$). Technical problems occurred during 4 RRT sessions including filter clotting ($n = 3$) or insufficient catheter output ($n = 1$), resulting in a session duration of less than 1 h in two cases. Systemic hypotension occurred in 16 of 36 continuous hemodiafiltration sessions (44.4%), which was not statistically different from that associated with IRRT ($p = 0.9$). These hypotensive episodes required initiation ($n = 1$) or an increase in the catecholamine infusion rate ($n = 10$). Two patients died of sudden cardiac arrest during a CRRT session.

Table 3. Renal replacement therapy settings

a Continuous hemofiltration settings

Blood flow rate, ml/min	150 (112–180)
Dialysis flow rate, ml/h	1,000 (1,000–1,500)
Filtration rate, ml/h	1,500 (1,125–2,000)
Ultrafiltration rate, ml/h	45.2 (30.6–63.1)
Duration of session, h	24 (20.5–50)
Anticoagulation with UFH (number of sessions)	25/36

b Intermittent hemodialysis settings

Blood flow rate, ml/min	200 (140–250)
Dialysate flow rate, ml/min	500 (500–500)
Ultrafiltration rate, ml/h	312 (125–405)
Duration of session, h	4.0 (3.75–4.5)
Anticoagulation, n	
UFH	5
LMWH	3
No anticoagulation, n	24

Values are presented as medians (25th to 75th percentiles) unless otherwise stated. UFH = Unfractionated heparin; LMWH = low molecular weight heparin.

Outcome

The median ICU length of stay was 5 days (2–12). The mortality rate for this cohort of PH patients undergoing RRT was 46.7% in the ICU, 66.7% at 28 days, and 73.3% at 3 months. No demographic, clinical, or biological differences were found between the patients according to ICU survival (data not shown). By comparison, the ICU length of stay and survival rates recorded for the previous cohort of PH patients hospitalized in the respiratory ICU without RRT were 14 days and 43.6%, respectively (fig. 1) [4]. These study groups are compared in table 4.

The two patients for whom long-term renal recovery could be evaluated recovered and did not require chronic RRT.

Discussion

This study reports for the first time the outcome of PH patients with acute right heart failure treated with RRT. Although the ICU mortality for this population is extremely high, it is comparable to that previously reported by our group for PH patients with acute clinical worsening in whom RRT was not required [4]. Nevertheless, the

Table 4. Comparison of baseline, treatment, clinical, and biological patterns between the presently described population and the one previously described

	RRT (n = 15)	No RRT (n = 46)	p
Age, years	64.5 (53.7–73.4)	50.1 (38.5–63.6)	0.009
Gender, F/M	9/6	31/15	0.6
Triggering factor	8/15	20/46	0.7
Prior hemodynamic data when last stable			
mPAP, mm Hg	58.5 (56.5–62)	52.0 (47–60)	0.06
CI, l/min/m ²	2.49 (2.34–3.27)	2.23 (2.01–2.67)	0.1
RAP, mm Hg	12 (8.9–15.5)	12.0 (7.0–16.0)	0.7
PVR, WU	14.3 (8.8–22.6)	12.7 (9.4–16.9)	0.9
Systemic mean arterial pressure, mm Hg	84 (63–91)	65.0 (58–71)	0.02
Sodium serum level, mmol/l	127 (124–133)	135 (130–137)	0.003
Creatinine serum level, µmol/l	496 (304–590)	100 (83.8–154)	<0.0001
CRP, mg/l	46 (27–188)	18 (3–59)	0.03
BNP, ng/l	3,580 (924–4,635)	809 (567–1,300)	0.04
Dobutamine treatment	14/15	41/46	0.9
Norepinephrine treatment	9/15	9/46	0.04
Norepinephrine rate, mg/h	2.0 (0.5–3.7)	0.5 (0.5–0.9)	0.04
Inhaled nitric oxide treatment	3/15	2/46	0.08

Values are presented as medians (25th to 75th percentiles) unless otherwise stated. mPAP = Mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; CI = cardiac index.

overall mortality at 3 months is higher in the group of patients receiving RRT although, as illustrated in table 4, this may result from the previous cohort being an older population with more severe disease.

In non-PH patients, considerable debate remains with regard to which RRT technique is preferable in unstable patients with AKI treated in the ICU setting. Recent review articles and meta-analyses have found no differences between the two modalities in terms of ICU mortality, hemodynamic instability, episodes of hypotension, or escalation in vasopressor therapy [12–15]. However, the relative potential merits of the different RRT approaches as they apply to PH patients have not been specifically addressed. The rate of hypotension during RRT sessions in our patients is comparable with that described in general ICU populations for both CRRT and IRRT [13]. Among our cohort, the two patients who died during CRRT had a low systemic arterial pressure despite vasopressor infusion at admission but underwent RRT because of anuria-associated severe hyperkalemia and fluid overload. Although intermittent dialysis was associated with a higher rate of hypotensive episodes in our study, this difference did not reach statistical significance. It has to be underlined that several mechanisms leading to systemic hypotension during RRT, regardless of the setting, can occur. Neurohormonal disturbances, fluid shifts, and osmotic

rapid modifications have been described [16]. We cannot be precise about the abnormalities involved in our cohort of patients, but one may hypothesize that all of the aforementioned mechanisms may play a part, with severe consequences due to the hemodynamic background of this population. Because of the relatively small number of patients studied, our series lacked power to detect statistical differences in patient outcomes when the two dialysis modes were compared. We therefore cannot provide a firm conclusion in support of one over the other.

AKI was defined according to the RIFLE classification in our study [11]. All of the patients exhibited biological or clinical criteria defining at least the ‘injury’ level of the classification. As in general ICU populations, the optimal timing RRT initiation in PH patients exhibiting AKI remains unclear. One might argue that earlier RRT might have led to improved outcomes, as is suggested in other patient populations [15, 17]. However, the current data confirm that introduction of RRT in unstable PAH patients may be hazardous and is associated with poor outcomes. In our cohort, RRT-induced systemic hypotension resulted in the death of two patients and in severe adverse events in two others (one episode of seizure and one episode of syncope). As a result, our policy is now to delay RRT in the absence of anuria, uremic complications or intractable severe acidosis or hyperkalemia.

Although we acknowledge that important limitations in the comparisons made between the two populations preclude firm conclusions, the higher mortality of patients undergoing RRT raises the question of whether it is the severity of these patients, the specific outcome associated with AKI, or RRT itself that confers a worse prognosis. Indeed, a recently published study identified RRT as an independent negatively prognostic factor in general ICU patients [18]. Nonetheless, it is widely accepted that RRT is the cornerstone for ICU patients with AKI [19]. Furthermore, studies specifically evaluating PH patients are lacking. As previously described, AKI arising as a complication of acute heart failure in PAH, without use of RRT, is a strong prognostic marker by itself [4]. The poor outcome of our patients treated by RRT may also be explained by the severity of heart failure, which is further underlined by the comparison of this cohort with the one we previously described [4]. Patients treated with RRT are older, are more often treated with norepinephrine, and have much higher levels of BNP and lower natremia, though kidney failure itself may have influenced some of these variables. While it is not possible to state the actual benefit conferred by RRT in that setting, it must be emphasized that RRT should be considered as an acceptable treatment option in PH patients with life-threatening complications of AKI.

Our data show that PH patients with clinical worsening who require RRT have a dismal prognosis, although we can not state whether RRT itself, the severity of the patients, or both can explain it. This raises the question of novel therapeutic approaches, such as early listing for lung transplantation (for eligible patients) and/or cardiac assist devices when AKI develops in the setting of heart failure [20–22]. RRT while on interventional lung assist membrane ventilator treatment in ARDS has been evaluated and proved favorable in ICU outcomes as a bridge in transplanted patients [23]. However, both pretransplantation kidney injury and inotropic support requirement are recognized as risk factors for increased posttransplantation mortality [24] and are associated with a complicated peri- and postoperative course [25]. Nevertheless, it seems of paramount importance to estimate very early the suitability of such new management strategies in these patients, as it might be the more favorable strategy for a subset of them.

Our study has several limitations that should be highlighted. Whether the two patients with preexisting chronic kidney failure should have been included is debatable as this may have biased baseline biological variables and/or survival analysis. Nevertheless, both pa-

tients had nonoliguric chronic renal failure prior to the acute episode of clinical worsening and otherwise met the inclusion criteria for our study. One of these patients died during ICU admission while the other was discharged from the hospital thereafter. Exclusion of these patients from the analysis did not significantly change the results (data not shown). Considering the retrospective design of the study, we could not evaluate the contribution of identified RV failure triggers such as sepsis, and we could not exclude a part of the baseline disease in kidney injury. No specific monitoring such as echocardiography or right heart catheter has been systematically performed and these data are not available for the vast majority of the included patients, preventing us from including it in the analysis. It has to be underlined that the retrospective design of the study prevented us from testing the RRT-induced relief of symptoms, or changes in the quality of life.

This is a retrospective single-center study. However, our respiratory ICU forms part of the National Reference Center for Pulmonary Hypertension which represents one of the largest pulmonary vascular units in the world. Approximately half of all French patients treated for PAH are followed up at our center [26]. In addition, it is one of the very few centers with an ICU dedicated to the care of PH patients. Our cohort was limited in size and our study lacked power to detect significant changes for several of the comparisons made. However, we chose to focus on a specific intervention (RRT) for an acute complication (AKI) for patients with evidence of decompensation of a rare condition (PH due to PAH or inoperable CTEPH), which explains the relatively small numbers of patients that could be identified for study. Indeed, Campo et al. [6] identified only 3 patients who underwent RRT among 90 PAH patients displaying acute heart failure over a 9-year study period, and Haddad et al. [7] identified 5 of such patients over a 10-year study period, further emphasizing the difficulty in studying this patient subgroup. Nevertheless, although rare, AKI in PH patients is a very challenging situation carrying an important prognostic significance. It has to be stressed that the risk of RRT in PH patients has been suspected for a long time by PH specialists, though never robustly evidenced. This might have led to a decrease in the number of situations in which RRT has been effectively proposed and performed. Indeed, one can hypothesize that this procedure has been delayed in a subset of patients because of the hypothetical hemodynamic risks and the absence of available circulatory assist or urgent lung transplantation.

Conclusion

Despite being a possible life-saving procedure, the use of RRT in our series of PH patients developing AKI in the setting of severe acute right heart failure was associated with a very poor patient outcome. This was, however, a retrospective survey of patient management rather than a prospective study powered to answer this question. These patients have a very poor prognosis when

admitted with acute right heart failure, and it would be important to ascertain any potential salvage therapies. Furthermore, identification of factors to guide clinicians with regard to the optimal timing of introduction of RRT and the choice of modality will also be important to study. The indication for novel therapeutic strategies such as mechanical circulatory assist devices in the setting of lung transplantation should also be carefully evaluated.

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