Reversible pulmonary hypertension in a kidney transplant with patent A-V fistula

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Abstract
Pulmonary hypertension (PH) occurs in end-stage renal disease (ESRD) patients on long-term haemodialysis (HD) using an arterio-venous (A-V) access and can be attenuated by either kidney transplantation per se or surgical fistula ligation/revision. We report an exceptional case with severe PH after kidney transplantation due to ESRD and prior chronic intermittent HD via a patent A-V fistula. Gold-standard right heart catheterization findings have—for the first time—proven that following surgical shunt ligation of the A-V fistula, haemodynamics normalized completely in this patient.

Keywords: arterio-venous access; end-stage renal disease; haemodialysis; right heart catheterization

Background
It is known that pulmonary hypertension (PH) might occur in patients with end-stage renal disease (ESRD) maintained on long-term haemodialysis (HD) as indicated by the current clinical classification of PH (4th World Symposium, Dana Point, California, 2008) [1]. An estimated 40% incidence of PH was reported in ESRD patients on chronic intermittent HD using an arterio-venous (A-V) access [2, 3].

Remarkably, kidney transplantation—whether the A-V fistula remained open or was surgically ligated—was reported to result in a notable pulmonary artery pressure (PAP) reduction [2]. This supports the hypothesis that PH in ESRD results largely from non-haemodynamic factors which can be resolved by normalization of the hormonal and metabolic changes as well as improvement of the inflammatory status following immunosuppressive therapy [2]. Furthermore, surgical ligation/revision of an A-V fistula was reported to attenuate PH in patients on chronic HD therapy and after kidney transplantation [4–6].

However, it remains to be demonstrated whether it is possible to completely normalize haemodynamics (in a kidney transplant recipient) after surgical shunt ligation of an A-V fistula and this should be achieved by the use of gold-standard right heart catheterization (RHC).

Case report
We report on a 68-year-old Caucasian female who presented with progressive hypoxic respiratory failure, recurrent pulmonary oedema, severe bilateral pleural effusions and shortness of breath worsening over the past few months (NYHA/WHO class IV).

Her past medical history revealed ESRD that was treated with chronic intermittent HD from 1995 to 2004, followed by cadaveric kidney transplantation 2004. HD had been performed using a native A-V fistula between the left radial artery and the left basilic vein that had remained patent throughout her renal replacement therapy and had become severely aneurysmatic during her HD treatment.

The patient also had a history of intermittent tachycardic atrial fibrillation and arterial hypertension.

Laboratory evaluation revealed a normal blood count, slightly elevated serum creatinine, moderately elevated liver enzymes and an N-terminal pro-brain natriuretic peptide (NT-proBNP) of >70 000 pg/mL.

Medication upon admission included mycophenolate mofetil, tacrolimus, prednisone, torsemide, metoprolol and enoxaparin.

Repeated chest radiographs during the hospital stay revealed progressive bilateral pleural effusions and bilateral enlargement of the central pulmonary vasculature. Transthoracic echocardiography displayed a normal left ventricular ejection fraction, no signs of diastolic left ventricular dysfunction, dilated left and right atria, slight mitral and tricuspid valve regurgitation and a hypertrophic right ventricle, and there was no inspiratory collapse of the enlarged inferior vena cava. Left coronary angiography did not reveal any relevant pathological findings. The results of the initial RHC after admission are summarized in Table 1. Due to clinical worsening over a few weeks, a second RHC was performed (Table 1). Here, short-term (60 s) external manual compression of the A-V fistula during RHC resulted in a reduction in cardiac
output (CO) from 5.7 to 3.8 L/min, suggesting a significant bypass volume. This corresponded well with an estimated flow via the A-V fistula of 2.6 L/min (46% of the CO) as assessed by duplex sonography.

Based on the clinical findings and the RHC results, the decision was made to surgically ligate the A-V fistula. At a follow-up visit 3 months later, the patient presented without shortness of breath, no signs of hypoxia and a marked decrease in NT-proBNP concentration from >70,000 to 9778 pg/mL. The chest radiograph displayed only marginal residual bilateral pleural effusions with slight bilateral enlargement of the central pulmonary vasculature. A subsequent RHC revealed normalization of both mean PAP and pulmonary vascular resistance (PVR), as well as normal oxygenation breathing ambient air (Table 1).

**Discussion**

Based on the Dana Point PH classification, this case is best categorized in Group 5 (Miscellaneous) as an ESRD patient maintained on long-term HD [1]. However, this patient fulfills criteria for pulmonary arterial hypertension (PAH) [1] and the pathophysiological conditions with increased CO due to systemic A-V shunting (over a total of 16 years) resemble those of patients with congenital systemic-to-pulmonary shunts (Group 1.3.2.). In this context, the development of PAH is associated with persistent exposure of the pulmonary vasculature to both increased blood flow and pressure, resulting in pulmonary obstructive arteriopathy that leads to an increase in PVR [1].

Our patient met several criteria for high-output cardiac failure, defined as symptoms of cardiac failure (dyspnoea at rest, pulmonary oedema) in the presence of a cardiac index above normal (>3.0 L/min/m²). Interestingly, unlike previous reports which suggested post-capillary PH in the presence of impaired left heart function with remarkably elevated pulmonary artery wedge pressures (PAWP) [4, 6], RHC results suggested pre-capillary PH in our patient. However, PAWP before shunt ligation reached borderline values which might further increase during physical exercise. This might contribute to the observed findings and symptoms. Importantly, PAWP achieved low-normal values after the intervention. This finding, along with results from echocardiography, makes the presence of (diastolic and/or systolic) left ventricular dysfunction very unlikely in this case.

Surprisingly, our patient presented with severe PH several years after successful kidney transplantation, suggesting that kidney transplantation per se does not necessarily prevent the abnormal haemodynamics associated with A-V access fistulas. PH in HD patients caused by an A-V fistula differs from other entities since it is (at least partially) reversible after correction of the increased CO, suggesting that unlike in other types of PH, the pulmonary vasculature remains largely intact, and only undergoes minor remodelling in HD patients [2]. It might be speculated that mainly the reduction in excessive pulmonary flow per se achieves the reduction in PAP in these cases. However, this is challenged by the aforementioned observation that kidney transplantation has been reported to result in normalization of the haemodynamics even if the A-V access fistula remained patent. Furthermore, if this assumption holds true, one would expect that elevated PAP levels normalize in all cases following shunt ligation. This, however, is obviously not the case as discussed in the following paragraph.

Our case is unique since it is—to the best of our knowledge—the first to demonstrate severe PH in the presence of A-V fistula the complete normalization of haemodynamics after surgical shunt ligation (unlike the case in which mean PAP remained pathological with 28 mmHg and the A-V shunt was revised rather than ligated [6]) by the use of gold-standard RHC prior to and after surgical intervention rather than sole trans-thoracic echocardiography and additional surrogate parameters like in earlier reports [2–5] and presents on pre-capillary PH (unlike cases in which PAWP was notably elevated [6]).

As suggested by MacRae et al. [4], we conclude that patients with persistent A-V fistulas (after kidney transplantation) should be carefully monitored for signs of PH and surgical shunt ligation/revision has the potential to avoid the considerable morbidity and mortality associated with this condition.

**Conflict of interest statement.** None declared.

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