PRESENTATION

A 74-year-old male initially presented to the cardiology service in 2011 for evaluation of possible ischemic heart disease. The patient reported shortness of breath without chest discomfort after walking 100 to 200 yards (91.4 to 182.8 meters) (NYHA FC III). A persantine nuclear examination prior to initiation of dialysis for end-stage renal disease (ESRD) and prior to dyspnea becoming severe was reported by the patient as unremarkable. Dyspnea had been troublesome the last 3 to 3.5 years, was relatively stable, but was limiting to activities of daily living and exertion.

Past medical history was pertinent for hypertension, right kidney neoplasm, insulin dependent diabetes mellitus type II, hypothyroidism, paralysis of right hemidiaphragm, chronic anemia, and ESRD due to diabetic nephropathy (hemodialysis via left upper extremity arteriovenous fistula [AVF]). Social history: Tobacco, 36 to 54 pack years; stopped 33 years ago. He denied alcohol consumption or recreational drug use.


EKG: Axis 90 degrees, normal sinus rhythm and first-degree heart block.

Echocardiogram (August 2011): Normal left ventricle size with mild to moderate left ventricle hypertrophy, left ventricular ejection fraction (LVEF) 65%, no wall motion abnormalities, grade 2 diastolic dysfunction, mildly dilated left atrium, right ventricle (RV) upper limit normal size with normal systolic function, trivial tricuspid regurgitation with pulmonary artery systolic pressure (PASP) 47 mm Hg, mildly dilated right atrium, unchanged from August 2010.

Chest fluoroscopy: Paralysis of the right-hemidiaphragm.

Pulmonary function testing: FVC 2.38 L (54% predicted), FEV1 1.82 L (52% predicted), FEV1/FVC 76, FEF25-75 1.42 L/sec (41% predicted), TLC 5.40 L (79% predicted), DLCO corrected for hemoglobin 23.08 (84% predicted).

Arterial blood gas (resting room air): pH 7.38, PaO2 61 mm Hg, PaCO2 45 mm Hg and calculated bicarbonate 27 mmol/L.

At that point, it was felt that symptoms were likely caused by diastolic dysfunction from severe hypertensive heart disease. Symptoms were not felt to be ischemic, although there were multiple risk factors for coronary artery disease.

Multiple echocardiographic studies showed gradual progression of PASP from 40 mm Hg (2006, pre-fistula) to 90 mm Hg (November 2013); the latter echocardiogram also demonstrated severe RV dilation, moderate right atrium (RA) enlargement, ventricular interdependence with normal LVEF and grade 1-2 diastolic dysfunction (Figures 1–4).

Because of the previous echocardiogram (November 2013) and worsening symptoms, right heart catheterization (RHC; February 2014) was performed after hemodialysis: RA 15/13(10), RV 90/0(16), pulmonary arterial pressure (PAP) 96/31(58), pulmonary capillary wedge pressure (PCWP) 10/13(10), cardiac output/cardiac index (CO/CI) (TD) 7.0/3.6, CO/CI (Fick) 4.9/2.5, pulmonary vascular resistance (PVR) 7.4 WU, TPG 48.

Further evaluation included a low probability V/Q scan, normal LFTs and TSH. Sleep study was refused by patient.

To determine if the symptoms and the pulmonary hypertension could be secondary to AVF rather than anemia alone, RHC was repeated pre- and post-occlusion of the AVF (Table 1).

There was a 22.5% drop in cardiac output after occlusion of AVF for 5 minutes. To ameliorate high cardiac
output from the AVF, the fistula was surgically ligated and a tunneled dialysis catheter placed. Repeat RHC (October 2014) again demonstrated marked pulmonary hypertension despite closure of AVF, suggesting progression of intrinsic pulmonary vascular disease. Therapy with a PDE-5 inhibitor (sildenafil) and, 1 month later, an ERA (macitentan) was initiated. The patient reported no symptomatic improvement with sildenafil and thought he was a little worse when macitentan was added. Overall, there was no clear benefit with these therapies; however, there were no side effects, especially peripheral edema. Sildenafil was discontinued because of low blood pressure, and macitentan was discontinued by the patient’s nephrologist.

Because of lack of change in symptoms and a 6-minute walk distance of 183 m, RHC was repeated and showed mPAP of 50 mm Hg, pulmonary capillary wedge pressure of 13 mm Hg, and cardiac output of 8.36 L/min. Because of the high cardiac output, the presumably closed AVF was re-evaluated by fistulogram and demonstrated collateral blood flow from the brachial artery to the cephalic vein. The patient then underwent complete resection of the AVF. RHC 6 months later showed PAP 88/27 (53), PCWP 7, and CO/CI (TD) 6.54/3.41.

### Additional Data
NT-proBNP 18 710 pg/mL (09/14), 4379 pg/mL (06/15), 29 469 pg/mL (11/15)
Hepatitis B surface AB 451 (high) (07/06), negative hepatitis A, hepatitis C and other hepatitis B markers. AST 8 IU/L; ALT 16 IU/L (03/2011) and remained normal.

### Table 1. Right Heart Catheterization Parameters Before and After Occlusion (5 Minutes) of AV Fistula*

<table>
<thead>
<tr>
<th></th>
<th>Pre-Occlusion</th>
<th>Post-Occlusion</th>
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<tbody>
<tr>
<td>RA</td>
<td>16/14 (12) mm Hg</td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>86/8 (15) mm Hg</td>
<td></td>
</tr>
<tr>
<td>PAP</td>
<td>90/34 (56) mm Hg</td>
<td>88/31 (53) mm Hg</td>
</tr>
<tr>
<td>PCWP (mean)</td>
<td>10 mm Hg</td>
<td>11 mm Hg</td>
</tr>
<tr>
<td>CO/CI (TD)</td>
<td>6.24/3.27 L/min</td>
<td>4.89/2.56 L/min</td>
</tr>
<tr>
<td>CO/CI (Fick)</td>
<td>8.03/4.20 L/min</td>
<td>6.28/3.29 L/min</td>
</tr>
<tr>
<td>PVR</td>
<td>577 dyne sec/cm²</td>
<td>687 dyne sec/cm²</td>
</tr>
<tr>
<td>MVO2</td>
<td>70% on 2 L/min</td>
<td>63% on 2 L/min</td>
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*Abbreviations: RA: right atrium; RV: right ventricle; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CO/CI: cardiac output/cardiac index; PVR: pulmonary vascular resistance; MVO2: mixed venous O2.
He was restarted on macitentan but noted no improvement in DOE/SOB. Selexipag was added and discontinued because of intolerable headache. Eventually, the patient was started on epoprostenol (Veletri), but up-titrations were limited by hypotension even with addition of midodrine. The patient continued to deteriorate, and he suffered multiple hospitalizations because of falls, weakness, and fluid overload. Repeat RHC now demonstrated elevated PCWP that responded to dialysis. He unfortunately died after a fall.

**DISCUSSION**

Pulmonary hypertension (PH) secondary to high cardiac output from an AVF is an under-appreciated but well-described entity in patients with ESRD undergoing hemodialysis (WHO Group 3). It is usually difficult to diagnose as an isolated, major contributing factor to elevated pulmonary pressures.

It has previously been reported that ESRD patients treated with chronic hemodialysis via arteriovenous access/fistula develop cardiovascular complications including vascular calcification, cardiac-vascular calcification, and atherosclerotic coronary artery disease. Using Doppler echocardiography, pulmonary hypertension and an increase in cardiac output has been reported in 40% of ESRD patients on chronic hemodialysis via arteriovenous access (Abassi et al). Temporary closure of the arteriovenous access and successful kidney transplantation have resulted in a decrease in pulmonary artery pressure, sometimes to the normal range. It has been postulated that the pulmonary circulation in chronic hemodialysis patients may be in a vasoconstrictive state because of metabolic and hormonal derangements. The increase in pulmonary arterial pressure and cardiac output is most likely related to the large size of the arteriovenous access and subsequent increased flow through it, or to altered vascular resistance as a result of local vascular tone and function resulting from an imbalance between vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1. As described by Abassi et al, ESRD has been associated with reduced production of nitric oxide and enhanced synthesis of endothelin-1 by pulmonary vasculature resulting in pulmonary vasoconstriction. Formation of AV access results in increased cardiac output, which worsens existing PH or precipitates PH. PH then worsens with initiation of dialysis. Decreased nitric oxide production and intact endothelin-1 production, the latter a known powerful mitogen, appears to be associated with reduced survival.

Increased endothelin-1 activity has independently been reported in uremia and therefore the possibility that local concentrations of endothelin-1 are enhanced in the pulmonary tissue of hemodialysis patients with PH cannot be excluded. Therefore, the presence of both uremia and arterio-venous access mediated cardiac output elevation is thought essential for development of PH. This type of PH has been demonstrated to be almost completely reversible following reduction in cardiac output or the uremic state (Clarkson in Nakhoul et al.).

Anemia and fluid overload are often present in ESRD patients and may also contribute to the increase in pulmonary arterial pressure and high cardiac output. Excessive pulmonary calcification is found in ESRD patients on chronic hemodialysis. Calcifications can occur in the heart, lungs, and kidneys. In the lungs, calcium deposits have been found in the interstitium of the alveolar septum, bronchial walls, large airways, and pulmonary vessels; these metastatic calcifications are thought to contribute to the pathogenesis of PH in chronic hemodialysis patients by causing increased stiffness of the pulmonary vasculature.

Renal transplantation has been associated with reversibility of PH. Alternatively, surgical reduction of outsized arteriovenous access has been beneficial in instances in which reduction in cardiac output and PH have been demonstrated following temporary closure of the AVF. Finally, peritoneal dialysis may be an alternative for some patients.

Most commonly, however, the PH in these patients is related to diastolic dysfunction (HFpEF), chronic volume overload from inadequate dialysis, and secondary hyperparathyroidism. Secondary hyperparathyroidism is highly prevalent in PH, might be related to low levels of vitamin D, and might contribute to bone and possibly pulmonary vascular disease. Formation of intravascular pulmonary lesions and calcifications have been associated with secondary hyperparathyroidism.

ElSaid et al found that PH is highly prevalent among patients on hemodialysis and may be associated with mild to moderate impairment of cardiac systolic function. In this clinical scenario, PH seems related to chronic fluid volume overload and increased interdialytic weight gain.

Baseline and regular echocardiographic evaluation of PASP in patients on hemodialysis is recommended. Careful assessment of volume state along with encouraging patients to limit interdialytic weight gain may help reduce PASP.

DiLullo et al report a 40% prevalence of elevated pulmonary pressures in hemodialysis patients from both central venous catheter and AVF vascular access. It is proposed that secondary PH in ESRD is related to impairment in pulmonary circulation, chronic volume overload and increased levels of cytokines and growth factors such as fibroblast growth factor, platelet derived growth factor, and tissue growth factor-beta leading to fibrosis. In addition, endothelial dysfunction, lower levels of nitrous oxide species, and increased levels of serum endothelin and fibrin stores result in complete obliteration of pulmonary vessels by endothelial cells. Proliferation of myointimal vessel wall, intimal laminated fibrosis, thrombosis and obliteration of arteries are typical pathologic features of disease progression.

The RV has thin muscular walls and lower blood pressure and is not able to generate high vascular pressures. Tricuspid regurgitation and further right heart overload develop because of PH secondary to pressure overload and loss of right chamber distensibility. Interestingly, in an overloaded RV resulting from such physiological stresses, a single hemodialysis session has been shown to significantly improve RV function as measured by tricuspid annular plane systolic excursion (TAPSE).
Diagnosis of PH is suggested by the following echocardiographic findings, including right heart chamber dilation, D-shape of the right ventricle caused by flattening of the interventricular septum, absence of inferior vena cava inspiratory collapse, and small or absent a (atrial) wave, the latter on M-mode transthoracic echocardiography.

Doppler evaluation is quantitative and allows assessment of pulmonary arterial pressure by tricuspid and pulmonary regurgitation speed assay. Tricuspid regurgitation speed \( (V_{TR}) \) is evaluated by 4-chamber echocardiographic apical view with ultrasound probe following transvalvular flow to collect regurgitation volume. \( V_{TR} \) reveals the systolic pressure gradient between the 2 right heart sections. If right atrial pressure \( (RAP) \) is added, PASP is obtained:

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PASP = 4(V_{TR})^2 + RAP
\]

Moreover, PH is an independent risk factor for mortality and morbidity for ESRD patients on hemodialysis via an AVF. Measures to decrease fistula-related PH and increased cardiac output, including shunt reduction, ligation of fistula, adoption of peritoneal dialysis, or expediting renal transplantation, should be considered. Raina further reports that pulmonary hypertension in chronic kidney disease is typically associated with left heart disease (WHO Group 2). Further contributing factors to pulmonary venous congestion include left ventricular hypertrophy, systemic hypertension, ischemic heart disease, and left ventricular diastolic dysfunction. Pulmonary arterial hypertension (WHO Group 1) is not common in this population. PH has been described as an independent predictor of mortality in chronic kidney disease patients, especially those receiving renal replacement treatment. PH has been associated with early renal allograft dysfunction and reduced survival after renal transplantation, and for these reasons significant PH is a relative contraindication to renal transplant.

### Teaching Points

1. A hyperdynamic circulatory state from AVF in ESRD patients should be considered in the differential for causes of PH. Improvement in cardiac output and/or pulmonary pressures after obliterating or bypassing the fistula confirms this hypothesis. 
2. Measures to decrease fistula-related PH, including shunt reduction, fistula ligation, peritoneal dialysis, or kidney transplantation, should be considered.
3. Early screening for PH by echocardiography in ESRD patients may enable early intervention such as aggressive treatment of anemia and fluid overload status.

### References