

## DIFFICULT CASES IN HEART FAILURE

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Editors

## A Comparison of Nesiritide vs. Epoprostenol in a Patient With Precapillary Pulmonary Hypertension Due to Scleroderma Complicated by Postcapillary Pulmonary Hypertension

*To the best of our knowledge, acute decompensated left-sided heart failure with preserved left ventricular ejection fraction in a patient with scleroderma has not been previously reported. We describe a patient with severe pulmonary hypertension due to limited scleroderma in whom nesiritide led to marked reductions in pulmonary arterial and capillary wedge pressure as well as resolution of symptoms and pulmonary edema. Subsequent epoprostenol use was associated with an increase in pulmonary capillary wedge pressure and a recurrence of pulmonary edema. Thus, nesiritide may be the preferred agent in scleroderma patients with severe pulmonary hypertension and preserved left ventricular systolic function since epoprostenol may lead to adverse hemodynamic effects. (CHF. 2005;11:331–334) ©2005 CHF, Inc.*

A 46-year-old African-American woman was admitted to our hospital with complaints of dyspnea at rest, cough productive of yellow sputum, and lower extremity edema. A diagnosis of scleroderma was made 12 years earlier by a gastroenterologist who had noted severe gastrointestinal reflux disease secondary to achalasia. Six years later, pulmonary hypertension by Doppler Echo was also diagnosed. The patient had smoked one pack of cigarettes per day for 6 years, but quit 10 years before the diagnosis of pulmonary hypertension was established. A subsequent ventilation-perfusion scan was normal. Pulmonary function tests revealed a moderately restrictive defect with a severely reduced oxygen diffusing capacity (34% of normal controls). High-resolution CT of the chest demonstrated mild interstitial lung disease.

All of the above tests were consistent with the diagnosis of pulmonary arterial hypertension in the setting of limited scleroderma. The patient was evaluated at that time for lung transplantation but then refused further workup.

The patient was referred to our care 1 year before admission on continuous home oxygen therapy at a rate of 3–5 L/min, with target arterial O<sub>2</sub> saturation >90%. At the time, she was so dyspneic at rest that she was unable to complete her sentences, and was clearly World Health Organization (WHO) class IV. Her therapy also included warfarin and omeprazole but no vasodilators.

At that time, a transthoracic Echo revealed severe pulmonary hypertension with an estimated right pulmonary artery systolic pressure of 80 mm Hg. In addition, there was paradoxical

interventricular septal motion consistent with right ventricular (RV) pressure overload, right atrial dilation, RV hypertrophy, and RV dilation, as well as a small circumferential pericardial effusion. On the left side, there was concentric left ventricular (LV) hypertrophy with a wall thickness of 1.3 cm, normal LV systolic function (ejection fraction of 60%), and grade I diastolic dysfunction (impaired LV relaxation).

Around the time that the transthoracic Echo was performed, serum B-type natriuretic peptide (BNP) was measured at 150 pg/mL (normal, 0–100 pg/mL). The patient again refused right-sided heart catheterization, precluding the use of epoprostenol, and still refused to be considered for lung transplantation.

The vasodilator sildenafil at a dosage of 50 mg q.i.d. was added to her medical therapy. Within several days,

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the patient noted marked improvement in exercise tolerance and was able to speak without difficulty. Two weeks later, bosentan and furosemide were added. Three months later, her BNP normalized to 85 pg/mL, and the patient remained clinically stable for approximately 10 months.

Over the 2-month period preceding her admission, the patient's dyspnea progressively worsened and started to occur even at rest. She also developed bilateral lower extremity edema. The patient was compliant with medications and denied any dietary indiscretion with regard to sodium intake. On the day of admission, her arterial O<sub>2</sub> saturation was down to 75% despite receiving oxygen via nasal cannula at a rate of 5 L/min. She was admitted to the intensive care unit for further work-up and management of respiratory failure presumed to be secondary to precapillary pulmonary hypertension in the setting of limited scleroderma.

Physical examination revealed a thin, tachypneic (respiratory rate of 24 BPM) woman in moderate respiratory distress. Her oral temperature was 97.0°F and blood pressure was 118/60 mm Hg; she had a regular pulse with an increased heart rate of 108 bpm. Cardiovascular examination revealed an elevated jugular venous pressure of 12 cm H<sub>2</sub>O, accentuated pulmonic component of the second heart sound, a right- and left-sided third heart sound, a grade II/VI holosystolic murmur heard best at the LV apex, and 3+ bilateral lower extremity edema up to the knees. On lung auscultation, rales were present over approximately the lower two thirds of the lung fields. ECG findings showed sinus tachycardia at a rate of 118 bpm, low voltage in limb leads, RV hypertrophy, and nonspecific T wave changes.

Laboratory investigations demonstrated a microcytic anemia with a hemoglobin of 12.6 g/dL (baseline, 11.8 g/dL–13.0 g/dL), a mean corpuscular volume of 68 fL, an elevated BNP of 302 pg/dL, and a respiratory alkalosis with severe hypoxia (arterial blood gas revealed a pH of 7.5, a partial carbon

dioxide pressure of 34 mm Hg, and a partial oxygen pressure of 44 mm Hg while receiving oxygen via nasal cannula at a rate of 5 L/min).

Chest radiography revealed extensive bilateral infiltrates more pronounced than those on the patient's baseline chest film, which was consistent with new superimposed pulmonary edema. Precapillary pulmonary hypertension alone could not account for all of the above findings. The clinical findings of rales, pulmonary edema on chest radiography, and significant elevation of serum BNP were suggestive of superimposed left-sided heart failure.

Pulmonary artery catheterization confirmed the diagnosis of concomitant left-sided heart failure characterized by severely elevated pulmonary capillary wedge pressure (PCWP) (Table, baseline column). The patient was started on an IV infusion of nesiritide at a rate of 0.03 µg/kg/min and furosemide at 15 mg/h. She was also placed on continuous positive airway pressure of 8 cm of H<sub>2</sub>O with a 40% fraction of inspired O<sub>2</sub> and moxifloxacin, since an underlying pneumonia could not be excluded. Sildenafil and bosentan were continued.

Six hours later, repeat pulmonary catheter measurements showed marked improvement in right- and left-sided filling pressures with preservation of cardiac index (Table, post-nesiritide infusion column). Concomitant with the decrease in PCWP, the patient's dyspnea markedly improved and the pulmonary edema nearly resolved, as evidenced on chest radiography.

A transthoracic Echo performed a few hours later revealed preserved LV systolic function (ejection fraction of 70%). Moderate-to-large pericardial effusion without signs of tamponade was the only new finding compared with Echo performed 1 year before.

Nesiritide was continued for a total duration of 24 hours with resolution of dyspnea and pulmonary edema with normalization of her PCWP. Nesiritide was then replaced with a continuous infusion of epoprostenol titrated to a rate of 4 ng/kg/min while continuing IV furosemide. Following a 24-hour

infusion of epoprostenol, the patient redeveloped pulmonary edema and PCWP rose to near-baseline levels without any changes noted on a repeat transthoracic Echo (Table, post-epoprostenol infusion column).

Subsequently, the patient was restarted on nesiritide infusions with improved hemodynamics and resolution of dyspnea and pulmonary edema. She was discharged in stable condition on continuous nesiritide infusion at 0.03 µg/kg/min, an aldosterone antagonist, and continued on bosentan, sildenafil, and warfarin with urgent referral for lung or heart-lung transplantation.

## Discussion

Pulmonary arterial hypertension occurs in approximately 30%–35% of patients with scleroderma and confers a high mortality rate.<sup>1,2</sup> In the vast majority of patients with scleroderma, pulmonary hypertension is of the precapillary type whose hallmark is a normal PCWP.

To the best of our knowledge, this is the first reported case of noniatrogenic postcapillary (high PCWP) pulmonary hypertension in a scleroderma patient with overt left-sided heart failure and preserved LV systolic function. In addition, this is the third reported patient with scleroderma in whom epoprostenol infusion led to pulmonary edema with an increased PCWP and the first in whom nesiritide was shown to have a beneficial effect.

Whether our patient had true diastolic heart failure or merely heart failure in the absence of LV systolic dysfunction is difficult to answer. Echocardiographically, LV diastolic dysfunction progresses from pure abnormal LV relaxation (defined as a mitral inflow E/A peak velocity ratio <1) to a combination of abnormal LV relaxation and elevated LV pressure (pseudonormal and restrictive patterns in which E/A >1.4).

It is clear from the data that our normotensive patient had underlying abnormal LV relaxation in the setting of LV hypertrophy as demonstrated on the Echo performed 1 year before acute decompensation and after successful

treatment with nesiritide. Unfortunately, mitral inflow filling patterns were not measured during acute decompensation.

Impaired LV relaxation occurs frequently in patients with scleroderma.<sup>3-6</sup> This may be due to direct cardiac involvement leading to myocardial fibrosis, collagen remodeling, and microvascular ischemia or merely secondary to predisposing conditions (e.g., pulmonary hypertension, LV hypertrophy, systemic arterial hypertension).<sup>7</sup>

Although myocardial fibrosis may lead to LV systolic and/or diastolic dysfunction, acute decompensated left-sided heart failure occurs in <5% of patients with scleroderma and is usually seen in patients with reduced LV systolic function.<sup>8</sup> However, symptoms (dyspnea, paroxysmal nocturnal dyspnea, orthopnea) and signs (rales, S<sub>3</sub> and S<sub>4</sub> gallops, increased pulmonary vascular markings on chest radiography) of congestive heart failure in patients with scleroderma who have preserved LV systolic function have been previously reported but without any confirmatory hemodynamic data.<sup>9</sup>

Furthermore, the existing diastolic dysfunction may be complicated by ventricular interdependence due to RV dilatation and pressure overload from severe pulmonary hypertension. Paradoxical interventricular septal motion that develops as a consequence of elevated RV systolic pressure has been shown to lead to abnormal LV end-diastolic shape and impairment of early diastolic filling.<sup>10,11</sup>

Although we were not aware of any prior reported use of nesiritide in a scleroderma patient with precapillary pulmonary hypertension, we decided to use this natriuretic peptide analog in our patient since she presented with acute decompensated left-sided heart failure, a known indication for nesiritide therapy.

Nesiritide is known to improve hemodynamics through multiple mechanisms, including the lowering of preload and afterload, indirect

**Table.** Hemodynamic Parameters Before and After Treatment

HEMODYNAMIC PARAMETER	BASELINE	POST-NESIRITIDE INFUSION (0.03 µg/ kg/min FOR 6 HR)	POST-EPOPROSTENOL INFUSION (4 NG/KG/ MIN FOR 24 HR)
Mean right atrial pressure (mm Hg)	10	5	12
Pulmonary artery pressure (mm Hg)			
Systolic	98	63	80
Diastolic	42	27	32
Mean	70	45	51
Pulmonary vascular resistance (dyne · sec/cm <sup>5</sup> )	500	558	286
Pulmonary artery capillary wedge pressure (mm Hg)	40	12	30
Cardiac index (L/min/m <sup>2</sup> )	3.0	2.9	3.6
Systemic vascular resistance (dyne · sec/cm <sup>5</sup> )	1000	800	1100
Left ventricular ejection fraction by Echo (%)	60	70	70

improvement in cardiac output, diuresis/natriuresis, and neurohormonal blockade leading to suppression of circulating levels of aldosterone, norepinephrine, and endothelin.<sup>12-14</sup> It has also been shown to have significant pulmonary vasodilator effects in patients with postcapillary pulmonary hypertension<sup>15,16</sup> and to be beneficial in patients with diastolic heart failure by increasing isovolumic relaxation time.<sup>17,18</sup> Its use as a pulmonary arterial vasodilator in patients with isolated precapillary pulmonary hypertension is currently under investigation.

Our patient demonstrated a dramatic response to nesiritide manifested by a 70% reduction in PCWP and a 36% reduction in mean pulmonary arterial pressure. The pulmonary vascular resistance did not decrease, but this can be explained by the marked reduction in PCWP compared with mean pulmonary arterial pressure (Table).

On resolution of the patient's pulmonary edema, we replaced nesiritide with epoprostenol, a prostacyclin analog considered to be mainstay therapy in patients with advanced precapillary pulmonary hypertension.

To our surprise, epoprostenol led to an increase in PCWP and recurrence of pulmonary edema. A similar

effect has been previously reported in two other scleroderma patients with pulmonary arterial hypertension and diastolic dysfunction who were treated with epoprostenol infusions.<sup>19,20</sup>

Epoprostenol-induced pulmonary edema in patients with scleroderma may be due to the significant inotropic effects of the drug on the right ventricle, leading to an increase in transpulmonary blood flow into a noncompliant left ventricle and subsequent elevation in PCWP.

Given the recurrence of pulmonary edema, we stopped epoprostenol and discharged our patient on continuous nesiritide infusion and oral furosemide at a standing dose of 80 mg, with additional doses as needed. Thereafter, she remained clinically stable for 6 months while awaiting lung or heart-lung transplantation.

In conclusion, given the high prevalence of diastolic dysfunction in patients with scleroderma, nesiritide may be a preferred agent in patients with severe pulmonary arterial hypertension in whom epoprostenol leads to adverse hemodynamic effects.

**Disclosure:** Dr. Berkowitz is an investigator and speaker for Scios Inc. and Biosite Incorporated.

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