

Right ventricular ST-elevation myocardial infarction as a cause of death in idiopathic pulmonary arterial hypertension

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Abstract

A 32-year-old woman with advanced idiopathic pulmonary arterial hypertension (PAH), treated with oral tadalafil and intravenous epoprostenol, presented with typical angina pectoris of one day's duration. Her electrocardiogram, previously typical of pulmonary hypertension, revealed an acute ST-elevation myocardial infarction in the anterior precordial leads. She had a prior coronary angiogram, in preparation for lung transplantation, that revealed normal coronary arteries. Urgent coronary angiography showed acute occlusion of several acute marginal coronary branches that feed the right ventricle (RV). Coronary angioplasty and stenting was unable to adequately restore coronary perfusion. Despite support, she developed progressive cardiogenic shock and died three days later. This is an unusual complication of PAH.

Keywords

coronary artery disease, myocardial infarction, pulmonary arterial hypertension, right ventricle, vasodilators

Date received: 10 January 2017; accepted: 21 March 2017

Pulmonary Circulation 2017; 7(2) 555–558

DOI: 10.1177/2045893217704435

Case description

A 32-year-old woman presented in February 2016 with retrosternal pressure and worsening dyspnea. In January 2012, she had been diagnosed with idiopathic pulmonary arterial hypertension (IPAH). She was previously well. She had taken an anorexigen, sibutramine, for three months in 2009, without symptoms. She denied illicit drug use. In June 2011, while in Mexico, she developed a severe respiratory infection, presumably viral, and returned to Montreal. A chest radiograph at that time revealed bilateral infiltrates, which resolved with antibiotics. However, she remained dyspneic in World Health Organization (WHO) Functional Class (FC) III. There was no orthodeoxia. A transthoracic echocardiogram showed normal right and left cardiac function, with no evidence of shunting by Doppler analysis, and an estimated systolic pulmonary artery pressure (PAP) of 33 mmHg. A radionuclide lung scan showed normal ventilation with heterogeneous perfusion, decreased in both lower lobes and non-segmental in both upper lobes. This, combined with a normal CT pulmonary angiogram, was not

suggestive of thromboembolic disease. Her serum transaminase, alkaline phosphatase, and bilirubin levels were normal, and there was no evidence of structural liver abnormalities, abnormal hepatic vasculature, portal hypertension, or hepatic shunting on contrast-infused CT scan of the abdomen. Her blood hemoglobin level was 137 g/L, serum thyroid stimulating hormone level 1.18 mU/L, and she was not iron deficient, with a serum iron level of 33 µmol/L. Pulmonary function tests revealed a FEV1 of 82% predicted, FVC 91%, total lung capacity 83%, and DLCO 64%. A CT scan of her lungs revealed a mild diffuse ground-glass pattern, thought to be a residuum of her recent respiratory illness infection. Cardiopulmonary exercise testing demonstrated a maximum oxygen uptake that was 50% predicted, with a cardiac but not a ventilatory limitation. The VE/VCO2 was markedly increased at 47, with an oxygen pulse of 5.4 (57% predicted),

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Fig. 1. Electrocardiogram in January 2016 prior to presentation (left), and in February 2016 upon presentation during the final admission (right).

and her transcutaneous oxygen saturation decreased from 97% to 91%. All the above prompted an open lung biopsy in November 2011 that showed pulmonary vascular narrowing with intimal thickening, without interstitial disease. Antinuclear antibody, extractable nuclear antigen panel, anticardiolipin antibody, and lupus anticoagulant assays were normal. In the absence of an explanation for her dyspnea, and with the biopsy findings, she underwent a cardiac catheterization in January 2012. Coronary angiography was normal. Her right atrial (RA) pressure was 5 mmHg, pulmonary artery wedge pressure (PAWP) 11 mmHg, PAP 66/35 mmHg, mean PAP (mPAP) 45 mmHg, and thermodilution cardiac output (CO) 5.3 L/min, cardiac index 3.24 L/min/m², pulmonary vascular resistance (PVR) 6.3 Wood units. A repeat echocardiogram at that time did not detect the pulmonary hypertension, and there was no evidence of intracardiac or transpulmonary shunting after intravenous injection of agitated saline. She was started on tadalafil 40 mg QAM but remained in WHO FC III.

A cardiac catheterization four months later showed a mPAP of 35 mmHg, PAWP 13 mmHg, RA 8 mmHg, cardiac output 4.8 L/min, and PVR 4.6 Wood units. Ambrisentan 10 mg QAM was added. After another four months, in October 2012, she entered into a blinded trial of added-on oral selexipag versus placebo.¹ She was able to up-titrate to a dose of 600 µg BID, but then downtitrated to 400 µg then 200 µg BID because of side effects.

She remained in WHO FC III, but her echocardiogram showed normal right ventricular size and function, with a dyssynergic septum. Her pulmonary function tests remained unchanged and her room-air transcutaneous oxygen saturation was 95%. Over the course of 2013 and early 2014, she became more dyspneic. She refused treatment with parenteral prostanoids and refused a lung transplant evaluation. She stopped the selexipag/placebo in May 2014 by her choice. In August 2014, the tadalafil was changed to riociguat. She did not feel better after four months and returned to tadalafil. A cardiac catheterization in March 2015 showed a PAP of 103/51, mPAP 68 mmHg, RA 15 mmHg, PAWP 19 mmHg, cardiac output 6.13 L/min,

and PVR 8 Wood units. Coronary angiography was normal. Her echocardiogram at that time showed worsening right ventricular function. In June 2015, she agreed to be evaluated for lung transplantation and was placed on the wait list. An echocardiogram in December 2015 showed worsening right ventricle dilatation and an N-terminal-pro-brain natriuretic peptide level of 3787 pg/mL. In January 2016, she agreed to receive intravenous epoprostenol. Her dyspnea continued to worsen.

Two days prior to presentation she developed intermittent retrosternal pressure. After 2 h of constant chest pressure and dyspnea she presented to the Emergency Room with a pulse of 110 bpm, blood pressure 121/76, oxygen saturation of 50% with a respiratory rate of 34. She was immediately placed on positive pressure ventilation with transient improvement of her oxygen saturation to 92%. An electrocardiogram showed sinus tachycardia at a rate of 105, a right bundle branch block, right axis deviation, right atrial enlargement, and ST elevation in leads I, aVL, and V2–V6, which was new since her last electrocardiogram (Fig. 1). A rapid CT pulmonary angiogram excluded pulmonary embolism as a cause of acute right heart strain. Subsequent emergent cardiac catheterization showed a normal left coronary system, but occlusions in large first and second acute marginal arteries (Fig. 2). The second acute marginal artery was stented with a 2.25 × 12 mm bare metal stent but the distal runoff was poor. The first acute marginal artery was deemed to be too small to stent, so angioplasty was performed, but it was complicated by dissection that required stenting that resulted in distal spasm.

She was then transferred to the cardiac intensive care unit, on vasopressor support. Cardiac troponin was elevated to 4066 pg/mL (normal < 15 pg/mL) with her previous values of < 3 pg/mL. An echocardiogram showed a markedly enlarged and hypokinetic RV with an estimated right ventricular systolic pressure of 100 mmHg. Her left ventricular ejection fraction was estimated at 70–75%. Saline injection showed early bubbles crossing the interatrial septum. She deteriorated before heart and lung transplant organs became available, and she died three days later of cardiogenic shock.

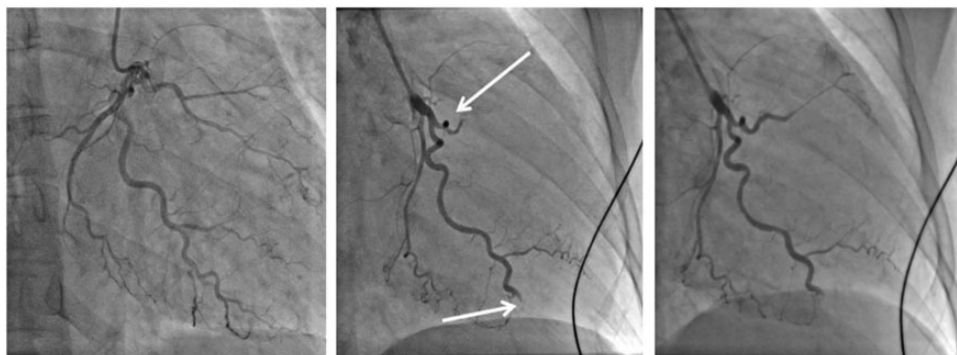


Fig. 2. Angiogram of the right coronary artery in March 2015 (left) showing normal coronary flow; at presentation with myocardial infarction in late Feb 2016 (center); and the same day after attempted stenting of the coronary artery (right). Arrows denote occlusions of the coronary artery.

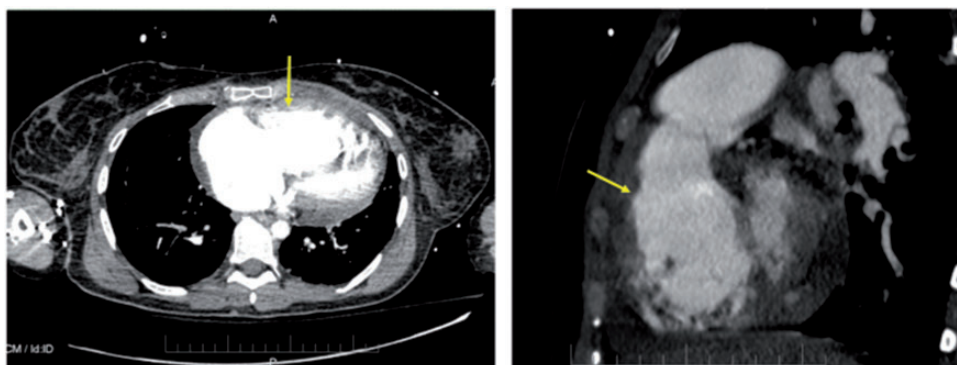


Fig. 3. Axial (left) and sagittal (right) images from the CT chest scan performed during the final presentation. Note the massive right ventricular enlargement and the abutment of the right ventricular epicardium on the anterior chest wall (arrows).

Discussion

IPAH is a proliferative process involving multiple cell lines in the pulmonary vasculature, leading to loss of perfused vasculature and increased PVR.^{2–4} Patients typically experience dyspnea and, when right ventricular ischemia is present, chest discomfort.^{5,6} Right ventricular failure is the most common cause of mortality in patients with IPAH.⁷ Unusual for this disease, our patient's echocardiograms were initially insensitive as a detection tool and were normal, despite pulmonary hypertension proven at catheterization. Moreover, her initial hemodynamic abnormalities seemed disproportionately mild compared to her degree of limitation, but exercise had not been performed during either echocardiography or catheterization and might have revealed a severe rise in PAP during effort.

Patients with PAH may have pre-existing coronary artery disease at the time of diagnosis. However, those patients tend to be older, and the presence of coronary artery disease in itself does not affect prognosis.^{8,9} The development of occlusive coronary disease must be highly unusual in a young PAH patient, as is presentation with an ST-elevation myocardial infarction. Coronary blood flow to the right

ventricle normally occurs during both systole and diastole. With pulmonary hypertension, and increased right ventricular wall stress and hypertrophy, right ventricular coronary flow becomes diastolic only, leaving the right ventricle more susceptible to ischemia.¹⁰ Complete occlusion of acute marginal branches resulting in right ventricular myocardial infarction would cause severe right ventricular dysfunction, cardiogenic shock, and an irreversible decline to death.

In a healthy right ventricle, oxygen extraction in the right coronary artery at rest is only 50%, as compared to 75% in the left coronary artery.¹¹ In this patient, there were numerous factors that contributed to oxygen supply–demand mismatch for the right ventricle. First, pulmonary hypertension significantly increased right ventricular wall stress and oxygen demand.¹² Second, the right ventricle was significantly dilated (Fig. 3). It extended across the whole precordium, which explained the extent of ST elevation on the electrocardiogram. Third, although the caliber of the acute marginal vessels was quite small (1.5–2 mm), they extended and supplied the large amount of RV free wall.

It is intriguing that several acute marginals were involved. She had angiographically normal coronary arteries less than

one year prior to the myocardial infarction. Rapid development of atherosclerotic lesions could only be attributable to highly altered flow and shear stress within the vessels, to spasm of the vessels, or to external trauma. The acute marginal branches lie on the anterior surface of the heart, and her massive right ventricular dilatation might have resulted in repeated compression or rubbing of those arteries between the RV myocardium and chest wall, with endothelial trauma and thrombus formation, and eventual occlusion (Fig. 3). Despite aggressive percutaneous intervention, she had “no-reflow,” and infarction and irreversible RV failure ensued. Some patients with IPAH experience rapid or sudden death, outside of a monitored environment. While arrhythmia is a likely culprit, acute massive right ventricular ischemia might also be a cause.

Acknowledgments

The authors thank the nursing and technical staff of the Cardiac Catheterization Laboratory and the Cardiovascular Intensive Care Unit of the Jewish General Hospital for their tender care of the patient. This work was supported in part by the Kendall Family Endowment, Pencer Family Endowment, Dimitrios Banousis PH Fund, and the Bank of Montreal Endowment for the Study of Heart Disease in Women, all at the Jewish General Hospital.

Conflict of interest

The authors declare the following conflicts of interest: Andrew Hirsch: Advisory board, speaker, and/or investigator for Actelion and Bayer, Advisory board and speaker for Boeringer Ingelheim; Lyda Lesenko: Advisory board and/or speaker for Actelion and Bayer; David Langleben: Advisory board, consultant, investigator, and/or speaker for Actelion, Bayer, Ikaria, Northern Therapeutics, United Therapeutics.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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