Received: January 2010; accepted: April 2010

CASE REPORT

Sildenafil getting it down

C Slagt[1], REJH Sentjens[1], G Veen[2], JJ Spijkstra[1], A Vonk Noordegraaf[3]

1 Department of Intensive Care, VU University Medical Center, Amsterdam, The Netherlands
2 Department of Cardiology, VU University Medical Center, Amsterdam, The Netherlands
3 Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, The Netherlands

Abstract - A patient is presented with multi-organ failure caused by pulmonary hypertension leading to right ventricular failure with low output state. The pulmonary hypertension was successfully treated by sildenafil. The patient was discharged home without any sequelae. Hence sildenafil can be used to lower high pulmonary artery pressures and to ameliorate right ventricular failure that leads to multi-organ dysfunction.

Keywords - pulmonary hypertension, multi-organ failure, sildenafil, haemodynamic monitoring

Introduction

Pulmonary hypertension (PH) can lead to right ventricular (RV) failure. RV dysfunction may result in a low cardiac output state or even cardiac arrest. Data from Hoeper et al. [1] show that cardiopulmonary resuscitation for circulatory arrest in patients with PH is rarely successful unless the cause of the cardiopulmonary decompensation can be eliminated. The prognosis is therefore grave in the critically ill patient. Here we describe a patient with cardiac arrest caused by pulmonary hypertension and right ventricular overload. After successful cardiopulmonary resuscitation, sildenafil was tried in an attempt to unload the right ventricle.

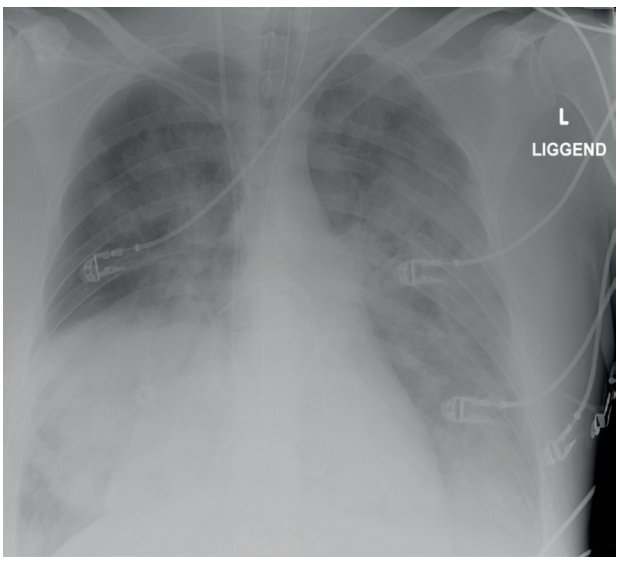
Case report

A 41-year-old man was transferred to our intensive care unit. Twenty-four hours earlier he had been admitted in another hospital for analysis of progressive dyspnoea. His family history was negative. He was a heavy smoker and had a dry cough in the morning. The initial symptoms started nine months before admission and consisted of dyspnoea, chest discomfort, anxiety, fatigue and depression. The symptoms remained stable until six weeks before admission. At that time the patient could walk only 50 metres and had even dyspnoea at rest. A computed tomography angiogram was performed which ruled out pulmonary emboli but showed diffuse consolidations of the upper and middle lobes of the right lung. Within hours after the angiogram, progressive dyspnoea resulted in a cardiac arrest with a pulseless electrical activity of 30 / min. Cardiopulmonary resuscitation was initiated and return of spontaneous circulation was achieved within 10 min. Admission to the ICU was arranged.

On admission the patient was intubated and pressure-control ventilated with an inspiratory O_2 fraction F_1O_2 of 1.0, positive end-expiratory pressure (PEEP) 18 cm H_2O and a minute ventilation of 14 L/min. Pulse O_2 saturation was 75%. His blood pressure was 73/44 mmHg with a sinus tachycardia of 116/min, and central venous pressure (CVP) of 18 mmHg. The patient was anuric. Capillary refill time was 11 seconds with enoxime 3 µg/kg/min, dobutamine 2 µg/kg/min and norepinephrine 1µg/kg/min. Arterial blood gas analysis showed pH 7.22, PCO_2 38 mmHg , PO_2 60 mmHg, bicarbonate 15.1 mmol/l and arterial saturation of 84%. A pulmonary artery catheter was placed in the right internal jugular vein. Pulmonary artery pressure (PAP) was 65/46 (53) mmHg. Systemic pressure was 75/52 (61) mmHg, cardiac index (CI) 1.5 l/min/m^2, pulmonary capillary wedge pressure (PCWP) 25 mmHg. Mixed venous saturation (SO_2) was 60%. Epinephrine was infused to increase blood flow and pressure. Laboratory results on admission showed lactate 11.7 mmol/l, anion gap 25 mmol/l, platelets 90 * 10^9/l, leucocytes 12.1 * 10^9/l, albumin 11 g/l, creatinine 192 µmol/l, bilirubin 24 µmol/l, elevated transaminases (up to 1008 U/l) and with a normal creatinine kinase level troponin-T 0.26 µmol/l, CK 138 E/l, MB 5.9 µg/l. The chest x-ray is shown in Figure 1.

Hence our patient had severe PH and RV failure with a low

Figure 1. Chest X ray shows bilateral extended pulmonary oedema with right paracardial consolidation of the lung



Correspondence

C Slagt
E-mail: Slagt.c@zaansmc.nl

output state. Transoesophageal echocardiography was performed and showed, with limited echocardiographic windows, a poorly contracting and severely dilated, but not hypertrophied RV (Figure 2). There was paradoxical movement of the septum which severely compromised left ventricular (LV) filling, and severe tricuspid valve regurgitation (Figure 3).

Despite haemodynamic and respiratory support, organ dysfunction was progressive. Four hours after admission PAP (79/55 (55) mmHG) equalled systemic blood pressures (79/53 (61) mmHg). Oxygenation deteriorated and arterial PO_2/F_iO_2 was 76 mmHg and peripheral O_2 saturation 87%. Prone ventilation increased arterial PO_2/F_iO_2 to 254 mmHg.

To reverse the negative chain of haemodynamic events, sildenafil citrate 3 x 50 mg was given as a rescue therapy. Forty-five minutes hereafter haemodynamic parameters improved. The arterial pressure was 92/55 mmHg, PAP 70/38 (48) mmHg, PCWP 21 mmHg, CI 3.3 L/min/m^2 and the mixed venous SO_2 77%. Over the next few hours urine output increased. Renal replacement therapy was needed to treat pulmonary fluid overload. In the acute setting the C-reactive protein peaked to 21 mg/L and leucocytes to 18.9 * 10^9/l. Tracheal aspirate cultures were initially negative but positive for *Stenotrophomonas maltophilia* on day 5. This was treated with co-trimoxazol 2x 960 mg IV. Over the next few days, inotropic support was tapered off and patient was weaned from the ventilator.

All organ dysfunction recovered and the patient was discharged to the ward eleven days after admission. After revalidation he was discharged home. A follow up echocardiography showed no signs of structural damage or PH. The exercise capacity of the patient slowly improved over the following months.

Discussion

Severe PH with RV dysfunction leading to multi-organ failure can thus be reversed with sildenafil treatment. Our patient had RV overload due to PH, resulting in tricuspid regurgitation and possibly decreased contractility by superimposed ischaemia exemplified by the elevated troponin-T levels. The elevated PCWP may have been caused by the septal shift. The PH can be a symptom of underlying disease, with a mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise [2]. It can be inherited or associated with numerous conditions (Table 1 [3]). Our patient was young and healthy but a heavy smoker.

Pulmonary embolism was ruled out as the cause of pulmonary hypertension. Although the patient was severely hypoxic on admission, the persistence of PH after hypoxia had been treated argues against the cause being hypoxia. No signs of underlying congenital heart disease, rheumatic disease or liver disease were found during diagnostic work up. *Stenotrophomonas maltophilia* is usually associated with nosocomial infection [4]. Taken together, the combination of chronic obstructive pulmonary disease and superimposed Gram- negative pneumonia [5] may have been responsible for the PH.

In our patient both hypoxia and RV failure were ameliorated by sildenafil. Sildenafil is a selective and potent inhibitor of phosphodiesterase (PDE) type 5. Under normal circumstances, endothelium-derived NO stimulated intracellular soluble guanylate cyclise resulting in increased levels of Cyclic guanosine monophosphate (cGMP) mediates smooth muscle relaxation. Sildenafil inhibits degradation of cGMP by PDE 5 thereby prolonging smooth muscle relaxation.

Stimulation of the cGMP pathway also inhibits cell proliferation in isolated pulmonary artery smooth muscle cells [6]. In a large international multicentre randomised controlled trail (SUPER 1 trail), 278 patients who mostly had idiopathic PH were randomised to receive placebo or sildenafil at a dose of 20, 40 or 80 mg three times daily. At all dosages, sildenafil reduced the PAP, improved exercise capacity and improved functional class compared to placebo [7]. After starting sildenafil in our patient, PAP halved within

Figure 2. Severe right ventricular dilatation

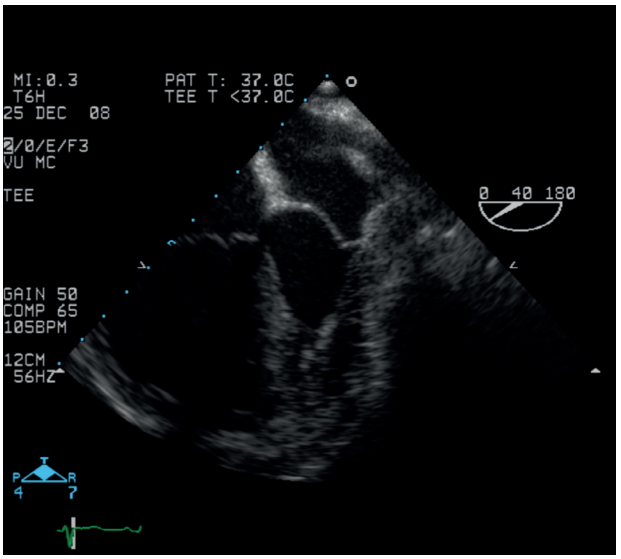
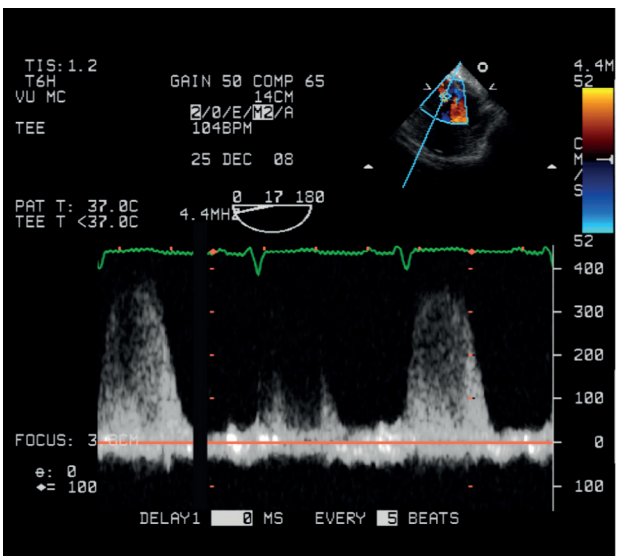


Figure 3. Severe tricuspid regurgitation



hours and returned to normal after a few days. Haemodynamics improved dramatically. The rapid response to sildenafil indicates that pulmonary vasoconstriction was the major contributor to PH rather the structural remodelling of pulmonary vessels. We may compare these effects to those of other drugs used in the treatment of PH induced RV failure.

RV dysfunction can be treated by reducing RV overload, but lowering arterial blood pressure may increase the risk of RV ischaemia [8]. Vasopressor therapy (epinephrine, dopamine) can be used to maintain coronary perfusion and to compensate for systemic hypotension caused by the vasodilatory effects of inotropics such as dobutamine, enoximone or by sildenafil [9,10]. Prostacyclin and prostaglandin E_1 act as pulmonary vasodilators but may aggravate ventilation-perfusion mismatching, increase hypoxia, and may cause systemic hypotension [11]. Inhaled and systemic nitric oxide may enhance the efficacy of inotropic therapy by reducing the afterload of the RV and improve hemodynamic without inducing systemic hypotension [12].

Recently, the calcium sensitizer levosimendan, a new inotrope used for the treatment of cardiac failure has been shown to reduce pulmonary vascular resistance with minimal systemic effects [13]. In acute pulmonary embolism-induced RV failure, levosimendan restores RV to pulmonary artery coupling better than placebo because of pulmonary vasodilation combination with increased RV contractility [14].

Conclusion

In the treatment of patients with PH-induced RV failure resulting in multi-organ failure, haemodynamics should be evaluated by transoesophageal echocardiography and/or a pulmonary artery catheter. Guided by the haemodynamic profile, the treatment should be optimised to suit individual needs. This case shows the acute pulmonary vasodilatatory and thereby beneficial effects of sildenafil.

Table 1. Classification of pulmonary hypertension adapted by Simonneau et al. [3].

1.	Pulmonary arterial hypertension		
	a.	Idiopathic	
	b.	Familial	
	c.	Associated with	
		i.	Collagen vascular disease
		ii.	Congenital left t right shunt
		iii.	Portal hypertension
		iv.	Infection with human immunodeficiency virus
		v.	Drugs and toxins
	d.	Persistent pulmonary hypertension of the newborn	
2.	Pulmonary hypertension with left heart disease		
	a.	Left sided atrial or ventricular heart disease	
	b.	Left sided valvular heart disease	
3.	Pulmonary hypertension assiciated with lung disease or hypoxemia or both		
	a.	Chronic obstructive pulmonary disease	
	b.	Interstitial lung disease	
	c.	Sleep disorderd breathing	
	d.	Alveolar hypoventilation disorders	
	e.	Chronic exposure to high altitude	
4.	Pulmonary hypertension due to chronic thrombotic or embolic disease or both		
	a.	Tromboembolic obstruction of proximal pulmonary arteries	
	b.	Thromboembolic obstruction of distal pulmonary arteries	
	c.	Nonthrombotic pulmonary embolism (tumor, parasites corpus alienum)	
5.	Miscellaneous		
	a.	Sarcoidosis, langerhans histiocytosis, lymphangiomatosis, compression of pulmonary vessels by tumor or fibrosis	

References

1 Hoeper MM, Galie N, Murali S, Olschewski H, Rubenfire M, Robbins IM, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2002; 165: 341-344.

2 Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43: 40S-47S.

3 Simoneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43: 5S-12S.

4 Muder RR, Yu VL, Dummer JS, Vinson C. Infections caused by Pseudomonas maltophilia: expanding clinical spectrum. Arch Intern Med 1987; 147: 1672-4.

5 Rossi P, Persson B, Boels PJM, Arner A, Beitzberg E, Oldner A. Endotoxemic pulmonary hypertension is largely mediated by endothelin-induced venous constriction. Intensive Care Med 2008; 34: 873-880.

6 Wharton J, Strang JW, Moller GMO, et al. Anti proliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. Am J Respir. Crit Care Med 2005; 172: 105-113.

7 Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J med 2005: 353 (20): 2148-2157.

8 Piazza G, Goldhaber SZ. The acutely decompensated right ventricle. Chest 2005; 128: 1836-1852.

9 Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection and therapeutic implications. Am Heart J 1995; 130: 1276-1282.

10 Goldstein JA. Pathophysiology and management of right heart ischemia J Am Coll Cardiol 2002; 40: 841-853.

11 Stobierska-Dzierzek B, Awand H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001; 38: 923-931.

12 Bhorade S, Christenson J, O'Connor M, et al. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 1999; 159: 571-579.

13 Slawsky MT, Wilson SC, Gottlieb SS, Greenberg BH et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000; 102: 2222-2227.

14 Kerbaul F, Gariboldi V, Giorgi R, Mekkaoui C et al. Effects of levosimendan on acute pulmonary embolism induced right ventricular failure. Crit Care Med. 2007; 35: 1948-1954