British Journal of Anaesthesia **99 (4):** 552–5 (2007)
doi:10.1093/bja/aem180 Advance Access publication July 27, 2007

BJA

OBSTETRICS

Case Report

Use of vasopressin after Caesarean section in idiopathic pulmonary arterial hypertension

L. C. Price[1 3]*, P. Forrest[4], V. Sodhi[5], D. L. Adamson[2], C. Nelson-Piercy[6], M. Lucey[3] and L. S. Howard[1]

[1]Department of Respiratory Medicine and Pulmonary Hypertension Service, [2]Department of Cardiac Services, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK. [3]Department of Intensive Care Medicine, and [4]Department of Anaesthesia, Royal Prince Alfred Hospital, Missenden Road, Camperdown, Sydney 2050, New South Wales, Australia. [5]Department of Anaesthesia and [6]Department of Obstetric Medicine, Queen Charlotte's and Chelsea Hospital, Du Cane Road, London, W12 0HS, UK

**Corresponding author: Pulmonary Hypertension Service, Department of Cardiac Services, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK. E-mail: lauracprice@hotmail.com*

We report the successful use of vasopressin in the management of hypotension in association with severe right ventricular (RV) failure in two patients with advanced idiopathic pulmonary arterial hypertension. Both patients were pregnant and developed systemic hypotension after delivery by Caesarean section. Placental autotransfusion and possibly oxytocin use were thought to be the major contributing factors in worsening RV function. After the use of vasopressin in both patients, cardiovascular variables improved without untoward effect on RV function, and provided rescue therapy for systemic hypotension in this setting. Vasopressin, a direct vasopressor acting via V1 receptors on the vascular endothelium, has been shown to cause pulmonary vasodilatation experimentally and in animal models of pulmonary hypertension. Its synthetic analogue, terlipressin, has been shown to reduce pulmonary vascular resistance in humans with cirrhosis. Vasopressin may therefore have differential effects on the pulmonary and systemic circulations, allowing systemic pressure to be supported without detrimental effects on the pulmonary circulation.

Br J Anaesth 2007; **99**: 552–5

Keywords: anaesthesia, obstetric; pregnancy; pulmonary hypertension; right heart failure; vasopressin

Accepted for publication: May 17, 2007

Idiopathic pulmonary arterial hypertension (IPAH) is a rare, progressive disease of uncertain aetiology characterized by increased pulmonary vascular resistance (PVR), leading to right ventricular (RV) failure and death.[1] A recent series of 15 pregnancies reported maternal mortality of 36% and neonatal mortality of 15%.[2] Pregnancy is therefore strongly discouraged.

Patients with pulmonary hypertension (PH) usually deteriorate in the second trimester of pregnancy, as the blood volume increases by up to 50%,[3] exacerbating an already pressure-loaded RV into worsening failure. In severe PH, the fixed cardiac output prevents circulatory adaptation to increase oxygen consumption, resulting in worsened hypoxaemia. During and after delivery, the contracting uterus increases RV preload, and may precipitate RV failure. This 'autotransfusion' effect may be exacerbated by decompression of the inferior vena cava (IVC) when the baby is delivered. In conjunction with either general or regional anaesthesia, this can lead to cardiovascular collapse.

In the acute setting, there are three main approaches to the treatment of systemic hypotension associated with severe PH: (i) selective reduction in PVR; (ii) the selective augmentation of systemic vascular resistance (SVR) to maintain right coronary perfusion pressure; and (iii) inotropic support of the right heart. The drugs most suited to

the acute reduction in PVR are inhaled nitric oxide (iNO) and inhaled prostacyclin because of their rapid onset and offset of action and minimal effect on SVR.[4] Most vasopressors used in anaesthesia and intensive care for the augmentation of SVR will also worsen PVR.[5] Reports have suggested that vasopressin may have differential effects on the systemic and pulmonary vascular circulations in several situations,[6–8] and even reduce PVR in a non-PH rat model.[9]

We report the use of vasopressin in the management of profound systemic hypotension shortly after Caesarean delivery in two patients with severe IPAH under general and regional anaesthesia. We discuss the challenge in managing this problem and specifically the choice of vasopressor in these patients.

Case 1

A 33-yr-old woman presented at 27 weeks gestation with a new diagnosis of IPAH, in New York Heart Association (NYHA) functional class IV.[10] She was transferred to the intensive care unit (ICU) for pulmonary vasodilator therapy before delivery by Caesarean section (CS). Initial pulmonary artery catheter (PAC) readings showed right atrial pressure (RAP) of 15 mm Hg, mean pulmonary artery pressure (mPAP) of 56 mm Hg, pulmonary capillary wedge pressure of 6 mm Hg, and cardiac index (CI) of 1.88 litre min^{-1}, measured by thermodilution. She was commenced on i.v. prostacyclin at 4 ng kg^{-1} min^{-1}, which was titrated to 6 ng kg^{-1} min^{-1}, and was anticoagulated with i.v. heparin. CI improved from 1.8 to 2.8 litre min^{-1} m^{-2} with a reduction in PVR and no consequent changes in mPAP. She improved from NYHA class IV to III.

Five days later, she proceeded to CS under general anaesthesia. Anaesthesia was induced using a modified rapid sequence induction, with midazolam 1 mg, fentanyl 350 μg, thiopentone 175 mg and suxamethonium 100 mg, and was maintained with sevoflurane in 100% oxygen. The prostacyclin infusion was continued and the lungs were ventilated to normocapnia. Immediately after delivery, a 0.25 IU oxytocin bolus was given, followed by a further 0.25 IU dose over 5 min. She became hypotensive to BP 79/55 mm Hg with a rise in mPAP to 59 mm Hg and in RAP from 15 to 22 mm Hg, suggesting acute RV failure. No further fluids or oxytocin were given. This acute increase in pulmonary arterial pressures proved unresponsive to a single ultrasonic nebulizer dose of 20 μg of iloprost and an increase in prostacyclin infusion rate to 8 ng kg^{-1} min^{-1}. Metaraminol (0.5 mg i.v, single bolus), norepinephrine (4 μg ml^{-1} infused at 6–12 ml h^{-1}), and dobutamine (5 ng ml^{-1} infused at 5–8 ml h^{-1}) were also ineffective in restoring her systemic MAP. After a bolus of 0.5 U of vasopressin, however, there was rapid improvement in MAP, with restoration of systemic pressures to 120/86 mm Hg and no associated change in mPAP.

She was transferred to ICU while being ventilated and on a vasopressin infusion at 0.06 U min^{-1}. With the addition of iNO, vasopressin was decreased to 0.04 U min^{-1}. Sildenafil was commenced at 25 mg twice daily, and her iNO and vasopressin were weaned. She was extubated 5 days after delivery, and 6 months later she was stable with NYHA class II symptoms.

Case 2

A 32-yr-old woman with known IPAH became pregnant despite pre-pregnancy counselling. Before pregnancy, she had been stable for 2 years with NYHA class III symptoms on dual therapy (bosentan 125 mg twice daily and sildenafil 25 mg thrice daily), but her symptoms deteriorated to NYHA class IV at 21 weeks, with significant peripheral oedema and dyspnoea at rest. She was admitted for diuresis and further pulmonary dilatation. Invasive arterial pressure and central venous pressure (CVP) monitoring were commenced. The latter was used to measure mixed venous oxygen saturation and the systolic and diastolic phases of the RAP, the diastolic phase reflecting RV end-diastolic pressure, and thus an indicator of worsening right heart function. Prostacyclin i.v. was started and she tolerated titration from 0.5 ng kg^{-1} min^{-1} up to 8 ng kg^{-1} min^{-1}. Intramuscular steroids were administered at 27 weeks for fetal lung maturation and CS was planned for 28 weeks.

CS was performed under incremental combined spinal-epidural anaesthesia using an initial intrathecal injection of diamorphine 400 μg, followed by epidural boluses of 3 ml levobupivacaine 0.5% at approximately 5–10 min intervals, to a total of 15 ml. After 40 min, the patient had a sensory level of T5 to touch, and surgery was commenced. This was technically challenging as the patient had previous extensive abdominal surgery and was positioned slightly head-up to avoid respiratory distress. A prophylactic B-lynch brace suture was inserted after delivery of the baby to prevent placental bleeding, and 5 IU of oxytocin in 50 ml of normal saline was administered as an infusion over 30 min. MAP became labile after delivery (lowest value, 50 mm Hg) with a gradual rise in RAP (up to 26 mm Hg) and was controlled temporarily with boluses of phenylephrine. With experience from the previous case, iNO and vasopressin were commenced at 12 ppm and 0.08 U min^{-1}, respectively. MAP was stabilized with no change in RAP and she was transferred to ICU. Vasopressin and iNO were weaned over the next 48 h, and prostacyclin continued at 8 ng kg^{-1} min^{-1}.

Discussion

Most deaths in women with PH associated with pregnancy occur in the days after delivery.[11] These two cases illustrate the haemodynamic problems that may occur at the

time of CS in patients with severe PH. The reasons for hypotension after delivery in these cases are likely to be multifactorial and relate mainly to uterine autotransfusion, decompression of the IVC, and the use of oxytocin. Autotransfusion will volume-load an already dilated, pressure-loaded RV, worsening RV systolic function. Other contributors to RV dysfunction may relate to the technique of anaesthesia. Disadvantages of general anaesthesia include reduced cardiac contractility from volatile agents and increased PVR from positive pressure ventilation and the use of NO. Reports also suggest that stimulatory effects of laryngoscopy and intubation may increase PAP and precipitate right heart failure.[2] Incremental regional anaesthesia may be better tolerated haemodynamically, although no controlled trials exist. However, care must be taken to avoid RV hypoperfusion by reducing SVR in the context of a fixed cardiac output, and also to minimize tachycardia. There is also a theoretical risk of spinal or epidural haematoma in the presence of i.v. prostacyclin because of its inhibition of platelet aggregation, although in both cases it was deemed necessary to continue this as a result of haemodynamic severity.

The use of PAC is also controversial. There is an increased risk of pulmonary artery rupture and thrombosis in IPAH,[12] notwithstanding the inherent risk of precipitating arrhythmias. It is also argued that monitoring mPAP may be misleading, because it may decrease as the RV fails. A surrogate marker for PVR is the CVP, as this will always increase in response to an acutely elevated PVR. In RV failure, owing to an increase in PVR, the diastolic component of the CVP will increase and the systolic component may show a prominent V-wave. However, the CVP is a relatively late marker of rising PVR, as it indicates that the RV is already failing.

Oxytocin boluses at the time of delivery have been shown to increase PVR by 40%, reduce SVR by 30%, and cause tachycardia in animal models,[13] and lead to tachycardia and hypotension in healthy women at CS under spinal anaesthesia.[14] Great caution is therefore required when using oxytocin in these patients. Thomas and colleagues[15] suggest that this haemodynamic instability is decreased if oxytocin is given by slow i.v. infusion. However, there is as yet no evidence that oxytocin is equally effective in decreasing blood loss when given at a slower administration rate. Consequently, a prophylactic brace suture was also inserted in Case 2. As an alternative to a slow infusion, smaller bolus doses may be considered. Recent data suggest that the minimal effective dose (ED_{90}) is 0.35 IU[16] with a 97% response rate at 0.5 IU, the total dose administered in Case 1 over two injections.

Over the last decade, many treatments have become available for the long-term management of pulmonary hypertension, including prostanoids (i.v., s.c. and nebulized), oral endothelin receptor antagonists, and phosphodiesterase inhibitors. Given the anticipated haemodynamic insults during pregnancy and delivery, it is critical that patients should have their PH management optimized during pregnancy and these new therapies provide greater flexibility to achieve that goal.

In the acute or acute-on-chronic setting, the ideal treatment for systemic hypotension associated with severe PH is a drug that lowers PVR and increases SVR. iNO may do the former, but will have no effect on SVR. Prostacyclin i.v. benefits from a short half-life, but also will reduce SVR, and evidence for its use comes predominantly from the long-term management of IPAH, where properties other than vasodilation, including effects on vascular remodelling, are important. Nebulized iloprost is effective in reducing PVR acutely, with fewer systemic effects, but has to be given frequently to maintain a continuous effect. It is, however, easier to administer by ultrasonic nebulizer than iNO in a non-intubated patient.

Much of the literature regarding haemodynamic support in animal models is in the setting of acute thromboembolic PH.[17] The acutely decompensated RV responds differently to the chronically hypertrophied one, requiring different management strategies including volume loading.[18] Furthermore, the pulmonary vasculature in chronic PH is different, having become remodelled and hypertrophied. Nonetheless, in this model, dobutamine increases CI and decreases PVR, probably because of the recruitment of pulmonary capillaries rather than a pulmonary vasodilatory effect.[19]

In chronic PH secondary to mitral valve disease, Kwak and colleagues[20] demonstrated that norepinephrine and phenylephrine corrected systemic hypotension after induction of anaesthesia and also that norepinephrine increased MAP to a greater extent, causing less elevation of mPAP than phenylephrine. However, this model of pulmonary hypertension differs from IPAH specifically as a result of elevated pulmonary venous pressure.

Vasopressin mediates vasoconstriction in the systemic circulation via the G protein-coupled V1 receptor on vascular smooth muscle cells.[21] In the pulmonary circulation, it appears that vasopressin causes vasodilatation, but only in preconstricted pulmonary arteries. This effect can be significantly attenuated either by blocking NO synthesis with L-NNA[22] or by blocking the V1 receptor, suggesting that vasopressin acts via the V1 receptor to increase NO production to cause pulmonary vasodilation. One of our patients (Case 2) was already receiving iNO when vasopressin was administered, and it may be that its benefit here simply related to sparing of the pulmonary circulation from a vasoconstrictor response.

The observation that the pulmonary vasodilatory effect is only seen in preconstricted pulmonary vessels (using either U46 619 or hypoxia)[21] in isolated perfused rat lungs and conscious rats is worth considering when reviewing data from studies in humans without PH. The effects of different analogues of vasopressin on humans have been reviewed by Smith and colleagues[23] and there are no studies in patients with PH. The most extensively studied cohort

includes patients with liver disease. Two studies using cardiac catheterization showed an increase in mPAP[24 25] but only as a result of increased left-sided cardiac filling pressures, and therefore there was no change in PVR. A conflicting echocardiographic study showed a decrease in systolic PAP after a 2 mg bolus of terlipressin.[26]

There are no data available on the dose range for vasopressin in pulmonary hypertension and the doses used in these patients were based upon the analysis of its use as a single vasopressor in patients with septic shock, where infusion rates of up to 1.8 U min^{-1} have been used.[27]

The cases presented illustrate the challenges in management of hypotension in patients undergoing delivery with severe IPAH. Hypotension in association with acute-on-chronic RV failure is a haemodynamic emergency, and our cases and the literature provide a rationale for the use of vasopressin in this setting. Data from animal studies suggest that it may be acting through an NO-dependent pathway on pre-constricted pulmonary arteries and this may suggest why patients with PH may benefit in particular from the use of this agent.

Acknowledgement

The authors would like to thank Dr A. Butwick for his helpful comments and suggestions.

References

1 Rubin LJ. Primary pulmonary hypertension. Chest 1993; **104**: 236–50

2 Bonnin M, Mercier FJ, Sitbon O, *et al*. Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology 2005; **102**: 1133–7

3 Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy. Blood and plasma volumes in multiple pregnancies. Am J Obstet Gynecol 1965; **93**: 1–15

4 Pepke-Xaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 1991; **338**: 1173–4

5 Barnes PJ, Liu SF. Review of pulmonary vascular tone. Pharmacol Rev 1995; **47**: 87–131

6 Wallace AW, Tunin CM, Shoukas AA. Effects of vasopressin on pulmonary and systemic vascular mechanics. Am J Physiol 1989; **257**: H1228–34

7 Dunser MW, Mayr AJ, Ulmer H, *et al*. The effects of vasopressin on systemic hemodynamics in catecholamine-resistant septic and postcardiotomy shock: a retrospective analysis. Anesth Analg 2001; **93**: 7–13

8 Braun EB, Palin CA, Hogue CW. Vasopressin during spinal anesthesia in a patient with primary pulmonary hypertension treated with intravenous epoprostenol. Anesth Analg 2004; **99**: 36–7

9 Walker BR, Haynes J Jr, Hang HL, Voekel NF. Vasopressin-induced pulmonary vasodilation in rats. Am J Physiol 1989; **257**: H415–22

10 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004; **351**: 1425–36

11 De Swiet M, Nelson-Piercy C. Cardiac disease. In: Lewis G, ed. Why Mothers Die 2000–2002: The Sixth Report of Confidential Enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press, 2004; 137–50

12 Barash PG, Nardi D, Hammond G, *et al*. Catheter induced pulmonary artery perforation. J Thorac Cardiovasc Surg 1981; **82**: 5–12

13 Roberts NV, Keast PJ, Brodeky V, Oates A, Ritchie BC. The effects of oxytocin on the pulmonary and systemic circulation in pregnant ewes. Anaesth Intensive Care 1992; **20**: 199–202

14 Pinder AJ, Dresner M, Calow C, *et al*. Haemodynamic changes caused by oxytocin during Caearean section under spinal anaesthesia. Int J Obstet Anesth 2002; **11**: 156–9

15 Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as intravenous bolus or infusion on women undergoing Caesarean section. Br J Anaesth 2007; **98**: 116–9

16 Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective Cesarean delivery: a dose-finding study. Obstet Gynecol 2004; **104**: 1005–10

17 Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. Chest 1997; **111**: 218–24

18 McNeil K, Dunning J, Morrell NW. The pulmonary physician in critical care: the pulmonary circulation and right ventricular failure in the ITU. Thorax 2003; **58**: 157–62

19 Kerbaul F, Rondelet B, Motte S, *et al*. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Critical Care Med 2004; **32**: 1087–9

20 Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. Anaesthesia 2002; **57**: 9–14

21 Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery: V1-receptor-mediated production of nitric oxide. Chest 1993; **103**: 1241–5

22 Russ RD, Walker BR. Role of nitric oxide in vasopressinergic pulmonary vasodilatation. Am J Physiol 1992; **262**: H743–7

23 Smith AM, Elliot CM, Kiely DG, Channer KS. The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension. QJM 2006; **99**: 127–33

24 Segel N, Bayley TJ, Paton A, Dykes PW, Bishop JM. The effects of synthetic vasopressin and angiotensin on the circulation in cirrhosis of the liver. Clin Sci 1963; **25**: 43–55

25 Mols P, Hallemans R, Vankuyk M, *et al*. Haemodynamic effects of vasopressin, alone and in combination with nitroprusside, in patients with liver cirrhosis and portal hypertension. Ann Surg 1984; **199**: 176–81

26 Atlintas E, Akkus N, Gen R, *et al*. Effects of terlipressin on systolic pulmonary artery pressure in patients with liver cirrhosis: an echocardiographic assessment. World J Gastroenterol 2004; **10**: 2278–80

27 Treschan TA, Peters J. The vasopressin system: physiology and clinical strategies. Anesthesiology 2006; **105**: 599–612