Vasopressin for Refractory Hypotension During Cardiopulmonary Bypass

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INTRODUCTION

Hypotension on initiation of cardiopulmonary bypass (CPB) occurs commonly. Causal factors are complex; however, it is thought that the sudden decrease in systemic vascular resistance due to abrupt haemodilution which decreases blood viscosity, is a significant cause (1). There is a direct relationship between haematocrit and blood viscosity and the perfusion pressure falls in proportion to the change in viscosity (1, 2). This shock-like state conferred by CPB is commonly met with a stress response which spontaneously increases the mean arterial pressure (MAP). Where the increase in MAP is inadequate or delayed, increased CPB flow rate and/or administration of an alpha-adrenergic agonist such as phenylephrine are usually effective. Occasionally, a more potent catecholamine, *eg* norepinephrine (NE), is required and is usually effective. Rarely, the hypotension is refractory to even the most potent sympathomimetic agents available and a potentially life-threatening situation arises. Only a few cases of refractory hypotension "*on-initiation*" of CPB (3, 4) have been reported. In one of these cases (3), vasopressin was administered with good response and a successful outcome. We report a case of severe refractory hypotension on initiation of CPB which also responded effectively to the administration of exogenous vasopressin (arginine vasopressin-AVP).

However, in this case, we observed a temporal association between administration of the drug and the development of a clinically significant lactic acidosis suggesting a cause and effect relationship. Other possible causes of elevated lactic acid levels during CPB will be discussed.

CASE REPORT

A 75-year-old man (weight, 85 kg; body surface area, 2.04 m^2) with a history of hypertension for 25 years, heavy cigarette consumption (20 pack-year) and two episodes of previous myocardial infarction, was referred for urgent coronary artery bypass surgery. The first episode of acute myocardial infarction occurred four months prior to surgery. At that time, he was treated conservatively, stabilized and referred for surgery following confirmation of 4-vessel coronary artery disease by coronary arteriography. One month prior to the planned surgery, he had another episode of cardiac decompensation for which he was again hospitalized. On this

occasion, he was diagnosed with congestive cardiac failure and was treated with a regimen of digoxin, furosemide, aldactone, slow K, lisinopril, fragmin and oral nitrates which were continued up to the time of surgery. Prior to surgery, he was classified as New York Heart Association class IV and found on echocardiographic examination to have a left ventricular ejection fraction of 35% with diffuse hypokinesia. The electrocardiogram showed signs of left ventricular hypertrophy, and bilateral pleural effusion was observed on chest X-ray. A 4-vessel coronary artery revascularization operation was scheduled.

The patient was admitted to the intensive care unit on the evening prior to surgery when the following procedures were carried out: left radial artery cannulation for direct arterial blood pressure (BP) monitoring, central venous catheterization *via* the right internal jugular vein, passage of an intra-aortic balloon pump with 1:2 augmentation and commencement of an intravenous heparin infusion. On arrival in the operating room and prior to the induction of anaesthesia, haemodynamic monitoring revealed a BP of 110/55 mm Hg, heart rate (HR) 64 beats/min, central venous pressure 15 mmHg and pulmonary artery pressure of 45/28 mmHg. A 16G peripheral venous catheter was also inserted. General anaesthesia was induced with iv midazolam 5 mg, fentanyl 200 μg and pancuronium 8 mg. Endotracheal intubation was performed and mechanical ventilation commenced with oxygen, nitrous oxide and isoflurane. A fall in BP occurred at induction but was readily responsive to 100–200 μg boluses of phenylephrine. Acute normovolaemic haemodilution was performed with the removal of two units of blood and replacement with an equal volume of a gelatin solution. The pre-CPB period was characterized by an unusually high blood loss (approximately 550 ml) but haemodynamic stability was maintained with adequate fluid replacement.

On initiation of normothermic cardiopulmonary bypass (CPB) and non-pulsatile blood flow, mean arterial pressure (MAP) fell to the 20–30 mm Hg range (Fig. 1). An ideal MAP for this patient was thought to be between 70 and 80 mmHg. The CPB pump flow rate was optimized and phenylephrine commenced by both continuous infusion and intermittent 100–200 μg boluses. The pressor response to phenylephrine was insignificant despite doses up to 2 μg. Kg^{-1}. min^{-1} and several 100–200 μg boluses. An infusion of norepinephrine was then commenced, initially at 5 μg.min^{-1} then progressively increased up to 25 μg.min^{-1} without significant response. An arterial blood gases analysis (ABG) performed around this time indicated a low haematocrit of 14.1; 600 mls of packed red blood cells was transfused into the CPB pump (the haematocrit subsequently increased to

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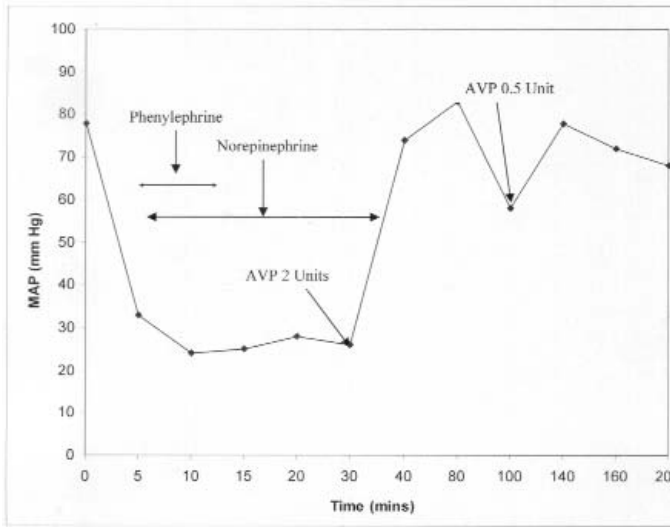
Fig. 1:   Chart of mean arterial pressure (MAP) and medication given after
         onset of cardiopulmonary bypass (CPB).
         Note that timeline is not to scale
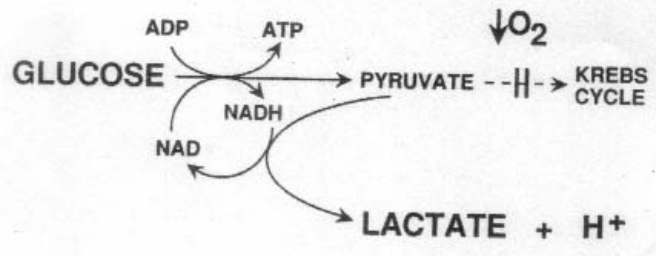   AVP = arginine vasopressin

Fig. 2:   Anaerobic metabolism

improvements in MAP, pump flow rate and, the plasma lactate levels continued to increase progressively from a pre-AVP level of 10.2 mmol/L to 23.9 mmol/L by the end of CPB.

Four-vessel coronary artery bypass surgery was performed; CPB and aortic cross clamp times were 200 minutes and 108 minutes respectively. A bilateral pleurodesis was also performed. Weaning from CPB was eventful: the patient had low cardiac output syndrome and required both inotropic support and intra-aortic balloon pump augmentation in order to enable successful weaning from CPB. The intensive care period was also eventful as high doses of varied combinations of inotropes (norepinephrine, dopamine, epinephrine and milrinone) were required to support cardiac output. On the third postoperative day (POD_3), the patient developed major organ failure, including acute respiratory distress syndrome and acute tubular necrosis. On POD_4 he had a cardiopulmonary arrest which failed to respond to resuscitative measures.

18.3). Despite these measures, the MAP failed to increase beyond 40 mmHg and the patient became anuric. Refractory hypotension was diagnosed and, in an urgent attempt to raise the MAP to a more acceptable range, a trial of vasopressin-2 units was administered (Pitressin, Parke Davis Pty Ltd–sterile, aqueous solution, containing 20 units per 1 ml ampoule of synthetic 8-arginine vasopressin in chlorbutol 0.5% preservative. This was diluted in water for injection to make a 1 unit/ml solution. The MAP promptly increased to 82 mmHg and stabilized in the 80–85 mmHg range. The phenylephrine infusion was discontinued and the norepinephrine infusion tapered. Subsequently, only one other bolus of vasopressin 0.5 unit was required to maintain the BP in the targeted range. The lactate and negative base excess levels, which had shown an initial increase in the early bypass period before trending down prior to the administration of AVP, began to increase once again following the administration of the vasopressin (Table). Despite the

DISCUSSION

Refractory hypotension after CPB, also called post-cardiopulmonary bypass distributive shock or post-cardiotomy syndrome, is well reported in the literature (5, 6). By contrast, only a few cases of refractory hypotension 'on-initiation' of CPB have been reported. Talbot et al (3) reported a case of refractory hypotension which was successfully managed with the use of vasopressin and in which there was a good outcome. Pappalardo et al (4) also reported a case of refractory

Table: Blood gas values during surgery (On-CPB 13:10; AVP 13:42 and 14:55)

Blood gas values						
Time	pre-CPB 9:30	CPB 13:31	CPB 13:40	CPB 14:50	post-CPB 15:31	end of surgery 17:13
pH	7.47	7.28	7.28	7.20	7.20	7.22
$PaCO_2$ (mm Hg)	32	44.5	45.6	48.4	42.6	42.3
PaO_2 (mm Hg)	207	547	537	476	343	402
Hct (%)	29.1	14.1	18.3	24.3	27.9	26.7
Base excess	-1.2	-5.2	-4.5	-8.3	-10.1	-12.4
Lactate (mmol/L)	2.1	12.1	10.2	16.1	18.4	23.9

hypotension on initiation of CPB but in that case the patient was not treated with vasopressin, experienced prolonged hypotension during CPB and suffered an eventful and prolonged postoperative period. Prolonged hypotension on CPB has been identified as a cause of multi-organ systemic dysfunction, including neurocognitive changes, renal failure and splanchnic hypoperfusion (7).

Refractory hypotension during CPB appears to have a similar pathophysiology and presentation to the refractory hypotension seen with the post-cardiotomy syndrome, severe septic shock and haemorrhagic shock unresponsive to volume replacement and catecholamine administration. This has been referred to as vasodilatory shock or the vasoplegic syndrome (VS) (8). No specific definition has been agreed upon but vasoplegic syndrome is characterized by severe hypotension, decreased systemic vascular resistance (SVR), decreased arteriolar reactivity, and increased requirements for filling volume and vasopressor therapy despite adequate cardiac output (or CPB flow rate). Landry *et al* (9) stated that the pathophysiology of intractable vasodilatation in sepsis, after cardiac surgery, or due to massive systemic inflammation, is very similar. This may explain the homogenous response to AVP therapy in patients with advanced vasodilatory shock originating from different underlying diseases (4, 5; 10–14).

Several case reports and studies have demonstrated that administration of vasopressin at doses that are nonpressor in normal subjects restores blood pressure in septic shock (15–17) and postcardiotomy shock patients with documented hyporesponsiveness to catecholamines (10). The vasopressin was most often administered as a last resort, after large doses of norepinephrine had failed to significantly improve the blood pressure. The vasopressin improved the mean arterial pressure (MAP) and decreased the amount of NE necessary.

Endogenous vasopressin is secreted by the posterior pituitary. It exerts antidiuretic, haemostatic and vasoconstrictive effects via stimulation of V1- and V2-receptors (18). Septic shock patients presenting with the VS have been shown to have vasopressin deficiency and a hypersensitivity to its exogenous administration (16, 18).

Some risk factors for the development of hypotension both during and after CPB have been identified. Several studies have established haemodilution, cardioplegia, preoperative intravenous heparin, chronic angiotensin-converting enzyme (ACE) inhibitor therapy and calcium channel blockers as independent risk factors (5, 19). Left ventricular ejection fraction lower than 0.35 have also been shown to increase the risk of vasoplegic syndrome in patients following cardiac surgery (5, 19). Many of these predisposing factors were present in the patient reported herein.

In our patient, the close temporal relationship between the administration of vasopressin and the increasing lactic acidaemia indicated that the AVP might have been the cause of or a major contributor to this complication. Other possible causes of an elevated plasma lactate concentration during cardiopulmonary bypass should also be considered. Hyperlactataemia is defined as a mild-to-moderate (2–5 mmol/L) persistent increase in blood lactate concentration without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually > 5 mmol/L) in association with metabolic acidaemia (pH < 7.35). Cohen and Woods (20) divided lactic acidosis into two categories, Type A and Type B. Type A is lactic acidosis occurring in association with clinical evidence of tissue hypoxia, including pulmonary problems (low PO_2), circulatory problems (poor delivery of oxygen) and haemoglobin problems (low O_2-carrying capacity, for various reasons). Type B is lactic acidosis occurring when no clinical evidence of poor tissue perfusion or oxygenation exists. By itself, an elevated arterial lactate concentration does not give any information on the underlying metabolic derangement which can modify lactate production, or lactate utilization, or both. Glycolysis, an anaerobic metabolic pathway in the cytoplasm of virtually all cells, produces the intermediate metabolite, pyruvate (Fig. 2). Under aerobic conditions, pyruvate is converted to acetyl CoA to enter another, more energy-efficient metabolic pathway, the Kreb's cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactate. The lactate diffuses out of the cells and is converted to pyruvate and then is aerobically metabolized to carbon dioxide and ATP. The heart, liver and kidneys use lactate in this manner. Alternatively, hepatic and renal tissues can use lactate to produce glucose via another pathway referred to as gluconeogenesis. The liver removes 70% of lactate. Less than 5% of lactate is renally excreted. Lactate synthesis increases when the rate of pyruvate formation in the cytosol exceeds its rate of use by the mitochondria. This occurs when a rapid increase in metabolic rate occurs or when oxygen delivery to the mitochondrion declines, such as in tissue hypoxia; the amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of hypoperfusion and the severity of shock. Lactate synthesis also occurs when the rate of glucose metabolism exceeds the oxidative capacity of the mitochondria, as observed with administration of catecholamines or errors of metabolism. Lactate clearance and uptake by the liver may be impaired by several factors, including acidosis, hypoperfusion and hypoxia. Lactic acidosis in cardiac surgical patients may also be a manifestation of systemic inflammation and excess pro-inflammatory cytokine production (21). Microvascular thrombosis is also an important cause of impaired peripheral oxygen utilization.

Hyperfusion of the gut during CPB may cause translocation of bacteria into the bloodstream and amplification of the inflammatory response. Also, intestinal infarction and gut hypoxia cause anaerobic metabolism. Bacterial translocation and profound fluid shifts contribute to circulatory collapse. Global oxygen delivery falls. Endogenous cate-

cholamine release attempts to support the circulation but will also increase glycolysis and lactate formation. As shock develops, hepatic blood flow falls and intracellular acidosis inhibits gluconeogenesis from lactate. The liver produces rather than clears lactate. Intestinal bacteria metabolize glucose and carbohydrate to D-lactate. This is only slowly metabolized by human LDH and contributes to the escalating lactic acidosis. Hyperlactataemia associated with metabolic acidosis is a major predictor of mortality in patients with sepsis or after cardiovascular shock (22, 23).

Our patient most likely had a Type A lactic acidosis, which may have resulted from increased production of lactate, decreased clearance of lactate or a combination of both. The complex array of factors which may have contributed include: tissue hypoxia, resulting from profound hypotension, profound haemodilution, the systemic inflammatory response syndrome, excessive neurohumeral activation, exogenous vasoactive agents such as the catecholamines and AVP, and impaired lactate clearance, resulting from poor liver perfusion and liver hypoxia.

The deleterious effects of VP on tissue perfusion is likely dose-dependent. Relatively high doses of vasopressin are used in emergency management of gastrointestinal bleeding because of its vasoconstrictive properties (24). Indeed, ischaemic lesions have been noted in patients receiving high doses of vasopressin to control upper gastrointestinal bleeding, and elevated liver enzymes (suggestive of a period of hepatic hypoperfusion) in patients receiving vasopressin for catecholamine-resistant shock have been reported (10). These effects were attributed to a compromise of splanchnic perfusion by the vasopressin. Klinzing and colleagues (25) investigated the effect of AVP when given in amounts adequate to replace the vasopressor effects of norepinephrine (mean vasopressin dose was 0.47 IU/min; range, 0.06–1.18 IU/min). Vasopressin decreased cardiac index, oxygen delivery and oxygen uptake. There was a tendency toward higher splanchnic blood flow but at the same time a significant increase in gastric mucosal PCO_2 gap. An increased gap suggests detrimental effects on mucosal gut blood flow.

In the studies above, the dose of VP was relatively high. Several studies have suggested that low-dose vasopressin (# 0.04 units/min) is safe and effective for the treatment of vasodilatory shock (10, 11, 16). In these studies, low-dose vasopressin improved or maintained blood pressure, decreased norepinephrine requirements and increased urine output without causing significant side effects.

In conclusion, we report here the case of a patient with severe refractory hypotension at the beginning of CPB. Persistent and prolonged hypotension during CPB is associated with a poor outcome; hence the need for urgent intervention. Administration of a 2-units bolus of vasopressin achieved an effective and persistent elevation in MAP. However, this was followed shortly after by the development of hyperlactataemia and lactic acidosis. The differential for this has been discussed, but vasopressin, by direct or indirect mechanisms, is a possible cause. Because of the potentially deleterious effects of vasopressin on the microcirculation, including that of the hepatosplanchnic region, we recommend that it be continued to be reserved for those patients with severe vasodilatory shock in whom other vasopressors fail. It should be used with the greatest caution and with careful titration to the desired effect. As well as further clinical studies on efficacy and safety, there is a need for pharmacodynamic and pharmacokinetic information on the use of vasopressin during cardiopulmonary bypass.

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