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CASE REPORT

Vasoplegia after cardiac surgery

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Abstract

A case of severe refractory hypotension following a cardiac transplant is presented. In the hours after surgery, vasoplegia was diagnosed in the intensive care unit after exclusion of common causes of hypotension after cardiac surgery. Vasoplegia after cardiac surgery is a condition characterised by severe systemic hypotension, low systemic vascular resistance and a normal to high cardiac output which is often refractory to conventional vasopressor therapy and fluid administration. The pathophysiology is still incompletely understood but seems to be related to several preoperative factors as well as the use of the cardiopulmonary bypass. As this phenomenon is associated with an increased morbidity and mortality, proper recognition is essential although treatment options are limited.

Introduction

Hypotension after major cardiothoracic surgery is a frequent phenomenon and it has a broad differential diagnosis. Emergent evaluation is obligatory to prevent further deterioration and eventually death of the patient. The vasoplegia syndrome causes a severe distributive shock which is regularly seen in patients post cardiac surgery. The underlying pathophysiology consists of resistance to vasopressors on the one hand and excessive activation of vasodilators on the other. Vasopressors such as norepinephrine and vasopressin are first choice for treatment but evidence is arising for new therapies such as methylene blue. To outline a comprehensive overview of the vasoplegia syndrome, the following case is presented.

Case

A 57-year-old man was admitted to the intensive care unit (ICU) after cardiac transplant. He was known with a non-ischaemic dilated cardiomyopathy and over the past few years, he underwent multiple aortic valve replacements because of recurrent aortic valve endocarditis. Because of recurrent episodes of arrhythmia and worsening biventricular cardiac function he was listed for cardiac transplant.

After 19 months on the waiting list, a cardiac transplant was performed. Despite a technically difficult but uncomplicated procedure (ischaemic time 173 minutes and cardiopulmonary bypass (CPB) time 303 minutes), transoesophageal ultrasound at the end of the procedure revealed dilatation of the right ventricle with a considerably reduced function, which was probably caused by both cardiac stunning due to the long procedure and recent pressure overload caused by pulmonary embolism in the donor. Furthermore, mild tricuspid insufficiency was seen. Additional right ventricular support was started consisting of inhaled nitric oxide and peripheral venoarterial extracorporeal membrane oxygenation (VA ECMO). Upon arrival to the ICU the patient was sedated, intubated and supported by high-dose vasopressors (norepinephrine at 0.667 µg/kg/min, vasopressin at 4 IU/hour) and inotropes (dobutamine at 7.8 µg/kg/min and milrinone at 0.31 µg/kg/min) because of refractory hypotension (mean arterial pressure <60 mmHg). Continuous invasive cardiac monitoring with a pulmonary artery catheter (PAC) revealed a cardiac output of 2.1-7.8 l/min (cardiac index 1.1-3.9 l/min/m^2), central venous pressure of 12-17 mmHg, mean pulmonary artery pressures of 18-25 mmHg and mixed venous saturation 68-88%. The systemic vascular resistance (SVR) was 1708-635 dyn·s/cm, but considering the corrected SVR for the total cardiac output (PAC and ECMO) this was even lower. Despite this, diuresis was still adequate. Because of low drainproduction and stable haemoglobin levels, bleeding as a cause of haemodynamic instability was ruled out. In addition, tamponade was excluded with cardiac ultrasound. Sepsis was not considered likely as there were no signs of infection immediately after surgery; neither was anaphylactic shock likely in the absence of other clinical signs such as erythema or angioedema. In the following 24 hours, fluid optimisation was

achieved by administering a total of 8 litres of blood products and balanced fluids. Nevertheless, refractory hypotension persisted and lactate levels were rising although the cardiac output increased in this same period to 7.8 l/min (cardiac index 3.9 l/min/m^2). Considering the mild tricuspid insufficiency seen directly postoperatively, the individual measurements of the PAC should be interpreted with caution, but the trend is thought to be reliable. Because of the striking persistent low vascular resistance, the hyperdynamic circulation and persistent need of high-dose vasopressors, vasoplegia was considered most likely in the absence of tamponade, persisting cardiac stunning, right ventricular failure or severe bleeding. Inotropes were discontinued. In the next 48 hours fluid administration could be ceased, and vasopressor dosage decreased. In the following days, the patient developed anuric acute kidney failure for which continuous venovenous hemofiltration (CVVH) was initiated on day 3, VA ECMO was weaned and successfully removed. Transoesophageal echocardiography revealed full recovery of the right ventricular function. After seven days, the patient was extubated and CVVH was successfully withdrawn. Ten days after cardiac transplant, he was discharged to the coronary care unit.

Discussion

The vasoplegia syndrome comprises a redistributive shock state which is diagnosed per exclusionem and is characterised by severe hypotension, low systemic vascular resistance and high cardiac output. In one of the first articles published in the 1990s, vasoplegia was characterised by hypotension (mean arterial pressure ranging from 40-65 mmHg, cardiac index between 2.9-3.8 l· min^{-1}· m^{-2}, and SVR index ranging from 700-1200 dyne· sec· cm^{-5}· m^2.[1] Until now, no universal definition has been defined.

In addition, there are no specific markers, strict criteria or tests to discriminate whether the cause of vasodilatory shock is due to vasoplegia or to one of the many other causes of hypotension.[2,3] In this case we excluded the most likely causes, namely haemorrhagic shock, tamponade and sepsis. The onset of the severe hypotension was postoperative, and the hypotension appeared resistant to vasopressors and inotropes. Altogether, these characteristics fit the diagnosis of the vasoplegia syndrome.

As widely described in literature, the vasoplegia syndrome is especially characterised by a low SVR, leading to end-organ hypoperfusion in spite of normal to high cardiac output in postoperative patients after cardiovascular surgery. In the absence of a strict definition, the variation in incidence is wide, varying between 5% to 45%.[4] As in our patient, vasoplegia syndrome usually occurs directly or within several hours after cardiopulmonary bypass, but some patients have a delayed onset of up to 39 hours.[5,6] A typical feature is the lack of effect of treating low systemic vascular resistance with high-dose vasopressors with persistent hypotension leading to end-organ hypoperfusion and failure. Vasoplegia contributes to increased morbidity and in-hospital mortality by causing renal failure, delayed extubation and prolonged stay in the ICU.[6,7] However, these adverse effects do not necessarily influence long-term outcome regarding patient survival, as shown by Chan et al.[8] The case presented here illustrates the short-term consequences of severe vasoplegia, but also shows that recovery is likely.

The underlying pathophysiology of vasoplegia syndrome is multifactorial in origin and not well understood but comprises an absent response to vasopressors on one hand and excessive stimulation of the vasodilator mechanism on the other. One of the causes of excessive vasodilation is a shortage of calcium influx into the cytoplasm of vascular smooth muscle cells by deactivation of calcium channels. In a physiological setting calcium generates contraction of the muscle. However, when these calcium channels are dysfunctional due to intracellular acidosis or depletion of adenosine triphosphate, muscle contraction is insufficient. Because the receptors which activate the calcium channels are the binding place for catecholamines, even with a high dose of these substances muscle contraction will not take place.

Another reason of vasodilation might be the presence of high concentrations of nitric oxide (NO).[2] This normally counteracts vasoconstriction but, in this situation of supraphysiological levels of NO, it leads to pathological vasodilation.

Finally, a relative vasopressin deficiency caused by prolonged shock induces vasodilatation. Extended stimulation of the arterial baroreflex due to prolonged hypotension leads to depletion of neurohypophyseal stores of vasopressin and the serum concentration falls to suboptimal levels. Whereas vasopressin is needed to oppose the effect and synthesis of NO, low concentrations of this hormone attribute to the vasoplegic state.[2,6,9]

A main contributing factor to both vasopressin deficiency and raised NO concentration seems to be the activation of a systemic inflammatory response caused by the CPB system. As reviewed by Hall et al. this is the consequence of blood contact with the CPB system, ischaemia-reperfusion injury of the heart and lung and the release of endotoxins from the gut. This may manifest clinically by haemodynamic instability, myocardial dysfunction, lactic acidaemia and low systemic vascular resistance.[10,11] Since the CPB is often used in major cardiovascular surgery, this is a major attributing risk factor for the development of the vasoplegia syndrome. And more specifically, the time on bypass is found to be of importance for the severity of vasoplegia to develop. Chan et al. found that a median bypass time of 189 minutes caused more severe vasoplegia in patients after heart transplantation than 147 minutes on the CPB.[12] Our patient was on bypass almost twice as long. Besides the systemic inflammatory response, CPB may also lead to cardiac stunning defined as systolic and diastolic myocardial dysfunction which in turn also contributes

to postoperative hypotension.[13] Other significant risk factors were found to be hypothyroidism, preoperatively reduced left ventricular systolic function and multiple sternotomies.[6] The preoperative use of medicaments such as amiodarone and angiotensin converting enzyme inhibitors also appears to be a contributing risk factor as they cause hypotension by blockade of the sympathetic nerve system and the renin-angiotensin system.[14,15] In addition, inotropes, such as milrinone, levosimendan and dobutamine, which are frequently used to improve postoperative myocardial contractility, are well-known for causing significant vasodilatation. Although clinically relevant, major trials confirming a significant negative effect of these drugs after cardiac surgery are lacking.[18-20]

Consequently, treatment of vasoplegia requires improving vascular tone and restoring adequate perfusion pressure to prevent end-organ hypoperfusion and failure (*figure 1*).

Synthetic catecholamines acting on alpha-1 adrenergic receptors, including phenylephrine, epinephrine, norepinephrine, and dopamine remain the hallmark for current treatment. Noradrenaline is a potent vasopressor and is associated with reduced mortality when used in patients with cardiogenic shock.[21] Other vasopressors are less favoured to treat vasoplegia because of lack of inotropic effect and less potency (phenylephrine), or due to causing hyperlactataemia (epinephrine) or arrhythmia (dopamine) (*table 1*).[3,22,23] Vasopressin, a non-catecholamine, can be used in addition to norepinephrine when high-dose levels of norepinephrine alone (>0.1 µg/kg/min) are not sufficient to achieve a minimal mean arterial pressure of 65-70 mmHg.[24,25] Dosage may be titrated up to 0.04 U/min, whereas in higher doses it is associated with

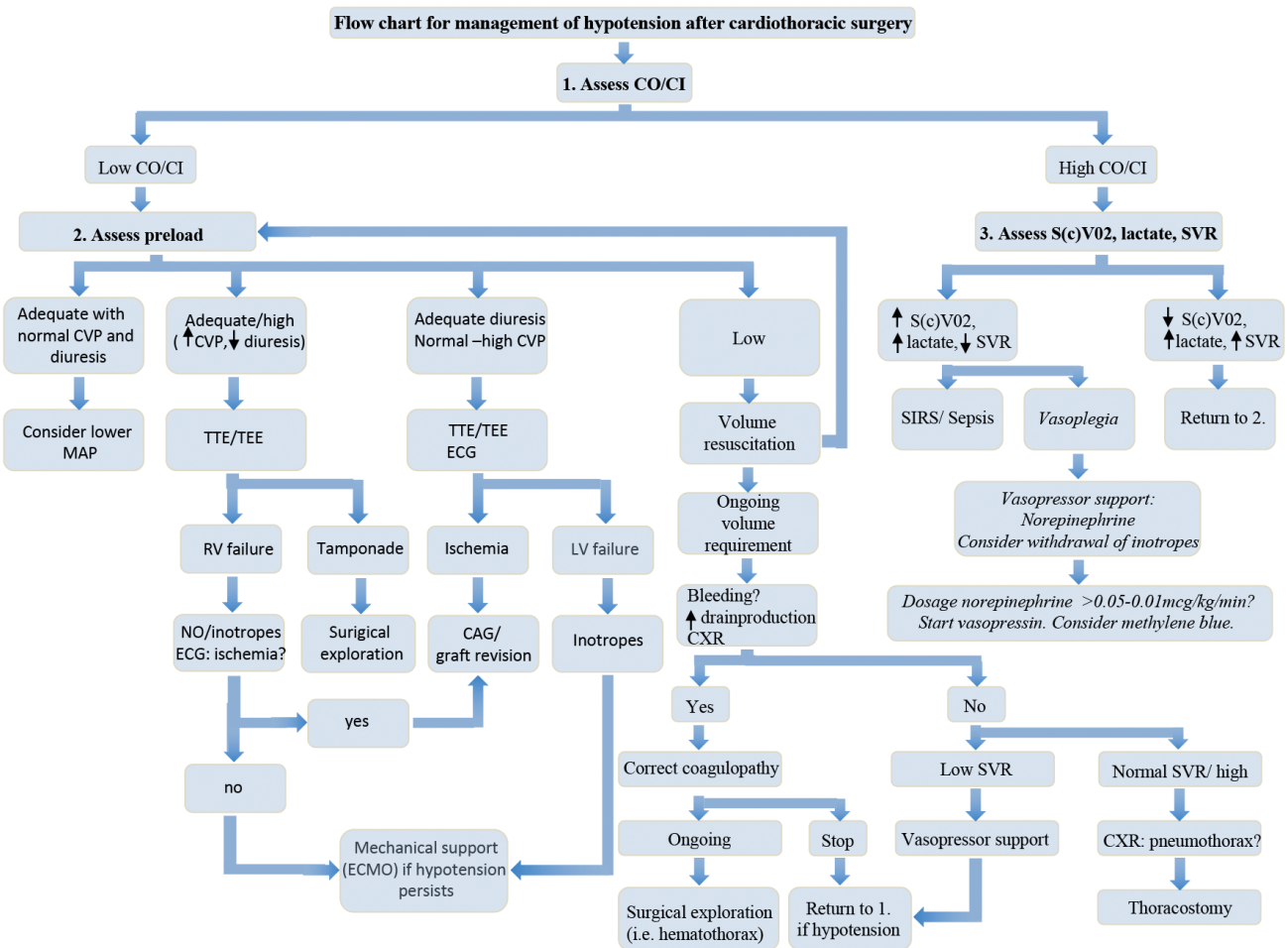

Figure 1. Flow chart for management of hypotension after cardio-thoracic surgery

CAG = coronary angiography; CI =cardiac index; CO = cardiac output; CVP = central venous pressure; CXR = chest X-ray; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; MAP = mean arterial pressure; NO = nitric oxide; SIRS = systemic inflammatory response syndrome; RV = right ventricle; LV = left ventricle S(c)V02 = (mixed) venous saturation; SVR = systemic vascular resistance; TTE = transthoracic echocardiography; TEE = transoesophageal echocardiography

Table 1. Summary of the mechanisms of action and effects of frequently used vasopressor and inotropic agents and their limitations when treating hypotension due to vasoplegia[3,16,17,22,23]

	Mechanism	Effects	Limitations (in vasoplegic patients)
Vasopressor agents			
Phenylephrine	α1-agonist	Peripheral vasoconstriction	No inotropic action and less potent
Norepinephrine	α1-, α2- and β1-agonist	Potent vasopressor	(Mesenteric ischaemia and increases pulmonary vascular resistance at higher dose)
Epinephrine	β1, β2-agonist with α1-, α2-effects at higher dose	Improves CO and vasoconstriction (α agonist effect)	Tachycardia and arrhythmias
Dopamine	β1-agonist with α1 effect at higher dose	Improves CO and vasoconstriction	Tachycardia and arrhythmias via β1-receptors
Vasopressin	Via vasomotor V1 and renal V2 receptors	Peripheral vasoconstriction	(Mesenteric ischaemia at higher dose)
Inotropic agents			
Dobutamine	β1-, β2-agonist	Improves CO	Hypotension via β2-receptors. Tachycardia and arrhythmias via β1-receptors
Milrinone	Phosphodie-sterase III inhibitor	Improves CO by lowering of afterload and increasing cardiac contractility	Hypotension by calcium removal by raising cAMP levels in vascular smooth muscle
Levosimendan	Phosphodie-sterase III inhibitor, calcium sensitizer	Improves CO by lowering of afterload and increasing cardiac contractility	Hypotension due to increased cAMP levels in smooth muscle cells by activation of specific K+-channels

CO= cardiac output, cAMP= cyclic adenosine monophosphate

mesenteric ischaemia.[4,6,25] Although not solidly proven in randomised clinical trials, intravenous vasopressin is used off label because of its potent effects.[25]

Our patient arrived at the ICU with a diagnosis of postoperative right ventricular failure due to stunning and pulmonary embolism in the donor. In the following hours in the ICU, we evaluated our patient thoroughly for refractory hypotension, finally diagnosing the vasoplegia syndrome. In the presence of a hyperdynamic circulation, infusion of dobutamine and milrinone was subsequently stopped because of their unwanted side effects consisting of vasodilation. Norepinephrine and vasopressin dosages were raised to achieve a mean arterial pressure of >65 mmHg which is important in the presence of right ventricular failure.

A therapy not considered in our patient is methylene blue. This dye, known for its treatment of methaemoglobinaemia, counteracts the vasodilation effect of NO. Several case reports and small prospective interventional studies have shown that infusion of methylene blue with a bolus of 1.5-2 mg/kg rapidly increases the systemic vascular resistance thereby decreasing norepinephrine dosage in patients diagnosed with vasoplegia. It can be initiated when reaching a norepinephrine dosage of at least 0.5 μg/kg/min.[27] Except for discoloration of skin and urine to greenish-blue, the adverse effects of methylene blue are dose dependent and do not occur with doses <2 mg/kg. When using higher doses, one should be aware of the risk of cardiac arrhythmia, coronary vasoconstriction, decreases in cardiac output, renal and mesenteric blood flow and haemolytic anaemia. Methylene blue should not be used in patients with severe renal insufficiency and hypersensitivity to the dye.[25,26] Considering this, methylene blue appears effective and safe as a treatment of vasoplegia but before using this in individual patients on our ICU dosing regimens and protocols need to be refined.

In conclusion, after major cardiovascular surgery patients may suffer from severe, refractory hypotension with a broad differential diagnosis. The vasoplegia syndrome is a diagnosis per exclusionem after excluding emergent causes, such as surgical bleeding, tamponade or myocardial dysfunction. Patients suffering from cardiac dysfunction are prone to develop vasoplegia because of medication used preoperatively, use of the CPB during the operation and use of inotropes postoperatively. Treatment consists of vasopressors such as noradrenaline and vasopressin, and discontinuation of inotropes which can further lower the SVR.

Disclosures

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