Review

Severe Refractory Vasoplegic Shock Syndrome After OPCABG: Our Experience and Review of Literature

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Review

Severe Refractory Vasoplegic Shock Syndrome after OPCABG: Our Experience and Review of Literature

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Abstract: Background: Vasoplegic shock syndrome(VSS) after an off-pump coronary artery bypass graft (OPCABG) is an extremely rare condition. Inotropic support is usually the first-line therapy though it can precipitate several complications or be ineffective. We report the first case of severe refractory VSS after OPCABG successfully treated with hydroxycobalamin. Methods: A 77-year-old gentleman underwent OPCABG for three vessels coronary artery disease. Preoperative LV ejection fraction was 28%, and the patient before surgery started sacubitril/valsartan titrated, then, to the highest dose. Surgery was uneventful and, by the end of the procedure, TEE showed improved biventricular contractility. Results: The patient was transferred to the ICU without inotropic support but he developed soon hypotension. TEE ruled out pericardial tamponade and confirmed fair contractility. Norepinephrine was titrated to a medium-high dose, vasopressin was started and a Swan-Ganz catheter was placed. SVR was 480 dyn·s·cm−5. Despite aggressive pharmacologic treatment (including Methylprednisolone and Methylene blue), no improvements were noticed. 10 g of hydroxycobalamin were administered. One hour later hemodynamic status re-assessment showed SVR > 800 dyn·s·cm−5. Afterward, vasopressors were gradually reduced. Conclusions: Our case demonstrated the importance of adequate early treatment in VSS after OPCABG. For the first time, hydroxycobalamin was effectively used to restore homeostasis.

Keywords: vasoplegic shock syndrome; off-pump CABG; Hydroxycobalamin

1. Introduction

Vasoplegic shock syndrome (VSS) is a complex condition that arises from a huge imbalance between the loss of systemic vasculature resistance and unresponsiveness to endogen/exogen vasopressor molecules despite a preserved cardiac index [1]. Despite no consensus has been obtained regarding its definition, VSS is frequently described as exhibiting a cardiac index of 2.2 L/min/m2, either normal or elevated, accompanied by difficulty maintaining a mean arterial pressure (MAP) of 60 mmHg due to a systemic vascular resistance (SVR) of less than 800 dynes*sec/cm5, despite receiving high doses of vasopressors and inotropes (equivalent to 0.5 mg/kg/min of norepinephrine) [2].

VSS has been also considered a distributive form of circulatory shock developing in the first 24 hours after cardiopulmonary bypass (CPB) [3]. VSS, in fact, has been reported in up to 40% of CPB and accounted for less than 5% of all circulatory shock [1]. Refractory VSS carries a mortality rate as high as 25% [4].

CPB can be a strong precipitant for VSS and in particular CPB duration, the employed oxygenator and drain types, priming, myocardial protection, drugs administered during CPB (heparin/protamine), and, most importantly, perfusion pressure.

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VSS incidence is higher in patients with preoperative use of angiotensin-converting enzyme inhibitor (ACE-I), calcium channel blockers, amiodarone, heparin, diabetes mellitus, or reduced cardiac function (EF < 35%), warmer core temperatures while on bypass, reperfusion injury and long CPB run [5].

Although VSS has been extensively studied and described as a post-CPB syndrome, a large question mark remains to explain and treat some reported cases of VSS after off-pump cardiovascular procedures.

Our study reports the first case of VSS refractory to standard medical treatment occurred after an off-pump cardiac surgery procedure successfully managed with hydrossycobalamin.

2. Relevant Sections

2.1. Case Report Description

A 77-year-old male with a history of untreated hypertension, dyslipidemia, diabetes mellitus type 1, and major depressive disorder underwent a pre-anesthesia check-up for inguinal hernia surgery. An electrocardiogram revealed a new left bundle branch block. Subsequently, the echocardiogram showed a severely reduced left ventricle ejection fraction (LVEF) of 26%, end-diastolic diameters of 76 mm, and end-diastolic volume of 224 ml with inferior basolateral wall, lateral wall, and apex akinesia. The left atrium was also dilated (area 25 cm^2) and there was mild mitral and tricuspid regurgitation (PAPS 52 mmHg). Therefore, the patient underwent an elective coronary angiogram that revealed 95% stenosis of the proximal left anterior descending artery (LAD), sub-occlusive stenosis of the left circumflex and obtuse marginal (OM) branches, and chronic total occlusion of the right coronary artery. Despite these findings, he had shortness of breath (class II NYHA). The patient was scheduled for elective off-pump coronary artery bypass grafting (OPCABG). Before the surgery, the patient was referred to the heart failure outpatient department for optimization of pharmacological therapy, and, starting two weeks before surgery, sacubitril/valsartan was titrated then to the highest dose. Pre-operative, in the operating room, an intra-aortic balloon pump (IABP) was placed. The patient underwent OPCABG and three grafts were performed. The patient received a skeletonized left internal mammary artery to LAD in situ, a skeletonized right internal mammary artery to OM in situ through transverse sinus, and a reverse saphenous vein graft to the posterior descending artery. Surgery was uneventful and by the end of the procedure, transesophageal echocardiography (TEE) showed improved biventricular contractility.

The patient was transferred to the intensive care unit with IABP and without inotropic support. After around one hour, the patient developed hypotension, tachycardia, and oliguria initially addressed with fluid management, and a low-dose vasopressor was started, but both failed to improve the hemodynamic. TEE ruled out any pericardial tamponade or pleural collections and confirmed fair contractility. Chest X-ray did not reveal abnormalities. Norepinephrine was titrated to a medium-high dose, vasopressin was started and a Swan-Ganz catheter was placed. SVR was 480 dyn·s·cm−5 and the cardiac index was > 8,3 L/min/m2. Broad spectrum antibiotic was started suspecting sepsis despite no evidence of infection. Despite aggressive pharmacologic treatment and optimization of mechanical ventilation, after 6 hours, no improvements in mean arterial pressure (MAP < 50 mmHg) were noticed and SVR was 500 dyn·s·cm−5. Blood lactate levels were continuously rising (peaked up 13mmo/d), and oliguria was also present. All vasopressors were titrated to the medium-high dose, trying to avoid beyond the safety threshold dose. Methylprednisolone 200 mg boluses were injected at regular intervals. An infusion of methylene blue was also started without success.

Being all common conditions that can lead to severe hypotension after cardiac surgery ruled out, VSS was suspected and it was the most reasonable diagnosis. Due to the hemodynamic status of the patient, mechanical circulator support would have not added any benefit to the clinic situation and might have been deteriorating the SIRS.

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10 g of hydroxycobalamin (labeled used for cyanide poisoning), (Figure 1) was administered as an intravenous infusion by central line. After around 30 minutes, MAP started rising and reached 60-65 mmHg. One hour later MAP was improving and hemodynamic status re-assessment showed SVR > 800 dyn·s·cm−5 and the cardiac index was 4,5 L/min/m2. In the following hours, the SBP reached levels above 90 mmHg and SVR was 1100 dyn·s·cm−5. Vasopressors were gradually reduced and blood lactate levels decreased.

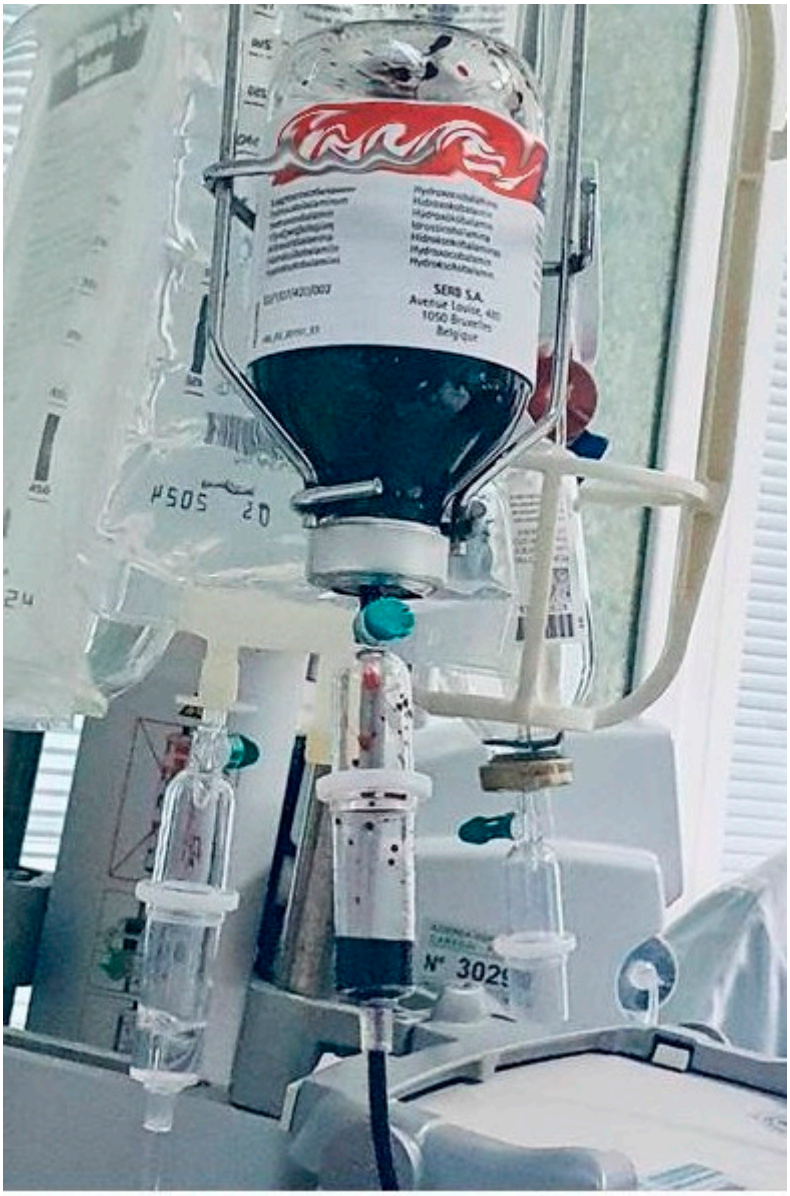

Figure 1. Infusion of hydroxycobalamin.

As a result of the VSS and its treatment, the patient developed chromaturia, prolonged mechanical ventilation, and percutaneous tracheostomy. The patient was discharged to a rehab facility on postoperative day 26. At the 3-month follow-up, the patient had completely recovered and he returned to normal life. Due to persistent reduced LVEF, an implantable cardioverter-defibrillator was implanted. The last echocardiography showed positive remodeling of the left ventricle and no residual regional wall motion abnormalities. No major adverse cardiac and cerebrovascular events were reported at 1-year follow-up.

2.2. Literature Review

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Studies were included if any of the following criteria were met: vasoplegic shock or syndrome after off-pump CABG.

Studies were excluded if any of the following criteria were met: (1) vasoplegic shock or syndrome after cardiac surgery; (2) not published in the English language; (3) not published in a peer-reviewed journal; and (4) was a conference abstract.

After the removal of duplicates and articles not in the English language there were four papers presenting VSS occurred in off-pump CABG (Table 1).

Table 1. Vasoplegic shock syndrome after OPCABG.

Study author	Year of the study	Type of the study	Patients included	Treatment
Sun et al.[3]	2008	comparative	10	-
Gomes et al.[8]	2003	retrospective	4	Norepinephrine
Raja et al.[10]	2004	case report	1	Norepinephrine and vasopressin
Vaidyanathan et al.	2017	case report	1	Norepinephrine and vasopressin

3. Discussion

Our literature review on VSS after off-pump cardiac procedures, Table 1, confirmed the need for an alternative effective medical treatment to inotropic support in case of severe refractory VSS, even in OPCABG. Despite early diagnosis can be challenging, the understanding of VSS pathophysiology is crucial to promptly start adequate therapy.

A delayed diagnosis especially in the initial phase, could result in an unpredictable prognosis. Aggressive treatment is usually required, yet this process has to be continuously tailored to the hemodynamic status of the patient.

The pathophysiology of VSS is multifactorial, and its underlying processes are often likened to septic shock [6]. The combination of exposure of blood to the foreign surfaces of CPB and surgical trauma triggers a systemic inflammatory response, which is considered a causative factor in the development of vasoplegia. During surgery, tissue injury and hypoperfusion can activate immune cells (i.e. macrophages and monocytes) leading to the release of pro-inflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), and IL-6. These cytokines decrease the responsiveness of vascular smooth muscle cells to vasoconstrictors, causing vasodilation and decreased SVR. They contribute also to activating inducible nitric oxide synthase (iNOS) enzymes, promoting the release of large volumes of NO. This prevents smooth muscle calcium influx and hyperpolarizing smooth muscle cells through activation of adenosine triphosphate (ATP)-sensitive potassium channels, leading to systemic vasodilatation [7]. The activation of the complement system can also contribute to vasoplegia by releasing vasoactive peptides, such as bradykinin and C5a, leading to vasodilation and increased vascular permeability [8]. Moreover, CPB not only increases NO production and ATP depletion, but it enhances also vascular smooth muscle acidemia, which results in decreased myosin phosphorylation and vasodilation. Simultaneously, neuro-hypophyseal deposits from endogenous vasopressin are depleted rapidly, adding to the vasodilation effect and creating vasoplegia [9].

In our case, VSS developed after OPCABG, despite two of the main pathways of VSS pathophysiology (systemic inflammatory response (SIRS) and cellular hyperpolarization through inactivation of Ca2+ voltage-gated channels) [1] being less exhibited. Therefore, other possible causes in the absence of extracorporeal circulation, should be considered.

In the case of off-pump procedures, the activation of pro-inflammatory cytokines and iNOs appears to be initiated by heparin-protamine administration with all the consequences of the development of SIRS and multi-organ failure due to hypotension refractory to catecholamines [5].

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In addition to this mechanism, it is possible that preoperative chronic congestive heart failure with low ejection fraction and the therapy with sacubitril/valsartan started at a high dose just before the surgery, could have precipitated the systemic inflammatory response related to surgery, and VSS. LVEF <35%–40%, in fact, is an independent predictor of vasoplegia after cardiac surgery with CPB. A pre-existing, increased inflammatory profile along with the compensatory chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system may be responsible for the development of postoperative vasoplegia in patients with heart failure [10].

To our knowledge, to date, this is the first case reporting the possible association of sacubitril/valsartan and VSS in OPCABG. Previous data regarding the use of sacubitril/valsartan and VSS after cardiac surgery are controversial [11], despite some case reports have described profound vasoplegia after CPB [12]. Haider et al. [11] reported the preoperative use of sacubitril-valsartan in patients undergoing heart transplantation or left ventricular assist device surgery and they found that the angiotensin receptor neprilysin inhibitor was not significantly associated with the development of vasoplegic syndrome. Similar results were described also by Domínguez et al. in their multicentric study in which the incidence of vasoplegic syndrome associated with the preoperative use of sacubitril-valsartan in a cohort of 96 patients undergoing heart transplant was 15.6% [13]. Conversely, Almufleh et al. [12] described in their case report the association of postoperative vasoplegia with the preoperative use of sacubitril-valsartan in a patient undergoing a heart transplant.

Nowadays, current management recommendations in cardiac surgery encourage stopping sacubitril-valsartan before the procedure. However, considering that the half-life of the drug and its metabolites reach 18 hours [14] and that not all cardiac surgery procedures can be scheduled, it is very likely that some patients undergoing treatment with this drug can be under its effect at the time of the surgical intervention.

The possible involvement of the sacubitril-valsartan in the mechanisms of vasoplegic syndrome is also supported by the fact that the Renin-Angiotensin-Aldosterone system (RAS) is one of the three different systems (together with the sympathetic, and vasopressinergic system), that are usually involved in the maintenance of blood pressure. RAS antagonists such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) block, in fact, the RAS response to hypotension. Therefore, a complete suppression of the RAS due to this treatment might play a crucial role in VSS [15]. In addition, considering that anesthetic drugs reduce the influence of the sympathetic system on cardiovascular tone, under general anesthesia there is an increased reliance on RAS and vasopressinergic system to maintain blood pressure.

Gomes et al [16]. described four patients who underwent VSS after OPCABG (total incidence 0,4% in 5 years). All patients were treated with high doses of norepinephrine, presented postoperative complications related to the VSS and one patient died. Interestingly, they found tumor necrosis factor α (TNF-α) soaring levels suggesting this cytokine is a likely mediator of this syndrome even in off-pump procedures.

Norepinephrine is usually the first-line therapy in case of hypotension associated with vasodilatory shock since it increases vascular and venous resistance, cardiac preload, and inotropy, and reduces vascular capacitance. Norepinephrine has vascular effects both on the arterial and on the venous side, with an increase of both arterial and venous pressure. Nevertheless, in some patients, the blood pressure constantly rises, whereas cardiac output might not increase. Because of this reason, restoring blood pressure with norepinephrine infusion may not always be associated with an improvement in tissue perfusion [17].

In addition to norepinephrine, vasopressin has gained popularity in restoring vascular tone and increasing the clinical outcome [18] as shown by Raja et al [19]. In this case report, however, before obtaining negative microbiology results, the patient was treated as a septic shock-like case, delaying the right diagnosis. Moreover, as suggested in the article, despite an off-pump procedure significantly decrease the systemic inflammatory response syndrome usually developed after a cardiac surgery intervention, there are still some cases of refractory vasoplegia developed after OPCABG. Therefore, the generation of proinflammatory mediators due to surgical stress, the use of resterilized disposable

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devices and protamine, the transfusion of blood products, or the occurrence of endotoxemia secondary to repeated episodes of hypotension throughout the surgery as a result of mobilization and displacement of the heart could precipitate the systemic inflammatory response and vasoplegic syndrome [19].

Other vasoactive drugs used include phenylephrine (alpha-1 receptor agonist), and angiotensin II (angiotensin II receptor type 1 agonist, causing vasoconstriction and upregulating endogenous vasopressin secretion) [19]. Dopamine can be also added since it increases systemic vascular resistance and inotropism, though it has been associated with an increased risk of arrhythmias compared with the other catecholamines [21]. If a single infusion of a single drug cannot achieve the target pressure, a second drug with a different mechanism of action should be used. Therefore, initial therapy usually involves volume expansion and administration of norepinephrine, and other inotropic drugs are then usually added. [18].

Despite the treatment of VSS is challenging, the aim is to address every single step in the pathophysiologic cascade of VSS to restore homeostasis. Inotropic agents are just a supportive therapy that can lead to resistance or even severe toxic effects at high doses [20]. Therefore, focusing the treatment towards hypotension using an uncontrolled escalade of vasopressors infusion, can be not only useless but also deleterious leading to a catastrophic vicious circle of malperfusion. It has been demonstrated that vasopressors have a non-responding threshold at the highest dose [22]. Once the splanchnic and peripheral malperfusion are established, these processes will further deteriorate the SIRS and the energetic status of the cells resulting in the complete loss of SVR.

Dysregulation of nitric oxide (NO) release, production, or signaling plays a key role in the systemic vasodilation of vasoplegic and septic shock. Therefore, targeted therapies such as methylene blue and hydroxocobalamin acting to interrupt this pathway might be promptly considered.

Hydroxycobalamin for catecholamine-resistant VSS during CPB was first described by Roderique et al [24].

To the best of our knowledge, our report is the first one on hydroxycobalamin treatment for VSS after OPCAB.

Hydroxycobalamin is usually used to counteract the excess of nitric oxide (NO) released into the bloodstream by cyanide poisoning. For this reason, it is considered a scavenging molecule for large amounts of NO released by inducible nitric oxide synthase [24]. Hydroxycobalamin also enhanced the clearance of vasodilators such as hydrogen sulfides and endothelium-hyperpolarizing factors, restoring, thus, the balance between vasodilator and vasoconstrictor molecules [25]. Besides, this re-established equilibrium most of the time may bring a recovery in the efficacy of vasopressors on vessels' smooth muscles. Given its off-label use in treating vasoplegia, the dosing of this drug is based on its primary indication of cyanide poisoning - 5-10 g IV infusion over 15 minutes. However, literature reports extended duration infusion of the same 5 g dose (median 6h, range 1-10h), to significantly and gradually reduce the vasopressor requirements throughout the infusion, which appeared to be sustained after cessation [26]. Hydroxycobalamin could be used as the last resource in an attempt to treat severe refractory VSS leading to an unfavorable prognosis or might be used as a vasopressor-sparing agent in an earlier stage trying to avoid the vasopressor-induced malperfusion.

Although hydroxycobalamin is a promising molecule, its response can be unpredictable [19], and, considering that it is also a very expensive drug [27], its usage should be balanced in a fair allocation of resources. Acknowledging that our case has the limitation of a single case report and further investigations are needed to evaluate the real strength of hydroxycobalamin in OPCABG, we strongly believe that this case could be a useful tool for the physician who faces this complex life-threatening complication, and it may be a starting point for future studies.

4. Conclusions

Our case demonstrates the importance of early recognizing severe refractory VSS in OPCABG since SIRS after reperfusion injury of a severe ischemic heart, even without CPB, can be extremely large. Moreover, with the increasing clinical use of sacubitril-valsartan in heart failure patients, accurate preoperative planning should be performed, when feasible, to reduce the possible effects of

this drug on the postoperative course. Finally, hydroxycobalamin can play a crucial role in restoring homeostasis in such a challenging situation. The usage of this molecule in a similar setting could pave the way for the next research.

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Informed Consent Statement: The patient provided informed consent to participate in this study and for the publication of any data included in this article.

Data Availability Statement: The data that support the findings of this study are available upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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