Vasoplegic syndrome after off-pump coronary artery bypass surgery

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Abstract

Objective: The vasoplegic syndrome (VS) has been implicated in life-threatening complications after open heart surgery, where the whole-body inflammatory reaction is attributed to the cardiopulmonary bypass (CPB). Off-pump coronary artery bypass grafting (OPCAB) has been recently achieving growing enthusiasm mainly due avoiding the side effects of CPB. However herein the occurrence of VS in OPCAB is reported. Methods: The vasoplegic syndrome usual findings occurring in the early postoperative period include severe hypotension, tachycardia, normal or elevated cardiac output and low systemic vascular resistance. Four patients underwent to OPCAB presented all the signs of VS intraoperatively or within the first 6 postoperative h. Results: The patients needed aggressive vasoactive drug support for hemodynamic stabilization and all of them developed complications. These patients also had tendency to require administration of blood and blood derivatives due to diffuse and oozing type bleeding. Mean intensive care unit stay of surviving patients was 70 h and mean period of postoperative hospitalization was 9 days. Tumor necrosis factor-α blood levels in one patient were elevated postoperatively though no signs of infection were observed. One patient died. Conclusions: Although vasoplegic syndrome can complicate OPCAB surgery, the rationale for avoiding CPB remains valid considering the benefits provided by OPCAB.

Keywords: Heart surgery; Coronary artery bypass surgery; Vasopelia; Systemic inflammatory response syndrome

1. Introduction

The vasoplegic syndrome (VS), i.e. a severe systemic inflammatory response syndrome (SIRS) following heart surgery using cardiopulmonary bypass (CPB) has been recently recognized and implicated in life-threatening complications [1,2]. The vasoplegic syndrome usual findings occurring in the early postoperative period include severe hypotension, tachycardia, normal or elevated cardiac output and low systemic vascular resistance [3]. These alterations are usually attributed to CPB, where induction of leukocyte activation plays a major role on releasing proinflammatory mediators [3,4].

Off-pump coronary artery bypass grafting (OPCAB) has been recently achieving growing enthusiasm mainly due avoiding the side effects of CPB related to the whole-body inflammatory reaction [5]. However we report here a series of patients submitted to OPCAB in whom a typical VS developed and added to perioperative morbidity and mortality.

2. Materials and methods

From November 1996 through January 2001, a total of 2541 patients underwent isolated coronary artery bypass grafting, being 1014 procedures (40%) performed without cardiopulmonary bypass (OPCAB technique).

This retrospective study was comprised of four patients submitted to OPCAB in the aforementioned period who developed in the early postoperative period a severe clinical picture of hypotension, tachycardia and oliguria which were firstly treated with fluid infusion. These signs and symptoms commenced at the end of the operation or within the first 6 postoperative h. Patients age varied from 57 to 85 years, with a mean of 71 years, including three males and one female. Preoperative cardiac function was normal in all patients, as demonstrated by left ventricle ejection fraction ranging from 55 to 62%. Demographic data are shown in Table 1.

Hypotension persistence eventually led to use of vasoconstrictor drugs, i.e. noradrenaline. Swan Ganz catheter, which is
not part of our routine in off-pump coronary artery bypass grafting (CABG), was immediately inserted. All patients were operated on using our standard technique, as previously described [5]. The anesthesia regime comprised intravenous midazolam hydrochloride, fentanyl citrate or sufentanil citrate or alfentanil hydrochloride, pancuronium bromide and inhalatory agents. Second-generation cephalosporin was used as antibiotic prophylaxis for 24 h. Heparin 200 IU/kg (Liquemin, Roche, São Paulo, Brazil) was administered at the beginning of the operation and reversed by protamine chloride (Protamina, Roche, São Paulo, Brazil). No patient received perioperative corticosteroids or antiinflammatory drugs. A mean of 2.25 grafts per patient was performed (ranging from 1 to 3). The mean operative time was 212 min, varying from 130 to 320 min (Table 1).

3. Results

Characteristically, patients presented with tachycardia, hypotension, decreased systemic vascular resistance, with normal or increased cardiac output. The onset of these signs was observed in the operating room or within the first 6 postoperative h. At the initial observation the patients exhibited systemic vascular resistance index (SVRI) ranging from 675 to 1159 dyn.s.cm⁻⁵/m² and cardiac index varying from 3.5 to 4.2 l.min⁻¹/m². The blood pressure showed mean arterial pressure between 40 and 51 mmHg and heart rate between 126 and 142 beats/min.

All patients required pharmacological support with norepinephrine (doses varying from 0.15 up to 4.0 µg/kg per min) in order to increase systemic vascular resistance and arterial pressure. It is worth noticing that all patients presented transient pre or intraoperative hypotension (during graft accomplishment), i.e. systolic blood pressure <60 mmHg requiring pharmacological support or fluid infusion for stabilization.

All patients presented postoperative complications related to the vasoplegic syndrome and one patient died (Table 1). No signs of infection were observed during the in-hospital stay.

These patients also had tendency to require administration of blood and blood derivatives due to diffuse and oozing type bleeding. Mean intensive care unit (ICU) stay of surviving patients was 70 h and mean period of postoperative hospitalization was 9 days.

Postoperative hemodynamic courses and drug responses of these patients are exemplified in Figs. 1 and 2 demonstrating a sequential evolution of two patients who presented opposite outcomes.

Interestingly, patient number 2, who died, had been

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>85</td>
<td>57</td>
<td>72</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Hypertension</td>
<td>–</td>
<td>Hypertension</td>
<td>Hypertension, diabetes</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56</td>
<td>60</td>
<td>55</td>
<td>62</td>
</tr>
<tr>
<td>Preoperative medication</td>
<td>Nifedipine, propranolol, aspirin</td>
<td>Isosorbide dinitrate, dipiridamol, aspirin</td>
<td>No</td>
<td>Isosorbide dinitrate, glibenclamide, aspirin</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Unstable angina</td>
<td>Unstable angina</td>
<td>Stable angina, failed angioplasty</td>
<td>Stable angina</td>
</tr>
<tr>
<td>Operation</td>
<td>CABGx3</td>
<td>CABGx2</td>
<td>CABGx1</td>
<td>CABGx3</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>240</td>
<td>160</td>
<td>130</td>
<td>320</td>
</tr>
<tr>
<td>24 h PO bleeding (ml)</td>
<td>1200</td>
<td>820</td>
<td>730</td>
<td>410</td>
</tr>
<tr>
<td>PO blood products (u)</td>
<td>5</td>
<td>4</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Vasopressor therapy (peak dose)</td>
<td>Norepinephrine</td>
<td>Norepinephrine</td>
<td>Norepinephrine</td>
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<tr>
<td></td>
<td>1.17 µg/kg per min</td>
<td>4 µg/kg per min</td>
<td>0.21 µg/kg per min</td>
<td>0.4 µg/kg per min</td>
</tr>
<tr>
<td></td>
<td>dopamine 14 µg/kg per min</td>
<td>dopamine 18 µg/kg per min</td>
<td></td>
<td>dopamine 10 µg/kg per min</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>15</td>
<td>48</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>ICU stay (h)</td>
<td>80</td>
<td>48</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>PO hospital stay (day)</td>
<td>10</td>
<td>–</td>
<td>8</td>
<td>9</td>
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<tr>
<td>Complications</td>
<td>Pyrexia, pleural effusion, pulmonary congestion</td>
<td>Pyrexia, renal failure, respiratory failure, MODS</td>
<td>Pulmonary congestion</td>
<td>Pyrexia, pulmonary congestion, pleural effusion</td>
</tr>
<tr>
<td>Outcome</td>
<td>Discharged</td>
<td>Died 2nd PO day</td>
<td>Discharged</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

a Abbreviations. F = female; CABG = coronary artery bypass grafting; ICU = intensive care unit; LVEF = left ventricle ejection fraction; M = male; MODS = multiple organ dysfunction syndrome; PO = postoperative; and u = unit.
previously enrolled in other scientific study and had pre and postoperative blood samples collected and frozen to −70°C. Tumor necrosis factor (TNF-α) was measured in these samples and revealed postoperative values of 1170 pg/ml, which is roughly 8-fold higher than the peak value found in our earlier work [6].

No intraoperative myocardial infarction was noticed as assessed by electrocardiogram (ECG) alteration or abnormal enzymes elevation.

4. Discussion

The current increased interest in OPCAB comes from the lower incidence of operative complications, mainly owing to avoidance of cardiopulmonary bypass. Reduction of systemic inflammatory response was demonstrated, including decreased cytokine release compared to on-pump CABG and that breakthrough was the great boost levering the expansion of this renewed technique [6,7].

Postoperative SIRS observed in cardiac surgery has been related to cardiopulmonary bypass and the main causative factors are surgical trauma, contact of blood components with the artificial surface of the bypass circuit and lung reperfusion injury. This inflammatory response is mediated by activation of complement, cytokines, kininogen/bradykinin pathways, coagulation cascade and fibrinolysis [8]. However, SIRS may follow any major surgery as a consequence of surgical stress. There is evidence that surgical trauma and hemorrhage induce release of a number of agents that include prostaglandins, catecholamines, corticosteroids and cytokines [9].

Undoubtedly the clinical and hemodynamic picture presented by these four patients is identical to those seen in on-pump patients evolving with vasoplegic syndrome, as previously described [1,3]. In practice, the clinical signs and symptoms of SIRS can vary from insignificant to very severe [10], as seen in the vasoplegic syndrome.

Although at first vasoplegic syndrome has been associated to cardiopulmonary bypass, the emergence of off-pump cases leads to theorize on other causal factors. Irrespective of the cause, the inflammatory response follows qualitatively similar activation patterns. Different forms of injury or infection result in initiation of decisive steps in tissue injury, the cytokine-mediated activation of platelets and leukocytes, being likely that the pattern of SIRS in the cardiac surgical patient is similar to one in the non-cardiac surgical patient [10].

Major surgical stress induces postoperative SIRS and is thought to be mediated by proinflammatory as well as neuroendocrine mediators such as cortisol and catecholamines [11]. TNF-α is one of the main proinflammatory mediators that are induced by surgical stress [12]. When leukocytes activated by surgical stress are further reactivated by other stimuli, they induce an increased production of the cytokines or inflammatory mediators. When monocytes activated by major surgical stress are further stimulated with lipopolysaccharides (LPS), a greater amount of TNF-α is produced. The activation of monocyte due to major surgical stress leads to production of TNF-α and correlate with the serum interleukin-6 levels, which are related to the degree of surgical stress [13]. Cardiovascular effects of cytokines are due to regulation of homeostasis of nitric oxide and by means of the interaction between leukocytes and endothelium [14].

The gastrointestinal tract has been recognized as a potential source of postoperative complications with the recognition that patients undergoing cardiopulmonary bypass sustain episodes of endotoxemia, which are self-limited in the majority of the patients and in others evolving to shock and multi-organ failure. Transient hypoperfusion or hypoxia following low flow states may injure the gut mucosa, allowing bacterial translocation, which is potentialized by reperfusion when oxygen supply is re-established. Moreover blood loss and shock have detrimental effects on immune and hepatic cells, reducing their capacity to clear bacteria and endotoxin [15]. Bacterial translocation and absorption of endotoxins, due to increased intestinal permeability, are triggers to widespread activation of proinflammatory cells and release of mediators of the metabolic response to sepsis. Intestinal ischemia may occur
due to a decreased blood flow confined to part of the splanchnic circulation related to atherosclerosis of the mesenteric vessels. The ischemic injury sustained and changes are dependent on the duration and severity of the ischemic insult. An increase in intestinal capillary permeability may occur after 20 min of regional ischemia and may be exacerbated by reperfusion [16]. An increase in plasma concentration of TNF-α has been found following intestinal ischemia with further increases of 5–10-fold after reperfusion. The TNF release is triggered by gut-derived endotoxin and leads, among others, to secretion of nitric oxide (NO) and platelet-activating factor (PAF). PAF is partially responsible for increased permeability in sepsis and shock [17].

Intermittent periods of hypotension throughout OPCAB surgery are not uncommon, since mobilization and displacement of the heart are necessary to achieve coronary exposure and perform the anastomosis. Multiple and relatively minor sequential insults might result in vasopлегic syndrome. Also resterilized disposable devices potentially may serve as a source of contamination and generate endotoxins or trigger the host mechanism [18].

Occasionally the onset of the vasopлегic syndrome have been perceived soon after blood products transfusion, although systematic culture of stored blood failed to show any sign of contamination. Blood transfusion is known to activate polymorphonuclear leukocytes and cytokine release [19]. Immunosuppression, with consequent postoperative bacterial infection and ABO incompatibility are now risks that physicians should consider as associated with allogeneic blood transfusion.

Preoperative use of ACE inhibitors have been suggested as a vasoplectic syndrome causal agent [20]. However, no patient in this series were in ACE inhibitor regime. Also a defective baroreflex-mediated secretion of arginine vasopressin has been incriminated for the emergence of vasoplectic syndrome [21].

It is known that protamine neutralization of heparin may cause circulatory side effects mediated via complement activation, histamine release, thromboxane and nitric oxide production, and antibody formation [22]. Following protamine infusion can be seen systemic hypertension, pulmonary hypertension and left ventricular dysfunction. It was shown that protamine causes activation of leukocytes and increases blood level of TNF-α may result in an increased NO production and this lead to contractile dysfunction and depression of cardiac function [23].

Methylene blue has been advocated in vasoplectic syndrome and reports have shown promising results. The effect is due to inhibition of the enzyme guanylyl cyclase which blocks the nitric oxide action and partially restores the systemic vascular resistance [24,25].

The incidence of VS in OPCAB in this series was 0.4%, and our finding of TNF-α soaring levels in one patient suggest this cytokine as a likely mediator of this syndrome. In conclusion, patients submitted to OPCAB could develop vasoplectic syndrome. However, the rationale for avoiding CPB remains valid considering the benefits yet proved by OPCAB and the infrequency of the mentioned complication.

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