1. Introduction

The hyperdynamic state (HS) seen in the postoperative period of heart surgery with extracorporeal circulation (ECC) is partly attributable to the rapid and highly amplified host cellular and humoral response triggered when the blood comes into contact with the surface of the extracorporeal circuit. Different proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) released in response to endothelial and blood cell activation after contact with the extracorporeal circuit participate in the pathogenesis of HS [1]. The incidence and risk factors underlying this inflammatory response – often reflected in the development of HS – vary greatly among studies [2]. The response too shows important individual variability. In this sense, the genes that encode for proteins implicated in transduction of the inflammatory process may help us to partially explain such variability [3].

The present study investigated the incidence of postoperative HS in our setting, together with its associated genetic and clinical risk factors. We hypothesized that a proinflammatory polymorphism, such as lymphotoxin alpha +250 [4], IL-10 [6] and IL-1ra [7], may predispose ECC patients to postoperative hyperdynamic state.

2. Patients and methods

2.1. Study design and patients

A prospective observational cohort study was performed between January and April 2004 to identify the incidence and risk factors associated with the development of HS in the postoperative period of elective heart surgery with ECC. Patients with acute endocarditis, preoperative fever or signs of infection or both, were excluded, as were those who underwent surgery without ECC, emergency operations, and cases requiring a counterpulsation balloon, or presenting perioperative cardiogenic shock. No patient was given corticoids, nonsteroidal anti-inflammatory drugs or immunosuppressors either before or after the surgical operation. Postoperative care took place in a 24-bed polyvalent Intensive Care Unit of a University Hospital. This study was approved by the Hospital Ethics Committee, in accordance with the principles of the Declaration of Helsinki.
2.2. Definition of hyperdynamic state

HS was defined as hyperthermia (>38 °C), cardiac index (CI) >3.5 ml/min/m² and systemic vascular resistance index (SVRI) <1600 dynes/cm²–m², without the use of inotropics in the first 4–6 h after admission to intensive care. All three criteria were required for patients to be classified in the HS group.

2.3. Intraoperative management

The same anesthetic method was used in all cases. Anesthesia was induced and maintained with propofol, midazolam, fentanyl and cis-atracurium. Etomidate was not used. The same anesthetic method was used in all cases. Anesthesia was induced and maintained with propofol, midazolam, fentanyl and cis-atracurium. Etomidate was not used. All the operations were performed by the same surgical team. The extracorporeal circuit was composed of a membrane oxygenator (Optima XP, Cobe, Denver, Colorado, or Quantum Lifestream International, Inc., Woodlands, TX, USA), a Tygon® extracorporeal circuit (Dieco, Mirandola, Italy), and a Medtronic Biopump® centrifuge pump (Minneapolis, MN, USA). No heparinized circuits or arterial filters were used. The primer solution consisted of 1000 ml of Ringer lactate, 500 ml of bicarbonate 1/6 molar, and 30 mg (10 mg/ml) of heparin sodium. A volume of 250 ml of 20% mannitol was administered at the start of ECC. Under conditions of hypothermia (30 °C), the pump flow rate was adjusted to ensure a mean arterial pressure of >45 mmHg and a flow index of 2.2 l/min/m². St Thomas 4:1 (12 °C) cardioplegia was used. The circuit was primed with 30 mg of heparin sodium, followed by a starting dose of 3 mg/kg, with additional doses to maintain an activated clotting time of 480 s. Heparin reversion was carried out with protamine, according to the blood heparin levels as measured with the Hepcon® system (HMS.Medtronic™, Minneapolis, MN, USA). Blood recovery was carried out in all patients. Blood product transfusion was carried out with haemoglobin values of <8 g/dl (erythrocytes), a prothrombin time of <50% (plasma), and a platelet count of <50,000/mm³.

Postoperative management has been previously described [5].

2.4. Data collection

The data collected included demographic variables, comorbidity, type of surgery and postoperative course (ICU and hospital stay). On admission to intensive care, and after 4 and 24 h during the postoperative period, hemodynamic data were collected using a Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA, USA). Surgical risk was calculated using the additive Parsonnet scale.

2.5. Determination of interleukin-6

The serum levels of IL-6 (range: <5.9 pg/ml; intratess variation: 4.5%) were determined using an automated immunoenzyme assay system (Immulite One™, Diagnostic Products Corporation (DPC). Los Angeles, CA, USA).

2.6. Genetic analysis

Following peripheral blood collection, 3 ml were added to EDTA tubes (Venoeject) and immediately subjected to DNA purification. The DNA samples were coded and stored at 4 °C in Tris-EDTA buffer, in compliance with the guidelines on patient privacy rights. Analysis was carried out in a blinded manner, with no knowledge of any clinical data.

The analysis of genetic polymorphisms (A/G) of tumor necrosis factor-beta (TNFβ +250), polymorphism G/A-1082 of the promoter of the gene encoding for interleukin-10 (IL-10), and polymorphism of intron two of the promoter region of the gene corresponding to interleukin-1 receptor antagonist (IL-1ra) was carried out according to the routine protocols established by the Laboratory of Molecular Biology, using previously described primers [4, 6, 7]. Likewise, seven neutral markers were genotyped following genomic control strategies to detect spurious associations attributable to population substructure [8]. The selected neutral markers consisted of bi-allelic repetitions distributed in different chromosomes.

2.7. Statistical analysis

Univariate analysis was based on the Pearson χ² or Fisher exact test for categorical variables, and Student t-test or Mann–Whitney U-test for continuous variables. Forward stepwise logistic regression analysis was used to identify risk factors independently associated with the development of HS, with inclusion in the model of those variables found in the univariate analysis to yield P < 0.15, along with the use of angiotensin-converting enzyme inhibitors (ACEIs) and the duration of ECC as known risk factors associated with HS. The results were expressed as mean ± S.D. or mean and percentiles 25–75. A P < 0.05 was considered statistically significant. The SPSS version 11.0 statistical package for Microsoft Windows (SPSS Inc, Chicago, IL, USA) was used throughout.

The genotypes were tested according to the Hardy–Weinberg equilibrium using ‘Online Encyclopedia for Genetic Epidemiology’ software (http://www.genes.org.uk/software/hardy-weinberg.shtml).

3. Results

A total of 100 patients were evaluated during the study period. Four were excluded due to surgery for infectious endocarditis, three because of cardiogenic shock, two due to the presence of an intraaortic balloon pump (IABP), four due to emergency surgery, and seven due to surgery without ECC. A total of 80 patients were thus finally included.

Twenty-two patients (27.5%) developed HS. The periperrative characteristics of the study population and their association with HS are reported in Table 1. The patients who underwent heart valve replacement surgery had a lower incidence of HS. These patients showed shorter ECC times than the others: 80 (range 65–94) min vs. 96 (70–126) min in the case of coronary and mixed surgery, P = 0.05.

Of the genetic polymorphisms studied, the presence of allele G of TNFβ +250 polymorphism was more frequent in the patients that developed HS than in those who did not (68% vs. 37%; P = 0.01) (Fig. 1). No association was found between IL-10 and IL-1ra polymorphisms and the development of HS (Table 2).
Table 1  
Perioperative patient characteristics and their association with hyperdynamic state (HS) *

<table>
<thead>
<tr>
<th>Variable</th>
<th>HS</th>
<th>No HS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.9±10.9</td>
<td>62.0±13.6</td>
<td>0.60</td>
</tr>
<tr>
<td>Sex (M/F) (%M)</td>
<td>17/5 (77)</td>
<td>34/24 (59)</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4±5.5</td>
<td>26.9±3.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Allele G (TNFβ +250) (%)</td>
<td>15 (68)</td>
<td>22 (37)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

- Coromorbidty (%) (n)
- Kidney failure 2 (9) (59) 0.99
- Arterial hypertension (mmHg) 6 (27) 22 (38) 0.37
- Diabetes (%) 10 (45) 19 (33) 0.29
- Surgery (%) 14 (64) 29 (50) 0.26
- Valve 3 (14) 23 (40) 0.02
- Mixed 5 (22) 6 (10) 0.16
- Reintervention 0 (0) 2 (3) 0.99
- Parsonnet 12.6±9.5 12.1±7.4 0.99
- Angiotensin-converting enzyme inhibitors (%) 6 (27) 22 (38) 0.37
- Extracorporeal circulation (min) 100.1±34.9 94.8±36.7 0.26
- Aortic clamping time (min) 60.4±27.0 56.7±24.7 0.39

*The numerical values correspond to mean±S.D. Numbers in parentheses are percentages of each column. *Can add more than 80 due to the presence of associated disease.

In order to determine which factors were independently associated with the development of HS, we introduced the presence of some allele G (P=0.01), sex (P=0.12), valve surgery (P=0.02), the administration of ACEIs (P=0.37) and the duration of ECC as independent variables (P=0.26). The duration of ECC presented an odds ratio (OR) of 1.02; 95% CI (1.02–1.04); P=0.001 while the presence of allele G of the genetic polymorphism of TNFβ +250 showed OR 5.57; 95% CI (1.7–18.6); P=0.004 – exhibiting a global χ² model: 15.8; df 3, P=0.001.

Lastly, the patients with HS required more vasopressor drugs [15/22 (68%) vs. 13/58 (22%), P=0.001], and had a longer stay both in the ICU (8.4±6.5 vs. 3.6±2.3, P=0.01) and in hospital (17.9±21.8 vs. 9.8±5.7, P=0.001). There were no deaths in this study.

4. Discussion

This prospective study was designed to explore the factors associated with the development of hyperdynamic state (HS) in 80 elective heart surgery patients. Our results suggest that the presence of allele G of the genetic polymorphism of TNFβ +250, and a prolonged duration of ECC are independently associated with the presence of perioperative HS.

The systemic response triggered by contact between the blood and the extracorporeal circuit gives rise to postoperative complications such as excessive bleeding [9] and HS, among other problems. The incidence of HS and its underlying factors are highly variable in the literature, and depend on the definition used – with figures ranging between 4% [10] and 44% [11]. The terminology has also been variable, with reference to low vascular resistance states, vasodilator shock or vasoplegic syndrome [11, 12].

We included hyperthermia (>38 °C), in addition to the inherent hemodynamic criteria, since this is probably the best clinical marker of the inflammatory response triggered during ECC, and reflected as HS. Due to the fact that vasodilator drugs may interact with vascular resistance, the inclusion of temperature as part of the clinical criteria rules out the confounding effect of these drugs [5].

Of the factors associated with the development of HS, a prolonged duration of ECC has already been reported as a

Table 2  
Distribution of the genetic polymorphisms TNFβ +250, IL-10 and IL-1ra, and their association with hyperdynamic state (HS)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>HS (n=22)</th>
<th>No HS (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFβ +250, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>7 (32)</td>
<td>37 (63)</td>
<td>0.037</td>
</tr>
<tr>
<td>AG</td>
<td>12 (54)</td>
<td>18 (31)</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>3 (14)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>IL-10, n (%)</td>
<td></td>
<td></td>
<td>0.238</td>
</tr>
<tr>
<td>AA</td>
<td>6 (27)</td>
<td>26 (45)</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>10 (46)</td>
<td>22 (38)</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>6 (27)</td>
<td>10 (17)</td>
<td></td>
</tr>
<tr>
<td>rIL-1, n (%)</td>
<td></td>
<td></td>
<td>0.413</td>
</tr>
<tr>
<td>1.1/1.3</td>
<td>12 (55)</td>
<td>26 (47)</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>10 (45)</td>
<td>26 (47)</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>0 (0)</td>
<td>4 (6)</td>
<td></td>
</tr>
</tbody>
</table>

*IL-10, interleukin-10. †rIL-1, receptor antagonist interleukin-1.

Table 3 shows the evolution of postoperative hemodynamic parameters for both groups.

Serum IL-6 levels 4 h after admission were significantly higher in patients with HS (236; range 171–400) than in those without HS (143; range 52–259), P=0.01.

Table 3  
Time-related haemodynamic parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>HS (n=22)</th>
<th>No HS (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>35.8±0.7</td>
<td>35.6±0.6</td>
<td>0.42</td>
</tr>
<tr>
<td>4 h</td>
<td>38.7±0.6</td>
<td>36.8±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h</td>
<td>36±0.3</td>
<td>36±0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Cardiac Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>2.53±0.7</td>
<td>2.19±0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>4 h</td>
<td>4.64±0.68</td>
<td>2.55±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h</td>
<td>3.8±0.45</td>
<td>3±0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>SVRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>1407±774</td>
<td>1327±364</td>
<td>0.301</td>
</tr>
<tr>
<td>4 h</td>
<td>1285±170</td>
<td>1833±643</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h</td>
<td>1854±685</td>
<td>1953±725</td>
<td>0.74</td>
</tr>
</tbody>
</table>

 SVRI, systemic vascular resistance index; †arrival to the ICU; ‡postoperative hours.
risk factor elsewhere [11]. This may explain the lower incidence of HS in the patients who underwent heart valve replacement surgery in our series, since these patients had shorter ECC times than the other patients. Likewise, higher IL-6 levels have been reported in patients with hemodynamic parameters of HS versus those without [5].

The other factor associated with HS was seen to be allele G of the genetic polymorphism of TNFβ +250. This polymorphism has recently been associated with the development of an inflammatory response in patients who underwent heart surgery with ECC [13, 14]. Furthermore, carriers of the G allele have been associated with a higher production of lymphotoxin alpha (LTA) [4], IL-6 and tumor necrosis alpha (TNFα) [15].

LTA can induce adhesion molecules and cytokines on the part of the vascular endothelial cells, thus contributing to the local inflammatory process. Although we did not determine serum LTA in our study, it seems reasonable to suggest that this may be the mechanism whereby carriers of allele G of the polymorphism of TNFβ +250 are more susceptible to the development of HS in the context of heart surgery.

Our findings may help explain, at least in part, the complexity of individual variability in host response to injury (in this case ECC), regardless of its intensity. In this context, conditions (genotype) that facilitate or promote a baseline inflammatory state in response to proinflammatory situations such as ECC (environmental factors) may favor an exaggerated (clinically manifest) hyperdynamic state. Operative morbidity is increased by the occurrence of post-ECC HS, with a consequent increased risk for the patient in the early postoperative period. We found a significantly longer intensive care unit and hospital stay among patients with HS when compared with controls. However, there was no intergroup difference on early mortality.

Limitations. This study has several limitations. Firstly, the number of patients studied was not high. Secondly, we did not determine serum levels of lymphotoxin-alpha and therefore did not analyze this parameter’s association with the development of HS; however, homozygotes G of the TNF-β gene polymorphism show greater production of this cytokine [4].

5. Conclusions

The presence of allele G of TNFβ +250 polymorphism, together with prolonged extracorporeal circuit times may favor the development of a hyperdynamic state after heart surgery with ECC.

Acknowledgments

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References