The profile of the systemic inflammatory response in children undergoing ventricular assist device support

Xiaoyang Yu, Bodil Larsen, Jennifer Rutledge, Lori West, David B. Ross, Ivan M. Reaney, Holger Buchholz and Jia Li*

* Division of Pediatric Cardiology, Department of Pediatrics, Stollery Children’s Hospital, University of Alberta, Edmonton, AB, Canada
* Nutrition Service, Alberta Health Services, Stollery Children’s Hospital, Edmonton, AB, Canada
* Division of Cardiac Surgery, Department of Surgery, Stollery Children’s Hospital, University of Alberta, Edmonton, AB, Canada

Corresponding author. Division of Pediatric Cardiology, Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Mazankowski Alberta Heart Institute, 8215-112th Street, Edmonton, AB, Canada T6G 2C8. Tel: +1-780-4928463; fax: +1-780-4926556; e-mail: jia.li@albertahealthservices.ca (J. Li).

Received 20 December 2011; received in revised form 26 March 2012; accepted 1 April 2012

Abstract

OBJECTIVES: Serum C-reactive protein (CRP) has been used as a systemic inflammatory response (SIR) marker in the critical ill, including children after cardiopulmonary bypass surgery. Ventricular assist devices (VAD) have been increasingly used as a bridge support to heart transplantation in children. We aimed to examine the profiles of CRP in children receiving VAD support.

METHODS: Charts of 13 children receiving Berlin Heart EXCOR® from 2005 to 2009 were reviewed. The data obtained prior to and during VAD support included: CRP, white blood cells, inotropes and steroid use, VAD mode and duration of VAD support. Ten patients received left VAD (LVAD) and 3 biventricular VAD (BiVAD).

RESULTS: The median duration of VAD support was 59 days (ranged 3–678 days). Pre-VAD CRP was 35 ± 51 mg/l and increased to 109 ± 59 mg/l on days 1–3 after the VAD implantation (P = 0.01), then gradually decreased to 28 ± 28 mg/l by 4 months and normalized by 5 months (P < 0.0001). CRP was higher in BiVAD than in LVAD patients throughout the study period (P = 0.003). CRP positively correlated with the doses of the epinephrine and norepinephrine and the monocyte counts, and negatively correlated with the lymphocyte count. The lymphocyte count was 2.5 ± 0.4 × 10^9/l prior to implantation, and decreased to 2.1 ± 1.3 × 10^9/l on days 1–3 (P = 0.5) and then to 0.6 ± 0.1 × 10^9/l by 6 months (P = 0.08). It tended to be lower in BiVAD patients (P = 0.06).

CONCLUSIONS: SIR exists in children prior to VAD support. VAD implantation is associated with a significant and prolonged increase in CRP and a decrease in lymphocyte count, indicating a suppressed immune function, being more pronounced in BiVAD patients.

Keywords: C-reactive protein · Systemic inflammatory response · Ventricular assist device · Berlin heart · Paediatrics

INTRODUCTION

Ventricular assist devices (VAD) have been increasingly used as a bridge to heart transplantation or to cardiac recovery in patients with end-stage heart failure [1]. Berlin Heart EXCOR® paediatric VAD has enabled the use in children with satisfactory outcomes. In 73 children from 17 North American institutions from 2000 to 2007 [1], 57% received a left VAD (LVAD) and the remaining received biventricular VAD (BiVAD). Overall, 70% was bridged to transplantation and 30% to recovery. Mortality remains substantial, being 35% in BiVAD patients and 14% in LVAD patients. While the factors that contribute to mortality are certainly complex, the systemic inflammatory response (SIR) may play an important role.

SIR can be evoked by critical illness [2]. It involves an acute-phase reaction with an increased synthesis of acute-phase proteins, such as C-reactive protein (CRP). CRP is a SIR marker and an independent predictor of outcomes in a varied group of patients, including those after a cardiopulmonary bypass (CPB) [3, 4]. However, the changes in CRP in children undergoing VAD support remain unknown. This group of children have a distinctive course of critical illness. Prior to VAD implantation, they experienced end-stage heart failure, and some had cardiogenic shock and received extracorporeal membrane oxygenation (ECMO) support. VAD implantation may require prolonged CPB. VAD itself, as an implantable device with external artificial components, may further induce a persistent SIR. This study examined the profile of SIR by evaluating the perioperative changes in CRP in children undergoing VAD support.

METHODS

After ethics approval, the charts of 13 children (aged 72 ± 87 months) receiving VAD at the Stollery Children’s Hospital between 2005 and 2009 were reviewed [Table 1]. Thirteen patients received Berlin Heart EXCOR® including 2 patients having Jostra for the initial 12 days (Patient 12) or Levitronix for
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>ECMO</th>
<th>CPB (min)</th>
<th>VAD mode</th>
<th>VAD duration (day)</th>
<th>ICU stay (day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 months</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>119</td>
<td>LVAD</td>
<td>25</td>
<td>25</td>
<td>Deceased</td>
</tr>
<tr>
<td>2</td>
<td>15 years</td>
<td>F</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>122</td>
<td>LVAD</td>
<td>145</td>
<td>191</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>1 months</td>
<td>M</td>
<td>Myocarditis</td>
<td>Weaned</td>
<td>112</td>
<td>LVAD</td>
<td>35</td>
<td>44</td>
<td>HTx</td>
</tr>
<tr>
<td>4</td>
<td>9 years</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>Yes</td>
<td>166</td>
<td>BlVAD</td>
<td>3</td>
<td>20</td>
<td>HTx</td>
</tr>
<tr>
<td>5</td>
<td>3 months</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>164</td>
<td>LVAD</td>
<td>56</td>
<td>72</td>
<td>HTx</td>
</tr>
<tr>
<td>6</td>
<td>17 years</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>Yes</td>
<td>102</td>
<td>LVAD</td>
<td>678</td>
<td>84</td>
<td>Discharge with LVAD</td>
</tr>
<tr>
<td>7</td>
<td>16 years</td>
<td>M</td>
<td>Friedreich's ataxia, cardiogenic shock</td>
<td>Yes</td>
<td>222</td>
<td>BiVAD</td>
<td>128</td>
<td>158</td>
<td>HTx</td>
</tr>
<tr>
<td>8</td>
<td>3 years</td>
<td>M</td>
<td>HLHS, failed Fontan</td>
<td>Yes</td>
<td>150</td>
<td>LVAD</td>
<td>173</td>
<td>195</td>
<td>HTx</td>
</tr>
<tr>
<td>9</td>
<td>15 years</td>
<td>M</td>
<td>Rheumatic mitral and aortic valve disease, bilateral above-knee amputation</td>
<td>Yes</td>
<td>465</td>
<td>BiVAD</td>
<td>192</td>
<td>515</td>
<td>HTx</td>
</tr>
<tr>
<td>10</td>
<td>1 months</td>
<td>M</td>
<td>Myocarditis</td>
<td>Yes</td>
<td>101</td>
<td>LVAD (Levitronix for 12 days)</td>
<td>59</td>
<td>32</td>
<td>HTx</td>
</tr>
<tr>
<td>11</td>
<td>5 months</td>
<td>M</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>136</td>
<td>LVAD</td>
<td>28</td>
<td>47</td>
<td>HTx</td>
</tr>
<tr>
<td>12</td>
<td>2 months</td>
<td>F</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>150</td>
<td>LVAD (Jostra for 10 days)</td>
<td>106</td>
<td>28</td>
<td>HTx</td>
</tr>
<tr>
<td>13</td>
<td>11 months</td>
<td>F</td>
<td>Cardiomyopathy</td>
<td>No</td>
<td>102</td>
<td>LVAD</td>
<td>23</td>
<td>75</td>
<td>HTx</td>
</tr>
</tbody>
</table>

BiVAD: biventricular assist device; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; HLHS: hypoplastic left heart syndrome; HTx: heart transplantation; ICU: intensive care unit; LVAD: left ventricular assist device; VAD: ventricular assist device.
the initial 10 days (Patient 10). There were 10 LVAD patients for 89 ± 77 days including the 2 with Jostra or Levitronix (aged 46 ± 80 months) and 3 BiVAD (aged 159 ± 44 months, \( P = 0.02 \)) for 108 ± 96 days (\( P = 0.80 \)). The devices were coated with heparin by the Carmeda process (Carmeda AB, Upplands Vasby, Sweden). Anticoagulation was standardized according to the Edmonton protocol [5]. The clinical protocol was to measure CRP twice weekly (Monday and Thursday) during VAD support, but the practice overall varied widely among clinicians.

Data collection

CRP was measured prior to VAD implantation (1–4 days, median 1 day), and twice weekly during support. Total and differential WBC counts were obtained concurrently with CRP measurements. Doses of epinephrine, norepinephrine, milrinone, nitroprusside and hydrocortisone were recorded within 8 h prior to CRP measurements. Cultures of blood and body fluids (sputum, urine, nasopharyngeal, sternum, throat and rectal swabs) were also collected. Demographic and clinical data included age, weight, gender, diagnosis, pre-VAD ECMO and duration of CPB. CRP was measured using UniCel DxI 800 (Beckman Coulter, Brea, CA, USA).

Data analysis

Data are expressed as mean ± SD. Mixed linear regression for repeated measures was used to compare the measurements prior to and first time after the VAD implantation, determine the nature of any time trend of the variables during VAD support and analyse the correlations of CRP with the other variables. The categorical data of culture in blood and other body fluid was numbered as 0 for the negative result and 1 for the positive, and then analysed in correlation with CRP. The strength and trend of correlations were indicated by a parameter estimate and \( P \)-value. The covariance structure was assumed to be compound symmetry. SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC, USA) was used.

RESULTS

Clinical data

Seven out of the 13 patients received pre-VAD ECMO because of a cardiovascular collapse [Table 1]. Among them, one had been weaned from ECMO for 10 days, and the remaining six were converted directly to VAD. Inotropes used concurrently with CRP measurements during VAD support included epinephrine (0.005–0.25 mcg/kg/min, \( n = 7 \)), norepinephrine (0.01–0.2 mcg/kg/min, \( n = 4 \)), milrinone (0.25–0.75 mcg/kg/min, \( n = 9 \)) and nitroprusside (0.25–5 mcg/kg/min, \( n = 8 \)). Hydrocortisone of 1 mg/kg was given Q6–8 h (\( n = 5 \)). During VAD support, positive culture results were found in the blood (\( n = 4 \)) and other body fluids including sputum, urine and sternum swabs (\( n = 7 \)). Patient 1 developed embolic strokes and died on day 25 of VAD support. Patient 9 had bilateral above-knee amputation on day 26 on VAD due to progressive tissue deterioration resulting from the cardiac arrest that occurred 5 days prior to VAD requiring ECMO support. Ten patients (7 LVAD and 3 BiVAD) were successfully bridged to heart transplantation.

Changes in C-reactive protein and other laboratory data before and after ventricular assist device implantation

CRP varied widely both between and within patients throughout the study period (Fig. 1A). Overall, pre-VAD CRP was 35 ± 51 mg/l (\( n = 12 \)). CRP was significantly higher in patients converted from ECMO to VAD (73.6 ± 61.7 mg/l, \( n = 6 \)) than in those who either did not require ECMO (\( n = 6 \)) or were weaned for 10 days (\( n = 1 \)) prior to VAD (7.2 ± 5.9 mg/l, \( P = 0.02 \)). All three BiVAD patients had been on ECMO. Pre-VAD CRP was not significantly different between the BiVAD (67 ± 51 mg/l) and the LVAD patients (24 ± 49 mg/l, \( P = 0.3 \)). The lymphocyte count was 2.5 ± 0.4 × 10^9/l in all patients. It was significantly lower in patients requiring pre-VAD ECMO (1.4 ± 0.4 vs 3.0 ± 1.5 × 10^9/l, \( P = 0.03 \)) and not significantly different between BiVAD vs LVAD patients (1.4 ± 0.5 vs 2.8 ± 1.5 × 10^9/l, \( P = 0.3 \)). The monocyte and neutrophil counts were 1.2 ± 0.7 and 7.9 ± 3.1 × 10^9/l in all patients, respectively, with no difference between those with pre-VAD ECMO or those with BiVAD vs LVAD. There were no significant correlations between pre-VAD levels of CRP, lymphocyte and monocyte and during VAD levels.

After VAD implantation, CRP increased significantly to 109 ± 59 mg/l on days 1–3 (\( P = 0.01, n = 13 \)), then decreased to 52 ± 53 mg/l by 1 month (\( n = 8 \)), 28 ± 28 mg/l by 4 months (\( n = 5 \)) and normalized by 5 months and thereafter (\( P < 0.0001, n = 2 \)) [Fig. 1A]. The lymphocyte count decreased insignificantly to 2.1 ± 1.3 × 10^9/l on days 1–3 (\( P = 0.5 \)) and then gradually decreased to 0.6 ± 0.1 × 10^9/l by 6 months (\( P = 0.08 \)) [Fig. 1B]. The monocyte count was 1.0 ± 0.5 × 10^9/l on days 1–3 of VAD support (\( P = 0.7 \)), and then significantly decreased to 0.7 ± 0.1 × 10^9/l by 6 months (\( P < 0.001 \)) [Fig. 1C]. The neutrophil count increased to 9.2 ± 4.0 × 10^9/l on days 1–3 after implantation, and significantly decreased to 7.8 ± 2.4 × 10^9/l by 6 months (\( P = 0.0001 \)).

CRP was significantly higher in the BiVAD compared with the LVAD patients throughout the support period (\( P = 0.003 \)) [Fig. 2A]. The lymphocyte counts in the BiVAD tended to be lower than in the LVAD patients (\( P = 0.06 \)) [Fig. 2B]. There were no significant differences between the two groups in other variables. No significant differences were found in any variable between patients with or without pre-VAD ECMO, and between the two patients on Jostra or Levitronix and the remaining patients on Berlin Heart EXCOR in the first 10 days on VAD.

Correlations of C-reactive protein with other laboratory and clinical variables during ventricular assist devices

CRP correlated negatively with the lymphocyte count (\( P = 0.02 \)), and positively with the monocyte count (\( P = 0.02 \)) and the doses of epinephrine (\( P < 0.0001 \)) and norepinephrine (\( P = 0.002 \)) [Table 2]. No significant correlations were found between CRP as well as total differential WBC counts and cultures of blood or body fluids. CRP did not significantly correlate with the length of stay in ICU and hospital. CRP in the deceased patient (Patient 1) was lower than average before and in the first 18 days on VAD,
but acutely increased to 69 mg/l on day 20 (2 days after the stroke), and then continuously increased to 138 mg/l until death. In Patient 9 who had a cardiac arrest prior to VAD and consequent progressive tissue deterioration of the legs during VAD, pre-VAD CRP was 102 mg/l. Post-VAD CRP was persistently higher than average, being ≏ 200 mg/l until a bilateral above-knee amputation on day 26 of support. It decreased to ≏ 50 mg/l by 1 week after the amputation, maintained at this level until 4 months of support and normalized from the fifth month of support.

**DISCUSSION**

This study examined the profile of SIR by evaluating the changes in serum CRP concentration in children undergoing VAD
support. Pre-VAD CRP was significantly higher in patients on ECMO. VAD implantation was associated with an intensified and prolonged SIR and immunosuppression, as indicated by the significantly elevated CRP and decreased lymphocyte count in the first 5 months. The SIR and immunosuppression tended to be greater in BiVAD than in LVAD patients, as indicated by the significantly higher CRP and lower lymphocyte count throughout the entire period of VAD support.

CRP has been used to indicate SIR in a wide range of patients, including those undergoing ECMO and CPB [6, 7]. CPB, ECMO and VAD share a common interaction of blood with the artificial surfaces of the system, and thus a common mechanism for inducing SIR [8]. ECMO and VAD may induce a SIR with a similar magnitude but a longer duration than CPB. In children undergoing CPB, preoperative CRP was normal, peaked to a mean of 50–80 mg/l after CPB and normalized within 3–10 days [3, 4]. In one report of ECMO patients, CRP was persistently elevated in the first 7 days of support, but no data were available afterward [7]. This is supported by our data. Pre-VAD CRP was significantly higher in patients on ECMO, whereas it was normal in those who were weaned off or did not require ECMO. A recent study has reported that a high preoperative CRP level is associated with an increased hospital mortality in children with VAD support [9].

Immediately after VAD implantation, CRP increased to a similar magnitude as reported in ECMO and post-CPB patients. Subsequently, there was a prolonged elevation of CRP up to 5 months after VAD implantation, indicating a persistent SIR. Of note, SIR was significantly greater in the BiVAD than in the LVAD patients as indicated by the significantly higher CRP throughout the support period. This may be due to more contact with artificial surfaces and a more severe myocardial dysfunction in the BiVAD patients. The latter factor is supported by the positive correlation between CRP and the dose of inotropes, indicating the role of cardiovascular functional status in SIR and vice versa [10].

SIR is associated with a depressed immune function [11]. This is supported by the reduced lymphocyte count during VAD support, along with the negative correlation between CRP and lymphocyte count. In concordance with the CRP profiles, the lymphocyte count tended to be lower in the BiVAD patients than in the LVAD patients.

This study examined the correlations of CRP with clinical outcomes. CRP has been reported to independently predict adverse clinical outcomes, such as longer ICU and hospital stays [3]. This correlation may not be appropriate in VAD patients, since their stay largely depends on the opportunity for heart

Figure 2: Comparison of (A) CRP concentrations and (B) lymphocyte counts between LVAD (n = 10) and BiVAD (n = 3) patients prior to and during VAD support.
CONCLUSIONS

SIR may exist in children prior to VAD support mainly related to ECMO. VAD implantation is associated with a significant and prolonged increase in CRP and decrease in lymphocyte count indicating SIR and suppressed immune status. It trend to be more pronounced in children receiving BiVAD than LVAD.

FUNDING

This study was supported by the start-up fund for J.L from Department of Pediatrics, University of Alberta.

Conflict of interest: none declared.

REFERENCES