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Perioperative measurements of IL-6 and α-melanocyte stimulating hormone in a cardiac transplant patient after ventricular assist device support

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Introduction

The ventricular assist device (VAD) has been used to support circulation in patients prior to cardiac transplantation. Although the hemodynamic characteristics of VAD have been studied thoroughly, their impact on the patient's immune system has not been well documented. VAD require two large-diameter tubes passing transcutaneously through the abdominal wall. Despite vigorous efforts to maintain sterility at the cannula sites and the use of velour sleeves to allow tissue ingrowth, the risk of infection persists throughout the time an assist pump is used. McBride et al. [1] reported a significant infection rate in patient supported with an external pulsatile VAD.

Interleukin-6 (IL-6) is one of the key mediators of the host response to tissue injury and invasion [2]. Induction of IL-6 synthesis is believed to be an early marker of activation of the acute phase response [3].

The α-Melanocyte-stimulating hormone (MSH), a peptide that occurs within the brain, the circulation, and other body sites, is a potent antipyretic agent when given centrally or peripherally [4]. The peptide likewise inhibits inflammation and aspects of the acute phase response [5]. Catania and Lipton [6] suggest that MSH may antagonize the effect of cytokines either directly or indirectly and play an important role in modulation of the acute phase response.

Plasma concentrations of IL-6 (pIL-6) and MSH (pMSH) in patients with VAD have not been studied previously, and perioperative changes in p IL-6 and pMSH with cardiac transplantation have not been studied either.

We report here a case of a patient with a VAD (Thermedics' Heartmate Blood Pump and Drive Console, Thermedics, Woburn, MA, USA) used as a bridge to cardiac transplantation. We also report the changes in pIL-6 and pMSH in this patient during and after cardiac transplantation.

Case history

A 50-year-old, 71.1 kg man was admitted for severe congestive heart failure and hypokalemia (2.2 mEq/L). On physical examination, he had signs of left ventricular failure with holosystolic murmur radiating to the axilla and bilateral rales. His echocardiogram showed increases in his left ventricular end-diastolic (11.9 cm) and end-systolic (8.8 cm) diameters. Estimated ejection fraction was less than 0.15. On his 3rd hospital day, he required tracheal intubation because of respiratory distress with a spontaneous respiratory rate of 45–50 breaths per minute. In addition, for management of his congestive heart failure, he required intravenous dopamine and dobutamine at high doses (13.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for both dopamine and dobutamine). His hemodynamics following dopamine and dobutamine administration showed low cardiac output with cardiac index of less than 2.0, elevated pulmonary capillary wedge pressure of 30–35 mmHg, and elevated pulmonary artery pressure at 55/40 mmHg. On the 7th hospital day, cardiac arrest occured shortly after he was begun on amrinone (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to improve his hemodynamics. Cardiopulmonary resuscitation (CPR) was immediately initiated. The patient required multiple cardioversions. In spite of this prolonged CPR for 90 min, he did not show any neurological damage. After he was successfully resuscitated, an intra-aortic balloon

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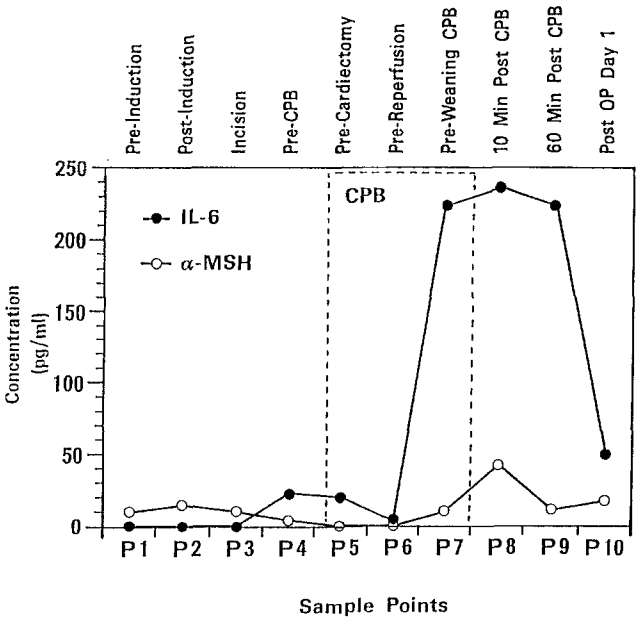

Fig. 1. Perioperative changes in plasma interleukin-6 (IL-6) and α-melanocyte stimulating hormone (α-MSH) concentrations. CPB, cardiopulmonary by pass

pump (IABP) was placed to stabilize his hemodynamics. Stabilization occurred with dopamine 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, dobutamine 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, sodium nitroprusside (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in addition to infusion of lidocaine 1 $mg \cdot kg^{-1} \cdot h^{-1}$ and bretylium 1 $mg \cdot min^{-1}$ for approximately 10 days. On the 20th hospital day, his clinical condition deteriorated with refractory hypotension in spite of IABP, increasing pulmonary artery pressure, decreasing cardiac output and deteriorating oxygenation. His cardiac index on high-dose dopamine and dobutamine declined to 1.8 $L \cdot min \cdot m^{-2}$. Since a donor for cardiac transplant did not become available during this period, a decision was made to implant a left VAD.

The patient was sedated with midazolam 2 mg i.v. upon his arrival in the operating room. Anesthesia was induced with midazolam 3 mg i.v. and sufentanil 15 μg i.v. Muscle relaxation was obtained with vecuronium 10 mg i.v., and endotracheal intubation was carried out without complications. Anesthesia was maintained with sufentanil in a mixture of air-O_2 with supplemental vecuronium. VAD implantation was performed without complications. The total aortic cross-clamp time was 30 min and total cardiopulmonary bypass (CPB) time was 60 min. Cardiac transplantation was done 60 days later.

The patient was sedated with midazolam 2 mg i.v. upon arrival in the operating room. After preoxygenation, anesthesia was induced with sufentanil 15 μg i.v. and midazolam 3 mg i.v. along with vecuronium 8 mg i.v. for muscle relaxation. Anesthesia was maintained with sufentanil and vecuronium.

Blood samples were drawn from an arterial catheter at the following times: (1) pre-induction of the anesthesia (P1); (2) post-induction of the anesthesia (P2); (3) post-incision (P3); (4) immediately before CPB (P4); (5) during CPB, immediately before removal of the old heart (P5); (6) during CPB, immediately before reperfusion of the new heart (P6); (7) during CPB, immediately before weaning from CPB (P7); (8) 10 min after discontinuation of CPB (P8); (9) 60 min after discontinuation of CPB (P9); and (10) 24 h postoperatively (P10). All 4-ml samples of arterial blood were collected in chilled tubes containing EDTA-Na_2 and 100 μl of aprotinin (0.67 trypsin-inhibiting units per milliliter of blood). The samples were immediately placed in ice and centrifuged within 10 min (3000 rpm, 4°C, 15 min). After transferral of the platelet-rich plasma to polypropylene Eppendorf tubes, the samples were centrifuged in a microfuge for 1 min. The plasma was stored at −70°C until the assay was performed.

IL-6 was measured using enzyme-linked immunosorbent (ELISA) techniques (R&D Systems, Minneapolis, MN, USA).

IL-6 could not be detected in the baseline, the post-induction, and the post-incision samples. Prior to CPB (P4), pIL-6 was 20 $pg \cdot ml^{-1}$. After onset of CPB (P5), the level of pIL-6 was similar to P4 (18 $pg \cdot ml^{-1}$). With reperfusion of the donor heart, there was a marked increase in IL-6 which persisted for at least 60 min (230 $pg \cdot ml^{-1}$). The concentration of IL-6 returned to 60 $pg \cdot ml^{-1}$ within 24 h.

The baseline pMSH was 10 $pg \cdot ml^{-1}$. pMSH increased to 16 $pg \cdot ml^{-1}$ after induction of anesthesia. After surgical incision, pMSH returned to the baseline level, and after onset of CPB pMSH continued to decrease. After removal of the diseased heart, pMSH was not detectable. With reperfusion of the donor heart, pMSH increased to the baseline level, and the peak pMSH was observed 10 min after discontinuation of CPB (P8). pMSH returned to the baseline level 60 min after discontinuation of CPB, and increased to 20 $pg \cdot ml^{-1}$ again 24 h postoperatively.

Discussion

IL-6 is a key member of an ever-expanding family of cytokines that play a major role in the regulation of the hematopoietic and immune systems[7,8]. IL-6 has emerged as one of the most pleiotropic of the members of the cytokine network and, therefore, at least in principle, it is one of the most important in integrating physiological responses in a variety of situations such as response to infection and tissue injury. Increases in plasma IL-6 have recently been observed following

burn injury [9] and during rejection of renal transplants [10].

This patient had no severe infective episodes for 60 days with a left VAD. IL-6 could not be detected at the baseline, post-induction of anesthesia, and post-incision. We reported that pIL-6 with patients underwent cardiac transplantation. the control level of those patients was 50 $pg \cdot ml^{-1}$, and anesthesia and surgical stress prior to CPB had no significant effect on pIL-6 [11]. Those patients had no episode of using a VSD. The present case indicated that VSD might influence nondetectable levels of pIL-6 before CPB. A marked and transient increase in IL-6 also occurred during cardiac transplantation [11]. The change in this patient (P7–P10) was same as in the patients without VAD[11]. Considering the short elimination half-life ($t^1/_2$) of IL-6 (3 min) and the sustained increase in IL-6 levels after CPB (minimum 60 min), it is unlikely that this increase represented a nonspecific response to CPB. Rather, the change may have been an immunologic response to the newly perfused donor heart, or a delayed nonspcific response to major surgery [12].

The functional significance of MSH is not clear, but the widespread distribution of MSH receptors in the body indicates that it may have one or more major physiological functions [4]. Our results show that changes in pMSH were not significant before CPB, but pMSH decreased to 0 before reperfusion of the donor heart. A marked increase in pMSH occurred after reperfusion of the donor heart. The peak in pMSH was observed 10 min after discontinuation of CPB, then pMSH decreased to the control levels immediately. With reperfusion of the donor heart, pIL-6 increased immediately and persisted for at least 60 min. pMSH also increased after reperfusion of the donor heart, and the peak pMSH was observed 10 min after discontinuation of CPB. Then pMSH decreased immediately. Lipton et al. suggest that MSH may antagonize the effect of cytokines either directly or indirectly [6]. The changes in pIL-6 and pMSH may indicate a relationship between IL-6 and MSH.

The possible influence of immunosuppressive therapy on the duration of elevated IL-6 and pMSH levels requires additional study. This transient, fourfold increase in IL-6 and the delayed increase and quick return to baseline levels of pMSH may play a significant role in the physiologic changes observed in the early postoperative period following cardiac transplantation.

Previous reports have described a reduction in total lymphocyte counts and T lymphocytes in patients undergoing mechanical circulatory support with VAD [13]. It is not entirely clear whether these effects are due to VAD themselves or to the influences of coincidental events. Recently, the decreased lymphocyte level has been recognized in conjuntion with CPB [14], transfursed blood products [15], or immunosuppressive therapy [16]. Corticosteroids are also known to cause lymphopenia by redistributing lymphocytes from blood into lymphoid tissues [17]. Brody et al. [18] pointed out that infectious complications are not a necessary consequence of decreased lymphocyte level.

The effect of VAD on pIL-6 and pMSH remains uncertain; however, cardiac transplantation may induce changes in pIL-6 and pMSH, which may help in understanding and managing the medical manifestations of the recovery from cardiac transplant surgery.

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