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Circulating soluble gp130, soluble IL-6R, and IL-6 in patients undergoing cardiac surgery, with or without extracorporeal circulation

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Abstract

Objective: Soluble forms of interleukin-6 (IL-6) receptors are known to modulate biological activities of IL-6. The purpose of the study was to measure circulating levels of IL-6, sIL-6R and sgp130 in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass (CPB group) or without CPB (non-CPB group). **Methods**: The CPB group included 19 patients and the non-CPB group 12 patients. Sera levels of IL-6, sIL-6R and sgp130 were measured by specific ELISA at the beginning of the operation (T0, 15 min before skin incision) and 6 h later (T1). **Results**: IL-6 sera levels were respectively 9 ± 20 pg/ml (mean ± SD) and 13 ± 19 pg/ml at T0 and reached 340 ± 250 pg/ml and 965 ± 1060 pg/ml at T1 in CPB and non-CPB groups, indicating a significant increase from T0 to T1, but no differences between the two groups. When compared to T0 values, sgp130 levels decreased in both groups (respectively 105 ± 37 and 115 ± 35 ng/ml at T0 for CPB and non-CPB groups, and 72 ± 25 and 84 ± 29 ng/ml at T1) while we are not able to detect differences between the groups. Whatever the group or the time, sIL-6R concentrations remained unchanged. **Conclusions**: We showed that the increase of IL-6 after artery bypass grafting was similar between patients operated with CPB or without CPB. We conclude that the main inductor of IL-6 release is linked to surgical trauma rather than a reaction to CPB. Since it is known that gp130 inhibits IL-6-biological activities, we suggest that the decrease of sgp130 sera levels could further enhance the inflammatory effects of IL-6 in cardiac surgery. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Interleukin-6; sIL-6R; sgp130; Cardiopulmonary bypass; Cardiac surgery

1. Introduction

Interleukin-6 (IL-6) is a 26 kDa cytokine involved in the regulation of a large variety of cellular responses in multiple organ systems. Among these pleiotropic activities, IL-6 plays a key role in the induction and keeping of inflammatory responses by promoting the synthesis by hepatocytes of acute phase proteins and is a potent inductor of cardiomyocyte hypertrophy [1–3]. IL-6 exerts its function through a cell surface receptor composed of two trans-membrane proteins belonging to the cytokine receptor family, an 80 kDa ligand-binding subunit designated as IL-6R and a transducing 130 kDa glycoprotein (gp130) [2,4]. Binding of IL-6 to IL-6R triggers the association of IL-6R and gp130, forming a high-affinity complex able to transduce activation signals via the Jak/STAT activation pathways. gp130 is also involved in the signaling pathway of leukaemia inhibitory factor, oncostatin, ciliary neurotrophic factor, IL-11 and cardiotrophin-1 [2] which explains the overlapping properties of these cytokines. Studies of gp130 knock-out mouse suggest that cytokines of the IL-6 family might play a critical role on heart development and in muscle cell survival in the onset of heart failure during biochemical stress [5,6]. Furthermore, in vivo continuous activation of gp130 causes myocardial hypertrophy in mice [7].

Whereas serum IL-6 levels are low (<20 pg/ml) in normal subjects, high levels have been reported in inflammatory diseases, hematologic diseases, a variety of tumors and several cardiac diseases such as acute myocardial infarction, congestive heart failure, myocarditis and myxoma [8–11]. Soluble forms of IL-6R (sIL-6R) with MW of 50 000–55 000 and soluble forms of gp130 (sgp130) (90 000–110 000) were reported to be present in

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Table 1
Characteristics of the two patients groups[a]

	CPB group	Non CPB group	*P*-value
No. of patients	19	12	
Age (years)	65 ± 7	66 ± 7	NS
Body surface area (m^2)	1.89 ± 0.04	1.81 ± 0.05	NS
Sex (M/F)	19/0	11/1	
Parsonnet index	6.2 ± 4.6	6.9 ± 6	NS
Diabetes (N/Y)	15/4	9/3	
ACC duration (mn)	46 ± 18	0	
CPB duration (mn)	92 ± 28	0	
Operation duration (min)	293 ± 39	225 ± 30	NS
No. of grafts per patient	1.91 ± 0.9	2.94 ± 0.52	0.049
Blood loss/24 h (ml)	1052 ± 413	954 ± 451	NS

[a] Data are presented as mean ± standard deviation; CPB, cardio-pulmonary bypass; ACC, aortic cross-clamping; NS, non-significant; N, no; Y, yes.

human serum and pleural fluid [12–15]. Stimulation of target cells with a complex of sIL-6R and IL-6 induces homodimerization and tyrosine phosphorylation of gp130 and transduces the IL-6 signal [15]. In contrast, sgp130 inhibits the effects of sIL-6R-IL-6 complexes [13]. These studies indicated that sgp130 and sIL-6R are able to modulate the biological activity of IL-6 in body fluids, and could be interesting parameters to measure in association with IL-6.

Cardiac surgery with cardiopulmonary bypass (CPB) causes a systemic inflammatory response associated with cytokine release. Numerous investigators studied circulating inflammatory cytokines during cardiac operations, and high IL-6, IL-8 and IL-10 sera levels have been reported, whereas the elevation of IL-1β and TNFα remains more controversial [15–20]. An increase of blood levels of soluble TNF receptors (sTNFR) has been also noticed during CPB [21] but, to the best of our knowledge, sera concentrations of the IL-6 receptor-soluble forms were not studied under these conditions.

The aim of our study was to measure blood levels of IL-6, sIL-6R and sgp130 during coronary artery bypass grafting undergoing normothermic CPB, and to compare with patients grafted without the use of CPB.

2. Materials and methods

2.1. Patients

Thirty-one patients with multi-vessel disease undergoing coronary artery bypass graft were enrolled for the study between January 1998 and December 1999. They included 19 patients undergoing coronary artery bypass grafting (CABG) with the use of CPB (CPB group), and 12 patients without CPB (non-CPB group). Patients with preoperative inflammatory disease, previous cardiac surgery or referred in emergency were excluded from the study. Choice of off-pump coronary surgery (non-CPB group) referred to surgeon preference, anatomy of the lesions, no possibility of revascularization on the circumflex artery branches and low ejection fraction. Patients gave informed consent for the study, as recommended by the local ethic committee. Characteristics of each patient group are shown in Table 1. There is no difference between the parameters analysed in the two groups excepted in the number of grafts ($P = 0.049$) which is dependent on angiographic aspect of vessels and choice of surgical strategy.

2.2. Intraoperative patient management

All patients received the same anesthesia protocol including hypnomidate as agent for induction, rocuronium to facilitate tracheal intubation, isoflurane and sufentanyl for maintenance. Aprotinin was infused throughout the intervention (1×10^6 kallicrein inactivators units (KIU) after induction of anesthesia and 0.5×10^6 KIU/h) in order to reach about 100 KIU /ml in serum. Heparin (300 UI/kg) was infused before cutting the distal part of the mammary artery; activated clotting time was maintained above 400 s throughout the CPB. For the non-CPB group, 100 UI heparin/kg was used. All patients were operated on by median sternotomy and receive left internal mammary artery graft on the left descending artery and saphenous graft for the other arteries. CPB was done in normothermia; however, as in the non-CPB group, temperature reached 34.5–35.5°C at the end of the operation. Cold blood anterograde cardioplegia was used and repeated every 20 min for myocardial preservation. In the non-CPB group, exposure and fixation of the anastomotic site were achieved with 4/0 polytetrafluoroethylene sutures. Pneumatic stabilization was not used. Hemostatics tourniquets, endoclamps and spurts of serum were used to obtain a bloodless field.

2.3. Blood sampling and ELISA

Blood samples were drawn from the central venous line, 15 min before skin incision (T0) and 6 h after (T1), in the intensive care unit. For eight patients (three from the CPB group, five from the non-CPB group, each of them receiving multiple grafts), blood samples were collected at T0 and 4, 6, 8, 10, 12 and 24 h after skin incision for a kinetic study. The time between blood sampling and freezing never exceeded 12 h. Preliminary experiments showed no differences between IL-6, sIL-6R, and sgp130 measurements in serum stored just after sampling or stored after keeping the collect tube 12 h at 4°C before centrifugation. Serums were kept in aliquots frozen at −20°C before ELISA. IL-6, sIL-6R and sgp130 levels were measured by ELISA, as previously described [10]. Briefly, the anti-IL-6 purified monoclonal antibodies (mAb) B-E4 was coated as a capture mAb on 96-well flat bottomed plates (Maxisorp, Nunc, Intermed, Denmark). The detection was achieved using an anti-IL-6 biotinylated mAb (B-E8) followed by detection with streptavidin-peroxidase (Dako, Trappes, France). sIL-6R ELISA was performed using the anti-sIL-6R mAb B-

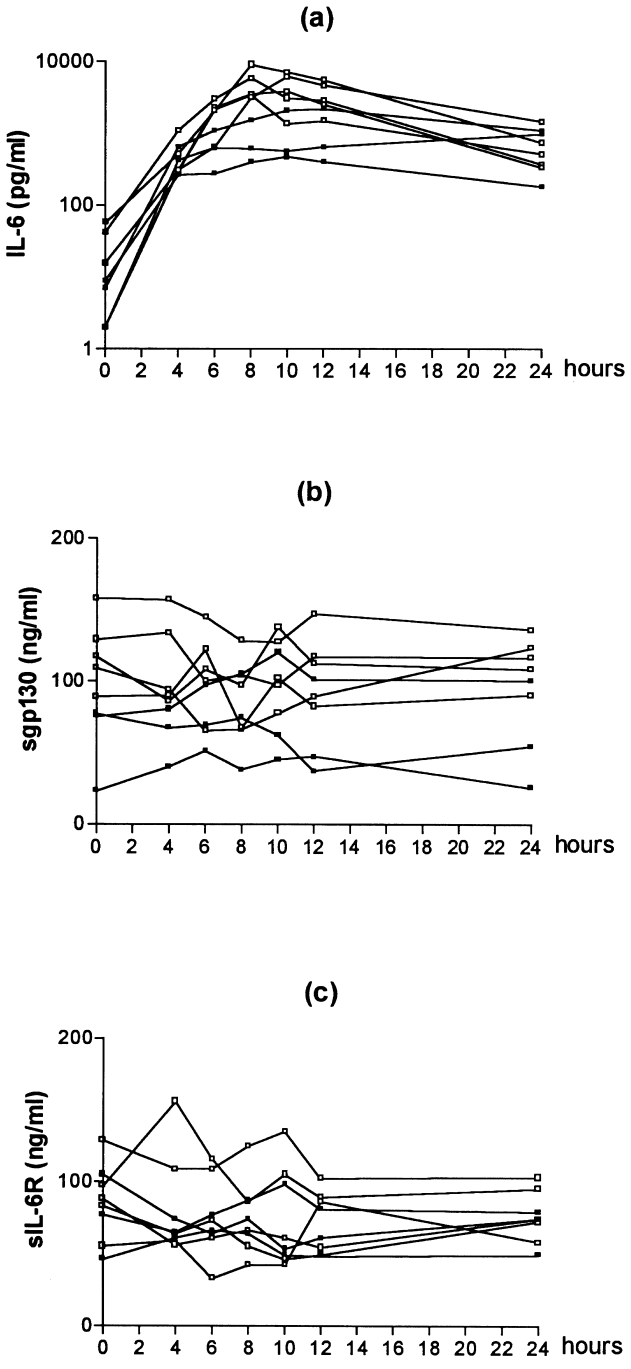

Fig. 1. Kinetic study of sera levels of IL-6 (a), sgp130 (b) and sIL-6R (c) measured by ELISA in patients undergoing CABG, either with CPB (■) or without CPB (□).

N12 as a capture mAb and the biotinylated anti-sIL-6R mAb B-R6 as a revealing mAb. sgp130 ELISA was similarly performed using the anti-sgp130 mAb B-K5 (capture) and the biotinylated anti-sgp130 mAb B-T12 (revelation). All the mAbs were kindly provided by Diaclone (Besançon, France).

The lowest detectable levels were 5 pg/ml for IL-6, 150 pg/ml for sIL-6R and 100 pg/ml for sgp130. Previous experiments showed no interference in the measurements of IL-6, sIL-6R and sgp130 by the addition of exogenous sIL-6R or sgp130, IL-6 or sgp130, and IL-6 or sIL-6R, respectively, or in any combinations of them. Furthermore, IL-6 measurements in HPLC fractions confirmed that monoclonal antibodies used in ELISA were able to detect monomeric as well as multimeric forms of IL-6 [10].

2.4. Statistical analysis

Data were expressed as mean ± standard deviation (SD). The differences between the two groups of patients were tested by the Mann–Whitney test. Comparison between serum parameters before and after surgery was done using the Wilcoxon's signed rank test.

3. Results

3.1. IL-6, sgp130 and sIL-6R sera levels

A kinetic study has been performed on eight patients at the beginning of the operation and 4, 6, 8, 10, 12, and 24 h after (Fig. 1). Kinetics for IL-6 release appeared comparable between the CPB and the non-CPB group, with the apex of secretion varying for individuals between 6, 8, or 10 h after the beginning of operation (Fig. 1a). sIL-6R and sgp130 levels were also comparable between the two groups, without noticeable variations along the kinetic study (Figs. 1b,c). Thereafter, IL-6, sgp130 and sIL-6R sera levels were measured by ELISA at the beginning of the operation (T0) and 6 h later (T1) (Fig. 2). IL-6 sera levels at T0 were respectively 9 ± 20 pg/ml (mean ± SD) in the CPB group and 13 ± 19 pg/ml in the non-CPB group, as found in healthy subjects [9]. At T1, IL-6 concentrations significantly raised at, respectively, 340 ± 250 ($P = 0.0001$) and 965 ± 1060 pg/ml ($P = 0.0005$) in CPB and non-CPB groups (Fig. 2a). No significant difference between the two groups at T0 and T1 has been pointed out. sgp130 levels in serum were 105 ± 37 ng/ml for the CPB group and 115 ± 35 ng/ml for the non-CPB group at T0, and significantly decreases to, respectively, 72 ± 25 ($P = 0.0052$) and 84 ± 29 ng/ml ($P = 0.0093$) at T1 (Fig. 2b). No significant difference of sgp130 levels can be detected between the two groups at T0 or T1. sIL-6R levels were, respectively, 122 ± 81 and 103 ± 37 ng/ml at T0 for CPB and non-CPB groups, and 92 ± 30 and 102 ± 38 ng/ml at T1. No significant difference can be noticed for sIL-6R between T0 and T1, as well as between the two patient groups (Fig. 2c).

4. Discussion

Previous reports have indicated that the proinflammatory cytokine IL-6 was produced undergoing coronary bypass with CPB [16–20]. In agreement with these reports, the present study shows the release of IL-6 during CABG,

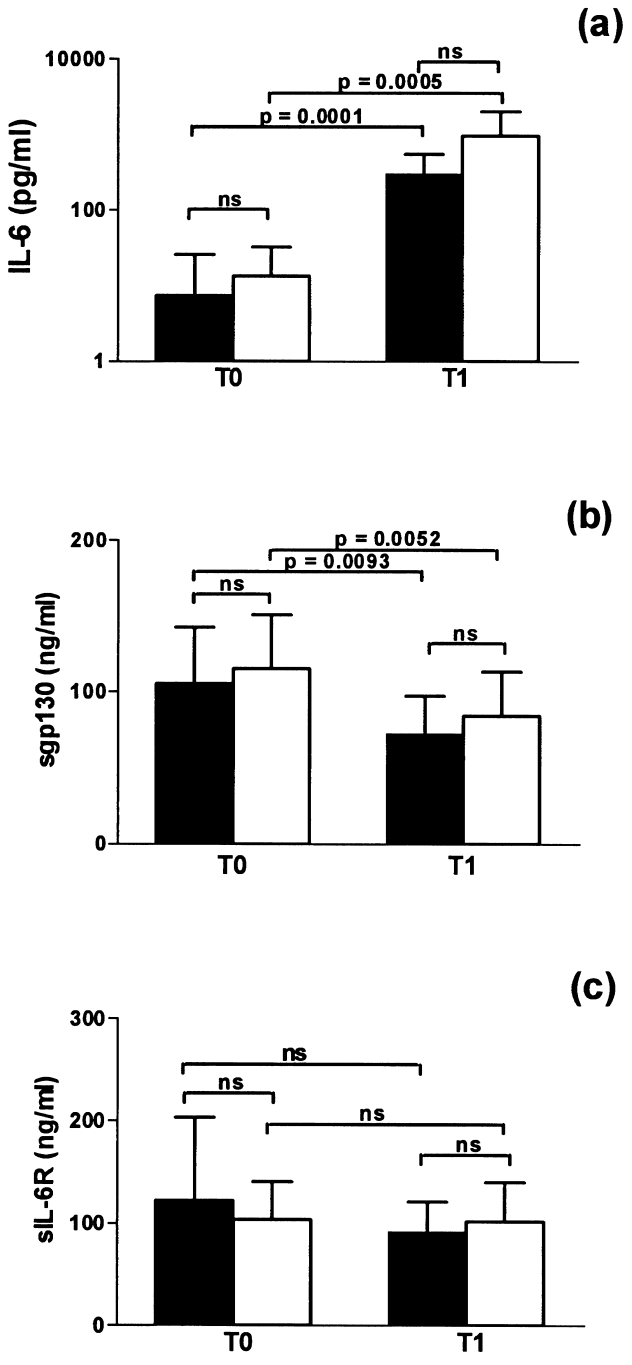

Fig. 2. Sera levels of IL-6 (a), sgp130 (b) and sIL-6R (c) measured by ELISA in patients undergoing CABG, either with CPB (■), ($n = 19$) or without CPB (□), ($n = 12$). Data are presented as mean ± SD. T0 corresponds to the beginning of the operation and T1 6 h later. Horizontal bars indicate statistical analysis between patient groups or between T0 and T1.

with a kinetic and serum concentrations closed to these previous results. This IL-6 release was expected since IL-6 is induced by a large number of stimuli such as inflammatory or mechanical stress [1]. Some authors suggested that the increase of IL-6 was an inflammatory response related with CPB [17,18,22,23]. Since CPB is associated with cardiac surgery such as CABG, it appeared to us of interest to further analyse the potential contribution of surgical trauma and CPB to IL-6 production. Variations between the groups of parameters such as blood loss, cardioplegia management or duration of ischemia may be potent modulators of cytokine release. In the present study, ischemic duration and time point of reperfusion appears to be equivalent for the two groups. Mean operation duration is not significantly different. Then, techniques for harvesting the grafts are the same for each group, as the time necessary to close the chest, proximal anastomosis required a very short time and distal anastomosis need more time in non-CPB group. Whatever, ischemia phenomena were indeed different between groups. For the non-CPB group, ischemia is localised on a working segment whereas in the CPB group, it concerns all the myocardium, which is cold and protected by blood cardioplegia. Regarding cardioplegia, it has been recently suggested that the use of cold or warm blood cardioplegia rather than cristalloid cardioplegia may attenuate inflammatory reactions [24,25]. Moreover, we have no significant differences between our groups regarding blood loss. Finally, we found in this study that the IL-6 increase after CABG was similar between a group of patients undergoing CPB and a control group of patients operated without CPB. We hypothesis that in cardiac surgery the main inductor of IL-6 release is linked to surgical trauma rather than to CPB. In agreement with this report, two recent studies demonstrated that the increase of IL-6 sera levels was the same in patients undergoing CABG with or without CPB [16,26]. In the Fransen et al. study [16], it could be noticed that only one coronary artery was grafted in the non-CPB group, vs. a mean of 3.8, reflecting a multivessel coronary artery disease in the CPB group. In the last group, patients were significantly older and per-operative temperatures were heterogeneous (normo- and hypothermia). Whatever, these authors reached the conclusion that the acute phase response was predominantly caused by the surgical procedure per se rather than CPB, as previously suspected. In their report, they only observed an early neutrophil activation when CPB was used [16]. As in our study, patient groups included in the Wan et al. study [26] were more homogeneous than in the Fransen et al. study since most of them suffered of multivessel coronary disease in both groups. A fortiori, they noted the absence of significant intergroup differences regarding IL-6 measurements, despite the fact that IL-8 and IL-10 sera levels after the operation were lower in the group without CPB than with CPB. By studying specific IL-6 levels in coronary sinus, arterial, pulmonary arterial, left atrial blood samples, Liebold et al. [20] also suggested that CPB is not per se the main inductor of the inflammatory response.

Our study also showed that sgp130 sera levels decreased during CABG with or without CPB but sIL-6R remained constant whatever kinetic and the patient group. Except a previous report [27] showing an increase of sgp130 levels in severe heart failure, it is the first study demonstrating a decrease of sgp130 during coronary surgery. Indeed,

CABG, independently of CPB, is able to induce a decrease of sgp130 by a mechanism that remains to be identified. Since sgp130 has been reported to inhibit the stimulatory effects of sIL-6-IL-6 complexes [13], we can hypothesis that the sgp130 decrease associated to unchanged sIL-6R levels and IL-6 increase could result in a stronger activation of the IL-6 transduction pathway. On another hand, the soluble cellular adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), and sTNFR were enhanced during heart surgery with CPB, though the control patient groups were missing to further indicate if the release is due to CPB rather than surgical trauma [20,28]. In this case, we can hypothesis that the sTNFR, which complexes with sera TNF, down regulates inflammatory processes. Whatever, sera levels of soluble inflammatory cytokine receptors during cardiac surgery are regulated by complex mechanisms able to enhance, inhibit or unaffect their release.

Taken together, these results suggest that phenomena regulating cytokine and cytokine receptor release are multiples, and that it is very difficult to identify a specific stimulus in a complex surgery procedure such as coronary artery bypass associated to CPB. To the best of our knowledge, we report the first case of decrease of sgp130 in patient serum secondary to surgical trauma. Whatever since it has been reported that serum sgp130 could negatively regulate the IL-6 signal [13], the decrease in sgp130 levels could further enhance the integrated biological response to IL-6 during CABG.

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