original research article

Interleukin-6 in cardiac surgery

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Abstract

Background and Purpose: Interleukin (IL)-6 is a multi-functional pro- and anti-inflammatory cytokine, and it has been a reliable biomarker of cardiac function status and myocardial damage. However, the characteristics of IL-6 expressions in the cardiac surgical patients have not been comprehensively described. The purpose of this review is to present the current knowledge on the role of IL-6 in the field of cardiac surgery.

Materials and Methods: Medical literature of IL-6 in cardiac surgical disorders of recent 3 decades were carefully collected as studying materials, and comprehensively reviewed and analyzed.

Results: Plasma IL-6 was significantly elevated 1 hour and peaked 3–6 hours after the start of cardiopulmonary bypass with a gradual decrease constant maintenance thereafter. No significant differences were found between patients with biological and mechanical heart valve replacements between on-poump and off-pump coronary artery bypass, or between cyanotic and acyanotic congental heart patients. The elevation of IL-6 was higher in mitral valve replacement than in coronary artery bypass grafting patients and in non-heart transplantation than in heart transplantation patients. Il-6 was involved in the pathogenesis of pulmonary artery hypertension and infective endocarditis, and predicted adverse cardiac events, such as coronary graft occlusion, aortic dissection progression and cardiac myxoma recurrence.

Conclusions: In cardiac surgical patients, the expression of IL-6 reflects the inflammatory situation of the patients and also predicts their prognosis. The higher elevation of IL-6 in mitral valve replacement and in non-heart transplantation might be attributed to cardiotomy suction, and to lack of sterioid use. Early administrations with steroid, α_2-adrenergic agonists, incretin hormones, or ischemic conditioning could reduce the inflammatory response and prevent from pertinent postoperative complications. Anesthetic agents and technique of choices may also reduce immune reactions and lower circulating cytokines. Extracorporeal IL-6 removal facilities have been successfully applied in clinical practice. The potential alternative therapies with IL-6 antibodies might be further developed and used in such patients for preventing myocardial apoptotic processes.

INTRODUCTION

Interleukin (IL)-6 is a multi-functional pro- and anti-inflammatory cytokine, and it has become a reliable biomarker of cardiac function status and myocardial damage *(1)*. IL-6 acts its biological functions via 2 signaling pathways: classic and trans-signaling pathways. The classic signaling mediates regenerative or anti-inflammatory activities of IL-6, whereas trans-signaling mediates pro-inflammatory processes. From the cellular level, IL-6 is produced principally by activated T lymphocytes

in the presence of macrophages or by macrophages alone, and secondarily by endothelial cells and fibroblasts. From the organ level, the heart would be a major source of IL-6 production as IL-6 levels were much higher in the coronary sinus blood than in the arterial blood *(2)*.

IL-6 plays an important role in the pathogenesis of coronary artery disease *(3)*. In animal experiments, IL-6 was illustrated to be an inducer of myocyte hypertrophy, and targeted deletion of the *IL-6* gene would not affect infarct size or left ventricular remodeling. Consequently, combination therapy involving IL-6 and soluble IL-6 receptor might inhibit cardiomyocyte apoptosis and reduce myocardial infarct size *(4)*. Moreover, patients with persistently elevated IL-6 levels demonstrate symptomatic congestive heart failure, larger end-diastolic and end-systolic diameters, increased left atrial size and a worse in-hospital outcome following admission with unstable angina *(5)*. In patients with paroxysmal atrial fibrillation, IL-6 concentration was elevated significantly and decreased gradually after recovery to sinus rhythm *(6)*. Furthermore, IL-6 has also been recognized to be involved in the postinterventional and postoperative complications. The roles of IL-6 expressions and *IL-6* gene polymorphism in the cardiac surgical patients have not been comprehensively described even though deliberations on respective disorders or operations were narrated. The aim of this review is to present the current knowledge on the role of IL-6 in the field of cardiac surgery.

IL-6 IN CARDIAC SURGERY

Cardiopulmonary bypass (CPB)

IL-6 is elevated in the conditions of surgical trauma, increased shear stress, ischemia-reperfusion injury and hypothermia *(1)*. Cardiac operations under CPB induce local and systemic inflammatory responses, thereby leading to multiple organ failure as a consequence of microcirculation disturbances. CPB activates inflammatory response by three mechanisms: contact activation, ischemia-reperfusion injury and endotoxemia. The triggering factors involved in the inflammatory process may be surgical procedure, duration of the ischemia and reperfusion in the heart, exposure of blood to the extracorporeal circuit, or release of endotoxin *(7)*. Usually, plasma IL-6 was significantly elevated 1 hour and peaked 3–6 hours after the start of CPB with a gradual decrease constant maintenance thereafter *(8)*. Plasma IL-6 increased within a few hours after the completion of CPB and lasted up to 24 hours. Plasma IL-6 increased during CPB comparing to baseline (42.1 ± 2.9 pg/mL to 71.1 ± 6.0 pg/mL, $p < 0.05$). The maximum concentration of IL-6 occurred before skin closure (116.6 ± 8.3 pg/mL) significantly higher than control *(9)*. The mechanism was considered to be circulating inflammatory cells activated by exposure to the extracorporeal circuit and moderate hypothermia. In contrast, the heart transplantation patients who received the immunosuppressive drugs, such as azathioprine and meth-

ylprednisolone, during the operation showed less elevated circulating IL-6 levels, and clinical observations revealed that early steroid administration before CPB could reduce the inflammatory response and enhance the release of IL-10 *(10)*.

Coronary artery bypass grafting (CABG)

IL-6 levels did not differ between on- and off-pump CABG patients. The peak values of IL-6 were found at the time protamine use in both groups, and then the IL-6 levels decreased gradually and recovered to baseline level at 30 day after operation (Figure 1) *(11)*. IL-6 levels in CABG patients may predict, 1) complement system activation, 2) postoperative inflammatory reaction, and 3) late cardiovascular events, such as occluded bypass grafts *(12)*. Hedman *et al*. *(12)* proposed a cut-off value of IL-6 of 3.8 pg/mL, a level above which in CABG patients might predict the adverse events.
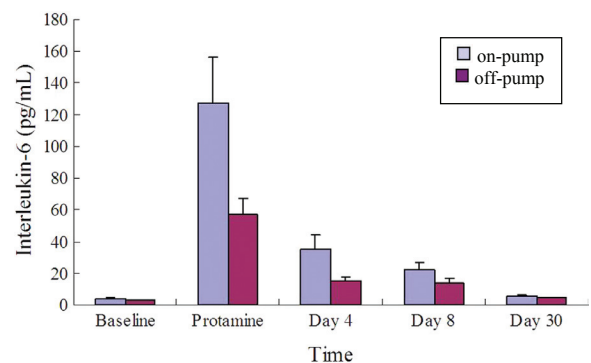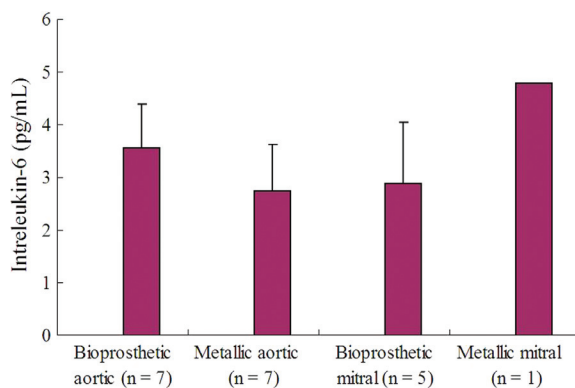

Figure 1. *A comparison of plasma interleukin-6 levels between on- and off-pump coronary artery bypass patients (11).*

It also illustrated that the IL-6 levels in patients receiving minimally invasive direct coronary artery bypass were significantly lower in the first 8 postoperative hours than those of the patients receiving conventional CABG, but a steady increase was observed during the postoperative course. After 24 hours, the level was comparable to that in the CABG group and significantly higher compared with the preoperative control *(13)*. Some inflammatory markers (IL-1, IL-6 and some leukocyte subsets) showed similar kinetics in both on- and off-pump CABG operations, whereas other cytokines (tumor necrosis factor-α, IL-8, IL-10 and elastase) showed earliest and highest peak levels. In brief, the inflammatory reactions occurring in the postoperative course of CABG were unrelated to the surgical strategy adopted, owing to the inflammatory reactions limited to the final phases of the operation *(11)*.

Heart valve operation

A retrospective analysis demonstrated that no differences were found in circulating IL-6 levels between the types of heart valve prostheses (mechanical or biological)

and implant sites (mitral or aortic postion) (Figure 2) *(14)*. A comparative study demonstrated that the serum IL-6 increased immediately after aortic crossclamp and reached its peak at the end of surgery in both CABG and heart valve groups. Serum IL-6 levels at the end of surgery and 24 hour after surgery were significantly higher in the valve group than in the CABG group (123.9 ± 21.7 pg/mL *vs.* 79.7 ± 10.4 pg/mL, *p* = 0.049; 113.6 ± 25.0 pg/mL *vs.* 39.9 ± 11.5 pg/mL, *p* = 0.006). It was explained as cardiotomy suction might be directly and specifically related to increased serum IL-6 levels after valve surgery *(15)*.

Figure 2. *A comparison of plasma interleukin-6 levels between the types of heart valve prostheses and implant sites (14).*

Infective endocarditis

The circulating IL-6 levels were noted to be increased in all patients with infective endocarditis (16.2 ± 15 pg/mL), and significantly higher than those of the control *(16)*. The IL-6 elevation was especially noted in patients with positive blood cultures, and a decrease of IL-6, during the whole treatment period, in comparison with that on admission, thereby reflecting the inflammatory protocol in the process of infective endocarditis *(17)*. However, differences of circulating IL-6 levels in infective endocarditis patients between different pathogens were not evaluated.

Congenital heart defect repair

The circulating IL-6 levels were found to be higher in both cyanotic (16.2 ± 6.9 pg/mL) and acyanotic patients with congenital heart disease (13.6 ± 5.8 pg/mL) when compared with the control, but the change of IL-6 was more pronounced in the cyanotic patients *(18)*. In such patients, the circulating IL-6 on postoperative day (POD) 1 increased to 271 ± 68 pg/mL from a preoperative baseline level of 46 ± 12 pg/mL, and declined on PODs 2 and 3, but insignificantly different from the baseline. Patients with single ventricle anatomy had the highest circulating IL-6 level on POD 1 as 629 ± 131 pg/mL, which was closely related to the elongation of CPB time to 106 ± 23 minutes *(19)*. Significant correlations of postoperative se-

rum IL-6 and IL-8 with increased inotropic requirements and reduced arterial oxygen tension 2 hours after CPB were also noted *(20)*.

Pulmonary artery hypertension (PAH)

Patients with idiopathic PAH have been noted an increased circulating and pulmonary tissue IL-6 expressions *(21)*. IL-6 may play a pathologic role through inflammation, cellular proliferation, interaction with bone morphogenetic protein pathways, decreasing prostacyclin and induction of the production of other nediators, such as serotonin, endothelin-1 and vascular endothelial growth factor (VEGF). Experimental studies demonstrated that hypoxic and monocrotaline-induced PAH was associated with increased IL-6 levels *(22)*. Overexpression of IL-6 in the mouse lungs resulted in increased pulmonary vascular resistance in the context of the pathological lesions similar to that seen in patients with PAH, including muscularization of the distal arterioles, plexogenic pulmonary arteriopathy and periarteriolar infiltration of T cells. These findings indicated that IL-6 directly or indirectly promoted proliferation of both smooth muscle and endothelial cells, triggering vascular smooth muscle cell proliferation through upregulated expression of VEGF and its receptor VEGF receptor II, through which it promoted the development and progression of pulmonary vascular remodeling *(21)*. Stimulated by IL-6, pulmonary artery endothelial cells form smooth concentric multilayers, leading to thickening of the intimal wall, narrowing the distal arteriolar lumen and forming a plexiform lesion. IL-6 might result in distal extension of the smooth muscle into the small peripheral pulmonary arteries at the level of the acinous, where the medial wall might become further hypertrophied with the added insult of hypoxia *(23)*. IL-6-induced VEGF expression might also indirectly increase the number of pulmonary artery smooth muscle cells by transforming into smooth muscle-like cells. Pulmonary endarterectomy is a potential curative treatment method for patients with chronic thromboembolic pulmonary hypertension. Plasma IL-6 in such patients peaked at 12 hours after termination of CPB and then decreased and recovered to baseline at 72 hours. Plasma IL-6 concentrations correlated inversely with cardiac index at the time of separation from CPB. Similarly, IL-8 concentrations correlated significantly with cardiac index at the same time. However, no significant relation was found between postoperative cytokine levels and mean pulmonary artery pressure or pulmonary vascular resistance *(24)*.

Aortic aneurysm/dissection

Aortic aneurysm formation is an inflammatory process according to contemporary theories. Many studies have identified associations between pro-inflammatory cytokines and abdominal aortic aneurysm formation, expansion, or rupture. IL-6 and tumor necrosis factor-α are

major inflammatory cytokines and have multiple important effects on human vascular pathophysiology. Research showed IL-6 concentrations were higher in acute aortic dissection than that in hypertension and healthy controls (25). Juvonen *et al.* (26) reported that IL-6 concentration was similar irrespective of dimensions of abdominal aorta aneurysms and presence of thrombus. Significant elevations of IL-6 and tumor necrosis factor-α levels were also detected in patients admitted at the acute phase of type A aortic dissection when compared with the other 2 control groups. However, no significant differences were noted between the chronic type A aortic dissection and hypertension patients. These findings accordingly confirmed that inflammation was closely involved into the pathogenesis of hypertension-induced aortic wall injury and the development of aortic dissection. Secretion of IL-6 occurred during open surgery as well in the endovascular treatment due to ischemia-reperfusion injury and after exposure of leukocyte to prosthetic materials. The plasma IL-6 increased on POD 1 of stent implantation of abdominal aorta (27). Increased IL-6 in supernatant of thrombotic contents of abdominal aortic aneurysms might explain the inflammatory response during endovascular repair (28). The aneurysm dimensions of the ascending and descending aorta did not correlate with serum C-reaction protein and IL-6. There was a strong linear correlation between the aneurysmal size and the C-reaction protein/IL-6 ratio for values above 0.8. The mean serum IL-6 levels of the ascending and descending aortic aneurysms were 7.58 and 6.86 pg/mL, respectively, with no significant difference (29). A recent study demonstrated a higher IL-6 level in acute aortic dissection than that in hypertension and healthy controls, no significant difference found between with and without endovascular treatment, and or between acute and chronic aortic dissection patients (30). A serological study supported the notion that endovascular repair might be rather less aggressive as evidenced by insignificant inflammatory modulations. The longer stent grafts were found to be associated with significant changes of IL-1β and IL-6 than shorter ones (31). This phenomenon was interpreted as stent graft deployment might definitely covered portions of spinal arteries, which might cause more severe hypoperfusion of the spinal cord by longer stents, thereby increasing the release of ILs in spite of the lack of clinical signs of paraplegia (31). An elevated circulating IL-6 has been proved to be a predictive risk factor of mortality in elderly patients with cardiovascular disorders. However, the circulating IL-6 changes in aortic aneurysmal patients receiving endovascular treatment remain to be clarified.

Cardiac myxoma

Various cytokines and growth factors including IL-6 were involved in tumor growth and angiogenesis. In one series of 37 cases of myxoma, 74% showed expression of IL-6 (32). Cardiac myxomas produce IL-6, which is a possible explanation for the inflammatory and immune features observed in the patients. The circulating IL-6 levels directly correlated the tumor size, *i.e.*, the number of IL-6-producing cardiac myxoma cells (33). A recent study demonstrated that circulation IL-6 level directly correlated with the tumor size, or with the recurrence of the tumors regardless of tumor size. According to the study, the overproduction of IL-6 by cardiac myxomas should be responsible for the constitutional symptoms and immunologic abnormalities in the patients, and might also serve as a marker of recurrence (34). The constitutional symptoms of cardiac myxoma patients for example, the onset fever of unknown origin of cardiac myxoma, might be mediated by IL-6 (35). Myxoma is highly aggressive due to IL-6 production irrespective of the tumor size, and the serum IL-6 level decreased rapidly after the cardiac myxoma resection and it remained in the normal range, but it would be elevated again when recurrent (34, 35). Therefore, IL-6 might also play a role in inducing the activation and proliferation of secondary foci in the event of multifocal recurrence.

Heart transplantation

A comparative study revealed that plasma levels of IL-6, IL-8 and IL-10 were increased in patients undergoing heart transplantation at the time of reperfusion, whereas IL-6 levels were higher in the non-heart transplantation group 24 hours after reperfusion (36). This inter-group disparity was considered to be a result of an absence of immunosuppressive therapy in the non-heart transplantation group (36). Research works also disclosed that the ischemic or CPB duration correlated circulating IL-6 or IL-8 levels, indicating the important role of ischemia duration that played in the inflammatory reactions. IL-6 elevation in the donor hearts might be due to the endogenous norepinephrine after brain death or to the exogenous norepinephrine administration to the donors. IL-6 can be produced from leukocytes, endothelial cells and vascular smooth muscle cells *in vitro* and has recently been detected in cardiac myocytes. Messenger ribonucleic acid of IL-6, IL-6 receptor and gp130 were observed to be strongly expressed in all chambers of donor hearts, whereas right ventricles of control patients did not express them. This phenomenon might explain the close relationship between elevated IL-6 levels and acute cardiac allograft dysfunction. An upregulation of IL-6 receptor in the donor heart after brain death was likely to illustrate that circulating IL-6, generated either by the donor heart or by the recipient due to advanced heart failure or after cardiac surgery, exerted its negative inotropic effects on the donor heart (37).

Left ventricular assist device (LVAD)

Cardiac content and expression of IL-6 might reflect an *in situ* inflammation due to the local infiltration of the inflammatory cells. Cardiac levels of IL-6 were less as-

sociated with the hemodynamic status of LVAD recipients, and did not predict to risks. In a cohort of LVAD-candidates, only patients with preoperatively elevated IL-6 levels, particularly >8.3 pg/mL, were more susceptible to serious complications, such as severe multiple organ failure (38). At the time of LVAD implantation, the mean serum IL-6 level was 33.6 ± 9 (range, 1.07–106.9) pg/mL. After a mean duration of LVAD support of 64 ± 8.4 days, IL-6 levels decreased to 11.3 ± 4 pg/mL. The patient with an infected device at time of explant had an increase in both IL-6 and tumor necrosis factor-α levels (39).

IL-6 GENE POLYMORPHISM

The IL-6 polymorphism might influence the circulating IL-6 levels and functioning activity of IL-6 protein and might indicate the postoperative outcomes of the patients (40). IL-6 gene G-174C polymorphism did not correlate with the number of stenosed coronary vessels. However, IL-6 gene G-174C polymorphism significantly associated with the prognosis of coronary patients: there were more cardiovascular events (revascularization, myocardial infarction and death) in the CC genotype carriers than in the GG/GC genotype carriers. There was no significant difference between patients with coronary revascularization (percutaneous transluminal coronary angioplasty with or without stent implantation and (or) CABG) and those without the need of revascularization. In addition, smokers with the CC genotype were an increased mortality risk compared to GG/GC carriers (41).

RISK FACTORS OF IL-6 ACTIVATION

The risk factors triggering IL-6 activities may include increasing age (in particular older age >70 years), obesity, atherosclerosis, diabetes (42), hepatic and renal dysfunction, high postoperative oxygen consumption and adrenaline infusions (43), etc.

IL-6 REMOVAL

Excessive circulating cytokines can be harmful. The cytokine antibodies to reverse hypercytokinemia seemed to be a vain in keeping the homeostatic balance (44). Anesthetics may reduce immune reactions and lower circulating cytokines including IL-6, by reducing the activity of adrenergic receptor, suppressing of inducible nitric oxide synthase/nitric oxide biosynthesis, and inhibiting nuclear factor-κB activation (45). The representative anesthetics include desflurane, propofol, fentanyl, remifentanyl, kesmine (44), sevoflurane (43) and thiopental (46), etc. Early steroid administration before CPB can reduce the inflammatory response. Dexmedetomidine, an α2-adrenergic agonists, was considered an anti-inflammatory agent for preventing inflammatory reaction to cardiac surgery with substantial efficacy and safety (47). Gluca-

gon-like peptide-1, an incretin hormone, was found to reduce circulating IL-6 levels in humans (48). Ischemic conditioning (pre and post) is a potential protective measure for prolonged ischemia and associated cytokine release (43). Plasma filtration was successful in cytokine removal but was associated with albumin loss. Hemodiafiltration with filters was not very encouraging due to a lower removal degree. Extracorporeal support systems may serve as cytokine removal facilities (44). Polymyxin B-immobilized cartridge has been successfully used in endotoxin elimination (49). CytoSorb® is effective in reducing postoperative systemic inflammatory response syndrome. Hemoadsorption by using CytoSorb® (CytoSorbents Corporation, USA) is a novel technique for removal of cytokines including IL-6, tumor necrosis factor and IL-10, when unresponsive to blood purification techniques. With the use of CytoSorb®, not only circulating IL-6 was removed, but inotropic support was also reduced and no complications were found (50). Recently, high cut-off hemofilters were proved to be effective in removing many cytokines including IL-6 in septic shock patients.

CONCLUSIONS

In cardiac surgical patients, the expression of IL-6 reflects the inflammatory situation of the patients caused by surgical trauma and CPB and it also predicts the prognosis of these surgical patients. IL-6 could be a reliable biomarker of cardiac surgery. Early administration with steroid, α2-adrenergic agonists, incretin hormones, or ischemic conditioning before CPB may reduce the inflammatory response and prevent from certain postoperative complications. Anesthetic agents and technique of choices may also reduce immune reactions and lower circulating cytokines. Extracorporeal IL-6 removal facilities have been successfully used in clinical practice. According to the kinetic features of the cytokines including IL-6, potential alternative therapies with IL-6 antibodies might be further developed and used in these patients to inhibit myocardial apoptotic processes.

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