REVIEW

Interleukin-6 and cardiac operations

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ABSTRACT. Interleukin (IL)-6 is a pleiotropic inflammatory cytokine with both pro- and anti-inflammatory capacities, produced by different cells and tissues, such as leukocytes, adipocytes, and endothelium. From the viewpoint of cardiologists, this cytokine is a reliable biomarker of cardiac dysfunction, occurrence of atrial fibrillation, cardiac myxoma with recurrence, remote metastasis or embolization, and atherosclerotic processes. Although IL-6 levels were detected in patients undergoing cardiac operations and reported sporadically, the perioperative kinetics of IL-6 in cardiac surgical patients was insufficiently elaborated. The influencing factors, clinical implications, and causative effects of IL-6 on clinical outcomes and potential treatment choices among cardiac surgical patients remained to be clarified as well. The purpose of this article is to discuss these aspects of IL-6 in patients undergoing a cardiac operation.

Keywords: cardiac surgical procedures, inflammation, interleukin-6

IL-6 is a dual functional cytokine with both pro- and anti-inflammatory capacities [1]. IL-6 exerts its biological functions via two signaling pathways: the classic signaling pathway via the membrane-bound IL-6 receptor (IL-6R), which is responsible for anti-inflammatory processes, and the trans-signaling pathway via the soluble IL-6R (sIL-6R), which participates in pro-inflammatory processes [2, 3]. IL-6 is ubiquitous and is secreted by all types of cells, including fibroblasts, endothelial cells, and cardiomyocytes [4]. The production of IL-6 may be influenced by many factors, both positive (the epinephrine and norepinephrine levels in the circulation and excitation of the sympathetic nervous system) and negative (use of β-blockers, angiotensin-converting enzyme inhibitor and angiotensin II type 1 receptor antagonist) [5]. The necrotic death of cells coincides with the upregulation of IL-6, mediated by NF-κB and p38MAPK. IL-6 is also involved in cellular apoptosis. Biffl *et al*. [6] reported the inconsistent effects of IL-6 on polymorphonuclear leukocytes, which was only effective prior to the concentration of polymorphonuclear leukocytes in culture reaching 10-20×10^6/mL. IL-6 and pertinent cytokines were found to be involved in the left ventricular remodeling, via cardiomyocyte hypertrophy and apoptosis, by upregulating the anti-apoptotic protein B-cell lymphoma-extra large (Bcl-xL) [5]. In a rat myocardial ischemia-reperfusion injury model, exogeneus IL-6 possibly induced cardiomyocyte apoptosis via inducible nitric oxide synthase (iNOS) action [7]. An experimental study also revealed that apoptotic cardiomyocytes in cardiac-specific gp130 knock out mice [8]. IL-6 can inhibit myeloma cell apoptosis by activating gp130 through IL-6R, whereas the IL-6/sIL-6R complex can inhibit myocardial apoptosis and limit infarct size in reperfused acute myocardial infarction [9].

Recent studies reported that IL-6 was elevated in the condition of acute and chronic infections [10], cardiac functional impairment [11] and geometric alterations [12], pulmonary artery hypertension [13], the occurrence of atrial fibrillation [14], and the presence, recurrence, and metastasis of cardiac myxoma [15, 16]. Plasma IL-6 strongly correlated with the six-minute walking distance and right atrial pressure, independently associated with mortality [17]. IL-6 participated in the development of coronary artery disease and was significantly expressed in unstable angina patients with unfavorable outcomes [18]. IL-6 is expressed in the infarcted left ventricle, especially in the bordering area of infarction [12]. Activation of the JAK/STAT pathway via IL-6 could mediate cytoprotective and antiapoptotic effects in acute myocardial infarction [19]. Although, in animal experiments, targeted deletion of the IL-6 gene did not alter myocardial infarct size or left ventricular remodeling [12], with combined IL-6 and sIL-6R, effects of the inhibition of cardiomyocyte apoptosis and the reduction of myocardial infarct size could be attained, thus providing a potential therapeutic alternative [20]. The mechanisms could relate to the fact that IL-6 plays its pro-inflammatory role by triggering the oxidant reactions resulting from intracellular adhesion molecule-1 and subsequent neutrophil adhesions. The use of the selective IL-6R antagonist MR16-1 may decrease inflammatory cell infiltrations, minimize the pro-inflammatory amplification and thus improve cardiac geometric and functional status [21]. In addition, IL-6 genotype studies have revealed that genotype CC patients presented the highest plasma IL-6 levels and

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highest cardiac death risks, followed by genotypes GC and GG [22].

Although continuous reports demonstrate that IL-6 is associated with postoperative adverse events [23], the kinetics of IL-6 in terms of operation types and surgical techniques have not been sufficiently described. Moreover, there have been conflicting results for IL-6 levels in terms of comparisons between certain cardiac operations and techniques, for instance, on-pump *versus* off-pump coronary artery bypass grafting (CABG). The clinical implications of IL-6 expressions entail further discussions. In order to highlight these aspects, a systematic review of IL-6 levels in cardiac surgical patients was made.

CARDIOPULMONARY BYPASS (CPB)

CPB may trigger an inflammatory cascade and lead to systemic inflammatory response syndrome (SIRS), while the cytokines, including circulating IL-6, in the inflammatory process can be triggered by many factors, such as anesthesia, surgical procedure, hemodynamic changes, ischemia-reperfusion injury, hypothermia and endotoxin release [1, 24]. As a result, both the immune and hematopoietic systems are involved, in response to local and systemic inflammatory reactions [25], leading to microcirculatory disorders and even multiorgan failure [26]. Usually, plasma IL-6 is significantly elevated 1 h and peaks 1-6 h after CPB, and then falls but remains significantly higher [27-34]. In patients receiving pulmonary endarterectomy, under profound hypothermic circulatory arrest, the peak of circulating IL-6 could be delayed until 12 h after the operation [35]. Lequier *et al*. [36] observed a delayed peak, which occurred 8 h after CPB. Beghetti *et al*. [37] noted, in pediatric cardiac surgical patients that the circulating IL-6 levels peaked 6 h after CPB and remained high for five days. Dehoux *et al*. [38] observed, in a prospective control study that IL-6 remained high 1-6 h after CPB, with no significant peak, but kinetics of IL-6 in lipopolysaccharide-induced whole blood cell cultures was contrary and in a parabolic curve form with a nadir appearing 2 h after CPB, implying the impact of CPB on lipopolysaccharide hyporesponsiveness.

Hauser *et al*. [39] noted that serum and alveolar IL-6 levels increased after CPB, which correlated with postoperative morbidity. Thus, IL-6 could be used to assess the severity of the systemic inflammatory response after CPB. In 32 children <two years of age with congenital heart disease repair under CPB, IL-6 in the bronchoalveolar lavage reached its peak 2 h and fell 14 h after CPB; however, corticosteroid inhalation did not influence the IL-6 release in comparison to control (*figure 1*), implying that corticosteroids did not affect the pulmonary inflammatory response [40].

Karube *et al*. [41] reported that IL-6 levels did not differ between the coronary sinus and the arterial blood. They explained that IL-6 levels in the arterial blood reflected the levels in the whole body, while precluding the myocardial source of IL-6. Wan *et al*. [42], who reported higher IL-6 levels in the coronary sinus than in the arterial blood, and higher IL-6 levels in the left atrium than in the pulmonary artery, proposed a contrary statement that myocardium was a main source of IL-6. Liebold *et al*. [34] found that plasma IL-6 levels from the arterial blood were much higher than those from the coronary sinus, and that those from the left

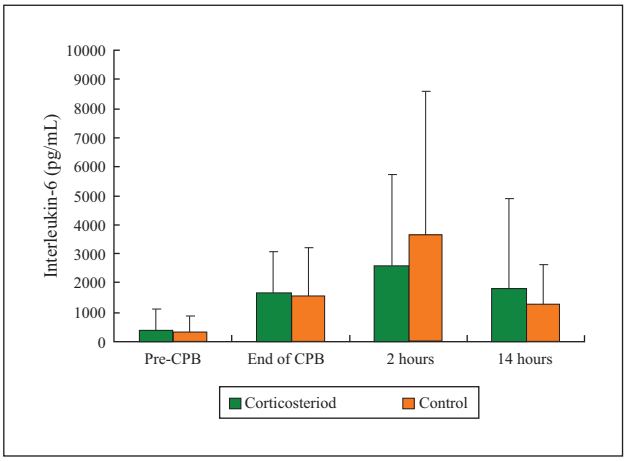

Figure 1
A comparison of bronchoalveolar interleukin-6 levels between patients receiving corticosteroid inhalation (■) and control (■) [40].

atrium were much lower than those from the pulmonary artery. Taken together, the disparities in IL-6 levels from blood samples of different sites taken during operations under CPB could be explained by a limitation in coronary sinus blood sampling.

Sablotzki *et al*. [43] found an increased IL-6 release after CPB with peak values 6 h after the operation, coinciding with a peak in body temperature. As observed in neonates and infants receiving cardiac operations, IL-6 started to increase at the end of CPB and peaked 2 h (at 298 and 254 pg/mL) following protamine injection, but there was no significant intergroup difference in spite of a more pronounced elevation in neonates [30].

In pediatric patients, it was found that the elevation of serum IL-6 did not correlate with the duration of the aortic cross-clamp time (either >80 min or <80 min), temperature (mild or moderate hypothermia) or surgical approach (ventriculotomy or atriotomy) on postoperative days 0, 1 and 4 [44]. Grünenfelder *et al*. [45] reported, in a prospectively controlled, randomized study, that IL-6 levels were significantly higher 24 h after the operation in the hypothermic than in the normothermic group. Menasche *et al*. [46] found that IL-6 levels were higher in patients having a normothermic bypass, while suggesting that vasodilation occurring with warm heart operations is mediated by a temperature-dependent release of cytokines. Ohata *et al*. [47] found no differences in IL-6 levels in normothermic and moderate hypothermic bypasses before and 0, 12 and 24 h after CPB in adult patients undergoing cardiac operations.

Steinberg *et al*. [48] reported increased plasma IL-6 and complement levels in response to CPB. Mareus *et al*. [49] found no correlation between serum IL-6 levels and CPB duration. Saatvedt *et al*. [50] noted a close correlation between IL-6 levels 48 h after CPB and CPB duration. Whitten *et al*. [51] found a positive correlation between IL-6 levels after CPB and CPB duration, other than aortic cross-clamp duration. Lequier *et al*. [36] demonstrated a significant increase in plasma IL-6 levels at all observed times in comparison to the preoperative baseline, but the insignificant difference in IL-6 levels between patients with and without endotoxemia following CPB indicated that IL-6 elevation could be due to CPB alone. In children undergoing major cardiovascular surgery, serum

levels of IL-6 increased dramatically during and/or after the operation, indicating that IL-6 elevation levels could result from an incorporated impact anesthesia, surgical trauma, and endothelial functional alterations [52]. Moreover, evidence has been presented to confirm the superior IL-6-eliminating effects of heparin-coated CPB over conventional CPB [53], membrane oxygenation over bubble oxygenation [54] and low tidal volume/high positive end-expiratory pressure (PEEP) over high tidal volume/low PEEP [55].

In addition, many authors have attempted perioperative conditioning on IL-6 production in cardiac surgical patients; in most situations, a good effect was obtained *(table 1)*.

CORONARY ARTERY BYPASS GRAFTING

Comparisons between CABG and valve replacement patients revealed serum IL-6 levels to be significantly higher in the valve group than in the CABG group at the end of surgery and 24 h after the operation (*figure 2A*) [66], which was explained as the result of cardiotomy suction in valve surgery.

Some authors [67, 68] found that IL-6 levels were similar in both on-pump and off-pump CABG patients with a baseline level of 3.9 and 2.7 pg/mL, respectively. It was also found that the peak values of IL-6 appeared at the time of protamine use in both groups, then decreased gradually and recovered to the baseline level 30 days after the operation (*figure 2B*) [67]. Uyar *et al*. [69] compared the kinetics of perioperative serum IL-6 levels in valve replacement, on-pump and off-pump CABG patients, finding that IL-6 was elevated 1 and 4 h after the operation, with similar trends seen in on-pump and valve replacement patients, whereas off-pump patients exhibited much higher IL-6 levels at each sampling time. They concluded that off-pump was associated with a reduced cytokine response. However, two reports on the kinetics of plasma IL-6 between on-pump and off-pump CABG by the same group from the Prince of Wales Hospital, Hong Kong, displayed similar trends for each group, but with conflicting results: no intergroup difference in one report [31], but significantly elevated plasma IL-6 levels in the on-pump group during and at the end of surgery in comparison to off-pump, which was interpreted as a reduced pro-inflammatory reaction to the off-pump maneuver [33].

In comparison to conventional CABG patients, Strüber *et al*. [70] found that the IL-6 levels in patients undergoing a minimally invasive direct coronary artery bypass (MIDCAB) procedure was significantly lower up to 8 h after the operation, followed by a gradual elevation and a match with the levels of the conventional CABG patients 24 h after the operation, indicating a less procedure-related inflammatory response in MIDCAB due to the lack of global ischemia, protamine use, and moderate hypothermia. Gunaydin *et al*. [71] disclosed similar IL-6 trends in both mini-CPB and conventional CABG patients, whereas, in the conventional CABG patients, IL-6 levels were significantly higher during CPB and at the end of CPB, and following protamine reversal with respect to mini-CPB patients (*figure 2C*). A comparative study of IL-6 levels in elective percutaneous transluminal coronary angioplasty (PTCA) without CPB, CPB-supported PTCA, and on-pump CABG patients demonstrated significant differences at 3, 6, and 24 h after the procedures, with the highest found in on-pump CABG patients, supporting the CPB relevance of IL-6 (*figure 2D*) [72]. On the contrary, Gulielmos *et al*. [73] observed that IL-6 levels started to increase in each group of CABG procedures within 2 h after ischemia, and peaked 12 h after ischemia. At 15 min, day 1 and day 2 after ischemia, IL-6 levels of patients with mini-thoracotomy CABG were significantly higher than those of conventional CABG patients. The result denied the relation of IL-6 production due to CPB.

The preoperative IL-6 level could be a biomarker for predicting postoperative complications, such as atrial fibrillation [74, 75]. Hedman *et al*. [76] proposed a cutoff value for IL-6 of 3.8 pg/mL, a level above which, in CABG patients, could predict early graft occlusion and late adverse cardiovascular events; patients with early graft occlusion or late adverse cardiovascular events were associated with a much higher plasma IL-6 levels (*figure 2E*). However, data from articles by Parolari *et al*. and Hedman *et al*. were somewhat inconsistent. The mean IL-6 level in on-pump CABG in the study by Parolari *et al*. was 3.9 pg/mL, whereas the cutoff for predicting adverse events, as proposed by Hedman *et al*., was 3.8 pg/mL. The detection of plasma IL-6 in both studies was the same, that is, by using commercially available enzyme-linked immunosorbent assay kits (R&D System). Clearly, the proposed cutoff was not suitable for the patient population similar to that in Parolari's study.

Some inflammatory biomarkers, including IL-6, displayed similar trends in on-pump and off-pump CABG procedures, while other biomarkers, such as tumor necrosis factor-α, exhibited advanced and elevated peaks. This revealed that the postoperative inflammatory response was unrelated to either on-pump or off-pump surgical techniques [67].

HEART VALVE OPERATION

Bacci *et al*. [77], who evaluated plasma IL-6 levels in patients receiving aortic or mitral valve replacement with a bio- or a mechanical prosthesis, found no difference in plasma IL-6 with respect to the prosthetic valve and the site of valve insertion (*figure 3A*). However, the authors failed to indicate the blood sampling time. Trikas *et al*. [78] conducted a prospective randomized control study on plasma IL-6 among 30 patients with mitral stenosis. In their study, the healthy controls had an IL-6 level of 3.8 pg/mL, whereas the mitral stenosis patients had a baseline IL-6 of 6.9 pg/mL and a postoperative value of 5.5 pg/mL at the six-month follow-up stage (*figure 3B*). The preoperative elevated IL-6 levels were explained as the result of an immune response to congestive heart failure, while the secondary significant decline in IL-6 was due to a reduced left atrial size and an improved cardiac function.

CONGENITAL HEART DEFECT REPAIR

Various studies revealed that the patients with a congenital heart defect, regardless of being cyanotic or acyanotic, presented higher circulating IL-6 levels compared to controls (*figure 4A*) [79-81]. The more distinctive changes in

Table 1
The influence of perioperative conditioning on IL-6 production

Year	Author	Study	Patient	Agent	Time of use	Effect on IL-6
1995	Kawamura *et al*. [29]	Prospective, randomized, controlled	27 patients undergoing elective CABG	Methylprednisolone (30 mg/kg)	Before CPB and before cross-clamp removal	Significantly reduced serum IL-6 levels 1-3 hours after operation
1996	Sawa *et al*. [56]	Prospective, randomized, double-blind	20 CABG patients	Nafamostat mesilate (FUT-175) 2 mg/kg/hour	During CPB	Significantly reduced the blood IL-6 level 2 hours after CPB in comparison to control (41 ± 14 pg/mL *versus* 79 ± 16 pg/mL, $p < 0.05$)
1996	Seghaye *et al*. [57]	Prospective, randomized	25 children	Aprotinin (20,000 kallikrein inactivation unit/kg body weight [2.8 mg/kg])	Short intravenous infusion (20 minutes) before sternotomy	No significant difference in peak values at 4 hours postoperatively in comparison to control (285 ± 48 pg/mL *versus* 205 ± 49 pg/mL, $p > 0.05$)
2002	Brull *et al*. [58]	Prospective, randomized	140 patients undergoing elective first time CABG	Angiotension converting enzyme inhibitors	At enrolment	Significantly decreased median (117 pg/mL *versus* 193 pg/mL) and peak IL-6 levels in comparison to non-treated patients (142 ± 19 pg/mL *versus* 196 ± 13 pg/mL, $p = 0.02$)
2003	Fansa *et al*. [59]	Prospective, randomized	15 adult patients for CABG	Diltiazem (1 g/kg/min)	Infused during CPB	Significantly lowered at the end of CPB and 3 hours later
2003	Greilich *et al*. [60]	Prospective, randomized, double-blind	60 CABG patients	ε-aminocaproic acid (100 mg/kg [load], 5 g [pump prime], 30 mg/kg/hour [infusion] *versus* aprotinin [2 $\times 10^6$kallikrein inactivation unit [load], 2×10^6 kallikrein inactivation unit [pump prime], and 5×10^5 kallikrein inactivation unit /hour [infusion])	Load, pump prime and infusion	No significance between, but significantly lower than the saline control group, indicating that the lysine analog ε-aminocaproic acid had a similar IL-6-eliminating effect to aprotinin

Table 1
(*Countinued*)

Year	Author	Study	Patient	Agent	Time of use	Effect on IL-6
2004	Sucu *et al*. [61]	Prospective, randomized, double-blind	40 CABG patients	N-acetylcysteine (50 mg/kg)	Intravenously for 3 days	Preventing pump-induced oxidoinflammatory response during CPB
2006	Nakanishi *et al*. [62]	Prospective, randomized, double-blind	CABG patients	Urinary trypsin inhibitor	Pretreatment	Lowered after separation from CPB and at the end of surgery
2007	Santos *et al*. [40]	Randomized, prospective, double-blind, placebo-controlled	32 children <2 years of age with congenital heart disease	Corticosteroid inhalation	After CPB	Not influence the IL-6 release
2007	Matsumura *et al*. [63]	Non-randomized, controlled	24 consecutive patients with a ventricular septal defect and pulmonary hypertension	Modified ultrafiltration (MUF)	After CPB	Significantly lower after modified ultrafiltration than before (306 ± 231 pg/mL *versus* 380 ± 328 pg/mL, $p<0.05$)
2011	Davies *et al*. [64]	Small non-randomized cohort	30 adult patients	Plasma-Lyte 148	Modifying priming solution	Increased over time peaking at 4 hours after CPB, but no difference was noted in comparison to control
2011	Xia *et al*. [65]	Prospective, randomized	32 patients with congenital heart defect	Propofol combined with low dose fentanyl *versus* midazolam combined with low dose fentanyl		The propofol group exhibited lower IL-6 levels at cross-clamp removal and 24 hours after operation than the midazolam group, implying propofol exerts greater inflammation-reducing potentials
2014	Ueki *et al*. [27]	Prospective, randomized, controlled	42 adult patients undergoing elective cardiac surgery with CPB	Dexmedetomide (1 μg/kg for 10 min after aortic cross-clamping, and 0.5 μg/kg/hour intraoperatively)	During operation	Suppressed plasma IL-6 levels during and after the operation

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IL-6: interleukin-6.

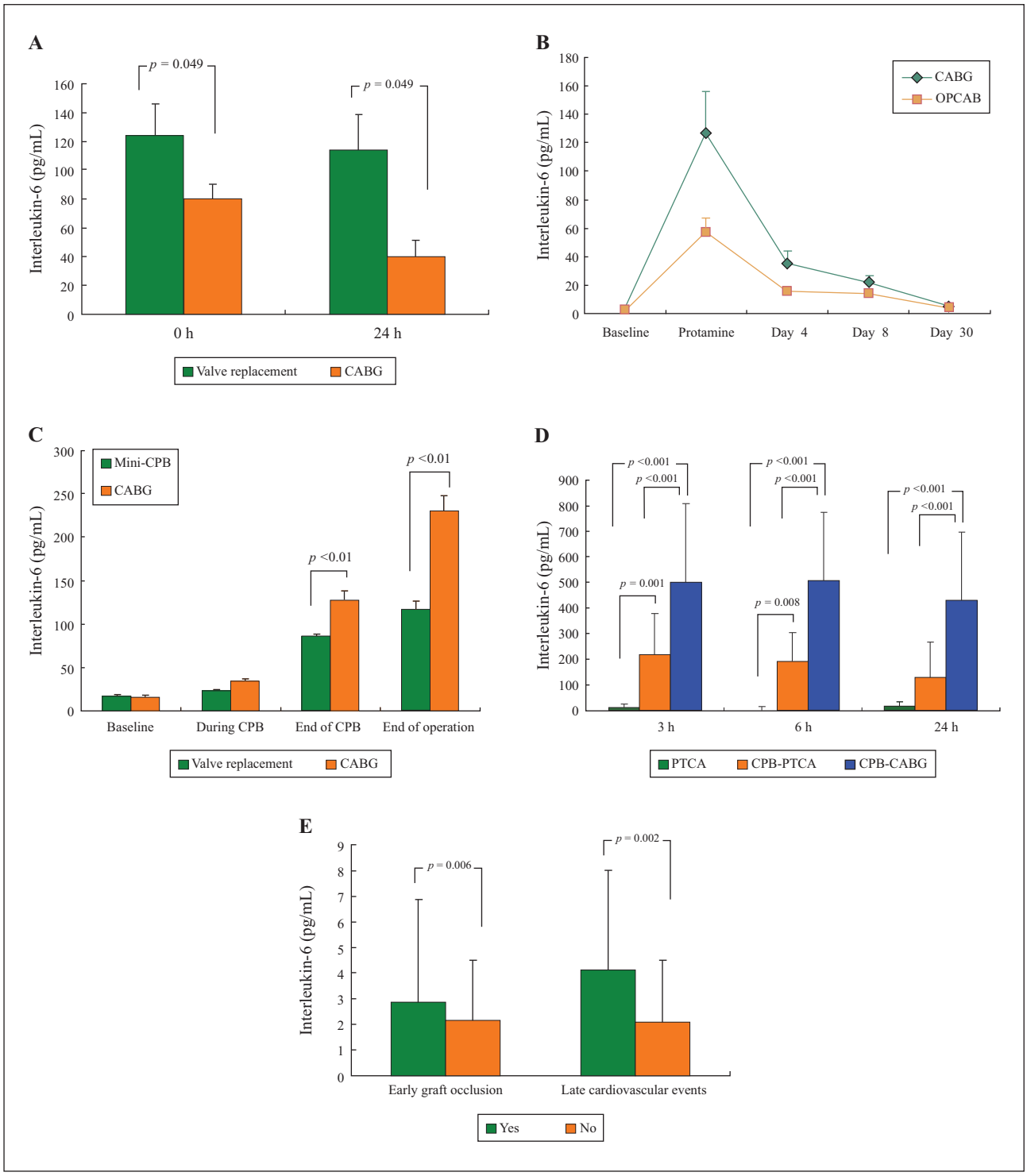

Figure 2

Comparisons of circulating interleukin-6 levels in CABG patients: (A) between patients with CABG (■) and those with heart valve replacement (■) [67]; (B) between on-pump (—◆—) and off-pump CABG patients (—■—) [68]; between min-CPB (■) and conventional CABG patients (■) [72]; and between patients with elective PTCA without CPB (■) , CPB-supported PTCA (■) and on-pump CABG patients (■) [73], and (E) between patients with (■) and without (■) early graft occlusion, and between patients with (■) and without (■) late cardiovascular events. CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; OPCAB: off-pump coronary artery bypass; PTCA: percutaneous transluminal coronary angioplasty.

the cyanotic patients may be explained by the possible effect of chronic congestive heart failure and chronic shunt hypoxemia [79]. Moreover, IL-6 levels were significantly higher in patients with pulmonary artery hypertension compared with non-pulmonary artery hypertension controls (*figure 4B*) [82, 83].

Madhok *et al*. [84] reported that, in pediatric patients receiving congenital heart defect repair, the circulating IL-6 on day 1 after the operation increased to 271 ± 68 pg/mL from a preoperative baseline of 46 ± 12 pg/mL, then declined on days 2 and 3 after the operation, but insignificantly different from the preoperative baseline. The highest circulating IL-6 level was seen on day 1 after the operation as 629 ± 131 pg/mL in patients with a single ventricle, which was proportional to the elongated CPB duration of 106 ± 23 min (*figure 4C*). Gupta *et al*. [85] reported that

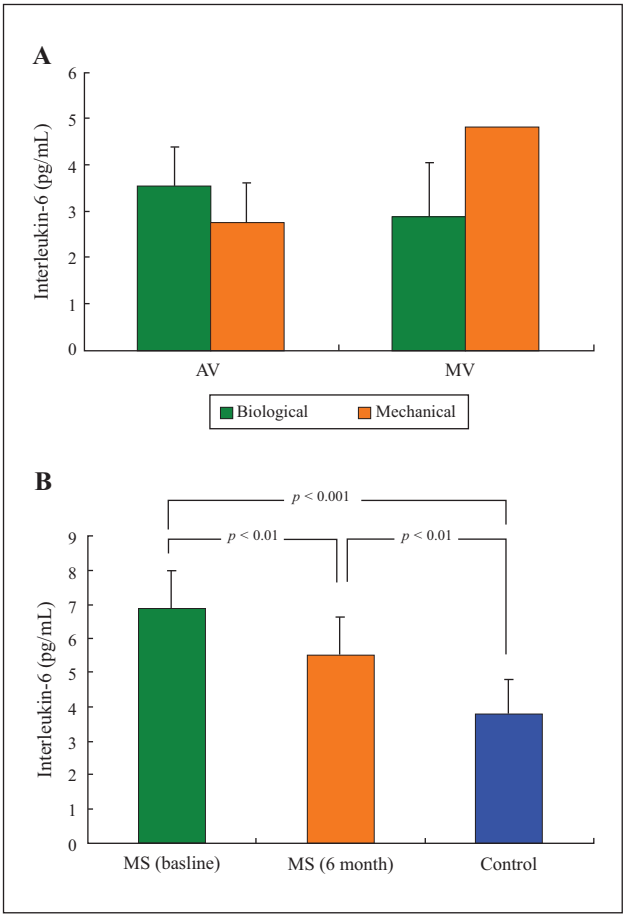

Figure 3
Comparison of circulating interleukin-6 levels in patients undergoing heart valve replacement: (A) between bio- (■) and mechanical (■) heart valve prostheses, and between aortic and mitral implant positions [78]; and (B) between mitral stenosis patients (preoperation (■) and 6 month postoperation (■)) and control (■) [79]. AV: aortic valve; MS: mitral stenosis; MV: mitral valve.

serum IL-6 levels did not differ significantly at post-bypass and at peak time between patients with cavopulmonary anastomosis and those with other corrective operations in the pediatric population (*figure 4D*). The postoperative 2-h IL-6 levels in pediatric congenital heart defect patients correlated with a long cross-clamp time (*figure 4E*) [86] and increased infusions of inotropics, as well as declined arterial oxygenation [87], other than in terms of relating to choices of either a centrifugal or a roller pump (*figure 4F*) [88].

PULMONARY ENDARTERECTOMY

IL-6 is a risk factor responsible for the development of pulmonary artery hypertension by mediating pulmonary artery remodeling via promoting the proliferation of pulmonary endothelial and smooth muscle cells [89]. In the chronic thromboembolic pulmonary hypertension piglet model, the pulmonary IL-6 gene was significantly overexpressed in comparison to sham controls or reperfused animals, indicating that IL-6 activities were associated with hemodynamic status caused by chronic pulmonary artery occlusion [90]. Maruna *et al*. [35] reported that plasma IL-6 peaked 12 h after pulmonary endarterectomy under profound hypothermic circulatory arrest, which was much higher than the preoperative baseline (25 ng/L *versus* 522 ng/L). Whether or not the delayed peak was due to profound hypothermia was unknown. In patients receiving pulmonary endarterectomy, however, IL-6 was significantly higher in the roller pump than in the centrifugal pump group 24 h after the operation (587 ± 38 ng/L *versus* 327 ± 37 ng/L, $p<0.001$) [91].

AORTIC ANEURYSM/DISSECTION REPAIR

According to contemporary theories, an inflammatory process is involved in the formation, expansion, or rupture of abdominal aortic aneurysms (AAAs) [92]. Research showed that IL-6 levels did not differ between patients with acute and chronic aortic dissections and chronic and hypertensive or healthy controls, but did differ between acute and hypertensive or healthy controls [93]. The results suggested differential pro-inflammatory cytokine activities between acute and chronic courses of aortic dissection. Artemiou *et al*. [94] found serum IL-6 levels did not differ between patients with ascending and patients with descending aortic aneurysms (7.58 pg/mL *versus* 6.86 pg/mL, $p = 0.449$). IL-6 levels detected in the aortic tissues were higher in patients with AAAs and thoracic aortic aneurysms compared with controls (*figure 5A*) [95]. Wallinder *et al*. [96] compared plasma IL-6 levels of patients with different sizes of AAAs and found increased IL-6 levels in patients with an AAA >5.0 cm, in comparison to those with an AAA <5.0 cm, albeit without significant difference. However, IL-6 levels in larger AAA patients were significantly higher than in controls (*figure 5B*). Juvonen *et al*. [97] reported that IL-6 concentration was similar, irrespective of dimensions of AAAs and the presence of thrombus. However, other authors [94, 96, 98] stated that IL-6 levels in AAA patients depended on aneurysmal dimensions and even aneurysmal growth rates. The discovery of increased IL-6 in the thrombus of the AAA hinted that the thrombus could be a source of IL-6 due to the leukocyte response and the production of other inflammatory cytokines, such as tumor necrosis factor-α [99]. The intramural thrombus *in situ* in endovascularly repaired patients could explain the stronger inflammatory response during endovascular repair [42]. Cheuk *et al*. [100] noted a rapid peak time for plasma IL-6 in patients with endovascular treatment of type B aortic dissection appearing within hours after treatment, but IL-6 reduced remarkably 6 h and returned to the baseline level 24 h after treatment. Another discovery in their study was that plasma IL-6 levels were directly proportional to the length of the endovascular graft deployed. Gabriel *et al*. [101] observed a plasma L-6 peak appeared 24 h after the endovascular treatment of aortic aneurysms. In their opinion, the IL-6 elevation was due to the contact between the leukocytes and the stent graft. Dawson *et al*. [102] compared the plasma IL-6 levels among three groups of AAA patients: unrepaired, endovascularly repaired, and surgically repaired. In their study, IL-6 levels descended in order in the three groups, namely, the endovascularly repaired AAA patients had a higher IL-6 than those receiving open surgery (*figure 5C*). This was explained by a still-active AAA in the endovascularly treated patients. Stamataki *et al*. [103] reported that, in patients receiving AAA repair, IL-6 levels elevated at the end of surgery, which directly correlated with the aortic cross-clamp time.

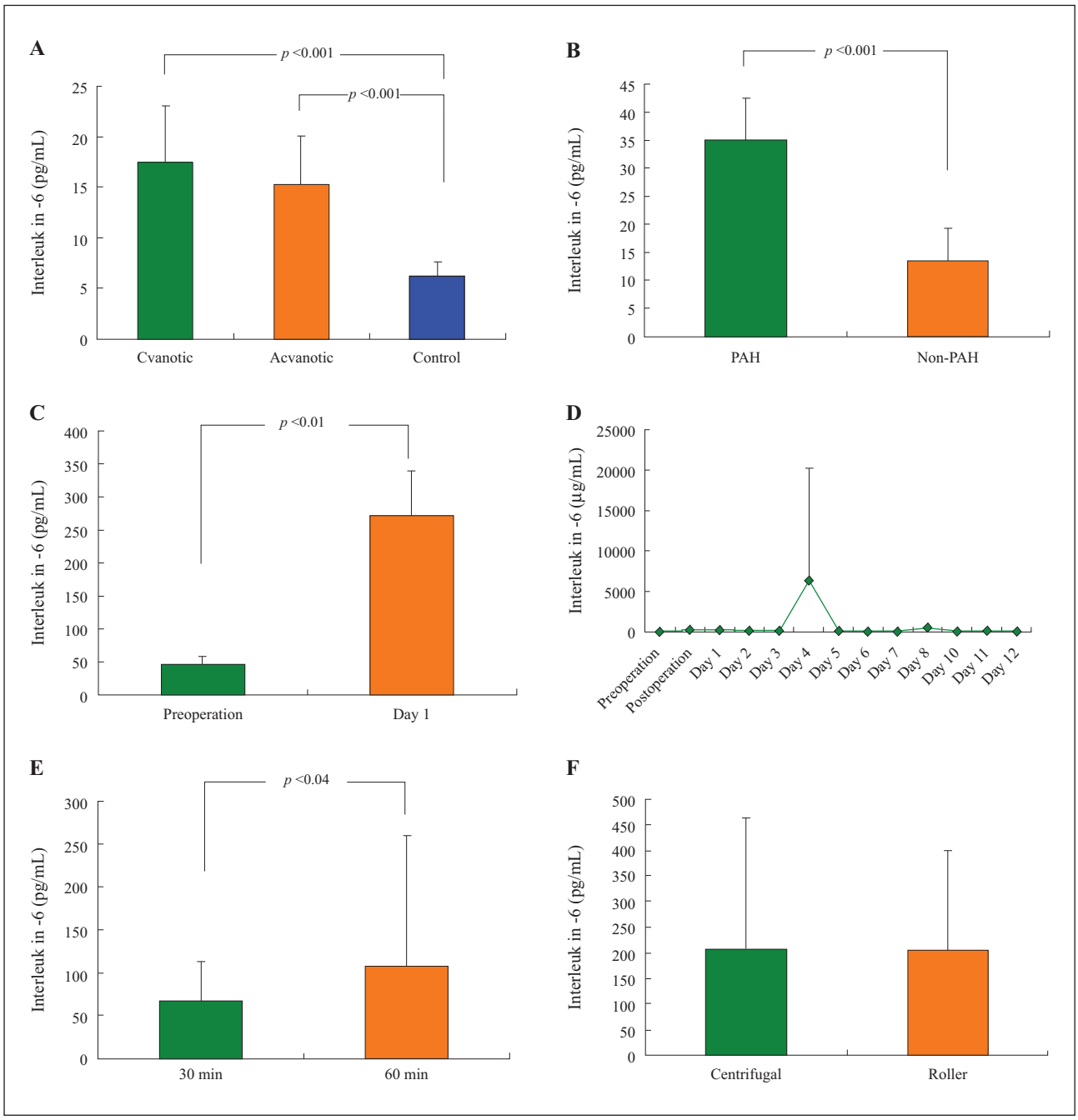

Figure 4

Circulating interleukin-6 levels in patients with congenital heart defects: (A) between cyanotic (■) and acyanotic (■) patients and control (■) [80-82]; and (B) between PAH patients (■) and non-PAH controls (■) [83, 84]; (C) of postoperative day 1 (■) in comparison to preoperative level (■) [85]; (D) kinetic changes in patients undergoing cogenital heart defect repair [86]; (E) between patients with shorter (30 minutes) (■) and longer (60 minutes) cross-clamp time [87]; and (F) between patients with the use of centrifugal (■) and roller pumps (■) [89].

Another study showed cytosolic IL-6 levels of ruptured AAA patients were significantly higher than those of either asymptomatic AAA patients or cadaveric kidney donor controls (*figure 5D*) [104]. The mechanisms of surgically and endovascularly repaired aortic aneurysms for IL-6 reversal remain to be clarified.

CARDIAC MYXOMA RESECTION

Seino *et al*. [105] reported serum IL-6 levels in two patients undergoing cardiac myxoma resections, revealing that serum IL-6 levels were higher before surgery (6 and 9 pg/mL), but fell afterwards (4 pg/mL). Clinical observations on a group of seven cardiac myxoma patients revealed a close correlation between tumor size and preoperative IL-6 levels (*figure 6A*), while myxoma resection led to a significant reduction in circulating IL-6 (*figure 6B*) [106]. Mochizuki *et al*. [15] observed a rapid decline in serum IL-6 after myxoma resection, along with sustained elevation after recurrence. In cases where cardiac myxoma induced intracerebral aneurysms, serum and cerebrospinal IL-6 levels could have been persistently high [16].

HEART TRANSPLANTATION

IL-6 was determined as a sensitive biomarker of allograft rejection based on the significantly elevated IL-6 levels in the severe rejection group, as opposed to the no or

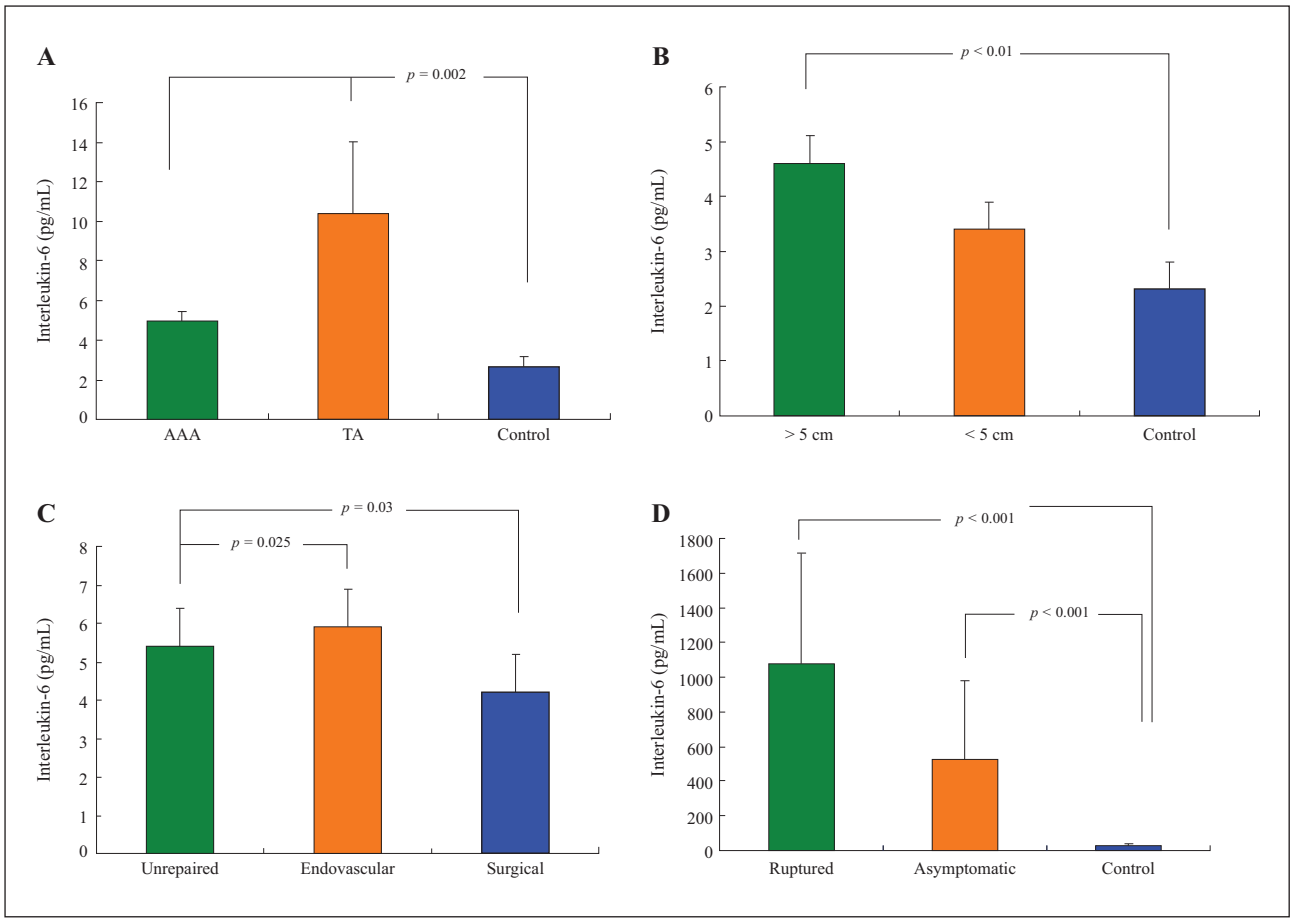

Figure 5

Comparisons of interleukin-6 levels in patients with aortopathies: (A) Aortic tissue interleukin-6 levels between AAA (■), thoracic aortic aneurysm patients (■) and control (■) [97]; (B) Plasma interleukin-6 levels between larger (■), smaller (■) AAA patients and control (■) [98]; (C) Plasma interleukin-6 levels between patients with AAA unrepaired (■), endovascularly repaired (■) and surgically repaired (■) [101]; and (D) Aortic tissue interleukin-6 levels between patients with ruptured AAA (■), asymptomatic AAA (■) and control (■) [104]. AAA: abdominal aortic aneurysm; TA: thoracic aortic aneurysm.

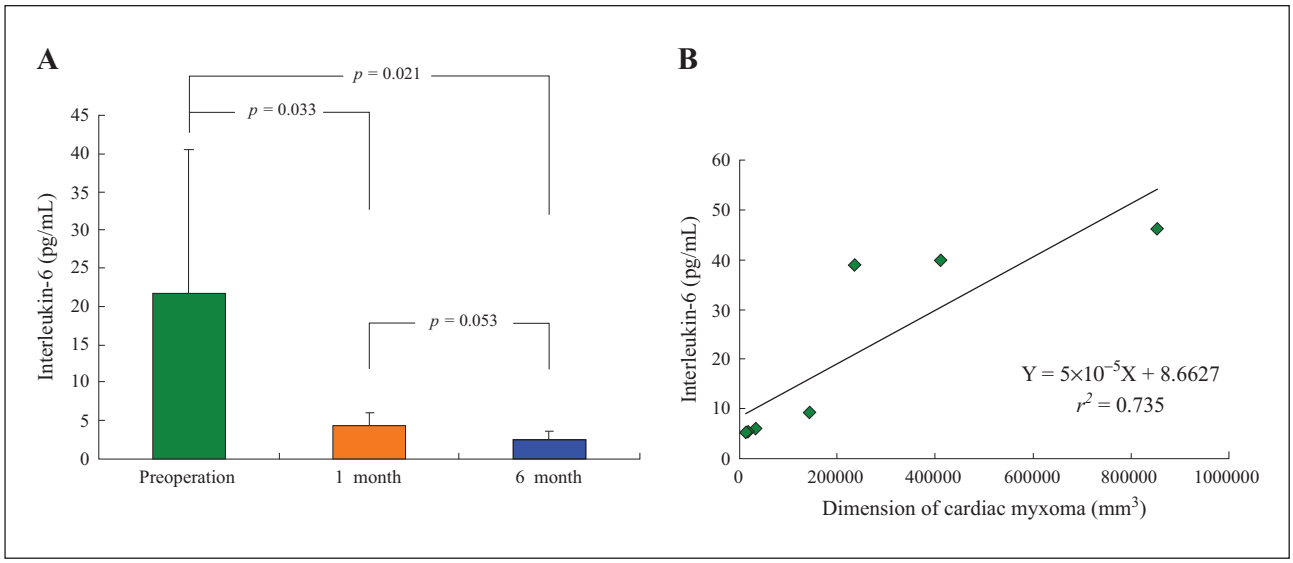

Figure 6

Plasma IL-6 in cardiac myxoma patients: (A) Plasma IL-6 levels were significantly reduced at postoperative 1-month (■) and 6-month follow-up (■) in comparison to preoperative baseline (■) [105]; and (B) A direct correction was shown between plasma IL-6 and dimension of cardiac myxoma [106].

mild rejection group [107]. Similarly, Perez-Villa *et al.* [108] reported that serum IL-6 levels were higher in heart transplant patients with a low grade (0-2) rejection than those with grade 3A or above (*figure 7A*). They stated that patients with serum IL-6 >30 pg/mL were unlikely to develop allograft rejection above grade 3A. Kubala *et al.*

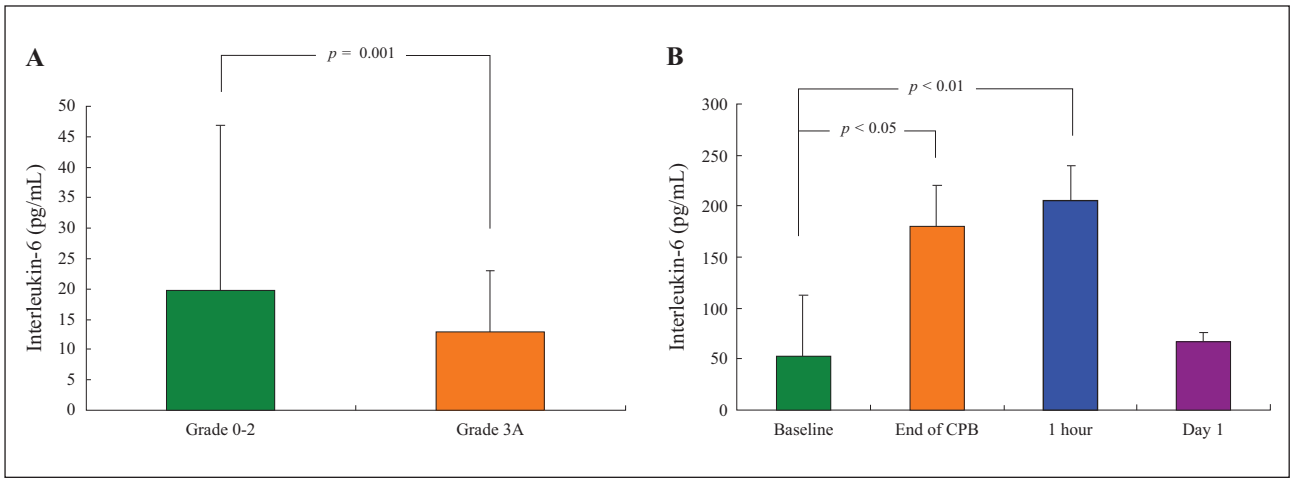

Figure 7

Interleukin-6 levels in heart transplant patients: (A) Grade 0-2 allograft rejection (■) was associated with higher serum IL-6 levels over grade 3A and above (■) [108]; and (B) dynamic changes of interleukin-6 in heart transplant patients [109]. CPB: cardiopulmonary bypass.

[109] reported that plasma IL-6 levels in the early reperfusion period (30 min) were higher in heart transplant patients than in non-heart transplant patients, but the situation was reversed in the late reperfusion period (24 h) with a higher IL-6 level in non-transplant patients, which was probably the result of a lack of immunosuppressive therapy. Wan *et al*. [24] reported a similar elevation-repression trend of plasma IL-6 from early (90 min) to late (12-24 h) reperfusion, finding that IL-6 at the 90-min reperfusion point correlated with ischemic time. As described by Sakai *et al*. [110], plasma IL-6 levels in heart transplant patients remained stable before the start of CPB, decreased after CPB and then increased significantly compared to controls at the end of CPB until 60 min after CPB, before returning to the control value 24 h after the operation (67 ± 9 pg/mL). In non-transplant cardiac surgical patients under CPB, a similar IL-6 elevation was only seen 60 min after CPB (290 ± 76 pg/mL), with the elevation remaining for 24 h (138 ± 42 pg/mL). The results suggested that CPB could have led to IL-6 elevation, but heart transplants brought about an IL-6 turndown due to immunosuppressive therapeutics (*figure 7B*). Birks *et al*. [111] compared serum and myocardial tissue IL-6 levels between unused and used heart donors; however, no significant difference was found in serum IL-6, but IL-6 mRNA was 2.4 times higher in unused than in used heart donors. They ascribed the increased IL-6 mRNA in unused donors to the aforehand infusions of inotropic agents. Plenz *et al*. [112] found that the mRNAs of IL-6, IL6R and gp130 were upregulated in donor and failure hearts, in comparison to controls, with no cardiac chamber difference noted, indicating that donor or failure hearts might produce IL-6 and mediate acute allograft rejection and late transplantation vasculopathy. Circulating IL-6, irrespective of its source (either from the donor heart or from the recipient), would negatively impact the donor heart [113].

LEFT VENTRICULAR ASSIST DEVICE (LVAD) IMPLANT

In all patients, circulating IL-6 levels were elevated shortly after assist device implantation, unless the candidates were not infected or had not deteriorated (*figure 8A*) [114]. Research revealed that LVAD implants were associated with an initial decrease in IL-6 levels up to 90 days after implantation, before recovering to pre-implantation levels (*figure 8B*) [115]. This phenomenon was attributed to cardiac function improvement after LVAD implantation, along with subsequent overt or significant infection or immunosuppression. Goldstein *et al*. [116] found an initial decrease in serum IL-6 at the time of LVAD implantation to 33.6 ± 9 (range: 1.07-106.9) pg/mL, followed by a secondary decline to 11.3 ± 4 pg/mL at the two-month follow-up stage (*figure 8C*), while a late elevation was only observed in patients with a serious device infection. Caruso *et al*. [52] defined a pre-implantation cutoff of serum IL-6 of 8.3 pg/mL, as patients with an IL-6 level above this cutoff point were found to have longer hospitalization duration, poorer cardiac function or more serious complications, such as multiorgan failure. Loebe *et al*. [117] compared two sorts of LVADs and found the axial flow MicroMed DeBakey device was associated with higher IL-6 levels than the pulsatile Novacor device (*figure 8D*). Myocardial and serum IL-6 levels of 23 LVAD implant patients showed higher myocardial IL-6 protein and serum IL-6 in comparison to those of heart transplant patients (*figure 8E*) [118]. However, myocardial IL-6 contents were unlikely to correlate with the cardiac function of LVAD recipients, and incapable of predicting clinical outcomes with respect to circulating IL-6 levels [119].

CONCLUSIONS

In cardiac surgical patients, the expression of IL-6 reflects the inflammatory process in relation to anesthesia, surgical trauma, CPB, and perioperative complications. It also predicts postoperative cardiac function and complications, such as infection, atrial fibrillation, cardiac dysfunction, and myxoma recurrence or metastasis. Preoperative preconditioning or immediate treatment by way of steroids, anesthetics, aprotinin, and ultrafiltration can benefit patients with eliminations of inflammatory cytokine and improvements in their outcomes. Novel therapeutic agents

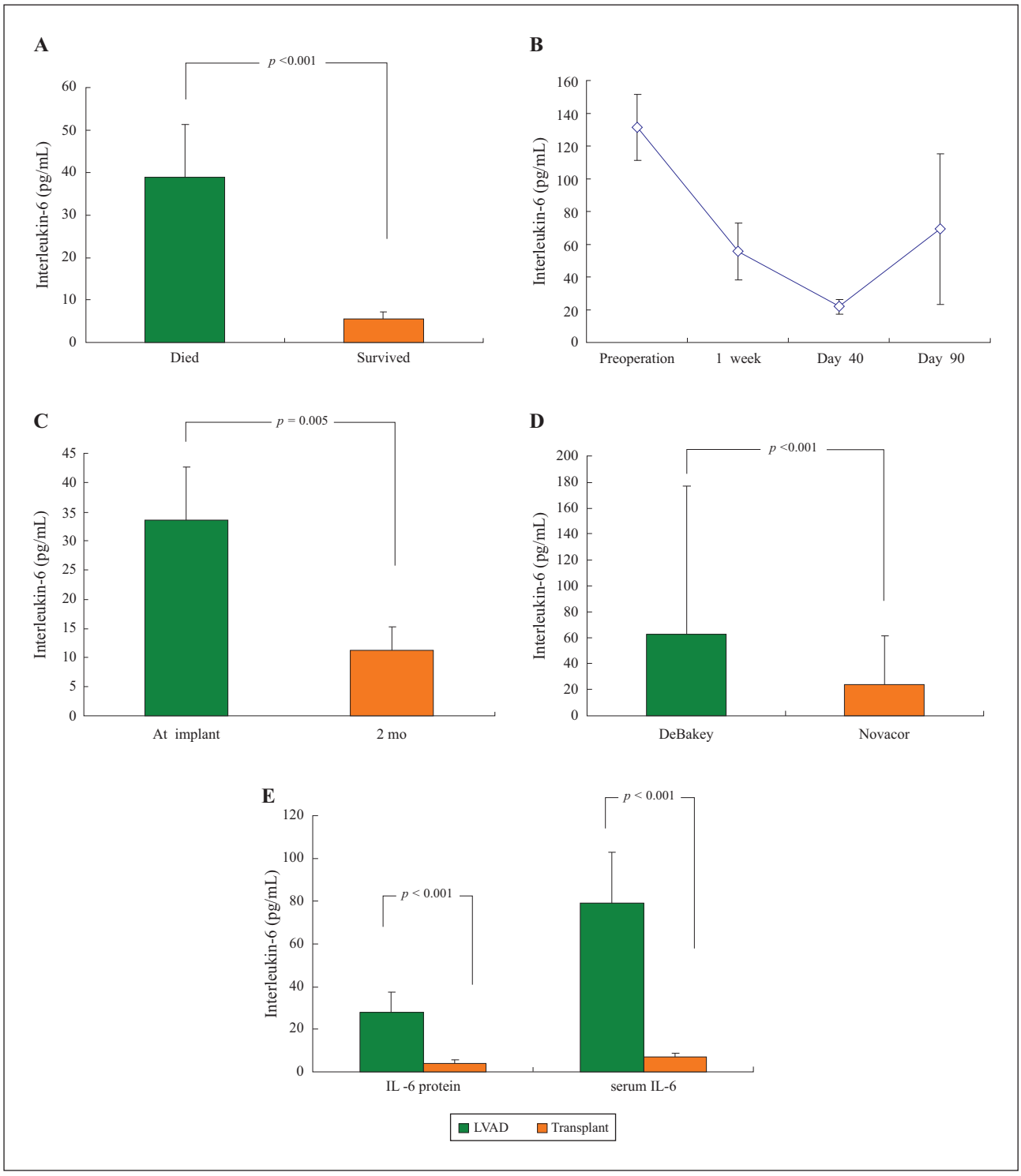

Figure 8

Interleukin-6 levels in patients receiving LVAD: (A) A reduced circulating interleukin-6 shortly after LVAD implant [114]; (B) An initial decrease of IL-6 remained till 90 days after LVAD implant [115]; (C) Initial interleukin-6 reduction (■) was followed by a second decline at 2 month after implant (■) [116]; (D) The axial DeBakey LVAD (■) was associated with higher interleukin-6 levels than pulsatile Novacor LVAD (■) [117]; and (E) Both myocardial and serum interleukin-6 levels did not differ between LVAD (■) and heart transplant patients (■) [118]. LVAD: left ventricular assist device.

for IL-6 elimination, by inhibiting myocardial apoptotic processes, are expected to be developed.

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