

Targeting the proinflammatory cytokine tumor necrosis factor- α to alleviate cardiopulmonary bypass-induced lung injury (Review)

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Abstract. Pulmonary dysfunction is one of the most frequent complications associated with cardiopulmonary bypass (CPB). Multiple factors, including the contact of blood with the artificial surface of the CPB circuit, ischemia-reperfusion and lung ventilator arrest elicit inflammatory reactions, consequently resulting in CPB-induced lung injury. The proinflammatory cytokine tumor necrosis factor- α (TNF- α) has been demonstrated to have a critical role in mediating CPB-induced pulmonary inflammation. The present review evaluated previous studies and summarized the effects of CPB on TNF- α level in the serum and lung tissue of patients and animal models of CPB, the underlying mechanism of TNF- α -mediated lung injury and the therapeutic strategies for the inhibition of TNF- α activity and production to attenuate CPB-induced lung injury. TNF- α level in the serum and lung tissue is significantly increased during and following CPB. TNF- α mediates CPB-induced lung damage by directly inducing apoptosis in alveolar epithelial cells and lung endothelial cells and by indirectly modulating the function of immune cells, including monocytes and macrophages. A functional neutralizing antibody to TNF- α can reduce pulmonary TNF- α production and attenuate CPB-induced lung injury in a rabbit model of CPB. Inhibition of TNF- α function and production using a neutralizing antibody to TNF- α appears to be a promising therapeutic strategy to alleviate CPB-induced lung injury.

Contents

1. Introduction
2. The underlying mechanism of TNF- α -mediated lung injury during CPB
3. Therapeutic strategies targeting TNF- α to attenuate CPB-induced lung injury
4. Effects of anti-inflammatory intervention on TNF- α level
5. Conclusion

1. Introduction

Postoperative pulmonary dysfunction is one of the most common complications associated with cardiopulmonary bypass (CPB) and it is particularly associated with an increased morbidity and mortality in high-risk patients having repeat coronary artery bypass surgery (1). The clinical presentation of CPB-induced lung injury varies from mild dyspnea to fully developed adult respiratory distress syndrome in ~2% of cases undergoing CPB, which, in itself, results in a 50% mortality rate (2,3). The damaged lung following CPB is characterized by abnormal functional, physiological, biochemical and histological alterations, including abnormal gas exchange and poor lung mechanics, increased lung permeability and pulmonary vascular resistance, the presence of neutrophil elastase and high expression of matrix metalloproteinases (MMPs) as well as alveolar edema and extravasation of erythrocytes and neutrophils (4).

Although impairment of lung function can occur following any major surgery, CPB appears to cause additional damage to the lung compared with off-pump coronary artery bypass grafting (5). It has been well recognized that the contact of blood cells with the artificial surface of the CPB circuit can activate polymorphonuclear cells (PMNs) and PMN activity can be further enhanced by proinflammatory factors (6), suggesting increased inflammation associated with CPB. Furthermore, ischemia-reperfusion also significantly contributes to CPB-induced inflammation. Diegeler *et al* (7) observed a significantly increased release of activated complement factors C5a and C3d, interleukin (IL)-8 and IL-10 and prolonged elevation of tumor necrosis factor- α (TNF- α) receptors p55 and p75 in patients undergoing CPB compared with

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the off-pump groups. In addition, postoperative white blood cell, neutrophil and monocyte counts and oxidative stress are also significantly higher in the on-pump than the off-pump group (8,9). Thus, CPB appears to be able to elicit or exacerbate a series of inflammatory reactions, ultimately leading to lung injury. The purpose of this review was to discuss the therapeutic strategies for reducing CPB-induced pulmonary inflammation with a particular focus on the intervention approaches targeting the proinflammatory cytokine TNF- α .

2. The underlying mechanism of TNF- α -mediated lung injury during CPB

Effects of CPB on TNF- α level in the serum and lung tissue. Numerous studies on clinical CPB and animal models of CPB have demonstrated that the serum levels of proinflammatory cytokines, including IL-1, IL-2, IL-4, IL-6, IL-8 and TNF- α are significantly increased during and following CPB (7-13). Wan *et al* (13) summarized the cytokine responses during clinical CPB and illustrated the complexity and diversity of the CPB-induced cytokine response. The present review aimed to focus on the proinflammatory cytokine TNF- α .

Studies on the effects of CPB on the serum level of TNF- α in patients are controversial. Zhang *et al* (10) revealed that the serum level of TNF- α in patients undergoing CPB significantly increases when CPB begins and reaches a maximum following CPB. By contrast, Welters *et al* (14) and Martínez-Comendador *et al* (15) reported that the plasma level of TNF- α is not statistically different pre- and post-surgery. The discrepancy may be due to the different trial design and different experimental procedure in these studies and also the complex chemistry of TNF- α in solution. The diverse baseline of TNF- α in different patients, which is associated with the unique genetic background of each individual may also contribute to this discrepancy. Previous studies have demonstrated that circulating TNF- α level in patients correlates with TNF- α polymorphisms. Boehm *et al* (16) analyzed two polymorphisms from the promoter region of the TNF- α gene, TNF- α -863 C/A and TNF- α -308 G/A. They revealed significant associations of the TNF- α 863 CC variant with higher TNF- α level preoperatively, following CPB and 6 h postoperatively, while the TNF- α 863 AA allele correlated with lower TNF- α level at all time points. Compared with the TNF- α 863 C/A polymorphism, fewer significant associations were detected between the TNF- α 308 G/A polymorphism and TNF- α level. The patients with the TNF- α 308 GG allele have lower TNF- α level immediately following CPB, whereas TNF- α 308 AA carriers are significantly associated with elevated TNF- α level preoperatively and immediately following CPB (16). Studies on the association between TNF- α 308 G/A polymorphism and serum level of TNF- α by other groups demonstrate varying results. Yoon *et al* (17) demonstrated that the TNF- α 308 AA variant correlated with increased TNF- α level, while Galiñanes *et al* (18) did not detect any correlation.

In animal models of CPB in which the genetic background of the experimental animal is more uniform than in humans, including rabbit, piglet and rat models, it is consistently observed that the serum level of TNF- α is significantly increased during and following CPB (11,12,19,20). Notably,

Qi *et al* (11) demonstrated that in a rabbit model of CPB, in addition to a significant increase of systemic levels of TNF- α , the serum level of TNF- α from the left atrium is significantly higher than that from the right atrium (Table I). Furthermore, TNF- α mRNA level in lung tissue is also increased markedly during CPB, suggesting that CPB can induce pulmonary TNF- α synthesis and release (11), which could further exacerbate CPB-induced lung injury.

TNF- α mediates lung injury during CPB. Although direct clinical evidence demonstrating that TNF- α can cause lung damage during and following CPB remains lacking, the association between increased level of TNF- α and pulmonary dysfunction has been indicated in multiple studies. Dauber *et al* revealed that peak circulating TNF levels correlate with CPB-induced coronary and pulmonary vascular injury (21). Studies on a rabbit model of CPB demonstrated that endotracheal administration or pulmonary perfusion of a neutralizing antibody against TNF- α significantly reduced pulmonary edema and alleviated histological damage in the lung (11,12). In a rat model, TNF- α markedly induced pulmonary vascular barrier dysfunction with increased lung water content and impaired oxygenation (22).

The molecular and cellular mechanisms underlying TNF- α -mediated lung injury remain to be elucidated. As a proinflammatory cytokine, TNF- α has been revealed to not only directly induce apoptosis in pulmonary endothelial and alveolar epithelial cells but also trigger a cascade of immune reactions to damage lung function indirectly. Petrache *et al* used bovine pulmonary artery endothelial cells to investigate the molecular mechanism underlying TNF- α -induced endothelial cell apoptosis and barrier dysfunction (23). They demonstrated that TNF- α significantly enhanced apoptosis and stimulated the formation of stress fibers and paracellular gaps by increasing myosin light chain (MLC) phosphorylation through MLC kinase and Rho kinase, which consequently resulted in the reduction of transcellular electrical resistance (23). Wang *et al* (24) demonstrated that human TNF- α induces dose-dependent apoptosis in pulmonary alveolar epithelial cells derived from the human lung carcinoma cell line A549 and primary cultures of well-differentiated type II alveolar epithelial cells from the rat. TNF- α -induced apoptosis requires the induction of angiotensinogen expression, proteolytic processing of the synthesized angiotensinogen protein and the subsequent binding of angiotensin II to its receptor.

At the cellular level, TNF- α has been found to activate and recruit PMNs (25,26). The activated PMNs secrete proteolytic enzymes, including MMPs and elastase and release oxygen-free radicals into the systemic circulation and lung tissue (25). Consequently, this leads to the degradation of pulmonary ultrastructure and permeabilization of pulmonary alveolar cells and endothelium. It has also been demonstrated that TNF- α can regulate the immune capacity of monocytes and macrophages by regulating the expression of toll-like receptors (TLRs). Tsai *et al* (26) used human monocytic THP-1 cells to elucidate that TNF- α can downregulate TLR4 expression and induce intracellular tristetraprolin (TTP) expression through the mitogen-activated protein kinase (MAPK)/extracellular-signal regulated kinase signaling pathway (Fig. 1). Their results from *in vitro* tissue culture are consistent with

Table I. TNF- α level in blood samples (pg/l).

Group	Prior to CPB			5 min after aortic clamp release			CPB termination		
	Right atrium	Left atrium	P-value	Right atrium	Left atrium	P-value	Right atrium	Left atrium	P-value
I	104.40 \pm 14.17	111.55 \pm 16.98	P>0.05	116.27 \pm 32.65	116.76 \pm 20.33	P>0.05	115.88 \pm 30.81	110.90 \pm 28.43	P>0.05
II	110.14 \pm 48.32	94.45 \pm 37.18	P>0.05	240.37 \pm 56.44 ^a	329.24 \pm 69.99	P<0.05	208.25 \pm 39.15 ^a	257.30 \pm 38.22	P<0.05
III	110.61 \pm 38.22	108.25 \pm 22.90	P>0.05	236.73 \pm 41.92 ^a	319.74 \pm 48.11	P<0.05	207.35 \pm 52.11 ^a	266.65 \pm 40.23	P<0.05
IV	110.49 \pm 47.56	113.63 \pm 33.05	P>0.05	212.98 \pm 55.30 ^a	215.49 \pm 56.28	P>0.05	189.84 \pm 37.09 ^a	192.79 \pm 39.43	P>0.05

Group I, open chest operation only; Groups II, CPB only; Group III, CPB+endotracheal intubation with phosphate-buffered saline; Group IV, CPB+endotracheal intubation with TNF- α antibody (2,400 pg/kg). P-values were obtained by the comparison of the right and left atriums in each group as compared with group I, ^aP<0.05 (11). CPB, cardiopulmonary bypass; TNF- α , tumor necrosis factor- α .

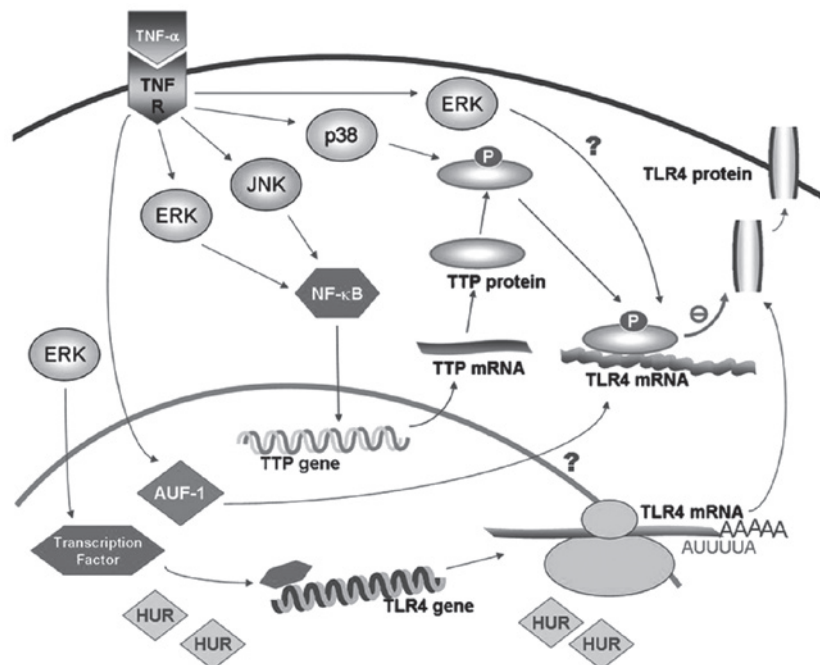


Figure 1. Mechanism underlying TNF- α mediated downregulation of TLR4 expression in monocytic cells. TNF- α and CPB cause MAPK-dependent activation and expression of TTP. ERK1/2 and JNK/SAPK-dependent TTP gene expression and subsequent p38 MAPK-dependent phosphorylation of TTP contribute to TLR4 downregulation of TNF- α -stimulated monocytes (26). TNF- α , tumor necrosis factor- α ; CPB, cardiopulmonary bypass; TLR, toll-like receptor; ERK, extracellular-signal regulated kinase; NF- κ B, nuclear factor- κ B; MAPK, mitogen-activated protein kinase; JNK/SAPK, c-Jun NH2-terminal kinase/stress-activated protein kinase; TTP, tristetraprolin; AUF-1, AU-rich element RNA-binding protein 1.

the observation of clinical samples, which demonstrate that TTP expression increases and TLR4 expression decreases in monocytes following CPB (26).

3. Therapeutic strategies targeting TNF- α to attenuate CPB-induced lung injury

Inhibition of TNF- α production. It has been revealed that p38 MAPK is involved in regulating TNF- α transcription (27). Thus, inhibition of p38 MAPK may be an effective approach to reduce TNF- α production. Dong *et al* pretreated rats using intravenous administration of the specific p38 MAPK inhibitor, SB203580 in 0.5 ml saline 30 min prior to establishing CPB and demonstrated that the pre-treatment not only significantly reduced the mRNA and protein level of TNF- α in lung tissue compared with those in rats undergoing CPB without adminis-

tration of the inhibitor, but also attenuated lung tissue water and CPB-mediated damage (28). However, the expression of other proinflammatory cytokines, including IL-1 β is also significantly reduced by the inhibitor. In addition, the p38 MAPK inhibitor affects the activity of nuclear factor (NF)- κ B, which is also a TNF- α transcription factor but with less specificity (28). Thus, it appears that inhibition of TNF- α transcription factors may induce a global effect on inflammatory reactions during CPB. The possible clinical application of such inhibitors remains inconclusive.

Inhibition of TNF- α activity. Functional neutralizing antibodies against TNF- α appear to be a more specific strategy for inhibiting TNF- α activity compared with the inhibition of TNF- α transcription. Qi *et al* (11) and Yu *et al* (12) demonstrated that in a rabbit model of CPB, neutralizing antibody against TNF- α

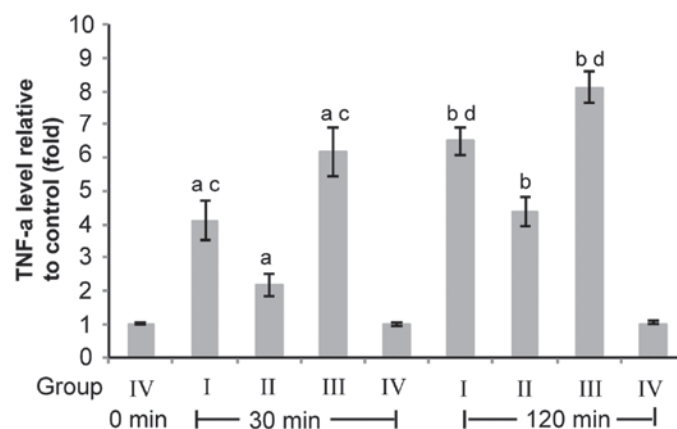


Figure 2. Pulmonary artery perfusion with TNF- α Ab reduces CPB-induced TNF- α overexpression in lung tissue. Group I, CPB+perfusion buffer; Group II, CPB+TNF- α Ab; Group III, CPB only; Group IV, Open heart no CPB. Rabbit lung tissues were collected following CPB for 30 and 120 min for group I-III or following the chest being opened for 30 and 120 min for group IV. β -actin was used as the reference gene. TNF- α level was normalized to the reference gene in each sample. The TNF- α level relative to that of the rabbits in group IV was calculated using the equation $2^{\Delta\Delta CT}$ ($n=10$). Data are presented as the mean \pm standard deviation. ^a $P<0.05$, group I, II and III vs. group IV for 30 min; ^b $P<0.05$, group I, II and III vs. group IV for 120 min; ^c $P<0.05$, group I and III vs. group II for 30 min; ^d $P<0.05$, group I and III vs. group II for 120 min (12). TNF- α , tumor necrosis factor- α ; CPB, cardiopulmonary bypass; TLR, toll-like receptor; Ab, antibody.

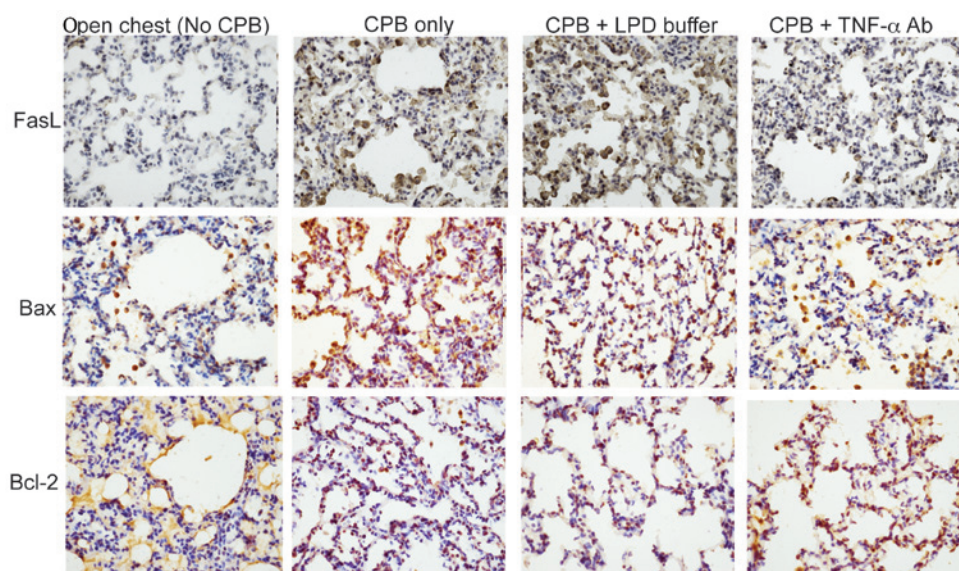


Figure 3. Pulmonary artery perfusion with TNF- α Ab reduces CPB-induced pulmonary apoptosis. Expression of FasL and Bax were significantly increased and the level of Bcl-2 was decreased in alveolar epithelial cells of the rabbits undergoing CPB for 30 min compared with the rabbits without CPB. By contrast, the rabbits that underwent CPB and received pulmonary artery perfusion with TNF- α Ab exhibited significantly less FasL and Bax expression and higher Bcl-2 expression compared with the rabbits that underwent CPB without TNF- α Ab (12). Magnification, x400. Protein expression visualized using immunohistochemical staining. TNF- α , tumor necrosis factor- α ; CPB, cardiopulmonary bypass; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; FasL, Fas ligand; Ab, antibody; LPD, low potassium dextran lung preservation solution.

administered either by endotracheal intubation or by pulmonary artery perfusion alleviates CPB-induced pulmonary tissue damage, prevents CPB-induced lung edema, significantly improves oxygenation index and reduces CPB-induced pulmonary inflammation. In addition to reducing the serum level of TNF- α , Yu *et al* demonstrated that pulmonary artery perfusion with an antibody against TNF- α markedly decreased TNF- α expression in lung tissue (Table I and Fig. 2) (11,12). Studies on ovarian cancer cells and keratinocytes revealed that TNF- α stimulates its own mRNA synthesis in an autocrine manner (29,30). Thus, functional inhibition of TNF- α was able to interrupt the autocrine TNF- α synthesis loop and ultimately reduce TNF- α production. Similar to the study by

Yu *et al*, Szlosarek *et al* also demonstrated that the TNF- α neutralizing antibody infliximab reduces TNF- α mRNA level in ovarian cancer cells by inhibiting the autocrine production loop (29). Thus, functional inhibition of TNF- α appears to be a strategy superior to inhibition of TNF- α transcription factors since it not only specifically inhibits TNF- α activity but also reduces its production. Yu *et al* (12) further investigated the molecular mechanisms underlying TNF- α antibody-mediated attenuation of PBC-induced lung injury. They revealed that TNF- α antibody administered either by endotracheal intubation or by pulmonary artery perfusion significantly reduces CPB-induced pulmonary apoptosis in a rabbit model of CPB (Fig. 3). In addition, Imai *et al* demonstrated that intratracheal

anti-TNF- α antibody attenuates ventilator-induced lung injury in rabbits (31).

TNF- α has been demonstrated to bind at least two receptors, TNFRI-p55 and TNFRII-p75 (32). The extracellular domain of these receptors can be shed into the circulation as soluble TNF- α receptors p55 and p75. Elevation of TNF- α level increases the levels of soluble receptors, which are generated by the cleavage of the membrane-bound TNF receptors by a metalloproteinase after TNF binds to its membrane-associated receptors (33). Elevated soluble TNF- α receptor concentrations have been revealed to be an indication of a systemic inflammatory response (34). The binding of the soluble receptors to TNF- α inhibits the biological activity and prolongs the half-life of circulating TNF- α (35). The inhibitory effect of soluble receptors on TNF- α activity has been demonstrated in an investigation into rheumatoid arthritis. Wooley *et al* demonstrated that a recombinant human TNF receptor, Fc-fusion protein significantly reduced the incidence and the severity of collagen-induced arthritis in mice (36). Thus, application of soluble receptors to inhibit TNF- α activity appears to be another rational strategy for attenuating TNF- α -mediated lung injury during CPB.

The clinical application of antibodies against TNF- α and the soluble TNF- α receptors p55 and p75 has been extensively investigated in human diseases where TNF- α has a critical role in disease development and progression, including sepsis and rheumatoid arthritis. They have been assessed in clinical trials of sepsis treatment. In phase I-III clinical trials, such agents appear to be safe and non-antigenic when they are administered intravenously to septic patients. However, the results of the sepsis trials varied significantly. Thus, the efficacy of TNF- α antibody and the soluble TNF- α receptors to treat human sepsis remains inconclusive. By contrast, the application of those agents in human rheumatoid arthritis has been demonstrated to be effective. In treating arthritis, these agents appear safe, improve disease symptoms in a dose-dependent manner and markedly reduce erythrocyte sedimentation rate and C-reactive protein level, which are indicators of systemic inflammation (37). Therefore, based on the results from studies on the rabbit model of CPB demonstrating that anti-TNF- α antibody can significantly attenuate CPB-induced lung injury (11,12) and the successful clinical application of TNF- α antibodies and soluble TNF- α receptors in human rheumatoid arthritis, it appears that anti-TNF- α antibodies and soluble TNF- α receptors could be promising therapeutic strategies for relief of the pulmonary dysfunction associated with CPB.

4. Effects of anti-inflammatory intervention on TNF- α level

In addition to the strategies directly targeting TNF- α , other anti-inflammatory interventions aimed at alleviating CPB-induced lung injury have been revealed to reduce TNF- α level. For instance, modification of artificial circuits, including heparin-coated and phosphorylcholine-coated circuits are found to significantly reduce systemic TNF- α level (38,39). Pharmacological interventions also appear to effectively inhibit TNF- α production during and following CPB. Administration of corticosteroids prior to CPB or aprotinin following CPB reduces the production of TNF- α and other proinflammatory cytokines (40), while the antibiotic agents moxifloxacin and cefuroxime, which have been demonstrated to inhibit cytokine

release from monocytes and neutrophils, do not attenuate the inflammatory cytokine response to CPB (41).

Statin drugs, which are increasingly recognized as having anti-inflammatory effects, have been widely investigated for their potential protective effects on patients undergoing CPB. Morgan *et al* published a systematic review of clinical trials examining the clinical benefits of pre-operative prophylactic statin therapy for patients undergoing CPB (42). Although the pooled data in their review support that pre-operative treatment with statins attenuates CPB-induced release of proinflammatory cytokines, including IL-6, IL-8 and TNF- α in patients, due to the limited number of studies and lack of rigorous study design in certain trials, the potential anti-inflammatory effects of pre-operative statin therapy remain inconclusive.

5. Conclusion

In the present review, the effects of CPB on TNF- α level in the serum and lung tissue in patients and animal models of CPB were summarized, the molecular and cellular mechanisms underlying TNF- α -mediated lung injury during CPB were discussed and several therapeutic strategies targeting TNF- α to attenuate CPB-induced pulmonary dysfunction were proposed. Although it remains to be elucidated how serum TNF- α level correlates with CPB-associated morbidity in patients and whether serum TNF- α level can predict post-CPB complications, it appears that pulmonary artery perfusion with neutralizing antibody for TNF- α , which can specifically inhibit pulmonary TNF- α production and activity, may be a superior strategy to attenuate CPB-induced lung injury.

The functions of other cytokines, including IL-6, IL-8 and IL-10 must not be ignored. The production and activity of these cytokines are also significantly affected by CPB. TNF- α and other cytokines may act synergistically, ultimately resulting in pulmonary dysfunction during CPB. Thus, restoration of the homeostasis of proinflammatory and anti-inflammatory cytokines may be the key to reducing CPB-induced lung injury.

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