Cytokines in myocardial injury: impact on cardiac surgical approach

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Abstract

Myocardial ischemia-reperfusion injury associated with cardiac surgery is an acute inflammatory process in which activated leukocytes and endothelial cells play a critical role. Recent data indicate that the release of cytokines is crucial in inducing leukocytes and endothelial cells activation during cardiopulmonary bypass (CPB). Some inflammatory cytokines can be produced locally from the heart, particularly interleukin (IL)-8, which may further enhance leukocyte activation and accumulation in the injured myocardium. In fact, postoperative levels of cardiac troponin-I, a highly specific marker of myocardial injury, correlated strongly with IL-8 values in patients undergoing coronary artery bypass grafting (CABG). Off-pump CABG is associated with less IL-8 production compared with conventional procedure, which may in turn reduce the degree of myocardial injury. On the other hand, reduced release of IL-8 and cardiac troponin-I has also been discovered following the use of heparin-coated CPB circuits. In addition, the balance between pro- and anti-inflammatory mediators may be even more crucial in determining the extent of injury. Hence, avoiding the use of CPB or improving the biocompatibility of CPB may lead to better myocardial preservation. Research along these lines is expected to help in the development of ideal therapeutic strategies to minimize the inflammatory response and subsequent myocardial injury associated with cardiac surgery. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Accumulating evidence confirms that the use of cardiopulmonary bypass (CPB) during open heart operations can trigger a whole body inflammatory response, which may induce postoperative morbidity including cardiac dysfunction [1]. The complex mechanisms involved in this inflammatory cascade are yet to be fully understood [1]. Recent investigations have clearly shown that cytokines, a group of low-molecular weight polypeptides which function as intercellular communication molecules, play a central role in inflammatory reactions and particularly in inducing myocardial injury during and after CPB [2-4]. The most studied proinflammatory cytokines include tumor necrosis factor α (TNF-α), interleukin (IL)-6, and IL-8. Meanwhile, the important anti-inflammatory capacity of IL-10 has also been widely known [4]. As our understanding of the underlying pathophysiology evolves, so must the therapeutic strategies. However, the question remains open regarding the clinical feasibility of anti-cytokine interventions (i.e. using various specific antibodies) [1-5]. This article gives a brief overview on the role of cytokines in myocardial injury associated with cardiac operations and, accordingly, discusses some possible treatments.

2. Recent observations

Myocardial ischemia-reperfusion injury is currently believed to be an acute inflammatory process in which activated leukocytes and endothelial cells are primarily involved. It has been noted that CPB can prime polymorphonuclear (PMN) leukocytes and increase the release of superoxide [6], which may be related to the production of cytokines, adhesion molecules, arachidonic acid metabolites, platelet activating factor, nitric oxide (NO), and endothelins (Fig. 1) [1]. The crucial role of cytokines in myocardial injury during CPB has attracted extensive investigations in the past decade [4]. While the influence of some individual mediators on myocardial function during and after CPB has been described, recent attention has focused on the combined effects of different mediators among this complex network. Aiming at reducing the degree of myocardial injury associated with cardiac operations, the
The nature of TNF-induced myocardial depression appears to be biphasic. TNF-α may depress α- and β-adrenergic responsiveness of myocyte in an NO-independent manner [13,14] in the early phase, which probably is mediated by sphingolipid metabolites and relates to the effects of TNF-α on the intracellular calcium transient [15]. TNF-α may also induce myocardial dysfunction through an NO-dependent mechanism in the delayed phase [4,15]. Furthermore, TNF-α has been recently suggested to be a critical factor in initiating the cytokine cascade responsible for myocyte intracellular adhesion molecule-1 induction and subsequent neutrophil-induced injury [16]. Experimental studies have shown that inhibition or neutralization of TNF-α by adenosine [17,18] or monoclonal anti-TNF antibody [19] may reduce myocardial ischemia-reperfusion injury and thereby improve the recovery of cardiac function. Nevertheless, evidence supporting the employment of anti-TNF strategies during clinical CPB has yet to be given.

Meanwhile, recent investigations have implicated TNF-α in the pathogenesis of myocardial ‘programed cell death’ [20]. This process, referred to as apoptosis, is characterized by cell death with the maintenance of cell membrane integrity. Apoptosis and necrosis generally have been considered to represent the two fundamental forms of cell death. Apoptotic cardiomyocytes do not release creatine kinase and may also retain their ability to contract in response to calcium ionophores [20]. It has been proposed that TNF-α may induce cardiac myocytes apoptosis through TNF receptors type 1 (TNFR1) and type 2 (TNFR2) [15]. However, Kurrelmeyer et al. [21] discovered that the frequency of apoptosis peaked significantly earlier in the TNFR1/TNFR2 knockout mice after myocardial infarction, indicating myocardial TNF-α expression may actually play an important homeostatic role. The potential beneficial effect of such an endogenous TNF-α production in myocardial preservation deserves further investigation.

2.2. Interleukin (IL)-6

IL-6 has been consistently associated with the production of IL-6 [4]. The ischemic and reperfused myocardium has been observed to be a major source of IL-6 during CPB [11]. IL-6 mRNA synthesis is accelerated by reperfusion and may be involved in inducing intracellular adhesion molecule-1 [22]. Hence, raised levels of IL-6 have been linked to cardiac dysfunction after CPB [2,8,23], although direct hemodynamic effects of IL-6 are doubtful [4].

Extensive recent investigations have provided insight into the role of IL-6 in the pathogenesis of acute inflammation. IL-6 may be a marker rather than a critical mediator of injury [4]. In the absence of transfusion of blood or blood product, a positive correlation was found between the magnitude of IL-6 release and duration of CPB (but not duration of aortic cross-clamp) [24]. Moreover, IL-6 may have anti-inflammatory effects through direct suppression as well as the induction of the natural antagonist of TNF-α [25]. Even though similar IL-6 production was noted in patients undergoing coronary artery bypass grafting (CABG) through median sternotomy with or without the use of CPB [26,27], a significantly lower release of cardiac troponin-I (a highly specific marker of myocardial injury) was observed in the off-pump group [27]. These findings indicate IL-6 production may be mainly influenced by the degree of surgical trauma (i.e. median sternotomy). Nevertheless, IL-6 is unlikely to be a crucial mediator inducing myocardial injury.

2.3. IL-8

IL-8 is a potent chemoattractant for neutrophil. IL-8 can activate neutrophils as well as T lymphocytes, and to control their trafficking. IL-8 may play a role in lung injury associated with pulmonary leukocyte sequestration following CPB and can also stimulate histamine release [4]. IL-8 is induced only after reperfusion of the ischemic myocardium in animal models [28,29]. A considerable body of clinical evidence has also documented that the myocardium is a
major source of IL-8 during reperfusion after longer duration of ischemia [4], or after acute myocardial infarction (AMI) [4,11]. The release of both superoxide and IL-8 were higher in patients with complicated AMI than in those with uncomplicated AMI, indicating IL-8 is a major contributor to the priming of neutrophils and may subsequently enhance the extent of injury [30]. Complement activation is also known to promote IL-8 expression [28,31]. Correlated with the reduced expression of IL-8, neutrophil influx into the infarcted area was decreased in C6-deficient rabbits subjected to regional ischemia and reperfusion [31]. Interestingly, the stimulus of CPB alone is sufficient to induce IL-8 mRNA production in human myocardium [32], which probably relates to the increased complement active split-products in a cascade sequence by the classic and the alternative pathways during CPB [1].

In as much as neutrophil activation is a critical initial step in ischemia-reperfusion injury, it has become evident that administration of anti-IL8 antibodies in rabbits prevents cardiopulmonary injury [3,33,34]. Indeed, a strong correlation between IL-8 production and postoperative cardiac troponin-I levels has been observed in patients undergoing CABG with or without CPB [27]. However, there is no substantial evidence so far for any relevant mediator (even IL-8) to be the ‘lethal activator’. It should be noted that, in addition to IL-8, other pathways exist for the recruitment of neutrophils to the inflammatory site. For instance, circulating neutrophils from patients undergoing aortic aneurysmectomy show delayed expression of constitutive apoptosis and such a prolonged neutrophil survival may contribute to the inflammatory injury [35]. Nevertheless, IL-8 blockade has no direct effect on PMN apoptosis [36].

2.4. IL-10

In the meantime, the release of an anti-inflammatory cytokine IL-10 is important. IL-10 may play a protective role by suppressing the production of proinflammatory cytokines [4]. IL-10 also exerts its cardioprotective function by inhibiting neutrophil-endothelial interaction [37]. IL-10 may reduce mortality rates and the development of acute lung injury, both experimentally [38] and clinically [39]. In addition, IL-10 can inhibit human vascular smooth muscle proliferation, representing an endogenous source of protection which is potentially important in patients following CABG [40]. Steroid-pretreatment and the use of aprotinin can markedly enhance IL-10 production [4,41], that originates primarily in the liver during CPB [42].

However, it is noteworthy that cytokines act both individually and within a network of interrelated and interacting signals. IL-10 production is often proportional to the release of IL-8 during clinical CPB. For instance, the release of IL-10 during off-pump CABG is lower than in conventional procedure, which could have been related to the reduced production of IL-8 [27]. In combination with the reduction of IL-6 and IL-8, reduced production of IL-10 has also been associated with the use of heparin-coated CPB circuits in patients undergoing heart and heart-lung transplantation [43]. Furthermore, this was associated with reduced postoperative myocardial injury as reflected by a lower release of cardiac troponin-I 12 and 24 h after reperfusion [43]. Thus, keeping a balance between pro- and anti-inflammatory reactions, instead of blocking some individual mediators, may be more crucial in determining the extent of the inflammatory response and the clinical outcome.

3. Therapeutic modalities

Based on an improved understanding of the underlying molecular biological mechanisms, ideal therapeutic strategies could be developed to reduce the inflammatory response and its subsequent damaging effects following open heart surgery. Considering the multifactorial nature of the inflammatory injury, combined interventions may be more efficient than a single approach to improve outcome. Aiming at reducing myocardial injury, some interventions may have clinical implications. These include:

1. Pharmacological strategies such as administration of corticosteroids, aprotinin, antioxidants, and other agents. These interventions mainly target on the inflammatory reactions on account of the material-independent factors during CPB (e.g. surgical trauma, ischemia-reperfusion to the organs, changes in temperature, etc.) [1].
2. Modification of mechanical devices such as the use of heparin-coated CPB circuits [1,43]. Obviously, these strategies are mainly dealing with the material-dependent factors (i.e. the exposure of blood to nonphysiological surfaces and conditions) during CPB.
3. Modification of surgical techniques, such as avoiding the use of CPB (off-pump CABG) [27,44,45].

An interesting example is the steroid pretreatment during CPB. This strategy has been extensively investigated within the past three decades [1,4]. Recent studies have provided further evidence for its role in myocardial preservation. First, although it remains controversial regarding their inhibiting effect on complement activation during CPB [4], steroids can reduce delayed complement activation (1–3 days after surgery) [46]. Such an effect may have important impact on cardiac recovery since the second phase of complement activation is closely associated with postoperative arrhythmia [47]. Second, steroid pretreatment can significantly inhibit the release of endotoxin-induced cytokines in patients undergoing CPB, such as TNF-α, IL-6, and IL-8, but greatly enhance IL-10 production [4]. However, endotoxin levels were found significantly higher at the end of CPB in steroid-pretreated patients than in control patients [48]. In a prospective randomized study, we [49] demonstrated that steroid pretreatment does not increase, but may actually reduce endotoxin release during CPB. These findings may help to understand the mechanism of steroid-
induced myocardial protection. In fact, steroid pretreatment has been reported to improve systolic and diastolic function and hemodynamic stability after CPB in a sheep heart transplantation model [50]. Applying to clinical practice, steroid pretreatment has become a fundamental component of the ‘fast-track recovery’ protocol [46] and has been shown to improve postoperative recovery in both pediatric [51] and adult [46] patients after CPB, as reflected by reduced length of stay in ICU and in hospital.

4. Summary

Numerous studies of the inflammatory response to CPB have implicated cytokine network in the pathogenesis of this ‘final common pathway for perioperative injury’. In particular, inflammatory cytokines play a critical role in inducing myocardial injury. Many investigators noted the importance of studying cytokines locally (on a specific organ) rather than systemically and, meanwhile, studying the interactions of the different cytokines rather than their individual effect. Considering therapeutic intervention, to keep a balance between pro- and anti-inflammatory cytokines may be more important than just simply blocking one of them. The continued explosion in molecular biological knowledge will help to develop ideal therapeutic strategies to reduce the inflammatory response and its subsequent damaging effects associated with open heart surgery.

References


