

# Traumatic Injury as the Inciting Event of Inflammation leading to Sepsis and Cardiovascular Disease: Review of the Literature

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## Abstract

This paper covers trauma as the inciting event of sepsis, complement, procalcitonin, neutrophils in trauma, innate inflammation, cardiovascular disease (CVD) and stress disorders related to posttraumatic stress disorder. Trauma exposure and elevated post traumatic stress disorder (PTSD) symptoms may increase risk of CVD and autoimmunity. Trauma can also induce immune function changes, which can lead to both pro-inflammatory activation known as systemic inflammation response syndrome (SIRS), coronary artery disease, neutrophil extracellular traps. Autoimmunity especially related to systemic lupus erythematosus and lupus nephritis, atherosclerosis, atherosclerotic plaques, reactive oxygen species, the role of interferons and the inflammasome is also included. Therefore, a review of the literature in these areas is important especially for cardiologists related to the many facets of cardiovascular disease.

**Keywords:** Sepsis; Trauma; Cardiovascular disease; Autoimmunity; Atherosclerosis, Reactive oxygen species

## Introduction

### Traumatic injury

One of the leading causes of death worldwide is traumatic injury and its driver to leading to significant mortality is not always related to the trauma itself, but generally due to the ensuing inflammatory process and cascade initiating severe organ injury, hypoxia, sepsis, and ischemia. This pro-inflammatory immune response has been correlated with the high morbidity and mortality in trauma patients. This pro-inflammatory state is referred to as the systemic inflammation response syndrome (SIRS). This review documents the immunological events after trauma and examines the mechanisms and pathways of the inflammatory immune response leading to sepsis and cardiovascular disease.

### Sepsis, SIRS, Complement and Procalcitonin

Severe sepsis and septic shock are among the leading causes of mortality in the intensive care unit where allergists-immunologists are frequently consulted and delay in both referral and admission to critical care can be associated with poor outcomes. Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS) involves multiple mechanisms, including cytokine release, activation of complement, coagulation and fibrinolytic systems [1]. An earlier article that considered some basic aspects of complement biology focused on addressing the complement deficiencies and the role of complement related to host cell entry, pathogenesis of infectious diseases, and apoptosis [2]. Procalcitonin is a biomarker that fulfills many of these requirements, especially in comparison to other commonly used biomarkers, and has demonstrated superior diagnostic accuracy for a variety of infections, including sepsis [3,4]. In sepsis, innate immunity and reactive oxygen species is important. Advances in the understanding of the innate immune response could be potential therapeutic targets for

sepsis since mechanisms involved in the clearance of pathogen toxin from the circulation and potential interventions could be aimed at enhancing clearance mechanisms [4]. In a surviving sepsis campaign, in addition to requiring early detection of sepsis and prompt initiation of antibiotics, early goal-directed therapy protocol requires invasive patient monitoring to guide resuscitation with intravenous fluids, vasopressors, red cell transfusions, and inotropes.

Development and validation of practical methods for accurately assessing optimal fluid administration is needed. Future studies that seek to address these issues will likely benefit from emerging novel techniques, including molecular diagnostics and adaptive trial designs [5].

The incidence of sepsis has increased over the last two decades, a trend likely driven by aging patient populations, the emergence of drug-resistant pathogens, and increased use of immunosuppressive drugs [6,7].

The surviving sepsis campaign develops and promotes evidence-based guidelines and performance-improvement practices aimed at reducing deaths from sepsis worldwide. The most recent guidelines, published in 2013, provide detailed management strategies for acute care, fluid resuscitation, and vasopressor use. In addition, the campaign has developed simple, short protocols for what to do within 3 and 6 hours of recognition of sepsis. These protocols are associated with reduced mortality rates [8].

Therapeutic interventions including fluid resuscitation, hemodynamic monitoring, glycemic control, corticosteroids, antimicrobial therapy and stewardship inform outcomes. Research on biomarkers, use of mesenchymal stem cells, blood purification, immunoglobulins, and antioxidative treatments apropos the immune response may soon yield viable therapies for sepsis [9]. The use of early and appropriate antibiotic therapy is crucial to improved survival rates in severe sepsis

and septic shock. Early antimicrobial therapy along with other supportive resuscitation goals should be achieved to avoid the further development of cellular dysfunction, tissue injury, and overwhelming inflammatory response. It is important to take into account that sepsis is a complex process where several factors play key roles in the pathogenesis: direct effects of bacterial compound, cytokine storm, activation of the endothelium, and subsequently the complement and coagulation process there are some promising therapies to be considered in the future, two of which are of special relevance: innate immunity modulation with the use of infused immunoglobulin (IgM enriched immunoglobulins) and antioxidative therapies [9]. Several biomarkers have been proposed, but it is important to note the use of procalcitonin for targeting treatment duration, and resolution of sepsis. Procalcitonin has also been found useful to implement an appropriate plan of treatment, to measure and tailor the response of the treatment and a good correlation with clinical severity. Monitoring immune status with the use of panels of biomarkers at regular intervals to assess the clinical and immune response seems to be a rational approach to better understand the value of the treatments provided [9].

### **Neutrophils in trauma and innate inflammation.**

The innate immune system has a very prominent role in organ failure after trauma [10]. Polymorphonuclear (PMN) phagocytes and monocytes are the main effector-cells of the innate immune system involved in organ failure and controlled by cytokines, chemokines, complement factors. Major torso trauma can prime and activate PMNs within 3 to 6 hours after injury and postinjury priming of PMNs may create a secondary operation or delayed hemorrhage that activates exuberant PMN cytotoxic superoxide anion  $O_2^-$  rendering the injured patient at high risk for multiple organ failure [11].

### **The impact of trauma on neutrophil function was evaluated**

With trauma-induced changes in neutrophil biology linked to the development of such post-traumatic complications as multiple organ failure and acute respiratory distress syndrome, an area of research within the field of trauma immunology is gaining considerable interest as the manipulation of neutrophil function as a means can potentially improve patient outcome [12].

To protect the host, these phagocytic cells possess an impressive array of microbicides that can be brought to bear on an invading pathogen, including a variety of toxic oxygen radical species and proteolytic enzymes [13].

Neutrophil extracellular traps (NETs) is a recently described cellular phenomenon of the innate immune system [14]. Neutrophils were isolated from 8 trauma patients requiring orthopedic surgery post injury and up to 5 days postoperatively and 4 healthy volunteers provided positive and negative controls [14]. NET formed after major trauma and subsequent surgery contain mtDNA and represented a novel marker of heightened innate immune activation. They could be considered when timing surgery after trauma to prevent systemic NET-induced inflammatory complications [14].

### **Trauma, inflammation and sepsis**

Undiagnosed preexisting comorbidities play a crucial role in determining outcomes following trauma and diagnosis of medical comorbidities may be a marker of access to health care and may be associated with treatment, which may explain the gap in mortality rates between insured and uninsured trauma patients [15]. Trauma can lead to both proinflammatory activation known as systemic inflammation response syndrome (SIRS) and an anti-inflammatory reaction with immunosuppression known as compensatory anti-inflammatory response syndrome. SIRS with proven infection is referred to as sepsis and

it is clinically often difficult to isolate the microbial inoculum, making the differential diagnosis crucial for further therapeutic decisions between SIRS and sepsis difficult [16]. Is an antimicrobial therapy and aggressive search for a septic focus with all its side-effects necessary or is a focused symptomatic therapy of the SIRS the adequate treatment concept? [16] In multiple trauma situations, both syndromes can develop simultaneously, recently described as the mixed antagonist response syndrome (MARS) [17].

Sepsis is the leading cause of mortality especially in non-cardiological critically ill patients with as many as 20 million cases annually with a worldwide and a mortality rate of around 35% [18].

Overall sepsis mortality is approximately 50% in a six-year period (2008-2013) sustained through 2014 and increased compliance with sepsis resuscitation bundle elements in the EDs and inpatient units in the 11 acute care hospitals. Improvements were achieved by engaging leadership; fostering inter professional collaboration, with other leading health care organizations; and developing meaningful, real-time metrics for all levels of staff [19].

Performance metrics can drive change in clinical behavior, improve quality of care, and may decrease mortality in patients with severe sepsis and septic shock [20].

Psychological stress is a proposed risk factor for cardiovascular disease (CVD), and posttraumatic stress disorder (PTSD). Trauma exposure and elevated PTSD symptoms may increase risk of CVD in this population of women, suggesting screening for CVD risk and reducing health risk behaviors in trauma-exposed women may be promising avenues for prevention and intervention [21].

A better understanding of the neurobiology of deleterious stress effects on extinction promises to yield novel approaches to improving therapeutic outcomes for PTSD and other anxiety and trauma-related disorders [22]. A recent retrospective, cross-sectional study evaluated the history of traumatic stress that predicts PTSD symptoms and severity in sudden cardiac arrest survivors [23]. Routine assessment and management were discussed as potential ways to expedite survivors' recovery [23].

### **Trauma and cardiovascular disease**

The relevance and prognostic significance of blunt cardiac injury in severely injured patients was evaluated in a retrospective multicentre study showing that multiple injured patients with blunt cardiac trauma are at high risk to be underestimated and careful evaluation of trauma patients is able to predict the presence of blunt cardiac injury [24]. The frequency of type 2 second-degree and third-degree atrioventricular block induced by blunt chest trauma in the emergency department was evaluated. Patients with blunt chest trauma must need an electrocardiographic evaluation for atrioventricular block upon admission and in the follow-up period [25].

### **Traumatic injury to the coronary tree and cardiac/ vascular Structure**

Acute myocardial infarction and coronary artery dissection following rugby-related blunt chest trauma in France was evaluated [26]. Coronary artery (CA) dissection following blunt chest trauma is a life-threatening and rare event. The study discussed the mechanism, diagnosis, and optimal management of blunt chest trauma-induced CA dissection [26]. Traumatic aortic regurgitation and descending aortic pseudoaneurysm secondary to blunt chest trauma was reported with traumatic aortic regurgitation combined with traumatic pseudoaneurysm of the aortic isthmus following blunt chest trauma, and its successful repair with a hybrid surgical strategy [27]. There are no previous reports in the literature of simultaneous injuries to both the descending aorta and the aortic valve [27].

A case of compression of the ostium of left main CA caused by aortic root intramural hematoma after blunt thoracic trauma was treated with

percutaneous coronary intervention (PCI) [28]. A 46-year-old man had exertional chest discomfort and dyspnea for 4 months, diagnosed as compression of the ostium of left main CA caused by aortic root intramural hematoma, severe stenosis in the ostium of the left main CA. The percutaneous coronary intervention was conducted, and a drug-eluting stent was implanted successfully. The symptoms were improved and the patient had a good recovery after PCI surgery [28].

### **Inflammation, autoimmunity and cardiovascular disease**

The pathogenesis of many autoimmune diseases is based on prolonged activation of the innate immune system [29]. Excessive activation of innate immunity is often the result of a chronic inflammatory process and this inflammation can be induced by exogenous and endogenous alarm factors. Recent discoveries implicate neutrophils as important regulators of both innate and adaptive immunity and in the development of organ damage in systemic autoimmune diseases, including SLE [30]. Thus, recent discoveries support the notion that neutrophils, low-density granulocytes and aberrant NET formation and clearance play important roles in lupus pathogenesis. Future studies should focus on how to selectively target these immunostimulatory pathways in this disease [30].

The incidence of atherosclerotic cardiovascular disease (CVD) is increased up to 50-fold in SLE compared to age- and gender-matched control subjects, and can partly be explained by traditional risk factors [31]. Pathogenic SLE immune responses and atherosclerotic plaques share some characteristics, due to impaired efferocytosis, skewed T cell activation, suggesting the possibility of identifying novel intervention targets [31].

Physicians should be knowledgeable regarding several aspects of autoimmune disorders, especially SLE which may masquerade as another condition [32]. This paper reviewed the link between NF- $\kappa$ B and SLE, B-cells, and cytokines which play a crucial role in the pathogenesis of SLE. These disorders can present to the clinician's clinic and private office regardless of their specialty. Various aspects of SLE, its mechanisms, role of accelerated atherosclerosis, proinflammatory cytokines, and therapeutic approaches were evaluated [33,34].

Multiple studies suggest that these patients have between a 9-fold and 50-fold increase in risk of developing CVD compared with non-SLE patients. These increases result from a combination of traditional risk factors, and dysfunctional immune and inflammatory mechanisms [35]. The relative risk of myocardial infarction is 5–8 times greater than that of the general population, and more than 1/3 of SLE patients exhibit evidence of carotid plaques of coronary artery calcifications [35].

Premature atherosclerosis has been recognized as a major comorbid condition in SLE. Women with SLE in the 35- to 44-year-old age group have an estimated 50-fold increased risk of myocardial infarction compared with age- and sex-matched controls, as well as an increased incidence of subclinical atherosclerosis [36].

Accelerated atherosclerosis is a major cause of morbidity and death in SLE. The purpose of this recent study was to determine whether the prevalence and extent of coronary artery calcium (CAC) is higher in female SLE patients compared with a non-SLE sample from the Multi-Ethnic Study of Atherosclerosis (MESA) [37]. The differences were most pronounced and statistically significant in those aged 45–54 years but were still observed among those aged 55–65 years after controlling for age, ethnicity, education, income, diabetes mellitus, hypertension, hyperlipidaemia, high-density lipoprotein levels, smoking, education and BMI, SLE patients still had a significantly higher prevalence of CAC than controls. Among those with CAC, the mean log Agatston score did not differ significantly between SLE and MESA participants. Women with SLE have a higher prevalence of CAC than comparable women without SLE, even after adjusting for traditional cardiovascular risk factors, especially among those aged 45–54 years [37].

Atherosclerosis is an inflammatory disease. Its lesions are filled with immune cells that can orchestrate and effect inflammatory responses. The first lesions of atherosclerosis consist of macrophages and T cells. Unstable plaques are particularly rich in activated immune cells, suggesting that they may initiate plaque activation [38].

Antiphospholipid syndrome is a rare autoimmune disease characterized by a high tendency of developing thrombotic events, diagnosed in the presence of specific laboratory criteria (positivity for lupus anticoagulant, and the presence of anticardiolipin and  $\alpha$ 2GPI antibodies) [39]. The heart is affected by direct autoimmune actions or thrombosis. Vascular inflammation may play a crucial role in the premature CVD in ARDs and be involved in the development and destabilization of both atherosclerotic lesions and of aortic aneurysms. Inflammation in subintimal vascular and perivascular layers frequently occurs in CVD with a higher frequency in ARD patients. This inflammation is caused by infections and/or autoimmunity, which might have consequences for treatment. Drugs targeting immunologic factors participating in the subintimal inflammation might have a protective effect on CVD and vasa vasorum and cardiovascular adipose tissue may play an important role in atherogenesis [40]. Inflammation and complement depositions are likely to contribute to vascular stiffness and there is a need for an improved CVD prevention in ARDs [40].

Atherosclerosis is a chronic disease of the arterial wall with immunoinflammatory mechanisms involved with formation of early fatty streaks when the endothelium is activated and expresses chemokines and adhesion molecules leading to infiltration into the subendothelium [41].

Inflammatory responses accompanying acute coronary syndrome (ACS) with that following coronary plaque rupture caused by coronary angioplasty (PCI) were evaluated [42]. Twenty-seven consecutive subjects with either ACS or treated with PCI in the subacute phase of ACS had serial evaluation of circulating interleukin (IL)-2, IL-8, IL-10, interferon (IFN)- $\gamma$  and tumor-necrosis-factor (TNF)- $\alpha$  levels. Coronary plaque rupture may be presumed as being the main responsible for increased circulating cytokine levels in this early phase [42].

Tenascin-C, a glycoprotein of the extracellular matrix increases the expression of metalloproteinases leading to plaque instability and rupture, resulting in ACS [43]. A high serum tenascin-C level could be associated with plaque rupture in ACS patients and tenascin-C levels are associated with pathologic conditions in ACS in the presence of ruptured plaque [43].

Epicardial fat volume (EFV) is increased in patients with ACS and lipid-rich plaques have been associated with acute coronary events. EFV was associated with lipid-rich plaque in patients with ACS, whereas no correlation between EFV and coronary plaque profile was apparent in SAP patients. Epicardial fat may have a role in the development of lipid plaque, which contributes to the pathogenesis of ACS [44].

### **Reactive Oxygen Species**

ROS plays an important role in both acute and chronic kidney injury. Quinones can be nephrotoxic or nephro-protective and many factors play a role in the interaction between quinones and the kidney [45].

Nanomaterials, are increasingly used in medical diagnosis and treatment every day. The use of such materials has helped deliver drugs across the blood-brain barrier [46]. The mechanisms by which the inflammatory response and ROS production occur was discussed [46].

ROS and oxidative stress are important features of CVD including atherosclerosis, hypertension, and congestive heart failure [47]. There are several sources of ROS known to be active in the cardiovascular system. This review addressed ROS sources in CVD, both animal and human data defining how ROS contribute to physiology and pathology [47].

## Role of Interferons

A paper in particular focused on progress over the past year in clinical and basic aspects of SLE-driven accelerated atherosclerosis [48]. CVD is a major complication of lupus and is now a leading cause of death. Type I IFNs may play a critical role in lupus CVD pathogenesis, and it is recommended that vascular outcomes be included in ongoing trials testing the efficacy of anti-IFN biologics [48].

A recent paper closely explored the role of interferons in endothelial cell apoptosis and vascular IFN in the development of premature atherosclerosis of SLE patients. An imbalance between endothelial cell damage and repair develops as a result of alterations in EPCs and CACs which is mediated by IFN- $\alpha$ , IFN- $\beta$  promotes atherosclerosis by various mechanisms by affecting adhesion and migration of leucocytes to plaques by promoting rupture. Understanding the role of IFN in promoting premature atherosclerosis is critical to the development of appropriate target therapy [49].

CVD due to accelerated atherosclerosis is the leading cause of death in patients with SLE. A recent paper associated with SLE stated. high levels of IFN- $\alpha$  production by TLR 9-stimulated pDCs is associated with an increased frequency of circulating pro inflammatory CD4+CXCR3+T cells, increased production of CXCR3 ligands by endothelial cells and an increased recruitment CD4+CXCR3+ T cells into the arterial wall and the development of atherosclerosis [50].

## Role of the Inflammasome

The effects of IFN- $\alpha$  are complex contributing to an elevated risk of CVD by suppression of IL-1 $\beta$  pathways and upregulation of the inflammasome machinery and potentiation of IL-18 activation [51]. Aside from CVD, the inflammasome is also involved with SLE.

## Conclusion

This paper documents the immunological events after trauma and examines the mechanisms and pathways of the inflammatory immune response leading to sepsis and cardiovascular disease. It has covered sepsis, SIRS, complement, procalcitonin, neutrophils and innate inflammation. Trauma exposure and elevated post traumatic stress disorder, symptoms may increase risk of CVD, induce immune changes, leading to both pro-inflammatory activation or SIRS and sepsis, neutrophil extracellular traps. Autoimmunity especially related to SLE, with atherosclerosis, atherosclerotic plaques, ROS, interferons and the inflammasome is also covered. These areas are important especially for cardiologists related to the many facets of cardiovascular disease.

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