International Journal of Surgery (2005) 3, 129–140

INTERNATIONAL JOURNAL OF SURGERY

www.int-journal-surgery.com

REVIEW

The systemic inflammatory response syndrome and cardiopulmonary bypass

J.R.S. Day*, K.M. Taylor

Department of Cardiothoracic Surgery, Hammersmith Hospital, Du Cane road, London W12 0HS, UK

KEYWORDS
Cardiopulmonary bypass;
Inflammation;
SIRS;
Cardiac surgery

Abstract Cardiac surgery using cardiopulmonary bypass (CPB) provokes a systemic inflammatory response. This is mainly triggered by contact activation of blood by artificial surfaces of the extracorporeal circuit. Although often remaining subclinical and resolving promptly at the end of CPB, in its most extreme form this inflammatory response may be associated with the development of the systemic inflammatory response syndrome (SIRS) that can often lead to major organ dysfunction (MODs) and death. Here, we review the pathophysiology behind the development of this ''whole body'' inflammatory response and some of the methods currently used to minimise it.

Introduction

When tissues are injured they attempt to eliminate the cause of injury by mounting an inflammatory response. When the injury is particularly severe, or when the injury is more generalised, a systemic inflammatory response can take place. This systemic inflammation manifests itself clinically as the systemic inflammatory response syndrome (SIRS).[1] Multiple factors associated with the use of cardiopulmonary bypass (CPB) contribute toward the generation of perioperative SIRS. These include the generation of shear forces from roller pumps driving blood through the bypass circuit, hypothermia as blood is passed through the extracorporeal circuit, and contact activation of plasma protein systems as circulating blood is exposed to artificial surfaces in the bypass circuit. This is then followed by the generation and release of endogenous inflammatory mediators leading to the development of SIRS. Here, we will review the pathophysiology of the plasma protein systems that become activated during CPB leading to SIRS and also some of the therapeutic strategies employed to counterbalance the deleterious effects of their activation.

Cardiopulmonary bypass activates the coagulation system

Although new concepts have been proposed,[2] the coagulation cascade which results in thrombus

* Corresponding author.
E-mail address: j.day@ic.ac.uk (J.R.S. Day).

1743-9191/$ - see front matter © 2005 Surgical Associates Ltd. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijsu.2005.04.002

formation is classically thought to be the result of two pathways, intrinsic and extrinsic, which consist of a series of enzyme cascades utilising blood coagulation factors, the most important being thrombin.[3]

The intrinsic pathway begins after contact activation of blood from exposure to collagen in a damaged vascular wall, or exposure of the blood to an artificial surface such as an extracorporeal circuit. In response to these stimuli, two events occur. Firstly, Factor XII (*Hageman Factor*) is converted from its inactive form (*zymogen*) to an active form Factor XIIa. Secondly, platelets are activated. This activation of Factor XII to XIIa is further amplified by plasma kallikrein via a positive feedback loop. Factor XIIa then enzymatically activates Factor XI to Factor XIa which then converts Factor IX to Factor IXa and Factor IXa then converts Factor X to Factor Xa. This activation of Factor X is greatly accelerated by the presence of Factor VIIIa — deficiency of which results in haemophilia. Activated Factor X functions as a protease to convert the inactive molecule prothrombin to the active form thrombin. Thrombin then cleaves fibrinogen to fibrin, which then polymerises to form fibrin strands.

In the extrinsic pathway, the initial stimulus is trauma to the vascular wall, resulting in exposure of blood to non-vascular tissue cells that express an integral membrane protein called 'tissue factor'. Factor VII is a circulating plasma protein that then binds to tissue factor, creating a complex. In doing so, Factor VII is activated to Factor VIIa. This complex, in the presence of Ca^{++} and phospholipids, activates Factor X to Factor Xa. Once Factor Xa is generated, the remainder of the cascade is similar to the intrinsic pathway (Fig. 1).

Surgery using CPB results in extensive activation of both intrinsic and extrinsic pathways of the coagulation system.[4] This necessitates the use of systemic heparinisation to prevent clot formation in the extracorporeal circuit, which brings with it risks of platelet activation (heparin induced thrombocytopenia)[5] and aldosterone inhibition leading to hyperkalaemia.[6] However, despite heparinisation inhibiting clot formation, activation of the coagulation system still occurs as heparin inhibits the coagulation system only at the end of the cascade (by promoting the activity of antithrombin III).[7,8] Molecular markers of thrombin generation such as thrombin—antithrombin III complex (TAT) and prothrombin fragment (PF1 + 2) remain elevated perioperatively in patients undergoing CPB demonstrating that thrombin generation is still occurring.[4]

Cardiopulmonary bypass activates the fibrinolytic system

To prevent excessive activation occurring, regulatory mechanisms exist that serve two main functions — firstly to limit the amount of fibrin clot formed to avoid ischaemia of tissues and secondly to localise clot formation to the site of tissue or vessel injury, thereby preventing widespread thrombosis. The continuous generation of cross-linked fibrin would create a clot capable of obstructing normal blood flow. Therefore, the fibrinolytic system exists as a counterbalance to the coagulation system. Plasminogen is an inactive protein synthesised mainly by the endothelium,[9] and can be converted to its active form plasmin by tissue plasminogen activator (t-PA). Plasmin then has the ability to degrade fibrin strands, preventing the build-up of excess clot.

The use of cardiopulmonary bypass results in increased fibrinolytic activity as shown by increases in D-dimer levels, and t-PA activity.[4] This activation of fibrinolysis is caused by elevated levels of Factor XIIa and kallikrein as well as by an increase in t-PA. Elevated D-dimer levels have been correlated with increased blood loss and postoperative bleeding time. Additionally, activation of fibrinolysis may also affect other aspects of haemostasis such as reduced platelet adhesion and aggregation capabilities due to redistribution of glycoprotein Ib and IIb/IIIa receptors.[10]

Cardiopulmonary bypass activates the complement system

The complement system provides an innate defence against microbial infection and is a ''complement'' to antibody mediated immunity. The complement system consists of 35 interacting plasma and membrane associated proteins which contribute to host defence by initiating and amplifying the inflammatory response. Also, contained within this system are several soluble factors that prevent spontaneous complement activation from occurring, as well as several regulatory proteins that protect host cells from accidental complement mediated attack.[11,12]

Activation of the complement system is achieved through three major pathways: the classical pathway, which is activated by certain antibodies bound to antigens (immune complexes); the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody; and the lectin pathway, which is activated by a plasma lectin that binds to mannose residues on microbes.[11—13]