

Review Article

Systemic Inflammation Induced by Cardiopulmonary Bypass: A Review of Pathogenesis and Treatment

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ABSTRACT

The acute respiratory distress syndrome (ARDS) is a severe alteration in lung structure and function that develops secondary to a traumatic stimulus. When ARDS develops following cardiopulmonary bypass (CPB) it is known as postpump syndrome (PPS). ARDS can be caused by a single massive insult ("hit"); however, sequential minor insults ("hits") are more common clinically. The concept of multiple sequential insults causing ARDS has been termed the "two-hit" model of ARDS. The purpose of this article is to summarize our studies testing the hypothesis that PPS is caused by multiple sequential insults. To confirm our hypothesis, we developed a porcine model of "two-hit" PPS. Our model was composed of sequential benign insults, with CPB as the "first hit" and low dose of endotoxin as the "second-hit." It is our hypothesis that the mechanism of PPS is CPB-induced priming of polymorphonuclear leukocytes (PMNs) ("first-hit") with subsequent PMN activation by a second insult ("second-hit") such as endotoxin. Our model confirms this clinically relevant postulate, and we provide strategies to disrupt the inflammatory cascade leading to PPS.

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INTRODUCTION

The acute respiratory distress syndrome (ARDS) is a severe alteration in lung structure and function characterized by hypoxemia and decreased compliance with diffuse radiographic infiltrate because of increased lung microvascular permeability. ARDS develops when a whole body inflammatory response occurs following severe trauma. In effect, the immune system over reacts to an inflammatory stimulus and attacks the major organ systems, with the lung being the first organ attacked. It is now believed that ARDS is caused in the majority of patients by multiple, sequential, relatively minor insults rather than by a single massive injury. This has been termed the "two-hit hypothesis of ARDS". The "two-hit" hypothesis was formulated following the observation that trauma patients ("first-hit") who experienced a second inflammatory stimulus, such as hypoxia, ischemia, or infection ("second-hit"), developed ARDS (1, 2). When ARDS develops following cardiopulmonary bypass (CPB), it is known as postpump syndrome (PPS)(3, 4). Because the pulmonary pathophysiology of ARDS and PPS are similar, our laboratory hypothesized a "two-hit" model of postpump syndrome similar to that suggested for ARDS. Much of this paper reviews our work investigating the "two-hit" hypothesis of PPS and various treatment regimens used to reduce morbidity and mortality in our PPS model.

PATHOPHYSIOLOGY OF POSTPUMP SYNDROME

Approximately 1.4% of CPB patients develop postpump syndrome every year (3, 4). CPB causes systemic activation of both plasma protein (complement cascade, coagulation cascade, and kallikrein-kinin) and cellular defense systems (endothelial cells, macrophages, monocytes, lymphocytes, and neutrophils) (5–8). The systemic inflammatory response syndrome (SIRS) is the term used to describe this whole body inflammatory response and suggests that CPB has elicited a "first-hit." In most cases, SIRS resolves without incident (9). We believe that if the CPB patient is subjected to a "second-hit," such as infection, SIRS will progress into the PPS. PPS is associated with a very high mortality (50%) (10).

The paradigm shown in Figure 1 depicts our hypothesis of the sequence of events that leads to postpump syndrome. Lung injury does not usually develop following CPB unless a second relatively minor insult ("second-hit") occurs that activates sequestered polymorphonuclear neutrophils (PMN). A "relatively minor" insult is one that by itself does not cause postpump syndrome. CPB constitutes the "first hit" and causes priming of PMN and alveolar macrophages (MØ). MØ reside in the alveolar air space and release chemokines. When activated through a "second hit," chemokines cause diapedesis of PMNs from the pulmonary capillaries into the alveolus. PMN diapedesis occurs by release of proteases that dissolve the al-

Pathophysiology of Post-Pump Syndrome

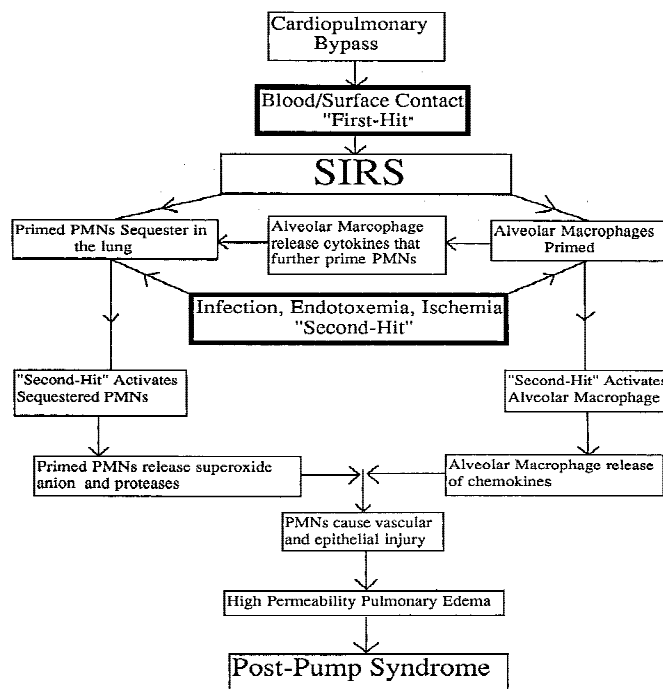


Figure 1: Diagram of the hypothesized development of postpump syndrome. CPB causes systemic inflammatory response syndrome (SIRS) mainly attributable to blood/perfusion circuit surface contact. Polymorphonuclear neutrophils (PMNs) are primed and sequester in the lung but do little damage until activated. Alveolar macrophages (MØ) release cytokines, which further recruit PMNs. A "second-hit" (in our model a small dose of endotoxin) following CPB activates both PMNs and MØ. Activated PMNs generate superoxide anions and proteolytic enzymes. Activated MØ release chemokines, which cause the diapedesis of PMNs into the alveolus. The diapedesis of PMNs is responsible for the vascular injury and high permeability edema, which ultimately results in postpump syndrome.

veolar-capillary basement membrane. Destruction of the basement membrane allows a protein-rich plasma to flood the alveolus causing a high pulmonary edema.

INITIATOR OF POSTPUMP SYNDROME: TUMOR NECROSIS FACTOR (TNF)

Tumor necrosis factor (TNF) is released during CPB and following exposure to endotoxin (8). TNF is one of the body's primary mediators of inflammation acting early in response to trauma and producing systemic inflammation. If injected systemically into test animals, TNF will mimic the symptoms of septic shock and cause ARDS (11). However, the biologic importance of TNF correlates with the magnitude and location of expression. In response to a local injury, TNF plays an important role in immune cell activation and propagation of the inflammatory response. Under these circumstances TNF orchestrates both autocrine and paracrine effects on surrounding cells that initiate, maintain, and resolve local inflammation. If

TNF reaches a concentration sufficient to spill into the systemic circulation, it causes immune cell activation and alteration in physiology. Increased circulating levels of TNF cause fever, lethargy, loss of appetite, and cachexia (12). Dysregulation of TNF production is associated with high morbidity and mortality rates and mediates the pathophysiology of sepsis and multiple organ failure (11). Thus, release of TNF into the circulation is one of the possible initiators of the systemic inflammatory response that causes PPS.

EFFECTOR OF POSTPUMP SYNDROME: POLYMORPHONUCLEAR NEUTROPHIL (PMN)

The primary inflammatory cell that effects the tissue damage responsible for PPS is the PMN. PMNs are believed to be responsible for the majority of the pathophysiology associated with ARDS. The "first-hit" primes the PMN. The "second-hit" activates PMNs causing the sequestered, primed PMNs to generate superoxide anions and proteases precipitating lung injury and ARDS (Figure 2).

Numerous studies support the theory of neutrophil priming and activation in the pathogenesis of postinjury multiple organ failure (13–18). The "first hit" in Moore's animal model consists of 45 minutes of gut ischemia followed by reperfusion (I/R). They demonstrated that gut ischemia activates gut phospholipase A₂ (PLA₂), which is a key enzyme in the generation of platelet activating factor (PAF). PAF is a potent PMN priming agent. PMN priming consists of up-regulation of both NADPH oxidase, which catalyzes the formation of superoxide anion and the adhesion receptors CD11/CD18. Primed PMNs begin to sequester in the pulmonary vasculature because of CD11/CD18 up-regulation, and, if activated, they have the ability to generate large amounts of superoxide anion. These investigators have demonstrated that gut I/R primes PMNs,

causing them to sequester in the lung without any associated lung injury. However, if a small and otherwise benign dose of endotoxin ("second hit") was introduced while the PMNs were sequestered in the lung, irreversible lung injury occurred (13).

It is our hypothesis that CPB acts similar to gut I/R and primes PMNs. Possible mechanisms for PMN priming by CPB include PAF formation secondary to reduced gut perfusion during CPB (19) or contact between blood and foreign surfaces in the perfusion apparatus (20). The primed PMNs up-regulate NADPH oxidase and CD11/CD18 and sequester in the lung (13). Subsequent exposure to a "second hit," such as endotoxin, which may also be released into the blood with reduced gut perfusion, activates the PMNs, and ultimately results in post-pump syndrome.

PMN-INDUCED TISSUE DESTRUCTION: OXYGEN METABOLITES OR PROTEASES

The mechanism by which PMNs cause lung injury in post-pump syndrome and ARDS is controversial. Two hypotheses have evolved and center on which of the toxic chemicals from PMNs is the primary source of tissue injury (21, 22). Although the PMN has approximately 50 toxins in its armamentarium, they are subdivided into two categories according to the location in the PMN: (1) *plasma membrane bound*, which consist of NADPH oxidase and the family of reactive oxidizing chemicals; and (2) *intracellular granules* consisting of microbicidal peptides, proteins, and enzymes. The first hypothesis identifies oxygen metabolites as being the most destructive toxins released from the PMNs (21). The most powerful oxidant generated by the PMN is hypochlorous acid (HOCl). *In vitro* experiments have demonstrated that HOCl can directly damage cellular membrane, and the less reactive chloramines can diffuse into the cell and damage cytosolic components (23). Blocking the generation of HOCl with such agents as HOCl scavengers prevented cell injury, and it was concluded that the reactive oxygen species were the most destructive toxins generated by the PMN (24). However, the above *in vitro* experiments were performed in plasma-free buffers. If the above experiments are performed in a plasma solution, HOCl reacts with plasma proteins to form chloramines. These chloramines have strong microbicidal activity but do not damage normal tissues. It has been demonstrated that 0.5% HOCl is toxic to human tissue only in simple buffer systems *in vitro* (23). Thus, HOCl in physiologic solutions is relatively harmless to tissue.

An alternative hypothesis states that HOCl is generated and deactivates the potent antiproteinase shield that is present in biological systems (Figure 3) (22). *In vivo*, PMNs are immersed in fluids containing huge excesses of α_1 -proteinase inhibitor. Normally, if elastase, a PMN-secreted protease, is released from PMNs, connective tissue would not be degraded, because elastase would be rapidly deactivated by α_1 -proteinase inhibitor in the surrounding tissue and blood. Deactivation of the antiproteinase shield with HOCl would enable PMN-generated elastase to degrade connective tissue. Thus, the se-

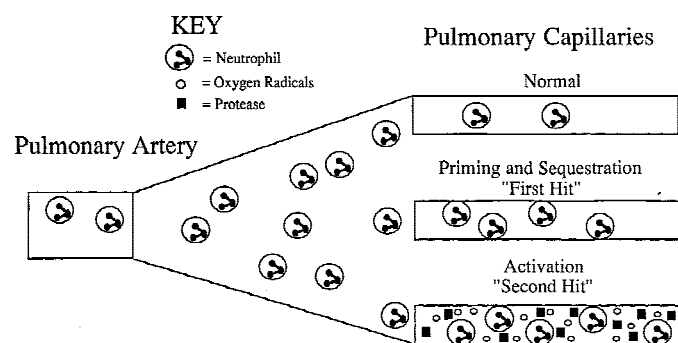


Figure 2: Diagram of the sequence of events leading up to the development of ARDS. Normally, PMNs circulate freely through the pulmonary microcirculation. Priming of the neutrophils by an inflammatory stimulus ("first-hit") causes PMN sequestration in the lung without injury, because PMNs have not released any injurious compounds. Activation of the primed and sequestered PMNs ("second-hit") results in release of superoxide anion and proteases, which destroy the alveolar-capillary membrane, resulting in the plasma flooding of the alveolus.

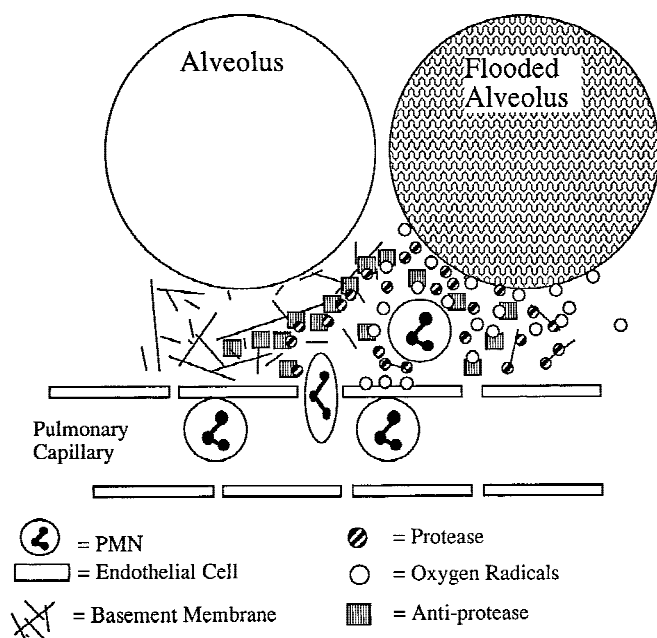


Figure 3: Proposed mechanism of PMN-induced lung injury. PMNs sequester in pulmonary capillaries and diapedesis into the interstitial space. Release of superoxide anion deactivates the antiprotease shield (area adjacent to the flooded alveolus), allowing protease to destroy the basement membrane. In areas where the antiprotease shield is intact (area adjacent to the nonflooded alveolus), protease activity is inhibited, and alveolar flooding is prevented. Loss of antiprotease activity allows such proteases as neutrophil elastase and collagenase released by PMNs to degrade the elastin and collagen components of the basement membrane. Plasma proteins flow through damaged microvessels and the basement membrane and also flood alveoli. This high permeability edema is the hallmark of PPS.

quence of events leading to ARDS would be PMN release of HOCl, deactivation of the α_1 -proteinase inhibitor shield, and finally, protease degradation of the alveolar-capillary basement membrane. Evidence to support this hypothesis includes detection of oxidatively inactivated antiproteases in bronchoalveolar lavage fluids from ARDS patients (25). In summary, the primary effectors of PMN-induced tissue damage are proteases.

MECHANISM OF TISSUE INJURY: NEUTROPHIL PROTEASES

Although the pathogenesis of ARDS is complex, protease disruption of the alveolar-capillary basement membrane is a key component (26, 27). This is evidenced by passage of plasma proteins from the vasculature into the alveolus, suggesting that not only is endothelial and epithelial permeability increased but that the basement membrane has been disrupted. Degradation products of type IV collagen, which are specific to alveolar basement membrane, have been found in the broncho-

alveolar lavage (BAL) fluid of ARDS patients, lending support to the above hypothesis (26). No clinical evidence exists demonstrating that proteases are the primary effectors of PMN-induced tissue damage in CPB patients. However, Carney et al. have shown that proteases play a key role in our animal model of PPS (28). The pathophysiologic significance of neutrophil proteases in ARDS is as follows.

Matrix Metalloproteinases (MMP): The MMPs are a family of enzymes involved in the homeostasis, remodeling, and response to injury of the extracellular matrix (ECM) (29). There are numerous MMPs that are distinguished, in part, by differences in specificity toward ECM components. MMPs are released as inactive pro-forms and are activated in the extracellular environment as a result of proteolytic cleavage and reactive oxygen intermediates (ROIs). Following activation, MMPs are regulated by the formation of complexes with tissue inhibitors of metalloproteinases (TIMPs) and α_2 -macroglobulin. Fibroblasts, endothelial cells, and epithelial cells (e.g., non-inflammatory cells) predominately secrete MMP-2 (gelatinase-A) and/or MMP-9 (gelatinase-B); whereas, PMNs and alveolar macrophages (e.g., inflammatory cells) release mainly MMP-9. The major substrates for MMP-2 and MMP-9 include gelatin, type IV and V collagens, and fibronectin. Consequently, the MMPs are of particular importance in ARDS pathophysiology (28–33). Elevated levels of MMPs in BAL have been measured in animals with endotoxin-induced lung injury (28) and in human ARDS patients (30–33). Torii et al. found that the concentrations of both MMP-2 and -9 were significantly higher in ARDS patients as compared to healthy volunteers, and that higher concentrations of MMPs correlated with the levels of the degradation products of basement membrane structures (32). These findings strongly suggest that MMPs play a major role in the pathogenesis of ARDS. Likewise, Delclaux et al. demonstrated that activated MMP-2 and MMP-9 in the epithelial lining fluid were elevated in ARDS patients and that this increase correlated with increased alveolar albumin concentration (31). This study provides evidence that the source of MMP during ARDS is from both inflammatory (neutrophils, MMP-9) and noninflammatory (fibroblasts, MMP-2) cells. It was concluded that these gelatinases are involved in the increased permeability of the alveolar-capillary membrane characteristic of ARDS.

Neutrophil Elastase (NE): The serine protease NE has also been implicated in the pathophysiology of ARDS (34–40). NE has been shown to be an important mediator in endotoxin-induced lung injury in cell culture (40), in animals, (35, 36, 38, 39) and in ARDS patients (34, 37). Anderson et al. found that low dose endotoxin caused PMN sequestration in the lung without lung injury (35). However, if the PMN activator, *N*-formyl-methionylleucyl-phenylalanine (FMLP), was administered while the PMNs were sequestered, lung injury occurred. This injury was prevented with a PMN elastase inhibitor. It

was concluded that the lung injury in this "two-hit" model of ARDS was attributable to release of NE from sequestered PMNs. In a clinical situation, elevated plasma NE was found in patients within minutes of multiple-trauma and NE level correlated with subsequent lung injury and progression to ARDS (37). NE increases the permeability of epithelial monolayers in a time- and concentration-dependent fashion without killing the cells (40). The activity of NE is controlled by α_1 -proteinase inhibitor (α_1 -PI) and, interestingly, MMPs have been implicated in the degradation of α_1 -PI during an inflammatory response, resulting in increased elastase activity (41). Addition of soy bean trypsin inhibitor or α_1 -PI prevented the increased permeability, suggesting that proteolytic activity was the mechanism of action. In addition, it has been shown that NE and superoxide anion act synergistically to mediate PMN-induced lung injury (37, 38). Serine protease inhibitors have been shown to be efficacious in reducing pulmonary PMN sequestration (42) and lung injury in various animal models of ARDS. However, these compounds are very specific and are limited to inhibition of specific protease types (43–49). Neutrophil elastase has been shown to increase during CPB, but this has not been correlated with the development of PPS (50).

PREVENTION OF POSTPUMP SYNDROME: BLOCKADE OF INITIATORS AND EFFECTORS

We have demonstrated that CPB or endotoxin alone did not change lung function. However, if CPB was followed by a low dose of endotoxin, serious lung dysfunction, typical of PPS, occurred (51). Both CPB and endotoxin alone also caused an increase in sequestered PMNs, although significantly less than the increase with CPB+ endotoxin. Because this increase did not cause lung injury, we speculate that CPB primes PMNs, causing them to sequester (51). Lung damage would occur if these primed PMNs were activated and released ROIs and proteases, as described by Partrick et al. (13). In our model, low dose endotoxin is the activator of PMNs (51). Our study demonstrated that PPS can be caused by multiple sequential insults. Thus, two basic strategies for preventing PPS arise. Blockade of inflammatory initiators, such as TNF, would buffer the "first-hit," priming and sequestration of PMNs, and ultimately prevent the development of PPS. However, if primed PMNs were activated by a "second-hit," tissue destruction could be prevented by blockade of neutrophil proteases.

BLOCKADE OF INITIATOR: TNF

TNF is recognized as a central initiator in the inflammatory process, which includes the priming and activation of PMNs (52–54). TNF primes PMNs for an enhanced response to subsequent insults (55), up-regulates adhesion molecules causing PMNs adherence to the vascular endothelium (53), and en-

hances neutrophil superoxide production (54). Preventing serum TNF levels from reaching pathologic concentrations is an attractive strategy for reducing the incidence of ARDS. However, without the availability of fast, accurate bedside measurement, it is impossible to predict when serum TNF concentrations are elevated in the critically ill patient. Obviously, TNF reduction strategies are only effective when administered preemptively or concurrent with elevated serum TNF. Consequently, clinical trials utilizing monoclonal antibodies against TNF (anti-TNF) and soluble TNF receptor to treat patients with well-developed sepsis and ARDS have failed (56).

Postpump syndrome is unique as compared with other forms of ARDS in that the timing of the initial insult (i.e., CPB) is known, and thus treatment regimens can be given prophylactically. We hypothesized that prophylactic treatment during CPB would be more effective than the therapeutic treatment in previous clinical trials (56). Using our model of PPS described previously, we tested the hypothesis that postpump syndrome could be averted if the CPB-induced rise in serum TNF was prevented. Serum TNF was scavenged with human recombinant tumor necrosis factor-binding protein (TNFbp) given concomitant with the initiation of CPB.

Although numerous studies have demonstrated that TNF is a primary mediator of information (6, 11, 12), our study suggested that TNF plays a larger role in PMN activation. TNFbp treatment blocked the rise in serum TNF levels and prevented the development of PPS in our CPB+ endotoxin model. Unexpectedly, TNFbp did not significantly reduce pulmonary PMN sequestration, which would be expected if TNF was solely responsible for the systemic inflammation of post-CPB. The important findings of this study were: (1) blocking the rise in serum TNF with TNFbp prevents PPS following CPB+ endotoxin; and (2) PPS is averted without a reduction in pulmonary PMN sequestration (57). These results suggest that PMN sequestration may occur independent of elevated serum TNF levels; whereas, high circulating levels of TNF plays a role in PMN activation. It is possible that other cytokines, such as Interleukin-1 (IL-1), may be responsible for PMN sequestration following the TNF blockade. From our results, we hypothesize that CPB primes PMNs, because they sequester in the pulmonary vessels but are not activated, because no lung damage occurs (51). TNFbp may prevent PMN activation, either by a direct effect of lowering serum TNF, or indirectly, by preventing TNF-induced production of other activating mediators, which, in turn, precludes lung injury.

Platelet activity factor (PAF) has been shown to be a powerful activator of PMNs (13–18). Others have shown that soluble TNF receptor (recombinant dimeric TNF receptor type II) strongly inhibits endotoxin-induced up-regulation of adhesion molecules by endothelial cells but did not inhibit release of secretory phospholipase A_2 (the enzyme responsible for PAF release) (58). We speculate that PAF may be released

during CPB and is responsible for PMN sequestration; whereas, TNF activates sequestered PMNs, causing lung injury.

BLOCKADE OF EFFECTOR: NEUTROPHIL PROTEASE AND MATRIX METALLOPROTEINASE

Two distinct strategies could be employed to protect against neutrophil-mediated injury and prevent the development of PPS. The first strategy attempts to block the early or "upstream" initiators of inflammation, and the second attempts to block neutrophil-derived toxic oxygen radicals or protease, which are the "downstream" effectors of tissue injury. First, circulating neutrophils could be depleted, but leukodepletion would reduce the number of PMNs available to kill pathogens and, thus, may do more harm than good. A second strategy would be to block adhesion molecules or to scavenge inflammatory cytokines (e.g., TNF, IL-1, etc), which would prevent neutrophil priming and sequestration. Adhesion molecule blockade would inhibit the immune response to a lesser extent than leukodepletion, because it is likely that high levels of cytokines generated at the site of an infection would override any adhesion molecules or cytokine blockade. The problem with inflammatory mediator blockade is that inhibition of bioactive lipids and cytokines would influence multiple cell lines, not neutrophils alone, which could have serious side effects. In addition, clinical trials employing these strategies have had limited success (56).

Because the onset of PPS cannot be anticipated or prevented, we chose to treat the "downstream," neutrophil-derived toxic mediators with chemically modified tetracycline (CMT). We utilized CMT-3, which antagonizes or neutralizes active neutrophil-derived oxygen metabolites, serine proteases, and MMPs. CMTs are powerful inhibitors of MMPs and prevent activation of pro-MMPs to MMPs by scavenging superoxide anion. This inhibits direct collagenolysis and protects against inactivation of endogenous antiproteases (26, 27–33). This inhibition of MMPs also prevents α_1 -protease inhibitors from

becoming either directly inactivated by MMPs or indirectly by oxidation from HOCl (33). This results in preserved antiprotease (anti-elastase) function, which attenuates neutrophil elastase activity and further protects the basement membrane (26).

We hypothesized that protease released from neutrophils is responsible for a majority of the lung injury during PPS. Therefore, treatment with CMT-3 will attenuate both MMP collagenolytic activity and MMP-induced inactivation of α_1 -protease inhibitor to prevent basement membrane degradation and protect against the development of acute lung injury in our porcine PPS model. CMT-3 prevented the development of PPS and significantly reduced the number of PMNs in pulmonary tissue (27). Reduced lung injury was associated with a fall in neutrophil elastase levels and collagenase in bronchoalveolar lavage fluid. CMT-3 likely precluded the onset of PPS by preventing elastase-mediated destruction of the alveolar-capillary basement membrane. Because nonantimicrobial tetracyclines have few side effects, they could be administered prophylactically to all high-risk CPB patients, which would likely reduce the morbidity and mortality associated with PPS.

SUMMARY

Postpump syndrome is a devastating lung injury that develops following cardiopulmonary bypass. The pathophysiology of PPS is caused by initiation of a systemic inflammatory response. The terminal effectors in this complex sequence of events are proteases released from neutrophils sequestered in the pulmonary vasculature. These proteases damage the alveolar-capillary membrane, resulting in a high permeability pulmonary edema typical of PPS.

It is now believed that PPS is caused by multiple, sequential insults and is termed the "two-hit" model of PPS. The "first-hit" occurs during bypass and is likely caused by contact of blood with the perfusion circuitry. The "second-hit" is most

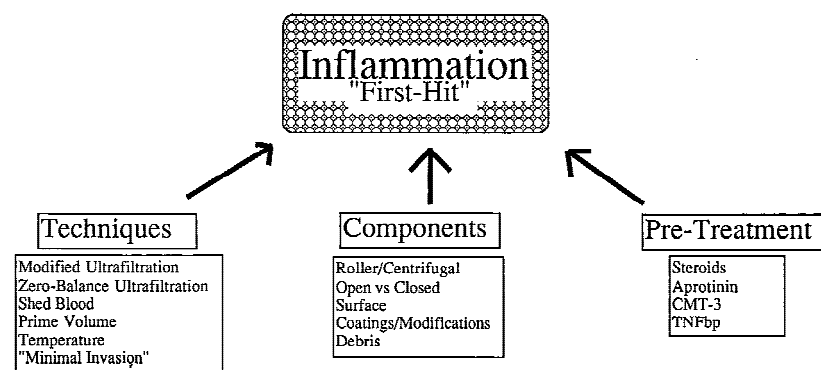


Figure 4: Constituents involved in the development and treatment of inflammation precipitated by cardiopulmonary bypass. *Techniques* include the volume of pump prime and shed blood handling technique, perfusion temperature, surgical technique (minimal invasion), modified ultrafiltration, and zero-balance ultrafiltration. *Components* of the perfusion setup: types of perfusion pumps include roller versus centrifugal with *open versus closed* perfusion systems. Coatings or modifications of the perfusion circuitry reduce inflammation. *Debris* may be liberated from certain components. In-line filters may reduce some of the embolic shower. Inflammation generated during CPB can be reduced by *pretreatment* with anti-

inflammatory drugs. Steroids block arachidonic acid metabolite mediators, such as thromboxane and prostaglandin, aprotinin blocks bradykinin generation and reduces coagulopathy. CMT-3 prevents neutrophil protease-induced lung injury, TNFbp prevents the rise in serum TNF level, eliminating a prime initiator of inflammation.

often caused by sepsis or endotoxemia, with sources being the gut or infected catheters.

These studies highlight the importance of minimizing the amount of inflammation generated during CPB. Treatment strategies in our laboratory focused on pretreatment regimens, although others have suggested alternative strategies to prevent CPB-induced inflammation. Although beyond the scope of this review, modification of perfusion techniques or the components of the pump circuit or use of other anti-inflammatory drugs may be effective in tempering the inflammation caused by CPB (Figure 4). A thorough knowledge of the procedures that produce the least inflammation during CPB are essential. Minimizing inflammation during CPB will reduce the morbidity and mortality of postpump syndrome.

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REFERENCES

1. Fry DE. Multiple system organ failure. In: Fry DE, ed. *Multiple System Organ Failure*. St. Louis: Mosby-Year Book; 1992; 3–14.
2. Deitch EA. Multiple organ failure: Pathophysiology and potential future therapy. *Ann Surg*. 1992;216:117–134.
3. Starr NJ. In: Casthely PA, Bergman D, eds. *Cardiopulmonary Bypass: Physiology, Related Complications, and Pharmacology*. New York: Futura; 1991.
4. Messent M, Anaes FC, Registrar K, et al. Adult respiratory distress syndrome following cardiopulmonary bypass: Incidence and prediction. *Anaesthesia* 1992;47:267–268.
5. Westaby S. Organ dysfunction after cardiopulmonary bypass. A systemic inflammatory reaction initiated by the extracorporeal circuit. *Intensive Care Med*. 1987;13:89–95.
6. Kirklin JK. The post perfusion syndrome: Inflammation and the damaging effects of cardiopulmonary bypass. In: Tinker JH, ed. *Cardiopulmonary Bypass: Current Concepts and Controversies*. Philadelphia: Saunders; 1989: 131.
7. Butler J, Rocker G, Westaby S. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg*. 1993;55:552–59.
8. Hirthler M, Simoni J, Dickson M. Elevated levels of endotoxin, oxygen-derived free radicals, and cytokines during extracorporeal membrane oxygenation. *J Ped Surg*. 1992;27:1199–1202.
9. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101:1644–55.
10. Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: Risk with common predispositions. *Ann Intern Med*. 1983;98:593–97.
11. Stephens KE, Ishizaka A, Larrick JW. TNF causes increased pulmonary permeability and edema. *Am Rev Respir Dis*. 1988;137:1364–70.
12. Kunkel SL, Remick DG, Strieter RM, et al. Mechanisms that regulate the production and effects of tumor necrosis factor alpha. *Crit Rev Immunol*. 1989;9:93–117.
13. Partrick DA, Moore FA, Moore EE, et al. Neutrophil priming and activation in the pathogenesis of postinjury multiple organ failure. *New Horiz*. 1996;4:194–210.
14. Barnett CC, Moore EE, Moore FA, et al. Intercellular adhesion molecule-1 provokes polymorphonuclear leukocyte elastase release by CD18. *Surgery*. 1996;120:395–401.
15. Franciose R, Moore E, Moore F, et al. Hypoxia/reoxygenation of human endothelium activates PMNs to detach endothelial cells via a PAF mechanism. *J Surg Res*. 1996;61:459–62.
16. Biffl WL, Moore EE, Moore FA, et al. Interleukin-6 delays neutrophil apoptosis via a mechanism involving platelet-activating factor. *J Trauma*. 1996;40:575–78.
17. Koike K, Moore EE, Moore FA, et al. Gut phospholipase A2 mediates neutrophil priming and lung injury after mesenteric ischemia-reperfusion. *Am J Physiol*. 1995;268: G397–G403.
18. Koike K, Moore EE, Moore FA, et al. Endotoxin after gut ischemia/reperfusion causes irreversible lung injury. *J Surg Res*. 1992;52:656–62.
19. Taggart DP, Sundaram S, McCartney C, et al. Endotoxemia, complement, and white blood cell activation in cardiac surgery: A randomized trial of laxatives and pulsatile perfusion. *Ann Thorac Surg*. 1994;57:376–82.
20. Edmunds LH, Ellison N, Coleman RW. Platelet function during open heart surgery: Comparison of membrane and bubble oxygenators. *J Thorac Cardiovasc Surg*. 1982;83: 805–12.
21. Malech HL, Gallin JI. Neutrophils in human diseases. *N Engl J Med*. 1987;317:687–94.
22. Weiss SJ. Destruction by neutrophils. *N Engl J Med*. 1989; 320:365–76.
23. Dakin HD, Cohen JB, Kenyon J. Studies in antiseptics (II): On chloramine: Its preparation, properties, and use. *Br Med J*. 1916;1:852–54.
24. Klebanoff SJ. Phagocytic cells: Products of oxygen metabolism. In: Gallin JI, Goldstein IM, Snyderman R., eds. *Inflammation: Basic Principles and Clinical Correlates*. New York: Raven Press; 1988: 391–444.
25. Cochrane CG, Spragg R, Revak SD. Pathogenesis of the adult respiratory distress syndrome: Evidence of oxidant activity in bronchoalveolar lavage fluid. *J Clin Invest*. 1983;71:754–61.

26. Kondoh Y, Taniguchi H, Taki F, et al. 7S collagen in bronchoalveolar lavage fluid of patients with adult respiratory distress syndrome. *Chest*. 1992;101:1091–1094.
27. Kawamura MF, Yamasawa F, Ishizaka R, et al. Serum concentration of 7S collagen and prognosis in patients with the adult respiratory distress syndrome. *Thorax*. 1994;49:144–46.
28. Carney D, Lutz C, Picone A, et al. Matrix metalloproteinase inhibitor prevents acute lung injury following cardiopulmonary bypass. *Circulation*. 1999;100:400–406.
29. Woessner JF. The family of matrix metalloproteinases. *Ann NY Acad Sci*. 1994;732:11–21.
30. d'Ortho MP, Jarreau PH, Delacourt C, et al. Matrix metalloproteinase and elastase activities in endotoxin-induced acute lung injury in guinea pigs. *Am J Physiol*. 1994;266:L209–L216.
31. Delcaux C, d'Ortho M-P, Delacourt C, et al. Gelatinases in epithelial lining fluid of patients with adult respiratory distress syndrome. *Am J Physiol*. 1997;272:L442–L451.
32. Torri K, Iida K-I, Miyazaki Y, et al. Higher concentrations of matrix metalloproteinases in bronchoalveolar lavage fluid of patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1997;155:43–6.
33. Ricou B, Nicod L, Lacraz S, et al. Matrix metalloproteinases and TIMP in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1996;154:346–52.
34. Lee DT, Fein AM, Lipmann M, et al. Elastase activity in pulmonary lavage fluid from patients with adult respiratory distress syndrome. *N Engl J Med*. 1981;304:192–96.
35. Anderson BO, Brown JM, Bensard DD, et al. Reversible lung neutrophil accumulation can cause lung injury by elastase-mediated mechanisms. *Surgery*. 1990;108:262–68.
36. Ferry G, Lonchampt M, Pennel L, et al. Activation of MMP-9 by neutrophil elastase in an in vivo model of acute lung injury. *Fed Eur Biochem Societies*. 1997;402:111–15.
37. Donnelly SC, MacGregor I, Zamani A, et al. Plasma elastase levels and the development of the adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151:1428–33.
38. Baird BR, Cheronis JC, Sandhaus RA, et al. O₂ metabolites and neutrophil elastase synergistically cause edematous injury in isolated rat lungs. *J Appl Physiol*. 1986;61:2224–229.
39. Yoshimura K, Nakagawa S, Koyama S, et al. Roles of neutrophil elastase and superoxide anion in leukotriene B₄-induced lung injury in rabbit. *J Appl Physiol*. 1994;76:91–6.
40. Peterson MW, Walter ME, Nygaard SD. Effect of neutrophil mediators on epithelial permeability. *Am J Respir Cell Mol Bio*. 1995;13:719–27.
41. Lee H-M LM, Golub D, Chan M, et al. Alpha-1-proteinase inhibitor in gingival crevicular fluid of humans with adult periodontitis: Serpinolytic inhibition by doxycycline. *J Periodont Res*. 1997;32:9–19.
42. Milano S, Arcoleo F, D'Agostino P, et al. Intraperitoneal injection of tetracyclines protects mice from lethal endotoxemia down-regulating inducible nitric oxide synthase in various organs and cytokine and nitrate secretion in blood. *Antimicrob Agents Chemother*. 1997;41:117–121.
43. Uchiba M, Okajima K, Murakami K, et al. Effect of nafamostat mesilate on pulmonary vascular injury induced by lipopolysaccharide in rats. *Am J Respir Crit Care Med*. 1997;155:711–18.
44. O'Donovan DA, Kelly CJ, Bouchier-Hayes DM, et al. Alpha-1 antichymotrypsin is an effective inhibitor of pancreatitis-induced lung injury. *Eur J Gastroenterol Hepatol*. 1995;7:847–52.
45. Okumura Y, Inoue H, Fujiyama Y, et al. Effects of serine protease inhibitors on accumulation of polymorphonuclear leukocytes in the lung induced by acute pancreatitis in rats. *J Gastroenterol*. 1995;30:379–86.
46. Sakamaki F, Ishizaka A, Urano T, et al. Effect of a specific neutrophil elastase inhibitor ONO-5046, on endotoxin-induced acute lung injury. *Am J Respir Crit Care Med*. 1996;153:391–97.
47. Kubo K, Kobayashi T, Hayano T, et al. Effects of ONO-5046, a specific neutrophil elastase inhibitor, on endotoxin-induced lung injury in sheep. *J Appl Physiol*. 1994;77:1333–40.
48. Miyazaki Y, Inoue T, Sawads M, et al. Effects of a neutrophil elastase inhibitor (ONO-5046) on acute pulmonary injury induced by tumor necrosis factor alpha (TNF α) and activated neutrophils in isolated perfused rabbit lungs. *Am J Respir Crit Care Med*. 1998;157:89–94.
49. Gossage JR, Kuratomi Y, Davidson JM, et al. Neutrophil elastase inhibitors, SC-37698 and SC-39026, reduce endotoxin-induced lung dysfunction in awake sheep. *Am Rev Respir Dis*. 1993;147:1371–79.
50. Ashraf S, Tian Y, Cowan D, et al. Release of proinflammatory cytokines during pediatric cardiopulmonary bypass: Heparin-bonded versus nonbonded oxygenators. *Ann Thorac Surg*. 1997;64:1790–94.
51. Picone AL, Lutz C, Finck C, et al. Multiple sequential insults cause post-pump syndrome. *Ann Thorac Surg*. 1999;67:978–85.
52. Van der Poll T, Buller HR, Cate HT, et al. Activation of coagulation after administration of tumor necrosis factor to normal subjects. *N Engl J Med*. 1990;322:1622–86.
53. Gamble JR, Harlan JM, Klebonoff SJ, et al. Stimulation of the adherence of neutrophils to umbilical vein endothelium by human recombinant tumor necrosis factor. *Proc Natl Acad Sci USA*. 1985;82:8667–71.

54. Larrick JW, Graham D, Toy K, et al. Recombinant tumor necrosis factor causes activation of human granulocytes. *Blood*. 1987;69:640–44.
55. Beutler B, Cerami A. Cachectin and tumor necrosis factor as two sides of the same biological coin. *Nature*. 1986; 320:584–88.
56. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: A reassessment. *Crit Care Med*. 1997;25:1095–1100.
57. Carney D, Lutz C, Picone A, et al. Soluble tumor necrosis factor receptor (TNFbp) prevents post-pump syndrome. *J Surg Res*. 1999;83:113–21.
58. Van der Poll T, Coule, SM, Levi M, et al. Effect of a recombinant dimeric tumor necrosis factor receptor on inflammatory responses to intravenous endotoxin in normal humans. *Blood*. 1997;89:3727–34.