Targeting the Proteolytic Arsenal of Neutrophils
A Promising Approach for Postpump Syndrome and ARDS
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Of patients who undergo cardiopulmonary bypass (CPB), a procedure essential to most cardiac operations, ≈1% to 2% develop a syndrome of pulmonary dysfunction called the postpump syndrome, which is analogous to the adult respiratory distress syndrome (ARDS) that develops as a complication of trauma, sepsis, inhalation injury, aspiration pneumonia, pancreatitis, and other disease states.1,2 This syndrome is characterized by evidence of pulmonary microvascular endothelial damage, increased microvascular permeability, increased lung water accumulation, increased intrapulmonary shunting, hypoxia, respiratory failure, and a variable severity of clinical expression. Despite many technical and therapeutic advances, the overall mortality associated with this syndrome continues to be high, ranging from ≈40% to ≈60%.1,2 The precise mechanisms responsible for microvascular damage and tissue destruction in postpump syndrome and ARDS are incompletely understood. An important role for inflammatory cells, specifically neutrophil sequestration and activation, is suggested by a number of experimental and clinical observations.3–7 It has been suggested that CPB primes the neutrophils, causing their sequestration in the pulmonary microvasculature, with subsequent activation resulting in the release of tissue-destructive mediators. Several cytokines, such as interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor-α, and leukemia inhibitory factor, have been implicated in neutrophil recruitment or activation in ARDS.6,8–14 Among various mediators of tissue injury released by activated neutrophils, serine proteases such as elastase and matrix-degrading metalloproteinases have been considered to be most relevant in ARDS.3–7,15,16 Experimental observations suggest that neutrophil elastase may serve as an activator of gelatinase B (matrix metalloproteinase [MMP]-9).17 Both elastase and metalloproteinases, when activated, can induce breakdown of extracellular matrix components such as elastin and basement membrane collagen type IV, resulting in microvascular endothelial damage and increased permeability.15 Furthermore, it has also been postulated that increased production of oxygen-derived free radicals (superoxide anion, hydrogen peroxide, hydroxyl radical, and hypochlorous acid) by activated neutrophils and tissues subjected to ischemia-reperfusion induces oxidation of the methionine-reactive site of α1-antiprotease, a natural irreversible inhibitor of neutrophil elastase, making it a less effective inhibitor of elastase, thereby contributing to enhanced elastolytic activity.4 Strategies aimed at reducing neutrophil accumulation or activation have been tried in experimental and clinical settings with variable results, possibly because of multiple redundant pathways through which such accumulation and activation could continue to occur despite the use of a specific inhibitor. Targeting the terminal effectors and mediator(s) through which activated neutrophils ultimately contribute to pulmonary microvascular injury could overcome some of these limitations. Neutrophil elastase and metalloproteinases are among the putative terminal effectors through which tissue destruction may be mediated.

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In this issue of Circulation, Carney et al18 have tested the hypothesis that increased metalloproteinase and elastase levels play a pathophysiological role in pulmonary microvascular injury in a porcine model of postpump syndrome. The authors used CPB plus endotoxin challenge to induce postpump-like syndrome on the basis of their previous experience showing that both a priming stimulus (CPB) and a secondary trigger (endotoxin) are necessary to create the syndrome in this model. To inhibit metalloproteinases, a chemically modified tetracycline derivative, CMT-3 (Collagenex Corp), that lacks antibacterial activity but has potent anti-MMP activity was used.19 In addition to inhibiting MMP activity, CMTs prevent the conversion of pro-MMP to active MMP by oxygen-derived free radicals, while at the same time preventing α1-antiprotease from inactivation by MMPs or oxygen-derived free radicals.20–24 This preservation of anti-protease activity may help reduce elastase activity, thereby further attenuating matrix breakdown. The authors demonstrated that the combined insult of CPB and endotoxin challenge produced anatomic evidence of pulmonary microvascular injury in this model, along with accumulation of neutrophils in lungs, increased lung water content, and increased elastolytic and gelatinolytic activity in the bronchoalveolar lavage fluid. These anatomic changes were associated with evidence of pulmonary dysfunction in the form of a decline in Pao2, increase in venous admixture, and a decline in ventilatory efficiency. When CPB plus endotoxin challenge was combined with CMT-3 administration, anatomic evidence of lung injury as well as the severity of pulmonary dysfunction was attenuated. This improvement in pulmonary
dysfunction was accompanied by a 40% reduction in neutrophil accumulation compared with controls and a reduction in elastase and gelatinolytic activity to control levels. The authors thus concluded that inhibition of elastolytic and gelatinolytic activity attributed to neutrophil elastase or MMPs represents a new approach for prevention of postpump syndrome and ARDS.

Although the observations reported by Carney et al provide new and important information in support of the potential involvement of matrix-degrading proteases in the postpump syndrome, several questions remain to be answered: (1) CMT-3 treatment was associated not only with normalization of elastase and MMP activity but also with a 40% reduction in neutrophil accumulation. The authors do not describe or discuss how the CMT-3 reduced neutrophil accumulation and to what extent this action of CMT-3 may have contributed to the salutary effects observed independently of the anti-MMP activity of the compound used. The possibility that alterations in pulmonary leukocyte count and proteolytic activity are simply epiphenomena rather than causally linked to postpump syndrome, although unlikely, cannot be fully dismissed. (2) The precise member(s) of the MMP family implicated in the microvascular injury and their source are not clearly defined. Neutrophils are known to produce gelatinase-B (MMP-9) as well as collagenase-2 (MMP-8), whereas gelatinase-A (MMP-2) is produced by epithelial cells and fibroblasts. Neutrophils have also been shown to activate endothelial cell–derived pro–gelatinase-A (MMP-2) through an as yet unidentified soluble mediator. Although the authors demonstrated increased total gelatinolytic activity attributed to MMPs and its normalization by CMT-3, the precise identity of all the MMPs involved remains unclear. (3) Finally, it is uncertain whether the favorable effects of CMT-3 observed in the porcine model of postpump syndrome can be extrapolated to other forms of ARDS.

Notwithstanding these limitations, the study by Carney et al provides important and useful information. Data provided are likely to lead to the development and investigation of novel therapeutic strategies targeting MMPs and possibly other terminal effectors of the tissue-destructive arsenal of the neutrophil for amelioration of pulmonary injury in postpump syndrome and ARDS.

References

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