Exploring molecular mysteries of the adrenal gland: Start with the basics

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Inflammatory molecular pathways induced by cardiopulmonary bypass.

Central Message

There are new and evolving molecular mechanisms relating to the adrenal gland that may affect the inflammatory response to cardiopulmonary bypass.

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The functional anatomy and physiology of the adrenal gland were fresh in the mind of the average cardiothoracic surgeon at some time during medical school training but were relegated to a slightly mysterious memory after that. The article by Mei and coauthors¹ in the current issue of the *Journal* challenges that memory. In this issue, Mei and coauthors¹ explore the adrenal gland molecular components of the inflammatory response to cardiopulmonary bypass (CPB). Extension of advances in molecular biology and molecular mechanisms to the adrenal gland offers new avenues that can affect outcomes after CPB.

Evidence supports the notion that there is relative adrenocortical insufficiency after CPB. This deficit is worsened by some anesthetic agents and is likely to cause more prominent findings of adrenocortical deficit in neonatal CPB.²⁻⁴ The impacts of the relative adrenal insufficiency and results of exogenously administered adrenal hormones during CPB are uncertain. A Cochrane Review suggests that post-CPB systemic inflammatory response syndrome is resistant to addition of corticosteroids during and after the operation.⁵ A subsequent meta-analysis found that steroid prophylaxis in patients undergoing coronary artery bypass grafting significantly reduced complications such as atrial fibrillation and prolonged hospital stay but slightly increased the duration of ventilation.⁶ Similarly, the infectious risks of adrenocortical insufficiency and of administering exogenous steroids in the perioperative setting are uncertain.^{6,7}

How should we respond to these adrenal function uncertainties during CPB? The short answer is to start with the basics. The basics involve the molecular substrates of CPB and the inflammatory response. The article by Mei and coauthors¹ in the current issue of the *Journal* begins the process of investigating the molecular underpinnings of the adrenal injury and of the inflammatory response associated with CPB. Mei and coauthors¹ studied adrenocortical cellular and molecular pathways in normal control dogs and in dogs exposed to CPB. They found that CPB induces local

inflammatory changes in the adrenal cortex including changes in architecture and in inflammatory molecular pathways. They introduce terms that might seem like reading ancient Greek to the average cardiothoracic surgeon. Terms such as *inflammasome* and *nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3' [NLRP3]* are not used in everyday conversation by most cardiothoracic surgeons. Nonetheless, these terms encompass the beginnings of the understanding of the adrenal gland molecular response to the inflammatory stimulus from CPB.

It is well known that CPB induces an inflammatory response and injury in sensitive organs such as the heart, lungs, and kidneys.⁸⁻¹⁰ In their animal model, Mei and coauthors¹ found that CPB induces significant local adrenal cortical inflammation resulting in cytological alterations. These adrenal inflammatory changes occurred along with a significant systemic inflammatory response. Mei and coauthors¹ found activation of one inflammasome pathway (NLRP3) that may be a target for intervention in subsequent studies. This NLRP3 inflammasome is a multiprotein oligomer that promotes the maturation and secretion of proinflammatory cytokines, especially interleukins 1 β and 18.¹¹ These oligomers are expressed in myeloid cells, but their finding in adrenal cells, although not surprising, is relatively new information.

Mei and coauthors¹ suggest that NLRP3 plays a prominent role in the adrenocortical component of CPB-

induced inflammation. They outlined the upregulation of NLRP3 and identified several proinflammatory actions, including interleukin 1 β expression. To implicate NLRP3 as a prominent mediator of the post-CPB inflammatory response, it would be necessary to identify the priming signal for NLRP3 expression and the targets after expression. A complete definition of the role of NLRP3 was beyond the study scope of Mei and coauthors,¹ but the possibilities are intriguing and should be explored. Ultimately, these studies may lead to new molecular targets to limit the harmful components of the CPB-induced inflammatory response. Studies directed at the CPB-induced cellular triggers for NLRP3 upregulation, and the NLRP3-induced cellular actions, may identify new targets to limit harmful proinflammatory responses. The article by Mei and coauthors¹ provides a glimpse into future experiments and is a beginning step in unravelling the molecular mechanisms involving the adrenal gland during CPB.

There are some questions about the study groups that Mei and coauthors¹ used. Clinically, many surgeons attempt to lessen the CPB-induced inflammatory response with empirically based steroid therapy during the perioperative period. I am surprised that Mei and coauthors¹ did not include a third group of dogs in their experiments. Specifically, a group of dogs that received high-dose steroids during CPB would have been an informative control group. There are multiple strategies to attenuate this response other than the administration of corticosteroids, including aprotinin and anticytokine monoclonal antibodies, as well as various modifications of the bypass circuit. CPB induces inflammation and subsequent organ dysfunction. It is very difficult to look only at the adrenal cortex in isolation as a trigger of the inflammatory response and of CPB-induced organ dysfunction without also considering multiple other organ-system effects of CPB. The interest of the readers revolves around clinical pathways and CPB outcomes. Mei and coauthors¹

identified specific post-CPB abnormalities associated with a single adrenocortical pathway activation. The clinical implications of their initial observations need to be expanded and defined with precision. One hopes that human trials, and ultimately clinical benefits, will follow this preliminary work.

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