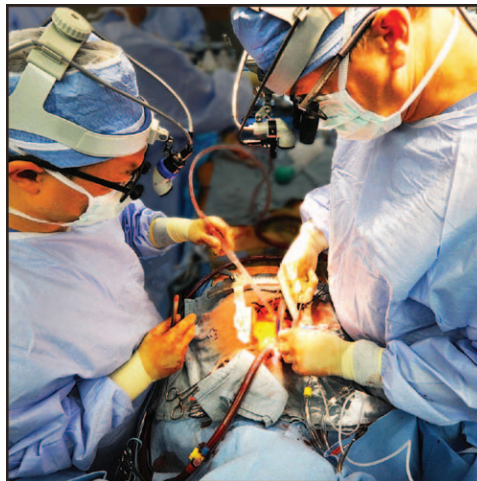


# Next Generation of Cardiovascular Studies

## *Transcriptional Responses of the Human Myocardium during Cardiac Surgery*

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**A**RGUABLY, one of the most significant directions for research in anesthesiology is finding new approaches to make surgical interventions safer. Interesting is the fact that despite a surgical procedure being performed for the correct indication and in a technically superb manner, patients may frequently be threatened by perioperative organ injury.<sup>1</sup> For example, myocardial injury is one of the leading causes of morbidity and mortality in surgical patients, including patients undergoing noncardiac surgery. As such, a recent study in over 15,000 patients undergoing inpatient noncardiac surgery demonstrated that elevated troponin—irrespective of the presence of an ischemic feature—independently predicts 30-day mortality, suggesting that myocardial injury occurs frequently in the perioperative period and is associated with dramatic increases of mortality.<sup>2</sup> Consistent with the notion that perioperative organ injury is one of the leading causes of morbidity and mortality of surgical patients, numerous experimental studies have tried to find novel therapeutic targets that would allow rendering a specific organ more resistant to the detrimental effects of limited supply with oxygen and nutrients, such as occurs during ischemia and reperfusion injury. Many of these studies have taken an approach to examine transcriptional changes as an indicator to find potentially important therapeutic targets. Frequently, such studies would set out with the notion that endogenous protective pathways could be activated during injurious conditions, thereby resulting in the enhanced transcription of protective genes that could be targeted to help adopt a



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Importantly, the authors can be congratulated on studying transcriptional responses during cardiac surgery in a translationally relevant model system. They were able to obtain left ventricular biopsies from 45 patients undergoing aortic valve replacement surgery at baseline and after an average of 79 min of cold cardioplegic arrest. This was achieved by utilizing left ventricular punch biopsies from the site of a routinely placed surgical punch in the anterolateral

specific organ to tolerate injurious conditions more efficiently. Subsequently, pharmacologic approaches that would directly target such pathways could be applied as novel organ-protective approaches. One of the main limitations of many of these studies is related to the model system that is being used. Indeed, such studies would most frequently expose mice to injurious conditions to elicit organ injury (*e.g.*, myocardial ischemia, acute kidney injury, and acute lung injury) and subsequently examine adaptive responses that could be important in perioperative organ protection. As published in the current edition of *ANESTHESIOLOGY*, Muehlschlegel *et al.*<sup>3</sup> took a different approach to identify transcriptional changes that could be targeted for perioperative organ protection.<sup>3</sup> Focusing on myocardial injury, they performed next-generation RNA sequencing to examine transcriptional changes that occur within the left ventricle of patients undergoing cardiac surgery. This innovative approach allows for the first

Image: J. P. Rathmell.

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Accepted for publication November 26, 2014. From the Department of Anaesthesiology, Ludwig-Maximilians-University, Munich, Germany (M.K.); and Organ Protection Program, Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado (T.E., H.K.E.).

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apical left ventricular wall of patients at baseline and following cold cardioplegic arrest. Their approach is superior to many previous studies examining cardioprotective responses during ischemia in several regards. As first, the authors are using a state-of-the-art approach to examine transcriptional responses in an unbiased approach (next-generation RNA sequencing). Second, the authors can be commended for performing these studies in surgical patients who are exposed to myocardial injury such as occurs in the context of cold ischemia exposure during cardiac surgery, as opposed to studying such responses in an animal model. Indeed, a common concern regarding animal models of acute organ injury is related to the question of how accurately mice, rats, rabbits, *etc.* display similar changes in gene expression and regulation as compared with humans. Finally, the authors were able to use the most important and relevant type of tissue—a freshly obtained biopsy of the left ventricle—to perform their studies.<sup>3</sup>

Previous studies have tried to identify changes in gene expression during myocardial injury in humans. For example, previous studies examined myocardial tissue samples from explanted hearts of patients undergoing cardiac transplantation for ischemic cardiomyopathy and compared them to heart samples of health explanted hearts that were not used for transplantation (*e.g.*, due to logistic reasons).<sup>4</sup> Similar to the study by Muehlschlegel *et al.*,<sup>3</sup> myocardial biopsies were obtained from a uniform area of the left ventricle. In contrast, however, these studies compare different patients and different pathological conditions. A great asset of the study by Muehlschlegel *et al.*<sup>3</sup> is related to the fact that each patient underwent two biopsies, and as such, each patient served as control for himself. Consequently, differences in gene expression are truly a reflection of the injury that occurred during cold ischemia associated with cardiopulmonary bypass and cardiac surgery. Again other studies have used samples obtained from the right atrium during cannulation during cardiac surgery. Such studies are limited by the fact that right atrial tissues are only a poor representation of the left ventricle, which is likely to have a very different exposure to cardioplegia, a different anatomic composition of cells, and a different functional role (*e.g.*, different loading conditions and contractility). Indeed, myocardial injury in surgical patients is predominantly considered a disorder of the cardiac ventricle and not the atrium. Together, this discussion highlights that the approach taken by Muehlschlegel *et al.*<sup>3</sup> provides extremely convincing and novel data describing alteration of RNA content in the setting of patients undergoing cardiac surgery.

The present study identified a large number of individual genes and pathways that were altered in their expression. Moreover, additional studies examining transcription factor-binding sites revealed even more targets. As such, the present studies provide an extremely rich and reliable resource for cardioprotective responses during cardiac surgery. An example of how such cardioadaptive responses could be further explored in a mechanistic direction comes from previous studies of

anesthetic-induced organ protection. Many studies have provided experimental evidence that organ-protection provided by volatile anesthetics—such as isoflurane—involves transcriptional responses. For example, a study in a model of acute kidney injury suggests that isoflurane-mediated kidney protection involves the transcriptional induction of CD73—an enzyme crucial in the extracellular production of the signaling molecule adenosine.<sup>5</sup> Indeed, the authors of this study found that anesthetic protection by isoflurane is abolished in mice with genetic deletion of *cd73*, thereby implicating CD73 and its function in generating extracellular adenosine in organ protection. Similar approaches can now be taken in subsequent studies, based on the large array of data provided by Muehlschlegel *et al.*<sup>3</sup> Indeed, changes in RNA content observed in the study by Muehlschlegel *et al.*<sup>3</sup> can be further examined by taking those findings from bedside back to the bench. Here, studies in murine models of *in situ* myocardial injury would be invaluable to confirm similar changes of transcript levels during coronary artery ligation. Moreover, functional studies utilizing mice with global or tissue-specific deletion of the examined gene will allow drawing functional conclusions. Similar to the above discussed studies of CD73-dependent organ protection elicited by volatile anesthetics, deletion of a specific gene product in mice could be associated with more profound myocardial injury. Once such studies have been performed, and pharmacologic studies targeting a specific pathway could be examined for cardioprotection in experimental models. As such, the study by Muehlschlegel *et al.*<sup>3</sup> provides an invaluable resource for many investigators interested in perioperative organ protection to find novel targets for cardioprotection or to take their own established findings into a translational direction.

### Acknowledgments

Support was received from the National Institutes of Health (Bethesda, Maryland) (grant nos. R01 DK097075, R01-HL092188, R01-HL098294, POI-HL114457, and R01-HL119837 to Dr. Eltzschig and K08HL102267 to Dr. Eckle).

### Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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