the presence of N-acetylcysteine. They suggest that N-acetylcysteine and allpurinol promote tolerance of the myocardium to ischemic injury by restoring adiponectin concentration, and thus, they propose that N-acetylcysteine might be effective in restoring sevoflurane postC in the diabetic heart.

The animal model used in the study was type I diabetes, i.e., uncorrected hyperglycemia for 1 month. Insulin was given in the last 48 h to bring the animals into a state of normoglycemia at the time of the experiment. I did not give insulin therapy to alleviate the symptoms of diabetes, but to perform the experiments in a normoglycemic state, with a goal to reduce blood sugar to less than 135 mg/dl, but I actually achieved better control as reflected in the study. The diabetic irresponsiveness of the myocardium is more complex than that expected by the hyperglycemic state alone. It might be attributed to multiple cellular changes in mitochondrial membrane potentials, which lead to certain degrees of mitochondrial uncoupling. This in turn leads to a glycation reaction, causing cellular injury and accumulation of glycation end products, depression of more signal transduction components such as phosphatidylinositol 3-kinase, STAT3, and nitric oxide synthase, as well as glycogen synthase kinase-3β activation, all leading to lipid accumulation, inflammation, and remodeling. Therefore, I do not agree with the comment that strict preservation of normoglycemia during the experiment might eliminate all changes accumulated during the month of diabetic state. The changes in the heart are too substantial to be prevented by a single maneuver of replenishing antioxidant state.

From a practical view, giving higher doses of insulin to an animal would be irresponsible, because hypoglycemia in animals who are not observed closely most of the time would be detrimental. I am not aware of any animal study evaluating diabetes for long-term outcome that used conventional glucose control levels. Extrapolating from human data that use conventional glucose control, as suggested in the current letter, to patients postoperative long-term outcome, is controversial at best. Strict control of diabetes at normal levels was found hazardous due to severe side effects. Attributing changes in sensitive cellular pathways, such as STAT3 and phosphatidylinositol 3-kinase, only to the natural lack of antioxidants seems simplistic. As discussed in the previous paragraph, diabetes effects on the heart are profound and the mechanism of injury is at multiple levels. The authors claim that a longer period of insulin therapy might have a beneficial effect on restoring postC in diabetes. Unfortunately, I suggested differently, that changes in the heart caused by diabetes were not restored by a short period of normoglycemia. Insulin administration before complete heart caused by diabetes were not restored by a short period of normoglycemia. I suggested differently, that changes in the heart caused by diabetes were not restored by a short period of normoglycemia. Insulin administration before complete heart caused by diabetes were not restored by a short period of normoglycemia. Insulin administration before complete heart caused by diabetes were not restored by a short period of normoglycemia. However, with regard to early detection of acute kidney injury (AKI) in adults by means of neutrophil gelatinase-associated lipocalin (NGAL), we feel that there has been a positive selection bias in their review of the available evidence.

Although they imply that, in adult patients after cardiopulmonary bypass cardiac surgery, plasma and urine NGAL con-
centrations are good predictors of renal injury with area under the receiver-operating characteristic curve (AUCROC) of 0.80 and 0.96, respectively, that is in fact an exceptional result from a single, small study.\(^2\) Wagener et al. reported an AUCROC for early diagnosis of AKI by urinary NGAL of 0.61 at 18 h post-cardiopulmonary bypass. The sensitivity and specificity of urinary NGAL in predicting AKI, as judged by AUCROC, was poor, varying from 0.57 to 0.61.\(^3\) Koyner et al.\(^4\) reported an AUCROC of 0.54 at 6 h postcardiopulmonary bypass for the diagnosis of AKI by plasma NGAL. Perry et al.\(^5\) documented increased plasma NGAL levels in patients who suffered AKI but the sensitivity was as low as 38.7%. Haase et al.\(^1\) in a recent meta-analysis derived an AUCROC of 0.78 for early diagnosis of AKI after cardiac surgery by plasma and urinary NGAL.

Given the limited sensitivity and specificity of individual biomarkers, it may be more realistic to use a panel of biomarkers to predict AKI and outcome. Furthermore, a number of key issues, including the wide variability in reported diagnostic performance, require clarification before adoption of NGAL into clinical practice.

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In Reply:
The authors thank Vives et al. for their interest in our Clinical Concepts and Commentary article.\(^1\)

Biomarkers in medicine are a rapidly evolving field that have generated a tremendous amount of interest for the promise of early, accurate diagnoses of a variety of conditions ranging from traumatic brain injury to acute kidney injury (AKI). Biomarkers in AKI have historically been studied in patient populations with a known and well-timed renal insult, like cardiopulmonary bypass or iodinated contrast exposure. The performance of a majority of these biomarkers tends to be poorer when studied in more heterogeneous populations than the original study population.\(^2\) Neutrophil gelatinase-associated lipocalin (NGAL) is no exception.

In the original article, we acknowledge the NGAL data in adult patients undergoing cardiopulmonary bypass is less clear than in the pediatric population, perhaps because of the associated comorbidities and their known and unknown influence on NGAL levels in adults.\(^1\)

The association of increased NGAL levels in patients developing AKI cardiopulmonary bypass is well documented in several studies, including the recent publication by the NGAL Meta-analysis Investigator Group.\(^3\) This largest meta-analysis to date used pooled data from 19 studies and found NGAL consistently to be a useful early predictor of AKI in a broad-based patient population, even though the area under the receiver-operating characteristic curve was 0.77 (as pointed out by Vives et al.). Receiver-operating characteristic analysis has been used to select the optimal threshold under a variety of clinical circumstances, balancing the inherent tradeoffs that exist between sensitivity and specificity.\(^4\) Currently there is no clear consensus on the plasma or urinary threshold levels to label patients as high risk for AKI-cardiopulmonary bypass. This may be in part to the variability in the cutoff values determined using research assays versus commercial standardized NGAL assays.

There have been more than 15 biomarkers described for AKI, and one of the likely reasons that NGAL is at the forefront is because of the availability of a commercial assay, rather than pure research assays, that allows clinicians and researchers across the globe to study AKI in varying patient populations.\(^1\) This also means that limitations of NGAL are likely to be reported in a higher frequency as we study it in more heterogeneous populations (e.g., intensive care unit patients and emergency department admissions).\(^5\)

We agree with the astute observation of the authors that in reality we may need a panel of biomarkers to better define the problem. We stated this in our article as well. Further studies are needed to validate and define the particular panels of biomarkers for AKI after cardiopulmonary bypass.

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References


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