clinical studies have highlighted the role of venous congestion in the development of acute kidney injury. An association between high venous pressure (i.e., right atrial pressure or central venous pressure) and worsening renal function has been described in many different clinical settings, including patients who have undergone cardiac surgery and patients with heart failure (5). We suggest that the observed protective effect on kidney function in this study might be due to a decreased right ventricular afterload, which would decrease the right filling pressure and prevent renal venous congestion after NO inhalation (6). The population investigated in this study furthermore suggests this. Cardiopulmonary bypass was prolonged and most of the surgical procedures were for rheumatic valvular disease, including tricuspid valve surgery. These patients, approximately half of whom had pulmonary artery hypertension, had a high risk of postoperative right cardiac failure. However, data regarding the postoperative hemodynamic parameters are not presented. Unfortunately, the authors point out that transesophageal echocardiography or pulmonary artery catheterization is not the standard of care during surgery in their center—but postoperative monitoring of cardiac function, including the cardiac index and filling pressures (such as the central venous pressure), certainly is. Insights into the impact of inhaled NO on hemodynamics and right filling pressure would help us to better understand the potential mechanisms of nephroprotection and identify the patients who would most benefit from this therapy. ■

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Reply to Coutrot *et al.*

From the Authors:

We read the comment by Dr. Coutrot and colleagues concerning our trial in Xijing Hospital (Xi'an, China) (1). They postulate that the observed effects on kidney function in patients undergoing cardiac surgery and receiving nitric oxide (NO) compared with control subjects receiving a placebo (nitrogen) could be due to NO improving right heart function.

In our trial, we found that delivering 24 hours of 80 ppm NO (both through the cardiopulmonary bypass circuit during surgery and subsequently through the ventilator) resulted in short-term and long-term renal benefits (1). A 22% relative risk reduction in acute kidney injury (AKI) (incidence: 64% for controls vs. 50% in the NO group, $P = 0.014$) translated into long-lasting renal protection. One year after surgery, stage 3 chronic kidney disease (defined as an estimated glomerular filtration rate below 60 ml/min/1.73 m^2) was found in 18% of patients in the NO group, compared with 31% in the control group (relative risk, 0.59; 95% confidence interval, 0.36–0.96; $P = 0.017$). We also found that although the two groups had similar levels of hemolysis (assessed by plasma levels of hemoglobin), plasma NO consumption activity was increased only in the placebo group, suggesting that the administration of NO successfully oxidized circulating plasma ferrous hemoglobin (oxy-hemoglobin) to ferric hemoglobin (met-hemoglobin), preventing depletion of vascular NO (2). Unfortunately, right heart function was not monitored in our trial. Intraoperative transesophageal echocardiography and pulmonary artery catheterization were not standard of care in Xijing Hospital at the time of the trial. Thus, we are unable to confirm the NO-mediated cardioprotective hypothesis of Dr. Coutrot and colleagues. This hypothesis is valid and thoughtful, and it builds on the knowledge that inhaled NO is a potent selective vasodilator of the pulmonary circulation (3). Right heart function might benefit greatly from a decreased workload, as pulmonary vascular resistance is decreased during NO therapy.

In a recent cardiac surgical randomized controlled trial (sample size $n = 71$) presented by Kamenshchikov and colleagues at the annual meeting of the American Heart Association, supplemental NO was added only during surgery to the cardiopulmonary bypass circuit (4). Gas was never delivered directly to the lungs. The authors reported a decrease in AKI from 44.4% in the control group to 14.3% in the NO

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group ($P = 0.0053$), suggesting a directly nephroprotective role of NO. However, no assesment of right heart function and no detailed hemodynamic measurements were presented.

To determine both the cardiac and renal protective effects of NO during cardiac surgery and the potential cardio–renal interactions that might occur, we are now conducting a randomized trial in 250 cardiac surgery patients at the Massachusetts General Hospital (Boston, MA) with intraoperative echocardiography and pulmonary artery catheterization. We will measure renal biomarkers, assess pre- and postoperative redox states, and evaluate pre- and postoperative levels of plasma NO metabolomics. The primary endpoint of this ongoing study in Boston is to determine whether NO is effective in the prevention of AKI as defined by Kidney Disease Improving Global Outcomes criteria (ClinicalTrials.gov Identifier: NCT02836899). However, in contrast to our first trial in China in patients primarily with rheumatic heart disease, Americans undergoing heart surgery are generally older and are affected by endothelial dysfunction. Endothelial dysfunction is a condition characterized by impaired endothelial NO synthase. In these patients, the diseased endothelium is unable to provide appropriate vasodilation during and after ischemic events, and is unable to replenish plasma NO after consumption of NO from intravascular hemolysis (5). At present (January 2019), we are halfway through enrollment ($n = 125$). We believe that the results of this ongoing trial will be able to address the hypothesis of Dr. Coutrot and colleagues. ■

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Enhancing the Expression of CFTR Using Antisense Molecules against MicroRNA miR-145-5p

To the Editor:

We read with great interest the article titled "MicroRNA-145 Antagonism Reverses TGF-β Inhibition of F508del CFTR Correction in Airway Epithelia" by Lutful Kabir and colleagues (1). In this paper, the authors demonstrate that miR-145 mediates TGF-β (transforming growth factor-β) inhibition of synthesis and function of CFTR (cystic fibrosis transmembrane conductance regulator) in cystic fibrosis (CF) airway epithelia. Interestingly, they found that antagonists of miR-145 were able to interrupt TGF-β signaling and restore F508del CFTR modulation. Therefore, they suggested that miR-145 targeting may provide a novel therapeutic opportunity to enhance the benefit of F508del CFTR correction in CF epithelia. In agreement with this, we have elsewhere published data supporting the use of miR-145 targeting in CF, based on an antisense peptide nucleic acid (PNA) to target miR-145-5p (PNA-a145) and enhance expression of the *CFTR* gene, which we analyzed at mRNA (qRT-PCR) and protein (Western blotting) levels (2). In support of the conclusion by Lutful Kabir and colleagues, our data suggest the use of suitably delivered antisense molecules targeting miR-145-5p to enhance the expression of CFTR (2).

With respect to a possible microRNA (miRNA)-based therapeutic option, one limitation is of course the presence of more than 300 *CFTR* gene disease-causing mutations (www.genet.sickkids.on.ca/cftr/) (3). Besides the *CFTR* mutation leading to the deletion of the phenylalanine in position 508 (F508del CFTR), accounting for 50–90% CF chromosomes, most CF-causing mutations are missense (42%), nonsense (10%), frameshift (15%), splicing (13%), in-frame deletion/insertion (2%), and promoter (0.5%) mutations, which are now operationally categorized in six classes of molecular defects of the CFTR protein (3).

In consideration of these different molecular defects, it is expected that targeting miR-145 could be useful for type IV (less function), V (less protein), and VI (less stable protein) CFTR defects. For CFTR defects such as type I (no protein), II (no traffic), and III

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