artery pressure during exercise in ePAH have been unclear. Dynamic pulmonary vasoconstriction has been previously implicated (9, 10); however, in comparison with control subjects and subjects with PAH, our findings show the presence of a distinct vascular pathology at rest in subjects with ePAH, represented by increased perfusion heterogeneity across image resolutions (length scale spectrum 10–110 mm). Whether this pattern heralds permanent vascular remodeling cannot be determined by our data, and a longitudinal study will be required to definitively evaluate whether this pathology relates to an intermediate PAH phenotype (10) or whether this unique perfusion pattern represents a distinct disease process. ■

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Is Nitric Oxide Nephro- or Cardioprotective?

To the Editor:

We read with interest the article recently published in the *Journal* by Lei and colleagues entitled "Nitric Oxide Decreases Acute Kidney Injury and Stage 3 Chronic Kidney Disease after Cardiac Surgery" (1). In a single-center, prospective, randomized, controlled trial, the authors compared inhaled nitric oxide (NO) versus inhaled nitrogen (N_2), administered via the gas exchanger during cardiopulmonary bypass and then by inhalation for 24 hours postoperatively, in adult patients undergoing multiple-valve cardiac surgery. A total of 244 patients were included. Inhaled NO was associated with a lower incidence of acute kidney injury (50% in the NO group vs. 64% in the control group; relative risk, 0.78; 95% confidence interval, 0.62–0.97; $P = 0.014$). These findings might appear to contrast with previously published literature suggesting that NO is nephrotoxic (2).

Inhaled NO-associated renal injury has been suggested to result from tissue hypoxia and oxidative stress through NO by-products, including methemoglobin, NO_2^-, and NO_3^- (3). In the present study, the authors suggest that the nephroprotective effect of inhaled NO would arise from the prevention of plasma depletion of NO secondary to circulating plasma hemoglobin, thereby preserving microvascular perfusion. Plasma hemoglobin oxidation by NO inhalation could also reduce free hemoglobin–related toxicity to the kidney. This is, however, highly speculative. We propose a unifying mechanism that may account for some degree of nephroprotection in this setting, i.e., a cardioprotective effect. Right ventricular dysfunction is common after cardiopulmonary bypass and has been found to be associated with renal dysfunction (4). Many experimental and

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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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