Is Preoperative Endothelial Dysfunction a Potentially Modifiable Risk Factor for Renal Injury Associated With Noncardiac Surgery?

David R. McIlroy, MBBS, MClinEpi, FANZCA,*† Matthew T.V. Chan, MBBS, FANZCA,‡ Sophie K. Wallace, BSc, MPH,* Arvinder Grover, MBBS, FANZCA,* Emily G.Y. Koo, MBBS, FANZCA,‡ Jiajia Ma, MBBS,‡§ Joel A. Symons, MBBS, FANZCA,* and Paul S. Myles, MBBS, MPH, MD, FCARCSI, FANZCA, FRCA*

Objectives: **To determine whether preoperative endothelial dysfunction provides risk stratification for perioperative renal injury in patients undergoing noncardiac surgery. The relationship between perioperative renal injury and myocardial injury after noncardiac surgery (MINS) was explored secondarily.**

Design: **An observational study.**

Setting: **Two academic medical centers.**

Participants: **A total of 218 patients scheduled to undergo intermediate or high-risk noncardiac surgery.**

Interventions: **None.**

Measurements and Main Results: **Endothelial dysfunction was identified preoperatively by a Reactive Hyperemia-Peripheral Arterial Tonometry (RH-PAT) index. Renal injury was defined by peak delta serum creatinine (ΔS_{Cr}) or creatinine-based kidney disease: Improving global outcomes acute kidney injury (AKI) criteria within 7 days postoperatively. MINS was defined by peak troponin $\geq$0.04 μg/L within 3 days postoperatively. AKI occurred in 22 patients (10.1%). Median RH-PAT index within the study cohort was 1.64 (range 1.03-4.96) and did not differ between patients with or without AKI. When adjusted for covariates, there was no association between RH-PAT index and either AKI or peak ΔS_{Cr}. MINS occurred in 32 patients (14.7%) and was associated independently with the outcome of AKI (odds ratio [OR], 3.7; 95% confidence interval [CI], 1.2-10.8; $p = 0.02$) and peak ΔS_{Cr} (β-regression coefficient 23; 95% CI, 9-37; $p = 0.002$). Co-occurrence of AKI and MINS portended a marked increase in 30-day mortality (OR, 43; 95% CI, 6-305; $p = 0.001$) and delayed time to discharge (hazard ratio, 0.27; 95% CI, 0.13-0.54; $p = 0.001$).**

Conclusions: **For patients undergoing noncardiac surgery, preoperative endothelial function assessed by noninvasive peripheral arterial tonometry was not associated with perioperative AKI. Perioperative renal injury was associated strongly with MINS, and this may represent a mechanism by which AKI increases adverse outcomes.**

KEY WORDS: myocardial infarction, complications, renal complications, endothelium complications, noncardiac surgery

Perioperative acute kidney injury (AKI) is a major health care burden associated with increased complications and mortality.[1,2] However, mechanisms leading to adverse outcomes, particularly with lesser degrees of renal injury, remain obscure. Although AKI occurring after cardiac surgery has been the focus of extensive research, the risk factors for AKI occurring after noncardiac surgery are less well defined. Recent studies confirm that AKI after noncardiac surgery occurs commonly, with reported incidences ranging from 6% to 33%,[1–4] and the lack of established preventive or therapeutic options highlights the urgent need to identify potentially modifiable risk factors with the hope of reducing this burden of injury. Identification of end-organ interactions through which AKI may promote perioperative adverse events also might offer a potential target for therapeutic intervention.

The vascular endothelium is an active participant in various forms of vascular disease, capable of releasing soluble factors, including nitric oxide, to induce vasodilation while also reducing the tendency toward platelet aggregation, white blood cell adhesion, and proliferation of vascular smooth muscle.[5–8] Endothelial dysfunction in the coronary vasculature consistently has been demonstrated to predict adverse cardiac events.[8–10] Although the etiology of AKI likely is multifactorial, endothelial dysfunction is thought to play an important mediator role in various models.[11,12] However, it is unknown whether the presence of preoperative endothelial dysfunction represents an important and potentially modifiable risk factor for AKI in the perioperative context. Endothelial dysfunction has been reported in >33% of patients with or at high risk for coronary artery disease,[13] and several interventions, including the use of statins, polyphenols, various antioxidant compounds, and even continuous positive airway pressure devices for patients with obstructive sleep apnea, have been suggested as potentially able to reverse such dysfunction.[14–16]

No diagnostic test specific for renal endothelial dysfunction has been described. However, the EndoPAT-2000 (Itamar Medical Ltd., Caesarea, Israel) is an automated noninvasive device capable of detecting endothelial dysfunction using peripheral arterial tonometry in response to reactive hyperemia (Reactive Hyperemia-Peripheral Arterial Tonometry [RH-PAT]

*From the *Department of Anaesthesia & Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, Australia; †Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY; ‡Department of Anaesthesia & Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; and §Department of Anaesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.*

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Address reprint requests to: David R. McIlroy MBBS, MClinEpi, FANZCA, Department of Anaesthesia & Perioperative Medicine, Alfred Hospital, 55 Commercial Road, Melbourne, Victoria, 3004 Australia. E-mail: D.Mcilroy@alfred.org.au

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index).[17] It has been approved by the FDA and has received CE mark. Although validated against endothelial dysfunction in the coronary vasculature, the generalized nature of endothelial dysfunction makes it reasonable to expect that the EndoPAT-2000 also may reflect dysfunction of the renovascular endothelium. The authors have demonstrated the prognostic utility of the EndoPAT-2000 for identifying patients at risk for myocardial injury after noncardiac surgery (MINS),[18] and the rapid and noninvasive nature of this testing makes it potentially applicable as a preoperative screening tool. Preoperative identification of AKI risk using an RH-PAT index would support endothelial dysfunction as a preoperative risk factor for AKI while also providing a potential target to facilitate meaningful risk reduction through preoperative optimization.

Adding to data from an existing cohort previously reported with respect to myocardial injury,[18] the authors sought to identify risk factors for perioperative AKI after noncardiac surgery, focusing on the prognostic utility of preoperative, noninvasively measured endothelial dysfunction while secondarily exploring the association between AKI and myocardial injury after surgery.

METHODS

The study was carried out in 2 academic medical centers (Alfred Hospital, Melbourne, Australia, and Prince of Wales Hospital, Hong Kong, China). After obtaining approval from the research and ethics committees of each participating institution (Ethics Committee Project numbers 08/07, CRE-2008.444 and CRE-2013.267) and written informed consent from all participants, the authors conducted an observational study in patients undergoing noncardiac surgical procedures. Patients aged >40 years and scheduled to undergo nonemergent surgery identified as intermediate or high risk for postoperative cardiac complications using American College of Cardiology/American Heart Association guidelines[19] were enrolled. Patients requiring preoperative renal replacement therapy, identified as undergoing partial or complete nephrectomy, or with no postoperative serum creatinine (S_{Cr}) measurement within 7 days of surgery were excluded from analysis.

In addition to routine preoperative evaluation and any additional testing performed at the discretion of the treating physician, all study patients underwent noninvasive endothelial function assessment using the automated EndoPAT-2000 device. The principles of peripheral arterial tonometry (PAT) in response to reactive hyperemia previously have been described in detail.[20] In summary, proprietary technology is used to noninvasively measure the magnitude and dynamics of arteriolar tone changes in peripheral arterial beds. Similar to conventional pulse oximetry, a thimble-shaped pneumatic probe is placed on the tip of 1 finger on each hand where the volume of blood in the fingertip with each arterial pulsation is photoplethysmographically detected. After a brief period to establish baseline, a blood pressure cuff is inflated to suprasystemic pressure on 1 arm for approximately 5 minutes. After cuff deflation, the hyperemic response in the ipsilateral finger is evaluated, measuring the ratio of the pulsewave amplitude in this period to baseline pulsewave amplitude. This ratio is further normalized to the signal simultaneously obtained from the contralateral arm, accounting for potential effects of systemic changes in vascular tone. Calculations are performed by the device software, providing a bedside quantitative assessment of peripheral endothelial function with the option for manual adjustment of calculation points as deemed appropriate. A previous study reported an RH-PAT index <1.35 to be a useful indicator of coronary artery endothelial dysfunction,[17] although an RH-PAT index ≤ 1.22 previously has been identified and reported to have prognostic utility for perioperative MINS within the current study cohort.[18]

In addition to baseline demographics, data were collected on various comorbidities, including factors thought to potentially affect endothelial function, including hypercholesterolemia, use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, diabetes, and smoking status. The most recent S_{Cr} recorded up to and including the day before surgery was used as baseline, with preoperative estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[21] Peak daily postoperative S_{Cr} was recorded on each of postoperative days 1 to 7 as available, with frequency of measurement and all clinical decisions at the discretion of the treating medical team. Serum troponin was measured daily for the first 3 postoperative days as previously described, with MINS defined as any troponin ≥ 0.04 μg/L.[18] Coprimary endpoints were the maximum delta serum creatinine (ΔS_{Cr}) occurring within 7 days postoperatively, as well as the incidence of AKI defined by recent creatinine-based Kidney Disease: Improving Global Outcomes guidelines.[22] Additional outcomes included 30-day mortality and time to hospital discharge.

Statistical Analysis

Statistical analyses were performed using Stata 12 (StataCorp, College Station, TX). Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as counts and proportions. Logistic regression and Cox proportional hazards first determined the association between both AKI and maximum ΔS_{Cr}, with 30-day mortality and time to hospital discharge, confirming the clinical significance of these endpoints. Patients who died before discharge were assigned the longest observed time to discharge within the study cohort, ensuring that early in-hospital mortality did not spuriously reflect a favorable outcome.

Univariate and multivariate logistic regression then determined the relationship between preoperative measures of endothelial dysfunction and postoperative AKI, adjusting for potentially confounding variables selected on the basis of existing data and biologic plausibility while limiting the number of variables included in any given model to avoid overfitting. A multivariate linear regression model identified factors associated with maximum ΔS_{Cr} within 7 days postoperatively. Variables were included in this starting model only if significant for the outcome of maximum ΔS_{Cr} at $p < 0.10$ on univariate analysis. Manual, backward, stepwise elimination proceeded, eliminating the least significant variable at each step. This procedure continued until likelihood testing confirmed either a parsimonious model or that all remaining explanatory variables were significant statistically.