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Automated preoperative assessment of endothelial dysfunction and risk stratification for perioperative myocardial injury in patients undergoing non-cardiac surgery

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Editor's key points

- Non-invasive preoperative assessment of endothelial dysfunction could provide additional information for risk stratification.
- The association of reduced reactive hyperaemia-peripheral arterial tonometry (RH-PAT) index with myocardial injury was studied prospectively in subjects undergoing intermediate-high risk non-cardiac surgery.
- Risk stratification for myocardial injury was improved with the addition of RH-PAT, although there were unexplained differences in prognostic utility between study sites that could limit application.

Background. Myocardial injury after non-cardiac surgery (MINS) is a common complication with associated serious morbidity and mortality. Endothelial dysfunction might play an important role in MINS, and its rapid assessment could provide a novel method of risk stratification before surgery.

Methods. We studied 238 subjects scheduled to undergo intermediate or high-risk surgery in a two-centre prospective study to determine whether preoperative endothelial dysfunction identified by a reactive hyperaemia—peripheral arterial tonometry (RH-PAT) index could provide effective risk stratification for MINS, defined as serum troponin $\geq$0.04 μg litre^{-1}, within 3 postoperative days.

Results. The primary outcome occurred in 35 subjects (14.7%). Endothelial dysfunction was defined as an RH-PAT index of $\leq$1.22. Adjusted for age, Lee index and a composite measure of the extent of surgery, endothelial dysfunction was associated with MINS [odds ratio 10.1, 95% confidence interval (CI) 3.3–30.9, P=0.001] and increased time to discharge from hospital after surgery (hazard ratio 0.39, 95% CI 0.23–0.65, P=0.001). Endothelial dysfunction identified MINS with a sensitivity of 31%, a specificity of 96%, and a positive diagnostic likelihood ratio of 8.0. Risk classification for MINS was improved by the addition of RH-PAT-defined endothelial dysfunction to the Lee index (*c*-statistic increased from 0.69 to 0.77; integrated discrimination improvement 0.11, P=0.003). However, prognostic utility varied widely between sites.

Conclusions. For patients undergoing non-cardiac surgery, non-invasive assessment of endothelial function might enhance preoperative risk stratification for perioperative myocardial injury. However, unexplained large inter-site variation in prognostic utility could limit widespread application and needs to be further understood.

Keywords: complications; myocardium; preoperative care; risk assessment

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Myocardial injury is estimated to occur in ~10% of patients over the age of 45 undergoing non-cardiac surgery resulting in increased mortality, hospital length of stay, and cost.[1–3] Despite extensive efforts to develop accurate methods for predicting the risk of such complications in individual patients, the pathophysiology of perioperative myocardial injury remains incompletely understood and important mechanistic variations contribute to the limited prognostic utility of risk-stratification methods currently in use.[4 5] While an imbalance between increased myocardial oxygen demand in the early postoperative period and limited myocardial oxygen supply secondary to significant obstructive coronary artery disease is believed to contribute to a substantial proportion of perioperative injury, rupture or complication of vulnerable coronary plaques might represent an additional mechanism.[6 7] Although significant obstructive coronary artery disease can be detected before operation with myocardial stress testing or coronary angiography, 'non-obstructive' but vulnerable plaques are likely to be missed.

The vascular endothelium is an active participant in vascular disease including coronary artery disease.[8–10] Vascular

endothelium releases various soluble factors including nitric oxide to induce vasodilation while also reducing platelet aggregation, white cell adhesion and proliferation of vascular smooth muscle.[11] Endothelial dysfunction is characterized by a reduction in this response, and multiple studies confirm that coronary artery endothelial dysfunction is associated with an increased incidence of adverse cardiovascular events.[10 12 13] The gold standard for identifying coronary artery endothelial dysfunction is the vasodilatory response to graded intra-coronary infusion of acetylcholine combined with quantitative coronary angiography and Doppler flow measurements.[8 14] However, endothelial dysfunction is a systemic disorder and less invasive methods have been developed and validated.[15–17] The EndoPAT 2000 (Itamar Medical Ltd, Caesarea, Israel) is an automated non-invasive device capable of detecting endothelial dysfunction using peripheral arterial tonometry (PAT) in response to reactive hyperaemia (RH-PAT index). The potential for rapid testing and relative operator independence[17] together with demonstrated reproducibility[18] represent potentially important strengths of this device. It is both approved by the US Food and Drug Administration and Conformité Européenne (CE) marked. Although previous studies have shown that the RH-PAT index identifies coronary artery endothelial dysfunction,[16] it is unknown whether this novel technique can provide information for cardiac risk stratification in patients undergoing non-cardiac surgery. We sought to determine whether endothelial dysfunction identified by an RH-PAT index could provide a useful risk-stratification tool for adverse cardiac events in at-risk adults undergoing non-cardiac surgery.

Methods

The study was carried out in two academic centres (Alfred Hospital, Melbourne, Australia and Prince of Wales Hospital, Hong Kong, China). After obtaining approval from the human research ethics committee of each participating institution and written informed consent from all participants, we conducted a prospective observational study in patients undergoing non-cardiac surgical procedures. Patients aged >40 yr and scheduled to undergo non-emergent surgery identified as intermediate or high risk for postoperative cardiac complications using American College of Cardiology/American Heart Association (ACC/AHA) guidelines[19] were screened.

In addition to routine preoperative evaluation and testing performed at the discretion of the attending physician, all study subjects underwent non-invasive endothelial function assessment using the automated EndoPAT 2000 device. The principles of PAT in response to reactive hyperaemia have been described.[20] In brief, it uses proprietary technology to measure the magnitude and dynamics of arteriolar tone changes in peripheral arterial beds non-invasively. A thimble-shaped pneumatic probe is applied to the tip of one 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, an arterial pressure cuff is inflated on one arm to supra-systemic pressure for a period of ~5 min. After cuff deflation, the hyperaemic response in the ipsilateral finger is evaluated, measuring the ratio of the pulse wave amplitude (PWA) in this period to baseline PWA. This ratio is further normalized to the signal simultaneously obtained from the contralateral arm, thus accounting for potential effects of systemic changes in vascular tone (Fig. 1). A previous study reported an RH-PAT index of <1.35 to be a useful indicator of coronary artery endothelial dysfunction.[16]

In addition to baseline patient characteristics, data were collected on known or suspected risk factors for perioperative cardiac morbidity (PCM) or mortality and factors that can impact on endothelial function. The revised cardiac risk (Lee) index was calculated for each subject,[21] while the treating clinician further assessed each subject's level of risk as low, moderate, or high for each of surgery-specific factors, clinical predictors, and functional status reflecting AHA/ACC guidelines[19] providing a global, albeit more subjective, metric of clinician-perceived risk. Additional preoperative investigations to further stratify or attenuate cardiac risk were performed at the discretion of the treating physician as part of the preoperative evaluation.

Serum troponin (Tn) was measured daily for the first 3 postoperative days with all management decisions at the discretion of the attending medical team. In Melbourne, Tn-I was measured with the Architect Stat System (Abbott Diagnostics, Lake Forrest, IL, USA), while in Hong Kong Tn-T was measured using the fourth-generation Elecsys assay (Roche diagnostics, Basel, Switzerland). For the Tn-T assay, despite a manufacturer-reported 99th percentile of 0.01 μg litre^{-1} for a normal population, the Hong Kong laboratory reports a 10% coefficient of variation (CV) of 0.035 μg litre^{-1} (unpublished data). For the Tn-I assay, the manufacturer reports the 99th percentile as 0.012 μg litre^{-1} in a normal population with 10% CV as low as 0.032 μg litre^{-1}. However, published data from the Melbourne laboratory reports the 99th percentile for Tn-I within a normal population as 0.03 μg litre^{-1} with a 10% CV near this level.[22] We subsequently considered Tn-I or Tn-T values of 0.03 μg litre^{-1} as normal with values above this representing myocardial injury, and therefore defined a common primary end-point of myocardial injury after non-cardiac surgery (MINS) as a peak Tn (I or T) of ≥0.04 μg litre^{-1} within the first 3 days of surgery across study sites.

Subjects were contacted by telephone 30 days after operation seeking to identify cardiac complications including coronary artery intervention or mortality occurring after discharge. Secondary end-points included PCM defined as the composite of coronary artery intervention or all-cause mortality within 30 days of surgery or Tn ≥0.04 μg litre^{-1} within 3 days of surgery. Time to hospital discharge was also assessed as a global measure of freedom from complications.

Statistical analysis

Statistical analyses were performed using Stata 12 (StataCorp, College Station, TX, USA). Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to distribution. Categorical variables are presented as counts and proportions. Receiver