BJA Advance Access published May 31, 2014

British Journal of Anaesthesia Page 1 of 9
doi:10.1093/bja/aeu135

BJA

Endothelial progenitor cell mobilization by preoperative exercise: a bone marrow response associated with postoperative outcome

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Editor's key points

- Mobilization of endothelial progenitor cells (EPCs) by preoperative exercise was studied as a predictor of postoperative complications.
- In 60 subjects undergoing major thoracic surgery, the exercised-induced increase in EPC number correlated with reduced postoperative complications.
- Whether this response is causative or associative is unknown, but it could provide a useful marker for preoperative risk stratification.

Background. Preoperative anaemia is associated with increased morbidity in patients undergoing major surgery. Whether erythrocytes are the only bone-marrow-derived cell lineage that associates with increased surgical complications is unknown. This prospective observational trial studied the mobilization of endothelial progenitor cells (EPCs) in response to exercise in association with postoperative complications.

Methods. After IRB approval, 60 subjects undergoing major thoracic surgery were exercised to exhaustion (peak $\dot{V}_{O_2}$). Peripheral blood collected before and after peak exercise was quantified for EPC lineages by fluorescence-activated cell sorter analysis. Complication analysis was based on the Clavien–Dindo classification.

Results. Exhaustive exercise increased EPC [CD45−133+34+ cells=150 (0.00–5230) to 220 (0.00–1270) cells μl^{-1}; median change (range)=20 (−4,180–860) cells μl^{-1}; P=0.03] but not mature endothelial cell (EC) subpopulations. Pre-exercise levels [odds ratio (OR)=0.86, 95% confidence interval (CI): 0.37–2.00, P=0.72), change after exercise as a continuous variable (OR=0.95, 95% CI: 0.41–2.22, P=0.91) and a positive response after exercise (change >0 cells μl^{-1}; OR=0.41, 95% CI: 0.13–1.28, P=0.12) were not statistically significantly associated with the incidence of postoperative complications. Post-hoc receiver operating characteristic curve analyses revealed that subjects with a CD45−133+34+ increase ≥60 cells μl^{-1} in response to exercise suffered fewer postoperative complications [86% sensitivity, 48% specificity and AUC=0.67 (95% CI: 0.52–0.81)].

Conclusions. Preoperative exercise induces EPC into the peripheral circulation. Subjects with a poor EPC response had a pre-existing propensity for postoperative complications. This warrants further research into the role of bone marrow function as a critical component to endothelial repair mechanisms.

Clinical trial registration. IRB 2003-0434 (University of Texas M.D. Anderson Cancer Center, Houston, TX, USA).

Keywords: training; vascular

Accepted for publication: 1 February 2014

A bone marrow-derived response that mobilizes cells into the peripheral circulation [e.g. reticulocytes with blood loss, leucocytes with infection, and endothelial progenitor cells (EPCs) for vascular repair] is crucial to regenerative responses that follow injury.[1] This cellular response is less appreciated (compared with the humoral/endocrine/metabolic response) component of the surgical stress response and the ensuing repair phase. Failure of a cellular response can have detrimental consequence(s). Preoperative anaemia is associated with increased morbidity and mortality in patients undergoing major surgery.[2]

Whether erythrocytes are the only bone marrow-derived lineage that associates with increased postoperative complications is unknown.

The mobilization of bone marrow-derived EPC plays a key role in vascular/endothelial repair. New vessel formation is regulated by paracrine effects via angiogenesis and endothelial colony-forming cells (ECFCs) potentially differentiate into mature endothelial cells (ECs) with vessel-forming ability.[3] Poor mobilization of EPCs into the peripheral circulation associates with reduced survival after critical illness, including septic shock;[4 5] however, it is unknown whether such poor mobilization is associated with postoperative complications.

Given that short-term exercise mobilizes EPCs into the peripheral circulation in healthy volunteers[6] and that EPC mobilization in response to critical illness has prognostic value,[5] we hypothesized that preoperative exhaustive exercise to mobilize EPCs, used as a surrogate stressor to mimic surgical stress, has prognostic potential for patients at risk of postoperative complications and potentially provide a novel therapeutic target for reducing postoperative complications. As such, this prospective observational study evaluated the dynamic bone-marrow responsiveness, characterized by EPC mobilization to a planned preoperative stressor, and whether poor bone marrow response is associated with postoperative complications.

Methods

Study population

After Institutional Review Board (The University of Texas, M.D. Anderson Cancer Center) approval, 60 consecutive adult subjects undergoing major thoracic surgery, including oesophagectomy, or lung resection (wedge resection, lobectomy or pneumonectomy), were enrolled in this prospective observational study. Major thoracic surgery was defined as procedures requiring thoracotomy. Thoracoscopic surgeries were not included taking into account the differences in complication rates between minimally invasive and open surgical procedures. A detailed list of surgery types is presented in Table 1.

Each subject gave written informed consent after receiving a thorough explanation of the study design and protocol. Predefined exclusion criteria included: inability to exercise above their anaerobic threshold (AT), thereby ensuring a valid cardiopulmonary exercise test (CPET) of sufficient exercise load was achieved, and any medical condition that deemed subjects unsatisfactory for surgery after their pre-anaesthetic evaluation, including a recent (<3 months prior) history of myocardial infarction, venous thromboembolism, and cerebrovascular accident.

Preoperative comorbidities were defined as: history of smoking, diabetes mellitus, cardiovascular disease (presence of hypertension, coronary artery disease, peripheral artery disease), history of chemoradiation therapy, modified Lee cardiac risk index >2, and ASA Physical Status Classification score >2 and the Charlson weighted index of comorbidity.

Postoperative complications were defined as: *cardiac events*, including myocardial ischaemia (with or without myocardial infarction), dysrhythmias, congestive heart failure, and postoperative requirement of vasopressors; *pulmonary events*, including prolonged intubation, postoperative re-intubation, pneumonia, acute lung injury (ALI), and acute respiratory distress syndrome; *wound healing events*, including wound infection, empyema, and sepsis; and *surgical events*, including prolonged air leak (>5 days), oesophageal leak, and any other re-operative event. Detailed definitions of these postoperative complications are displayed in the Supplementary Appendix. Complications were analysed according to the Clavien–Dindo classification.[7]

A blinded researcher reviewed the medical records for occurrence of these predefined perioperative comorbidities and postoperative complications according to the Clavien–Dindo classification. These data were collected for the period of subjects' hospital stay.

Study design and intervention

Cardiopulmonary exercise testing

Before exercise, baseline observations (heart rate, arterial pressure, pulse oximetry, ECG) and static pulmonary function tests (forced expiratory volume at 1 s, forced vital capacity, maximal voluntary ventilation) were recorded for all subjects. CPET was performed as a multi-stage incremental ('ramp workload') study using a cycle ergometer and a metabolic cart with standardized exercise software (Medgraphic Cardio-2CP system, Medical Graphics Corporation, St Paul, MN, USA) for breath-by-breath analysis of gas exchange.

An initial acclimation period consisted of breath-by-breath gas exchange analysis performed in the supine resting position for 5 min. After acclimation the subject pedalled in the upright position at 60 rpm with minimal resistance (unloaded work) for 3 min. After 3 min, loaded work (increasing pedal resistance, watts per minute) followed a standardized ramp protocol to maximal symptom limited exertion that typically lasted 9–12 min. Exercise was terminated by the subject or by the study investigator if symptoms of cardiovascular, pulmonary distress, fatigue, or both were observed. Gas exchange analysis recorded oxygen consumption ($\dot{V}_{O_2}$, ml min kg^{-1}) and carbon dioxide production ($\dot{V}_{CO_2}$, ml min kg^{-1}) at all phases of exercise. AT (ml min kg^{-1}) was defined as peak $\dot{V}_{O_2}$ at the inflection point as determined by the modified V-slope method of plotting carbon dioxide excretion ($\dot{V}_{CO_2}$) against oxygen uptake ($\dot{V}_{O_2}$) during increasing exercise intensity, as described by Wassermann.[8] The peak $\dot{V}_{O_2}$ was defined as the highest oxygen consumption achieved during the exercise test.

To ensure a comparable amount of perceived exertion, subjects were required to reach the individual AT during the exercise session and encouraged during exercise to achieve true peak $\dot{V}_{O_2}$. Subjects failing to reach the AT were excluded.

EPC analysis by flow cytometry

Blood was collected before and 10 min after peak exercise, using EDTA as an anticoagulant. Blood samples were frozen according to the freezing/thawing procedure described by Norden-Zfoni and colleagues.[9] In brief, blood was collected in