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Cardiopulmonary exercise testing before and after blood transfusion: a prospective clinical study

S. E. Wright[1]*, B. Pearce[1], C. P. Snowden[1], H. Anderson[1] and J. P. Wallis[2]

[1] Perioperative and Critical Care Directorate and [2] Department of Haematology, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK

* Corresponding author. E-mail: stephen.wright@nuth.nhs.uk

Editor's key points

- Anaemia reduces exercise tolerance and increases risks after major surgery.
- However, the effect of red cell transfusion on exercise capacity in anaemic patients is unknown.
- In this small study, patients with chronic anaemia underwent cardiopulmonary exercise testing before and after allogeneic red cell transfusion.
- Mean anaerobic threshold and other measures of exercise capacity increased after transfusion.
- These effects were not universal and further studies are needed.

Background. Cardiopulmonary exercise testing (CPET) is used to risk-stratify patients undergoing major elective surgery, with a poor exercise capacity being associated with an increased risk of complications and death. Patients with anaemia have a decreased exercise capacity and an increased risk of morbidity and mortality after major surgery. Blood transfusion is often used to correct anaemia in the perioperative period but the effect of this intervention on exercise capacity is not well described. We sought to measure the effect of blood transfusion on exercise capacity measured objectively with CPET.

Methods. Patients with stable haematological conditions requiring blood transfusion underwent CPET before and 2–6 days after transfusion.

Results. Twenty patients were enrolled and completed both pre- and post-transfusion tests. The mean (SD) haemoglobin (Hb) concentration increased from 8.3 (1.2) to 11.2 (1.4) g dl^{-1} after transfusion of a median (range) of 3 (1–4) units of packed red cells. The anaerobic threshold increased from a mean (SD) of 10.4 (2.4) to 11.6 (2.5) ml kg^{-1} min^{-1} (P=0.018), a mean difference of 1.2 ml kg^{-1} min^{-1} (95% confidence interval (CI)=0.2–2.2). When corrected for the change in Hb concentration, the anaerobic threshold increased by a mean (SD) of 0.39 (0.74) ml kg^{-1} min^{-1} per g dl^{-1} Hb.

Conclusions. Transfusion of allogeneic packed red cells in anaemic adults led to a significant increase in their capacity to exercise. This increase was seen in the anaerobic threshold, and other CPET variables.

Keywords: adult; anaemia; anaerobic threshold; erythrocyte transfusion; exercise test; humans; oxygen consumption; physical exertion; pulmonary gas exchange

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Cardiopulmonary exercise testing (CPET) provides a non-invasive, objective assessment of cardiorespiratory function during exercise. In the preoperative setting, CPET is increasingly used to risk-stratify patients undergoing major elective surgery.[1] Decreased exercise capacity has been associated with an increased risk of postoperative complications and death after a variety of major surgical procedures.[2–5] Decreased exercise capacity is also a feature of anaemia,[6] along with subjective symptoms of lethargy and fatigue. Preoperative anaemia is common, occurring in ∼30% of patients presenting for major non-cardiac surgery, and is independently associated with an increased risk of 30-day morbidity and mortality.[5 7 8] This association between preoperative anaemia and perioperative risk is likely to be at least partly because of the reduced oxygen carrying capacity of blood leading to decreased oxygen delivery to the tissues.[9] Residual confounders are also likely because of the association of anaemia with other risk factors such as chronic disease, malnutrition, and frailty.[10–12]

Blood transfusion is often used to correct preoperative anaemia and acute anaemia resulting from blood loss in the perioperative period. In contrast to the situation in the critically ill, the optimum target haemoglobin (Hb) concentration for patients undergoing major non-cardiac surgery is not known.[13] A better understanding of the relationship between preoperative Hb concentration, exercise capacity, and perioperative risk will require a broad programme of research, including observational studies using existing perioperative datasets, large-scale epidemiological studies,[7 13 14] and interventional studies to measure the effect of blood transfusion on exercise capacity objectively. We identified two studies of the effects of transfusion on exercise in children or young adults with thalassaemia,[15 16] and studies in healthy volunteers or athletes transfused autologous red blood cells.[17] We could find no studies measuring the change in exercise capacity using CPET in anaemic adult patients transfused with allogeneic red cells.

We undertook this study to evaluate the effects of blood transfusion on exercise capacity, measured objectively using CPET.

Methods

The study was approved by the Newcastle and North Tyneside 1 Research Ethics Committee (11/H0906/9) and written informed consent was obtained from all participants. Between May 2011 and July 2012, patients attending either the haematology outpatient clinic or the haematology day ward in our hospital were screened by the investigators. Patients over the age of 18 yr requiring a transfusion of packed red blood cells for chronic anaemia were identified. Patients undergoing chemotherapy for a haematological malignancy were excluded, as were those where the blood transfusion was judged clinically urgent by the patient's haematologist. The other exclusion criteria were: a lack of capacity to give informed consent; inadequate understanding of English to undertake CPET; a physical disability preventing CPET; angina or intermittent claudication on moderate exercise; shortness of breath at rest; or any contraindication to exercise testing in either our local CPET policy, or the CPET guidelines published by the American College of Cardiology/American Heart Association.[18]

After giving informed consent, the first CPET was arranged for the morning of the patient's scheduled blood transfusion and the second CPET for 3–5 days later. The second test was delayed at least 72 h to allow time for regeneration of 2,3-diphosphoglycerate (DPG) in stored red blood cells.[19] A blood sample was obtained at the time of each test to determine Hb concentration, unless one had been taken in the previous 24 h. The number of units of packed red cells transfused was determined by the patient's haematologist and was not influenced by the patient's participation in the study. All transfusions were given in our haematology day ward using leucodepleted, allogeneic packed red blood cells in optimum additive solution. The mean (SD) age of red cells transfused was 19 (6) days.

CPET was performed in the Pre-Assessment Clinic by one of two specialist CPET practitioners. CPET equipment included an electronically braked cycle ergometer, 12 lead electrocardiogram (ECG), and a metabolic cart. The metabolic cart has oxygen and carbon dioxide analysers with a rapid response time enabling breath-by-breath measurement. Flow and gas calibration were performed manually before each test. VO_2, VCO_2, heart rate, minute ventilation, and work rate are displayed continuously throughout the test. The increment in work rate was determined using equations to estimate the expected work capacity, aiming for a test duration of between 6 and 10 min. Initially, 2–5 min of resting data were recorded, followed by 1–3 min of unloaded cycling, followed by a ramped increase in workload. The test was stopped by the patient if requested because of fatigue, pain, light headedness, or by failure to maintain >40 rpm for more than 30 s despite encouragement. The test was stopped by the specialist CPET practitioner if any of the premature stopping criteria in our local CPET policy were met; these include cardiac chest pain, ischaemic ECG changes, hypertension (systolic blood pressure (BP) >250 mm Hg or diastolic BP >120 mm Hg), hypotension (fall in systolic BP >20 mm Hg during the test), or severe oxygen desaturation (Sp_{O_2}<80%). On completion of the exercise phase of the test, monitoring continues until the heart rate is within 10% of baseline.

Patients were given a unique identifying number on the CPET database. The CPET reports were displayed in the standard 9-panel format and V-slope comparison plot compiled by Breeze (Medical Graphics Corporation, St Paul, MN, USA) but presented without any data identifying the patient, the Hb concentration, or whether the test was done before or after transfusion. The reports were interpreted independently by two Consultant Anaesthetists, who compared results and agreed a consensus on all reports.

Statistical analysis was performed using Minitab 16 (Minitab, Inc., State College, PA, USA). Descriptive statistical terms have been used to describe the patient characteristics in our study. Hb concentration and CPET data were checked for normality with the Ryan–Joiner test, a correlation-based test similar to the Shapiro–Wilk test. Paired *t*-tests were used to compare variables measured before and after blood transfusion including Hb concentration, anaerobic threshold, peak VO_2, and other CPET variables. The CPET variables that are ratios (VE/VCO_2) were log-transformed before performing the paired *t*-test. After checking for normality, an unpaired *t*-test was used for the *post hoc* analysis of the patients who failed to increase their anaerobic threshold with transfusion. All tests were two-sided with a significance level of 0.05.

Results

Twenty patients were enrolled in our study. One patient developed an ischaemic ECG during their first test, which was stopped immediately as per protocol; their data have not been included in the analysis. Another patient did not attend for their second test as they felt unwell but returned 3 months later and completed both tests at the time of their next transfusion. In one patient the anaerobic threshold could not be determined from the V-slope plot, and consequently, the CPET variables dependent on the anaerobic threshold are reported for 18 patients, while the other CPET variables are reported for 19 patients. Hb concentration and all CPET variables were normally distributed.

The patient characteristics, including their underlying haematological diagnoses, are given in Table 1. After their first CPET, patients were transfused a median (range) of 3 (1–4) units of packed red cells. Blood transfusion increased the patients' Hb concentration from a mean (SD) of 8.3 (1.2) to 11.2 (1.4) g dl^{-1} (P<0.001), a mean (SD) increase in Hb of 2.9 (1.2) g dl^{-1}, 95% CI=2.3–3.4. The second CPET was performed a median (range) of 4 (2–6) days after blood transfusion. After transfusion, the mean (SD) anaerobic threshold increased from 10.4 (2.4) to 11.6 (2.5) ml kg^{-1} min^{-1} (P=0.018), a mean difference of 1.2 ml kg^{-1} min^{-1}, 95% CI=0.2–2.2. Within this overall