

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

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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. $\dot{V}O_2$, $\dot{V}CO_2$, 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 $\dot{V}O_2$, and other CPET variables. The CPET variables that are ratios ($\dot{V}E/\dot{V}CO_2$) 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

Table 1 Patient characteristics. Values are expressed as mean (range), mean (SD), or frequency

Variable	n=19
Age (yr)	66 (40–77)
Height (cm)	170 (8)
Weight (kg)	76 (16)
Primary haematological diagnosis	
Myelodysplasia	8
Hypoplastic anaemia	1
Sideroblastic anaemia	1
Pure red cell aplasia	1
Autoimmune haemolytic anaemia	1
Thalassemia intermedia	1
Chronic lymphocytic leukaemia	3
Chronic myeloid leukaemia	2
Non-Hodgkin's lymphoma	1

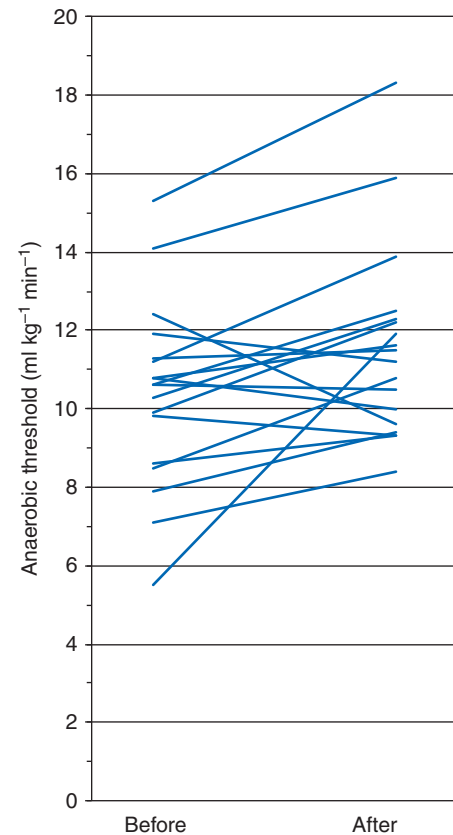
result, there was some individual variation in the response to blood transfusion: anaerobic threshold increased in 13 patients, decreased in one patient, and showed little change in four patients (Figs 1 and 2). After blood transfusion, peak VO_2 increased from 13.9 (3.6) to 15.4 (3.4) $\text{ml kg}^{-1} \text{min}^{-1}$ ($P=0.016$), a mean difference of 1.5 $\text{ml kg}^{-1} \text{min}^{-1}$ (95% CI=0.3–2.7). The changes seen in other CPET variables are given in Table 2. When adjusted for the change in Hb concentration, the mean (SD) anaerobic threshold increased by 0.39 (0.74) $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} increase in Hb, and the mean (SD) peak VO_2 increased 0.57 (0.77) $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} increase in Hb.

We undertook a *post hoc* analysis of the five patients in whom the anaerobic threshold failed to increase after transfusion. In these patients, blood transfusion had resulted in a smaller increase in Hb, mean (SD) 1.9 (0.6) g dl^{-1} , compared with 3.1 (1.2) g dl^{-1} in those patients in whom anaerobic threshold had increased after transfusion ($P=0.014$).

Discussion

We found that transfusion of packed red cells, in adults anaemic because of chronic haematological conditions, led to a significant increase in exercise capacity measured objectively with CPET. The improvement was seen in sub-maximal exercise variables (anaerobic threshold and oxygen-uptake efficiency slope) and effort-related variables (work and peak VO_2). On average, the anaerobic threshold increased by 0.4 $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} increase in Hb.

We believe that this study is the first to assess the change in anaerobic threshold seen after blood transfusion in anaemic adults. Our results are consistent with those of a similar study involving 11 children with beta-thalassaemia who underwent a treadmill CPET before and after allogeneic blood transfusion. Exercise duration and oxygen consumption (VO_2) were significantly higher 2 h after blood transfusion, although the average baseline VO_2 was higher than in our study group.¹⁵ Another study in children and young adults with beta-thalassaemia¹⁶ failed to show any benefit in peak VO_2 with

**Fig 1** Change in anaerobic threshold before and after blood transfusion.

blood transfusion, although the average baseline Hb concentration was 11.1 g dl^{-1} compared with 8.1 g dl^{-1} in the study by Marinov and colleagues¹⁵ and 8.3 g dl^{-1} in our study.

Two other studies in healthy adults assessed the effect of blood donation, rather than transfusion, on exercise capacity; both found a significant decrease in VO_2 and anaerobic threshold following donation of 450–500 ml of blood.^{20 21} Similar to our findings, the effect of blood donation was not consistent from individual to individual with some participants having either no change or an improvement in exercise capacity with blood donation.

The effects of raising the Hb concentration with erythropoietin (EPO) on exercise capacity have also been studied. In young patients with end-stage renal failure,²² and in patients with chronic heart failure,^{23 24} treatment with EPO was associated with a significant increase in exercise capacity. In the study by Metra and colleagues,²² anaerobic threshold increased by 1.28 $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} Hb at 1 month and 0.45 $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} Hb at 3 months. The 3-month value is similar to that found in our study (0.43 $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} Hb). Mancini and colleagues²³ found that anaemic patients with moderate-to-severe chronic heart failure given EPO had an improvement in peak VO_2 of 0.51 $\text{ml kg}^{-1} \text{min}^{-1}$ per g dl^{-1} of Hb. While Cohen and

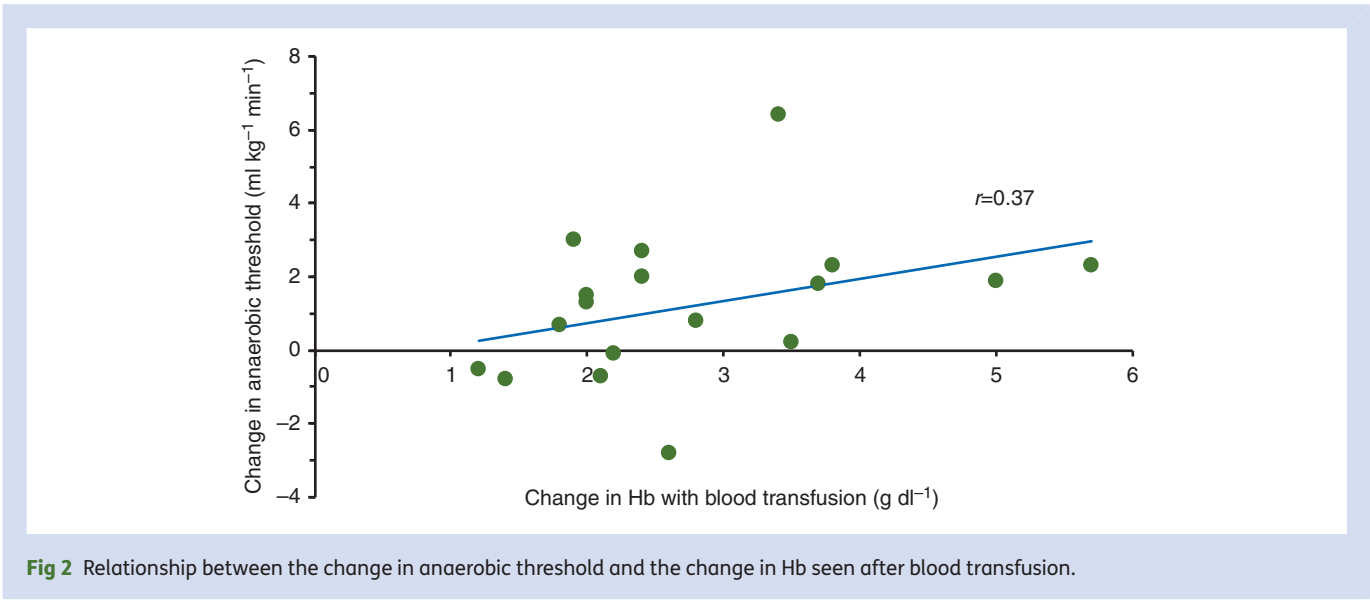


Fig 2 Relationship between the change in anaerobic threshold and the change in Hb seen after blood transfusion.

Table 2 Cardiopulmonary exercise test results from before and after blood transfusion. Values are expressed as mean (SD). VO₂, oxygen consumption; AT, anaerobic threshold; OUES, oxygen-uptake efficiency slope; and VE/VCO₂, ventilatory equivalent for carbon dioxide

	Before	After	Mean difference (95% CI)	P-value	n
Work (W)	82.3 (25.8)	93.6 (28.3)	11.3 (6.0, 16.6)	<0.001	19
Peak VO ₂ (ml kg ⁻¹ min ⁻¹)	13.9 (3.6)	15.4 (3.4)	1.5 (0.3, 2.7)	0.016	19
AT (ml kg ⁻¹ min ⁻¹)	10.4 (2.4)	11.6 (2.5)	1.2 (0.2, 2.2)	0.018	18
OUES	1133 (369)	1311 (300)	178 (64, 293)	0.004	19
VE/VCO ₂ at AT	36.3 (5.9)	34.1 (4.2)	-2.2 (-0.9, -3.6)	0.004	18

colleagues²⁴ found that in anaemic patients with diastolic heart failure, 3-month treatment with EPO increased peak VO₂ by 0.86 ml kg⁻¹ min⁻¹ per g dl⁻¹ Hb. These results are similar to those of our study where peak VO₂ increased by 0.57 ml kg⁻¹ min⁻¹ per g dl⁻¹ Hb.

The changes we observed in CPET variables can be considered with regard to the principles of oxygen transport and the physiological adaptation to anaemia.²⁵ From the Fick principle, oxygen consumption (VO₂) is equal to the product of cardiac output and the arterial-venous oxygen difference (C_A - C_V), where C_A and C_V are the arterial and mixed-venous O₂ content. During exercise, VO₂ is increased by an increase in cardiac output and an increase in arterial-venous oxygen difference (attributable to the decrease in the mixed-venous O₂ content). After blood transfusion, arterial-venous oxygen difference will also increase because of an increase in arterial oxygen content (C_A). The effect of blood transfusion on cardiac output in patients with normovolaemic anaemia is less predictable. In some patients, particularly those where cardiac output is limited by cardiac ischaemia, blood transfusion may increase peak VO₂ by a direct beneficial effect on cardiac function.⁹ The improvement in ventilatory efficiency (VE/VCO₂) we observed during exercise could be explained by an improvement in pulmonary perfusion (because of improved

cardiac output), an augmented Haldane effect arising from the greater C_A - C_V,²⁶ or by a decrease in the hyperventilation that tends to accompany exercise in patients with anaemia.²⁷

Five of our patients failed to increase their anaerobic threshold after transfusion and we reviewed their CPET reports, clinical records, and blood transfusion data for any possible reasons. We could find no documented evidence of an acute illness or other clinical problem at the time of the testing that might account for the apparently anomalous results. Other CPET variables were not always consistent with the measured anaerobic threshold; two patients had an increase in oxygen-uptake efficiency slope and three patients had an increase in peak VO₂ after blood transfusion. The potential for the age of red blood cells to influence the results was difficult to assess, although we found no difference in the mean age of blood received. In any case, the time between transfusion and the second CPET (median 4 days) should have been sufficient for 2–3 DPG levels to be restored. The apparent lack of effect in these patients may be partly accounted for by a smaller than average increment in Hb concentration with transfusion and also by the small but recognized test-to-test variability of CPET.²⁸ It is possible that other factors, such as outflow obstruction, may have limited cardiac output in some patients independent of Hb concentration.

Our study had several weaknesses. The study group was relatively small and although the paired test study design is efficient, the small sample size decreases the precision of our results. The study participants were not blinded to the intervention or hypothesis raising the possibility that they gave more effort to the second test. While this may have impacted on the peak VO_2 , the sub-maximal parameters (anaerobic threshold and oxygen-uptake efficiency slope) should be unaffected by patient effort. Similarly, we believe it is unlikely that a learning effect could explain the increase in anaerobic threshold seen in the second tests.²⁸

Care is needed in extrapolating the results of this study directly to the perioperative setting. The patients all had significant haematological conditions and are unlikely to be representative of the population typically presenting for major elective surgery. These data do not show, nor was it an aim of our study, that improving a patient's exercise capacity by transfusion decreases their perioperative risk. A low preoperative Hb may be associated with a higher risk of perioperative complications or death, but the concentration of Hb below which blood transfusion is beneficial remains to be determined. Indeed, the limited data available from high-quality randomized controlled trials would support a more conservative approach to blood transfusion in the perioperative period.²⁹ Further information should be gained from an ongoing trial assessing preoperative i.v. iron to treat anaemia in patients undergoing major abdominal surgery.³⁰

In conclusion, in a cohort of adults anaemic because of underlying haematological conditions, blood transfusion led to an increased capacity to exercise; this effect was seen in the anaerobic threshold, and other CPET variables.

Authors' contributions

J.P.W., C.P.S., S.E.W., and B.P. conceived the study. B.P., S.E.W., and J.P.W. recruited participants. C.P.S. and H.A. interpreted the CPET reports. S.E.W. carried out the statistical analysis. S.E.W. and B.P. drafted the manuscript, with revision by the other authors. All the authors read and approved the final manuscript.

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Declaration of interest

None declared.

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