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CLINICAL INVESTIGATION

The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference

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Abstract

Background: Cardiorespiratory fitness can inform patient care, although to what extent natural variation in CRF influences clinical practice remains to be established. We calculated natural variation for cardiopulmonary exercise test (CPET) metrics, which may have implications for fitness stratification.

Methods: In a two-armed experiment, critical difference comprising analytical imprecision and biological variation was calculated for cardiorespiratory fitness and thus defined the magnitude of change required to claim a clinically meaningful change. This metric was retrospectively applied to 213 patients scheduled for colorectal surgery. These patients underwent CPET and the potential for misclassification of fitness was calculated. We created a model with boundaries inclusive of natural variation [critical difference applied to oxygen uptake at anaerobic threshold ($\dot{V}O_2$-AT): 11 ml O_2 kg^{-1} min^{-1}, peak oxygen uptake ($\dot{V}O_2$ peak): 16 ml O_2 kg^{-1} min^{-1}, and ventilatory equivalent for carbon dioxide at AT (V_E/VCO_2-AT): 36].

Results: The critical difference for $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT was 19%, 13%, and 10%, respectively, resulting in false negative and false positive rates of up to 28% and 32% for unfit patients. Our model identified boundaries for unfit and fit patients: AT <9.2 and ≥13.6 ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak <14.2 and ≥18.3 ml kg^{-1} min^{-1}, $\dot{V}_E/\dot{V}CO_2$-AT ≥40.1 and <32.7, between which an area of indeterminate-fitness was established. With natural variation considered, up to 60% of patients presented with indeterminate-fitness.

Conclusions: These findings support a reappraisal of current clinical interpretation of cardiorespiratory fitness highlighting the potential for incorrect fitness stratification when natural variation is not accounted for.

Keywords: anaerobic threshold; cardiopulmonary exercise test; risk assessment

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Editor's key points

- Cardiorespiratory fitness affects outcome from major surgery and may be assessed using cardiopulmonary exercise testing (CPET) but there are few data on the natural variation in CPET measures.
- The critical difference accounts for both imprecision in measurements and biological variation and indicates clinically important changes in a variable.
- This study found significant variability in the critical differences in CPET values in healthy adults and when applied retrospectively to a patient cohort.
- Using the boundaries of critical difference, a large proportion of patients were classified as being of indeterminate fitness for surgery.
- If confirmed, this suggests that fitness stratification should be based on a range of values for a CPET variable rather than a single value.

Cardiopulmonary exercise testing (CPET) is a non-invasive procedure to determine the level of cardiorespiratory fitness (CRF) of patients during a progressive exercise challenge to symptom limited maximum. CPET is used as a tool for preoperative assessment of physical fitness for intra-abdominal surgery to aid clinical decision-making given its increasingly proved association with postoperative outcome.[1–7] Furthermore, The American Heart Association recently published a scientific statement promoting CRF as a clinical vital sign.[8] Despite increasing support for CPET, the mechanisms underpinning CRF that provide protection require further investigation.

The seminal work of Older and colleagues[9] documented an 18% mortality rate in elderly surgical patients with a pulmonary oxygen uptake at the anaerobic threshold ($\dot{V}O_2$-AT) of <11 ml oxygen (O_2) kg^{-1} (total body mass) min^{-1} compared with 0.8% recorded in patients with a $\dot{V}O_2$-AT$\geq$11 ml O_2 kg^{-1} min^{-1}. Other biomarkers including peak oxygen uptake ($\dot{V}O_2$ peak) <15 ml O_2 kg^{-1} min^{-1} and ventilatory equivalent for carbon dioxide at AT ($\dot{V}_E/\dot{V}CO_2$-AT) >42 have predicted postoperative survival after abdominal aortic aneurysm surgery.[2] Studies have further attempted to define threshold values in an effort to optimise risk prediction; for example a range of AT values from 9.0 to 11 ml O_2 kg^{-1} min^{-1} have been reported,[4,5,9–12] thus demonstrating that variation is present and that a single cut-point cannot be recommended.

Like most biomarkers, CRF is a dynamic metric subject to natural variation and thus needs to be interpreted with caution. Such variation encompasses both analytical and biological components that collectively contribute to the critical difference (CD) as originally described by Fraser and Fogarty.[13] The CD represents random variation around a homeostatic point indicative of the change that must occur before a true difference of clinical significance can be claimed. The concept of CD, yet to be applied to clinical CPET variables, emanates from the field of clinical biochemistry and has been applied to metabolic biomarkers of exercise stress and clinical patients.[14,15]

The current study reflects the first attempt within the clinical setting to quantify the CD of established CPET markers of CRF with corresponding implications for patient management. We hypothesise that natural variation is present in markers of CRF and will thus impact upon patient fitness stratification.

Methods

Ethical approval

The University of South Wales Ethics Committee (LSE1636-GREO), and Cardiff and Vale University Health Board (15/AIC/6352) approved the study. All procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association.[16] Written informed consent was obtained from participants in study arm 1. Study arm 2 constituted a retrospective analysis of an anonymised database and thus patient consent was waived.

Design

We conducted a two-armed study. First, to determine the CDs of selected CPET variables (reported as independent predictors of postoperative outcome), analytical variation was calculated, and biological variation derived using repeated CPET results from a young apparently healthy population (arm 1). Subsequently, these CD values were retrospectively applied to an anonymised database of patients who had CPET before colorectal surgery, to re-appraise fitness stratification (arm 2).

Study arm 1: Critical difference determination

Analytical variation (CV_A); the first component of CD, was determined by repeatedly passing inspired and expired gases through a MedGraphics Ultima metabolic cart (MedGraphics™, Gloucester, UK) in a manner that replicated typical ventilatory responses during the latter stages of a patient CPET (i.e. pulmonary minute ventilation of 25 litres min^{-1}). In a series of eight repeated trials, each lasting 10 respiratory cycles, a 250 litre Douglas bag containing saturated expired gas (17% O_2, 5% CO_2) and an equivalent volume of ambient gas was passed through a pneumotach and gas analyser. Inspiration and expiration were simulated using two-way non-rebreathing valves (2700 Series) connected to two factory-calibrated 3 litre syringes (Hans Rudolph, Kansas City, KS, USA) operated simultaneously (Fig 1). Before sampling, calibration was undertaken in accordance with manufacturer's guidelines using a 3 litre syringe and a known precision gas. During data collection the middle five of seven breaths were averaged.

The within participant coefficient of variation (CV_W) from which biological variation could be calculated, was determined by completion of three repeat CPETs separated by a minimum of 24 h, for 12 healthy participants (Table 1). Tests were conducted in a randomised order at three time points across operating hours for patient CPET clinics (09:00–10:30, 12:00–13:30, and 15:00–17:00). All CPETs were conducted to volitional fatigue using the Wasserman protocol,[17] the same metabolic cart and investigator, and calibration undertaken as previously described. Following 3 min of resting data collection, participants cycled at 60 rpm on an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands) for 3 min in an unloaded 'freewheeling' state. A progressively ramped period of exercise (10–30 W min^{-1} based on stature, age, and predicted $\dot{V}O_2$)[17] was then undertaken to volitional termination and followed by 3 min recovery. Heart rate (Polar Electro, Oy, Finland) was recorded throughout.

MedGraphics Breeze™ software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ during the final 30 s of exercise reported), oxygen uptake efficiency slope, and peak oxygen pulse (O_2 pulse). The AT was manually interpreted by a