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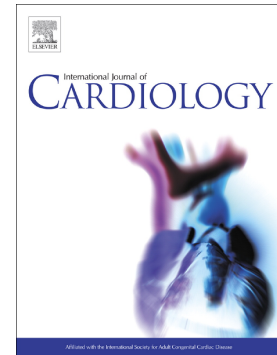**Title:** A potential case for the routine assessment of cardiorespiratory fitness level in clinical practice

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A potential case for the routine assessment of cardiorespiratory fitness level in clinical practice

Brief Title: fitness and hospitalization

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Editorial

Cardiorespiratory fitness (CRF), as measured directly using respiratory gases, is the most accurate indicator of the ability to transport oxygen from the lung to the mitochondria to perform physical exercise. Left ventricular stroke volume, exercise heart rate, and arteriovenous oxygen differences at exercise are major determinants of CRF levels. Directly measured oxygen uptake (VO2), an objective and quantitative measure of CRF, is the gold standard for assessing the amount of oxygen consumption during exercise (1). It has been suggested that about half of the variance in CRF is attributable to heritable factors (2). CRF is significantly correlated with measures of pulmonary, cardiovascular, skeletal muscle, and metabolic function.

Large clinical studies have shown the importance of an easily available submaximal testing for CRF assessment, which has relatively good reliability and validity (1). The use of CRF as a determinant of cardiac risk, specifically as a predictor of major cardiovascular (CVD) outcomes, has remained underused in clinical practice, e.g. due to proficiency constraints and the lack of very sophisticated equipment. Submaximal exercise test with the use of heart rate assessment is relatively easy to implement in clinics. However, consideration needs to be given for the fact that prevalent medical conditions, medication use (especially β-blockers), body size and severity of cardiac symptoms may have an effect on exercise-based heart rate response, which is commonly used in formulae to estimate CRF levels. Submaximal exercise testing can be an appropriate modality for patients with coronary heart disease (CHD) to assess CRF when a cardiopulmonary exercise test is not available or when resources are limited (3). In our previous studies, CRF (measured using peak oxygen uptake, $VO2_{peak}$) was demonstrated to be inversely and independently associated with a lower risk of cardiovascular events, although $VO2_{peak}$ yielded only a modest improvement in sudden cardiac death risk prediction on the top of cardiovascular risk factors (4-6). Good CRF is also associated with attenuated coronary calcification and increased plaque stabilization, potentially reducing the

risk of unexpected coronary events due to plaque rupture (7). The observed association on CRF and all-cause mortality has persisted across the lifespan (4).

Given that normal reference standards for $VO2_{peak}$ are controversial because they tend to be population and protocol specific and need to be accurately interpreted with respect to age, gender and body weight, the use of $VO2_{peak}$ relative to an age and gender predicted value ie. percent-predicted $VO2_{peak}$ has been recommended. To date, there are only few published reports on the prognostic utility of percent-predicted $VO2_{peak}$ in patients with pre-existing cardiac disease. Furthermore, it is unknown whether analyses using only single baseline measurements of percent-predicted $VO2_{peak}$ would underestimate associations with outcomes. Due to measurement errors, lifestyle changes, aging and chronic diseases, assessments using baseline measurements of an exposure could underestimate the true strength of an association between an exposure and disease outcome in long-term cohort studies due to the phenomenon of regression of dilution bias (8). Our substudies on repeat assessments of CRF measurements within the Kuopio Ischemic Heart Disease prospective study show a within-person variability in CRF levels measured many years apart (regression dilution ratio=0.58) (9). In the current issue of the International Journal of Cardiology, Chiaranda and colleagues evaluated the association between percent-predicted $VO2_{peak}$ and all-cause hospital readmission in 1283 male patients with stable CHD recruited into the Fitness Registry and the Importance of Exercise National Data Base (FRIEND) (10). To account for regression dilution bias, the authors also assessed whether serial changes in percent-predicted $VO2_{peak}$ were associated with new readmissions. For the estimation of CRF (measured by $VO2_{peak}$), patients were instructed to keep a moderate pace for 10 to 20 minutes using a 1km treadmill-walking test. $VO2_{peak}$ was estimated using an algorithm that was initially included age, height, weight, time to walk 1000 m and heart rate (10). The percent-predicted $VO2_{peak}$ was derived from the FRIEND equation (henceforth referred to as $FRIEND_{\%PRED}$) (3).

Rates of readmission were significantly lower across tertiles of improved FRIEND$_{\%PRED}$ and persisted after adjustment for relevant confounders, including the use of β-blockers and diuretics (10). An important clinical finding was that the total hospital days were 2.0 and 3.2 times higher among patients with low and intermediate FRIEND$_{\%PRED}$ levels compared to subjects in the highest CRF tertile. The authors also showed a strong inverse association between improvement in FRIEND$_{\%PRE}$ and all-cause readmission rates. Cardiac patients with the highest increases in FRIEND$_{\%PRE}$ had significantly lower readmission rates observed during the longer-term of follow-up. The current findings are relevant especially for healthcare systems and clinicians who have to consider appropriate use of resources. There were a number of drawbacks to this study which merit consideration, though the majority were acknowledged and discussed by the authors. Of much importance is the observation that the authors did not conduct formal risk prediction analyses to assess the prognostic relevance of FRIEND$_{\%PRE}$ when added on top of risk factors for hospitalization, using measures of discrimination (eg, Harrell's C-index) and reclassification (eg, net-reclassification-improvement). CRF is a clinically useful indicator of the effectiveness of exercise-based rehabilitation. After an acute cardiac event, CRF levels may be partly explained by the timing of participation in cardiac rehabilitation programs and exercise testing. Secondly, the assessment of predicted CRF by using a submaximal test with heart rate is dependent on the population to be tested, and the use of medication such as β-blockers; data on cardiovascular interventions or other causes of hospitalization were not available in the current study. Furthermore, the percentages of patients taking aspirin and statins three years after baseline were not optimal.

Considering the observational nature of the study, a causal association cannot be implied between low CRF and hospital readmissions. Nevertheless, the efforts of the authors must be applauded, having shown that CRF as a percentage of an age-specific value using the FRIEND equation (estimated using a simple walking test) may be a risk indicator for hospitalization rates in outpatients with CHD. To conclude, the authors' suggestions on age-predicted VO2$_{peak}$ being a

predictor of hospital readmission need interpretation with caution as no risk prediction analyses were conducted.

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