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Clinical Perspectives on Incorporating Cardiorespiratory Fitness in Clinical Practice

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Abstract

Cardiorespiratory fitness (CRF) has been documented as a strong, independent predictor of non-communicable disease and mortality in both clinical and apparently healthy populations. This well-established relationship has impelled organizations, including the American Heart Association, to release scientific statements highlighting the importance of accurate quantification of CRF. Current knowledge of the relationship between CRF and mortality is predominantly based on estimated CRF obtained from varying indirect methods. Cardiopulmonary exercise testing (CPX), the gold standard method of CRF measurement, provides a more accurate and reliable quantification of CRF compared to estimated methods. This review provides support for the diagnostic and prognostic use of CRF based on the current literature and makes a case for the use of CPX when available, as well as the need for standardization of normative values defining CRF levels to increase the efficacy of the risk assessment. Further, clinical applications of CPX-derived CRF are discussed, providing clinicians with recommendations on how to use and interpret this measure in practice to guide clinical decisions and improve patient outcomes.

Key words: Cardiopulmonary exercise testing, Aerobic capacity, Exercise, Physical Fitness

Cardiorespiratory fitness (CRF) is related to the integrated function of numerous physiological systems, including the circulatory, respiratory, and musculo-skeletal, and thus is considered a reflection of total body health[1]. Over the past three decades, substantial evidence has emerged supporting the value of CRF as a predictor of non-communicable disease and premature mortality. The strong, inverse, and independent relationship between CRF and these adverse health outcomes has been reported in several cohorts with varying demographics and baseline health statuses, speaking to its robustness as a diagnostic and prognostic tool[2-5]. In fact, CRF has been documented to be a stronger predictor than other traditional risk factors [1, 3, 6]. This established relationship prompted the American Heart Association (AHA) to publish a scientific statement in 2016 promoting CRF as a clinical vital sign[1]. Although the importance of CRF is well-established, several factors need to be refined in order for CRF to be routinely and effectively incorporated in clinical practice (standardization, normative values defining fitness levels, etc.). In this review, we provide support for the diagnostic and prognostic use of CRF based on the current literature assessing the relationship between CRF and health outcomes. We also discuss clinical applications of CRF, providing clinicians with recommendations on how to use and interpret this measure in practice to increase the efficacy of the risk assessment and improve patient outcomes.

1. Incorporating Cardiorespiratory Fitness into Practice: What Needs to be Refined

The relationship between CRF and mortality, when studied in apparently healthy, disease free populations, has almost exclusively been studied using estimated CRF (CRF_e). These estimates were obtained from various indirect methods, such as exercise workload or duration on a maximal exercise test, [2, 3, 7, 8] heart rate at a submaximal workload [4, 8-11], or more recently using non-exercise prediction equations[12-15]. In 2009, Kodama et al published a meta-analysis using data from 33 studies to assess the quantitative relationship of CRF with cardiovascular disease (CVD) and all-cause mortality in apparently healthy adults. Together these studies utilized over 20 different methods for obtaining CRF, including both direct and indirect measurements [16]. A more recent paper by Harber et al reviewed the research advances on this relationship since 2009. Data were reported from studies that have utilized ~16 different CRF measurement methods[17]. This highlights the robust relationship between CRF and health outcomes, but also underscores the need of standardization.

Varying criteria used to define low CRF in these research cohorts is also a concern, as it presents challenges to clinicians' interpretation[18]. Some defined CRF levels by achievement of a specific metabolic equivalent (MET), with the classification of low CRF ranging from 4 to 9 METs for exercise capacity [2, 19]. Others use cohort-specific CRF classifications, most commonly tertiles (≤ 33%) [4, 9, 11], quartiles (≤25%)[14, 20, 21], and quintiles (≤20%) [3, 12]. For example, Jensen et al [4] report <8.3 METs to represent low CRF in their cohort of men, whereas the low CRF in the cohort assessed by Park et al [9] corresponded to ≤6.3 METs. To add to the problem, the majority of studies do not account for sex or age in the defining criteria. However, it has been clearly shown that CRF is influenced by these factors, with men typically having higher CRF values than women, and CRF progressively decreasing with age in a non-linear fashion [22]. The varying methods used to obtain CRF_e, along with the differing cohort specific criteria to define CRF_e levels, have led to inconsistencies between studies in the degree of risk reduction associated with each increment increase in CRF_e (8 to 35% risk reduction per MET increment increase [1]) and the magnitude of protection associated with achieving higher CRF_e levels, all of which reduce generalizability of past study results. Kokkinos et al address this issue in a recent report calling for standardization of CRF categories to ameliorate methodological discrepancies between studies[18].

All methods used to predict CRF have established estimation errors of ~1 to 2 METs. This would equate to an error of up to 40% in those with low CRF (≤ 5 METs)[23]. This variability may result from exercise-related factors including maximal effort criteria, handrail use, protocol selection, exercise mode, i.e. [24]. Small differences in CRF have been shown to have important clinical application as Kodama et al reported 1 MET increment increase to be associated with 13 and 15% reductions in risk for all-cause and CVD mortality[16], respectively. Therefore, the use of CRF_e has the potential to over- or underestimate one's risk for mortality by ~ 30%.

Longitudinal studies have assessed the influence of the change in CRF over time (>4 years) on mortality risk, reporting approximately 30 to 40% reduction in risk by improving one's CRF level from unfit to fit [19, 25]. However, similar to prior cross-sectional studies, these longitudinal studies used varying criteria to define fit and unfit levels, and primarily used CRF_e. This may significantly impact the risk assessment, as error may be introduced into both the baseline and follow-up exercise tests, which could lessen the sensitivity of the risk stratification.

The findings from these longitudinal analyses suggest that prescribing exercise to increase CRF will improve longevity. Most of these past studies did not directly assess lifestyle changes between tests. CRF is considered to be an objective measure of physical activity (PA), and it has been reported that 5 to 30% (1-2 MET) improvements in CRF typically occur following 3 to 6 months of an aerobic exercise training program, with higher improvements seen in those with lower baseline CRF [23]. The influence of post-training improvements in CRF_e on prognosis has only been assessed in CVD patients, showing a 30% reduction in all-cause mortality per MET increase after 12 weeks of cardiac rehabilitation in patients classified as low fit at baseline. Studies are needed to assess the influence of short-term improvements in CRF following initiation of aerobic exercise training on mortality risk in apparently healthy populations.

2. The Clinical Value of Cardio-pulmonary Exercise Testing

Cardiopulmonary exercise testing (CPX) provides direct measurement of CRF, expressed as maximal oxygen consumption (VO_{2max}), which minimizes the exercise related factors that result in variability in the estimated methods [24]. For example, the use of handrails when performing a maximal exercise test without gas analysis will increase exercise test duration and allow the attainment of higher workloads (ex. speed and/or grade), which would result in a higher value of CRF_e. As a direct measurement of gas exchange, CPX-derived CRF is not altered by handrail use, increasing the accuracy and reliability, with technical and biological variability estimated to be only ~3 to 4% [23]. While CPX has been historically underutilized due to requirements for additional equipment and trained personnel, these factors are no longer significant barriers. Improvements in technology and training, as well as the growing awareness of its diagnostic and prognostic value [26, 27] now allow CPX to be considered for use more routinely in clinical practice.

Hemodynamic responses to maximal exercise testing, including heart rate recovery and chronotropic incompetence have also been shown to have prognostic power. The prognostic value of these measures is even more evident when combined with CPX responses[28, 29]. CPX can provide additional physiological measurements that are valuable in optimizing risk assessment in clinical populations. These measurements include minute ventilation (V_E), ventilatory threshold (VT), ventilatory efficiency (V_E/VCO_2 slope), circulatory power, exercise ventilatory power, exercise oscillatory ventilation (EOV), partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), and oxygen uptake efficiency slope (OUES)[28]. Guazzi et al describe the scientific evidence behind the value of these CPX variables in their 2012 recommendations and the 2016 update [26, 27]. These scientific statements promote the use of these emerging CPX variables to increase diagnostic and prognostic sensitivity, as they allow for greater insight into physiological factors that cause functional limitations, potentially indicating underlying disease[1, 17, 22, 26]. For example, V_E/VCO_2 slope is a commonly used prognostic measure with elevated V_E/VCO_2 slope values (≥34 indicating decreased efficiency) associated with ventilation-perfusion abnormalities commonly experienced by heart failure, pulmonary hypertension, and intrinsic lung disease patients. Patients' prognosis is progressively worsened when V_E/VCO_2 becomes ≥40 [28, 30, 31]. Moreover, when heart rate recovery is combined with V_E/VCO_2 slope, the multivariable score provides clinicians with an integrated method that powerfully predicts outcomes in cardiac patients [29]. Continued research is needed to gain further insight into these emerging CPX variables in order to increase the evidence-base for their clinical value.

CPX-derived CRF has been used as a diagnostic and prognostic tool in clinical populations, with peak VO_2 values < 20 ml/kg/min warranting strong consideration of more aggressive medical treatment and <10 ml/kg/min indicating particularly poor prognosis. However, the use of CPX in apparently healthy adults, free from medical diagnosis of disease, is less established[27]. To date, only one research cohort has assessed the relationship between CPX-derived CRF and all-cause and disease-specific mortality in an apparently healthy population. Laukkanen et al assessed the association of CPX-derived CRF with mortality outcomes in middle-aged men from eastern Finland[32-36]. The results showed 20%, 31%, 12%, and 23% reductions in sudden cardiac death, CVD mortality, cancer mortality, and all-cause mortality, respectively [33, 36]. Further, each unit (ml/kg/min) change in CRF after 11 years was associated with a 9% reduction in mortality risk in this cohort[35]. The use of CPX-derived CRF make the findings from this study promising, as they confirm the well-established relationship between CRF_e and mortality, but the higher accuracy and reliability of the method may improve the risk assessment for mortality outcomes. However, the generalizability of the results beyond middle-aged Finnish men is unknown. Therefore, research focusing on the association of CPX-derived CRF with clinical end-points, in diverse populations, including both healthy women and men, across a wide distribution of ages, ethnic and racial groups, geographical locations, and socioeconomic statuses is warranted. The studies will help to more accurately guide clinical decisions for these diverse populations.

3. Clinical Application of Cardio-pulmonary Exercise Testing

The current literature suggests clinician utilization of CPX would better predict patient outcomes compared to estimated methods. Currently, variability in physician utilization and understanding of CRF may be a limiting factor, even in a physician office equipped with CPX equipment. The Guazzi et al scientific statements provide clear risk stratification algorithms, using CPX evidence-based research results which can provide guidance to clinicians for both prognostic and diagnostic applications. These statements also provide algorithms specific to patient populations who are healthy, undergoing a pre-surgical evaluation, or with underlying pulmonary or cardiac abnormalities [26, 27].

Consequently, functional classification beyond evaluation of clinical populations (along with delineation of their unhealthy habits) would suggest the need for two tiers of disease- specific patients. The first would be a functionally stable participant for a rehabilitation program, with long term follow-up testing. The second group including patients in the pre-surgical or pre-treatment (such as toxic chemotherapy) phase, with their post-surgical or post-treatment outcome. The goal in this group would be an eventual transition to a more conventional rehabilitation program when more acute goals are achieved. Measurement of CPX-derived CRF in the pre- and post-phases would provide a more objective and accurate reflection of the change in CRF in response to their overall treatment, including lifestyle behavioral modifications.

There remains a distinct discrepancy between the value of CPX and a clinician's utilization of the service. Enthusiasm for the ability to assess risk and detect underlying disease based on clinical variables obtained from CPX, as well as the possibility to change a patient's prognosis by improving CRF through a fitness program should herald a change in physician interest. Previously, there was high physician hesitation for ordering an exercise test, out of their concern for patient discomfort or anxiety. However, current standard-of-care procedures can be more intensive, while only providing risk evaluation similar to CPX outcomes. A few of these include cardiac stress tests with or without intravenous catheter placement, mammography, 24-hour gastric pH probes, colonoscopies and esophagogastroscopy. Therefore, the physician hesitations towards the use of CPX should be reconsidered, as it provides a wealth of clinical information and significantly adds to the risk assessment with minimal risk to the individual[23].

The establishment of the Fitness Registry and the Importance of Exercise National Database, called for by the American Heart Association in 2013, allows physicians to more easily interpret non-communicable disease and mortality risk based on CPX derived CRF. This registry provides population based age and sex-specific reference values developed from > 12,000 CPX tests [22, 37], increasing generalizability of CRF percentiles to the US adult population that physicians see on a regular basis. The use of CPX-derived CRF along with age and sex-specific reference values from the FRIEND registry would reduce inconsistencies between studies and help ease clinician interpretation of risk.

4. Conclusion

CRF has been shown to reflect total body health and has important prognostic and diagnostic value. Clinicians should assess CRF routinely as a vital sign, which can easily be done with CRF_e methods. CPX-derived CRF provides the most accurate data, which will reduce misclassification of risk, thus it should be increasingly considered for use in clinical practice. A wealth of clinical information is also obtained through the measurement of CPX variables which increase prognostic power when combined with CRF and hemodynamic measures. When used, CPX-derived CRF can be interpreted with age and sex-specific reference standards from the FRIEND registry, which should help guide clinical decisions. Those identified with low CRF, via the routine CRF assessments, should be recommended for therapy (i.e. regular exercise training), similar to how clinicians currently respond by prescribing therapies for other CVD risk factors.

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