Progress in Cardiovascular Diseases 62 (2019) 86–93

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Cardiorespiratory fitness and cardiovascular disease - The past, present, and future

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ARTICLE INFO

Keywords:
Exercise training
Morbidity
Mortality
Prevention
Reference standards
Vital sign

ABSTRACT

The importance of cardiorespiratory fitness (CRF) is now well established and it is increasingly being recognized as an essential variable which should be assessed in health screenings. The key findings that have established the clinical significance of CRF are reviewed in this report, along with an overview of the current relevance of exercise as a form of medicine that can provide a number of positive health outcomes, including increasing CRF. Current assessment options for assessing CRF are also reviewed, including the direct measurement via cardiopulmonary exercise testing which now can be interpreted with age and sex-specific reference values. Future directions for the use of CRF and related measures are presented.

Contents

Abbreviations and acronyms: ACLS, Aerobics Center Longitudinal Study; ACSM, American College of Sports Medicine; AHA, American Heart Association; BALL ST, Ball State Adult fitness program Longitudinal Lifestyle STudy; CRF, cardiorespiratory fitness; CDC, Centers for Disease Control and Prevention; CERG, Cardiac Exercise Research Group; CHD, coronary heart disease; CI, confidence interval; CPX, cardiopulmonary exercise test; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; EOV, exercise oscillatory ventilation; FRIEND, Fitness Registry and the Importance of Exercise National Database; HLM, healthy living medicine; HR, hazard ratio; LRC, Lipid Research Clinics; MET, metabolic equivalent; NCD, non-communicable diseases; OUES, oxygen uptake efficiency slope; PA, physical activity; $P_{et}CO_2$, partial pressure of end tidal carbon dioxide; RR, relative risk; SBP, systolic blood pressure; Ve/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen uptake; VO_{2max}, maximal oxygen uptake; VT, ventilatory threshold.

Statement of conflict of interest: See page 91.

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https://doi.org/10.1016/j.pcad.2019.01.002
0033-0620/

Exercise can certainly be recognized as a form of medicine, which is used to prevent or treat disease. For example medicine, including exercise, is used to control cardiovascular (CV) disease (CVD) risk factors. Healthy lifestyle behaviors are commonly the first line of therapy for CVD risk factors, followed by medications as necessary. For example, diuretics may be prescribed for treatment and control of hypertension, and similarly statins for hyperlipidemia. When considered as the form of treatment, exercise as medicine is associated with benefit across a wide range of outcomes, of which perhaps the most important is improvement in cardiorespiratory fitness (CRF). While adherence to exercise, and/or regular physical activity (PA) programs is the desired behavior, attention should be focused on evaluating measurable outcomes. Thus, CRF should be a key variable of interest for clinicians and patients related to health.

This report provides a brief overview of the importance of CRF as a key factor associated with CV health. The report contains three sections: 1) a summary of the research that established the importance of CRF related to CVD; 2) an overview of exercise as medicine and the importance of assessing CRF; and 3) suggestions for future research objectives related to the importance of CRF.

CRF and CVD – the past

For more than a half century, a wealth of epidemiologic studies has documented the health benefits of regular PA. It is now widely appreciated that higher CRF and PA patterns are not only beneficial for the prevention of CVD, but also site-specific cancers, type 2 diabetes, improved bone health, reduced disability, and increased both longevity and healthspan (i.e., "the number of years an individual is healthy and free from debilitating disease").[1] PA patterns provide information on risk that is independent from traditional CVD risk factors.[2,3] Expert panels convened by organizations such as the Centers for Disease Control and Prevention (CDC), the American College of Sports Medicine (ACSM), the European Working Group on Cardiac Rehabilitation and Exercise Physiology, and the American Heart Association (AHA),[4–8] along with the US Surgeon General's Report on Physical Activity and Health[9] have synthesized and reinforced the volume of scientific evidence linking regular PA to various measures of health.

Association between CRF and health outcomes

The relationships between oxygen uptake (VO_2) and the severity of exercise were first described by A.V. Hill et al. in 1923–24.[10,11] In these early years Hill and colleagues performed a series of elegant experiments in which they ultimately described the classic relationships between exertion and VO_2 and coined the term *maximal* VO_2 or VO_{2max}. In these studies, Hill and colleagues suggested there is an upper limit to oxygen uptake (VO2max) which will vary between individuals and is limited by the ability of the cardiorespiratory system to transport O2 to the muscles, which generally speaking holds true to this day. Subsequently, the improvement in VO_{2max} became a primary target of athletes seeking to enhance endurance performance. It was not until the early 1980's that the associations between VO_{2max} or CRF and health outcomes was described. Over the last 3 decades, evidence has accumulated that demonstrates a strong, inverse, graded and independent association between CRF and health outcomes in both apparently healthy individuals and those with existing CVD. In many studies, this association has been demonstrated to be even more powerful than the traditional CVD risk factors.[2,3,12] The body of evidence and strength of this association over the last 3 decades was the impetus behind a recent AHA Scientific Statement making the case for CRF as a vital sign.[12]

Studies assessing CRF by standardized exercise tests have quantified the association between CRF and risk of mortality, CVD, or both. In 1985, Lie and colleagues studied >2000 healthy Norwegian subjects and a smaller group of middle-aged and elderly cross-country skiers followed over 7 years.[13] They observed a strong association between reduced coronary risk and higher levels of CRF, which was also inversely associated with CVD mortality. In 1987, Sobolski et al. assessed ooccupational and leisure time PA, conventional risk factors, and CRF in the Belgian Physical Fitness Study, a prospective evaluation of 2383 healthy male factory workers followed for 5 years.[14] CRF was estimated using an interpolation of working capacity at a heart rate 150 bpm. CRF was a strong and independent risk marker for CVD, along with smoking and high-density lipoprotein cholesterol, while PA scores were not significant predictors of CVD incidence. In a seminal 1989 study by Blair and colleagues, using the Aerobics Center Longitudinal Study (ACLS) cohort, 10,244 men and 3120 women were studied who underwent a maximal exercise test and were prospectively followed for a mean of 8 years.[15] Subjects were divided into quintiles of CRF and adjusted for age and other known CVD risk factors. With the least fit group as the reference, the relative risk for mortality among men in the highest quintile of fitness was 0.29; among women in the highest quintile of CRF, the relative risk was 0.22. Simply changing from the lowest quintile of CRFs to the second lowest quintile cut the mortality rate in half for women (relative risk, 0.52) and by 60% in men (relative risk, 0.40). This pattern, in which the greatest health outcome benefits occur at the low end of the CRF spectrum, has been a consistent finding in epidemiologic studies for several decades.[16] The results of Blair et al.[15] were groundbreaking at the time, being one of the early studies to prospectively assess CRF in women, to include a large sample size, and to document that gradations in CRF lead to significant differences in mortality. The ACLS analysis closely paralleled a report from about the same time among asymptomatic men enrolled in the Lipid Research Clinics (LRC) Mortality follow-up, in which each 2 SD decrement in CRF was associated with 2- to 5-fold reductions in CVD or all-cause death rates.[17]

Studies over the following decade, including studies from the ACLS, the LRC, the Mayo Clinic, the Cleveland Clinic and US Veterans, reinforced the strength of the association between CRF and health outcomes.[16,18–21] A growing body of data began to emerge suggesting that CRF frequently outperformed traditional CVD risk factors in predicting risk for adverse outcomes. In addition, a consistent observation was the fact that the strength of CRF in predicting risk applies to women who were healthy at the time of evaluation.[18,22] Gulati et al. suggested that the strength of CRF in predicting risk of mortality in women, 17% reduction in risk for every 1 - metabolic equivalent (MET) increase in CRF, was greater than the 12% reduction observed in men.[21,22] In the LRC, nearly 3000 asymptomatic women underwent exercise testing and were followed for up to 20 years.[18] A 20% decrease in survival was observed for every 1-MET decrement in CRF. The study also pointed out the relative weakness of ischemic ECG responses in predicting CVD and all-cause mortality among women, similar to that observed among men.[21,23] Recently, directly measured CRF from cardiopulmonary exercise testing (CPX) demonstrated a CVD mortality risk reduction of 16.1% for every 1-MET increase in the Ball State Adult fitness program Longitudinal Lifestyle STudy (BALL ST) cohort of over 4000 men and women.[24]

Prospective studies with a one-time assessment of CRF may be questioned because of concerns about the influences of hereditary factors, pre-existing disease, and/or uncertainty about the influence of potential changes in PA and/or CRF during follow-up. Prospective studies that include multiple assessments of CRF (e.g. two time points) allow for the assessment of relationships between change in CRF and the given outcome thereby controlling for these and other potentially confounding factors.

Early studies that examined the association between changes in CRF and mortality outcomes in healthy[15,25] and diseased populations[26,27] confirmed earlier observations based on a single baseline measure. Blair et al. were the first to demonstrate that men who remained fit over 5 years between assessments had a relative risk of 0.33 (95% CI 0.23–0.47) for all-cause mortality and relative risk of 0.22 (95% CI

0.12–0.39) for CVD mortality compared to those who were unfit, after adjusting for all known confounders.[28] Erikssen et al.[25] observed that changes in CRF among 1756 Norwegian 40–60 year old men followed for 22 years was an independent predictor of all-cause mortality and CVD mortality (independent of smoking, resting heart rate, blood pressure and vital capacity).[25] Those with the highest change in CRF (Quartile 4) had a RR of 0.45 (95% CI 0.29–0.69) for all-cause mortality and RR of 0.47 (95% CI 0.26–0.86) for CVD mortality compared to those with the lowest CRF change (Quartile 1). These early findings have been confirmed by Laukkanen et al. who observed that a 1 $mL \cdot kg^{-1}$ min^{-1} increase in CRF over an 11-year period between assessments was independently associated with an all-cause mortality decrease of 9% (HR 0.91; 95% CI 0.87–0.95) compared to those with no change in CRF.[29] De Schutter et al. examined the effect of CRF improvement in 1171 CHD patients over 140 days of cardiac rehabilitation therapy.[30] They observed that CRF improvements were independently associated with decreases in risk of mortality compared to those who did not improve CRF by at least 2.5 $mL \cdot kg^{-1}$ min^{-1} (HR 1.78; 95% CI 1.19–2.65). In summary, the literature consistently demonstrates that CRF improvements in healthy and diseased populations are independently associated with reduced risk of mortality and other adverse outcomes. Practitioners may confidently convey that adults who have a higher CRF have a lower risk of premature mortality and adverse health events. Moreover, increasing general PA levels and/or participating in an exercise training program are effective strategies to improve CRF and health outcomes.

CRF and CVD – the present

Relevance to exercise as medicine

Clinicians rely on assessing vital signs (i.e., blood pressure, body mass index, heart rate, tobacco use, blood profile) to gain perspective on the clinical status of patients and to forecast risk of future morbidity. Interpretation of each vital sign initiates clinical therapeutic action and strong endorsement of healthy living medicine ([HLM][1]; reduce sedentary time, increase PA, diet modification, smoking cessation) to slow or reverse the progression of deteriorating health, with the aim of attenuating the risk of developing non-communicable diseases ([NCD]; i.e., CVD, cancer, diabetes, sarcopenia, etc.). The adoption of CRF as a vital sign has been slow despite a robust body of epidemiologic and clinical investigations that reinforced the strong prognostic utility of CRF compared to traditional vital signs.[12] Moreover, when CRF is included in NCD risk calculators with traditional vital signs, the prediction of ominous outcomes is markedly enhanced (Table 1).[31] Accordingly, the AHA published a Scientific Statement that recognized and endorsed CRF as a vital sign that should be regularly implemented in clinical practices.[12]

Although CRF is a seemingly simple metric, testing an individual's capacity to perform physical work characterizes the ability of multiple physiologic processes to occur synergistically in order to achieve and sustain high levels of PA. Thus, CRF is significantly correlated with measures of pulmonary,[32] CV,[33] skeletal muscle,[34] and metabolic function.[35] Insufficiencies in one or more systems involved in delivering atmospheric oxygen to the mitochondria of the working organ and/or removal of metabolic byproducts from the body, reduces CRF. Advancements in quantifying and interpreting CPX data have enhanced the ability to detect suspected impairments in key organ systems, guide diagnosis, and assess the efficacy of certain pharmacologic interventions that have been shown to improve CRF.[36] This exemplifies the versatile applications of CPX in the clinical management of patients across the spectrum of risk assessment, diagnosis, and treatment efficacy.

In addition to optimizing the clinical management of patients at risk for developing or those who have been diagnosed with NCD, prescribing exercise as medicine has been widely promoted.[37,38] The accumulation of recommended levels of PA is a potent component of HLM that positively impacts health outcomes, independent of the presence or absence of NCDs.[39] Certainly, the degree to which one responds to PA is dependent on genetic factors[40,41] as well as the frequency, duration and intensities of PA performed.[42] Similar to utilizing CPX outcomes to facilitate the detection and clinical management of cardiopulmonary insufficiencies, identification of individuals with low CRF who are at high risk for future NCDs should trigger referrals to HLM practitioners (clinical exercise physiologists, dietitians, etc.) for personalized HLM therapy.[1,21,43–45] Mounting evidence is supporting the addition of CRF to classic risk algorithms as it significantly improves the classification of an individuals' risk.[12] CPX outcomes (i.e., peak or maximal VO_2, heart rate, and work rate) may also be utilized by HLM practitioners to optimize exercise prescriptions with the goal of maximizing improvements in CRF. Additionally, a recent report from the Veterans Exercise Testing study has demonstrated that low CRF is associated with higher healthcare costs, thus improving CRF may also lower these costs.[46]

CRF assessment options

CPX is regarded as the criterion clinical procedure for assessing CRF by quantifying peak VO_2 which represents an individuals' capacity to produce energy to perform strenuous exercise. Original approaches for collecting and analyzing expired gases during exercise tests were

Table 1
Net Reclassification Improvement (NRI) by Addition of CRF.

Author	Sample	Correctly reclassified as higher risk	Correctly reclassified as lower risk	NRI (%)
Stamatakis et al.[94]	32,319 adults from English and Scottish Health Survey			
	Men (n)	97/3108	26/3338	27.2
	Women (n)	59/3727	22/3863	21
Gupta et al.[31]	66,371 Adults from Aerobics Center Longitudinal Study			
	With CVD death (n)	49	19	11.3
	Without CVD death (n)	1622	1882	12.1
Myers et al.[95]	6962 exercise test referrals for clinical reasons			
	BRF + CRF (%; all-cause mortality)	25.8	17.6	43.5
Chang et al.[96]	1288 patients undergoing angiogram given questionnaire about vigorous exercise			
	All-cause mortality (%)	64.6	−31.9	32.6
	CVD mortality (%)	64.1	−32.0	32.0
Holtermann et al.[97]	8936 men and women from the Copenhagen City Heart Study			
	CVD Mortality (%)	−23.3	55.8	30.5
	All-Cause Mortality (%)	−20.6	46.0	24.5

BRF = Baseline risk factors; CRF = Cardiorespiratory fitness.
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quite cumbersome, time consuming, and therefore impractical for clinical applications. However, with rapid technological advancements commercial metabolic exercise testing units that are compact, easy to use, provide breath-by-breath analysis in real time and can include built in electrocardiogram equipment are now readily available at competitive prices. Coupled with the wealth of clinically meaningful cardiopulmonary data that can be acquired by these units, the implementation of CPX in hospitals is now more feasible and should be pursued. Yet, many institutions have not committed to CPX due to remaining perceptions of high equipment cost or need for multiple technicians. Instead, more commonly CRF is estimated based on the peak speed and grade, or workload (i.e., watts) achieved during symptom limited exercise tests. Although symptom limited exercise tests are not the "gold standard" method of assessing CRF, many seminal investigations that established or reinforced the clinical significance of this measure did so through these estimates of CRF.[21,47,48]

In many clinical settings, the indication for an exercise test is reserved to explore the underlying cause of PA induced signs and symptoms of ischemia or arrhythmias. Therefore, many patients that are symptom free do not receive a physician order for an exercise test, despite its established clinical utility. Furthermore, specialty clinics may not have access to exercise testing equipment and as a result referring patients to exercise testing facilities may not be considered. In any case, field-based tests, such as the 6-minute walk test can be easily administered in hallways by nurses, medical assistance or other HLM practitioners. This test has previously been shown to predict CRF,[49] serve as a prognostic tool in advanced NCDs[50,51] and be used by clinicians to identify patients that are in great need of HLM. If any degree of physical functional testing is not feasible in a clinical setting, CRF prediction equations that rely upon individual characteristics (i.e., sex, age, waist circumference, resting heart rate, PA habits) may be an initial option. Recently, CRF estimated in a large cohort of older adults was shown to be an independent and strong predictor of future (median 16 years) CVD and all cause-mortality.[52] While predicting an individual's CRF with equations is an effective initial approach to allow communicating the importance of increasing or maintaining CRF, it should be recognized that large individual variations may exist due to prediction errors. Therefore, exercise testing with CPX is considered the optimal method for determining an individual's CRF (Table 2).

Table 2
Recommended procedures for measurement of CRF during routine clinical visits.

General recommendations:
1. At a minimum, all adults should have CRF estimated each year using a non-exercise algorithm during their annual healthcare exam†. Clinicians may consider the use of submaximal exercise tests or field tests** as alternatives as these involve individual-specific exercise responses.
2. Ideally all adults should have CRF estimated using a maximal test*, if feasible using CPX***†, on a regular basis similar to other preventative services[a]. The specific age of first assessment and schedule for follow-up are yet to be established. However, patients with higher CVD risk profiles should have an initial test at an earlier age and be tested more frequently than patients with lower risk profiles.
3. Adults with chronic disease should have CRF measured with a peak or symptom-limited CPX on a regular[b] basis.

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†Recommendation to estimate CRF is for the purpose of assessing fitness and not coronary heart disease. Non-exercise estimates of CRF provide clinicians the opportunity to counsel patients regarding the importance of performing regular physical activity. *See section "Maximal exercise testing without CPX measurements", **See section "Submaximal exercise and Field and Clinical Tests, ***See section "Maximal exercise testing with CPX measurements"; CRF – cardiorespiratory fitness, CPX – cardiopulmonary exercise test.
[a] https://www.healthcare.gov/preventive-care-adults/.
[b] The schedule for this is specific to the chronic disease status (http://circ.ahajournals.org/content/126/18/2261).

Interpretation of CRF-development of FRIEND

Despite its established importance to CVD risk, CRF is the only major CVD risk factor that is not routinely assessed in clinical practice. However, even when it is obtained, there are challenges associated with CRF assessment in not having a clear standard for interpreting the results. The most common approach used in research studies is comparing the results to other existing values within the study population (i.e. cohort-specific). Although this approach has been helpful in determining that CRF is a major CVD risk factor, it is difficult to generalize the results from these studies to other populations. For example highest risk CRF levels have been defined as <5 METs,[23,53–55] < 6METs,[55] < 8.8 METS,[11,52,56], and < 11.2 METs.[52]

This approach has also been used specific to submaximal exercise tests (e.g. YMCA and Astrand cycle tests) and also field tests like the Cooper 1.5-mile or 12-minute running tests.[57,58] Possibly the most widely used reference for classifying an individual's VO_{2max} has been those provided in the ACSM Guidelines for Exercise Testing and Prescription, first appearing in 1995.[59] These tables used data from the Cooper Clinic (Dallas, TX) and provided percentiles for men and women for individuals' results from either maximal Balke treadmill test time, 12-minute run time, or 1.5-mile run distance. The tables also provided estimates of VO_{2max} values derived from the exercise test time or work rate (speed and grade).

Recognizing the lack of any reference standards for interpreting CRF, and specifically CRF determined from maximal exercise tests using CPX, the AHA issued a Policy Statement in 2013 describing a need for a National CRF Registry.[60] This resulted in the formation of a CRF Registry Advisory Board, who developed policies and procedures for establishing a data registry in the US. This Board then solicited data from clinical and exercise physiology labs experienced in CPX to contribute to this registry. In 2015, the CPX data from treadmill testing ($n = 7783$) was released from a group of 8 laboratories in the US to provide the first reference standards for CPX-derived VO_{2max} from the Fitness Registry and the Importance of Exercise National Database (FRIEND).[61] This was followed with a FRIEND report on reference standards for cycle ergometer testing ($n = 4494$) from a group of 10 laboratories in the US (Table 3).[62] The 2 FRIEND reference standards provide percentile data for men and women between the ages of 20–79 years for the US population. These data now allow for VO_{2max} data to be interpreted as an age and sex standardized percentile or as a percentage of test mode specific predicted values.[63] FRIEND can be used to provide standardizations or interpretations of studies analyzing the influence of CRF on chronic disease. More overview of the reports from FRIEND was provided in a recent review.[64] The FRIEND treadmill values were compared to previously published data from the HUNT study in Norway.[65] The US values were notably lower at each age range than those from HUNT and the rate of decline was greater (~10% vs. ~7% per decade) in the US. Less comparative data was found for cycle testing, however the limited comparisons suggested a similar difference of lower VO_{2max} in the US population than the groups from Lithuania[66] and Finland.[67] These findings clearly point to the need for expanding the registry effort worldwide to identify any regional differences which could lead to subsequent studies to determine the factors associated with these differences and to potentially, guide region specific PA recommendations.

CRF and CVD – the future

As the accumulation of research over the past few decades has established the strong inverse association between CRF and CVD, even prompting the AHA to promote CRF as a clinical vital sign,[12] it is prudent to look forward to assess what advances are necessary for the assessment of CRF to be routine in patient care. In fact, the 2005 AHA scientific statement on exercise testing in asymptomatic individuals concluded the following: "Given the strong evidence linking exercise test findings with risk in asymptomatic subjects, we believe that the

Table 3
Percentiles by age group for CRF from CPX on a cycle ergometer with measured VO2max (mlO2·kg-1·min^{-1}). Data obtained from the *FRIEND Registry* for men and women who were considered free from known CVD.

Percentile	Men [age group (y)]						Women [age group (y)]					
	20–29	30–39	40–49	50–59	60–69	70–79	20–29	30–39	40–49	50–59	60–69	70–79
90	55.5	41.7	37.1	34.0	29.9	28.1	42.6	30.0	26.2	22.6	20.5	18.0
80	51.4	36.2	34.2	30.7	26.7	24.5	38.8	26.0	23.4	20.7	18.8	16.9
70	47.9	33.9	30.4	28.2	24.5	21.9	35.6	24.2	22.0	19.3	17.8	16.1
60	44.5	31.1	28.6	26.3	23.2	20.4	33.6	22.5	20.7	18.2	16.7	15.4
50	41.9	30.1	27.1	24.8	22.4	19.5	31.0	21.6	19.4	17.3	16.0	14.8
40	38.3	28.1	25.4	23.6	21.4	18.5	28.1	20.1	18.4	16.6	15.4	14.2
30	36.2	26.9	24.0	22.6	20.2	17.5	25.6	18.8	17.1	15.7	14.7	13.6
20	33.2	25.4	22.2	21.5	19.0	16.7	21.6	17.0	15.8	14.9	14.0	12.8
10	29.5	21.8	20.6	20.4	17.3	15.8	19.3	20.9	14.6	13.7	13.0	12.0

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CRF = cardiorespiratory fitness; CPX = cardiopulmonary exercise testing; CVD cardiovascular disease; FRIEND = Fitness Registry and the Importance of Exercise National Database; VO2max = maximal oxygen uptake.
Sample size men ($n = 1717$); By age group: 20–29 ($n = 191$); 30–39 ($n = 182$); 40–49 ($n = 373$); 50–59 ($n = 475$); 60–69 ($n = 337$); 70–79 ($n = 159$).
Sample size women ($n = 2777$); By age group: 20–29 ($n = 235$); 30–39 ($n = 282$); 40–49 ($n = 562$); 50–59 ($n = 876$); 60–69 ($n = 602$); 70–79 ($n = 220$).

next major priority is the design and implementation of large-scale randomized trials to determine whether an exercise screening strategy leads to an improvement in outcomes".[68] To date, as the evidence has continued to mount in support of broadening the clinical application of CRF since publication of this AHA scientific statement 13 years ago, these types of trials have not been conducted even though there has been and currently remains a strong justification. A great challenge currently facing the healthcare system is the expanding demographic of older adults. Age is an independent risk factor for CVD, thus the burden of CVD is expected to rise as it is estimated that over 40% of the US population will have a form of CVD by 2030.[69] CRF inevitably declines with age,[61,62,70] independent of changes in body composition,[69] likely contributing to the increased prevalence of CVD as CRF is strongly related to health outcomes in older adults (>65 years).[71] As CRF is known to be influenced by age, body composition, and physical activity status, future work should explore the contribution of each of these factors to the change in CRF as it relates to predicting health-related outcomes. Amplifying this burden is the trend for declining CRF levels that was noted at the beginning of the 21st century.[72] Thus, the need for routine assessment of CRF, particularly in older adults, to identify those with low CRF and potentially higher risk of CVD, is warranted.

CRF assessed at any point during adulthood is a strong predictor of long-term health outcomes.[73] However, higher CRF at a younger age during mid-life (age 45–65 years) appears to be more protective against CVD mortality.[74] Currently, the association between CRF assessed during adolescence and long-term risk of CVD in unknown. A troubling trend is a secular decline in CRF among American youth,[75] suggesting the near future will see a greater proportion of young adults with low CRF, and thus elevated risk of CVD. Collectively, these trends support the routine assessment of CRF for all individuals, across the lifespan, and not only in older adults or those considered to be high risk.

While the prognostic power of CRF has been firmly established, standard practices for interpretation of CRF values are needed for CRF to be effectively used in clinical practice.[48] CRF is known to be influenced by age, sex, ethnicity, and nationality, as well as the myriad of lifestyle behaviors, thus establishing universal thresholds to identify individuals at elevated risk is not feasible.[61,76,77] Most epidemiological studies examining the association between CRF and CVD have used cohort specific thresholds or have identified low CRF based on bottom quartiles or quintiles, which in many cases is not generalizable to other populations. The FRIEND was established to provide age and sex-specific reference values for CRF derived from CPX for apparently healthy individuals that are representative of the US population.[61,62] A recent investigation utilized these normative values to categorize individuals as low (<34th percentile), moderate (34th to 66th percentile), and high (>66th percentile) fit and found that low fit individuals had a >2-fold risk of CVD mortality compared to high fit, even after adjustment for traditional risk factors (Fig. 1).[24] This study provides a framework for clinicians to interpret CVD mortality risk based on population derived CRF reference values, but more work is needed before this approach can be uniformly utilized. While the inverse relation between CRF and CVD is independent of race and nationality,[53,78] CRF values are known to differ. Specifically, Black men and women have lower CRF compared to White,[79] and CRF is lower in Americans compared to Norwegian cohorts.[61] Thus, additional reference values need to be established for specific ethnic/racial groups worldwide so that race and nationality-specific thresholds can be identified to guide clinical decisions.

The recent scientific statement by the AHA recommended that CRF be routinely assessed from a maximal exercise test, incorporating CPX if feasible (Table 2).[12] CPX generally involves exercise testing of submaximal or maximal exertion combined with ventilatory expired gas analysis. These measurements allow the assessment of numerous cardiopulmonary measures at rest, during the transition from rest to exercise, in response to a progressively increasing workload, and at maximal exertion. Thus, CPX provides unique information beyond traditional exercise testing (non-CPX) that may be useful in the diagnosis and management of numerous suspected or confirmed cardiopulmonary disease processes.[80,81] While CPX has been used routinely in populations with known CV or pulmonary disease, it has been relatively underutilized in apparently healthy individuals. There is currently only one available study that has examined a CPX derived variable, VO_2 @ ventilatory threshold (VT), on mortality outcomes in an apparently healthy population.[82] A study of men in the Kuopio Ischemic Heart Disease Risk Factor Study concluded that VO_2 @ VT showed a graded, inverse relationship with all-cause and CV mortality. Further, the addition of VO_2@VT to established risk factors improved classification of individuals into CVD mortality risk categories. While this study only investigated middle aged Finnish men, it does provide initial evidence for the utility of CPX derived variables in mortality risk estimations. Despite limited evidence, given the overall compelling case for assessing CRF regardless of health status, a recent AHA/European Society of Cardiology/European Association for Cardiovascular Prevention & Rehabilitation focused update on the clinical application of CPX included an algorithm for apparently healthy individuals.[81]

Additional CPX derived variables including the VO_2 efficiency slope (OUES),[83] Ve/VCO_2 slope,[84,85] exercise oscillatory ventilation,[86,87] exercise ventilatory power (ratio of peak SBP and Ve/VCO_2 slope),[88,89] circulatory power (product of peak VO_2 and SBP),[90,91] and end tidal volume pressure of CO_2 ($P_{et}CO_2$),[85,92] have been used in the diagnosis

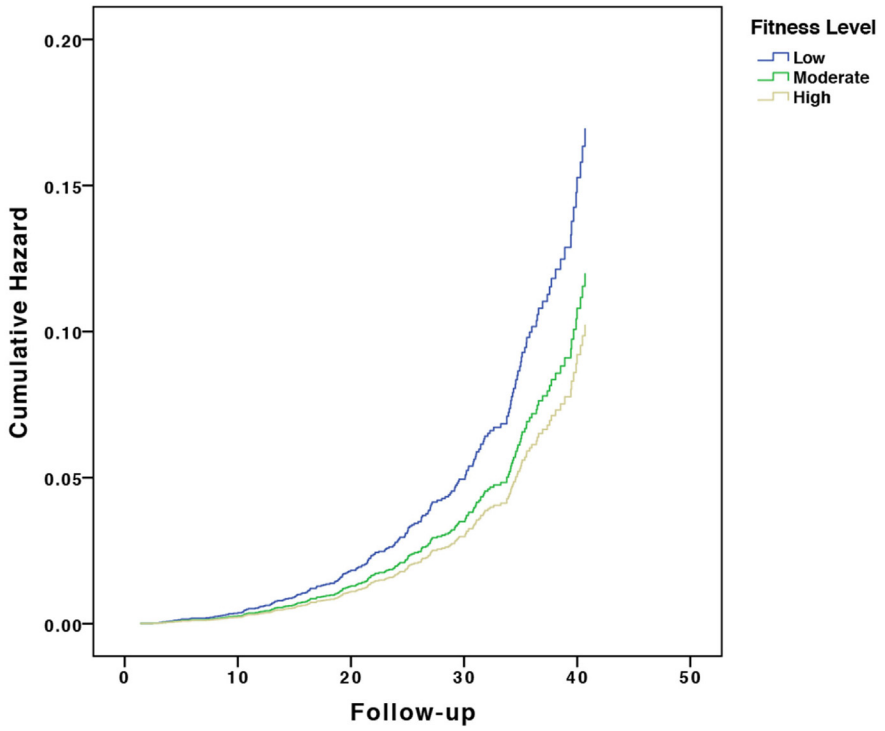

Fig. 1. Cumulative Hazard of CVD mortality by cardiorespiratory fitness group. Hazard plot for CVD mortality according to CRF level. Low, moderate, and high CRF corresponds to ≤33rd, 34–66th, and ≥67th percentiles of FRIEND normative values. Low-fitness was associated with increased risk of all-cause, CVD, and cancer mortality compared to both moderate- and high-fitness groups over the follow-up period. Reprinted from the Journal of the American College of Cardiology 72(19):2283–2292, 2018; Mary T. Imboden, Matthew P. Harber, Mitchell H. Whaley, et al. Cardiorespiratory Fitness and Mortality in Healthy Men and Women; with permission from Elsevier.

and management of numerous patient populations including heart failure, pulmonary arterial hypertension and chronic obstructive and interstitial pulmonary disease, valvular heart disease, patients with unexplained exertional dyspnea, and in presurgical assessment. Moreover, given the integrative physiological coordination of the pulmonary and CV systems to meet the metabolic demands of exercise, it is possible that the presence of subclinical CVD in apparently healthy men and women may result in abnormal ventilatory responses to exercise, that if detected could enhance CVD risk predictions. A recent update to a AHA – European Society of Cardiology/European Association for Cardiovascular Prevention and Rehabilitation CPX statement included a diagnostic/prognostic algorithm specifically for apparently healthy individuals as a guide for interpreting responses during CPX.[81] Additionally, new approaches using machine learning applications with exercise test and individuals' health data are being evaluated.[93]

The ideal outlook is for CRF to be routinely measured in the future, however, it is important to recognize that estimates of CRF can be effective at identifying risk. Indeed, the recent AHA statement clearly points out that CRF estimated by non-exercise algorithms is now able to be calculated through electronic medical records and thus should be available to all clinicians. Until CPX-derived CRF becomes more available, clinicians and patients can also use submaximal exercise tests and/or field tests such as the one-mile walk to evaluate CRF as these methods can identify individual-specific exercise responses.

Conclusions

A Policy Statement by the AHA in 2013 stated that CRF "is currently the only major risk factor that is not routinely and regularly assessed in either the general or specialized clinical settings."[60] Although much progress has been made in the past 5 years, including recognition of CRF as a clinical vital sign, there needs to be accelerated efforts to include CRF as a routine health measure. The evidence base for the importance of CRF is now firmly established as are reference values for interpreting CRF. Presently, estimates of CRF are available for all using non-exercise algorithms. Additionally, the potential for enhanced recognition of CRF and additional measures obtained during the CPX procedure suggests CRF is a key variable of interest for clinicians and patients related to health.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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