Truth About Physical Fitness and Risk of Acute Myocardial Infarction: The HUNT Is On

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Cardiorespiratory fitness (CRF), a measure of the body's maximal ability to use oxygen to perform physical work, relies on interconnected functioning of the cardiovascular system, lungs, and skeletal musculature. A large body of work, spanning 3 decades, has shown that CRF is a potent predictor of key health outcomes, including incident cardiovascular disease (CVD) and mortality.[1] More important, measurement of CRF has the capacity to improve the estimation of CVD risk afforded by traditional risk factors,[2,3] leading some to advocate that CRF be considered a clinical "vital sign."[4] However, routine clinical assessment of CRF is limited by the time, effort, and expertise involved in the assessment of maximal oxygen consumption during incremental intensity maximal effort limited exercise. Thus, the use of CRF as a determinant of risk, specifically as a predictor of incident CVD in clinical practice, remains sorely underused.

Algorithms for the estimation of CRF (eCRF) have been developed to provide a more convenient, readily accessible metric for routine clinical use.[4,5] In addition to common clinical variables, such as age, sex, and body size, all available eCRF models include a metric of self-reported physical activity, which is an important, although not sole, determinant of CRF. Thus, calculation of eCRF requires the addition of an assessment of habitual physical activity to standard components of a routine clinical encounter. The limited validation data available to date suggest that eCRF models appear reasonably accurate when compared with CRF derived from the measurement of oxygen uptake during exercise testing.[4]

In this regard, eCRF may have an advantage both in ease of use and cost over the direct measurement of CRF. A growing literature suggests that eCRF may provide similarly powerful prognostication of health outcomes compared with conventional direct determination of CRF.[6–9]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Shigdel and colleagues present data describing the relationship between eCRF and first acute myocardial infarction (AMI).[10] This relationship was studied in cohort of 26 163 participants (age, 56±11 years; 52% women) who were free of baseline CVD at baseline and then followed up prospectively in the HUNT (Nord-Trøndelag Health Study), a community-based survey assessment of Norwegians. A major strength of this study is that the primary outcome, AMI, was ascertained via a regional registry derived from a small network of hospitals, therefore leading to comprehensive and accurate event capture. Covariate adjustment included the consideration of traditional cardiovascular risk determinants (ie, hypertension, dyslipidemia, diabetes mellitus, and tobacco use) and additional characteristics, including alcohol consumption, marital status, and highest achieved education level. Over a mean follow-up of 13 years, there were 1566 AMI events, yielding an incidence of 4.5 per 1000 person-years. In the aggregate cohort inclusive of both men and women, the fully adjusted risk of AMI was 15% and 7% lower, respectively, among participants in the highest (SHR (standardized hazard ratio), 0.85; 95% CI, 0.75–0.97) and middle (SHR, 0.93; 95% CI, 0.82–1.05) eCRF tertiles compared with those in the lowest eCRF tertile. Perhaps somewhat surprisingly, this result was driven largely by AMI risk reduction in women rather than men. Specifically, fully adjusted models demonstrated strong associations between eCRF and incident AMI among women but only demonstrated similar nonsignificant trends among men.

There are several notable strengths of this study that deserve attention. First, data from this effort establish a clear and compelling association between eCRF and incident AMI, rather than the incrementally broader outcomes of composite CVD events, CVD mortality, or all-cause mortality that have been the focus of previous work.[4,6,7] Data from this study thus permit us to consider AMI risk as a function of eCRF

without dilution by other CVD events that may have a different relationship with eCRF. Within the constraints of observational research, this discrete focus provides the opportunity to generate credible quantitative associations and perhaps mechanistic speculations about the relationship between exposure and outcome. Second, the present study appears to have revealed interesting sex-based differences on how eCRF may mediate CVD risk that was not captured in prior studies. The nearly equal number of men and women in this large cohort afforded the authors the ability to perform amply powered sex-specific analyses that suggest a stronger protective effect of high eCRF among women than men. Notably, women in the highest eCRF tertile had a 25% lower AMI risk than women in the lowest eCRF tertile (SHR, 0.75; 95% CI, 0.60–0.95) and an overall AMI risk attenuation of 11% lower for each 1–metabolic equivalent of task increase in eCFR. The message herein is clear and unambiguous: the fitter the woman, the less likely the risk of future AMI.

The apparent lack of AMI risk reduction in men is puzzling, and potential explanations deserve consideration. It is almost certain that a true beneficial relationship between eCRF and AMI risk exists but was not captured because of the nature of the HUNT cohort. Among this relatively healthy and physically fit group of men, the average eCRF of the *lowest* tertile of male participants was 37 mL/kg per minute or 10.4 metabolic equivalents of task. This value approximates the average exercise capacity of healthy 55-year-old men rather than the large swath of the global population who lives with impaired or underdeveloped fitness. Prior work suggests that most risk reduction for all-cause mortality is observed when comparing those with low CRF (<5 metabolic equivalents of task) with those with marginally higher CRF (5–7 metabolic equivalents of task).[4] In HUNT, grouping men with low and average eCRF together for use as a referent tertile, without isolation of a truly low eCRF subgroup, may explain the lack of significant incremental AMI risk reduction among fitter men. But if exercise is medicine for the least fit, should it not be similarly so for the most fit? At some level of fitness, probably a lower level than many aging athletes and exercise zealots wish to acknowledge, further increases in physical activity and/or higher levels of fitness yield diminishing health returns. Practically speaking, data from HUNT remind us that aging men with conventional coronary artery disease risk factors cannot completely "outrun," "outcycle," "outswim," or "outplay" the risk of future heart disease. Knowing well that increasing levels of physical activity have a beneficial effect on most traditional risk factors, the fact that high levels of exercise are incompletely protective remains poorly understood. To what degree unmeasured risk factors or complex interactions between traditional risk factors, both which may vary as a function of sex, are explanatory remains unclear. Future work, focusing on defining the mechanistic and

intrinsic sex-based differences for physical activity, CRF, and heart health, is badly needed. In the interim, there lies a time-honored lesson for both the patient and the clinician. Physically fit people and the cardiovascular specialists who care for them are often tempted to underplay the importance of and, thus, to undertreat risk factors, such as mild hypertension or dyslipidemia. Data from HUNT serve as a sobering reminder that this is nothing short of an avoidable mistake. No matter how fit your patient is or how much he or she does, no level or fitness or activity is the ticket for coronary immunity.

Finally, we consider several key unanswered questions that emerge from this study. As the authors rightfully point out, eCRF provides an inexpensive and informative opportunity to refine AMI risk assessment in clinical practice. As we and other authors have previously advocated, physical activity, perhaps using a tool that derives eCRF, should be assessed and documented as a standard part of all clinical patient encounters. Yet, at present, we are far from knowing what to do with this information for 2 fundamental reasons. First, estimates of CRF do not permit one to differentiate the relative importance of habitual physical activity from objective measures of fitness. Although they are related, their relationship is neither simple nor well understood. Work comparing the prognostic power of habitual physical activity with direct measures of CRF is badly needed as this uncertainty impacts the way we counsel and manage patients. For those with a genetically endowed high CRF, is superimposed physical activity of any incremental value? Conversely, for those who meet or exceed physical activity guidelines but do so with low levels of CRF, are they wasting their time? Future work designed to address this area of uncertainty is of critical importance. Second, the impact of change in eCRF over time on AMI risk and other important health outcomes remains largely unknown. Although we think that targeted efforts to improve eCRF may improve clinical outcomes, this has yet to be established. The impact of longitudinal eCRF trajectories, as affected by common perturbations, including exercise interventions, pharmacotherapy, medical procedures, and the development of disease, has yet to be determined. Delineating the true modifiability of eCRF and its impact on health and wellness represents a critical area of future work.

While we await progress in the aforementioned areas of critical scientific uncertainty, findings from HUNT represent a step in the right direction. The routine assessment of physical activity habits and or the determination of eCRF in clinical practice provides an opportunity to improve coronary artery disease risk stratification.[11] A tool that integrates traditional markers of risk with the metrics of physical activity and/or CRF, either measured or estimated, promises to represent the next major advance in AMI risk stratification and, thus, disease prevention. As for such a tool, "*the HUNT is on*."

Disclosures

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