ORIGINAL RESEARCH

Cardiorespiratory Fitness and Highly Sensitive Cardiac Troponin Levels in a Preventive Medicine Cohort

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***Background*—**Cardiorespiratory fitness (CRF) and highly sensitive cardiac troponin T (hs-cTnT) are associated with risk of all-cause and cardiovascular mortality as well as incident heart failure. A link of low CRF to subclinical cardiac injury may explain this association. We hypothesized that CRF would be inversely associated with hs-cTnT measured in healthy adults over age 50.

***Methods and Results*—**We evaluated 2498 participants (24.7% female, mean age 58.7 years) from the Cooper Center Longitudinal Study between August 2008 and January 2012. Plasma specimens obtained shortly before CRF estimates by Balke treadmill testing were used for hs-cTnT assays. CRF was grouped into low CRF (category 1), moderate CRF (categories 2–3), and high CRF (categories 4–5). Multivariable logistic regression was used to estimate the association of CRF with hs-cTnT. The prevalence of measurable hs-cTnT (≥3 ng/L) was 78.5%. In multivariable analyses, low-fit individuals were significantly more likely than high-fit individuals to have elevated hs-cTnT (≥14 ng/L) (odds ratio 2.47, 95% CI 1.10–5.36).

***Conclusions*—**In healthy older adults, CRF is inversely associated with hs-cTnT level adjusted for other risk factors. Prospective studies are needed to evaluate whether improving CRF is effective in preventing subclinical cardiac injury. **(*J Am Heart Assoc*. 2016;5:e003781 doi: 10.1161/JAHA.116.003781)**

Key Words: cardiorespiratory fitness • exercise capacity • hs-cTnT • troponin

Low cardiorespiratory fitness (CRF) is known to be a strong and independent predictor for risk of all-cause mortality, cardiovascular disease mortality, and morbidity, including incident heart failure.[1–4] While it is thought that associations of CRF with atherosclerotic coronary heart disease risk are largely mediated through traditional atherosclerotic coronary heart disease risk factors,[5,6] the mechanisms underlying the association of low CRF with heart failure risk are less well defined. In asymptomatic adults, low CRF has recently been shown to be associated with a higher prevalence of cardiac echocardiographic abnormalities such as concentric remodeling and smaller left ventricular chamber size as well as diastolic dysfunction.[7] These results suggest an underlying cardiac structural etiology for the low CRF.

The recent development of a high-sensitivity assay for cardiac troponin T (hs-cTnT) allows characterization of cTnT levels in the general adult population. Of note, studies utilizing these more sensitive troponin assays in patients with existing coronary artery disease or congestive heart failure have shown higher levels to be associated with increased cardiovascular mortality and heart failure morbidity.[8,9] In general, community-based populations, however, low but detectable levels of hs-cTnT have been associated with structural heart disease and with heart failure and mortality risk.[10,11] Thus, the ability to measure highly sensitive cTnT has facilitated exploration of the role of minor, subclinical myocardial injury in the pathogenesis of heart failure and can be used to assess the possible relationship of subclinical myocardial injury with low CRF.

As both CRF and cTnT are predictive of cardiovascular risk, a common underlying pathophysiologic mechanism is possible, and therefore improving CRF may prevent or mitigate cardiac injury at an early subclinical stage. To investigate the potential link of low CRF with myocardial injury, we studied the association of CRF and hs-cTnT, hypothesizing that higher CRF would be associated with lower measured levels of hs-cTnT.

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Methods

Study Population

The Cooper Center Longitudinal Study (CCLS) is a prospective cohort study that began in 1971 and consists of men and women who received a preventive medicine examination at the Cooper Clinic in Dallas, TX. In general, CCLS participants are well-educated and self-referred or referred by their employer for the preventive examination. All participants signed an informed consent to participate in the CCLS. The data are maintained by The Cooper Institute, a nonprofit research organization, with the goal of examining the association between lifestyle factors and health outcomes. The study is reviewed and approved annually by The Cooper Institute Institutional Review Board.

The current study is cross-sectional, with participants drawn from 10 039 CCLS men and women who had clinic examinations including maximal exercise treadmill tests and stored plasma samples between 2008 and 2012. We excluded participants who were less than 50 years old (n=4671), those with a personal history of myocardial infarction, cerebrovascular accident, or cancer (n=617), and those with creatinine ≥1.5 mg/dL (n=26). After all exclusions, 4725 participants remained eligible for the present study. From this pool of eligible individuals, we randomly selected 2500 participants for study. An additional 2 participants were excluded during sample processing because of technical issues with the plasma assay, leaving a final study sample of 2498 (1881 men and 617 women) as shown in Figure 1.

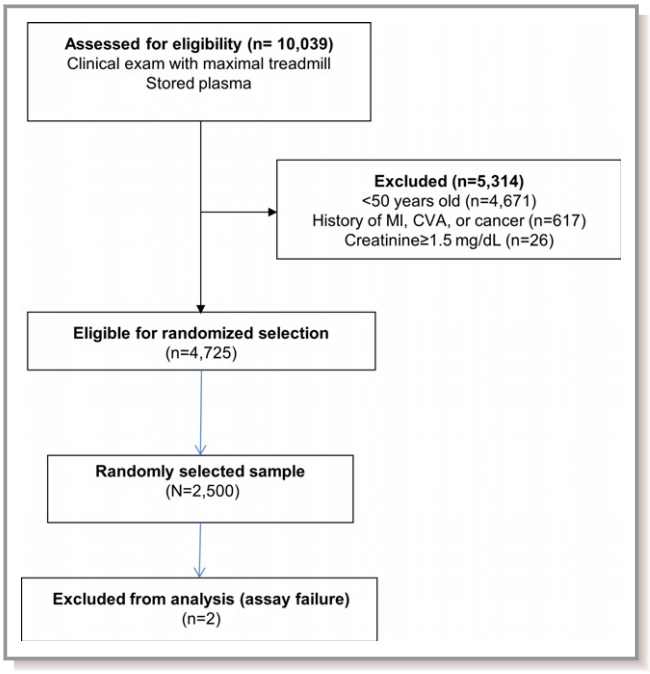

Figure 1. Study sample derivation. CVA indicates cerebrovascular accident; MI, myocardial infarction.

Medical Examination

The preventive medical examination occurred after a 48-hour period of no leisure-time physical activity and a 12-hour fast. As part of the examination, participants were asked to complete an extensive medical history questionnaire that included detailed questions on demographics, personal and family health histories, and physical activity habits. Physical activity was based on 11 questions from the medical history questionnaire. Specifically, participants were asked to provide the frequency and duration of 11 specific physical activity types, including walking, running, treadmill, swimming, stationary cycling, bicycling, elliptical, aerobic dance, racket sports, vigorous sports, and other activity. Summary estimates were computed by weighting the product of the reported frequency and duration (in minutes per week [min·week^{-1}]), by a standardized estimate of the metabolic equivalent (MET) of each activity type[12], which was then summed across all activities performed. Leisure-time physical activity was expressed as MET·min·week^{-1}.

Clinic staff measured the participant's height and weight using a standard clinical stadiometer and scale. Seated resting blood pressure was measured with a calibrated sphygmomanometer. Fasting venous blood was assayed for blood glucose and lipids using automated techniques at the Cooper Clinic Laboratory following standard procedures.

All participants completed a symptom-limited maximal exercise treadmill test using a modified-Balke protocol. The Balke protocol has been used since the establishment of the CCLS and for consistency across decades of measurements; it has remained the standard at the Cooper Clinic for maximal exercise testing. Duration of the treadmill test has a strong correlation with measured maximal oxygen uptake in men (r=0.92) and women (r=0.94).[13,14] For the current study, we computed maximal METs (metabolic equivalents, 1 MET=3.5 mL O_2 uptake/kg/min) based on the final treadmill speed and grade in order to standardize exercise test performance. We classified men and women into age- and sex-specific categories of CRF level based on normative data on treadmill time within the CCLS. Participants were then classified into 3 groups: low CRF (category 1), moderate CRF (categories 2 and 3), and high CRF (categories 4 and 5).[2] As the CRF categories are based on normative data, they do not represent 5 equal samples.

Biomarker Analysis

Hs-cTnT was measured from plasma obtained prior to the maximal exercise treadmill test. Plasma samples were stored at −70 to −80°C and were thawed immediately before testing, with a maximum of 2 freeze–thaw cycles. Hs-cTnT concentrations were measured on an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN) at the University of

Maryland. The analytical measurement range was 3 to 10 000 ng/L. The manufacturer's reported 99th percentile cutoff value for this assay in healthy controls is 14 ng/L, and values above this level are considered elevated.[15] All technologists involved in the measurement and recording of the hs-cTnT were blinded to participant outcomes.

Statistical Analyses

Means and frequencies were calculated for patient characteristics by age- and sex-specific CRF groups: low CRF (category 1), moderate CRF (categories 2 and 3), and high CRF (categories 4 and 5). For analysis, hs-cTnT levels were stratified into 5 categories: undetectable, <3.0 ng/L (the limit of blank of the assay) as the lowest category (1), ≥14.0 ng/L, the level greater than or equal to the 99th percentile as the highest category (5), and levels between 3.0 and 14.0 divided into tertiles for the intermediate categories 2, 3, and 4, as previously described.[10,15] The proportion of individuals in each hs-cTnT category was determined for each CRF category. Trends across CRF categories for means and proportions of cTnT categories were tested using the Jonckheere-Terpstra test. Multivariable logistic regression was used to estimate the association of CRF with the presence of hs-cTnT ≥14.0 ng/L. Models were adjusted for age, sex, body mass index, systolic blood pressure, fasting glucose, total cholesterol, and current smoking status. A *P* value of <0.05 was considered statistically significant. All analyses used SAS for Windows (release 9.2; SAS Institute Inc, Cary, NC).

Results

Characteristics of the 2498 participants are shown in Table 1. The prevalence of hs-cTnT ≥3 ng/L (the limit of blank for the assay) was 78.5%. Those with low CRF (Category 1) had

Table 1. Participants' Characteristics Stratified by CRF Categories

	Low Fitness (Category 1)	Moderate Fitness (Categories 2 & 3)	High Fitness (Categories 4 & 5)	*P* Value for Trend
n (%)	93 (3.7)	581 (23.3)	1824 (73.0)	
Female, n (%)	19 (20.4)	109 (18.8)	489 (26.8)	<0.001
Age, y	62.7 (10.0)	60.3 (8.1)	58.0 (6.9)	<0.001
Current smoker, n (%)	12 (12.9)	51 (8.8)	92 (5.0)	<0.001
Body mass index, kg/m^2	30.8 (5.5)	28.7 (3.8)	25.5 (3.1)	<0.001
Systolic blood pressure, mm Hg	123.9 (14.8)	122.4 (13.2)	119.6 (13.2)	<0.001
History of high blood pressure, n (%)	40 (43.0)	191 (32.9)	382 (20.9)	<0.001
Glucose, mg/dL	100.9 (18.5)	97.3 (12.5)	93.4 (9.2)	<0.001
History of diabetes mellitus, n (%)	1 (1.1)	7 (1.2)	1 (0.1)	<0.001
Total cholesterol, mg/dL	170.8 (35.4)	180.6 (40.4)	182.0 (36.2)	0.042
HDL cholesterol, mg/dL	49.7 (13.7)	52.6 (14.9)	61.7 (18.3)	<0.001
LDL cholesterol*, mg/dL	94.6 (30.6)	102.4 (33.5)	101.3 (30.9)	0.772
Triglycerides, mg/dL	136.3 (85.1)	130.1 (121.6)	95.1 (51.0)	<0.001
History of high cholesterol, n (%)	40 (43.0)	224 (38.6)	543 (29.8)	<0.001
Creatinine, mg/dL	1.02 (0.17)	1.00 (0.17)	0.97 (0.17)	0.001
Creatinine phosphokinase* (CPK), mg/dL	129.7 (125.1)	140.7 (300.9)	124.2 (196.3)	0.135
C-reactive protein* (CRP), mg/dL	3.46 (5.7)	2.05 (3.3)	1.31 (3.3)	<0.001
High-sensitivity cardiac troponin, ng/L	7.78 (5.15)	7.00 (5.52)	5.95 (9.89)	<0.001
Physical activity*, MET min/week	553.5 (964.8)	891.3 (1012.4)	1539.3 (2091.2)	<0.001
Cardiorespiratory fitness, METs	6.7 (0.9)	8.8 (1.1)	11.6 (1.9)	<0.001
Maximum heart rate, BPM	149.1 (16.7)	160.1 (15.7)	168.9 (13.0)	<0.001
Heart rate recovery* (HRR), BPM	17.6 (8.5)	21.8 (7.7)	24.4 (7.5)	<0.001
10-y Framingham Risk, %	5.1 (2.5)	4.9 (2.7)	3.7 (2.5)	<0.001

Data presented as mean (SD) unless otherwise indicated. BPM indicates beats per minute; CRF, cardiorespiratory fitness; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent. Heart rate recovery (HRR)=maximum heart rate−heart rate at 1 minute of recovery.
*Variables with N < 2498: LDL cholesterol N=2490; CPK N=2494; CRP N=2456; physical activity MET min/week N=2209; HRR N=2494.

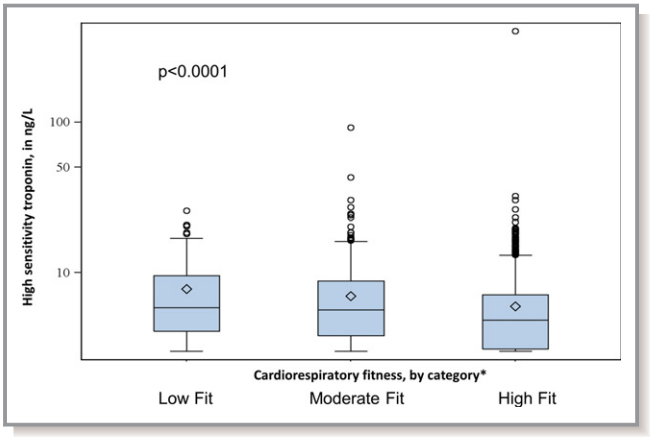

Figure 2. Box and whisker plot of high-sensitivity troponin by cardiorespiratory fitness category. Boxes indicate the interquartile range (IQR). Diamonds indicate the mean. Horizontal bars within boxes indicate the median. Outlying data points are >1.5 IQR beyond the 75th percentile. Whiskers indicate the range of data excluding outliers.

higher levels of traditional risk factors compared with moderate fit and high fit individuals as seen in Table 1. The trend in hs-cTnT levels across low fit, moderate fit, and high fit groups is illustrated in Figure 2. Persons who were classified as low fit had approximately half the prevalence of hs-cTnT <3 ng/L compared with high CRF individuals (11.8% versus 23.7%, *P* for trend <0.001) and conversely >4 times the prevalence of elevated hs-cTnT ≥14 ng/L (12.9% versus 2.5%, *P*<0.001) (Figure 3).

Unadjusted Spearman correlation showed an inverse continuous relationship between CRF and hs-cTnT: CRF by METs predicting hs-cTnT was −0.191, *P*<0.001 in men and −0.159, *P*<0.001 in women. In multivariable analyses, low fit individuals were significantly more likely than high fit individuals to have hs-cTnT ≥14 ng/L (odds ratio 2.47, 95% CI [1.10–5.36]). Moderate fit individuals tended to be more likely than high fit people to have hs-cTnT ≥14 ng/L (odds ratio 1.53, 95% CI [0.91–2.57]), but the estimate for moderate fit was not statistically significant in the adjusted model (Table 2).

Discussion

In this study, we demonstrate an inverse association between CRF and hs-cTnT in a cohort of generally healthy men and women. Higher levels of CRF were associated with lower levels of hs-cTnT and lower odds of having significant elevated levels of hs-cTnT of 14 ng/L or greater. The inverse association remained significant after adjustment for age and traditional cardiac risk factors. This represents the first study looking at the relationship between measured CRF and hs-cTnT and suggests that low CRF may be associated with chronic low-level myocardial injury.

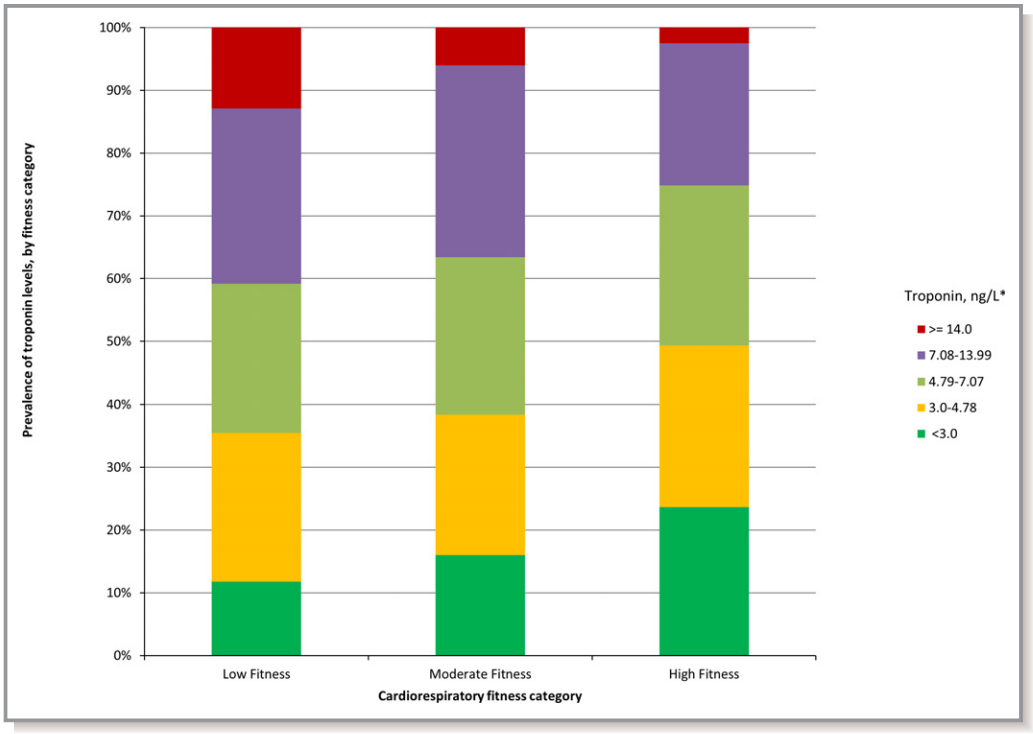

Figure 3. Prevalence of troponin levels, by cardiorespiratory fitness category. *Troponin levels were defined as: 99th percentile (≥14.0 ng/L), tertiles (3.0–13.99 ng/L), and lower limit of assay (<3.0 ng/L). Low fit=category 1, moderate fit=categories 2 and 3, high fit=categories 4 and 5 of maximal treadmill time.

Table 2. Odds Ratios (OR) and 95% CI for the Association Between Fitness Categories and Presence of hs-cTnT ≥14 ng/L

	Low Fitness (Category 1)	*P* Value	Moderate Fitness (Categories 2 & 3)	*P* Value	High Fitness (Categories 4 & 5) Referent
Unadjusted OR (95% CI)	5.73 (2.92–11.23)	<0.001	2.48 (1.58–3.89)	<0.001	1.0
Adjusted OR (95% CI)*	2.98 (1.42–6.24)	0.004	1.81 (1.13–2.89)	0.014	1.0
Adjusted OR (95% CI)†	2.92 (1.37–6.22)	0.005	1.63 (1.01–2.62)	0.044	1.0
Adjusted OR (95% CI)‡	2.42 (1.08–5.40)	0.031	1.44 (0.86–2.40)	0.168	1.0
Adjusted OR (95% CI)§	2.47 (1.10–5.36)	0.029	1.53 (0.91–2.57)	0.109	1.0

hs-cTnT indicates high-sensitivity cardiac troponin T.
*Covariates: age.
†Covariates: age and sex.
‡Covariates: age, sex, and body mass index (BMI).
§Covariates: age, sex, BMI, systolic blood pressure, glucose, total cholesterol, and current smoking status (Y/N).

Higher levels of physical activity and CRF have been associated with lower rates of incident heart failure and cardiovascular mortality.[1,16] Until recently, few data have been available characterizing the potential mechanisms of the benefits of CRF on heart failure risk. Higher CRF appears to favorably influence cardiac structure and function,[7,17] contributing to lower rates of heart failure morbidity and mortality.

The use of hs-cTnT for screening of the general population has been evaluated. In the Dallas Heart Study, a multiethnic population-based study, over a median of 6.4 years of follow-up, the prevalence of measurable cTnT above the limit of blank with the highly sensitive assay (≥3 ng/L) was 25% (versus 0.7% with standard assays).[10] Of note, in the current study, the prevalence of hs-cTnT >3 ng/L was notably higher (78.5%), presumably due to the older age and larger proportion of males in the CCLS compared with the Dallas Heart Study. In the Dallas Heart Study, all-cause mortality and left ventricular hypertrophy increased significantly from the lowest hs-cTnT category (<3 ng/L) to the highest (≥14 ng/L).[10] In an older population enrolled in the Cardiovascular Health Study, the prevalence of hs-cTnT ≥3 ng/L was 66.2% and both the baseline hs-cTnT level and changes in troponin levels were found to provide prognostic information.[11] In the Cardiovascular Health Study, we previously reported an association between regular exercise and smaller increases in hs-cTnT over time.[18] However, the association with objectively measured CRF has not been reported previously.

In the current study, we found that compared with the high fit group, those individuals in the low fit group had over 2.5 times the odds of having hs-cTnT ≥14 ng/L, and those in the moderate fit group had 1.5 times higher odds, suggesting that lower CRF may be associated with subclinical cardiac injury. It appears that the relationship may be nonlinear, with the association of CRF and hs-cTnT more apparent in the lower range of CRF and the higher range of the troponin distribution. Furthermore, the question of which comes first, low CRF or higher hs-cTnT, cannot be determined based on this cross-sectional study. However, baseline physical activity has been shown to correlate with changes in biomarkers, including hs-cTnT and NT-pro-BNP, over up to 3 years.[18] Further research is needed with prospective studies to fully evaluate the underlying pathophysiology and whether improving CRF is an effective strategy to prevent or limit chronic subclinical cardiac injury.

Strengths of our study include the well-characterized measure of CRF among the participants who also had plasma collected shortly before actual treadmill testing, allowing a cross-sectional analysis of troponin and CRF. An important limitation is that the CCLS comprises predominantly non-Hispanic white patients, which may limit the generalizability of our findings to other racial groups. However, this feature allows assessment of a homogeneous, generally well cohort free of potential confounding health and socioeconomic issues. Participants were well-educated and often self-referred, so a volunteer effect would also limit the generalization of the results to the general population. Because of resource limitations, we were unable to study women and men separately with sufficient power to detect associations of CRF with hs-cTnT in sex-specific subgroups.

In conclusion, this study shows that CRF is inversely associated with hs-cTnT, which may be related to subclinical myocardial cellular injury. Further research should be done to assess whether modifying CRF through increased physical activity would prevent cardiac injury and potentially the longer term risk of cardiovascular disease outcomes.

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Disclosures

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