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Sarah Gorgis

Jonathan K. Ehrman

Michael J. Blaha

Waqas T. Qureshi

Steven J. Keteyian

See next page for additional authors

Authors

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Relation of Exercise Capacity to Incident Heart Failure Among Men and Women With Coronary Heart Disease (from the Henry Ford Exercise Testing [FIT] Project)

Sarah Gorgis, MD[a], Jonathan K. Ehrman, PhD[b], Michael J. Blaha, MD[b], Waqas T. Qureshi, MD, MS[c], Steven J. Keteyian, PhD[a], Mouaz H. Al−Mallah, MD[d], and Clinton A. Brawner, PhD[a,*]

Exercise capacity (EC) is inversely related to the risk of cardiovascular disease and incident heart failure (HF) in healthy subjects. However, there are no present studies that exclusively evaluate EC and the risk of incident HF in patients with known coronary heart disease (CHD). We aimed to determine the relation between EC and incident HF in patients with an established clinical diagnosis of CHD. We retrospectively identified 8,387 patients (age 61 ± 12 years; 30% women; 33% non-White) with a history of myocardial infarction (MI) or coronary revascularization procedure and no history of HF at the time of a clinically indicated exercise stress test completed between 1991 and 2009. EC was quantified in metabolic equivalents of task (METs) estimated from treadmill testing. Incident HF was identified through June 2010 from administrative databases based on ≥3 encounters with International Classification of Diseases, Ninth Revision 428.x. Cox regression analysis was used to evaluate the risk of incident HF associated with METs. Covariates included age; gender; race; hypertension, diabetes, hyperlipidemia, smoking, and MI; medications for CHD and lung diseases; and clinical indication for treadmill testing. During a median follow-up of 8.2 years (interquartile range 4.7 to 12.4 years) after the exercise test, 23% of the cohort experienced a new HF diagnosis. Lower EC categories were associated with higher HF incidence compared with METs ≥12, with nearly fourfold greater adjusted risk among patients with METs <6. Per unit increase in METs of EC was associated with a 12% lower adjusted risk for HF. There was no significant interaction based on race (p = 0.06), gender (p = 0.88), age ≤61 years (p = 0.60), history of MI (p = 0.31), or diabetes (p = 0.38). This study reveals that among men and women with CHD and no history of HF, EC is independently and inversely related to the risk of future HF. **(Am J Cardiol 2022;181:66−70)**

Cardiorespiratory fitness (i.e., exercise capacity [EC]) is inversely related to the risk of cardiovascular disease and incident heart failure (HF) in healthy subjects.[1] Despite improvements in cardiovascular disease treatment, the prevalence of HF continues to increase with projected numbers estimated to affect over 8 million Americans and result in total costs of $70 billion by 2030.[2] Given the significant burden of disease, identifying factors that correlate with future HF can serve to target preventative efforts, especially in higher-risk populations. A recent meta-analysis by Qiu et al[3] evaluated 4 studies and found a consistent inverse relation between EC and incident HF with a relative risk of 0.82 (95% confidence interval [CI] 0.80 to 0.84). There are no present studies that exclusively evaluate EC and the risk of incident HF in patients with known coronary heart disease (CHD). This study aimed to determine the relation between EC and incident HF in patients with an established clinical diagnosis of CHD. We hypothesized that EC would be inversely related to incident HF in patients with CHD and no history of HF.

Methods

The Henry Ford Exercise Testing (FIT) Project is a retrospective cohort study containing 69,885 patients (aged ≥18 years) who underwent a clinically indicated exercise stress test between January 1991 and May 2009. Details of the FIT project design were published previously.[4] A brief overview is provided here. Exercise tests were performed at Henry Ford Hospital and affiliated medical centers. All patients underwent routine sign and symptom-limited maximal exercise tests on a treadmill following the standard Bruce protocol. Clinical exercise physiologists and nurses collected relevant clinical, medication, and exercise data at the time of testing and entered the data into a clinical reporting tool that directly populated the system's electronic medical record. Incident HF was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification codes (428.x) through June 2010 providing a minimum of 1 year of follow-up. All-cause mortality was obtained by way of the Social Security Death Index Master File through April 2013. EC was quantified in METs of task as reported by the clinician who administered

[a]Henry Ford Hospital and Medical Group, Detroit, Michigan; [b]Johns Hopkins Medicine, Lutherville, Maryland; [c]University of Massachusetts School of Medicine, Worcester, Massachusetts; and [d]Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas. Manuscript received May 19, 2022; revised manuscript received and accepted July 5, 2022.

See page 69 for disclosure information.

*Corresponding author: Tel: 313.972.4108; fax: 313.972.1921.
E-mail address: cbrawne1@hfhs.org (C.A. Brawner).

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the test based on peak treadmill speed and grade. The cardiorespiratory fitness groups were as previously defined in the rationale and design of the FIT project.[4] METS <6 was used to define the lowest fitness category based on previous analyses of the group's association with high risk for early mortality.[4]

For the present analysis, we identified 8,387 patients with CHD, defined as a history of myocardial infarction (MI) and/or coronary revascularization, who also had no history of HF at the time of the exercise stress test. Patients with a diagnosis of HF at the time of testing or during the first 90 days of follow-up were excluded. The FIT project was approved by the Henry Ford Health System's institutional review board and informed consent was waived.

Between group comparisons were performed using the chi-square test for categorical variables, two-sample *t* test for normally distributed numerical variables, and Mann-Whitney U test for non-normally distributed numerical variables. Non-normally distributed numerical variables were summarized as median (interquartile range [IQR]). Cox regression analysis was used to determine the hazard ratio (HR) associated with the relation between METs and time to incident HF. Covariates included age; gender; race; history of hypertension, diabetes, hyperlipidemia, smoking, and MI; medications for CHD and pulmonary diseases; and clinical indication for exercise testing. Patients without incident HF were censored based on the date of their last clinic visit or death occurring before June 2010. Interactions with METs were assessed for gender, age, race, hypertension, diabetes, history of MI, history of percutaneous intervention (PCI), and history of coronary artery bypass grafting (CABG). Finally, for patients who had coronary revascularization after the baseline exercise test, a sub-analysis based on the type of revascularization procedure (i.e., PCI or CABG) was also performed. Alpha level was set at 0.05. IBM SPSS version 24 (IBM, Somers, New York) with the advanced statistics module was used for all analyses.

Results

A total of 8,387 patients met all inclusion and no exclusion criteria. Over a median follow-up of 8.2 years (IQR 4.7 to 12.4), 22.5% of patients had incident HF. Demographics of the cohort are shown in Table 1. The mean age was 61 ± 12 years, 30.3% were female, and 33.4% were of non-White race. The most common cardiovascular co-morbidity was hypertension (87.9%), followed by prior MI (78.3%), prior revascularization (57.7%), tobacco use (44.1%), and diabetes (26.8%).

Among patients with CHD, those who experienced incident HF were more likely to be older and have hypertension, diabetes, atrial fibrillation, prior MI, and prior CABG.

Table 1
Demographics of patients with CHD, with and without incident HF

Characteristics	All patients (n = 8,387)	Incident HF		P-value*
		Yes (n = 1,883)	No (n = 6,504)	
Age (years)	61 ± 12	64 ± 11	60 ± 12	<0.001
Women	2538 (30.3%)	595 (31.6%)	1943 (29.9%)	0.15
Body mass index (kg·m^{-2})	29.0 ± 5.3	29.2 ± 5.5	28.9 ± 5.2	0.09
Race				<0.001
White	5587 (66.6%)	1167 (62.0%)	4420 (68.0%)	
Black	2445 (29.2%)	668 (35.5%)	1777 (27.3%)	
Other	355 (4.2%)	48 (2.5%)	307 (4.7%)	
Hypertension	7375 (87.9%)	1704 (90.5%)	5671 (87.2%)	<0.001
Diabetes (type 1 or 2)	2246 (26.8%)	684 (36.3%)	1562 (24.0%)	<0.001
Hyperlipidemia	4867 (58.0%)	939 (49.9%)	3928 (60.3%)	<0.001
Smoking	3699 (44.1%)	749 (39.8%)	2950 (45.4%)	<0.001
Myocardial infarction	6563 (78.3%)	1511 (80.2%)	5052 (77.7%)	0.02
PCI	2659 (31.7%)	438 (23.3%)	2221 (34.1%)	<0.001
Coronary artery bypass	2180 (26.0%)	638 (33.9%)	1542 (23.7%)	<0.001
Atrial fibrillation	480 (5.7%)	144 (7.6%)	336 (5.2%)	<0.001
Medications				
ACE inhibitor	2588 (30.9%)	633 (33.6%)	1955 (30.1%)	0.003
ARB	228 (2.7%)	29 (1.5%)	199 (3.1%)	<.001
Beta-adrenergic blocker	4452 (53.1%)	949 (50.4%)	3503 (53.9%)	0.008
Calcium channel blocker	1822 (21.7%)	484 (25.7%)	1338 (20.6%)	<0.001
Diuretic	1770 (21.1%)	540 (28.7%)	1230 (18.9%)	<0.001
Lipid lowering	3476 (41.4%)	608 (32.3%)	2868 (44.1%)	<0.001
Oral antiglycemic	965 (11.5%)	285 (15.1%)	680 (10.5%)	<.001
Insulin	548 (6.5%)	212 (11.3%)	336 (5.2%)	<.001
Exercise test data				
% age-predicted HR max	81 ± 14	80 ± 15	82 ± 14	<.001
Peak METs	7 (5, 10)	5 (4, 7)	7 (5, 10)	<.001

Data are mean ± standard deviation, median (25th, 75th percentile), or n (% of group).

ARB = angiotensin receptor blocker; HF = heart failure; HR max = heart rate maximum; METs = metabolic equivalents of task; PCI = percutaneous coronary intervention.

* Comparison of patients with vs. without incident HF.

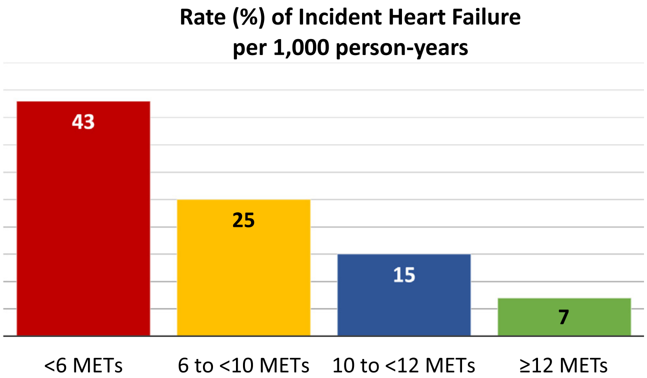


Figure 1. Rate of incident heart failure per 1,000-person-years across categories of METs of task.

Patients without incident HF were more likely to have hyperlipidemia, be on statins, and have prior PCI (Table 1).

Patients with incident HF achieved lower median METs as compared with those without incident HF (5 METs [IQR 4 to 7] vs 7 METs [IQR 5 to 10], p <0.001). The unadjusted incidence of HF across MET categories is illustrated in Figure 1. There is an early and sustained higher incidence of HF with lower EC. Based on Cox regression analysis adjusted for baseline characteristics (age, gender, race, medical history, medications, reason for test), there continued to be a significant inverse association between EC and HF incidence (Table 2). Patients with EC <6 METs had 3.8 times higher adjusted risk for incident HF compared with EC ≥12 METs. For per unit increase in METs, there was a 12% lower adjusted risk of incident HF.

Adjusted survival curves by gender are shown in Figure 2. There was no significant interaction between METs and time of incident HF based on gender (p = 0.88), nor the following characteristics at baseline: age (<50, 50 to 59, or 60+ years; p = 0.09), race (Black or White; p = 0.06), hypertension (p = 0.93), diabetes (p = 0.41), history of MI (p = 0.31), history of PCI (p = 0.76), or history of CABG (p = 0.99).

However, there was a significant interaction (p <0.001) based on coronary revascularization status (yes/no) occurring during follow-up after the exercise test and before the incident HF. Among patients (n = 842) who underwent follow-up coronary revascularization (PCI or CABG) after the exercise test, the adjusted HR associated with METs and time to incident HF was 0.96 (95% CI 0.93 to 0.99, p = 0.01). The adjusted HR was 0.86 (95% CI 0.84 to 0.88, p <0.001) among patients without revascularization after the exercise test (n = 7,545).

Finally, in a sensitivity analysis in which 832 patients who experienced an MI after the exercise test and before incident HF were excluded, METs were associated with an adjusted HR= 0.86 (95% CI 0.84 to 0.89; n= 7,555).

Table 2
Risk of incident heart failure based on exercise capacity expressed in metabolic equivalents of task (METs)

MET categories	n	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
< 6	2,835	6.33 (4.77, 8.40)	3.83 (2.86, 5.13)
6 to < 10	2,814	3.40 (2.55, 4.52)	2.44 (1.83, 3.27)
10 to <12	1,999	2.20 (1.63, 2.97)	1.82 (1.35, 2.46)
≥ 12	739	Referent	Referent
Per 1 unit METs	8,387	0.84 (0.83, 0.86)	0.88 (0.87, 0.90)

CI = confidence interval; HR = hazard ratio.

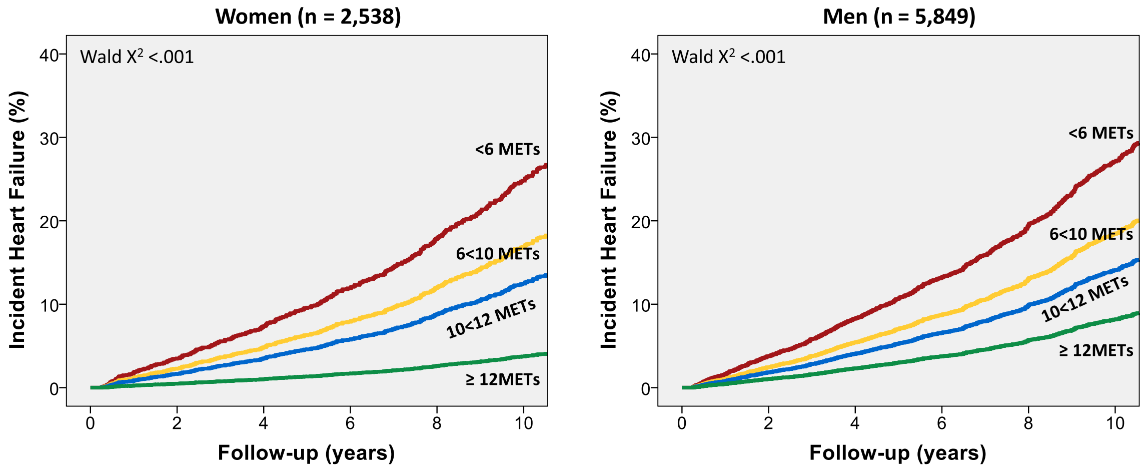
* Covariates include age, sex, race, medical history, medications, and reason for test.

Discussion

In this retrospective study, we showed that in a demographically heterogeneous cohort of patients with CHD and no history of HF, EC is independently and inversely related to the risk of future HF. We found that for every 1 MET achieved in patients with known CHD, there was a 12% lower adjusted risk of incident HF. Although several previous studies showed this same inverse relation between EC and HF in healthy subjects, this is, to the best of our knowledge, the first to exclusively study patients with known CHD.

Over the past several decades, cardiovascular medicine has experienced extensive growth in its ability to treat coronary artery disease medically and invasively. This improvement in treatment modalities has resulted in an increased prevalence of patients living with CHD, and leading many to subsequently develop HF.[5−7] Efforts are now aimed at aggressively controlling risk factors in patients with CHD to reduce the progression of the disease and development of HF. However, other than aggressive blood pressure control, no other strategy has been shown to reduce the risk of incident HF. Exercise-based cardiac rehabilitation (CR) is a class 1a indication in this patient population and likely the only therapy known to improve EC, yet only 20% to 30% of eligible patients participate in CR.[8,9] Although studies have shown that participation in CR improves symptoms and reduces hospitalizations[8], our study suggests that CR might also reduce progression to HF though the 10% to 20% increase in EC that is often observed through exercise training. Supporting this notion, we previously showed that EC at the conclusion of CR was inversely associated with a combined outcome of all-cause mortality, non-fatal MI, and HF hospitalization among patients with CHD and no HF.[10]

The lower risk of incident HF with increasing METs was independent of gender, race, age, or co-morbidities (hypertension, diabetes, history of MI, history of PCI, history of CABG). This suggests that there are mechanisms associated with higher fitness that prevent MI, independent of the presence of traditional risk factors. The ways by which higher EC relates to lower risk of incident HF are likely multifactorial. EC is best improved through a planned program of progressive physical activity (i.e., exercise training) and the latter has been shown to improve metabolism and positively impact HF risk factors such as hypertension, diabetes, lipid levels, and obesity.[11,12] Physical activity is also known to reduce sympathetic tone,[13] reduce myocardial stress,[14] improve coronary endothelial function,[15] and promote myocardial remodeling.[16,17] These physiologic and mechanical changes result in improved myocardial performance through more effective oxygen utilization, increased collateral artery formation, and improvement in left ventricular size and function.[16,17]



Number at Risk

METs	0	2	4	6	8	10	0	2	4	6	8	10
<6	1259	1126	976	812	638	485	1576	1328	1110	915	731	540
6<10	827	748	672	570	438	328	1987	1826	1629	1395	1121	871
10<12	401	364	326	278	177	131	1598	1481	1314	1102	794	618
≥12	51	49	43	33	25	16	688	630	576	504	384	313

Figure 2. Adjusted survival curves based on Cox regression for incident heart failure by metabolic equivalents of task (METs) stratified by gender. Covariates included age, race, medical history, medications, and reason for test.

There was a difference in the association of HF risk with METs in patients who underwent coronary revascularization (PCI or CABG) during follow-up compared with patients who did not undergo revascularization. The relation was significant in both groups, but the risk per MET was larger in the group of patients who did not undergo revascularization (14% reduction in risk per MET) compared with patients who underwent coronary revascularization (4% reduction in risk per MET). This may be because chronic ischemia in the group that subsequently needed revascularization had limited their baseline EC, and thus affected the relation between METs and incident HF. Our results and implications are strongest in people with stable CHD who do not have a large burden of non-revascularized ischemia. The association of fitness and risk of acute MI and other non-fatal cardiovascular outcomes is well known.[18] Perhaps early and aggressive exercise programs would have averted events in some patients.

Our results continue to support the long-term benefits of higher fitness in the CHD population. The rate of incident HF per 1,000 person-years is sixfold higher in patients with <6 METs compared with those with ≥12 METs in patients with known CHD. As we find ourselves caring for an increasing number of patients with CHD, it is critical to focus on interventions aimed at improving EC as it may lead to lower HF incidence.

Although our cohort includes both men and women and is racially diverse (33% non-White), it is derived from a single medical group in the Detroit area. The diagnosis of HF was based on International Classification of Diseases, Ninth Revision codes and may not have captured all patients, given the variation in provider coding. Given the limitation of International Classification of Diseases coding during that time, we could not distinguish between HF with reduced versus preserved ejection fraction. Further, data regarding co-morbidities were obtained from administrative data sources; therefore, the accuracy, duration, and severity of each co-morbidity is unknown. EC was based on a single exercise test and was not tracked over time, therefore these data do not directly support the premise that increasing EC lowers the risk for incident HF. The timing of exercise testing after the cardiac event is unknown, and it is probable that some patients were tested shortly after the cardiac event and others were tested at a much later time. Finally, although adjustments were made for potential confounders, there is always a potential for residual confounding as with all observational studies. Some examples of potential confounding factors include association of EC with socioeconomic status, nutritional decisions, and education.

In conclusion, among men and women with CHD and no history of HF, who were referred for an exercise test, EC was independently and inversely related to risk of future HF.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.07.016.

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