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Subclinical Cardiac Dysfunction is Associated with Reduced Cardiorespiratory Fitness and Cardiometabolic Risk Factors in Firefighters

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ABSTRACT

BACKGROUND: Past studies have documented the ability of cardiopulmonary exercise testing to detect cardiac dysfunction in symptomatic patients with coronary artery disease. Firefighters are at high risk for work-related cardiac events. This observational study investigated the association of subclinical cardiac dysfunction detected by cardiopulmonary exercise testing with modifiable cardiometabolic risk factors in asymptomatic firefighters.

METHODS: As part of mandatory firefighter medical evaluations, study subjects were assessed at 2 occupational health clinics serving 21 different fire departments. Mixed effects logistic regression analyses were used to estimate odds ratios (ORs) and account for clustering by fire department.

RESULTS: Of the 967 male firefighters (ages 20-60 years; 84% non-Hispanic white; 14% on cardiovascular medications), nearly two-thirds (63%) had cardiac dysfunction despite having normal predicted cardiorespiratory fitness (median peak $VO_2 = 102\%$). In unadjusted analyses, cardiac dysfunction was significantly associated with advanced age, obesity, diastolic hypertension, high triglycerides, low high-density lipoprotein (HDL) cholesterol, and reduced cardiorespiratory fitness (all P values < .05). After adjusting for age and ethnicity, the odds of having cardiac dysfunction were approximately one-third higher among firefighters with obesity and diastolic hypertension (OR = 1.39, 95% confidence interval [CI] = 1.03-1.87 and OR = 1.36, 95% CI = 1.03-1.80) and more than 5 times higher among firefighters with reduced cardiorespiratory fitness (OR = 5.41, 95% CI = 3.29-8.90).

CONCLUSION: Subclinical cardiac dysfunction detected by cardiopulmonary exercise testing is a common finding in career firefighters and is associated with substantially reduced cardiorespiratory fitness and cardiometabolic risk factors. These individuals should be targeted for aggressive risk factor modification to increase cardiorespiratory fitness as part of an outpatient prevention strategy to improve health and safety.
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KEYWORDS: Cardiac dysfunction; Firefighters; Prevention; Risk stratification; Stress testing

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INTRODUCTION

Cardiovascular disease is the leading cause of mortality in the United States and is of specific concern in firefighters because approximately 50% of duty-related deaths are attributable to cardiac events and 80% of cardiac fatalities occur among those with evidence of coronary artery disease and structurally enlarged hearts.[1,2] Individuals with demand ischemia at high workloads, such as during strenuous firefighting activities may experience myocardial injury, type II myocardial infarction, or arrhythmias resulting in cardiac events and possibly death. In this context, there is a need to identify markers of early disease and to implement accepted therapeutic interventions at an earlier stage to improve job safety and longevity.

Peak oxygen consumption (Peak VO_2) objectively quantifies exercise capacity and is a primary component of cardiorespiratory fitness. It is recognized as the best predictor of all-cause mortality and has been proposed as a vital sign to objectively quantify the functional health of the cardiorespiratory system.[3,4] Directly measured cardiorespiratory fitness in healthy men and women reveals an inverse linear relationship with mortality.[5,6] In an outcomes study of men and women with coronary heart disease, peak VO_2 was a strong predictor of all-cause death with every 1 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ increase in peak VO_2 associated with an approximate 15% decrease in mortality.[7] Cardiopulmonary exercise testing (CPET) is the gold standard for quantifying cardiorespiratory fitness, including peak VO_2 as well as for determining the mechanism of exercise limitation (cardiac vs pulmonary vs other).[8] With enhanced analysis of data from CPET performed on a cycle, inducible myocardial dysfunction caused by coronary artery disease can be assessed.[9,10] Inducible myocardial dysfunction results from mechanical dysfunction caused by myocardial energy depletion and has been shown to be superior to stress electrocardiogram (ECG) for detecting coronary artery disease in symptomatic patients.[11,12] Recent outcomes data reveal that patients with inducible myocardial dysfunction on CPET have a 3-fold increased risk of near-term annualized mortality compared to patients without inducible myocardial dysfunction, independent of cardiorespiratory fitness.[13]

Current US guidelines for firefighters recommend the quantification of cardiorespiratory fitness as part of an annual medical assessment.[14] CPET performed to maximal exercise is superior to submaximal tests on a treadmill as it more precisely quantifies cardiorespiratory fitness. The purpose of this cross-sectional, observational study was to investigate the relationship between cardiometabolic risk factors and inducible myocardial dysfunction detected by CPET in a population of asymptomatic career firefighters for whom CPET is part of the annual medical evaluation.

CLINICAL SIGNIFICANCE

- Cardiopulmonary exercise testing (CPET) can detect subclinical cardiac dysfunction in asymptomatic individuals undergoing annual physicals.
- Subclinical cardiac dysfunction was found in 63% of firefighters and was strongly associated with reduced cardiorespiratory fitness, obesity, and diastolic hypertension.
- Aggressive risk factor modification in individuals with cardiac dysfunction can improve outpatient strategies for heart disease prevention.

METHODS

Subjects

Firefighters were assessed at 2 occupational health clinics serving 21 different fire departments in Arizona and Texas. Eligible study subjects included all consecutive firefighters who underwent mandatory firefighter medical evaluations between January 2018 and August 2020 and for whom medical records were available. All firefighters were asymptomatic and on active duty at the time of their evaluations. Firefighters who did not meet our inclusion criteria (20-60 years of age) or who were missing key demographic or clinical information (n = 257) were excluded from the analysis. For the present investigation, our sample included 967 firefighters. Only male firefighters were included because the number of women in the data set was too small to test for differences due to sex. The study protocol was reviewed and approved by Skidmore Colleges' institutional review board.

Data Collection

Annual occupational medical evaluations were consistent with current guidelines[14] and included demographic measurements, standard blood chemistries, lipid panels, medical examinations, and CPET. Blood draws were obtained in the morning after an overnight fast and sent to a commercial laboratory for the determination of blood lipids and chemistries. All CPET equipment, technician training, clinical support, and data analysis were provided by a central laboratory (MET-TEST).

CPET was performed on an electronically braked cycle ergometer with breath-by-breath gas analysis as previously described.[10] Major prognostic variables include measurements of peak VO_2, and peak O_2-pulse defined as peak VO_2 corrected for peak heart rate (VO_2/HR). Relative values for peak VO_2 and peak O_2-pulse were expressed as $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ and mL/beat, respectively. These parameters were also expressed relative to predicted values based on age, height, weight, and sex from population studies.[15] Increase of the O_2-pulse during exercise has been shown to be a close surrogate for the stroke volume response in a variety of cardiac abnormalities and is a key variable to diagnosing inducible myocardial dysfunction.[16] The change

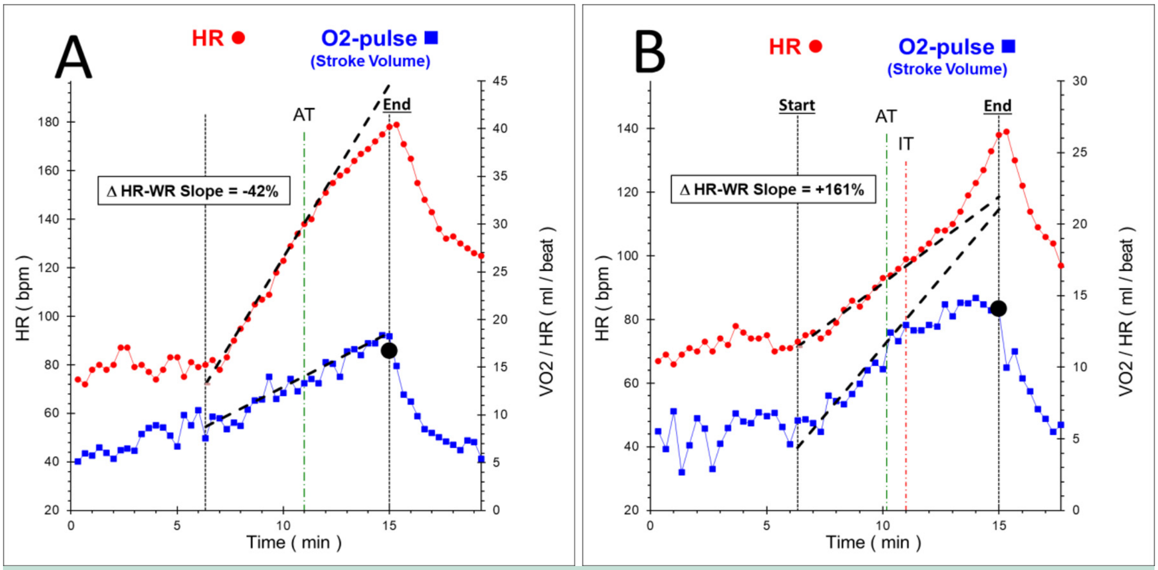

Figure 1 Classification based on cardiac function. Graphical display of heart rate (*top line*) and O_2-pulse response, which reflects stroke volume (*bottom line*). Cardiac output is the product of stroke volume and heart rate and plotting both parameters in the same graph allows for assessment of their relative dependence in real time. Data from every test was optimized for averaging, filtering, scaling, and trend analysis prior to classification: **(A)** Normal cardiac response: The O_2-pulse rises from start (6-min mark) to end (15-min mark) in a linear manner to slightly above predicted value (*black dot*) without plateau. The heart-rate response is linear in early and middle exercise and slows in late exercise as it approaches physiological peak resulting in a negative ΔHR-WR slope (−42%). The mean value of the ΔHR-WR slope was −7% for individuals with normal cardiac function. **(B)** Abnormal cardiac response - IMD: The O_2-pulse response is linear in early and middle exercise but shortly after reaching AT (*green dotted line*), abruptly slows starting at the IT, then plateaus and is decreasing by the end of exercise. The plateau/decreasing trend in stroke volume reflects the start of mechanical dysfunction at the IT. Heart rate is linear in early and middle exercise but at the IT, abruptly starts to accelerate in an exponential manner to the end of exercise resulting in a highly positive ΔHR-WR slope (+161%). The upper limit of increase in ΔHR-WR slope is +15-20% and represents increased sympathetic discharge to compensate for loss of stroke volume after the IT. Note that heart rate acceleration is independent of oxygen consumption measurement and changes in both parameters occurs near simultaneously. The mean value of ΔHR-WR slope was +61% for individuals with IMD. AT = anaerobic threshold; IT = inducible threshold; IMD = inducible myocardial dysfunction; ΔHR-WR slope = change in heart rate vs work-rate slope.

in heart rate to work rate slope (ΔHR-WR slope) is a novel CPET parameter that was calculated as described in a previous publication.[12] Simultaneous changes in O_2-pulse trajectory and ΔHR-WR slope were the primary determinants for identifying inducible myocardial dysfunction. All CPET studies were analyzed per protocols of the central CPET laboratory. Each test with sufficient effort (ie, peak respiratory exchange ratio ≥1.05) was classified as either normal cardiac function or abnormal with inducible myocardial dysfunction as illustrated in Figure 1.[17]

Statistical Analysis

Summary statistics were computed for all variables, including means and standard deviations for quantitative variables and frequencies and proportions for categorical variables. Two-sample *t*-tests were used to test for mean differences in cardiometabolic risk factors, including CPET-derived measurements, between subjects with and without inducible myocardial dysfunction. Two-sample *t*-tests were also repeated after stratifying by age (younger than 45 years or 45 years and older) and ethnicity (non-Hispanic whites vs others). Differences between the proportion of younger and older subjects or non-Hispanic whites and others with and without inducible myocardial dysfunction were tested using a standard 2-sample *z*-test.

To account for clustering by fire department, we fit mixed effects logistic regression models, with fire department as a random effect, to estimate odds ratios and 95% confidence intervals for the association between each cardiometabolic risk factor and inducible myocardial dysfunction. Age- and ethnicity-adjusted models were also fit to account for the potential confounding effects of age (younger than 45 years or 45 years and older) and ethnicity (non-Hispanic white vs others). To examine whether the association between each cardiometabolic risk factor and inducible myocardial dysfunction differed by age or ethnicity, we also included and tested the significance of an interaction term in each model. To explore whether traditional cardiometabolic risk factors were associated with inducible myocardial dysfunction after accounting for cardiorespiratory fitness, we fit age, ethnicity, and peak VO_2 adjusted mixed effects logistic regression models. All statistical tests were 2-sided, and *P* values< .05 were considered statistically significant. All analyses were conducted using R/RStudio (version 1.3.959).

RESULTS

The mean age of the firefighters was 40 years and the majority were non-Hispanic white (84%) with approximately 10% being Hispanic. Demographic and clinical characteristics of the 967 firefighters with and without myocardial dysfunction are summarized in Table 1 and in Supplementary Tables S1, S2, and S3, available online, after stratifying on ethnicity (non-Hispanic whites vs others). Overall, firefighters with inducible myocardial dysfunction were older and heavier with higher blood sugars and triglycerides and lower cardiorespiratory fitness.

Table 1 Characteristics of Firefighters by Myocardial Dysfunction

	Myocardial dysfunction		
	No	Yes	*P* Value
Number (proportion)	356 (0.37)	611 (0.63)	-
Ethnicity (non-Hispanic white)*	299 (0.37)	515 (0.63)	.97
Age (y)	39 ± 9	41 ± 9	**<.01**
Height (in)	71 ± 3	71 ± 3	.66
Weight (lb)	204 ± 31	207 ± 34	.12
BMI (kg/m^2)	28.5 ± 3.8	29.1 ± 4.3	.05
Body fat (%)	18 ± 6	19 ± 6	**<.01**
SBP (mm Hg)	120 ± 9	121 ± 10	.12
DBP (mm Hg)	77 ± 7	78 ± 7	.05
Triglycerides (mg/dL)	106 ± 54	115 ± 61	**.02**
Total cholesterol (mg/dL)	190 ± 34	189 ± 38	.85
LDL (mg/dL)	117 ± 30	116 ± 33	.62
HDL (mg/dL)	52 ± 13	51 ± 13	.07
Fasting glucose (mg/dL)	94 ± 14	96 ± 17	**.03**
Hemoglobin A1C (%)	5.4 ± 0.4	5.4 ± 0.7	.10
Peak VO_2 ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$)	36 ± 6	32 ± 6	**<.01**
Peak VO_2 (L/min)	3.3 ± 0.5	3.0 ± 0.5	**<.01**
Predicted peak VO_2 (%)	109 ± 15	101 ± 15	**<.01**
Peak O_2-pulse (mL/beat)	20 ± 3	19 ± 3	**<.01**
Predicted peak O_2-pulse (%)	122 ± 17	114 ± 17	**<.01**
SBP at peak exercise (mm Hg)	172 ± 18	172 ± 19	.99
DBP at peak exercise (mm Hg)	82 ± 12	83 ± 12	.29
Resting heart rate (beats per min)	73 ± 13	75 ± 12	.09
Peak heart rate (beats per min)	162 ± 16	159 ± 15	**<.01**
Predicted peak heart rate (%)	89 ± 8	89 ± 7	.53
Heart rate recovery (beats per min)	37 ± 10	37 ± 14	.58
ΔHR-WR slope (%)	−7 ± 32	61 ± 59	**<.01**

BMI = body mass index; DBP = diastolic blood pressure; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; SBP = systolic blood pressure; VO_2 = oxygen uptake; ΔHR-WR slope = change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

*Data are number (proportion); *P* values based on 2-sample *z*-tests for difference in proportions.

Based on dichotomizing cardiometabolic risk factors per threshold values (Table 2), approximately one-third of firefighters (n = 347) were 45 years of age or older, and approximately one-third (n = 325) were obese (body mass index [BMI] >30 kg/m^2). Based on national hypertension thresholds, approximately 18% had high systolic blood pressure (≥130 mm Hg) and 48% had high diastolic blood pressure (≥80 mm Hg). Similarly, about one-third had elevated cholesterol (total cholesterol >200 mg/dL^{-1}). Only 2% had blood glucose levels indicative of diabetes (fasting glucose ≥126 mg/dL^{-1}). Fourteen percent of firefighters were on 1 or more cardiovascular medications.

Nearly two-thirds of firefighters (63%) had evidence of inducible myocardial dysfunction (Table 1), despite having a median percentage of predicted peak VO_2 of 102% (or median of 100% and 107% in those with and without inducible myocardial dysfunction, respectively; Figure 2). There was no difference in the prevalence of inducible myocardial dysfunction by ethnicity (Table 1). On average, firefighters with evidence of inducible myocardial dysfunction were slightly but significantly older (41 vs 39 years) and heavier (19% vs 18% bodyfat) than those without inducible myocardial dysfunction (Table 1). Those with inducible myocardial dysfunction also had significantly higher mean triglycerides and fasting glucose levels. Peak VO_2, percentage of predicted peak VO_2, peak O_2-pulse, and percentage of predicted peak O_2-pulse were also significantly lower, on average, in those with inducible myocardial dysfunction (Table 1). The change in heart rate-work rate slope (ΔHR-WR slope) is one of the salient diagnostic markers for inducible myocardial dysfunction and had a mean acceleration of +61% in the inducible myocardial dysfunction group and a mean deceleration of −7% in the noninducible myocardial dysfunction group (Table 1).

Firefighters were stratified by age based on the cutoff value of when age becomes a risk factor for men (<45 y vs ≥45 y); BMI, body fat, and triglyerides were slightly but significantly higher and HDL lower in firefighters with inducible myocardial dysfunction compared with those without among younger but not older firefighters (Table 3). In contrast, fasting glucose levels were significantly higher in firefighters with inducible myocardial dysfunction versus those without among older but not younger firefighters.

In mixed effects logistic regression models (Table 2), inducible myocardial dysfunction was significantly associated with obesity, diastolic hypertension, and low percentage of predicted peak VO_2 before and after adjustment for age and ethnicity. In contrast, inducible myocardial dysfunction was significantly associated with high triglycerides and low HDL cholesterol before but not after adjustment for age and ethnicity. In adjusted models, the odds of inducible

Table 2 Association of CVD Risk Factors with Myocardial Dysfunction

	Number (proportion)	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)†
Ethnicity (non-Hispanic white)	814 (0.84)	1.01 (0.70-1.46)	-
Age (≥ 45 y)	347 (0.36)	**2.07 (1.54-2.80)**	-
Obesity (BMI ≥ 30 kg/m^2)	325 (0.34)	**1.52 (1.13-2.03)**	**1.39 (1.03-1.87)**
Systolic hypertension (SBP ≥ 130 mm Hg)	169 (0.18)	1.22 (0.85-1.75)	1.11 (0.77-1.60)
Diastolic hypertension (DBP ≥ 80 mm Hg)	459 (0.48)	**1.48 (1.12-1.95)**	**1.36 (1.03-1.80)**
High triglycerides (>150 mg/dL)	184 (0.19)	**1.46 (1.03-2.09)**	1.27 (0.88-1.83)
High cholesterol (total cholesterol >200 mg/dL)	350 (0.36)	1.11 (0.84-1.47)	1.08 (0.81-1.43)
High LDL cholesterol (LDL ≥ 130 mg/dL)	303 (0.31)	1.18 (0.88-1.58)	1.15 (0.86-1.55)
Low HDL cholesterol (HDL <40 mg/dL)	177 (0.18)	**1.51 (1.05-2.16)**	1.39 (0.97-2.01)
Hyperglycemia (fasting glucose ≥ 126 mg/dL)	20 (0.02)	2.55 (0.83-7.82)	2.00 (0.64-6.20)
High hemoglobin A1C (≥5.7 %)	174 (0.18)	1.29 (0.90-1.84)	1.09 (0.75-1.58)
Low predicted peak VO_2 (<90%)	162 (0.17)	**5.23 (3.19-8.57)**	**5.41 (3.29-8.90)**
High resting heart rate (>90 beats per min)	94 (0.10)	1.14 (0.72-1.81)	1.08 (0.68-1.73)

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; OR = odds ratio; SBP = systolic blood pressure; VO_2 = oxygen uptake.

*Based on unadjusted mixed effects logistic regression.

†Based on mixed effects logistic regression adjusted for age (≥ 45 y vs <45 y) and ethnicity (non-Hispanic white vs other).

myocardial dysfunction were about a third higher among firefighters with obesity and diastolic hypertension (odds ratio [OR] = 1.39, 95% confidence interval [CI] = 1.03-1.87 and OR = 1.36, 95% CI = 1.03-1.80, respectively) and more than 5 times higher among firefighters with low percentage of predicted peak VO_2 (OR = 5.41, 95% CI = 3.29-8.90). However, there was a significant interaction between obesity and age consistent with obesity being a significant predictor of inducible myocardial dysfunction in younger but not older firefighters (Table 3).

In age- and ethnicity-adjusted models, inducible myocardial dysfunction was significantly associated with obesity and diastolic hypertension before and after adjustment for percentage of predicted peak VO_2 (Supplementary Table S4, available online). After adjusting for age, ethnicity, and percentage of predicted peak VO_2, the odds of having inducible myocardial dysfunction were 51% and 44% higher, respectively, among obese firefighters and those with diastolic hypertension.

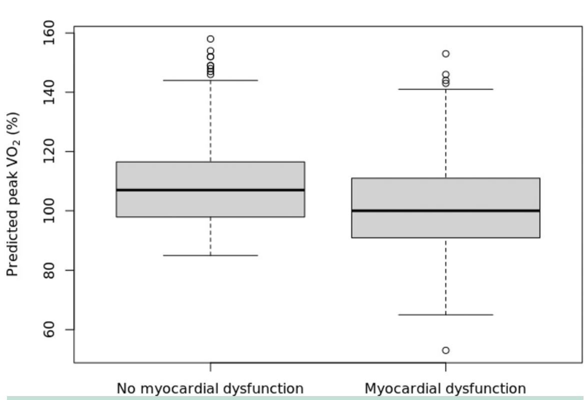

Figure 2 Predicted peak VO_2 (%) stratified by myocardial dysfunction. VO_2 = oxygen uptake.

DISCUSSION

To our knowledge, this is the first study to demonstrate that subclinical cardiac dysfunction as evidenced by inducible myocardial dysfunction on CPET is a common finding among asymptomatic career firefighters (63% prevalence). Although cardiorespiratory fitness was well preserved overall with a median peak VO_2 of 102% predicted, the absolute mean peak VO_2 was 4 mlO_2·kg-1·min-1 lower in the group with inducible myocardial dysfunction compared with those without inducible myocardial dysfunction, corresponding to 15%-20% increased risk for cardiovascular mortality.[5-7] Inducible myocardial dysfunction was significantly associated with age but not ethnicity in our predominantly non-Hispanic white sample. On average, firefighters with inducible myocardial dysfunction were older and heavier with higher blood sugars and triglycerides and lower cardiorespiratory fitness. In unadjusted mixed effects logistics regression analyses, inducible myocardial dysfunction was significantly associated with obesity, diastolic hypertension, low HDL, high triglycerides, and low cardiorespiratory fitness. After accounting for age and ethnicity, inducible myocardial dysfunction remained significantly associated with obesity and diastolic hypertension both before and after adjustment for cardiorespiratory fitness.

Inducible myocardial dysfunction detected by CPET has been attributed to mechanical dysfunction induced by myocardial ATP depletion resulting from the ischemic cascade.[17] The compensatory acceleration of heart rate (HR) observed when the rise in O_2-pulse (surrogate for stroke volume) abruptly plateaus after the ventilatory anaerobic threshold is the hallmark pathological sign of inducible myocardial dysfunction (Figure 1). Van De Sande et al[18] compared asymptomatic individuals with ischemic ECG changes to matched individuals without ECG changes in a population of healthy middle-aged athletes. They found that athletes with ischemic ECG changes had a lower peak

Table 3 Characteristics of Firefighters by Age and Myocardial Dysfunction

	Age < 45 y			Age ≥ 45 y		
	Myocardial dysfunction			Myocardial dysfunction		
	No	Yes	*P* Value	No	Yes	*P* Value
Number (proportion)*	258 (0.42)	362 (0.58)	—	98 (0.28)	249 (0.72)	—
Ethnicity (non-Hispanic white) *	214 (0.42)	294 (0.58)	.66	85 (0.28)	221 (0.72)	.73
Age (y)	35 ± 6	35 ± 6	.85	**50 ± 4**	**51 ± 4**	**.04**
Height (in)	71 ± 3	71 ± 3	.37	71 ± 3	71 ± 3	.45
Weight (lb)	201 ± 32	206 ± 35	.11	210 ± 30	210 ± 33	.82
BMI (kg/m^2)	28.1 ± 3.7	28.9 ± 4.4	**.02**	29.7 ± 3.8	29.4 ± 4.0	.46
Body fat (%)	17 ± 5	18 ± 6	**<.01**	20 ± 6	20 ± 6	.87
SBP (mm Hg)	119 ± 9	120 ± 9	.65	122 ± 10	123 ± 11	.29
DBP (mm Hg)	76 ± 7	77 ± 7	.70	78 ± 7	79 ± 7	.08
Triglycerides (mg/dL)	99 ± 49	108 ± 59	**.04**	127 ± 62	126 ± 63	.97
Total cholesterol (mg/dL)	187 ± 32	187 ± 37	.89	197 ± 39	193 ± 39	.43
LDL (mg/dL)	115 ± 28	115 ± 33	.92	123 ± 33	117 ± 34	.16
HDL (mg/dL)	53 ± 13	50 ± 13	**<.01**	50 ± 13	51 ± 14	.28
Fasting glucose (mg/dL)	93 ± 13	93 ± 12	.68	**96 ± 16**	**101 ± 23**	**.02**
Hemoglobin A1C (%)	5.3 ± 0.3	5.3 ± 0.3	.44	5.5 ± 0.5	5.6 ± 1.0	.18
Peak VO_2 ($mlO_2 \bullet kg^{-1} \bullet min^{-1}$)	37 ± 6	34 ± 6	**<.01**	**32 ± 6**	**29 ± 6**	**<.01**
Peak VO_2 (L/min)	3.4 ± 0.5	3.1 ± 0.5	**<.01**	**3.0 ± 0.5**	**2.8 ± 0.5**	**<.01**
Predicted peak VO_2 (%)	108 ± 14	99 ± 14	**<.01**	**112 ± 16**	**104 ± 16**	**<.01**
Peak O_2-pulse (ml/beat)	20 ± 3	19 ± 3	**<.01**	**20 ± 3**	**18 ± 3**	**<.01**
Predicted peak O_2-pulse (%)	121 ± 17	113 ± 17	**<.01**	**127 ± 18**	**116 ± 18**	**<.01**
SBP at peak exercise (mm Hg)	169 ± 17	168 ± 16	.55	178 ± 18	176 ± 21	.46
DBP at peak exercise (mm Hg)	81 ± 13	81 ± 12	.71	84 ± 12	85 ± 12	.72
Resting heart rate (beats per min)	74 ± 13	75 ± 12	.25	72 ± 13	74 ± 12	.12
Peak heart rate (beats per min)	166 ± 13	164 ± 13	**.03**	151 ± 17	152 ± 14	.49
Predicted peak heart rate (%)	90 ± 6	88 ± 6	**.03**	89 ± 10	90 ± 8	.24
Heart rate recovery (beats per min)	38 ± 10	38 ± 13	.78	35 ± 10	35 ± 15	.69
ΔHR-WR slope (%)	−9 ± 34	53 ± 49	**<.01**	**−2 ± 25**	**73 ± 69**	**<.01**

BMI = body mass index; DBP = diastolic blood pressure; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; SBP = systolic blood pressure; VO_2 = oxygen uptake; ΔHR-WR slope = change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

*Data are number (proportion); *P* values based on 2-sample *z*-tests for difference in proportion

VO_2 and lower peak O_2-pulse with an average 19% increase in the HR slope in late exercise (our inducible myocardial dysfunction group had a mean acceleration of +61%). The nonischemic ECG athletes had an average deceleration of −20% in HR slope during the same period (our noninducible myocardial dysfunction group had a mean deceleration of −7%). Interestingly, peak VO_2 in their inducible myocardial dysfunction group was also 4 $mlO_2 \cdot kg$-1·min-1 less than those with normal cardiac function, similar in magnitude to our findings. The authors concluded the ischemic ECG changes were likely due to early-stage atherosclerosis and unlikely to represent false positive findings.[18] In a recent study based on firefighter autopsies, we found that only 20% of cardiac deaths had evidence of intracoronary thrombi, suggesting that many cardiac events during job-related strenuous activity are likely caused by demand ischemia.[19] The data suggest that inducible myocardial dysfunction in firefighters could be caused by microvascular ischemia. If left untreated, microvascular ischemia can lead to symptomatic nonobstructive and obstructive coronary artery disease, atrial fibrillation, heart failure, and persist as angina after revascularization.[20-23]

In this study, the primary cardiometabolic risk factors associated with inducible myocardial dysfunction were obesity and diastolic hypertension. We recently reported that across all age groups, male firefighters had a higher prevalence of hypertension (based largely on a greater prevalence of elevated diastolic blood pressure) than the general population.[24] We have also shown that firefighters have a concerning prevalence of obesity and hypercholesterolemia and that these risk factors increase over a 5-year period.[25] Asymptomatic obese individuals are recognized to have subclinical cardiac dysfunction that is thought to be linked to endothelial dysfunction and non-endothelium-dependent coronary microvascular dysfunction.[26] Obesity is a major driver of metabolic syndrome[27] and accelerates atherosclerosis even after accounting for the impact of traditional cardiovascular risk factors[26] and even in obese individuals considered to be metabolically healthy.[28,29] Visceral adipose tissue related systemic inflammation, decreased nitric oxide bioavailability, insulin resistance, and oxidized low-density lipoprotein are primary drivers of endothelial dysfunction in obesity.[30] Likewise, the increased hemodynamic load of hypertension has also been linked to endothelial dysfunction regardless of the underlying mechanism.[31] Obesity has also been linked to abnormalities in non-endothelium-dependent coronary microvasculature involved in regulating myocardial blood flow.[32,33] Coronary microvascular dysfunction is associated with a higher BMI, is linked to increased microvascular resistance, and provides independent prognostic information for cardiovascular risk in obese patients.[34,35] Asymptomatic diabetic patients undergoing cardiac magnetic resonance imaging (MRI) have also been shown to have decreased myocardial blood flow from microvascular dysfunction, a finding that was linked to reduced peak VO_2.[36] Thus, inducible myocardial dysfunction may be the result of endothelial dysfunction and coronary microvascular dysfunction.

These findings provide evidence that inducible myocardial dysfunction is a distinct "physiological phenotype" associated with undertreated cardiometabolic risk factors that can result in progressive decrease in cardiorespiratory fitness over time. Because 80% of cardiovascular disease is considered preventable, inducible myocardial dysfunction could help to identify individuals who would benefit from more aggressive risk factor modification with the goal of increasing cardiorespiratory fitness from baseline. The current standard of care is to recommend exercise as the primary treatment modality for individuals with modifiable cardiometabolic risk factors as well as those with established cardiovascular disease. CPET provides individualized exercise prescriptions for precise HR training in the low-, moderate-, and high-intensity zones. Training in the moderate HR zone (corresponding to 40%-60% of measured peak VO_2) is safe, well tolerated, and highly efficacious to reverse cardiometabolic risk factors, promote weight loss, improve coronary circulation, and increase cardiorespiratory fitness if performed for the recommended 150 min/wk or more.[37] For individuals not compliant with exercise training or for whom exercise alone may not be sufficient to stop disease progression, intensification with medications proven to reduce cardiovascular mortality should be the next step. Longitudinal changes in cardiorespiratory fitness provides a robust and recognized mechanism to track response to medical therapy on an individualized basis. Serial CPET in a high-risk individual on aggressive lipid-lowering therapy for primary prevention for 3.3 years (without lifestyle changes) revealed a significant reversal of the baseline inducible myocardial dysfunction pattern with a concomitant 2.6 mlO_2·kg-1·min-1 increase in peak VO_2.[38] In the same individual, nearly complete normalization of inducible myocardial dysfunction and cardiorespiratory fitness was achieved with the addition of exercise to his daily routine.[17] Implementing precise, individualized physiological data in this manner can be used to improve cardiovascular health and safety as part of an outpatient heart disease prevention program. The establishment of multidisciplinary cardiometabolic health clinics to accomplish similar goals have been proposed for the general population.[39]

There are several strengths of the current study. We analyzed data from nearly 1000 firefighters from a geographically diverse population including 21 departments from 2 states. Because the annual medical evaluations were mandatory, referral and selection bias were minimized. To improve diagnostic accuracy, the collection, processing, and interpretation of all CPET data were standardized by a central laboratory. Despite these strengths, there were also several limitations. Our sample was a convenience sample, and due to administrative constraints, we were unable to account for smoking, a potentially significant confounder. Fourteen percent of firefighters were also on cardiovascular medications, another potential confounder. There were some small but significant differences between the 967 firefighters included in our analyses and the 257 who were excluded due to missing data. Notably though, there was no evidence that the outcome of interest (inducible myocardial dysfunction) differed between the 2 groups (Supplementary Table S5, available online). Our sample was exclusively male and primarily non-Hispanic white with a well-defined occupational exposure. Thus, these findings may not be generalizable to other populations. Although microvascular ischemia may be the likely mechanism of inducible myocardial dysfunction, validation and further study by other modalities are needed to better characterize this physiological phenotype. Future research should also determine the significance of inducible myocardial dysfunction to predict cardiovascular events and mortality independent of cardiorespiratory fitness.

CONCLUSION

Firefighters are an important occupational group that requires adequate cardiorespiratory fitness and cardiovascular health to safely perform high-risk duties. Myocardial ischemia during strenuous firefighting work increases the risk for adverse events and sudden cardiac death. This study found that nearly two-thirds of firefighters have signs of subclinical cardiac dysfunction as evidenced by inducible myocardial dysfunction during CPET. Moreover, inducible myocardial dysfunction was significantly associated with reduced cardiorespiratory fitness and undertreated cardiometabolic risk factors. Aggressive risk factor interventions with exercise and medical therapy have the potential to treat these risk factors with the intent to reverse inducible myocardial dysfunction and increase cardiorespiratory fitness from baseline. Comprehensive cardiovascular disease prevention programs could benefit by using this information to improve the health and safety of career firefighters.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.12.025.

Supplementary Table S1 Characteristics of Non-Hispanic White Firefighters by Myocardial Dysfunction

	Overall	Myocardial dysfunction		
		No	Yes	*P* Value
Number (proportion)	814	299 (0.37)	515 (0.63)	—
Age (y)	41 ± 9	39 ± 9	42 ± 9	**<.01**
Height (in)	71 ± 3	71 ± 3	71 ± 3	.63
Weight (lb)	207 ± 34	204 ± 31	208 ± 35	.14
BMI (kg/m^2)	28.8 ± 4.1	28.4 ± 3.8	29.0 ± 4.3	.06
Body fat (%)	18 ± 6	17 ± 5	19 ± 6	**<.01**
SBP (mm Hg)	121 ± 10	120 ± 9	121 ± 11	.08
DBP (mm Hg)	77 ± 7	77 ± 7	78 ± 7	.08
Triglycerides (mg/dL)	111 ± 58	105 ± 56	114 ± 59	**.03**
Total cholesterol (mg/dL)	190 ± 36	190 ± 35	189 ± 36	.70
LDL (mg/dL)	116 ± 32	117 ± 30	116 ± 32	.70
HDL (mg/dL)	51 ± 13	53 ± 14	51 ± 13	.03
Fasting glucose (mg/dL)	95 ± 15	94 ± 15	96 ± 15	**.04**
Hemoglobin A1C (%)	5.4 ± 0.5	5.4 ± 0.4	5.4 ± 0.5	.56
Peak VO_2 (mlO_2^{-1-1})	34 ± 6	36 ± 6	32 ± 6	**<.01**
Peak VO_2 (L/min)	3.1 ± 0.5	3.3 ± 0.5	3.0 ± 0.5	**<.01**
Predicted peak VO_2 (%)	104 ± 15	109 ± 15	102 ± 15	**<.01**
Peak O_2-pulse (mL/beat)	19 ± 3	20 ± 3	19 ± 3	**<.01**
Predicted peak O_2-pulse (%)	117 ± 18	123 ± 17	114 ± 18	**<.01**
SBP at peak exercise (mm Hg)	172 ± 19	172 ± 18	172 ± 19	.66
DBP at peak exercise (mm Hg)	82 ± 12	82 ± 13	83 ± 12	.22
Resting heart rate (beats per min)	74 ± 12	73 ± 13	75 ± 12	.09
Peak heart rate (beats per min)	160 ± 15	162 ± 15	159 ± 14	**.02**
Predicted peak heart rate (%)	89 ± 7	89 ± 7	89 ± 7	.94
Heart rate recovery (beats per min)	37 ± 12	37 ± 10	37 ± 13	.54
ΔHR-WR slope (%)	37 ± 60	−7 ± 33	62 ± 58	**<.01**

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; VO_2 = oxygen uptake; ΔHR-WR slope = change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

Supplementary Table S2 Characteristics of Hispanic and Non-white Firefighters by Myocardial Dysfunction

	Overall	Myocardial dysfunction		
		No	Yes	*P* Value
Number (proportion)	153	57 (0.37)	96 (0.63)	—
Age (y)	39 ± 10	38 ± 9	39 ± 10	.73
Height (in)	70 ± 3	70 ± 3	70 ± 3	.96
Weight (lb)	204 ± 31	202 ± 32	205 ± 31	.62
BMI (kg/m^2)	29.5 ± 4.0	29.2 ± 3.7	29.6 ± 4.2	.47
Body fat (%)	20 ± 6	19 ± 6	20 ± 6	.46
SBP (mm Hg)	120 ± 9	121 ± 8	120 ± 9	.82
DBP (mm Hg)	77 ± 7	77 ± 6	78 ± 8	.36
Triglycerides (mg/dL)	118 ± 63	113 ± 46	121 ± 71	.44
Total cholesterol (mg/dL)	190 ± 39	188 ± 31	191 ± 44	.72
LDL (mg/dL)	116 ± 35	117 ± 28	115 ± 39	.73
HDL (mg/dL)	51 ± 13	50 ± 12	51 ± 13	.70
Fasting glucose (mg/dL)	99 ± 23	97 ± 9	100 ± 28	.36
Hemoglobin A1C (%)	5.7 ± 1.0	5.5 ± 0.3	5.8 ± 1.2	.07
Peak VO_2 (mlO_2^{-1-1})	33 ± 6	35 ± 7	32 ± 6	**<.01**
Peak VO_2 (L/min)	3.0 ± 0.5	3.2 ± 0.5	2.9 ± 0.5	**<.01**
Predicted peak VO_2 (%)	102 ± 15	107 ± 14	98 ± 14	**<.01**
Peak O_2-pulse (mL/beat)	19 ± 3	20 ± 3	19 ± 3	**.02**
Predicted peak O_2-pulse (%)	117 ± 16	122 ± 15	114 ± 16	**<.01**
SBP at peak exercise (mm Hg)	169 ± 17	172 ± 16	168 ± 17	.24
DBP at peak exercise (mm Hg)	82 ± 11	83 ± 11	82 ± 11	.77
Resting heart rate (beats per min)	74 ± 11	74 ± 13	74 ± 11	.78
Peak heart rate (beats per min)	158 ± 17	161 ± 19	157 ± 16	.13
Predicted peak heart rate (%)	87 ± 8	89 ± 9	87 ± 7	.11
Heart rate recovery (beats per min)	39 ± 15	39 ± 11	38 ± 18	.97
ΔHR-WR slope (%)	34 ± 60	−6 ± 26	58 ± 61	**<.01**

BMI = body mass index; DBP =diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; VO2 = oxygen uptake; ΔHR-WR slope = change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

Supplementary Table S3 Characteristics of Firefighters by Ethnicity

	Overall	Non-Hispanic white	Others	*P* Value
Number (proportion)	967	814 (0.84)	153 (0.16)	—
Myocardial dysfunction (yes)*	611 (0.63)	515 (0.63)	96 (0.63)	.97
Age (y)	40 ± 9	41 ± 9	39 ± 10	**<.01**
Height (in)	71 ± 3	71 ± 3	70 ± 3	**<.01**
Weight (lb)	206 ± 33	207 ± 34	204 ± 31	.38
BMI (kg/m^2)	28.9 ± 4.1	28.8 ± 4.1	29.5 ± 4.0	.05
Body fat (%)	18 ± 6	18 ± 6	20 ± 6	**<.01**
SBP (mm Hg)	121 ± 10	121 ± 10	120 ± 9	.74
DBP (mm Hg)	77 ± 7	77 ± 7	77 ± 7	.66
Triglycerides (mg/dL)	112 ± 59	111 ± 58	118 ± 63	.20
Total cholesterol (mg/dL)	190 ± 36	190 ± 36	190 ± 39	.97
LDL (mg/dL)	116 ± 32	116 ± 32	116 ± 35	.93
HDL (mg/dL)	51 ± 13	51 ± 13	51 ± 13	.76
Fasting glucose (mg/dL)	96 ± 16	95 ± 15	99 ± 23	**<.01**
Hemoglobin A1C (%)	5.4 ± 0.6	5.4 ± 0.5	5.6 ± 1.0	**<.01**
Peak VO_2 (ml$O_2$$^{-1-1}$)	33 ± 6	33 ± 6	33 ± 6	.39
Peak VO_2 (L/min)	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.5	.06
Predicted peak VO_2 (%)	104 ± 15	104 ± 15	102 ± 15	.08
Peak O_2-pulse (mL/beat)	19 ± 3	19 ± 3	19 ± 3	.26
Predicted peak O_2-pulse (%)	117 ± 18	117 ± 18	117 ± 16	.99
SBP at peak exercise (mm Hg)	172 ± 18	172 ± 19	169 ± 17	.10
DBP at peak exercise (mm Hg)	82 ± 12	82 ± 12	82 ± 11	.97
Resting heart rate (beats per min)	74 ± 12	74 ± 12	74 ± 11	.57
Peak heart rate (beats per min)	160 ± 15	160 ± 15	158 ± 17	.18
Predicted peak heart rate (%)	89 ± 7	89 ± 7	87 ± 8	**<.01**
Heart rate recovery (beats per min)	37 ± 13	37 ± 12	39 ± 15	.11
ΔHR-WR slope (%)	36 ± 60	37 ± 60	34 ± 60	.59

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; VO2 = oxygen uptake; ΔHR-WR slope change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

*Data are number (proportion); *P* values based on 2-sample *z*-tests for difference in proportions.

Supplementary Table S4 Association of CVD Risk Factors with Myocardial Dysfunction Before and After Adjustment for Percentage of Predicted Peak VO_2

	Number (proportion)	Unadjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)†	*P* Value
Obesity (BMI kg/m^2)	325 (0.34)	1.39 (1.03-1.87)	**.03**	1.51 (1.11-2.06)	**<.01**
Systolic hypertension (SBP mm Hg)	169 (0.17)	1.11 (0.77-1.60)	.57	1.15 (0.79-1.67)	.47
Diastolic hypertension (DBP mm Hg)	459 (0.48)	1.36 (1.03-1.80)	**.03**	1.44 (1.08-1.93)	**.01**
high triglycerides (>150 mg/dL)	184 (0.19)	1.27 (0.88-1.83)	.20	1.12 (0.77-1.62)	.56
High cholesterol (total cholesterol >200 mg/dL)	350 (0.36)	1.08 (0.81-1.43)	.60	1.05 (0.78-1.41)	.75
High LDL cholesterol (LDL mg/dL)	303 (0.31)	1.15 (0.86-1.55)	.34	1.12 (0.83-1.51)	.47
Low HDL cholesterol (HDL <4 0 mg/dL)	177 (0.18)	1.39 (0.97-2.01)	.08	1.23 (0.84-1.78)	.29
Hyperglycemia (fasting glucose mg/dL)	20 (0.02)	2.00 (0.64-6.20)	.23	1.59 (0.48-5.28)	.45
High hemoglobin A1C (%)	174 (0.18)	1.09 (0.75-1.58)	.65	1.03 (0.70-1.52)	.87
Low predicted peak VO_2 (<90%)	162 (0.17)	5.41 (3.29-8.90)	**<.01**	—	—
High resting heart rate (>90 beats per min)	94 (0.10)	1.08 (0.68-1.73)	.75	0.78 (0.48-1.27)	.32

BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; HDL = high density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; OR = odds ratio; SBP = systolic blood pressure; VO2 = oxygen uptake.

*Based on mixed effects logistic regression adjusted for age (≥45 y vs <45 y) and ethnicity (non-Hispanic white vs other).

†Based on mixed effects logistic regression adjusted for age (≥45 y vs <45 y), ethnicity (non-Hispanic white vs other), and percentage of predicted peak VO_2.

Supplementary Table S5 Characteristics of Included and Excluded Firefighters

	N*	Overall	Included	Excluded	*P* Value
Ethnicity (non-Hispanic white)†	1224	1025 (0.84)	814 (0.84)	211 (0.82)	.48
Myocardial dysfunction (yes)†	1195	769 (0.64)	611 (0.63)	158 (0.61)	.67
Age (y)	1224	40 ± 9	40 ± 9	37 ± 9	**<.01**
Height (in)	1224	71 ± 3	71 ± 3	71 ± 3	.57
Weight (lb)	1224	207 ± 34	206 ± 33	208 ± 35	.34
BMI (kg/m^2)	1224	28.9 ± 4.2	28.9 ± 4.1	29.1 ± 4.4	.46
Body fat (%)	1191	19 ± 6	18 ± 6	19 ± 6	.39
SBP (mm Hg)	1149	121 ± 10	121 ± 10	124 ± 11	**<.01**
DBP (mm Hg)	1149	77 ± 7	77 ± 7	79 ± 8	**<.01**
Triglycerides (mg/dL)	1194	111 ± 60	112 ± 59	107 ± 64	.22
Total cholesterol (mg/dL)	1220	190 ± 38	190 ± 36	192 ± 45	.40
LDL (mg/dL)	1195	116 ± 32	116 ± 32	114 ± 33	.23
HDL (mg/dL)	1217	51 ± 13	51 ± 13	49 ± 13	.06
Fasting glucose (mg/dL)	1216	95 ± 16	96 ± 16	95 ± 15	.70
Hemoglobin A1C (%)	1105	5.4 ± 0.6	5.4 ± 0.6	5.5 ± 0.9	.55
Peak VO_2 ($mlO_2{}^{-1-1}$)	1223	33 ± 6	33 ± 6	33 ± 7	.20
Peak VO_2 (L/min)	1224	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.6	.26
Predicted peak VO_2 (%)	1223	103 ± 16	104 ± 15	99 ± 17	**<.01**
Peak O_2-pulse (mL/beat)	1224	19 ± 3	19 ± 3	18 ± 4	**<.01**
Predicted peak O_2-pulse (%)	1224	116 ± 18	117 ± 18	110 ± 20	**<.01**
SBP at peak exercise (mm Hg)	1224	171 ± 19	172 ± 18	169 ± 22	.10
DBP at peak exercise (mm Hg)	1224	83 ± 12	82 ± 12	84 ± 11	.05
Resting heart rate (beats per min)	1222	75 ± 13	74 ± 12	78 ± 13	**<.01**
Peak heart rate (beats per min)	1224	161 ± 16	160 ± 15	165 ± 17	**<.01**
Predicted peak heart rate (%)	1224	89 ± 8	89 ± 7	90 ± 8	**.04**
Heart rate recovery (beats per min)	1222	37 ± 13	37 ± 13	37 ± 13	.69
ΔHR-WR slope (%)	1224	34 ± 60	36 ± 60	25 ± 59	**<.01**

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; VO_2 = oxygen uptake; ΔHR-WR slope = change in heart rate vs work-rate slope.

Data are restricted to men 20 to 60 years of age.

Data are mean ± standard deviation unless indicated otherwise; *P* values based on 2-sample *t*-tests for difference in means.

*Number of firefighters with nonmissing values for each variable.

†Data are number (proportion); *P* values based on 2-sample *z*-tests for difference in proportions.