Relation of Coronary Artery Diameters With Cardiorespiratory Fitness

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Cardiorespiratory fitness is associated with reduced cardiovascular morbidity and mortality when adjusted for traditional risk factors. Mechanisms by which fitness reduces risk have been studied but remain incompletely understood. We hypothesize that higher fitness is associated with larger coronary artery diameters independent of its effect on traditional risk factors. Two independent measurements of the proximal diameters of the left main, left anterior descending, left circumflex, and right coronary arteries were obtained from gated multidetector computed tomography scans in 500 men from the Cooper Center Longitudinal Study (CCLS). Men with coronary artery calcium scores ≥10 were excluded. Fitness was measured with a maximal exercise treadmill test and reported by quintiles and as a function of METs. We then evaluated the relation between coronary artery diameters and fitness using mixed effect regression models. Higher fitness was associated with larger coronary artery diameters after adjustment for body surface area, smoking status, low-density lipoprotein and high-density lipoprotein cholesterol, resting systolic blood pressure, and serum glucose. When examined continuously, each MET increase in fitness was associated with a mean 0.03 ± 0.01 mm larger diameter of the left main, a 0.04 ± 0.01 mm larger diameter of the left anterior descending, a 0.05 ± 0.01 mm larger diameter of the left circumflex, and a 0.07 ± 0.01 mm larger diameter of the right coronary artery (p = 0.002). This correlation between fitness and coronary artery diameters was most prominent for fitness levels above 10 METs. In conclusion, higher fitness is associated with larger coronary artery diameters. **(Am J Cardiol 2018;■■:■■–■■)**

Physical inactivity is an independent risk factor for atherosclerosis and cardiovascular disease.[1] Low cardiorespiratory fitness has also been proven to be a strong independent predictor of all-cause mortality.[2] Conversely, high fitness is inversely related to all-cause and cardiovascular mortality.[3] Mechanisms through which fitness reduces cardiovascular morbidity and mortality have been extensively studied but are not fully understood. Adverse changes in cardiovascular risk factors have been suggested as a possible explanation for the increased cardiovascular risk associated with chronic inactivity. However, recent studies suggest that the negative changes in traditional cardiovascular risk factors with inactivity can only partially explain the strong association between physical inactivity and cardiovascular mortality and morbidity.[4–6] In addition, the association of high fitness with reduced mortality in several exercise training studies persisted after adjustment for known traditional cardiovascular risk factors.[4,7] With this background, we propose a novel mechanism for the association of high fitness with reduced cardiovascular mortality and morbidity; specifically, high fitness is associated with larger coronary artery diameters. In the present study, we aimed to determine the association, if any, of coronary artery diameters with increased cardiorespiratory fitness in 500 men.

Methods

The study population consisted of 500 men randomly selected from the Cooper Center Longitudinal Study (CCLS), with approximately 100 from each quintile of fitness as described more fully further in the present study. The CCLS is an ongoing cohort study of patients who underwent a preventive medicine evaluation at the Cooper Clinic.[8] All participants in the CCLS cohort had undergone a detailed medical history, a physical examination, and fasting blood analysis, including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and glucose. Diabetes was defined as a fasting blood glucose level of ≥126 mg/dl or treatment with antidiabetic medication. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 (or both) or current treatment for hypertension. Hyperlipidemia was defined as a total cholesterol level of ≥200 or concurrent treatment for such.

All participants also underwent a cardiovascular fitness assessment with a maximal treadmill stress test using a modified Balke protocol. Exercise duration with this protocol correlates highly with directly measured maximal oxygen uptake

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(r = 0.92).[9] Maximal MET levels of cardiorespiratory fitness (1 METs = 3.5 ml O_2/kg min) were estimated from the final treadmill speed and grade. Age-specific distributions of treadmill exercise duration were then stratified into quintiles of cardiorespiratory fitness based on the previously described CCLS database.

To more accurately assess the cardiovascular risk, all men included in this study also had a gated multidetector computed tomography scan (GE VCT, Milwaukee, Wisconsin) of the heart to assess the extent, if any, of coronary artery calcium (CAC).[10] These scans were also utilized to measure the diameters of proximal coronary artery segments. Because the presence of significant CAC may cause vascular remodeling and distortion of the size of the coronary arteries, we excluded men whose CAC scores were ≥10 Agatston units. An Agatston score of less than 10 units is equivalent to a zero score because of the unavoidable baseline "noise" in the equipment and procedure.

Two investigators independently measured the diameter of the proximal left main (LM), left anterior descending (LAD), left circumflex (LC), and right coronary artery (RCA) of each study within 2 cm from its ostium. These measurements were performed without knowledge of the associated demographics or cardiorespiratory fitness. Appropriate statistical evaluation of the accuracy and reproducibility of these measurements was carried out as discussed further. The average of the 2 readings was used for the analysis.

Descriptive characteristics for the study participants were summarized by fitness quintiles, and trends across quintiles were tested using the nonparametric Jonckheere-Terpstra method. Smooth curves were fit to scatterplots of coronary artery diameter versus fitness using the LOESS method. Mixed effect regression models were used to estimate the linear relation between fitness and each of the 4 coronary artery diameters. One set of models was used to estimate and test linear trends of diameter across fitness quintiles, adjusted continuously for body surface area (BSA). Another set of models included fitness entered continuously: (1) adjusted for BSA; (2) adjusted for BSA, age, and smoking status; and (3) adjusted for BSA, age, smoking status, LDL, HDL, systolic blood pressure, and glucose. Random participant effects were included in each mixed effect regression model to account for correlation between the 2 measures of each artery in the same participant. A fixed observer effect was also included to account for the difference between the observations of the 2 investigators.

Interobserver reliability was assessed using mixed effect regression models to estimate intraclass correlation. These models included random participant effects and a fixed investigator effect but no other covariates. Calculations of intraclass correlation coefficients for single and average measurements incorporated the estimated residual and between-participant variance components but not the between-investigator variance component. All p values presented are 2-sided, with p <0.05 considered statistically significant. Data analyses were performed using SAS/STAT version 9.4 (SAS Institute, Inc, Cary, North Carolina).

Results

Table 1 depicts the characteristics of the participants in the present study, with quintile 1 representing those with the lowest age-adjusted fitness and quintile 5 representing those with the highest age-adjusted fitness. Not surprisingly, there was a higher frequency of adverse traditional cardiovascular risk factors with worsening fitness. The clinical and laboratory demographics of the study also corroborated the association of an adverse health status with worsening fitness. Finally, there was also a trend toward lower HDL cholesterol levels, higher triglyceride levels, and higher fasting glucose levels with worsening fitness.

Table 1
Study participant characteristics

	Quintile				
	1	2	3	4	5
Variable	(n = 100)	(n = 100)	(n = 100)	(n = 99)	(n = 101)
Age (years)	45.8 ± 6.7	47.5 ± 6.7	46.7 ± 6.0	48.0 ± 7.2	50.2 ± 6.8
Weight (lbs)	232.6 ± 39.5	213.1 ± 30.3	203.9 ± 26.4	197.7 ± 26.8	182.7 ± 24.6
Height (in)	70.9 ± 2.7	71.0 ± 2.4	71.0 ± 2.5	71.2 ± 2.7	70.9 ± 2.6
Body Mass Index (kg/m^2)	32.5 ± 5.0	29.6 ± 3.7	28.4 ± 3.0	27.4 ± 3.0	25.5 ± 2.9
Body Surface Area (m^2 Du Bois Formula)	2.24 ± 0.19	2.17 ± 0.16	2.13 ± 0.16	2.10 ± 0.16	2.03 ± 0.15
Systolic Blood Pressure (mm Hg)	122.6 ± 13.4	122.5 ± 14.0	119.2 ± 9.5	116.9 ± 9.7	118.6 ± 10.9
Diastolic Blood Pressure (mm Hg)	83.7 ± 9.8	82.0 ± 10.0	81.0 ± 7.3	79.1 ± 7.9	79.7 ± 8.9
Total Cholesterol (mg/dL)	196.7 ± 39.2	193.8 ± 35.5	191.5 ± 35.7	193.0 ± 38.1	190.5 ± 28.8
Low Density Lipoprotein Cholesterol (mg/dL)	119.4 ± 34.2	118.5 ± 30.9	119.3 ± 33.4	118.4 ± 32.7	113.2 ± 26.2
High Density Lipoprotein Cholesterol (mg/dL)	44.2 ± 14.9	45.4 ± 11.0	48.1 ± 11.1	51.0 ± 12.3	57.9 ± 13.5
Triglycerides (mg/dL)	165.9 ± 81.1	149.6 ± 88.3	120.6 ± 52.9	118.3 ± 65.9	96.9 ± 53.5
Glucose (mg/dL)	105.8 ± 31.5	97.9 ± 12.1	95.1 ± 8.2	94.5 ± 7.6	93.9 ± 7.7
Current Smoker	18 (18.0%)	19 (19.0%)	11 (11.0%)	8 (8.1%)	8 (7.9%)
Hypertension	32 (32.0%)	33 (33.0%)	20 (20.0%)	11 (11.1%)	13 (12.9%)
Diabetes mellitus	4 (4.0%)	3 (3.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)
Hyperlipidemia	31 (31.0%)	26 (26.0%)	31 (31.0%)	25 (25.3%)	15 (14.9%)
Treadmill time (min)	11.0 ± 2.2	14.2 ± 1.7	16.6 ± 1.6	19.1 ± 2.2	23.3 ± 2.6
Maximum METs	8.43 ± 1.01	9.89 ± 0.78	10.95 ± 0.74	12.11 ± 1.03	14.15 ± 1.45

Values are mean (SD) unless otherwise noted.