Zeng et al. Cardiovascular consequences of secondhand smoke

SUPPLEMETAL APPENDIX

Remote exposure to secondhand tobacco smoke is associated with lower exercise capacity through effects on oxygen pulse, a proxy of cardiac stroke volume

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TABLE OF CONTENTS

Zeng S, *et al. BMJ Open Resp Res* 2022; 9:e001217. doi: 10.1136/bmjresp-2022-001217

SUPPLEMENTAL METHODS

Study Overview

This was a prespecified analysis of data collected as part of the Secondhand Smoke Respiratory Health Study, an observational cohort study of nonsmoking participants with a range of occupational SHS exposure, as previously described.[1-3] Briefly, between July 2007 and July 2015, we recruited US airline flight crewmembers with a history of occupational exposure to SHS, along with nonsmoker controls without such occupational exposure, who were participating in a larger study of cardiopulmonary health effects of prolonged remote exposure to SHS.[3] The participants were characterized by respiratory symptom questionnaires, full pulmonary function testing (PFT), and a maximum effort cardiopulmonary exercise testing (CPET). We used the data from this cohort to perform a prespecified analysis to determine the associations among exercise capacity (highest workload completed [$Watts_{Peak}$ in Watts], volume of oxygen uptake at peak exercise [VO_{2Peak} in L/min], and cumulative work achieved [$Work_{Total}$ in Watts-Minutes]), cardiovascular responses to maximum effort CPET (oxygen-pulse [O_2-Pulse; a proxy for cardiac stroke volume], systolic and diastolic blood pressures [SBP and DBP], and heart rate [HR]), years of airline employment during which the participants worked in smoky cabin (cabin SHS exposure), and their interactions with each other as well as with air trapping (ratios of residual volume, or functional residual capacity, to total lung capacity; RV/TLC or FRC/TLC), which we had previously shown to be associated with exercise capacity ($Watts_{Peak}$ and VO_{2Peak}).

Study Population

The Secondhand Smoke Respiratory Health Study recruited the United States (U.S.) airline flight crewmembers as part of an investigation of the potential adverse health effects of the cabin environment on those employed before and after introduction of the ban on smoking in U.S.

commercial aircraft. Crewmembers were eligible to participate in the study if they had worked ≥5 years in aircraft. A referent group of "sea-level" participants who lived in San Francisco Bay area and had never been employed as airline crewmembers was also recruited. All participants were nonsmokers defined by never-smoking or, in ever smokers, a cumulative history of smoking <20 pack-years and no smoking for ≥20 years prior to enrollment. Participants with known history of pulmonary (such as asthma or COPD) or cardiovascular disease (such as coronary artery disease or heart failure) were excluded. Participants with known history of hypertension were included if their blood pressure was medically controlled as defined by SBP≤145 and DBP≤90 mmHgat the time of visit. Overall, out of the 283 participants who underwent cardiopulmonary exercise testing (CPET), 245 individuals were included in this analysis after such exclusions (**Figure 1**).[3]

Institutional Review Board Approval

The UCSF Institutional Review Board (IRB) and the San Francisco VA Medical Center Committee on Research and Development approved the study protocols. Written IRB-approved informed consent and Health Insurance Portability and Accountability Act (HIPAA) were obtained from all study participants. All participants received monetary compensation for their participation in the study.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. However, the participants did act as a referral source and referred other interested potential people to participate in our study, and in that sense participated in dissemination of the study.

SHS Exposure Characterization

SHS exposure was characterized by a questionnaire developed by the UCSF Flight Attendant Medical Research Institute (FAMRI) Center of Excellence,[4] and modified to acquire information on airline-related occupational history, as described previously (UCSF FAMRI SHS Questionnaire).[1,2] Briefly, this included employer airlines, duration of employment, and flight routes with quantification of "cabin SHS exposure" as the number of years during which the crewmembers were exposed to SHS in aircraft. Other possible sources of SHS exposure were also explored by questioning participants about their non-cabin exposures in additional settings, as described previously.[5]

Pulmonary Function Testing

Lung function measurement procedures were conducted according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.[6-11] Routine pulmonary function tests were performed in the seated position using a model Vmax 229 CareFusion (CareFusion Corp., Yorba Linda, CA) and nSpire body plethysmograph (nSpire Health Inc., Longmont, CO) as described previously.[1] This included the spirometry measurements of flows at low lung volumes;[12] lung volume by single breath dilution and plethysmography;[13-15] airway resistance during panting at FRC;[16,17] and single breath carbon monoxide diffusing capacity.[18] Bronchodilator responsiveness was not performed. Hyperinflation and air trapping, which is inferred from an increase in FRC or RV, were quantified using the ratios of FRC or RV to TLC (FRC/TLC or RV/TLC).

Cardiopulmonary Exercise Testing

Participants performed physician-supervised, symptom-limited, progressively increasing exercise tests in the supine position on an electromagnetically braked, supine cycle ergometer (Medical Positioning Inc. Kansas City, MO). The protocol consisted of 3-minute rest, 1-minute

unloaded (freewheeling) cycling at 60 to 65 revolutions per minute (rpm), followed by increasing work rate of 20 to 40 Watts at 2-minute intervals (stages) to a maximum toleration, and ending with 5-minutes of recovery. Participants were encouraged to give their best effort and were encouraged to continue exercise until a VO_2 plateau effect on a breath-to-breath analysis of oxygen consumption was visually observed during testing; however, they were advised that they could stop voluntarily at any time they believed they could not continue.

Twelve-lead electrocardiogram (ECG), heart rate (HR), and oxyhemoglobin saturation by pulse oximetry (SpO_2) were monitored continuously, and blood pressure (BP) (measured manually by a physician using a sphygmomanometer) was recorded every 2 minutes during the second minute of each stage. Minute ventilation (V_E), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were measured breath-by-breath with an open-circuit metabolic cart (model Vmax 229, CareFusion, Yorba Linda, CA). Immediately before all tests, the gas analyzers were calibrated using reference gases of known concentrations and the ventilometer was calibrated using a 3-liter syringe (Hans Rudolph, Kansas, MO). The metabolic system was verified using four trained technicians who provided monthly exercise values as biological standards for the laboratory.

Peak exercise gas exchange variables (VO_2, VCO_2, and V_E) were estimated as the last 30-second average value obtained during the highest stage of the exercise test that the participant was able to complete ($Watts_{Peak}$), as defined by continuous cycling at the required 60 to 65 rpm during that stage for greater than 1 minute. The volumes of the flow meter, mouthpiece, and filter (70 mL x breathing frequency) were subtracted from V_E for the V_E/VCO_2 calculations. Anaerobic threshold (AT) was determined by the V-slope method.[19,20]

The participant's perception of level of effort and exertion, breathlessness, and fatigue was documented during the second minute of every stage using the modified Borg Rating of Perceived Exertion (Borg), with the Category-Ratio Scale anchored at number 10 (CR10).[21]

Respiratory Symptom Scoring

Respiratory symptoms were assessed using modified Medical Research Council (mMRC) Dyspnea Scale[22] and another self-reported questionnaire (UCSF FAMRI SHS Questionnaire) that elicited symptoms of dyspnea, cough, and participants' perception of a decreased level of exertion compared to peers over the year preceding enrollment.[4] A dichotomous indicator of respiratory symptoms was defined by mMRC ≥1 or report of at least one respiratory symptom on the UCSF FAMRI SHS Questionnaire. A dichotomous cause of exercise cessation (dyspnea versus fatigue or effort; $Dyspnea_{Peak}$) was determined based on the highest modified Borg Dyspnea Scale category reported by the participants at the end of the maximum effort exercise testing.

Data Analysis

Percent predicted as well as lower and upper limits of normal (LLN and ULN) values for measures of spirometry and lung volumes at rest and cardiopulmonary responses to exercise were calculated using Global Lung Function Initiative (GLI), Quanjer et al., and Wasserman predicted formulas, repectively.[23-25] American Thoracic Society guidelines were also used for assessment of normal ranges of cardiopulmonary exercise indices.[26]

Distributions of participants' characteristics, pulmonary function, cardiopulmonary exercise, and SHS exposure quantification variables were examined. Changes in HR, SBP, DBP, and O_2-Pulse with respect to the workload were approximated by estimating the slopes from linear regression modeling of those measures (HR, SBP, DBP, and O_2-Pulse) over workload at each

stage. Peak cardiopulmonary exercise variables were estimated using the last 30-second average values obtained during the highest stage of the exercise test as described above. Cumulative work achieved throughout the exercise ($Work_{Total}$), or the area under the curve of workload in Watts vs. time in minutes, was computed as the sum of the product of watts completed and time spent at each stage in the unit of Watts-Minute.

Associations between exercise capacity ($Watts_{Peak}$, $Work_{Total}$, or VO_{2Peak}, as dependent variables) and each of the cardiovascular outputs (including SBP, DBP, and O_2-Pulse, as independent variables) were examined in multivariable linear regression models with adjustment for covariates (age, sex, height, and BMI unless noted otherwise). Because O_2-Pulse (proxy for stroke volume) estimates were calculated using VO_2 and HR, the associations and mediation analyses of O_2-Pulse was only examined with $Watts_{Peak}$ and $Work_{Total}$ measures of exercise capacity and not with VO_{2Peak} to prevent bias from "mathematical coupling".[27]

Similarly, associations between presence of respiratory symptoms (mMRC or UCSF FAMRI SHS Questionnaire, as dependent variables) and each of the cardiovascular outputs (as independent variables) were examined in multivariable logistic regression models with adjustment for covariates. The respective baseline variable was also adjusted whenever a slope variable was used in a model. Additionally, associations between each of the cardiovascular outputs (SBP, DBP, and O_2-Pulse) and baseline air trapping (FRC/TLC or RV/TLC) as a pulmonary factor affecting exercise capacity and cardiovascular outputs,[28-31] and SHS exposure were examined using linear regression models.

To assess whether associations between exercise capacity and SHS exposure or air trapping (FRC/TLC or RV/TLC) were potentially mediated through cardiovascular outputs, we performed mediation analyses with exercise capacity (dependent variable), SHS exposure or air

Zeng S, *et al. BMJ Open Resp Res* 2022; 9:e001217. doi: 10.1136/bmjresp-2022-001217

trapping (independent variable), and cardiovascular outputs (mediator variables), with inclusion of covariates using the "mediation" package in R.[32] To achieve robust estimations, the bootstrap method with 1000 resamples from the data was applied to obtain the estimated proportion of mediation and the corresponding P-value. Absolute proportion of mediated effects with corresponding P values were reported.

For each analysis, the total number of participants who had complete set of data for that analysis was reported along with the results from the regression modeling or mediation analysis. Statistical significance was defined as a P-value <0.05.

SUPPLEMENTAL RESULTS

Participant Characteristics

The characteristics of the 245 individuals included in this analysis are shown in **Table 1**. The participants were predominantly women (213 [87%]). All were never-smokers (<100 cigarettes lifetime) with the exception of three who had smoked ≤3 pack-years (0.7, 1, and 3 pack-years) ≥20 years prior to participation in the study. All participants had exposure to SHS with 47% and 24% reporting childhood and adult home SHS exposure, respectively. One-hundred-thirty-nine (57%) had been exposed to cabin SHS during their airline employment for an average of 16.5±9.2 years (median [IQR] <total range> of 17.1 [8.6-24.0] <0.3-35.0> years). None of the participants included in the analysis reported any history of cardiovascular or pulmonary diseases. There were eleven participants who had a history of well-controlled hypertension, nine of whom were on medical management (three on lisinopril, two on atenolol, one on verapamil, one on an unknown beta-blocker, one on combination hydrochlorothiazide and benazepril, and one on an unknown medication). None of the participants had history of diabetes mellitus.

All participants had preserved spirometry (normal FEV_1/FVC and FEV_1 by LLN criterion) but some had mildly reduced diffusing capacity at 81±10 (median [IQR] <total range> of 80 [73-88]) <55-114> %predicted). The participants had FRC/TLC of 0.53±0.07 (at 99±13 %predicted; median [IQR] <total range> of 99 [91-106] <54-129> %predicted) and RV/TLC of 0.33±0.07 (at 90±13 %predicted; median [IQR] <total range> of 90 [82-98] <53-129> %predicted).

Overall response to exercise

All participants reported ceasing exercise due to dyspnea or leg fatigue. Modified Borg Dyspnea Scale rating of perceived exercise scales were 4.2±1.9 for dyspnea, 5.1±1.9 for effort, and 4.7±1.9 for fatigue at peak exercise. When pressed to identify a single cause for ceasing exercise, 117 (48%) identified dyspnea as opposed to fatigue or effort as the main cause ($Dyspnea_{Peak}$) (**Table 2**).

Pulmonary response to exercise

The average volume of oxygen consumption at peak exercise (VO_{2Peak}) was 1,557±476 mL/min at 100±24 %predicted (median [IQR] <total range> VO_{2Peak} of 98 [82-113] <52-208> %predicted) with 71 (29%) having a VO_{2Peak} <84 %predicted, a presumed threshold for abnormal results. The volume of oxygen consumption by weight at peak exercise ($VO_{2Peak/kg}$) was 23.8±7.0 $mL.kg^{-1}.min^{-1}$ at 85±18 %predicted (median [IQR] <total range> $VO_{2Peak/kg}$ of 85 [72-94] <44-163> %predicted by FRIENDS reference equation)[33] with 33 (14%) having a value below the LLN. This VO_{2Peak} was achieved at a peak workload of 156±46 watts (135±33 %predicted) (median [IQR] <total range> $Watts_{Peak}$ of 135 [112-155] <64-273> %predicted). The ratio of oxy-hemoglobin to total hemoglobin (oxygen saturation or SpO_{2Peak}) at peak exercise was 98±1% (median [IQR] <total range> SpO_{2Peak} of 99 [98-100] <94-100> %) with nearly all participants but one having a SpO_{2Peak} of ≥95% (one had SpO_{2Peak} of 94%, eleven had SpO_{2Peak} of 95%, and all other >95%).

The pulmonary response to exercise was also remarkable for a peak-exercise minute ventilation (V_{EPeak}) of 57.0±17.0 L/min at 50±12 %predicted (median [IQR] <total range> of 50 [42-58] <18-90> %predicted) with only 12 (5%) exceeding the 70% threshold for inappropriate ventilatory response to maximum effort exercise. This level of minute ventilation at peak

exercise was achieved through a tidal volumes at peak exercise (V_{TPeak}) of 1.73±0.47 L at 86±17 %predicted (median [IQR] <total range> of 85 [76-96] <42-146> %predicted), and a peak-exercise respiratory rate (RR_{Peak}) that remained below the 50 breaths/minute in 93% (218 out of 235) and below the 60 breaths/minute threshold in all but 1 participant (35±9 breaths/min; median [IQR] <total range> of 33 [28-40] <15-69> breaths/min) (**Table 2**). All participants reached their anaerobic threshold (VO_{2AT}) as determined by V slope method. The VO_{2AT} was 994±327 mL/min at 63±13% of VO_{2Peak} (median [IQR] <total range> of 63 [56-71] <27-100> % of VO_{2Peak}) (**Table 2**). The volume of oxygen consumption by weight at anaerobic threshold ($VO_{2AT/kg}$) was17.8±4.9 $mL.kg^{-1}.min^{-1}$, which was 54±14 % of the maximum VO_2 predicted (median [IQR] <total range> of 54 [43-63] <18-96>) % of the maximum VO_2 predicted.

Furthermore, ventilatory efficiency (V_E/VCO_2) at peak exercise was 30.7±3.8 (108±12 %predicted; median [IQR] <total range> of 107 [99-114] <79-181> %predicted). The lowest V_E/VCO_2 was 29.4±3.4 (103±11 %predicted; median [IQR] <total range> of 104 [97-110] <45-129> %predicted) (**Table 2**).

Cardiovascular response to exercise

None of the participants reported any chest pain, chest tightness, lightheadedness, or dizziness during the CPET. None had any clinically significant electrocardiographic (ECG) changes or arrhythmia besides occasional premature ventricular contractions that did not increase in frequency with exercise testing. Nevertheless, many had abnormal cardiovascular response to exercise as described below.

Although only 11 (4%) of participants had reported history of hypertension (with their hypertension well-controlled), 66% percent of the participants (149 out of 226) showed a

hypertensive response to exercise by at least one established criterion (**Table 2**). The heart rate at peak exercise was 142±18 beat/min (85±10 %predicted; median [IQR] <total range> of 85 [79-93] <58-119> %predicted). Oxygen-pulse at peak exercise (O_2-$Pulse_{Peak}$) was 11.0±3.0 mL/beat (116±25 %predicted; median [IQR] <total range> of 113 [99-133] <64-224> %predicted), with 8 (3.3%) participants not achieving their 80% predicted values. (**Table 2**).

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SUPPLEMENTAL TABLES

Table S1- Associations of cardiovascular response to exercise with years of exposure to cabin SHS or air trapping.

	Independent variables								
	Cabin SHS exposure			**RV/TLC**			**FRC/TLC**		
Dependent variables	**N**	**PE±SEM (95% CI)**	**P value**	**N**	**PE±SEM (95% CI)**	**P value**	**N**	**PE±SEM (95% CI)**	**P value**
Peaks									
O_2-Pulse$_{Peak}$	**241**	**-0.032±0.015 (-0.062 to -0.001)**	**0.040**	235	-0.058±0.032 (-0.121 to 0.005)	0.069	220	-0.005±0.025 (-0.055 to 0.044)	0.829
HR_{Peak}	241	-0.009±0.124 (-0.253 to 0.235)	0.941	**235**	**-0.521±0.257 (-1.028 to -0.014)**	**0.043**	**220**	**-0.397±0.195 (-0.782 to -0.012)**	**0.043**
SBP_{Peak}	223	-0.070±0.151 (-0.368 to 0.228)	0.642	220	0.259±0.304 (-0.340 to 0.858)	0.394	213	0.064±0.236 (-0.402 to 0.530)	0.786
DBP_{Peak}	223	-0.109±0.078 (-0.262 to 0.044)	0.162	220	0.069±0.159 (-0.244 to 0.382)	0.663	213	0.009±0.123 (-0.233 to 0.251)	0.942
Slopes									
O_2-Pulse$_{Slope}$	234	0.001±0.001 (-0.001 to 0.002)	0.345	229	0.001±0.002 (-0.002 to 0.004)	0.475	218	0.001±0.001 (-0.002 to 0.003)	0.605
HR_{Slope}	234	0.016±0.007 (0.001 to 0.030)	0.034	229	-0.001±0.015 (-0.031 to 0.028)	0.929	218	-0.012±0.011 (-0.034 to 0.010)	0.289
SBP_{Slope}	224	0.004±0.010 (-0.016 to 0.023)	0.724	221	0.024±0.020 (-0.015 to 0.064)	0.228	214	-0.005±0.016 (-0.036 to 0.026)	0.758
DBP_{Slope}	224	0.001±0.005 (-0.009 to 0.012)	0.814	221	0.002±0.011 (-0.019 to 0.023)	0.820	214	0.005±0.008 (-0.011 to 0.022)	0.508

Footnote: The association between each of the cardiovascular response to exercise (dependent variable) and years of exposure to cabin SHS or air trapping (independent variable) was individually assessed by linear regression modeling with adjustment for age, sex, height, BMI, and corresponding baseline values (for slope variables). Statistically significant values (P<0.05) are shown in bold. Air

trapping was represented by the ratio of residual volume to total lung capacity (RV/TLC) and the ratio of functional residual capacity to total lung capacity (FRC/TLC). Abbreviations- SHS: secondhand smoke, O_2-Pulse: oxygen uptake per heartbeat; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table S2- Effect of air trapping on exercise capacity through mediators.

	Mediation analysis of effect of FRC/TLC to								
	$Watts_{Peak}$			$Work_{Total}$			VO_{2Peak}		
Mediators	**N**	**% mediated (95% CI)**	**P value**	**N**	**% mediated (95% CI)**	**P value**	**N**	**% mediated (95% CI)**	**P value**
Cardiovascular outputs									
Peaks									
O_2-$Pulse_{Peak}$	220	28.1(-705 to 396.6)	0.628	219	22.2(-328.5 to 414.5)	0.658		N/A *	
HR_{Peak}	220	51.2(-648.3 to 515.8)	0.396	219	56.5(-814 to 660.2)	0.364	220	53.0(-416.6 to 693.5)	0.230
SBP_{Peak}	213	1.4(-171.2 to 172.6)	0.920	213	1.4(-212.2 to 210.7)	0.932	213	2.1(-111.4 to 130)	0.848
DBP_{Peak}	213	0.002(-49.3 to 73.3)	0.999	213	0.1(-58.3 to 38.1)	0.960	213	0.03(-29.3 to 27)	0.962
Slopes									
O_2-$Pulse_{Slope}$	218	12.9(-217.9 to 193.5)	0.540	218	10.4(-166.8 to 188.6)	0.560		N/A *	
HR_{Slope}	218	16.3(-370 to 336.6)	0.570	218	10.3(-256.1 to 224.6)	0.590	218	8.2(-138.9 to 148.5)	0.496
SBP_{Slope}	214	3.1(-160.8 to 229.7)	0.864	214	1.4(-91.4 to 140.6)	0.852	214	2.2(-82.1 to 110.7)	0.808
DBP_{Slope}	214	9.8(-176.3 to 190.4)	0.544	214	6.5(-108.8 to 145.6)	0.570	214	9.0(-92.7 to 110.1)	0.520
Pulmonary outputs									
RR_{Peak}	214	41.3(-446 to 482.9)	0.302	214	50.0(-540.2 to 635.1)	0.348	214	63.2(-544 to 619.5)	0.222
VE_{Peak}	220	73.3(-991 to 1198.2)	0.368	219	76.0(-920.1 to 1072.6)	0.340	220	81.1(-812.4 to 781.2)	0.202
VT_{Peak}	218	21.1(-289.9 to 261.4)	0.512	218	16.8(-279.5 to 251.4)	0.546	218	13.6(-140 to 209.2)	0.506

Footnote: To see if the association of air trapping (independent variable) with exercise capacity (dependent variable) was mediated through the cardiovascular or pulmonary outputs, mediation analyses were performed with adjustment for age, sex, height, and BMI and inclusion of one mediator at a time. Statistical significance was determined by a P value<0.05. * The associations of VO_{2Peak} with O_2-$Pulse_{Peak}$ and O_2-$Pulse_{Slope}$ were not computed due to existence of "mathematical coupling" between VO_2 and O_2-Pulse, which

depends on VO_2 for its calculation (O_2-Pulse=VO_2/HR). Abbreviations- VO_{2Peak}: peak oxygen uptake; SHS: secondhand smoke; O_2-$Pulse_{Peak}$: oxygen uptake per heartbeat at peak exercise; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR_{Peak}: peak respiratory rate; VE_{Peak}: peak minute ventilation value; VT_{Peak}: peak tidal volume; FRC: functional residual capacity; TLC: total lung capacity.

Table S3- Associations of exercise capacity with cardiopulmonary exercise outputs when adjusting for respiratory symptoms measured by mMRC.

	Dependent variables								
	Peak Workload (watt) ($Watts_{Peak}$)			Cumulative Work (watt-minute) ($Work_{Total}$)			Peak volume of O_2 consumption (mL/min) (VO_{2Peak})		
Independent variables	**N**	**PE±SEM 95% CI**	**P value**	**N**	**OR±SEM 95% CI**	**P value**	**N**	**OR±SEM 95% CI**	**P value**
Cardiovascular outputs									
Peaks									
O_2-$Pulse_{Peak}$	**245**	**10.1±0.7 (8.7 to 11.5)**	**<0.001**	**239**	**53.0±4.6 (44 to 62)**	**<0.001**		N/A *	
HR_{Peak}	**245**	**0.6±0.1 (0.4 to 0.8)**	**<0.001**	**239**	**4.2±0.7 (2.9 to 5.5)**	**<0.001**	**245**	**7.6±1.2 (5.4 to 9.9)**	**<0.001**
SBP_{Peak}	**226**	**0.3±0.1 (0.1 to 0.6)**	**0.001**	**224**	**2.3±0.6 (1.1 to 3.6)**	**<0.001**	**226**	**3.3±1.1 (1.1 to 5.6)**	**0.003**
DBP_{Peak}	226	0.1±0.2 (-0.4 to 0.5)	0.791	224	-0.1±1.2 (-2.6 to 2.3)	0.905	226	-0.2±2.2 (-4.6 to 4.1)	0.918
Slopes									
O_2-$Pulse_{Slope}$	**238**	**-61.6±17.7 (-96.6 to -26.7)**	**<0.001**	**238**	**-238.0±108.3 (-451.4 to -24.6)**	**0.028**		N/A *	
HR_{Slope}	**238**	**-11.4±1.9 (-15.1 to -7.8)**	**<0.001**	**238**	**-39.5±11.6 (-62.3 to -16.8)**	**<0.001**	**238**	**-61.5±20.6 (-102.0 to -21.1)**	**0.003**
SBP_{Slope}	**227**	**-6.4±1.5 (-9.5 to -3.4)**	**<0.001**	**225**	**-19.3±9.4 (-37.7 to -0.8)**	**0.040**	**227**	**-38.1±16.7 (-70.9 to -5.2)**	**0.023**
DBP_{Slope}	**227**	**-12.0±2.9 (-17.8 to -6.2)**	**<0.001**	**225**	**-46.5±17.6 (-81.2 to -11.7)**	**0.008**	**227**	**-107.1±31.1 (-168.4 to -45.7)**	**<0.001**

Footnote: The association between exercise capacity (dependent variable) and each of the cardiopulmonary exercise measures (independent variables) were individually assessed by multivariable linear regression modeling with adjustment for age, sex, height,

BMI, and corresponding baseline values (for slope variables). In addition, modified Medical Research Council dyspnea scale (mMRC) was also included as a binary independent variable (mMRC<1 versus mMRC≥1) in the models. In those models, the likelihood of having an mMRC≥1 remained negatively associated with the work achieved (with the exception of the models of VO_{2Peak} and $Work_{Total}$ versus HR_{Peak} in which mMRC was not significant) (mMRC data not shown). Statistically significant values ($P<0.05$) are shown in bold. * The associations of VO_{2Peak} with $O_2\text{-}Pulse_{Peak}$ and $O_2\text{-}Pulse_{Slope}$ were not computed due to existence of "mathematical coupling" between VO_2 and O_2-Pulse, which depends on VO_2 for its calculation ($O_2\text{-}Pulse=VO_2/HR$). Abbreviations- VO_{2Peak}: peak oxygen uptake; $O_2\text{-}Pulse_{Peak}$: oxygen uptake per heartbeat at peak exercise; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table S4- Associations of Oxygen-Pulse at peak exercise (O_2-$Pulse_{Peak}$) with cardiopulmonary exercise outputs.

Independent variables	N	PE±SEM (95% CI)	P value
Cardiovascular outputs			
Peaks			
SBP_{Peak}	226	0.008±0.007(-0.006 to 0.023)	0.250
DBP_{Peak}	226	-0.018±0.014(-0.046 to 0.009)	0.196
Slopes			
SBP_{Slope}	**227**	**-0.257±0.105(-0.464 to -0.05)**	**0.015**
DBP_{Slope}	**227**	**-0.774±0.197(-1.163 to -0.385)**	**<0.001**

Footnote: The association between O_2-$Pulse_{Peak}$ (dependent variable) and each of the cardiopulmonary exercise measures (independent variable) were individually assessed by multivariable linear regression modeling with adjustment for age, sex, height, BMI, and corresponding baseline values (for slope variables). Statistically significant values ($P<0.05$) are shown in bold. Abbreviations- O_2-$Pulse_{Peak}$: oxygen uptake per heartbeat at peak exercise; SBP: systolic blood pressure; DBP: diastolic blood pressure; Peak: SBP and DBP measure at peak of exercise; Slope: change in SBP and DBP over change in workload during exercise.