Article:

Coffman, KE, Carlson, AR, Miller, AD et al. (2017) The effect of aging and cardiorespiratory fitness on the lung diffusing capacity response to exercise in healthy humans. Journal of Applied Physiology, 122 (6). pp. 1425-1434. ISSN: 8750-7587

https://doi.org/10.1152/japplphysiol.00694.2016

Articles in PresS. J Appl Physiol (March 23, 2017). doi:10.1152/japplphysiol.00694.2016

The effect of aging and cardiorespiratory fitness on the lung diffusing capacity response to exercise in healthy humans

Authors
Kirsten E. Coffman[1], Alex R. Carlson[2], Andrew D. Miller[2], Bruce D. Johnson[2], Bryan J. Taylor[2,3]

Author Affiliations
[1]Mayo Graduate School, Mayo Clinic, Rochester, MN, USA
[2]Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
[3]School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, UK

Contact Information for Corresponding Author
Bryan J. Taylor, PhD
University Academic Fellow
School of Biomedical Sciences
Faculty of Biological Sciences
University of Leeds
Garstang 5.68
Leeds, UK
LS2 9JT
Office: +44(0)113 343 0482
E-mail: b.j.taylor@leeds.ac.uk

ABSTRACT

Aging is associated with deterioration in the structure and function of the pulmonary circulation. We characterized the lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C) response to discontinuous incremental exercise at 25, 50, 75, and 90% of peak work (W_{peak}) in four groups: 1) Young [27 ± 3 y, maximal oxygen consumption ($\dot{V}O_{2max}$) 110 ± 18% age-predicted]; 2) Young Highly-Fit (27 ± 3 y, $\dot{V}O_{2max}$ 147 ± 8% age-predicted); 3) Old (69 ± 5 y, $\dot{V}O_{2max}$ 116 ± 13% age-predicted); and 4) Old Highly-Fit (65 ± 5 y, $\dot{V}O_{2max}$ 162 ± 18% age-predicted). At rest and at 90% W_{peak}, DLCO, Dm_{CO}, and V_C were decreased with age. At 90% W_{peak}, DLCO, Dm_{CO} and V_C were greater in Old Highly-Fit vs. Old adults. The slope of the DLCO-cardiac output ($\dot{Q}$) relationship from rest to end-exercise at 90% W_{peak} was not different between Young, Young Highly-Fit, Old and Old Highly-Fit (1.35 vs. 1.44 vs. 1.10 vs. 1.35 $ml_{CO}\cdot mmHg^{-1}\cdot Lblood^{-1}$, $P = 0.388$), with no evidence of a plateau in this relationship during exercise; this was also true for Dm_{CO}-$\dot{Q}$ and V_C-$\dot{Q}$. $\dot{V}O_{2max}$ was positively correlated with: 1) DLCO, Dm_{CO}, and V_C at rest; 2) the rest to end-exercise change in DLCO, Dm_{CO}, and V_C. In conclusion, these data suggest that despite the age-associated deterioration in the structure and function of the pulmonary circulation, expansion of the pulmonary capillary network does not become limited during exercise in healthy individuals regardless of age or cardiorespiratory fitness level.

KEY WORDS: Maximal aerobic capacity, lung diffusing capacity, pulmonary circulation, alveolar-capillary membrane conductance, pulmonary-capillary blood volume

NEW & NOTEWORTHY

Healthy aging is a crucial area of research. This manuscript details how differences in age and cardiorespiratory fitness level affect lung diffusing capacity, particularly during heavy exercise. We conclude that highly fit older adults do not experience a limit in lung diffusing capacity during heavy exercise. Interestingly, however, we found that highly fit older individuals demonstrate greater values of lung diffusing capacity during heavy exercise than their less fit age-matched counterparts.

INTRODUCTION

Maximal aerobic capacity ($\dot{V}O_{2max}$) has been shown to, at least in part, determined by the structure and function of the pulmonary vasculature in health and chronic disease (1, 10, 22, 23, 25). For example, it has been shown that $\dot{V}O_{2max}$ is positively correlated with resting pulmonary capillary blood volume (V_C) and pulmonary vasculature distensibility, and inversely related to pulmonary vascular resistance at maximal exercise in healthy individuals (23). This suggests that a larger, more distensible pulmonary vascular network is associated with greater aerobic exercise capacity in humans.

Measures of lung diffusing capacity for carbon monoxide (DLCO) and nitric oxide (DLNO), alveolar-capillary membrane conductance (Dm_{CO}) and pulmonary capillary blood volume (V_C) are considered to reflect the pulmonary vascular response to whole-body exercise. Indeed, increased cardiac output and pulmonary perfusion pressure during exercise cause a marked expansion of the highly compliant pulmonary capillary network that is associated with an increase DLCO, DLNO, Dm_{CO} and V_C (17, 27, 34). Additionally, it is thought that the DLNO/DLCO ratio provides insight into the mechanism by which expansion of the pulmonary capillary network during exercise occurs, with an increase in the ratio indicating a thinning of the pulmonary capillary sheet (i.e. predominant vessel recruitment) and a decrease in the ratio indicating a thickening of the blood sheet (i.e. predominant vessel distension) (13, 23).

Heathy aging is associated with a progressive deterioration in the structure and function of the pulmonary circulation that is characterized by an increase in pulmonary vascular stiffness, pulmonary vascular pressures and pulmonary vascular resistance (20, 24, 28). Additionally, from maturity to senescence there is a decrease in resting V_C and Dm_{CO} that is consistent with a reduction in alveolar-capillary surface area (1, 15). These age-related changes in the pulmonary vasculature may impair recruitment and/or distension of the pulmonary capillaries during exercise in healthy older adults, subsequently impairing the increase in alveolar-capillary surface area needed for effective gas exchange and resulting in an excessive rise in pulmonary vascular pressures relative to the metabolic demand of exercise. However, it has been shown that DLCO and V_C increase linearly relative to exercise intensity in old as well as young healthy adults (34), indicating that expansion of the pulmonary capillaries does not become limited during exercise in these individuals. This finding implies that the changes in the pulmonary circulation that occur with healthy aging are somewhat mild and not sufficient to affect pulmonary vascular expansion and the recruitment of effective alveolar-capillary surface area for gas exchange during exercise in healthy older adults.

The pulmonary vascular response to exercise in aged adults who have maintained a high cardiorespiratory fitness is, however, currently less well characterized. Theoretically, better maintenance of $\dot{V}O_{2max}$ through conditioning may cause the demand for $\dot{Q}$ and pulmonary blood flow during exercise to remain elevated in endurance trained highly fit older subjects compared to their younger counterparts. This, in the face of age-related alterations in the structure and function of the pulmonary circulation, may predispose highly fit older adults to impairments in pulmonary vascular expansion and pulmonary gas exchange relative to metabolic demand during exercise. Accordingly, the aim of the present study was to characterize the DLCO, Dm_{CO}, and V_C response to incremental exhaustive exercise in healthy, aerobically-trained older adults relative to their age-matched less aerobically fit counterparts, as well as younger adults of various cardiorespiratory fitness levels. We hypothesized that those older individuals who had maintained an elevated cardiorespiratory fitness would encroach upon their maximal ability to expand the pulmonary vascular network during severe exercise, as evidenced by a plateau and/or decrease in the rate of rise in one or more of DLCO, Dm_{CO} or V_C.

METHODS

Subjects

Sixteen young adults (27 ± 3 y) and 15 older adults (67 ± 6 y) who had pulmonary function within normal limits participated in the study (Table 1). The subjects were sub-divided into four groups according to age (≤ 30 y = "young"; ≥ 60 y = "old") and cardiorespiratory fitness ($\dot{V}O_{2max}$ ≥140% of age predicted = "highly-fit"). Group 1) Young: age 27 ± 3 y (range 22 – 29), $\dot{V}O_{2max}$ 110 ± 18% predicted (range 85 – 133) (*n* = 9); Group 2) Young Highly-Fit: age 27 ± 3 y (range 23 – 30), $\dot{V}O_{2max}$ 147 ± 8% predicted (range 140 – 163) (*n* = 7); Group 3) Old: age 69 ± 5 y (range 60 – 76), $\dot{V}O_{2max}$ 116 ± 13% predicted (range 100 – 132) (*n* = 7, 1 female); Group 4) Old Highly-Fit: age 65 ± 5 y (range 60 – 74), $\dot{V}O_{2max}$ 162 ± 18% predicted (range 140 – 198) (*n* = 8, 1 female) (Table 1). All subjects were healthy and had no history of respiratory, cardiovascular, or metabolic disease. Each participant gave written informed consent after being provided a detailed description of the study requirements. The experimental procedures were approved by the Mayo Clinic Institutional Review Board and were performed in accordance with the ethical standards of the Declaration of Helsinki.

Experimental Procedures

The experimental procedures were conducted during two laboratory visits separated by at least 2 but no more than 14 days. The subjects abstained from caffeine for 12 h and exercise for 24 h prior to each visit. During visit 1, pulmonary function was assessed via full body plethysmography (MedGraphics Elite Series Plethysmograph, Medical Graphics Corporation, St. Paul, MN, USA) according to standard procedures (26). Next, subjects performed a maximal incremental exercise test on an electromagnetically braked cycle ergometer (Lode Corival, Lode B.V. Medical Technology, Groningen, The Netherlands) for determination of peak work rate (W_{peak}) and maximal oxygen consumption ($\dot{V}O_{2max}$). Exercise was initiated at 60, 80, or 100 Watts (W), depending on self-reported fitness, and work rate was increased by 20 W every 2 min until volitional exhaustion. W_{peak} was calculated as the sum of the final work rate completed plus the fraction of the partially completed work rate before exhaustion. $\dot{V}O_{2max}$ was taken to be the highest mean value within the final 20 seconds of exercise.

During visit 2, subjects performed discontinuous graded cycle exercise. Following 5 minutes of quiet rest, participants cycled for 6 minutes at 25, 50, and 75% of W_{peak}, before cycling at 90% of W_{peak} to volitional exhaustion. Between exercise bouts, subjects recovered quietly until heart rate returned to within 10 bpm of resting values (at least 4 minutes). Additionally, a 1 min 'warm-up' at 40% of the workload about to be completed was allowed before each exercise bout. Lung diffusing capacity for carbon monoxide (DLCO) and nitric oxide (DLNO) and cardiac output ($\dot{Q}$) were measured in duplicate at rest and during the final 90 s of each exercise bout via a rebreathe technique.

Lung diffusing capacity and cardiac output

Lung diffusing capacity for carbon monoxide (DLCO), lung diffusing capacity for nitric oxide (DLNO), and cardiac output ($\dot{Q}$) were assessed using a rebreathe technique as we have described previously (5, 36). Using this technique, DLCO, DLNO, and $\dot{Q}$ are determined via the rate of disappearance of CO, NO, and acetylene (C_2H_2), respectively. Briefly, subjects sat upright on a cycle ergometer and breathed through a two-way switching valve (Hans Rudolph 4285 series, Hans Rudolph, Kansas City, MO, USA) connected to a pneumotachometer (MedGraphics PreVent Pneumotach, Medical Graphics Corporation, St. Paul, MN,USA), mass spectrometer (Marquette 1100 Medical Gas Analyser, Perkin-Elmer, St. Louis, MO, USA) and NO analyzer (Sievers 280i NOA, Sievers, Boulder, CO,USA). The inspiratory port of the switching valve was open to room air or a 6-L anesthesia bag filled with 0.3% CO ($C^{18}O$), 40 ppm NO, 9% He, 0.6% C_2H_2, 35% O_2 and N_2 balance. The total volume of gas added to the rebreathe bag was determined as the average tidal volume of the subject during the 20-30 s immediately prior to each measurement. To ensure the volume of the test gas was consistent across multiple rebreathe maneuvers the bag was filled using a timed switching circuit that, given a constant flow rate from the gas tank, resulted in the desired volume. The test gas volume given by the switching circuit was verified before exercise using a 3 L syringe. Following a normal expiration, subjects were switched into the rebreathe bag and instructed to nearly empty the bag with each breath for 8-10 consecutive breaths. A respiratory frequency of 32 breaths per min was maintained by following a metronome with inspiratory and expiratory tones; this respiratory rate was necessary in order to collect enough data to correctly trace NO decay. If the subject's respiratory frequency was above 32 breaths per min during exercise, the subject was allowed to breathe at a higher rate. This maneuver was performed in duplicate at rest and during the final 90 s of each exercise bout.

From the measurements of DLCO and DLNO, alveolar-capillary membrane conductance (Dm_{CO}) and pulmonary capillary blood volume (V_C) were calculated (5, 32). The coefficient relating DLNO to Dm_{CO} (α-ratio) was set at 2.26 (5) such that Dm_{CO} was calculated as DLNO/α-ratio. Next, the reaction rate of CO with hemoglobin (θ_{CO}) was calculated using the equation derived by Reeves and Park (5, 29) in which θ_{CO} is dependent on the capillary partial pressure of oxygen ($P_{cap}O_2$):

$$\frac{1}{\theta_{CO}} = 0.008 * P_{cap}O_2 + 0.0156 \qquad \text{Equation (1)}$$

where $P_{cap}O_2$ is estimated as alveolar $PO_2 - VO_2/(DLCO \times 1.23)$ with partial pressures in mmHg and VO_2 in ml/min. Finally, the values of Dm_{CO} and θ_{CO} were used to solve for V_C according to the following equation derived by Roughton and Forster (31):

$$\frac{1}{DLCO} = \frac{1}{DmCO} + \frac{1}{\theta_{CO} * Vc} \qquad \text{Equation (2)}$$

Capillary blood was sampled from an earlobe and measured for hemoglobin (Hb) concentration via centrifugal hematology (QBC Autoreader, Bector Dickinson, Port Matilda, PA). V_C was then corrected for standard concentrations of Hb in men (14.6 g/dl) and women (13.4 g/dl) as calculated V_C × (standard Hb concentration/measured Hb concentration).

Lung Diffusing Capacity-Cardiac Output Slope

We calculated the slope of the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$, and V_C-$\dot{Q}$ relationship from rest to end-exercise in each experimental group by plotting DLCO, Dm_{CO} or V_C as a function of $\dot{Q}$. These slopes represent unit DLCO, Dm_{CO}, and V_C changes per unit change in pulmonary vascular blood flow ($\dot{Q}$) and provide an indirect measure of the hemodynamic response of the pulmonary circulation to exercise.

Statistical Analysis

One-way ANOVA with Tukey-Kramer post-hoc analysis (*two-tailed*) was used to compare 1) subject characteristics, 2) pulmonary function, and 3) measures of DLCO, Dm_{CO}, and V_C at rest and at 90% of W_{peak}. The effect of exercise on DLCO, Dm_{CO}, V_C, and DLNO/DLCO was tested using a linear mixed effects model. In this model, the dependent variable was DLCO, Dm_{CO}, V_C or DLNO/DLCO, and the five exercise levels (rest, 25, 50, 75 and 90% W_{peak}) were treated as repeated measures with $\dot{Q}$ as the continuous variable. Age (young or old) and cardiorespiratory fitness (normal or highly-fit) were included as independent predictor variables. That is, using this model the response of a given variable to exercise as well as the offset in baseline values are assessed as a function of age and/or cardiorespiratory fitness. Coefficient of determination (r^2) was computed to assess the proportion of $\dot{V}O_{2max}$ that was predicted by 1) resting DLCO, resting Dm_{CO}, and resting V_C; 2) the change (Δ) in DLCO, Dm_{CO}, and V_C from rest to end-exercise; and 3) the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$, and V_C-$\dot{Q}$ slope in response to exercise. In all analyses, the acceptable type I error was set at $P < 0.05$. Results are expressed as mean ± SD. The linear mixed effects model was performed in Matlab (version R2016a, MathWorks, Natick, MA); all other statistical analyses were performed using IBM SPSS Statistics 20 for Windows (IBM, Armonk, NY).

RESULTS

Subjects

Subject characteristics and pulmonary function are shown in Table 1. Group mean age was not different in Young vs. Young Highly-Fit, or in Old vs. Old Highly-Fit. In addition, all subject groups were well matched for height, body mass, and BMI. Absolute and relative (*to body mass*) $\dot{V}O_{2max}$ and W_{peak} were greater in Young Highly-Fit compared to Young, Old and Old Highly-Fit (all $P < 0.01$, Table 1). In addition, $\dot{V}O_{2max}$ (absolute and relative) and W_{peak} were lower in Old versus Young, Young Highly-Fit and Old Highly-Fit (all $P < 0.01$, Table 1). Interestingly, however, neither $\dot{V}O_{2max}$ nor W_{peak} was different in Young vs. Old Highly-Fit (Table 1).

Lung Diffusing Capacity at Rest and at 90% W_{peak}

At rest, group mean DLCO, Dm_{CO}, and V_C were lower in Old vs. Young ($P \leq 0.003$) and Young Highly-Fit ($P < 0.001$) (Table 2 and Figure 1). In addition, group mean resting DLCO, Dm_{CO}, and V_C were lower in Old Highly-Fit compared to Young Highly-Fit ($P < 0.001$, 0.016, and 0.021, respectively) (Table 2 and Figure 1). No other differences in resting measures of DLCO, Dm_{CO}, and V_C were observed between the four experimental groups (Table 2).

At 90% of W_{peak}, group mean DLCO, Dm_{CO}, and V_C were lower in Old vs. Young ($P < 0.001$), Young Highly-Fit ($P < 0.001$), and Old Highly-Fit ($P \leq 0.050$) (Table 2 and Figure 1). Also, group mean DLCO and Dm_{CO} at 90% of W_{peak} were lower in Old Highly-Fit compared to Young ($P \leq 0.019$) and Young Highly-Fit ($P \leq 0.001$). Moreover, V_C was lower in Old Highly-Fit vs. Young Highly-Fit at 90% of Wpeak ($P = 0.016$) (Table 2 and Figure 1). These data suggest that, at rest and during exercise, lung diffusing capacity and its component parts (i.e. DLCO, Dm_{CO}, and V_C) are decreased with age. Additionally, lung diffusing capacity and its component parts are greater during near-maximal exercise highly-fit older adults compared to their age matched less fit counterparts.

Lung Diffusing Capacity Response to Exercise: effect of age and cardiorespiratory fitness

DLCO, Dm_{CO}, and V_C rose steadily with increasing $\dot{Q}$ during exercise, with no evidence of a plateau and/or decrease in the rate of rise in these variables from rest to end-exercise in any of the experimental groups (Figure 1). These data suggest that no group encroached upon their maximal ability to expand the pulmonary vascular network and increase lung surface area for gas exchange during exercise. Throughout exercise, DLCO was significantly lower with greater age ($P < 0.001$) but significantly higher with greater fitness ($P = 0.016$) (Figure 2). Dm_{CO} and V_C were significantly lower with greater age ($P < 0.001$) throughout exercise; the effect of fitness was not significant (Figure 2). The relationships between lung diffusing capacity and its component variables (i.e. DLCO, Dm_{CO}, and V_C) and $\dot{Q}$ from rest to end-exercise are shown in Figure 2. The rate of rise in DLCO, Dm_{CO}, and V_C relative to $\dot{Q}$ during exercise was remarkably similar between the four experimental groups. Indeed, there was no significant effect of age or fitness on the slope of the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$ and V_C-$\dot{Q}$ response to exercise (Figure 2). These data suggest that all groups experienced a similar pulmonary vascular response to exercise.

The DLNO/DLCO ratio decreased from rest to throughout exercise in Young ($P = 0.033$), Old ($P = 0.028$), and Old Highly-Fit ($P = 0.004$), indicating that pulmonary capillary expansion during exercise was at least partially achieved via vessel distension; this fall was not significant in the Young Highly-Fit individuals ($P = 0.051$) (Figure 6). Furthermore, there was no significant effect of age ($P = 0.055$) or fitness on the rate of fall in DLNO/DLCO from rest to end-exercise (Figure 6).

Relationship of Lung Diffusing Capacity and $\dot{V}O_{2max}$

The relationships between $\dot{V}O_{2max}$ and 1) resting measures of DLCO, Dm_{CO}, and V_C, 2) the change (Δ) in DLCO, Dm_{CO}, and V_C from rest to end-exercise, and 3) the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$, and V_C-$\dot{Q}$ slope in response to exercise for all 31 subjects are shown in Figure 3, Figure 4 and Figure 5, respectively. A significant positive correlation was found between $\dot{V}O_{2max}$ and resting measures of DLCO ($r^2 = 0.587$, $P < 0.001$), Dm_{CO} ($r^2 = 0.402$, $P < 0.001$), and V_C ($r^2 = 0.584$, $P < 0.001$) (Figure 3). Similarly, there was a significant positive relationship between $\dot{V}O_{2max}$ and the rest to end-exercise change (Δ) in DLCO ($r^2 = 0.502$, $P < 0.001$), Dm_{CO} ($r^2 = 0.412$, $P < 0.001$), and V_C ($r^2 = 0.273$, $P = 0.003$) (Figure 4). Finally, there was a positive relationship between $\dot{V}O_{2max}$ and the DLCO-$\dot{Q}$ slope in response to exercise ($r^2 = 0.152$, $P = 0.030$); the relationship between $\dot{V}O_{2max}$ and the Dm_{CO}-$\dot{Q}$ and V_C-$\dot{Q}$ slope in response to exercise was not statistically significant (Figure 5). Together, these data suggest that a higher baseline DLCO, Dm_{CO}, and V_C, as well as a larger increase these values in response to exercise are associated with greater maximal aerobic capacity in young and older adults regardless of cardiopulmonary fitness level.

DISCUSSION

Major Findings: comparison to previous findings

In the present study, we characterized the lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C) response to discontinuous incremental exercise in healthy, aerobically-trained older adults relative to their age-matched less fit counterparts as well as younger adults. We hypothesized that healthy older adults (~65 years old) with a high cardiorespiratory fitness level ($\dot{V}O_{2max}$ ~162% of age-predicted) would encroach upon their maximal ability to expand the pulmonary capillary network during severe cycle exercise, as evidenced by a limit in DLCO, Dm_{CO}, and V_C near maximal end-exercise. The main findings were: 1) healthy aging was associated with a decrease in DLCO, $Dm_{CO,}$ and V_C at rest and during near maximal exercise (Table 2); 2) better maintained cardiorespiratory fitness was associated with greater DLCO, $Dm_{CO,}$ and V_C during near-maximal exercise in older adults (Table 2); 3) there was no plateau (i.e. a limitation) in the DLCO, Vc and Dm_{CO} response to exercise in any subject group **r**egardless of age or cardiorespiratory fitness level (Figure 1); 4) throughout exercise, DLCO, Dm_{CO}, and V_C were systematically lower in older individuals regardless of fitness, and DLCO was systematically higher with maintained cardiorespiratory fitness regardless of age; and 5) the slope, or rate of rise, of the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$, and V_C-$\dot{Q}$ relationship from rest to end-exercise was not different between subjects regardless of age or cardiorespiratory fitness level (Figure 2).

Our findings are confirmatory that healthy aging is associated with a progressive decline in resting DLCO (1, 6, 9, 11, 15, 33, 34). For example, Guénard and Marthan demonstrated that both DLCO and DLCO relative to minute ventilation (DLCO/$\dot{V}_E$) are negatively correlated with age according to the equations DLCO = 126 – 0.90 × age and DLCO/$\dot{V}_E$ = 13.5 – 0.85 × age, respectively (15). Likely contributors to this age-related reduction in DLCO are a decrease in the number of capillaries perfusing the lungs with a reduction in Vc (6, 7, 12), as well as a decrease in alveolar surface area with a consequent reduction in membrane diffusing capacity (6, 12). Our findings are also in agreement with previous reports that exercise is associated with a marked, mostly linear, increase in DLCO, Vc and Dm_{CO} in healthy adults (16, 18, 27, 34). This increase, at least in part, reflects expansion of the highly compliant pulmonary capillary network secondary to the elevation in $\dot{Q}$ and pulmonary perfusion pressure that occurs with exercise.

To date, however, there is a relative paucity of data regarding the effect of healthy aging on the lung diffusing capacity response to exercise. In a limited number of subjects ($n = 12$) of a broad age range (23 to 79 years), Tamhane et al. reported that DLCO, Dm_{CO} and lung diffusing capacity for nitric oxide (DLNO) increased linearly with $\dot{Q}$ from rest to exercise regardless of age (34). However, while the authors found that age was a significant determinant of *resting* DLNO, no such analysis was done examining the influence of age on the lung diffusing capacity response to *exercise*. Additionally, we are unaware of any previous study that has examined the influence of healthy aging *plus* maintained cardiorespiratory fitness on lung diffusing capacity during exercise. In combination, the present findings suggest that despite the age-associated deterioration in the structure and function of the pulmonary circulation, expansion of the pulmonary capillary network does not become limited during severe exercise (i.e. there is still a reserve to recruit the pulmonary vasculature) in healthy individuals regardless of age or cardiorespiratory fitness level. In addition, we suggest that maximal oxygen consumption ($\dot{V}O_{2max}$) is positively related DLCO, Dm_{CO}, and V_C, both at rest and in response to exercise, across all ages and cardiorespiratory fitness levels.

Lung Diffusing Capacity Response to Exercise: effect of age and cardiorespiratory fitness

Exercise is associated with an increase in cardiac output and pulmonary perfusion pressure that causes both recruitment of under-perfused pulmonary capillaries and distension of already perfused pulmonary blood vessels, as evidenced by an increase in DLCO, Dm_{CO}, and V_C (16, 18, 22, 23, 36). The resulting increase in pulmonary blood flow and marked expansion of the highly compliant pulmonary vasculature acts to increase the alveolar-capillary surface area available for effective gas exchange.

Healthy aging is associated with a deterioration in the structure and function of the pulmonary vasculature that is characterized by an increase in pulmonary vascular stiffness, pulmonary vascular pressures and pulmonary vascular resistance (20, 24, 28), as well as reductions in resting V_C and Dm_{CO} (1, 9, 12, 15). It has been shown, however, that despite these age-related changes DLCO does not become limited during heavy to maximal exercise in the older adult of average cardiorespiratory fitness (34). This is likely because the age-associated decline in the maximal metabolic demand of exercise occurs at rate equal to or greater than the deleterious changes in the pulmonary circulation (14, 19, 37). However, it is conceivable that healthy older individuals who have maintained cardiorespiratory fitness, and thus metabolic demand, at an exceedingly high level may experience a limit in the capacity of the pulmonary vasculature to expand relative to the demand for pulmonary blood flow during exercise.

In the present study, we found that DLCO, Dm_{CO}, and V_C increased steadily with increasing cardiac output ($\dot{Q}$), with no evidence of a plateau in these variables in both young and old subjects, regardless of cardiorespiratory fitness level (Figure 1). Moreover, the slope of the DLCO-$\dot{Q}$, Dm_{CO}-$\dot{Q}$, and V_C-$\dot{Q}$ relationship from rest to end-exercise was not different between Young, Young Highly-Fit, Old and Old Highly-Fit subjects (Figure 2). This suggests that the recruitment and/or distension of the pulmonary capillaries and thus expansion of alveolar-capillary surface area remain adequate for the metabolic demand of exercise regardless of age and cardiorespiratory fitness level. In agreement with previous findings, DLCO, Dm_{CO}, and V_C

at rest and during exercise were decreased with advanced age (1, 6, 11, 12, 15, 33, 34). Interestingly, however, we also found that DLCO, Dm_{CO}, and V_C were greater during near-maximal exercise in highly fit older individuals compared to their less fit counterparts (Figure 1). Additionally, regardless of age, maintained cardiorespiratory fitness was associated with a significantly greater DLCO from rest through to maximal exercise.

It has been suggested previously that exercise training has no effect on DLCO and its components parts (8, 30). For example, Reuschlein et al. reported no change in DLCO or Vc at rest and during submaximal exercise from before to after 5 months of combined strength and endurance training (30). By contrast, it has been shown that cardiac and great vessel function is better in older, habitually active, fit adults relative to their more sedentary counterparts. Indeed, Arbab-Zadeh et al. reported that prolonged, sustained endurance training improves stroke volume for a giving filling pressure and preserves left ventricular compliance in aged adults such that the capillary wedge pressure-LV end diastolic volume curve in Masters athletes was indistinguishable from that of young, sedentary control subjects (2). In addition, central arterial compliance is 20-35% greater in endurance-trained middle-aged and older men compared to their less active age matched counterparts (35). Furthermore, 3 months of aerobic exercise training increases central arterial compliance (~25%) in middle-aged men (~53 years) to a level similar to that observed in older endurance-trained men (35), possibly due to modified cross-linking of "stretched" collagen fibres and/or a reduction in the chronic suppressive influence exerted by sympathetic adrenergic tone (4, 35). Theoretically, it is entirely possible that habitual physical activity may also better preserve the function of the pulmonary circulation, attenuating the age-related decline in pulmonary vascular distensibility (28) and compliance, allowing for greater expansion of the pulmonary capillary network with increasing cardiac output, and thus facilitating a greater DLCO, Dm_{CO}, and V_C response to exercise in highly fit older individuals compared to their less fit counterparts. However, whether preservation of cardiorespiratory fitness does indeed ‘protect’ against the age-related deterioration of the pulmonary circulation cannot be deduced from the present findings, and as such remains purely speculative.

Expansion of the Pulmonary Capillary Network during Exercise: Recruitment vs. Distension

The mechanism by which the pulmonary vasculature expands to accept increased blood flow and increase effective alveolar-capillary surface area during exercise is also of interest. In the healthy pulmonary circulation, vessel distensibility is largely independent of vessel size, location and animal species (21), but appears to be lower in older adults relative to their younger counterparts (28). Assessing the change in the ratio between DLNO and DLCO during exercise may allow insight into whether pulmonary vascular volume increases due to recruitment or distension of the pulmonary capillaries (13, 23, 27). Specifically, a fall in the DLNO/DLCO ratio with exercise is thought to indicate a disproportionate rise in V_C relative to Dm_{CO}, which in turn suggests predominant pulmonary capillary distension over recruitment (13). In the present study, all groups with the exception of the Young Highly-Fit (P = 0.051) demonstrated a significant reduction in the DLNO/DLCO ratio from rest to end-exercise (Figure 3). This finding suggests that despite the previously reported decay in pulmonary vascular distensibility associated with healthy aging, increased blood flow through the pulmonary circulation during exercise is at least partially achieved via distension of the pulmonary capillaries in old as well as young individuals.

Relationship between Lung Diffusing Capacity Response to Exercise and $\dot{V}O_{2max}$

The importance of pulmonary vascular hemodynamics in determining $\dot{V}O_{2max}$ in both health and disease is well known (10, 23). Fujii et al. reported that slope of the mean pulmonary artery pressure-to-cardiac output relationship was negatively correlated with $\dot{V}O_{2max}$ in COPD patients (10). That is, a more compliant pulmonary vasculature, or one that experiences lower vascular pressures, allows for greater maximal aerobic capacity in healthy individuals as well as diseased patients.

In this study, we did not examine pulmonary vascular pressures in response to exercise. Conceptually, however, a greater increase lung diffusing capacity relative to cardiac output in response to exercise could be indicative of a greater ability of the pulmonary vasculature to expand and accept the increase in pulmonary blood flow whilst minimizing the increase in pulmonary vascular pressure. That is, it is conceivable that a steeper DLCO-$\dot{Q}$ slope during exercise is reflective of a more compliant pulmonary vascular network. In support of this notion, we found that DLCO-$\dot{Q}$ was positively correlated to $\dot{V}O_{2max}$ across all subjects (Figure 6). In addition, resting values of DLCO, Dm_{CO}, and V_C, as well as the absolute change in these variables from rest to maximal exercise, are positively correlated with $\dot{V}O_{2max}$ across all subjects (Figures 3 and 4). That expansion of the pulmonary vasculature appears not to reach a maximum during exercise (Figure 1) likely serves to allow an increase in the alveolar-capillary surface area for effective gas exchange whilst minimizing the exercise-induced increase in pulmonary arterial pressure, pulmonary vascular resistance and right-ventricular afterload, and thus allowing a greater maximum cardiac output and maximum oxygen consumption in healthy adults regardless of age and cardiorespiratory fitness (22, 23, 27).

Technical Considerations

Effect of acetylene solubility upon calculation of cardiac output

A concern with the use of acetylene uptake in the noninvasive determination of $\dot{Q}$ is that an assumption, rather than direct assessment, of acetylene solubility (λ) in individual subjects can result in considerable error in the measurement of $\dot{Q}$. For example, Barker et al. suggested that failure to account for inter-subject variability in λ can lead to substantial underestimation (up to 27%) or overestimation (up to 13%) of $\dot{Q}$ in young healthy adults (3). In the present study, we did not measure, and subsequently account for, between-subject differences in λ upon the calculation of $\dot{Q}$. However, while any such error may have negatively impacted the *accuracy* of our measure of $\dot{Q}$, we are able to demonstrate good within-session within-subject *reliability* of our acetylene derived $\dot{Q}$ measure at rest (CV; coefficient of variation = 8.5%). This is comparable with the CV reported previously by our group for open-circuit acetylene wash-in estimated $\dot{Q}$ (17). In addition, although not assessed in the present study, it is likely that the variability in our measure of $\dot{Q}$ *improved to* ~4% during exercise (17). As such, based on the relatively low CV (i.e. good reproducibility) along with the repeated measures design of our study, we are confident that our findings are not greatly affected by any underlying variability in λ between individual subjects.

CONCLUSION

In conclusion, DLCO, Dm_{CO}, and V_C are decreased with age and increased with greater cardiorespiratory fitness in older individuals near maximal exercise. Interestingly, there is a systematic increase in DLCO throughout exercise with maintained cardiorespiratory fitness, regardless of age. Older highly fit individuals do not appear to encroach upon a pulmonary vascular limit, and expansion of the pulmonary capillary network is able to adequately increase DLCO, Dm_{CO}, and V_C, even during heavy exercise. Furthermore, the response (i.e., rate of increase) of DLCO, Dm_{CO}, and V_C to exercise is not altered by age and/or cardiorespiratory fitness level. Future studies should incorporate measures of pulmonary vascular pressures in order to elucidate the relationship between increases in lung diffusing capacity and the pulmonary vascular response to exercise.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Josh O'Malley for his work as a research technologist during these studies. KEC is supported by Mayo Graduate School and National Heart, Lung, And Blood Institute of the National Institutes of Health (NIH) grant F31HL131076. BJT is supported by American Heart Association grant AHA12POST12070084. This study was funded by NIH grant HL71478.

REFERENCES

1. **Al Dandachi G, Londner C, Caumont-Prim A, Plantier L, Chevalier-Bidaud B, Toussaint JF, Desgorces FD, and Delclaux C**. Ageing and endurance training effects on quantity and quality of pulmonary vascular bed in healthy men. *Respir Res* 15: 8, 2014.

2. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD**. Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.

3. **Barker RC, Hopkins SR, Kellogg N, Olfert IM, Brutsaert TD, Gavin TP, Entin PL, Rice AJ, and Wagner PD**. Measurement of cardiac output during exercise by open-circuit acetylene uptake. *J Appl Physiol (1985)* 87: 1506-1512, 1999.

4. **Bruel A, Ortoft G, and Oxlund H**. Inhibition of cross-links in collagen is associated with reduced stiffness of the aorta in young rats. *Atherosclerosis* 140: 135-145, 1998.

5. **Ceridon ML, Beck KC, Olson TP, Bilezikian JA, and Johnson BD**. Calculating alveolar capillary conductance and pulmonary capillary blood volume: comparing the multiple- and single-inspired oxygen tension methods. *J Appl Physiol (1985)* 109: 643-653, 2010.

6. **Chang SC, Chang HI, Liu SY, Shiao GM, and Perng RP**. Effects of body position and age on membrane diffusing capacity and pulmonary capillary blood volume. *Chest* 102: 139-142, 1992.

7. **Crapo RO, Morris AH, and Gardner RM**. Reference values for pulmonary tissue volume, membrane diffusing capacity, and pulmonary capillary blood volume. *Bull Eur Physiopathol Respir* 18: 893-899, 1982.

8. **Dempsey JA, Gledhill N, Reddan WG, Forster HV, Hanson PG, and Claremont AD**. Pulmonary adaptation to exercise: effects of exercise type and duration, chronic hypoxia and physical training. *Ann N Y Acad Sci* 301: 243-261, 1977.

9. **Ehrsam RE, Perruchoud A, Oberholzer M, Burkart F, and Herzog H**. Influence of age on pulmonary haemodynamics at rest and during supine exercise. *Clin Sci (Lond)* 65: 653-660, 1983.

10. **Fujii T, Kurihara N, Fujimoto S, Hirata K, and Yoshikawa J**. Role of pulmonary vascular disorder in determining exercise capacity in patients with severe chronic obstructive pulmonary disease. *Clin Physiol* 16: 521-533, 1996.

11. **Garcia-Rio F, Dorgham A, Galera R, Casitas R, Martinez E, Alvarez-Sala R, and Pino JM**. Prediction equations for single-breath diffusing capacity in subjects aged 65 to 85 years. *Chest* 142: 175-184, 2012.

12. **Georges R, Saumon G, and Loiseau A**. The relationship of age to pulmonary membrane conductance and capillary blood volume. *Am Rev Respir Dis* 117: 1069-1078, 1978.

13. **Glenet SN, De Bisschop C, Vargas F, and Guenard HJ**. Deciphering the nitric oxide to carbon monoxide lung transfer ratio: physiological implications. *J Physiol* 582: 767-775, 2007.

14. **Goldspink DF**. Ageing and activity: their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. *Ergonomics* 48: 1334-1351, 2005.

15. **Guenard H, and Marthan R**. Pulmonary gas exchange in elderly subjects. *Eur Respir J* 9: 2573-2577, 1996.

16. **Hsia CC, McBrayer DG, and Ramanathan M**. Reference values of pulmonary diffusing capacity during exercise by a rebreathing technique. *Am J Respir Crit Care Med* 152: 658-665, 1995.

17. **Johnson BD, Beck KC, Proctor DN, Miller J, Dietz NM, and Joyner MJ**. Cardiac output during exercise by the open circuit acetylene washin method: comparison with direct Fick. *J Appl Physiol (1985)* 88: 1650-1658, 2000.

18. **Johnson RL, Jr., Spicer WS, Bishop JM, and Forster RE**. Pulmonary capillary blood volume, flow and diffusing capacity during exercise. *J Appl Physiol* 15: 893-902, 1960.

19. **Kasch FW, Boyer JL, Van Camp S, Nettl F, Verity LS, and Wallace JP**. Cardiovascular changes with age and exercise. A 28-year longitudinal study. *Scand J Med Sci Sports* 5: 147-151, 1995.

20. **Kovacs G, Berghold A, Scheidl S, and Olschewski H**. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 34: 888-894, 2009.

21. **Krenz GS, and Dawson CA**. Flow and pressure distributions in vascular networks consisting of distensible vessels. *Am J Physiol Heart Circ Physiol* 284: H2192-2203, 2003.

22. **La Gerche A, MacIsaac AI, Burns AT, Mooney DJ, Inder WJ, Voigt JU, Heidbuchel H, and Prior DL**. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. *J Appl Physiol (1985)* 109: 1307-1317, 2010.

23. **Lalande S, Yerly P, Faoro V, and Naeije R**. Pulmonary vascular distensibility predicts aerobic capacity in healthy individuals. *J Physiol* 590: 4279-4288, 2012.

24. **Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, and Redfield MM**. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation* 119: 2663-2670, 2009.

25. **Lewis GD, Bossone E, Naeije R, Grunig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, and Rubenfire M**. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 128: 1470-1479, 2013.

26. **Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, and Force AET**. Standardisation of spirometry. *Eur Respir J* 26: 319-338, 2005.

27. **Pavelescu A, Faoro V, Guenard H, de Bisschop C, Martinot JB, Melot C, and Naeije R**. Pulmonary vascular reserve and exercise capacity at sea level and at high altitude. *High Alt Med Biol* 14: 19-26, 2013.

28. **Reeves JT, Linehan JH, and Stenmark KR**. Distensibility of the normal human lung circulation during exercise. *Am J Physiol Lung Cell Mol Physiol* 288: L419-425, 2005.

29. **Reeves RB, and Park HK**. CO uptake kinetics of red cells and CO diffusing capacity. *Respir Physiol* 88: 1-21, 1992.

30. **Reuschlein PS, Reddan WG, Burpee J, Gee JB, and Rankin J**. Effect of physical training on the pulmonary diffusing capacity during submaximal work. *J Appl Physiol* 24: 152-158, 1968.

31. **Roughton FJ, and Forster RE**. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J Appl Physiol* 11: 290-302, 1957.

32. **Sackner MA, Greeneltch D, Heiman MS, Epstein S, and Atkins** N. Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measured by a rebreathing technique. *Am Rev Respir Dis* 111: 157-165, 1975.

33. **Stam H, Hrachovina V, Stijnen T, and Versprille** A. Diffusing capacity dependent on lung volume and age in normal subjects. *J Appl Physiol (1985)* 76: 2356-2363, 1994.

34. **Tamhane RM, Johnson RL, Jr., and Hsia CC**. Pulmonary membrane diffusing capacity and capillary blood volume measured during exercise from nitric oxide uptake. *Chest* 120: 1850-1856, 2001.

35. **Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, and Seals DR**. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 102: 1270-1275, 2000.

36. **Taylor BJ, Carlson AR, Miller AD, and Johnson BD**. Exercise-induced interstitial pulmonary edema at sea-level in young and old healthy humans. *Respir Physiol Neurobiol* 191: 17-25, 2014.

37. **Trappe SW, Costill DL, Vukovich MD, Jones J, and Melham T**. Aging among elite distance runners: a 22-yr longitudinal study. *J Appl Physiol (1985)* 80: 285-290, 1996.

FIGURE LEGENDS

Fig. 1 Group mean values of lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C) as a function of cardiac output ($\dot{Q}$) during exercise. DLCO, Dm_{CO}, and V_C increase relatively linearly from rest to exercise at 90% W_{peak} in all groups. Error bars denote standard deviation from the mean. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Fig. 2 Individual values of lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C) as a function of cardiac output ($\dot{Q}$) during exercise. The mean and standard deviation of the slope of the lung diffusing capacity-cardiac output relationship is given for each group; there was no significant difference in slope between groups for any measure. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Fig. 3 Individual values of $\dot{V}O_{2max}$ as a function of resting values of lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C). A linear regression was fit to all data points for each measure. $\dot{V}O_{2max}$ is positively correlated with resting values of DLCO, Dm_{CO}, and V_C. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Fig. 4 Individual values of $\dot{V}O_{2max}$ as a function of the absolute change (Δ) in values of lung diffusing capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}), and pulmonary-capillary blood volume (V_C) from rest to exercise at 90% of W_{peak}. A linear regression was fit to all data points for each measure. $\dot{V}O_{2max}$ is positively correlated with the absolute change in values of DLCO, Dm_{CO}, and V_C from rest to exercise at 90% of W_{peak}. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Fig. 5 $\dot{V}O_{2max}$ as a function of the lung diffusing capacity-cardiac output slope for each individual subject (from Figure 2). A linear regression was fit to all data points for each measure. $\dot{V}O_{2max}$ is positively correlated with the DLCO-$\dot{Q}$ slope; $\dot{V}O_{2max}$ is not significantly correlated with the Dm_{CO}-$\dot{Q}$ or V_C-$\dot{Q}$ slopes. DLCO, lung diffusing capacity for carbon monoxide; Dm_{CO}, alveolar-capillary membrane conductance; V_C, pulmonary-capillary blood volume. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Fig. 6 Group mean values of the ratio of lung diffusing capacity for nitric oxide to carbon monoxide (DLNO/DLCO) as a function of cardiac output ($\dot{Q}$) during exercise. DLNO/DLCO falls from rest to exercise at 90% W_{peak} in YNGm, OLDm, and OLDh. Error bars denote standard deviation from the mean. Closed circles = Young Highly-Fit (HF); Open circles = Young; Closed squares = Old Highly-Fit (HF); Open squares = Old.

Table 1 Subject characteristics

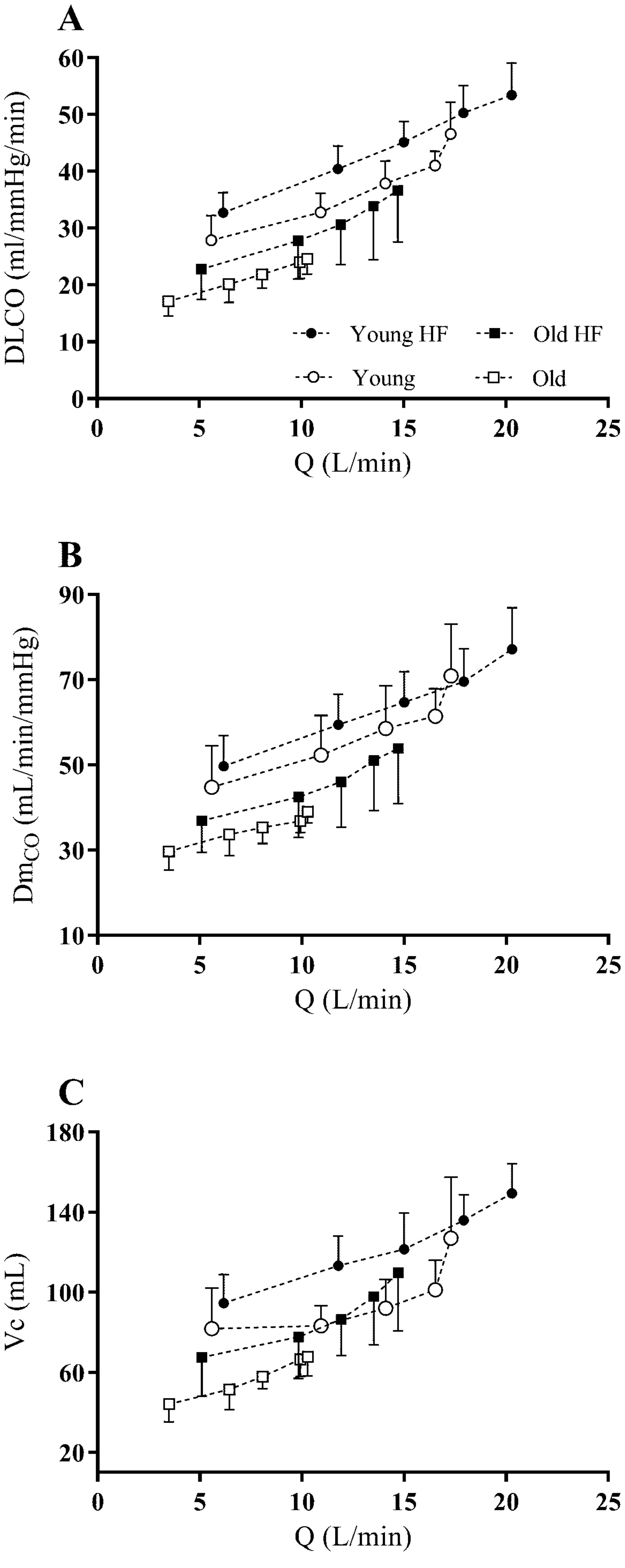
	Young	Young Highly-Fit	Old	Old Highly-Fit
Age, y	27 ± 3	27 ± 3	69 ± 5*†	65 ± 5*†
N (female)	9 (0)	7 (0)	7 (1)	8 (1)
Height, cm	178 ± 4	178 ± 4	173 ± 4	176 ± 7
Mass, kg	78.0 ± 5.8	72.5 ± 6.8	73.6 ± 8.8	75.4 ± 9.0
BMI, kg/m^2	24.7 ± 2.0	22.8 ± 2.1	24.8 ± 3.4	24.5 ± 2.2
W_{peak}, W	269 ± 43	338 ± 28*	157 ± 26*†	239 ± 29†#
$\dot{V}O_{2max}$, ml/min	3519 ± 449	4577 ± 419*	2050 ± 381*†	3140 ± 368†#
$\dot{V}O_{2max}$, ml/kg/min	45.3 ± 6.5	63.4 ± 6.0*	28.2 ± 6.4*†	41.8 ± 3.8†#
% Pred. $\dot{V}O_{2max}$	110 ± 18	147 ± 8*	116 ± 13†	162 ± 18*#
FEV_1/FVC	82 ± 6	80 ± 4	78 ± 5	74 ± 5*
% pred.	99 ± 8	96 ± 5	105 ± 7	98 ± 5
FEV_1, L	4.8 ± 0.4	5.0 ± 0.8	3.2 ± 0.3*†	3.7 ± 0.9*†
% pred.	106 ± 9	110 ± 13	110 ± 12	112 ± 21
FVC, L	5.9 ± 0.7	6.3 ± 0.9	4.2 ± 0.4*†	5.0 ± 1.2†
% pred.	106 ± 10	114 ± 12	104 ± 11	114 ± 21
$FEF_{25\text{-}75}$, L	4.6 ± 0.7	4.5 ± 1.1	2.9 ± 0.7*†	2.8 ± 1.0*†
% pred.	100 ± 19	97 ± 21	126 ± 32	104 ± 30
TLC, L	7.7 ± 0.9	8.0 ± 1.3	6.9 ± 1.0*†	8.2 ± 1.2*†
% pred.	112 ± 10	116 ± 16	106 ± 12	121 ± 11

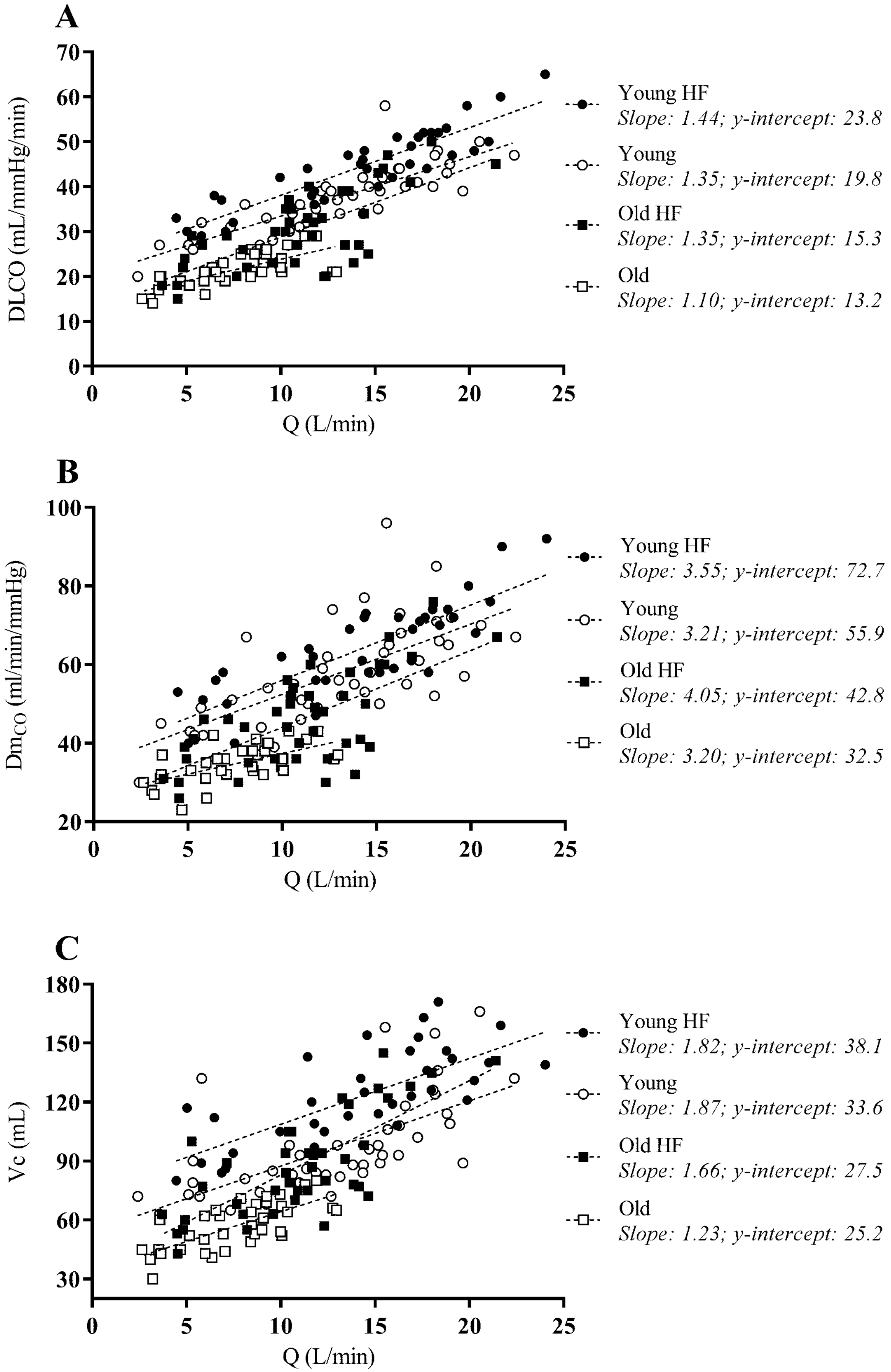
Values are reported as mean ± SD. BMI, body mass index; W_{peak}, peak power output during maximal exercise test; $\dot{V}O_{2max}$, maximal oxygen consumption; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; $FEF_{25\text{-}75}$, average forced expiratory volume during middle portion of FVC; TLC, total lung capacity. Significance set at $P < 0.05$; *significantly different vs. Young, †significantly different vs. Young Highly-Fit, $^\#$significantly different vs. Old.

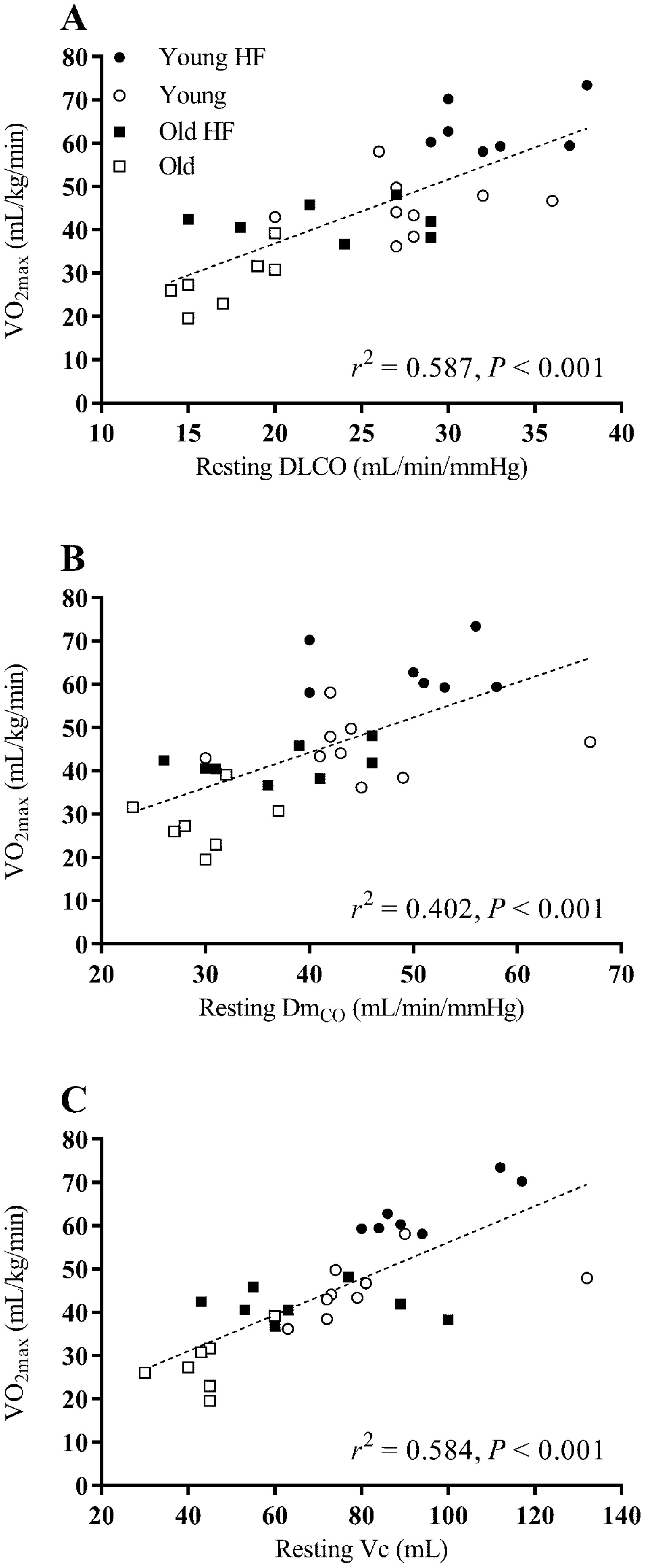
Table 2 Lung diffusing capacity and cardiac output

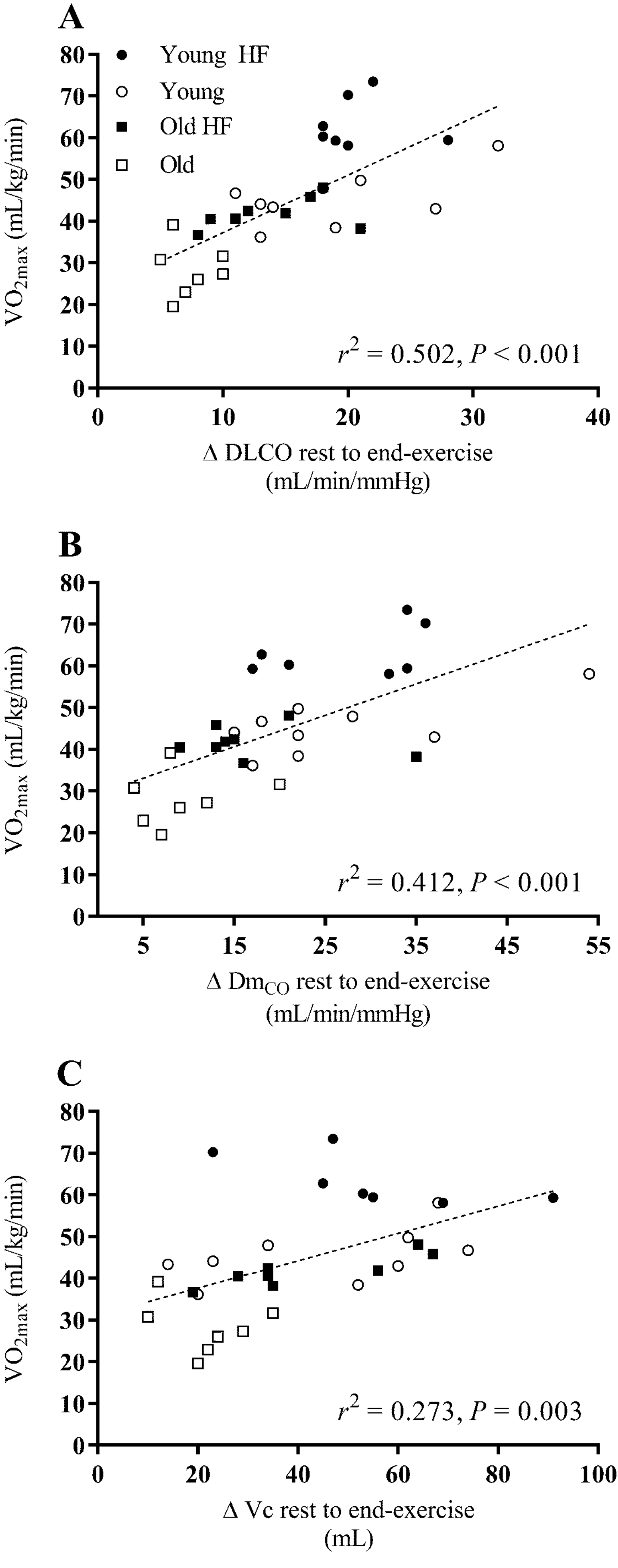
	Young	**Young Highly-Fit**	**Old**	**Old Highly-Fit**	**Young**	**Young Highly-Fit**	**Old**	**Old Highly-Fit**
	Rest				*Exercise at 90% of W_{peak}*			
DLCO, ml/min/mmHg	28 ± 4	33 ± 4	17 ± 3*†	23 ± 5†	47 ± 6	53 ± 7	25 ± 3*†	37 ± 10*†#
DLNO, ml/min/mmHg	101 ± 22	112 ± 16	67 ± 10*†	85 ± 18†	153 ± 16	171 ± 18	87 ± 7*†	122 ± 30*†#
DLNO/DLCO, unitless	3.6 ± 0.4	3.4 ± 0.4	4.0 ± 0.6	3.8 ± 0.4	3.3 ± 0.3	3.2 ± 0.2	3.6 ± 0.2	3.3 ± 0.2
Dm_{CO}, ml/min/mmHg	45 ± 10	50 ± 7	30 ± 4*†	37 ± 8†	71 ± 12	77 ± 10	39 ± 3*†	54 ± 13*†#
V_C, ml	82 ± 20	95 ± 14	44 ± 9*†	68 ± 20†	127 ± 30	149 ± 15	66 ± 10*†	110 ± 29†#
$\dot{Q}$, L/min	5.6 ± 2.0	6.2 ± 1.1	3.5 ± 0.6*†	5.1 ± 1.0	17.3 ± 3.1	20.3 ± 2.2	10.3 ± 1.6*†	14.7 ± 3.5†#

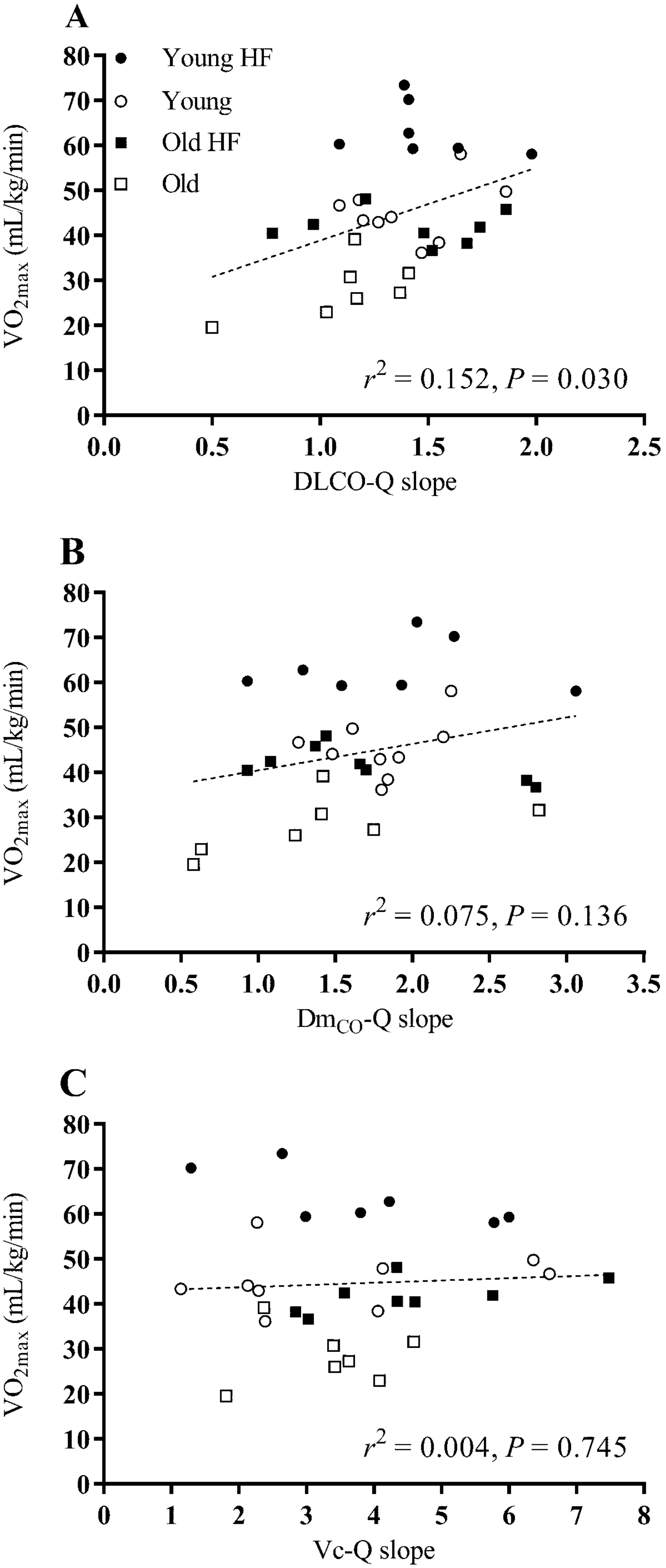
Values are reported as mean ± SD. DLCO, lung diffusing capacity for carbon monoxide; DLNO, lung diffusing capacity for nitric oxide; Dm_{CO}, alveolar-capillary membrane conductance; V_C, pulmonary-capillary blood volume; $\dot{Q}$, cardiac output. Significance set at $P < 0.05$; *significantly different vs. Young, †significantly different vs. Young Highly-Fit, #significantly different vs. Old.

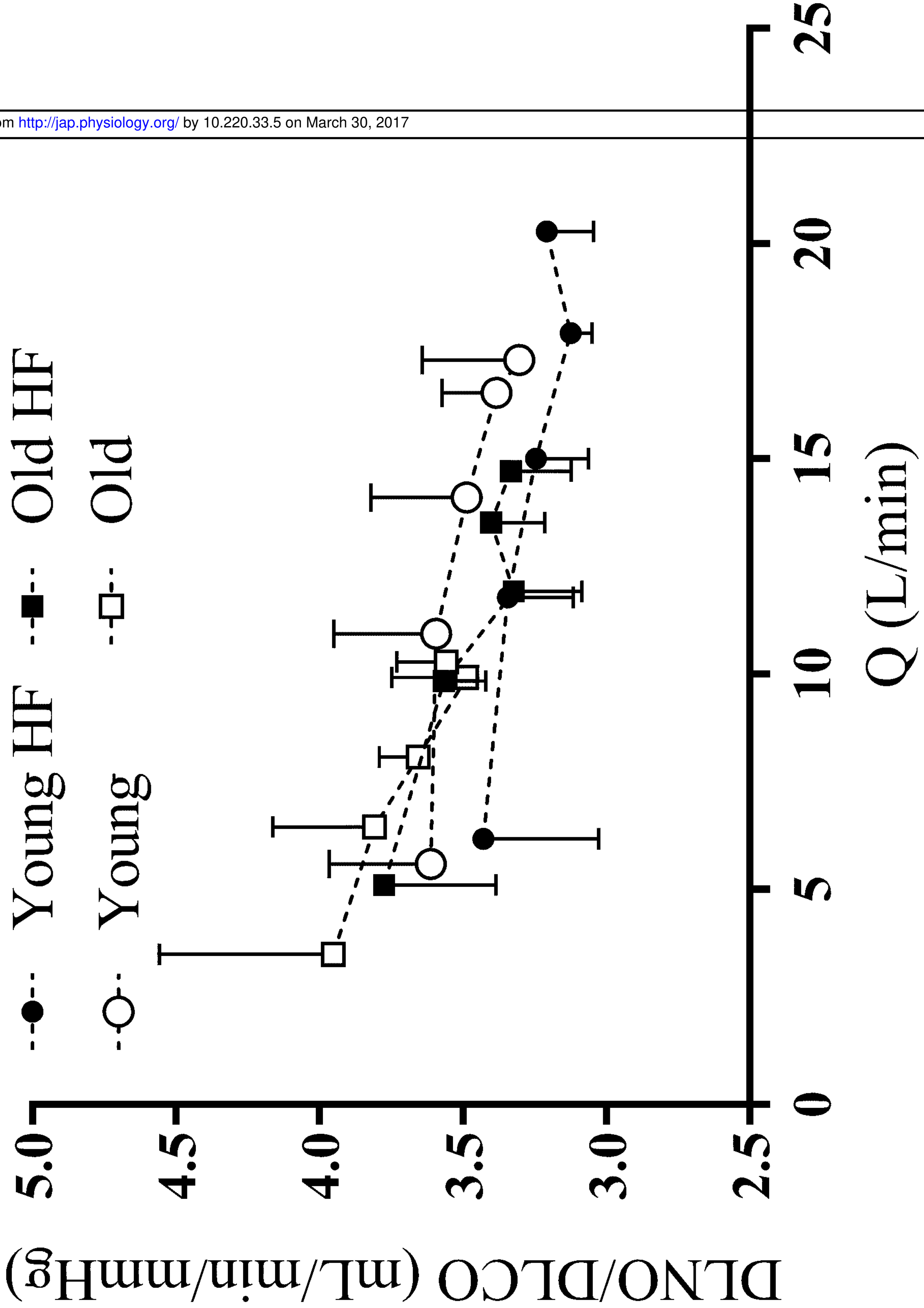

A
DLCO (ml/mmHg/min)
60
50
40
30
20
10
0
Young HF
Old HF
Young
Old
0
5
10
15
20
25
Q (L/min)
B
Dm$_{CO}$ (mL/min/mmHg)
90
70
50
30
10
0
5
10
15
20
25
Q (L/min)
C
Vc (mL)
180
140
100
60
20
0
5
10
15
20
25
Q (L/min)


A
DLCO (mL/mmHg/min)
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Q (L/min)
Young HF
Slope: 1.44; y-intercept: 23.8
Young
Slope: 1.35; y-intercept: 19.8
Old HF
Slope: 1.35; y-intercept: 15.3
Old
Slope: 1.10; y-intercept: 13.2
B
Dm$_{CO}$ (ml/min/mmHg)
100
80
60
40
20
0
5
10
15
20
25
Q (L/min)
Young HF
Slope: 3.55; y-intercept: 72.7
Young
Slope: 3.21; y-intercept: 55.9
Old HF
Slope: 4.05; y-intercept: 42.8
Old
Slope: 3.20; y-intercept: 32.5
C
Vc (mL)
180
150
120
90
60
30
0
5
10
15
20
25
Q (L/min)
Young HF
Slope: 1.82; y-intercept: 38.1
Young
Slope: 1.87; y-intercept: 33.6
Old HF
Slope: 1.66; y-intercept: 27.5
Old
Slope: 1.23; y-intercept: 25.2


A
Young HF
Young
Old HF
Old
VO2max (mL/kg/min)
0
10
20
30
40
50
60
70
80
10
15
20
25
30
35
40
Resting DLCO (mL/min/mmHg)
r2 = 0.587, P < 0.001
B
VO2max (mL/kg/min)
0
10
20
30
40
50
60
70
80
20
30
40
50
60
70
Resting DmCO (mL/min/mmHg)
r2 = 0.402, P < 0.001
C
VO2max (mL/kg/min)
0
10
20
30
40
50
60
70
80
20
40
60
80
100
120
140
Resting Vc (mL)
r2 = 0.584, P < 0.001


A
● Young HF
○ Young
■ Old HF
□ Old
VO$_{2max}$ (mL/kg/min)
0
10
20
30
40
50
60
70
80
$r^2 = 0.502$, $P < 0.001$
0
10
20
30
40
Δ DLCO rest to end-exercise
(mL/min/mmHg)
B
VO$_{2max}$ (mL/kg/min)
0
10
20
30
40
50
60
70
80
$r^2 = 0.412$, $P < 0.001$
5
15
25
35
45
55
Δ Dm$_{CO}$ rest to end-exercise
(mL/min/mmHg)
C
VO$_{2max}$ (mL/kg/min)
0
10
20
30
40
50
60
70
80
$r^2 = 0.273$, $P = 0.003$
0
20
40
60
80
100
Δ Vc rest to end-exercise
(mL)


A
Young HF
Young
Old HF
Old
VO2max (mL/kg/min)
0
10
20
30
40
50
60
70
80
0.0
0.5
1.0
1.5
2.0
2.5
DLCO-Q slope
r2 = 0.152, P = 0.030
B
VO2max (mL/kg/min)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
DmCO-Q slope
r2 = 0.075, P = 0.136
C
VO2max (mL/kg/min)
0
1
2
3
4
5
6
7
8
Vc-Q slope
r2 = 0.004, P = 0.745


DLNO/DLCO (mL/min/mmHg)
5.0
4.5
4.0
3.5
3.0
2.5
0
5
10
15
20
25
Q (L/min)
Young HF
Old HF
Young
Old