# Exercise Stroke Volume in Adult Cystic Fibrosis: A Comparison of Acetylene Pulmonary Uptake and Oxygen Pulse

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine
Volume 12: 1–9

DOI: 10.1177/1179548418790564

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**ABSTRACT:** Cardiac hemodynamic assessment during cardiopulmonary exercise testing (CPET) is proposed to play an important role in the clinical evaluation of individuals with cystic fibrosis (CF). Cardiac catheterization is not practical for routine clinical CPET. Use of oxygen pulse ($O_2$pulse) as a noninvasive estimate of stroke volume (SV) has not been validated in CF. This study tested the hypothesis that peak exercise $O_2$pulse is a valid estimate of SV in CF. Measurements of SV via the acetylene rebreathe technique were acquired at baseline and peak exercise in 17 mild-to-moderate severity adult CF and 25 age-matched healthy adults. We calculated $O_2\text{pulse} = \dot{V}O_2 \cdot HR^{-1}$. Baseline relationships between SV and $O_2$pulse were significant in CF ($r = .80$) and controls ($r = .40$), persisting to peak exercise in CF ($r = .63$) and controls ($r = .73$). The standard error of estimate for $O_2$pulse-predicted SV with respect to measured SV was similar at baseline (14.1 vs 20.1 mL) and peak exercise (18.2 vs 13.9 mL) for CF and controls, respectively. These data suggest that peak exercise $O_2$pulse is a valid estimate of SV in CF. The ability to noninvasively estimate SV via $O_2$pulse during routine clinical CPET can be used to improve test interpretation and advance our understanding of the impact cardiac dysfunction has on exercise intolerance in CF.

**KEYWORDS:** Cardiac output, peak $VO_2$, cardiopulmonary exercise test, pulmonary function, exercise capacity

**RECEIVED:** September 22, 2017. **ACCEPTED:** June 28, 2018.

**TYPE:** Original Research

**FUNDING:** The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This research was supported by the National Institutes of Health (HL108962 to EMS).

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Introduction

Individuals with cystic fibrosis (CF) demonstrate a lethal cascade of events involving sodium (Na+) and chloride ($Cl^-$) ion channel dysregulation underpinned by mutations of the gene encoding the CF transmembrane regulator (CFTR) protein.[1,2] Closely following is a hallmark airway obstruction phenotype.[1–3] These pulmonary-centric features of CF are potent contributors to impaired peak oxygen uptake ($\dot{V}O_{2peak}$) and exercise intolerance.[3,4]

By contrast, there is a separate line of evidence from studies of CF involving cardiopulmonary exercise testing (CPET) and/or exercise training suggesting this disease also affects cardiac function.[5–10] Individuals with CF have been observed to demonstrate an impaired cardiac hemodynamic response to increased metabolic demand, which, in part, precipitates exercise intolerance and contributes to poor prognosis.[5–10] Unfortunately, however, it has been a challenge to routinely test the exact role impaired exercise cardiac hemodynamics play in CF. Clinical exercise physiology research involving individuals with CF and invasive measurement of cardiac output ($\dot{Q}$) and stroke volume (SV) is not practical.

Although noninvasive echocardiography is an established clinical diagnostic tool useful for assessing exercise cardiac hemodynamics, it is also physiologically relevant that the recommended body position to acquire images for the derivation of $\dot{Q}$ and SV is supine.[11] By contrast, optimal CPET posture to acquire key prognostic measurements such as $\dot{V}O_{2peak}$ is upright.[4,12,13] Accordingly, to advance the understanding of what role cardiac dysfunction contributes to exercise limitations in CF, there is an important need to identify alternative noninvasive laboratory methods that can be used to closely estimate cardiac hemodynamics during routine clinical CPET.

In contrast to inspired and expired $O_2$ and $CO_2$ gases commonly measured during CPET, inert gas such as acetylene ($C_2H_2$) is nonphysiological and demonstrates low affinity for hemoglobin.[14–16] Still, because of its robust Bunsen solubility coefficient in blood, $C_2H_2$ is a perfusion sensitive gas.[14–16] Laboratory techniques based on the principle that there is rapid uptake of inspired inert gas within the pulmonary circulation have been validated for use at rest as well as during exercise for the measurement of $\dot{Q}$ and SV in adults with or without advanced cardiopulmonary disease (eg, pulmonary hypertension).[17–21]

Alternatively, it has also been shown that when $\dot{V}O_2$ is combined with measurements of heart rate (HR), the oxygen pulse ($O_2$pulse) response correlates with SV during exercise in healthy adults as well as those with heart failure.[22–25] Separately, it has also been suggested for adult CF that an improved $O_2$pulse response during CPET as a result of exercise training is reflective of cardiac adaptations and increased SV.[9]

Nevertheless, it has not been tested to what extent $O_2$pulse aligns with SV during CPET in these individuals. This is a question that warrants testing not only because of the proposed importance impaired cardiac hemodynamics play in worsened CF prognosis[5–9,26,27], but also because exercise cardiac catheterization is impractical for routine clinical practice. There is safety and a practical ease in which $O_2$pulse can be readily acquired in clinical and research settings.

Therefore, this study tested the hypothesis that peak exercise $O_2$pulse is a valid estimate of SV acquired via the $C_2H_2$ gas pulmonary uptake technique in young adults with modest-to-moderate severity CF.

## Methods

This study is a subanalysis of the original study reported in Van Iterson et al.[5] However, data as they pertain to this study hypothesis have not been previously reported. All aspects of this study were reviewed and approved by the University of Arizona Institutional Review Board. All individuals included in this study provided voluntary written informed consent prior to study participation.

In brief, 17 young adults with mild-to-moderate severity CF and a convenience sample of 25 healthy young adults serving as controls participated in this study. Study inclusion criteria for CF required confirmation of a positive $Cl^-$ sweat test ($\geq$60 mM/L $Cl^-$) and presence of at least one copy of the ΔF508-CFTR mutation (71% in this study were homozygous for ΔF508-CFTR). Individuals with CF interested in this study were excluded from participation for any of the following reasons: (1) experienced a pulmonary exacerbation within the last 2 weeks or pulmonary hemorrhage within 6 months resulting in greater than 50 $cm^3$ of blood in the sputum, (2) taking any antibiotics for pulmonary exacerbation, or (3) taking any experimental drugs related to CF. Exclusion criteria for any participant included (1) medical records demonstrating the diagnoses of hypertension, cardiac and/or vascular disease, metabolic disease (including diabetes), orthopedic disease, or other diseases affecting the neuromuscular system; (2) currently smoking or history of smoking, or (3) those who were not able to engage in exercise (eg, known orthopedic limitations or musculoskeletal disorders).

Eligible and enrolled participants performed testing on a single day. Participants were asked to avoid engaging in exercise (other than physical activity associated with tasks of daily living) 24 hours prior to a study visit. We also asked that participants avoid caffeine ingestion for at least 8 hours leading up to a study visit.

### *Overview*

Briefly, after arriving to our human physiology laboratory and providing voluntary written informed consent, basic measurements of body anthropometry were performed on participants. This included measurements of height and body weight (not corrected for fat-free mass), which were used to calculated body surface area (BSA) as, $0.024265 \times W^{0.5378} \times H^{0.3964}$.[28] Following, participants performed flow volume loop spirometry (CPFS/D spirometer; MGC Diagnostics, St. Paul, MN, USA) in the upright seated position according to guidelines of the American Thoracic Society.[29] Measurements acquired included forced vital capacity (FVC) and forced expiratory volume in 1 second ($FEV_1$), whereby the $FEV_1$/FVC ratio was calculated. For each of these parameters, we calculated percent of predicted values using equations of Hankinson et al.[30] After being given the opportunity to rest for at least 30 minutes following airway function testing, participants finally performed CPET.

### *Cardiopulmonary exercise testing*

In an environmentally controlled human physiology laboratory, incremental stepwise CPET to volitional fatigue was performed by participants in the upright seated position on a cycle ergometer (Corival Lode B.V., Groningen, Netherlands).[5,31] To accommodate the time needed for measurements performed for this study (ie, SV, described below), the CPET protocol instituted for this study was a modified version of that reported by others.[31] Each CPET stage was 3 minutes in length, whereas workload in watts (W) was individualized based on participant physical activity history (questionnaire) and body size (range: 15-40 W/stage).[5,31] An excellent effort and achievement of peak exercise was defined as a rating of perceived exertion (RPE; Borg scale 6 to 20) $\geq$17 and reaching a respiratory exchange ratio (RER) $\geq$1.10.[4,12,13]

Oxygen saturation ($Sao_2$) was monitored noninvasively throughout CPET using finger pulse oximetry (Nellcor N-600, Pulse Oximeter; Boulder, CO, USA). Breath-by-breath measurements of gas exchange and ventilation occurred throughout CPET via an open-circuit indirect calorimetry system (Medical Graphics CPX/D, St. Paul, MN, USA). Recording of beat-to-beat HR occurred throughout CPET via 12-lead ECG (Marquette Electronics; Milwaukee, WI, USA). Measurements of HR and breath-by-breath gas exchange were temporally aligned. Manual sphygmomanometry was used to take measurements of blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) at baseline as well as near the end of each CPET stage. Mean arterial pressure (MAP) was calculated as DBP + 1/3(SBP – DBP).

Absolute values for $\dot{V}O_2$, $\dot{V}CO_2$, HR, minute ventilation ($\dot{V}_E$), mixed expired $CO_2$ ($PECo_2$), and end-tidal $CO_2$ ($P_{ET}Co_2$) reported for rest and peak exercise represent the average of the final 30 seconds of the baseline period or the last 30 seconds of the final completed exercise stage (ie, peak exercise).[4,5,12,13] We calculated the ratio of $PECo_2$ to $P_{ET}Co_2$ ($PECo_2/P_{ET}Co_2$) as a noninvasive estimate of ventilation-perfusion matching during exercise, where Hansen et al[32] reports that values approximately equal to 0.60 are consistent with chronic obstructive pulmonary disease, 0.70 are consistent with heart failure, and $\geq$0.75 are healthy adults.

### *$C_2H_2$ gas pulmonary uptake technique*

Measurements of SV via the $C_2H_2$ gas pulmonary uptake technique occurred in temporal alignment with periods used to acquire breath-by-breath and HR data at both rest and peak exercise. A full description of the $C_2H_2$ gas pulmonary uptake rebreathe technique has been reported previously.[5,20,33]

Briefly, the apparatus from which participants respired through during the $C_2H_2$ gas pulmonary uptake maneuver included a mouthpiece attached to a pneumotachometer (Hans Rudolph, Kansas City, MO, USA), which was connected to a nonrebreathing Y valve (Hans Rudolph). The inspiratory port of the Y valve was interconnected to a pneumatic sliding switch valve allowing for rapid change between open-circuit room air and a hanging rebreathe bag containing the $C_2H_2$ gas mixture (described below). Placed within the pneumotachometer exposed to inspiratory and expiratory flows was a gas sampling line, which was connected on the other end to a mass spectrometer (Perkin Elmer MGA-1100, Wesley, MA, USA) for continuous breath-by-breath gas fraction sampling. Gas sampling via mass spectrometry was integrated with a PC and custom analysis software for the determination of $\dot{Q}$ and SV.[5,20,33]

For a given $\dot{Q}$ and SV measurement, the gas mix containing $C_2H_2$ was respired during a 8- to 10-breath period from a 5-L anesthesia rebreathe bag (Hans Rudolph), which contained 1 to 3 L of total gas comprising 0.65% $C_2H_2$, 9% helium (He), balance $N_2$, and 35% $O_2$ depending on an initial tidal volume for a given participant as well as exercise intensity (i.e., to promote nearly complete emptying of the rebreathe bag in the absence of bag collapse). Participants were immediately switched out of respiring from the rebreathe bag following a given $C_2H_2$ uptake maneuver back into room air breathing.

Compared with the blood insoluble He gas, $C_2H_2$ gas demonstrates not only high blood solubility but also low affinity for hemoglobin.[5,20,33] Therefore, uptake of inspired $C_2H_2$ gas within pulmonary capillary blood occurs rapidly and also readily washes out of the circulation during subsequent expiration in the absence of high levels of recirculation. Accordingly, with concurrent measurements of HR, and because of the unique gas properties of both He and $C_2H_2$ gases, the breath-by-breath slope of the exponential end-tidal decrease in $C_2H_2$ concentration with respect to that of He gas can be used to quantify beat-to-beat pulmonary blood flow and, hence, SV.[5,20,33]

The quotient of $\dot{V}O_2$ and HR was calculated for $O_2$pulse.[22–25] In addition, because of the gas properties of $CO_2$,[34–36] which demonstrate closer semblance to diffusion-perfusion characteristics of $C_2H_2$ gas within the pulmonary system compared with $O_2$,[35,37] we also calculated the quotient of $\dot{V}CO_2$ and HR ($CO_2$pulse) to compare against SV.

### *Statistical analyses*

Data are presented as mean ± SEM or otherwise noted. Where appropriate, between-group differences were assessed using Wilcoxon rank sum or $\chi^2$ tests for continuous or categorical data, respectively.

The following statistical routines were used to test the validity of $O_2$pulse (or $CO_2$pulse) as an estimate of SV[38,39]: (1) univariate least squares linear regressions were performed separately for comparisons involving SV via the $C_2H_2$ uptake technique (dependent and criterion method) and $O_2$pulse (or $CO_2$pulse) (independent and practical method) at time periods of baseline and peak exercise; (2) output parameters from each linear regression (ie, calibration equation in the form of, $y = mx + b$, and coefficient of determination [$R^2$]) were used to determine validity as the standard error of estimate (SEE) variable equal to, $SD \times \sqrt{(1 - R^2)}$, accompanied by 95% confidence limits, where SD is the standard deviation of dependent variable values from respective calibration equations; and finally (3) the distribution of residuals (criterion SV minus predicted SV) relative to predicted SV (computed using $O_2$pulse and calibration equations) were plotted.[38,39]

Correlation coefficients ($r$) from Pearson product moment tests were used to assess relationships between SV measurements using the $C_2H_2$ uptake technique vs $O_2$pulse (or $CO_2$pulse) at both baseline and peak exercise. Strength of a given $r$ value was interpreted based on thresholds of Cohen[40]: small = 0.10, medium = 0.30, and large ⩾ 0.50, power ⩾ 0.80. We tested between-group differences for $r$ values using Fisher $r$-to-$z$ transformations and computing respective Fisher $Z$ tests to obtain $P$ values.[40] Two-tailed significance was determined using an $\alpha$ level set at .05. All computations were performed using SAS statistical software (v.9.4.; SAS Institute, Cary, NC, USA).

## Results

### *Baseline characteristics*

There were no differences for age (27 ± 2 vs 23 ± 2 years, $P = .17$) and percentage of men participants (60% vs 76%, $P = .27$) between healthy controls and CF, respectively. Alternatively, compared with controls, height (174 ± 2 vs 168 ± 2 cm, $P = .04$), weight (72 ± 3 vs 62 ± 3 kg, $P = .01$), and BSA (1.86 ± 0.04 vs 1.73 ± 0.05 m2, $P = .01$) were reduced in CF, respectively. Measurements of resting FVC (4.8 ± 0.2 vs 3.6 ± 0.3 L and %predicted 96% ± 2% vs 80% ± 5%, both $P < .01$), $FEV_1$ (3.8 ± 0.2 vs 2.6 ± 0.2 L and %predicted 94% ± 35 vs 69% ± 6%, both $P < .01$), and the $FEV_1$/FVC ratio (0.82 ± 0.02 vs 0.72 ± 0.03 and %predicted 98% ± 2% vs 86% ± 4%, both $P < .01$) were also all greater in controls compared with CF, respectively. Participants of both groups in this study completed all aspects of testing as described and in the absence of experiencing adverse events.

### *Cardiopulmonary exercise testing*

For the baseline period immediately preceding the exercise on-transition, there were no group differences for $\dot{V}O_2$ (5.9 ± 0.3 vs 6.5 ± 0.4 mL/kg/min), $\dot{V}CO_2$ (0.34 ± 0.02 vs 0.37 ± 0.03 L/

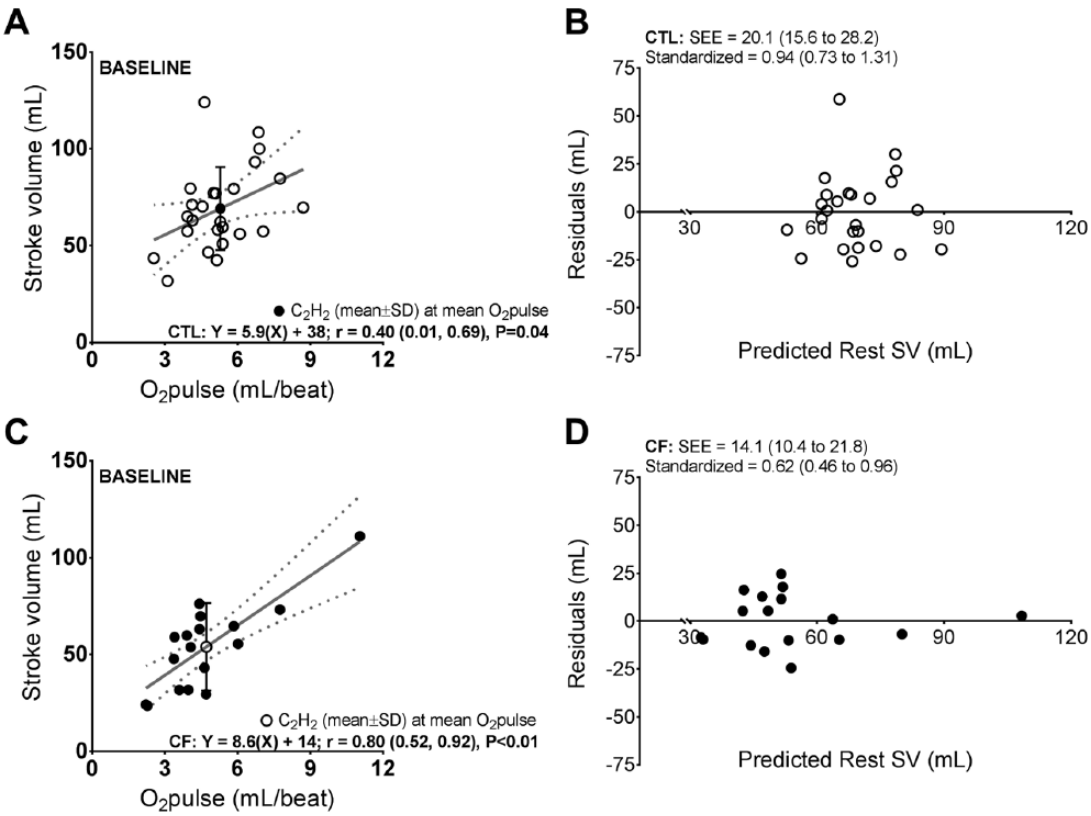


**Figure 1.** Correlations and validity between stroke volume (SV) assessed via the acetylene ($C_2H_2$) pulmonary uptake technique (criterion method) and oxygen pulse ($O_2$pulse) (practical method) at baseline in healthy controls (CTL) and individuals with cystic fibrosis (CF). Panels (A) and (C): solid gray line and dotted gray lines (lower and upper 95% confidence limits [CLs]) represent the line of best fit for respective regressions. Correlation coefficient (*r*) is presented with lower and upper 95% CLs. Interpretation of *r* values: small = 0.10, medium = 0.30, and large ⩾ 0.50, power ⩾ 0.80. Panels (B) and (D): regressions (ie, calibration equations) from panels (A) and (C), respectively, were used to calculate predicted SV. Residuals = criterion SV minus predicted SV. Validity is represented by the standard error of estimate (SEE, with lower and upper 95% CLs) variable.

min), $\dot{V}_E$ (14 ± 1 vs 16 ± 1 L/min), $P_{ET}Co_2$ (30 ± 1 vs 30 ± 1 mm Hg), SBP (110 ± 2 vs 106 ± 2 mm Hg), DBP (71 ± 1 vs 70 ± 2 mm Hg), and MAP (84 ± 1 vs 82 ± 2 mm Hg) between controls and CF (all $P > .05$), respectively. Alternatively, $Sao_2$ (98% ± 0% vs 96% ± 0%) and $PECo_2/P_{ET}Co_2$ (0.69 ± 0.01 vs 0.63 ± 0.02) were significantly greater in controls compared with CF, respectively, whereas HR was decreased in controls compared with CF (81 ± 3 vs 93 ± 4 beats/min) (all $P < .05$).

Workload (power) achieved (2.57 ± 0.16 vs 1.64 ± 0.14 W/kg, $P < .01$) at peak exercise by participants per kilogram of body weight was greater in controls compared with CF, respectively. Peak exercise RPE (18 ± 0 vs 17 ± 0) and RER (1.11 ± 0.02 vs 1.11 ± 0.01) did not differ between controls and CF (both $P > .05$), respectively. In contrast to baseline, peak exercise responses across $\dot{V}O_2$ (33 ± 2 vs 23 ± 2 mL/kg/min), $\dot{V}CO_2$ (2.6 ± 0.2 vs 1.6 ± 0.2 L/min), $\dot{V}_E$ (82 ± 4 vs 56 ± 3 L/min), $PECo_2/P_{ET}Co_2$ (0.79 ± 0.02 vs 0.63 ± 0.04), $Sao_2$ (97% ± 0% vs 94% ± 0%), SBP (158 ± 4 vs 142 ± 6 mm Hg), and HR (177 ± 2 vs 145 ± 7 beats/min) were increased in controls compared with CF (all $P < .05$), respectively. Alternatively, peak exercise responses for $P_{ET}Co_2$ (35 ± 1 vs 36 ± 1 mm Hg), DBP (61 ± 4 vs 67 ± 4 mm Hg), and MAP (93 ± 3 vs 92 ± 4 mm Hg) did not differ between controls and CF (all $P > .05$), respectively.

### *Cardiac hemodynamics and estimates*

Baseline $\dot{Q}$ (5.5 ± 0.4 vs 4.8 ± 0.4 L/min), $\dot{Q}$ index (3.1 ± 0.2 vs 2.6 ± 0.2 L/min/m$^2$), $O_2$pulse (5.3 ± 0.3 vs 4.7 ± 0.5 mL/beat), $O_2$pulse index (2.87 ± 0.15 vs 2.68 ± 0.23 mL/beat/m$^2$), $CO_2$pulse (4.2 ± 0.2 vs 4.2 ± 0.4 mL/beat), and $CO_2$pulse index (2.30 ± 0.13 vs 2.37 ± 0.18 mL/beat/m$^2$) did not differ between controls and CF (all $P > .05$), respectively. However, SV (70 ± 4 vs 54 ± 5 mL) and SV index (40 ± 3 vs 31 ± 3 mL/m$^2$) were greater in controls compared with CF (both $P < .05$, respectively).

In contrast to baseline, compared with controls, peak exercise $\dot{Q}$ (16.5 ± 0.4 vs 11.9 ± 0.9 L/min), $\dot{Q}$ index (9.1 ± 0.3 vs 6.7 ± 0.5 L/min/m$^2$), SV (94 ± 4 vs 78 ± 5 mL), $O_2$pulse (13.1 ± 0.7 vs 9.3 ± 0.8 mL/beat), $O_2$pulse index (7.08 ± 0.31 vs 5.38 ± 0.43 mL/beat/m$^2$), $CO_2$pulse (14.6 ± 0.7 vs 10.4 ± 0.9 mL/beat), and $CO_2$pulse index (7.88 ± 0.34 vs 5.97 ± 0.48 mL/beat/m$^2$) were reduced in CF (all $P < .05$). However, SV index (51 ± 2 vs 45 ± 3 mL/m$^2$) did not differ between controls and CF ($P = .11$), respectively.

### *Correlations and validity*

Baseline correlations in Figure 1 between SV and $O_2$pulse for both controls and CF were significant. However, compared

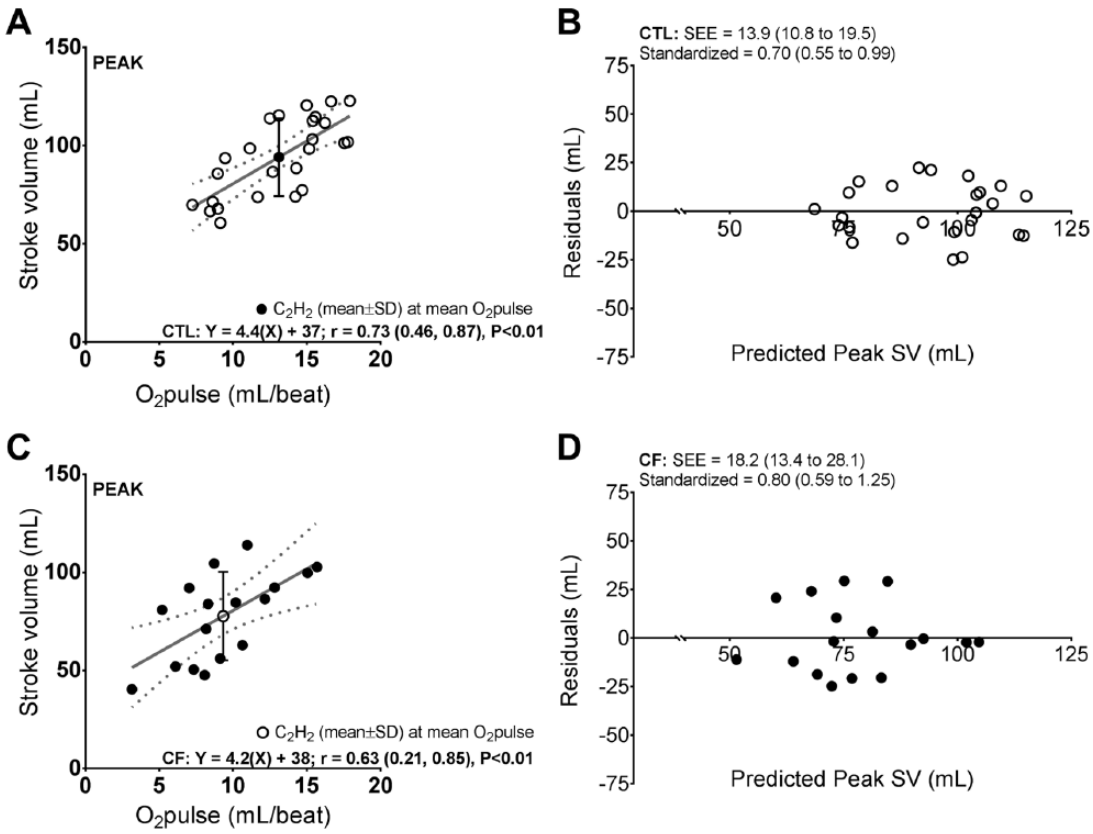


**Figure 2.** Correlations and validity between stroke volume (SV) assessed via the acetylene ($C_2H_2$) pulmonary uptake technique (criterion method) and oxygen pulse ($O_2$pulse) (practical method) at peak exercise in healthy controls (CTL) and individuals with cystic fibrosis (CF). Panels (A) and (C): solid gray line and dotted gray lines (lower and upper 95% confidence limits [CLs]) represent the line of best fit for respective regressions. Correlation coefficient (*r*) is presented with lower and upper 95% CLs. Interpretation of *r* values: small = 0.10, medium = 0.30, and large ⩾ 0.50, power ⩾ 0.80. Panels (B) and (D): regressions (ie, calibration equations) from panels (A) and (C), respectively, were used to calculate predicted SV. Residuals = criterion SV minus predicted SV. Validity is represented by the standard error of estimate (SEE, with lower and upper 95% CLs) variable.

with controls, *r* was stronger in CF ($P = .05$). The difference in baseline *r* between controls and CF did not persist to peak exercise ($P = .58$) as both groups demonstrated correlations that were significant and similar in magnitude.

Correlations between SV and $CO_2$pulse illustrated in Figures 3 and 4 generally mirrored respective $O_2$pulse counterparts in Figures 1 and 2, with the exception of the baseline correlation in controls, which was not significant. Similar to Figure 1, the correlation between baseline SV and $CO_2$pulse was also weaker controls compared with CF ($P < .01$). However, SV and $CO_2$pulse correlations at peak exercise did not differ between groups ($P = .73$).

Accompanying correlations in Figures 1 to 4 are respective values for SEE (absolute and standardized). Consistent with correlations showing increasing strength from baseline to peak exercise for controls, SEE lessened in size while improving the distribution of residuals over the range of predicted SV values for this same time course. Although baseline to peak exercise SEE improvements were not observed for CF, SEE values for these individuals at both time points in Figures 1 to 4 remained within limits observed for healthy controls. Moreover, the nearly even distribution of residuals over the range of predicted SV for CF was mirrored across baseline and peak exercise. Finally, for both groups at each time point, Figures 1 to 4 illustrate that predicted SV using either $O_2$pulse or $CO_2$pulse could be expected to remain within ±1 SD of measured SV with an approximate magnitude of over- or underestimation consistently <20 mL (absolute) or <0.5 mL (standardized).

## Discussion

The present observations support our hypothesis that peak exercise $O_2$pulse is a valid estimate of SV in young adults with modest-to-moderate severity CF. Although CF is traditionally identified as a disease having a severe impact on airway function, these data are consistent with those of other studies involving adults with or without cardiac and/or pulmonary disease, for whom $O_2$pulse has been reported to demonstrate close agreement with SV.[22–25] Separate studies consistent with the present have also shown that the $C_2H_2$ gas pulmonary uptake technique provides a valid means to assess $\dot{Q}$ in adults with advanced chronic pulmonary disease (eg, pulmonary hypertension).[17]

Because of the proposed role that cardiac dysfunction plays in contributing to exercise intolerance and poor prognosis in CF,[5–10,27] another important aspect of this study is we included methodology and resources that are immediately clinically

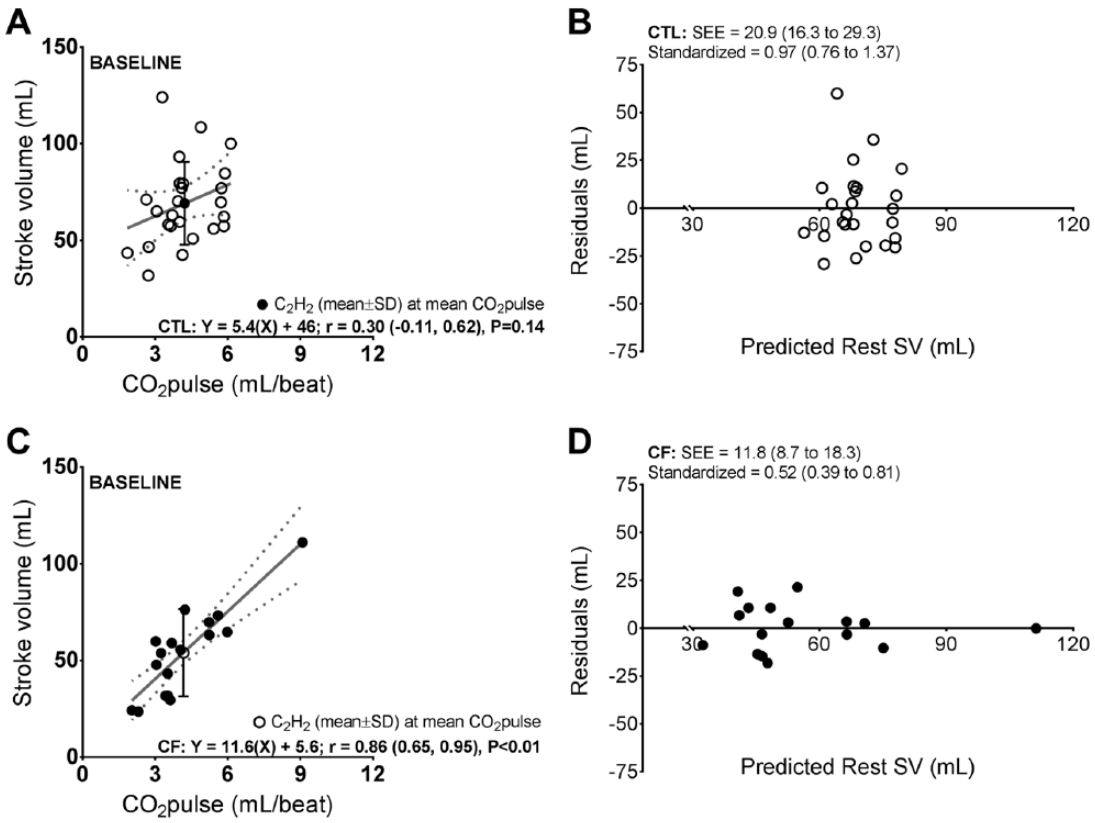


**Figure 3.** Correlations and validity between stroke volume (SV) assessed via the acetylene ($C_2H_2$) pulmonary uptake technique (criterion method) and carbon dioxide output pulse ($CO_2$pulse) (practical method) at baseline in healthy controls (CTL) and individuals with cystic fibrosis (CF). Panels (A) and (C): solid gray line and dotted gray lines (lower and upper 95% confidence limits [CLs]) represent the line of best fit for respective regressions. Correlation coefficient (*r*) is presented with lower and upper 95% CLs. Interpretation of *r* values: small = 0.10, medium = 0.30, and large ⩾ 0.50, power ⩾ 0.80. Panels (B) and (D): regressions (ie, calibration equations) from panels (A) and (C), respectively, were used to calculate predicted SV. Residuals = criterion SV minus predicted SV. Validity is represented by the standard error of estimate (SEE, with lower and upper 95% CLs) variable.

translational. Most medical centers with the advanced infrastructure and expert personnel available to provide care for individuals with CF are also likely to have CPET facilities. Accordingly, the application of $O_2$pulse as an estimate of SV can be used as a tool to strengthen the ability to interpret CPET in adult CF. Perhaps with greater utilization over time, $O_2$pulse may also demonstrate usefulness as a key prognostic indicator in CF similar to what has been reported for other patient groups.[41–44] This study addressed a need-based practical knowledge gap in adult CF by highlighting there are safe, noninvasive, and accessible ways in which SV can be closely estimated during CPET. The addition of $O_2$pulse and/or SV (via $C_2H_2$ uptake) measurements to routine clinical CPET can be expected to advance our understanding of cardiac contributions to exercise limitations in CF.

Despite the absence of performing direct measurements of ventilation-perfusion matching or magnitude/distribution of airway recruitment, we suggest that participant responses across SV, $O_2$pulse, $CO_2$pulse, $P_{ET}Co_2$, $PECo_2/P_{ET}Co_2$, and lack of severe hypoxemia ($Sao_2$ <88%)[45] lend indirect evidence signifying that the $C_2H_2$ gas pulmonary uptake technique is not appreciably limited by airway factors in modest-to-moderate severity CF. The underlying physiological rationale used to support our interpretation of these data includes but is not limited to the following comments: (1) only during severely impaired alveolar-capillary diffusion has it been established that pulmonary transfer of $O_2$ and $CO_2$ gases is limited and markedly influential to exercise capacity[35,36]; (2) $C_2H_2$ is not a diffusion limited gas[14,46,47]; (3) because of the robust Bunsen solubility coefficient in blood for $C_2H_2$ (~30 times that of $O_2$ and ~1.5 times that of $CO_2$), this gas demonstrates high perfusion sensitivity[14,20,37,46]; (4) therefore, severe shunt (ie, alveolar ventilation = 0.0) causing ventilation-perfusion mismatch (equal to 0.0) coupled with patent maldistributed ventilation and prolonged emptying of long time-constant airspaces ($PECo_2/P_{ET}Co_2$ <0.60)[32] for most lung regions would be needed to prevent $C_2H_2$ gas from being taken up by pulmonary capillary blood flow; (5) extreme shunt (eg, due to alveolar edema and atelectasis) resulting in no $C_2H_2$ gas pulmonary transport could also be expected to result in a condition where CF would not have achieved peak exercise as described in this study; and finally (6) $CO_2$ cannot be expired if pulmonary capillary perfusion and alveolar ventilation does not occur.[39,48] Without adequate ventilation-perfusion matching, the ability to expire metabolically produced $CO_2$ is transient, and therefore, $P_{ET}Co_2$ recorded for such instances is confounded by high contributions from $CO_2$ previously trapped in airways. The overall result of severe ventilation-perfusion mismatch is

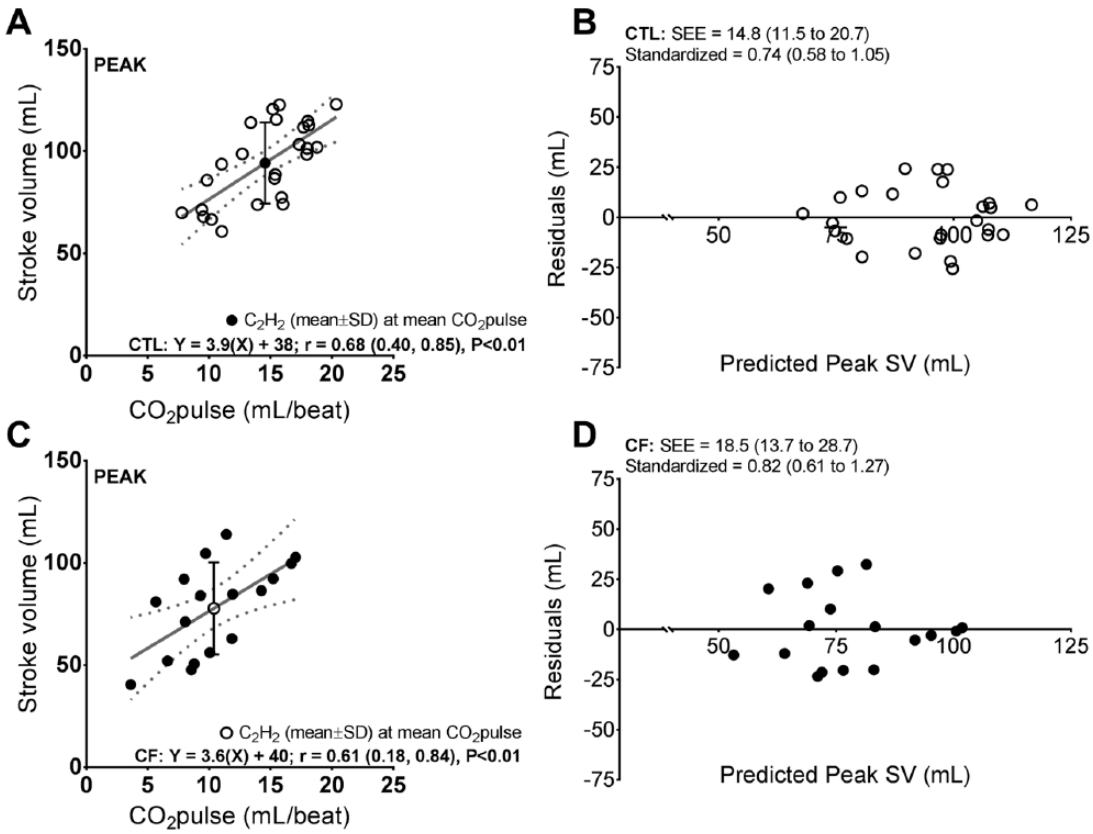


**Figure 4.** Correlations and validity between stroke volume (SV) assessed via the acetylene ($C_2H_2$) pulmonary uptake technique (criterion method) and carbon dioxide output pulse ($CO_2$pulse) (practical method) at peak exercise in healthy controls (CTL) and individuals with cystic fibrosis (CF). Panels (A) and (C): solid gray line and dotted gray lines (lower and upper 95% confidence limits [CLs]) represent the line of best fit for respective regressions. Correlation coefficient (*r*) is presented with lower and upper 95% CLs. Interpretation of *r* values: small = 0.10, medium = 0.30, and large ⩾ 0.50, power ⩾ 0.80. Panels (B) and (D): regressions (ie, calibration equations) from panels (A) and (C), respectively, were used to calculate predicted SV. Residuals = criterion SV minus predicted SV. Validity is represented by the standard error of estimate (SEE, with lower and upper 95% CLs) variable.

$P_{ET}CO_2$ which would have appreciably dropped to far greater levels than demonstrated in this study.

These data are also compatible with those of Hoeper et al,[17] who in an earlier study involving adults with mild-to-severe pulmonary hypertension reported $\dot{Q}$ measurements using the $C_2H_2$ gas pulmonary uptake technique demonstrated clinically acceptable agreement with $\dot{Q}$ measurements acquired using the direct Fick method. Equally noteworthy, measurements acquired in Hoeper et al[17] occurred as patients rested. This is of practical relevance because efficacy of the $C_2H_2$ gas pulmonary uptake technique is highly dependent on alveolar recruitment.[20,33] This suggests that even at rest where there is less alveolar recruitment compared with exercise,[49] the inert gas pulmonary uptake approach provides a valid means to assess SV in patients with obstructive pulmonary disease who are also at high risk for diffusion impairment (eg, due to alveolar and/or interstitial edema).[17,50] The observations of Hoeper et al[17] have since been replicated by Saur and colleagues[19,21] who used the nitrous oxide gas pulmonary uptake method (ie, inert gas with blood solubility less than $C_2H_2$) compared with cardiac magnetic resonance imaging to assess resting $\dot{Q}$ across a spectrum of patients with advanced pulmonary disease including both obstructive and restrictive classifications.

Although this is the first study to test relationships between $O_2$pulse and SV during CPET in adult CF, we are not the first to report on $O_2$pulse as an indirect means to suggest that the SV response to exercise is impaired in this population. In an earlier study, Gruber et al[9] reported young adults with CF demonstrate impaired exercise $\dot{V}O_2$, HR, and $O_2$pulse responses, which do not collectively respond favorably to exercise training. In contrast to improved exercise $\dot{V}O_2$ and $O_2$pulse, exercise training had no effect on HR. Accordingly, while Gruber et al[9] did not perform direct measurements of SV, we are in agreement with their interpretation that cardiac adaptations leading to improved posttraining exercise $O_2$pulse were in-large part attributable to heightened SV responsiveness to increased metabolic demand.

While it is plausible that widening of the arteriovenous $O_2$ content gradient may have driven the training benefit previously observed for exercise $O_2$pulse in CF,[9] we suggest that this is unlikely because in the steady-state condition (ie, submaximal exercise), the arteriovenous $O_2$ content gradient is expected to be invariable, and most of the rise in $O_2$pulse from the rest to submaximal exercise transition is commensurate with changes that occur in SV.[51] Again, the effect of training on $\dot{V}O_2$, $O_2$pulse, and HR responses reported in Gruber et al[9]

was generally mirrored across submaximal and maximal exercise performance. There is also no evidence to date suggesting widening of the arteriovenous $O_2$ content gradient in response to increased $O_2$ metabolic demand is enhanced and/or an adaptive mechanism able to compensate for impaired cardiac hemodynamics in CF.[52,53]

### *Limitations*

To benefit the wide-scale translation of these data across CF in the real world, it is necessary to test the present hypothesis in CF demonstrating a broader spectrum of disease severity and age. Still, the encouraging nature of these data acquired in young adults with modest-to-moderate severity CF provides support to warrant such a follow-up study. Separately, we also acknowledge that performing concurrent cardiac catheterization studies would have strengthened the interpretability of these data. However, as noted above, the practicality and feasibility of performing exercise cardiac catheterization for research in CF is unrealistic. Cardiac catheterization is also not a practice that can be deployed for routine clinical CPET in CF.

Along with the impact that severe pulmonary disease due to obstruction, fibrosis, etc, may have on the accuracy of inert gas uptake techniques for the measurement of $\dot{Q}$ and SV, such pulmonary factors could also be expected to affect $O_2$ transport and, hence, the validity of $O_2$pulse. Accordingly, for those and other possible reasons (eg, chronotropic incompetence or other arrhythmias),[54] we recognize that $O_2$pulse is imperfect and should not be instituted as a replacement for SV when direct measurements of cardiac hemodynamics are warranted to guide advanced clinical decision making (eg, need for mechanical circulatory support and/or heart transplantation). Instead, we propose $O_2$pulse, similar to SV via the $C_2H_2$ gas pulmonary uptake technique, can be useful when deployed as a routine screening tool during the interpretation of clinical CPET to assess whether cardiac limitations may be present, necessitating the need for advanced follow-up diagnostic testing.

## Conclusions

The present observations suggest that $O_2$pulse provides a valid means to estimate SV at peak exercise in young adults with mild-to-moderate severity CF. These data are immediately clinically translational because $O_2$pulse is a parameter that can be safely and easily assessed during CPET in these individuals. The routine acquisition of $O_2$pulse during CPET can be expected to improve and advance our knowledge of what role cardiac dysfunction plays in limiting exercise in CF.

## Acknowledgements

The authors thank the individuals who participated in this study.

## Author Contributions

Conception and design: EMS and WJM. Acquisition of data: EMS, CMW, and SEB. Analysis and interpretation: EHV and EMS. Drafting the article for important intellectual content: EHV, EMS, TPO, CMW, SEB, and WJM. All authors contributed to the intellectual content of the manuscript and were consulted for final approval of the submitted version.

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