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The relationship between resting lung-to-lung circulation time and peak exercise capacity in chronic heart failure patients

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Abstract

Background—Peak exercise capacity (VO_{2peak}) is a measure of the severity of chronic heart failure (CHF), however few indices of resting cardiopulmonary function have been shown to predict VO_{2peak}. A prolonged circulation time has been suggested as an index of increased severity of CHF. The aim of this study was to investigate the relationship between resting lung-to-lung circulation time (LLCT) and VO_{2peak} in CHF.

Methods—30 CHF patients (59±13 yr, NYHA: 1.9±1.0) undertook the study. Each subject completed resting pulmonary and echocardiography measures and an incremental exercise test. LLCT was measured using the reappearance of end tidal acetylene (P_{ET,C_2H_2}) following a single inhalation. Univariate and multivariate stepwise linear regression was used to determine the predictors of VO_{2peak}.

Results—Univariate correlates of VO_{2peak} (group mean: 1.53 ±0.44.l.min^{-1}) included LLCT (r = −0.75), inspiratory capacity (r = 0.41), ejection fraction (r=0.33), peak early flow velocity (r=−0.39) and the ratio of early to late flow velocity (r=−0.31). LLCT was the only independent predictor where VO_{2peak}=3.923–0.045 (LLCT); R2 = 54%.

Conclusion—These results suggest that resting LLCT determined using the soluble inert gas technique represents a simple, non-invasive method that provides additional information regarding exercise capacity in CHF.

INTRODUCTION

Peak oxygen consumption (VO_{2peak}) measured during maximal cardiopulmonary exercise testing has been shown to be a strong predictor of the severity of CHF[1]. However the measurement of VO_{2peak} is not routine in the clinical setting. Currently there are few indices of resting cardiopulmonary function that correlate strongly with VO_{2peak} in CHF. Indices of resting left ventricular (LV) systolic function such as ejection fraction (EF) have been shown to be poor correlates VO_{2peak} in this patient group.[2]

Recent studies have reported that indices of resting pulmonary and LV diastolic function may be better predictors of VO_{2peak} in CHF patients[3, 4] when compared to other indices of resting LV systolic function. Nannas and colleagues[3] reported that inspiratory capacity (IC) was an independent predictor of VO_{2peak}. Likewise, Meyer and colleagues[4] found that resting indices of LV diastolic function such as peak early flow velocity (E), peak late flow velocity (A), the

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ratio of the early transmitral flow velocity to atrial flow velocity (E/A) were univariate correlates of VO_{2peak} in CHF patients.

While these resting cardiopulmonary measures may provide some insight into the severity of disease in CHF, changes in the resting circulation time may provide additional information. The lung-to-lung circulation time (LLCT) represents the transit time for a bolus of blood through the pulmonary and systemic circulations. Given this, alterations in LLCT at rest in CHF patients may reflect not only changes in CO but also changes in blood volume and blood flow distribution.

We have recently developed a non-invasive measurement of LLCT using the soluble gas acetylene (C_2H_2). Using this method, we are able to determine the time taken for a bolus of C_2H_2 to travel from the lungs, through the systemic circulation and then back to the lungs i.e. the lung-to-lung circulation time. This technique was developed from methods for determining cardiac output (CO) using soluble gases[5], where recirculation is a well-described phenomenon. While other methods for estimating circulation time exist, these either require invasive techniques[6], extensive monitoring using polysomnography[7] or the inhalation of hypoxic gas mixtures.[8] The method we propose has advantages over others in that it is non invasive and a relatively simple maneuver for the patient to perform that does not require the inhalation of a hypoxic gas mixture. Moreover the LLCT reflects the time taken to circumnavigate the entire pulmonary and systemic circulations, rather than the arterial circulation time alone.[6–8] Given this, changes in LLCT at rest for CHF patients may reflect changes in CO and blood flow distribution.

Recent studies have suggested that a prolongation or lengthening of the resting circulation time may be a potential index of underlying cardiac dysfunction in CHF, particularly in patients with central sleep apnea.[7, 9–11] In a separate study Wolff et al [8] found that resting lung to ear circulation time was approximately 25% longer in 8 patients with CHF when compared with 6 healthy age matched controls.

To date, there has been no examination of the relationship between LLCT and VO_{2peak} in CHF. We propose that LLCT may be an index of the severity of CHF and that individuals with a longer resting LLCT will have a lower VO_{2peak}. We hypothesized that resting LLCT determined using a soluble gas method would be a independent predictor of VO_{2peak} in patients with CHF over and above other previously published resting indices of pulmonary[3] and LV diastolic function.[4] To assess this hypothesis we measured VO_{2peak}, resting LLCT, pulmonary function and resting indices of LV systolic and diastolic function of 30 CHF patients referred to the Mayo laboratory.

METHODS

Subject Details

The characteristics of the subjects that volunteered for this study are outlined in Table 1. In total, 30 subjects with CHF (NYHA I–IV) aged 27–79 years who had a clinical diagnosis of heart failure for at least 3 months participated in the study. The percentages for the broad etiological classification for heart failure were as follows: ischemic dilated cardiomyopathy (38%); idiopathic dilated cardiomyopathy (48%); valvular heart disease (10%) and other (4% i.e. one patient, secondary to radiation therapy). Details of the medications prescribed to the patients are outlined in Table 1. The Mayo Clinic Institutional review board approved the study and all subjects signed a written consent form prior to commencing.

Incremental Exercise Test

Each subject completed an incremental exercise test on a treadmill to determine VO_{2peak}. Subjects commenced walking on the treadmill at 2 mph, 0% grade for a warm up period of 3–4 min. Following the warm up period the grade and/or speed of the treadmill was increased by approximately 2 mets every 2 minutes until the subject could no longer exercise because of either exhaustion or cardiac symptoms or significant ECG or blood pressure changes.[4]

During the incremental exercise test, oxygen uptake (VO_2) was measured breath-by-breath using a metabolic measuring system (CPX-D, Medical Graphics Corporation, St. Paul, MN, USA). The gas exchange and heart rate data were averaged over 30-s intervals.

Ideally we would have determined maximal oxygen consumption (VO_{2max}) for each subject. The technical criteria for achieving VO_{2max} has typically been defined as achieving two the following during the incremental exercise test: 1) a plateau in oxygen uptake (VO_2) despite an increasing exercise intensity 2) a respiratory exchange ratio of 1.1 or better.[12] In our study few subjects achieved the technical criteria for achieving VO_{2max} and hence the highest VO_2 measured during the final minute of the incremental exercise was designated as VO_{2peak}. Peak exercise values were calculated as the average of the two highest consecutive 30-s values obtained prior to termination of exercise. At the completion of the test, ventilation (V_E) was plotted against carbon dioxide production (VCO_2) to determine the V_E/VCO_2 slope for each subject.

Spirometry

Forced vital capacity (FVC); forced expiratory volume in 1 second (FEV_1) and IC were measured with the subject in seated position with a closed-circuit pulmonary function testing system (Medical Graphics, USA) using American Thoracic Guidelines[13].

Echocardiography

All measurements were made using standard two-dimensional echocardiography with the patient in a supine position according to the recommendations of the American Society of Echocardiography.[14] Left ventricular stroke volume and CO were calculated using the methods of Lewis et al[15], whereas LV EF was determined using the modified Simpson's rule.[16] Transmitral inflow velocity was obtained from a 2-dimensional apical window with pulsed wave Doppler function facilitating the calculation of the E, A and E/A ratio.

Circulation Time Measurement

Lung-to-lung circulation time was measured using a acetylene bolus tracking method with the subject in a seated position. Each subject inhaled a single breath of a 0.65% C_2H_2, 9.0% Helium (He), normoxic gas mix. With end tidal gas monitoring in place, the subject then continued to breathe room air. Acetylene is an inert gas that is highly soluble in blood. Helium is an insoluble tracer gas that is used to account for any breath-by-breath variation in the distribution of C_2H_2 within the lung. Following inhalation, the $P_{ET,C_2H_2}/P_{ET,He}$ will fall as C_2H_2 is carried away from the lungs via both perfusion and ventilation (Figure 1). The dissolved C_2H_2 is distributed through the systemic circulation and eventually appears in mixed venous blood, which causes a slight rise in alveolar (end-tidal) air, at which point the $P_{ET,C_2H_2}/P_{ET,He}$ will start to rise (Figure 1). The time take for $P_{ET,C_2H_2}/P_{ET,He}$ to rise following the initial inhalation is measured as the LLCT. To determine the point at which $P_{ET,C_2H_2}/P_{ET,He}$ begins to rise we assumed an initial exponential decay in $P_{ET,C_2H_2}/P_{ET,He}$ signal. The rise in $P_{ET,C_2H_2}/P_{ET,He}$ following recirculation was assumed to be linear (Figure 1). The end tidal point representing the intersection between the exponential decay in $P_{ET,C_2H_2}/P_{ET,He}$ and the linear rise in $P_{ET,C_2H_2}/P_{ET,He}$ following recirculation was designated the final point prior to recirculation

(Point A, Figure 1). LLCT was calculated from the difference in time at Point A to time zero (time at the peak C_2H_2 value during inhalation of the test gas, Figure 1). Using this particular method, the within tester reliability was r=0.92 for 28 resting LLCT assessments healthy subjects. The coefficient of variance for repeated measures of resting LLCT was 4.9 ± 2.8% (mean ± SD).

Currently there is no gold standard estimate of LLCT. Previous invasive studies evaluating arterial circulation time used invasive techniques with a labeled dye (indocyanine green) introduced into the pulmonary artery and measuring the time taken for a detectable amount of dye to arrive at the pulmonary artery.[6] While these techniques introduce dye directly into the pulmonary artery, they are still dependent on the distribution of the dye throughout the circulatory system, similar to the soluble gas method that we propose.

Given that we are unable to establish a gold standard measure for LLCT validation, we chose to examine whether the measurement behaved in a manner we would predict in normal subjects during exercise. We measured LLCT and CO during exercise (25%, 50%, 75% and 100% VO_{2peak}) in 8 healthy subjects (mean age 52 ± 5 yr). Sowton et al[6] reported an inverse relationship between arterial circulation time and CO during exercise. That is, as CO rose, arterial circulation time fell. Extending this finding to LLCT, we therefore expected to find a fall in LLCT as CO rises during exercise.

Statistical Analysis

All data is presented as mean ± standard deviation (SD). Individual correlates of VO_{2peak} and LLCT were assessed using univariate linear regression. Multivariate stepwise linear regression was used to evaluate independent predictors of VO_{2peak}. Based on our hypothesis and the findings of previous studies we chose the following univariate correlates of VO_{2peak}: resting hemodynamics (systolic and diastolic blood pressure, EF, HR, cardiac output and LLCT); resting pulmonary function (IC, FVC, FEV_1, FEV_1/FVC); resting echocardiographic measures (EF, E, A and E/A) and V_E/VCO_2. For the stepwise linear regression, predictive variables were chosen on the basis of high univariate regression and a low level of multicollinearity.[17]

RESULTS

The subjects that participated in this study had stable heart failure. The majority of patients were taking Angiotensin-converting Enzyme (ACE) inhibitors, beta blockers and digoxin (Table 1). Note that while 23 patients were taking ACE inhibitors, a further 4 patients were taking angiotensin receptor blockers. Of the subjects that participated in the study, the majority (45%) were NYHA classification I, 24% NHYA classification II, 24% were NYHA classification III and 7% were NYHA classification IV.

Figure 2 shows the relationship between LLCT and CO during exercise in 8 healthy subjects. Panel A clearly shows that, as CO increased there was a fall in our estimate of LLCT. Panel B shows the relative change in LLCT as a function of the relative change in CO during exercise. The relative change in LLCT was correlated (r =0.79) with the relative change in cardiac output.

For the 30 CHF patients, the mean VO_{2peak} was 1.53 ±0.44.l.min^{-1}. The mean peak oxygen uptake for the group relative to body mass was 19.1 ± 5.6 ml.kg^{-1}·min^{-1}. The mean peak heart rate achieved was 124 ± 22 beats.min^{-1} and the peak RER was 1.16 ±0.22.

The relationship between VO_{2peak} and LLCT is shown in Figure 3. Individuals with a longer resting LLCT generally had a poorer exercise capacity, whereas individuals with a shorter resting circulation time tended to have a greater exercise capacity. Hence we found that VO_{2peak} was inversely related to LLCT (r=−0.75, P <0.001).

Other univariate correlates of VO_{2peak} are presented in Table 2. Apart from LLCT, significant univariate correlates of VO_{2peak} were IC (P=0.01), EF (P=0.04), E wave (P=0.02), V_E/VCO_2 (P=0.04) and E/A ratio (P=0.05).

Univariate correlates of LLCT are presented in Table 2. Significant univariate correlates of LLCT were VO_{2peak} (P<0.001), IC (P=0.01), V_E/VCO_2 (P=0.01), E (P=0.02) and E/A (P=0.05).

Stepwise multivariate analysis indicated that the only independent predictor of VO_{2peak} was LLCT accounting for 54% of the variance. The equation for VO_{2peak} using LLCT as an independent predictor was:

$$VO_{2peak} = 3.923 - 0.045\,(\text{LLCT});\quad R^2 = 54\%$$

DISCUSSION

There are two important findings from this particular study. Firstly, we demonstrated that a non-invasive soluble gas technique provides a potentially valid and reliable estimate of LLCT in CHF and that as CO increased, LLCT fell. Secondly we showed that resting LLCT is an independent predictor of VO_{2peak} in CHF.

The advantages of the soluble gas technique is that it is non invasive and relatively simple to perform. Recent studies have measured circulation times in CHF patients using polysomnography[7, 18]. This method however, requires extensive monitoring and the detection of apneic episodes in order to estimate circulation time. If no apneic episodes are detected then circulation time cannot be calculated. Other methods require the inhalation of 100% N_2 mixture[8], which may be unsafe in severe CHF patients.

Our results suggest that resting LLCT is an independent predictor of VO_{2peak} in CHF over and above other recently published indices of resting cardiopulmonary function.[3, 4] Nanas and colleagues[3] found that IC was correlated (r=0.71, P<0.001) and an independent predictor of VO_{2peak} in 51 CHF patients (Mean NYHA classification: 2.8) who had a normal FEV_1/FVC ratio. The results of the current study support those of Nannas et al[3], albeit with a slightly lower univariate correlation coefficient. The finding that individuals with a lower IC tended to have a lower exercise capacity is not surprising. Typically CHF has been associated with a restrictive lung pattern[19] resulting in a decrease in TLC and hence IC. The mechanism for the loss of TLC in CHF remains controversial with factors such as changes in lung fluid balance, cardiomegaly, increased central blood volume, respiratory muscle weakness and airway remodeling being cited as potential causes.[20–23]

However unlike Nannas et al[3], we did not find that IC was an independent predictor of VO_{2peak} in CHF. After accounting for the variance due to LLCT, we found that adding IC did not significantly improve the model for determining VO_{2peak}. This would suggest that any variance in VO_{2peak} due to IC is accounted for the variance in the LLCT measurements. Indeed, Table 2 shows that there was a significant correlation between LLCT and IC. The strong relationship between LLCT and VO_{2peak} would therefore explain the fact that IC is not an independent predictor in the current study.

The results of this study are similar to those of Meyer et al[4] who reported that indices of resting LV diastolic function correlated with VO_{2peak} in CHF patients. In the current study E, E/A and EF were significantly univariate correlates of VO_{2peak}. Indeed, Meyer et al[4], showed such indices (LV chamber stiffness parameter –k, E, A. E/A) were all univariate correlates of VO_{2peak} in CHF patients with defined LV systolic dysfunction. Of these, only the LV chamber

stiffness parameter was an independent predictor of VO_{2peak} which accounted for which for 56% of the variance. Unfortunately, we were unable to examine LV chamber stiffness and thereby make any conclusions on the relationship between this index and LLCT. Notably, there was a weak but significant relationship between LLCT and E and E/A and as such, when the variance in VO_{2peak} due to LLCT was taken into account, the addition of either E or E/A did not alter the model for VO_{2peak}.

Overall, our results suggest that resting LLCT is a 'better' predictor of exercise capacity than the other measures of pulmonary and LV diastolic function obtained in the current study. As such we may have expected to find a significant relationship between resting CO and LLCT in this patient group. However the finding that there is a relationship between resting CO and circulation time appears controversial. On one hand, Hall and colleagues[7] reported an inverse relationship between lung to ear circulation time and resting CO ($r=-0.72$, $P<0.006$), in 13 individuals with central sleep apnea (8 of whom were CHF patients). Alternatively a recent study by Wolff et al[8] failed to find a significant relationship between resting lung to ear circulation time and resting CO in CHF patients.

The lack of a statistical relationship between LLCT and resting CO reported in the current study indicates that factors other than resting CO may affect LLCT in CHF patients. These may include factors which may affect blood flow distribution and a variation in blood volume[7, 24, 25]. Recent findings that an increased blood volume is associated with a poorer hemodynamic status in CHF suggest resting blood volume may be an important prognostic indicator in CHF[24, 25]. Moreover blood volume has been hypothesized to contribute changes in circulation time in CHF[9]. One would hypothesize that for a given CO, patients with a larger blood volume would have a longer LLCT. Hence some of the variation in resting LLCT we have observed may be due to variations in blood volume in the CHF group.

While we found no statistically significant relationship between resting LLCT and CO we did find that resting indices of LV diastolic function (E and E/A) had a weak but significant relationship with LLCT. This may suggest that LLCT is more sensitive to changes in resting indices of cardiac function rather than global changes in CO per se.

Finally we note that there may have been limitations in the method used to measure CO in the particular study. While echocardiograph provides a well-defined clinical measure of CO, other more accurate methods exist such as thermo dilution. A better correlation between LLCT and CO may have been found if the CO had been measured by a more accurate method like thermo dilution.

Limitations and Future Study

We acknowledge that we have not comprehensively validated the soluble inert gas method for determining LLCT with a gold standard measure of circulation time. While other invasive measures of circulation time exist (dye dilution), these rely on similar principles as the soluble inert gas we have proposed. As such any attempt to validate the soluble inert gas with a similar method would be a comparison of two similar techniques. Another potential limitation in our study was a lack of comprehensive measurements of diastolic function such as LV stiffness. The inclusion of LV stiffness may have resulted in the development of a more comprehensive model for predicting VO_{2peak} using resting indices of cardiopulmonary function. While we have shown a significant relationship between resting LLCT and VO_{2peak} in CHF, future studies should explore and compare the relationship between exercising LLCT in CHF and healthy subject populations. Moreover further studies may be necessary to confirm their results in other study groups, including, for instance, higher percentages of patients with more

advanced heart failure. Further insight into specific factors that affect LLCT during exercise may be elucidated with this investigation.

In conclusion, this study found that resting LLCT could be reliably measured using an soluble gas technique and that LLCT was an independent predictor of exercise capacity in CHF. Our results support the hypothesis that CHF patients LLCTs may be an index of the severity of disease and that the assessment of resting LLCT may provide additional clinical information.

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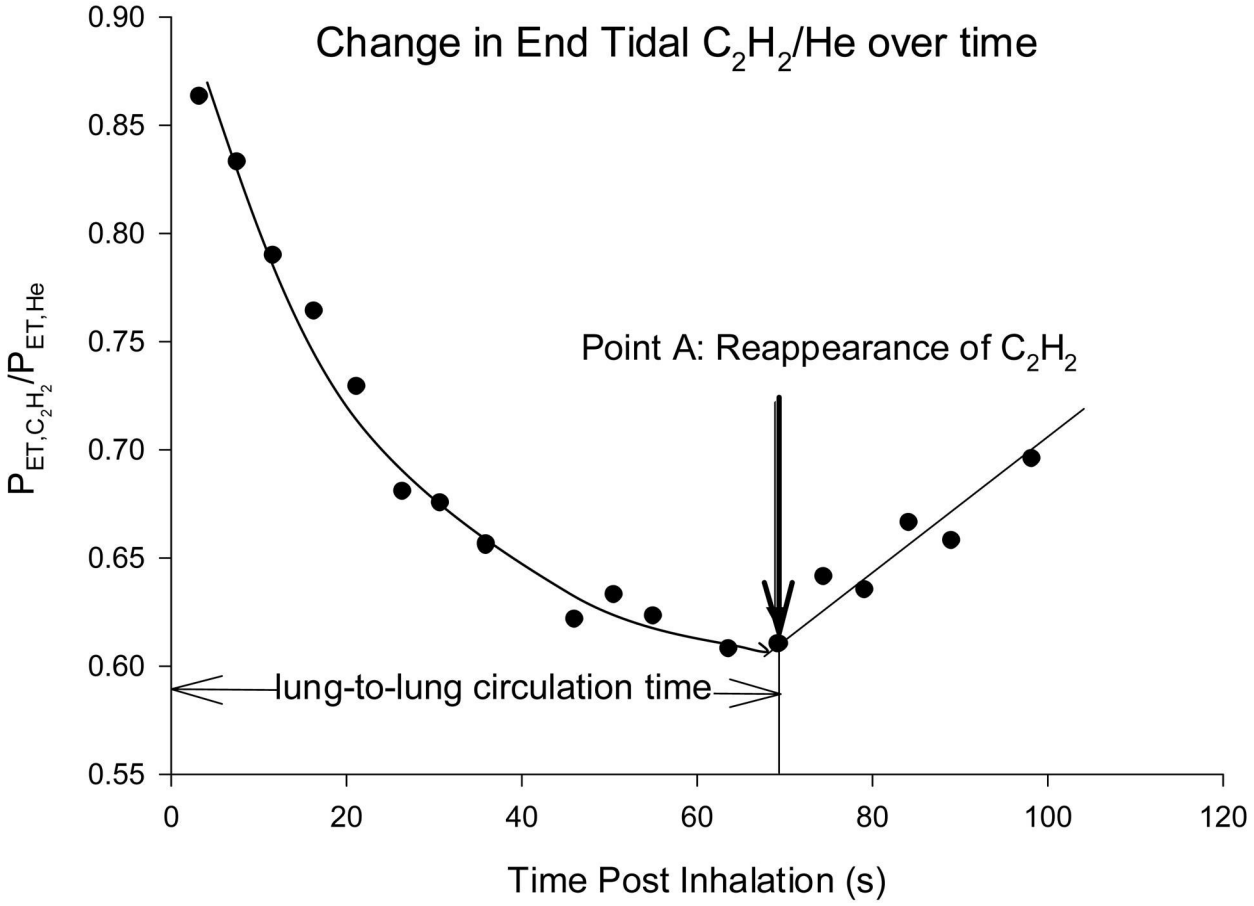

Figure 1.

Graphical representative of the change in breath-by-breath end tidal C_2H_2/He following a single inhalation of 0.9% C_2H_2, 9% He for a single subject. Following inhalation C_2H_2/He falls as C_2H_2 is distributed in the pulmonary blood volume. At the point when a significant volume of C_2H_2 is returned to the right side of the heart and re-enters the pulmonary circulation, C_2H_2/He will start to rise. The time taken from inhalation (time 0) until where C_2H_2/He shows a significant rise and consistent rise was calculated as being the circulation time.

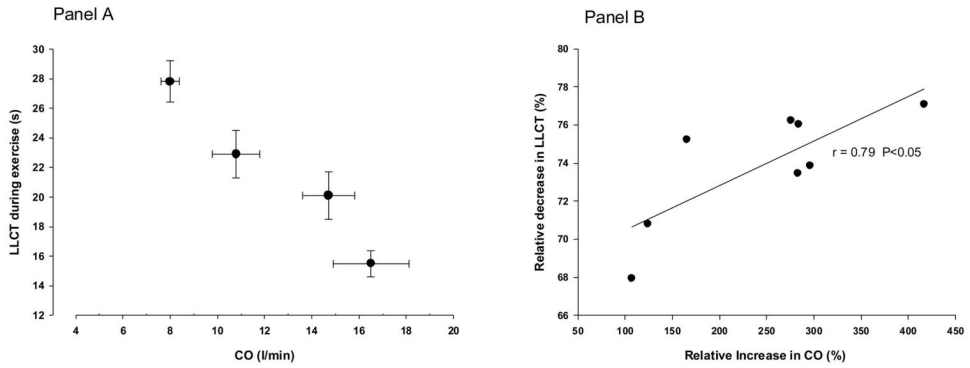

Figure 2.

Panel A: Change in CO and lung-to-lung circulation time during exercise at 25%, 50%, 75% and 100% VO_{2peak} in 8 healthy subjects; Panel B: Correlation of the relative change in CO with the relative change in lung-to-lung circulation time; Change in CO was positively correlated with the change in lung-to-lung circulation time (r=0.79, P<0.05). CO: Cardiac output; LLCT: Lung to lung circulation time.

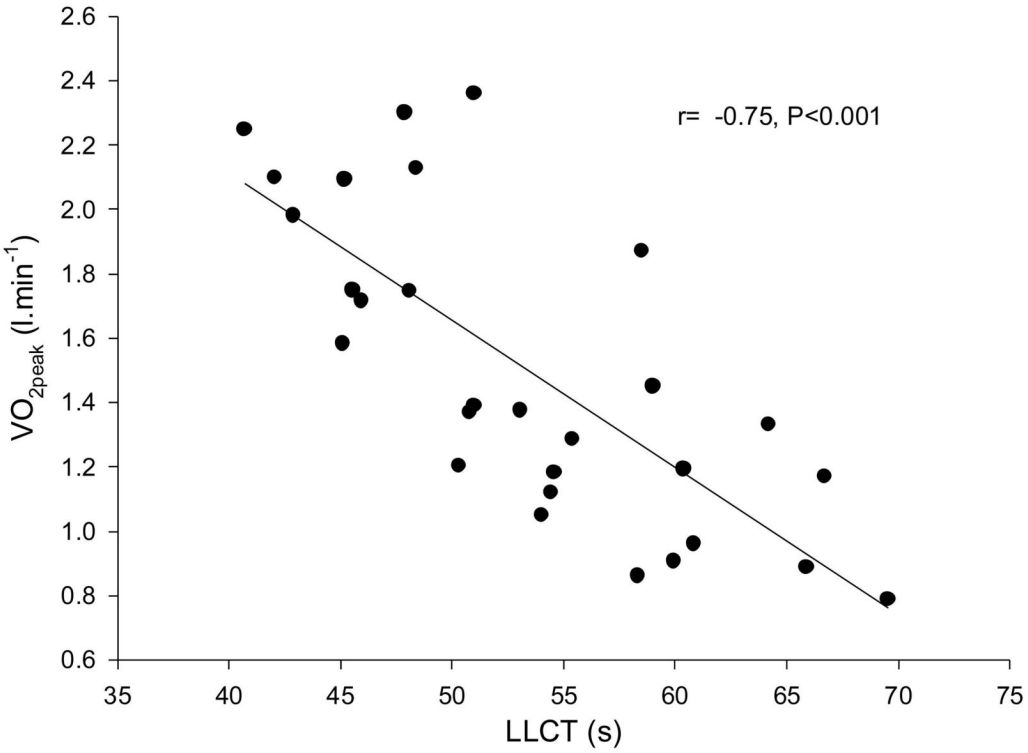

Figure 3.
Relationship between circulation time and peak exercise capacity in 30 patients with chronic hear failure. Circulation time was inversely related to peak exercise capacity, (r=−0.75, P<0.001)

Table 1

Subject Characteristics and Etiology of Chronic Heart Failure. Results are mean ± SD. BMI: Body mass index; NYHA: New York Heart Association Classification. ACE: Angiotensin-converting Enzyme Inhibitor; For cardiovascular medications, data reflect the ratio of the number of patients on the medication to the total number of patients.

Age (yr)	59 ± 13
Male/Female	20/10
BMI ($kg \cdot m^{-2}$)	27.7 ± 7.3
NYHA Functional Classes	
I	14
II	7
III	7
IV	2
Etiology of Heart Disease	
Ischemic dilated cardiomyopathy	12
Idiopathic dilated cardiomyopathy	14
Valvular heart disease	3
Other (chemotherapy)	1
Cardiovascular Medications	
ACE	23/30
Digoxin	23/30
Beta Blocker	26/30
Diuretic	22/30

Table 2

Univariate predictors of Peak Exercise Capacity and Lung-to-Lung Circulation Time for Chronic Heart Failure Patients. Results are mean ± SD. r: Univariate correlation coefficient; VO_{2peak}: Peak oxygen uptake; LLCT: Lung-to-lung circulation time; NYHA: New York Heart Association Classification. SBP systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart Rate; CO: Cardiac output; IC: Inspiratory capacity; FEV_1: Forced expired volume in 1s; FVC: Forced vital capacity; EF: Ejection Fraction; E: Maximal early flow velocity; A: Maximal late flow velocity; E/A ratio: Maximal early to late flow velocity ratio.

		r (VO_{2peak})	r (LLCT)
Resting Hemodynamics			
SBP (mmHg)	109 ± 20	0.12	−0.06
DBP (mmHg)	65 ± 11	0.17	−0.29
HR (beats·min^{-1})	72 ± 17	−0.29	0.05
CO (l·min^{-1})	4.6 ± 1.2	−0.09	−0.15
LLCT	53.7 ± 7.9	−0.75‡	
Peak Exercise Capacity			
VO_{2peak} (l·min^{-1})	1.53 ± 0.44		−0.75‡
V_E/VCO_2	36.5 ± 6.0	−0.32*	0.44‡
Pulmonary Function			
IC (l)	2.5 ± 0.7	0.41*	−0.50‡
FEV_1 (l)	2.8 ± 0.6	0.07	−0.25
FVC (l)	3.7 ± 0.8	0.18	−0.27
Echocardiography			
EF (%)	27.1 ± 8.7	0.32*	−0.19
E (m·s^{-1})	0.82 ± 0.34	−0.39*	0.35*
A (m·s^{-1})	0.65 ± 0.30	0.21	−0.16
E/A ratio	1.8 ± 1.0	−0.31*	0.32*

*P<0.05;

‡P<0.01