Methods

# A Multicenter Study of Noninvasive Cardiac Output by Bioreactance During Symptom-limited Exercise

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**ABSTRACT**

**Background:** Hemodynamic responses to exercise were assessed in patients with varying degrees of chronic heart failure (CHF) to determine the feasibility of using bioreactance during exercise testing in multicenter studies of CHF.

**Methods and Results:** A total of 210 symptomatic CHF patients and 22 subjects without heart failure were subjected to symptom-limited exercise testing on a bicycle (105) or treadmill (127) while measuring gas exchange for $VO_2$, cardiac output (CO) noninvasively by a bioreactance technique, heart rate, and blood pressure. Peak CO (pCO) and $VO_2$ ($pVO_2$) during exercise were lower in patients with higher New York Heart Association (NYHA) class, in females and in older patients. Multiple linear regression analysis showed that pCO (L/min) = $19.6 + 4 \cdot M - 2.1 \cdot NYHA + 1.9 \cdot G - 0.09 \cdot Age$, where M = 1 for treadmill and 0 for bicycle and G = 1 for males and 0 for females. Similarly, $pVO_2$ (mL/kg/min) = $24 + 2.1 \cdot M - 2.9 \cdot NYHA + 1.26 \cdot G - 0.08 \cdot Age$. $VO_2$ and CO were also highly correlated to each other: pCO (mL/kg/min) = $0.059 + 0.007 \cdot pVO_2 + 0.036 \cdot M - 0.025 \cdot G$. Similar correlations were determined for other parameters of exercise, including left ventricular power, and the ratio of peak/resting $VO_2$ (cardiovascular reserve), the ratio of peak/resting CO (cardiac reserve), and total peripheral vascular resistance.

**Conclusion:** Bioreactance-based noninvasive measurements of CO at rest and during exertion identified abnormalities of cardiovascular function consistent with those identified by $pVO_2$ and in prior studies using invasive CO measurements. This technique might therefore be useful for indexing disease severity, prognostication, and for tracking responses to treatment in clinical practice and in clinical trials. (*J Cardiac Fail 2009;15:689–699*)

**Key Words:** Heart failure, cardiac output, oxygen uptake, exercise testing, New York Heart Association class, total peripheral resistance, LV power, cardiac reserve.

The cardiopulmonary exercise tolerance test (CPX) has been widely used in the management of patients with chronic heart failure (CHF). Its applications include classifying the severity of disease, evaluating the effects of therapy, estimating prognosis, and developing effective exercise prescriptions.[1,2] Numerous studies have demonstrated the value of peak oxygen uptake (peak $VO_2$) measured during CPX for estimating risk in patients with CHF.[3–7] However, peak $VO_2$ can be difficult to determine in some patients, can be difficult to define,[8–10] is influenced by motivation, and varies considerably in some patients with similar cardiac function.[11–14] Wilson et al[11–13] reported dissociations between exertional symptoms, peak $VO_2$, and circulatory function in patients with CHF. Chomsky and colleagues[15] observed that the cardiac output (CO) response

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to exercise was a stronger predictor of survival than peak $VO_2$ among cardiac transplant candidates. These and other investigations[16–19] have therefore suggested that the CO response to exercise can be very useful when assessing the degree of cardiac dysfunction or when estimating risk in patients with CHF. Furthermore, Weber and colleagues showed how hemodynamic responses to exercise (including CO, total peripheral resistance, and arterial-venous difference) vary in CHF and help explain the mechanisms of effort intolerance in different degrees of heart failure.[4,5] Most recently, Lang et al showed that peak cardiac power (the product of CO and mean arterial pressure [MAP]) and peak CO itself were of equal or greater value than peak $VO_2$ in prognosticating outcomes in heart failure patients.[20]

Drawbacks to the routine measurement of CO by thermodilution (the current gold standard) during exercise include the fact that it is invasive, time consuming, carries an inherent risk, is not always accurate, is expensive, and is particularly difficult to measure during exercise. Thus, it is impractical for routine clinical use. For these reasons, a noninvasive and easily applied method to quantify CO and other hemodynamic indices during exercise could have important applications for the routine clinical evaluation of CHF patients. Although a number of noninvasive approaches have been proposed and concur with the direct Fick, thermodilution, or other techniques at rest,[21–24] few previous studies have validated noninvasive estimates of CO during exercise in patients with CHF.

Bioreactance, a recently introduced noninvasive approach for CO measurement, involves the analysis of blood flow–dependent changes in the phase shifts of electrical currents applied across the chest. Bioreactance has an improved signal-to-noise ratio and is less susceptible to physical factors such as body features, body motion, and ambient conditions than other electrical-based approaches.[25] The accuracy and precision of this technique has been demonstrated previously in comparison to invasive measurements with thermodilution in a variety of clinical settings at rest.[26,27] This approach has also been introduced previously as a means of measuring CO during symptom limited exercise simultaneous with gas exchange in a small number of subjects.[28]

The purpose this multicenter study was to test the hypothesis that, similar to peak $VO_2$, measurement of CO and other parameters derived from CO, blood pressure, and heart rate during symptom limited exercise provides information that correlates with the severity of CHF. In so doing, we determined the feasibility and utility of using bioreactance exercise testing in large-scale studies of CHF patients. In addition, further validation of the bioreactance system was obtained by direct comparison of CO measurements by the Fick method with an inert gas rebreathing technique.[29–32]

## Methods

Basic demographic data and medical history were obtained from 232 subjects referred for stress testing at 4 institutions. The medical history included the primary clinician's assessment of New York Heart Association (NYHA) functional classification. This study was approved by each Institutional Review Board and all subjects gave written informed consent to participate. The only inclusion criterion was that each subject was already referred for a stress test; a small group of patients (n = 22) without a history of heart failure were included. The only exclusion criterion was if the subject had heart failure with a normal ejection fraction, including diastolic heart failure from restrictive, amyloid, or idiopathic hypertrophic cardiomyopathy. All subjects underwent symptom limited CPX testing. Because this was mainly an observational, feasibility study, sites were instructed to use the exercise modality (bicycle, n = 105; or treadmill, n = 127) and exercise protocol that was indicated for use based on their individual standards of practice. One site (Columbia University) exclusively used bicycle testing; the protocol consisted of a 3-minute rest period on the bicycle followed by 3-minute stages starting at 0 watts and increasing by 25 watts every stage until test termination. Treadmill tests included modified Bruce and modified Naughton in approximately equal numbers and a small number (n = 16) of Balke protocols. As per standard routine, all subjects were requested to abstain from eating or smoking at least 3 hours before the test. Ventilatory oxygen uptake was measured and gas exchange data were acquired breath-by-breath and expressed in 10-second intervals of rolling 20- or 30-second averages. Oxygen uptake, carbon dioxide production, minute ventilation, and respiratory exchange ratio were calculated online. A 12-lead electrocardiogram was monitored continuously and recorded every minute. Systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded manually at each stage of exercise throughout the test. Mean arterial pressure (MAP) was estimated as DBP + (SBP − DBP)/3. All subjects were encouraged to provide a maximal effort.

### Bioreactance-Based Continuous Noninvasive CO Measurement

Each patient was connected to the bioreactance-based CO measurement (NICOM, Cheetah Medical, Wilmington, DE) device that allowed continuous monitoring of CO throughout exercise. The NICOM system has CE mark in Europe and has 510(k) clearance from the US Food and Drug Administration. The NICOM technology, described in detail previously,[25–27] is based on an analysis of time-dependent relative phase shifts of an oscillating current that occur when traversing the thoracic cavity during each beat. Briefly, the NICOM system comprises a radiofrequency generator for creating a high-frequency current that is injected across the thorax, 4 dual-surface electrode stickers that are used to establish electrical contact with the body, a receiving amplifier for recording the transthoracic voltage in response to the injected current, and circuitry for determining the relative phase shift between the injected current and the recorded voltage. Within each dual electrode stickers, 1 electrode is used for delivery of the high-frequency current and the other is used for measuring the resulting voltage. Signals are applied to and recorded from the left and right sides of the thorax; these signals are processed separately and averaged after digital processing. The signal processing unit of the system determines the relative phase shift ($\Delta\Phi$,) between the input signal relative to the output signal. $\Delta\Phi$, in turn, is due to instantaneous changes in blood flow in the aorta. It has been shown that stroke volume (SV) is estimated by:

$$SV = C \cdot VET \cdot d\Phi/dt_{max,}$$

where C is a constant of proportionality and VET is ventricular ejection time, which is determined from the NICOM

and electrocardiogram signals. The value of C has been optimized in prior studies and accounts for patient age, gender and body size.[26] CO is then calculated as the product of SV and heart rate.

Proper management of the electrode wires during exercise testing is important to ensure good signal quality. As detailed previously,[28] electrodes are placed on the patients' back: 1 set above each scapula and the other set at the lower edge of the rib cage. The skin is prepared by light exfoliation and alcohol wipe and applying the self-adhesive dual electrode stickers. The wires are attached to the electrodes with clips that are then taped securely to the body surface. The electrode cables are bunched and secured to minimize cable motion during body motion. Before starting each test, be it on a bicycle or on a treadmill, the patient sits or stands at rest for 2 to 3 minutes to allow stabilization of signals before proceeding.

### Exercise Variables

Availability of CO measurements allowed calculation of several other fundamental hemodynamic variables at rest and during exercise. These include SV, total peripheral resistance (TPR ≡ MAP/CO), and left ventricular power (LVPower ≡ CO · MAP/451, in watts). Each of these parameters was presented in absolute values and also indexed to body surface area (stroke volume index (SVI), total peripheral resistance index (TPRI), LVPower Index). Similar to $VO_2$, we also expressed CO in units of mL·kg·min (which we called normalized cardiac output (COn)). In addition, the ratio of peak $VO_2$ to resting $VO_2$ was taken as an index of *cardiovascular reserve*, the ratio between peak CO and resting CO was taken as an index of *cardiac reserve*, and the percent reduction in TPR was taken as an index of *vascular reserve*.

### NICOM-Innocor Substudy

In a substudy involving 27 patients at 1 center (Columbia University), NICOM was measured during CPX testing on a bicycle ergometer in which CO was also measured at rest and peak exercise using the Innocor system (Innovision A/S, Odense, Denmark).[29–32] The Innocor device employs a rebreathing system that uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) from a 4-L prefilled anesthesia bag. Photoacoustic analyzers measure gas concentrations over a 5-breath interval. Tidal volume is progressively increased in the closed circuit to match the physiologic increase. Nitrous oxide concentration decreases during the rebreathing maneuver at a rate proportional to pulmonary blood flow allowing estimation of CO. Three to 4 respiratory cycles are needed to obtain a value for nitrous oxide washout. The technique for measuring $VO_2$ in these patients was identical to that used in all other patients; the inert gas measurements were coupled with a standard metabolic cart. Patients were instructed to give an approximately 1-minute warning before they feel they will end exercise so that a final rebreathing measurement is obtained at the peak of exercise; this is because the Innocor device takes approximately 45 seconds to boot up followed by 15 seconds to make the measurement. The patient continues to exercise through the measurement and cool down is started after it is complete. The value for peak CO from the NICOM device is taken as the peak value during exercise so that the 2 measurements are taken as close in time as possible.

### Statistical Analysis

Variables measured at rest and at peak exercise were summarized using descriptive statistics are presented as mean ± SD. Multiple linear regression analysis (MLRA) was used to assess statistical significance of specific parameters on variables describing exercise performance. These parameters included mode of exercise testing (treadmill coded as 1; bicycle coded as 0), the degree of heart failure (based on NYHA class), gender (male coded as 1, female coded as 0), age, and ejection fraction (continuous variables). The impact of β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker use were also explored. All parameters were included initially in each MLRA model; parameters were removed stepwise if the coefficient quantifying their contribution failed to exhibit statistical significant (ie, parameters were removed if $P > .05$).

Standard Bland and Altman analysis[33] was used to compare Innocor and NICOM measurements. This consisted of constructing the plot of the average of Innocor and NICOM CO values plotted versus the difference between Innocor and NICOM CO values. Bias between the measurements is defined as the average of the differences between the 2 techniques; the limits of agreement between the methods is defined by the range spanning the bias ± 1.96 multiplied by the standard deviation of the differences between the 2 techniques.

For all tests, a $P$ value $< .05$ was considered statistically significant.

## Results

Typical NICOM signals obtained at rest, approximately halfway to peak exercise, and at peak exercise from a test performed during treadmill testing are shown in Fig. 1. All tracings, including 3 leads of an electrocardiogram, the NICOM phase signal (Φ(t)), and the first derivative of phase (dΦ(t)/dt)) represent signals that were averaged over a 1-minute period. With increasing amounts of exercise, heart rate increases, the peak-to-peak amplitude of the Φ(t) signal increases (indicating increase stroke volume), and the dΦ(t)/dt signal increases in amplitude (increased peak aortic flow) and narrows (decreased ventricular ejection time); all these features are expected to occur during exercise. Also as shown in Fig. 1, the NICOM signals are stable and free of noise even during vigorous motion during exercise.

Figure 2 shows the time courses of change of $VO_2$ and CO during exercise for a patient during a treadmill test (A) and from a different patient during a bicycle test (B, additional details in the figure inserts). $VO_2$ and CO increase in proportion to each other throughout exercise, as revealed by the relatively linear relationship between these two parameters (C). Similar relationships for additional patients are shown in Fig. 3. As shown in these examples from both bicycle (Fig. 3A) and treadmill tests (Fig. 3B), $VO_2$ and CO vary in a roughly linear manner in all cases, but the precise nature of the relationship varies considerably from patient to patient.

### NICOM-Innocor Comparison Substudy

CO was measured by NICOM and the Innocor system in a subset of 27 subjects during bicycle testing at 1 investigative site (Columbia University). Seventy-seven percent of these subjects were male, with an average age of 55 ± 11

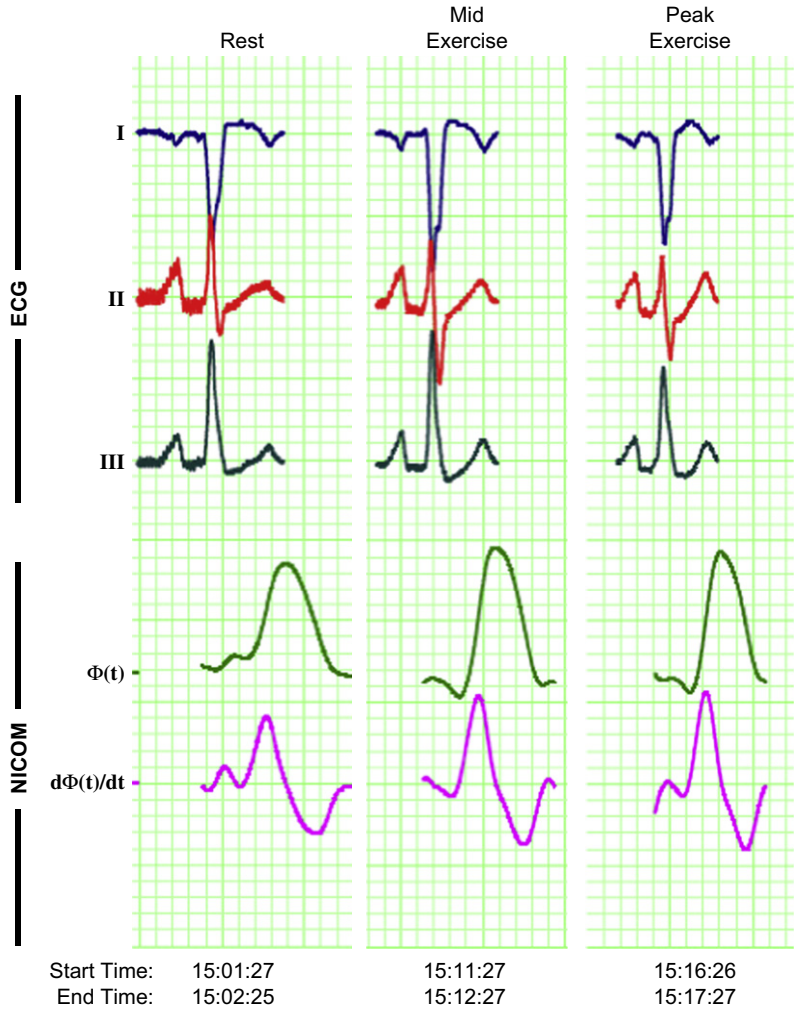


**Fig. 1.** Physiologic signals provided by the bioreactance system. The signals include 3 leads of electrocardiogram (leads I, II, and III), the time-dependent phase shift (Φ(t), that is the fundamental bioreactance signal) and its first derivative (dΦ(t)/dt, which is related to aortic flow). Each column shows tracing that represent 1-minute signal averages.

years, and weighing 87 ± 22 kg. All patients had a history of heart failure with an average ejection fraction of 20 ± 16% and NYHA Class of 1 (n = 3), 2 (n = 16), or 3 (n = 8) (average 2.2 ± 0.7). Exercise duration averaged 701 ± 246 seconds, achieving a peak work load of 78 ± 33 watts. Systolic/diastolic blood pressures were 113 ± 15/71 ± 13 mm Hg at rest, compared with 140 ± 38/80 ± 13 mm Hg at peak exercise. Oxygen consumption was 3.9 ± 0.9 mL $O_2$·kg·min at rest versus 14.7 ± 4.4 mL $O_2$/kg/min at peak exercise, at which point the respiratory exchange ratio averaged 1.06 ± 0.10. The relationship between CO measured by the 2 techniques is summarized in Fig. 4A, with the corresponding Bland and Altman plots in Fig. 4B. With the exception of 2 points on the graph of Fig. 4A, the data fell close to the line of identity ($CO_{Innocor} = 0.94 + 0.79$ $CO_{NICOM}$, $r = 0.834$). Combining data from rest and peak exercise, the overall average CO by NICOM was 7.1 ± 3.1 L/min versus 6.7 ± 3.2 L/min for the Innocor system; the mean difference (ie, bias) 0.4 L/min, which was not statistically different than 0 ($P = .10$). The limits of agreement between the techniques ranged from 2.3 and −1.5 L/min and the difference between the measurements did not vary systematically with the average value of the measurements.

The relations between CO and $VO_2$ (including both resting and peak exercise data) are shown in Fig. 4C with CO measured by NICOM and Fig. 4D with CO measured by Innocor, along with their respective regression lines (solid red lines). Also shown in each graph are similar data obtained from prior studies in which COs were measured by invasive techniques (either direct Fick method with blood drawn from a right heart catheter[34] or with the indicator dilution method using venous injections and arterial sample on indocyanine green dye[35]). As seen, the data from the current study generally conform to the data obtained in these prior studies for both CO measurement devices.

### Effect of Exercise on Hemodynamics in Different NYHA Classes and Different Modes of Exercise

The basic clinical features and stress test results are summarized in Table 1 for the 105 subjects who underwent bicycle testing and in Table 2 for the 127 subjects who underwent treadmill testing. For each mode of exercise

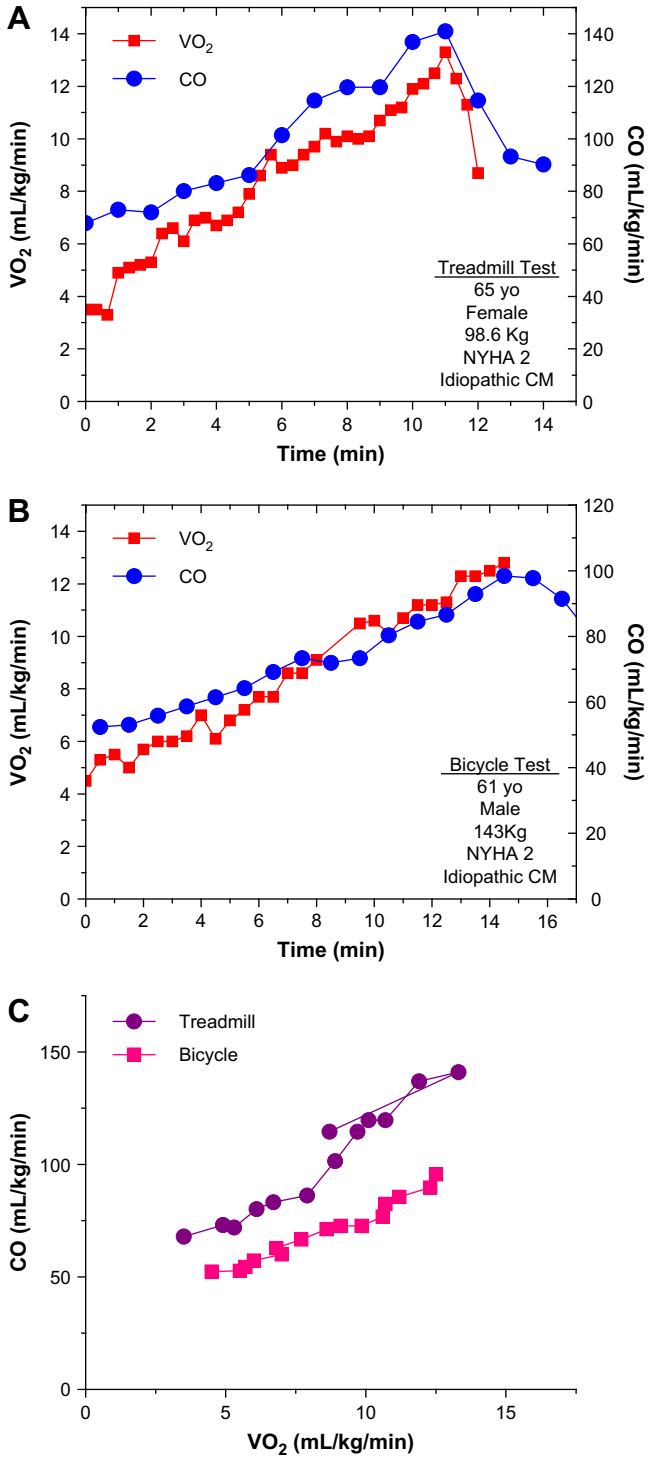


**Fig. 2.** Time course of changes in $VO_2$ and cardiac output (CO) during treadmill (A) and bicycle (B) tests. Correlations between $VO_2$ and CO (C) reveal proportional changes in these parameters throughout exercise. Other clinical details related to these examples in the figure inserts.

testing, results are grouped according to NYHA functional classification. Twenty-two of the participants in the treadmill group had no history of heart failure (these are designated, for convenience, as NYHA 0). This group consisted of 16 patients referred for evaluation of coronary artery

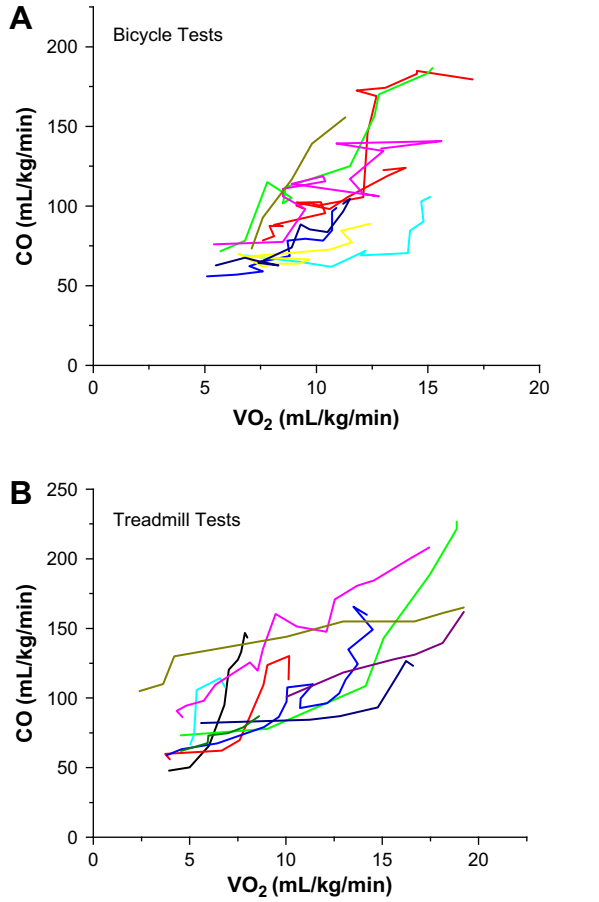


**Fig. 3.** Additional examples showing the relationship between $VO_2$ and cardiac output from the start to the peak of exercise for bicycle (A) and treadmill (B) tests. Although these variables are reasonably linearly correlated for a given patient, this relationship varies significantly from patient to patient.

disease, 3 patients with corrected congenital heart disease, 1 patient with a history of mitral regurgitation, 1 patient with a history of pericarditis, and 1 patient with Raynaud disease. The majority of study participants were NYHA Class II or III. Nine patients in the bicycle group had NYHA Class 4 symptoms. Therefore, overall, patients in the bicycle group were slightly more compromised, with NYHA averaging 2.6 versus 1.9 in the treadmill group. There were also small but statistically significant differences between the cohorts in age ($P = .02$, older in the bicycle group), ejection fraction ($P = .04$, lower in the bicycle group), and gender (77% male in the bicycle group versus 61% male in the treadmill group, $P = .03$) (all $P$ values adjusted for the other covariates using MLRA). Additionally, ejection fraction decreased ($P < .0001$) and age increased with worsening NYHA ($P = .0003$). Medication use, summarized in Table 3, did not differ between groups. β-blocker and either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was high, but was lower in the NYHA Class IV patients.

Each measured variable differed between rest and at peak exercise. The results of statistical testing of the determinants

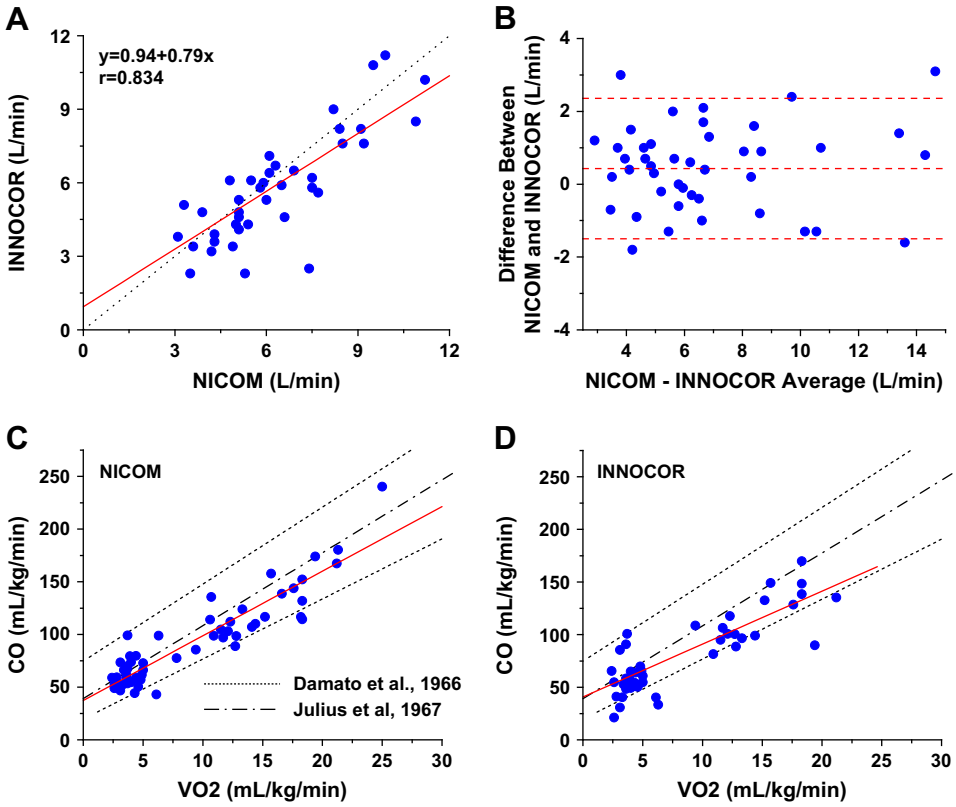


**Fig. 4.** (A) Relationship between cardiac output (CO) measured by the bioreactance technique (NICOM) and the inert gas rebreathing Fick method (Innocor). (B) Bland and Altman plot summarizing the concordance between NICOM and Innocor measurements of CO. Dashed lines (from top to bottom) show the upper limit of agreement, the bias, and the lower limit of agreement. (C) Relation between CO and $VO_2$, with CO measured with the bioreactance-based NICOM. (D) Relation between CO and $VO_2$, with CO measured with the Innocor system. Data in all panels include measurements at rest and at peak exercise. In (C) and (D), prior results obtained by invasive CO measures by Damato et al[34] and by Julius et al,[35] as indicated in the legend of (C) panel.

of hemodynamic factors at peak exercise incorporating data from all 232 study participants and accounting for the impact of mode of exercise testing (bicycle versus treadmill testing), NYHA class, gender, age, and EF are summarized in Table 4. The value of the intercept signifies the average value of each parameter obtained from all study participants; the value of each coefficient signifies the quantitative contribution of the specified parameter to each hemodynamic variable; values are only provided when the contribution is statistically significant ($P < .05$). For example, referring to the data in Table 4, peak exercise CO = 19.6 + 4 · M-2.1 · NYHA + 1.9 · G−0.09 · Age, where M = 1 for a treadmill test and 0 for a bicycle test, G = 1 for male and 0 for female, and age is in years; note that peak exercise CO was not dependent on ejection fraction.

Test duration was lower with treadmill than bicycle testing, was lower with worse NYHA class, and with increasing age, but was higher in male subjects. Peak exercise heart rate was higher during treadmill testing, was lower in males, and decreased with increasing NYHA. Systolic and mean pressures increased with EF; SBP was higher in males.

Resting $VO_2$ did not differ between subgroups. Respiratory exchange ratio at peak exercise increased slightly with ejection fraction, but did not otherwise differ between groups indicating similar degrees of effort during exercise. Despite this, peak $VO_2$ was higher during treadmill than bicycle exercise, was lower with increasing NYHA class and increasing age, and was higher in males. Peak $VO_2$ was not impacted by ejection fraction.

Resting values of CO, CI, COn, SV, and SVI trended lower with increasing NYHA class, but where not consistently dependent on other factors. Peak exercise values of CO, CI, COn, SV, and SVI all decreased with increasing NYHA class. Values for these variables at peak exercise were all greater during treadmill exercise and all decreased with increasing values of NYHA. Gender and age differences existed in some of these variables as summarized in Table 4. None of these parameters were dependent on EF.

Resting values for TPR and TPRI were higher as NYHA class increased ($P = .01$ and .03, respectively). At peak exercise, these parameters decreased more significantly during treadmill compared to bicycle testing and were higher in subjects with higher NYHA classes. Furthermore, *vascular reserve* (indexed by the percent reduction in TPR at peak exercise) was greater during treadmill testing and was also greater with increased NYHA classes.

Left ventricular power and power index were lower at increased NYHA classes at rest and at peak exercise. These

**Table 1.** Baseline Demographic and Exercise Data from Bicycle Tests*

| | | NYHA 1 Mean ± SD | NYHA 2 Mean ± SD | NYHA 3 Mean ± SD | NYHA 4 Mean ± SD |
|---|---|---|---|---|---|
| n | | 10 | 35 | 51 | 9 |
| AGE | | 48.1 ± 20.8 | 52.6 ± 12.1 | 57.3 ± 116 | 59.5 ± 7.1 |
| % Male | | 80 | 82 | 74 | 75 |
| Ejection fraction | | 38 ± 18 | 28 ± 11 | 26 ± 13 | 26 ± 9 |
| Stress test results | | | | | |
| Test duration | | 943 ± 196 | 742 ± 173 | 539 ± 179 | 397 ± 96 |
| HR (bpm) | Resting | 75 ± 11 | 75 ± 13 | 75 ± 16 | 82 ± 19 |
| | Peak | 130 ± 21 | 117 ± 23 | 102 ± 21 | 100 ± 21 |
| SBP (mm Hg) | Resting | 118 ± 19 | 115 ± 15 | 111 ± 15 | 105 ± 18 |
| | Peak | 165 ± 28 | 140 ± 31 | 131 ± 25 | 115 ± 22 |
| MAP (mm Hg) | Resting | 89 ± 16 | 86 ± 9 | 83 ± 9 | 83 ± 12 |
| | Peak | 111 ± 17 | 100 ± 16 | 95 ± 15 | 86 ± 15 |
| VO2 (mL/kg/min) | Resting | 4.1 ± 06 | 3.8 ± 0.8 | 3.7 ± 0.9 | 3.7 ± 1.1 |
| | Peak | 20.2 ± 4.0 | 15.3 ± 3.1 | 11.1 ± 2.5 | 7.8 ± 0.8 |
| RER | Peak | 1.03 ± 0.12 | 1.09 ± 0.10 | 1.06 ± 0.11 | 1.05 ± 0.17 |
| CO (L/min) | Resting | 4.8 ± 2.0 | 5.3 ± 1.3 | 4.5 ± 1.3 | 3.7 ± 0.9 |
| | Peak | 15.1 ± 8.1 | 11.9 ± 4.2 | 9.6 ± 4.4 | 9.7 ± 5.4 |
| CI (L/min/M$^2$) | Resting | 2.3 ± 0.8 | 2.6 ± 0.5 | 2.2 ± 0.5 | 2.0 ± 0.3 |
| | Peak | 7.3 ± 3.4 | 5.8 ± 2.1 | 4.8 ± 1.8 | 4.9 ± 2.6 |
| COn (mL/kg/min) | Resting | 56.7 ± 21.7 | 61.1 ± 11.9 | 52.8 ± 12.5 | 50.6 ± 8.6 |
| | Peak | 177.0 ± 81.9 | 139.0 ± 59.5 | 110.3 ± 34.3 | 118.1 ± 61.3 |
| SV (mL) | Resting | 65.9 ± 32.2 | 71.4 ± 20.4 | 60.8 ± 18.1 | 46.7 ± 10.6 |
| | Peak | 121.5 ± 72.1 | 101.2 ± 32.9 | 96.7 ± 43. | 93.6 ± 61.6 |
| SVI (mL/M$^2$) | Resting | 32.0 ± 13.2 | 35.3 ± 8.4 | 30.6 ± 8.4 | 25.6 ± 5.5 |
| | Peak | 58.6 ± 30.8 | 50.7 ± 17.4 | 47.9 ± 18.6 | 48.4 ± 28.5 |
| TPR (mm Hg·min/L) | Resting | 22.4 ± 11.3 | 17.1 ± 3.9 | 20.1 ± 6.6 | 21.9 ± 5.4 |
| | Peak | 10.4 ± 9.0 | 9.4 ± 3.2 | 11.4 ± 4.7 | 12.4 ± 7.3 |
| TPRI (mm Hg·min/L/M$^2$) | Resting | 44.4 ± 20.8 | 33.9 ± 6.8 | 39.3 ± 11.7 | 41.9 ± 8.8 |
| | Peak | 20.2 ± 16.0 | 18.8 ± 6.7 | 22.2 ± 7.9 | 22.3 ± 11.8 |
| % Vasodilation | | 54.8 ± 17.6 | 43.0 ± 18.8 | 41.0 ± 20.3 | 45.2 ± 23.3 |
| LV power (watts) | Resting | 0.95 ± 0.47 | 1.01 ± 0.30 | 0.83 ± 0.27 | 0.69 ± 0.22 |
| | Peak | 3.83 ± 2.41 | 2.57 ± 0.90 | 2.08 ± 1.09 | 1.70 ± 0.87 |
| LV power index | Resting | 0.46 ± 0.18 | 0.50 ± 0.11 | 0.41 ± 0.11 | 0.37 ± 0.08 |
| (watts/M$^2$) | Peak | 1.83 ± 1.01 | 1.29 ± 0.49 | 1.02 ± 0.44 | 0.8 ± 0.39 |
| Peak/rest $VO_2$ | | 5.14 ± 1.50 | 4.18 ± 1.27 | 3.14 ± 1.03 | 2.23 ± 0.52 |
| Peak/rest CO | | 3.20 ± 1.46 | 2.32 ± 1.00 | 2.32 ± 1.58 | 2.53 ± 1.76 |

*All parameters measured at rest and at peak exercise differed from each other ($P < .05$); see Table 4 for $P$ values for other comparisons.

parameters were greater at peak exercise during treadmill compared with bicycle exercise. Similarly, metabolic reserve (indexed by peak/rest $VO_2$) and cardiac reserve (indexed by peak/rest CO) were greater during treadmill exercise and decreased with increasing NYHA.

We also assessed the role of background medication on the hemodynamic responses to exercise. The only parameter that emerged was that peak exercise heart rate was decreased in the setting of β-blocker use (coefficient = −14, $P = .001$). Importantly, neither β-blocker nor angiotensin blockade impacted CO or vascular resistance at rest or at peak exercise.

Finally, using MLRA, we directly explored the correlations between peak exercise CO and peak $VO_2$, including potential covariates. We found a strong correlation between peak $VO_2$ and peak COn (both in units of mL/kg/min), with mode of exercise and gender as significant contributing cofactors: $COn = 59 + 6.6 \cdot pVO_2 + 36.2 \cdot M\text{-}24.8 \cdot G$ ($P < .001$, $r = 0.69$). Factors such as age, ejection fraction, NYHA, and medication use did not significantly influence this relationship. There were weak, though statistically significant, correlations between peak systolic blood pressure and peak CO ($P = .01$, $r = 0.16$) and between peak systolic blood pressure and peak $VO_2$ ($P < .001$, $r = 0.33$).

## Discussion

The present study, performed in a relatively large number of patients, demonstrates that CO can readily be measured at rest and throughout symptom limited treadmill or bicycle exercise using the bioreactance technique in patients with heart failure spanning a wide range of NYHA classes recruited from multiple centers. The physiologic information obtained about heart failure conforms well with data from several prior studies in which CO was measured invasively and reinforces the concept that assessment of key hemodynamic parameters derived from measurement of stroke volume and CO during stress is significantly more useful for assessing disease severity than is assessment of these same parameters at rest. The data also reinforce several important features about the pathophysiology of heart failure.

Although resting values of CO, SV, and left ventricular power were slightly lower in heart failure than in controls, these parameters did not vary significantly with NYHA class. However, the ability to augment cardiac performance as indexed by these parameters was progressively impaired with increasing NYHA class (Tables 1, 2, and 4). This is consistent with the well documented progressive decline in peak $VO_2$ with increasing NYHA class that was also

**Table 2.** Baseline Demographic and Exercise Data from Treadmil Tests*

| | | NYHA 1 Mean ± SD | NYHA 2 Mean ± SD | NYHA 3 Mean ± SD | NYHA 4 Mean ± SD |
|---|---|---|---|---|---|
| n | | 22 | 13 | 51 | 41 |
| AGE | | 49.7 ± 12.3 | 55.0 ± 17.0 | 58.1 ± 12.7 | 59.2 ± 9.7 |
| % Male | | 50 | 69 | 62 | 63 |
| Ejection fraction | | 58 ± 5 | 36 ± 16 | 37 ± 14 | 28 ± 9 |
| Stress test results | | | | | |
| Test duration | | 586 ± 149 | 682 ± 243 | 604 ± 185 | 507 ± 212 |
| HR (bpm) | Resting | 70 ± 16 | 73 ± 10 | 73 ± 14 | 73 ± 13 |
| | Peak | 145 ± 28 | 144 ± 30 | 128 ± 20 | 11 ± 520 |
| SBP (mm Hg) | Resting | 115 ± 13 | 110 ± 18 | 113 ± 15 | 110 ± 17 |
| | Peak | 148 ± 15 | 154 ± 26 | 149 ± 29 | 136 ± 23 |
| MAP (mm Hg) | Resting | 88 ± 13 | 84 ± 11 | 84 ± 9 | 83 ± 12 |
| | Peak | 101 ± 17 | 102 ± 13 | 100 ± 16 | 94 ± 13 |
| VO2 (mL/kg/min) | Resting | 4.0 ± 1.0 | 3.1 ± 1.2 | 3.6 ± 2.0 | 3.5 ± 1.1 |
| | Peak | 22.1 ± 4.7 | 19.8 ± 6.9 | 16.1 ± 4.3 | 13.9 ± 4.2 |
| RER | Peak | 1.14 ± 0.10 | 1.09 ± 0.08 | 1.08 ± 0.10 | 1.05 ± 0.12 |
| CO (L/min) | Resting | 6.5 ± 1.7 | 5.8 ± 1.9 | 5.1 ± 2.3 | 5.0 ± 1.7 |
| | Peak | 20.5 ± 5.8 | 17.0 ± 4.4 | 16.1 ± 4.6 | 12.8 ± 4.6 |
| CI (L/min/M$^2$) | Resting | 3.2 ± 0.9 | 3.0 ± 0.9 | 2.6 ± 1.0 | 2.6 ± 0.8 |
| | Peak | 10.1 ± 2.8 | 8.8 ± 2.2 | 8.3 ± 2.0 | 6.7 ± 2.4 |
| COn (mL/kg/min) | Resting | 75.7 ± 23.8 | 75.0 ± 27.4 | 60.0 ± 20.1 | 61.7 ± 21.8 |
| | Peak | 236.4 ± 76.2 | 215.9 ± 70.3 | 190.9 ± 49.2 | 159.8 ± 67.6 |
| SV (mL) | Resting | 95.4 ± 27.2 | 79.0 ± 28.0 | 71.7 ± 32.7 | 70.9 ± 30.4 |
| | Peak | 146.7 ± 47.0 | 123.1 ± 44.1 | 129.0 ± 43.2 | 113.0 ± 40.8 |
| SVI (mL/M$^2$) | Resting | 47.2 ± 12.4 | 42.0 ± 14.0 | 36.5 ± 13.8 | 36.9 ± 15.1 |
| | Peak | 72.0 ± 21.5 | 63.2 ± 19.0 | 66.2 ± 19.2 | 59.3 ± 23.0 |
| TPR (mm Hg·min/L) | Resting | 14.7 ± 5.1 | 16.7 ± 6.7 | 19.3 ± 10.5 | 18.1 ± 5.3 |
| | Peak | 5.5 ± 1.9 | 6.7 ± 2.9 | 6.7 ± 2.4 | 8.3 ± 3.2 |
| TPRI | Resting | 29.9 ± 11.1 | 31.2 ± 12.9 | 37.2 ± 21.5 | 34.1 ± 8.0 |
| (mm Hg·min/L/M$^2$) | Peak | 10.9 ± 3.0 | 12.4 ± 3.9 | 13.0 ± 4.4 | 15.5 ± 5.1 |
| % Vasodilation | | 60.7 ± 15.1 | 56.7 ± 15.9 | 60.8 ± 17.1 | 52.5 ± 17.4 |
| LV power (watts) | Resting | 1.28 ± 0.48 | 1.02 ± 0.28 | 0.96 ± 0.43 | 0.93 ± 0.34 |
| | Peak | 4.60 ± 1.04 | 3.83 ± 1.04 | 3.59 ± 1.05 | 2.71 ± 1.22 |
| LV power index | Resting | 0.64 ± 0.23 | 0.55 ± 0.15 | 0.49 ± 0.16 | 0.48 ± 0.16 |
| (watts/M$^2$) | Peak | 2.27 ± 0.57 | 2.00 ± 0.54 | 1.84 ± 0.47 | 1.42 ± 0.62 |
| Peak/rest $VO_2$ | | 5.77 ± 1.66 | 7.06 ± 3.30 | 4.97 ± 1.80 | 4.55 ± 2.85 |
| Peak/rest CO | | 3.33 ± 1.07 | 3.22 ± 1.16 | 3.51 ± 1.38 | 2.68 ± 0.92 |

*All parameters measured at rest and at peak exercise differed from each other ($P < .05$); see Table 4 for $P$ values for other comparisons.

observed in the present study. Importantly, the inability to increase CO was due both to a NYHA class-dependent progressive blunting of the ability to increase heart rate (a well-established finding) and SV. In turn, the inability to increase SV is contributed to by the statistically significant reduced vasodilatory capacity with worsening NYHA class.

Availability of CO measurements allows for calculation of several less widely recognized indexes that served to differentiate between different NYHA classes. The *cardiac reserve index* (defined as the ratio of peak to resting CO) and left ventricular power (the product of MAP and CO) are 2 such examples. Left ventricular power, along with peak $VO_2$ and peak CO, has been proposed as an important predictor of outcomes in heart failure.[7] In particular, one recent study showed that peak cardiac power was the most powerful single predictor of outcome and that peak CO was equal to peak $VO_2$ as a predictor of outcome.[20]

In addition, the bioreactance technique allows for continuous CO measurement throughout exercise. Data revealed a reasonably linear relationship between $VO_2$ and CO in individual patients. However, this relationship differed significantly from patient to patient (Fig. 3). The interpretation of this relationship is complex, however, because it is dependent on the rate of oxygen extraction ($AVO_2$) from the periphery, so that: $VO_2(t) = CO(t) \cdot AVO_2(t)$. Because the ability to extract oxygen can vary during exercise and differs based on the level of physical fitness and with different degrees of heart failure, the relation between $VO_2$ and CO throughout exercise is expected to vary from patient to patient. Future studies could readily employ this technique to study these factors, which could yield new insights into the relationship between $VO_2$ to CO at varying levels of exercise.

The present study allowed use of exercise tests performed on either treadmill or upright bicycles. We analyzed results of these testing modalities separately and our results confirm prior studies by showing that peak $VO_2$ is lower during bicycle than treadmill testing.[36] Our results extend these findings by demonstrating that a wide range of hemodynamic parameters differ between bicycle and treadmill testing, all in a fashion consistent with the idea that treadmill exercise imposes significantly greater cardiovascular stress than bicycle testing. Such differences include higher peak values for heart rate, CO, SV, LV power, and the degree of vasodilation on the treadmill.

The accuracy of the NICOM device to measure CO noninvasively and to accurately detect changes in CO as compared with thermodilution has been demonstrated in 2

**Table 3.** Summary of the Percent of Study Participants in each Group Taking Various Classes of Medications

| | NYHA0 | | NYHA1 | | NYHA2 | | NYHA3 | | NYHA4 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B | T | B | T | B | T | B | T | B | T |
| Diuretic | n/a | 9.1 | 40.0 | 69.2 | 82.4 | 75.0 | 81.3 | 92.7 | 88.7 | n/a |
| ACEI | n/a | 9.1 | 80.0 | 76.9 | 76.5 | 75.0 | 56.3 | 82.9 | 33.0 | n/a |
| ARB | n/a | 4.5 | 10.0 | 15.4 | 11.8 | 25.0 | 20.8 | 12.2 | 11.1 | n/a |
| β-blocker | n/a | 68.2 | 80.0 | 84.6 | 91.2 | 94.2 | 91.7 | 95.1 | 77.8 | n/a |
| aldosterane blocker | n/a | 0.0 | 40.0 | 61.5 | 47.1 | 48.1 | 39.6 | 70.7 | 55.6 | n/a |
| statin | n/a | 59.1 | 40.0 | 38.5 | 50.0 | 73.1 | 62.5 | 73.2 | 44.4 | n/a |

B, subjects in the bicycle group T, subjects in the treadmill group, n/a, not applicable; NYHA, New York Heart Association; ACEI, angiotenisin converting enzyme inhibitor; ARB angiotensin receptor blocker.

prior studies.[26,27] These studies compared invasive thermodilution and NICOM-based measurements of CO over long periods (up to 24 hours), in varied clinical settings spanning wide ranges of CO values. Results of 1 other prior study[28] also showed a fairly tight relationship between $VO_2$ and CO at rest and at peak exercise that was similar to that reported in earlier studies.[34,35] The best approach to obtain additional validation of NICOM during exercise would be to measure CO by thermodilution at peak exertion (similar to what was done in the prior studies of patients in the intensive care unit already having a pulmonary artery catheter). We did not take that approach in the context of this multicenter study in which we aimed to study a relatively large number of patients, however, because of the added risks associated with such an approach. Instead, we turned to another noninvasive approach to CO measurement: the Fick method using an inert gas rebreathing technique that has also been studied previously during rest and exercise.[29–32] Although that system has also not been extensively validated and acknowledging that there is no other truly validated noninvasive method of CO measurement applicable during exercise testing, the good correlation between bioreactance and Fick-based measurements of CO at rest and at peak exercise provides additional support for accuracy of these techniques. The fact that the relationships between CO and $VO_2$ observed with both systems conform well to those of prior studies using invasive techniques to measure CO[34,35] (Fig. 4) further strengthens this argument. The Bland and Altman analysis resulted in limits of agreement that were ± 1.9 L/min around a statistically insignificant 0.4 L/min bias; importantly, the difference between the 2 techniques was uniform across the range of COs measured. These limits of agreement are very similar to what is obtained in the comparison of almost any 2 methods of CO measurement *at rest*, including comparisons between thermodilution and the Fick

**Table 4.** Results of Multiple Linear Regression Summarizing Coefficients of the Impact of Mode of Exercise Testing, NYHA, Gender, Age, and EF on Specified Parameters

| | | | Mode of Exercise | | NYHA | | Gender* | | Age | | EF | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Intercept | Coef | *P* | Coef | *P* | Coef | *P* | Coef | *P* | Coef | *P* |
| Peak Exercise | | | | | | | | | | | | |
| Test duration | | 893 | −90 | .001 | −79 | <0.0001 | 83 | 0.003 | −2.2 | .03 | | ns |
| HR (bpm) | | 158 | 14 | <.0001 | −9 | <0.0001 | | ns | −0.45 | <.0001 | | ns |
| SBP (mm Hg) | | 110 | | ns | | ns | 7.4 | 0.05 | | ns | 0.8 | <.0001 |
| MAP (mm Hg) | | 84 | | ns | | ns | | ns | | ns | 0.39 | <.0001 |
| VO2 (mL/kg/min) | | 24 | 2.1 | .0002 | −2.9 | <0.0001 | 1.26 | 0.02 | −0.08 | <.0001 | | ns |
| RER | | 1.03 | | ns | | ns | | ns | | ns | 0.39 | <.0001 |
| CO (L/min) | | 19.6 | 4.0 | <.0001 | −2.1 | <0.0001 | 1.9 | 0.004 | −0.09 | .0007 | | ns |
| CI (L/min/$M^2$) | | 9.3 | 2.2 | <.0001 | −1 | <0.0001 | | ns | −0.03 | .03 | | ns |
| COn (mL/min/kg) | | 204 | 45 | <.0001 | −25 | <0.0001 | −18 | 0.032 | | ns | | ns |
| SV (mL) | | 110.00 | 21.7 | .0004 | −10.5 | 0.0006 | 21.5 | 0.0005 | | ns | | ns |
| SVI (mL/$M^2$) | | 60.0 | 12.1 | <.0001 | −4.0 | 0.01 | | ns | | ns | | ns |
| TPR (mm Hg·min/L) | | 5.40 | −3.5 | <.0001 | 1.4 | <0.0001 | | ns | | ns | 0.07 | .004 |
| TPRI (mm Hg·min/L/$M^2$) | | 12.40 | −7.0 | <.0001 | 2.2 | 0.0002 | | ns | | ns | 0.1 | .01 |
| % Vasodilation | | 50.60 | 12.0 | <.0001 | 2.6 | 0.05 | | ns | | ns | | ns |
| LV power | Resting | 1.60 | | ns | −0.1 | <0.0001 | | ns | −0.008 | <0.0001 | | ns |
| (watts) | Peak | 4.30 | 0.85 | <.0001 | −0.60 | <0.0001 | 0.48 | 0.004 | −0.01 | 0.017 | | ns |
| LV power index | Resting | 0.74 | | ns | −0.04 | <0.0001 | | ns | −0.003 | 0.001 | | ns |
| (watts/$M^2$) | Peak | 1.92 | 0.42 | <.0001 | −0.29 | <0.0001 | | ns | | ns | | ns |
| Peak/rest $VO_2$ | | 5.33 | 1.10 | <.0001 | −0.68 | <0.0001 | | ns | | ns | | ns |
| Peak/rest CO | | 2.92 | 0.62 | .0008 | −0.19 | 0.03 | | ns | | ns | | ns |

Comparisons are for values at peak exercise except as otherwise noted; see text for further details. NYHA, New York Heart Association; EF, ejection fraction; HR, heart rate; SBP, Systolic blood pressure; MAP, mean arterial pressure; RER, respiratory exchange ratio; CO, Cardiac output; CI, cardiac index; COn, normalized cardiac output; SV, stroke volume; SVI, stroke volume index; TPR, total peripheral resistance; TPRI, total peripheral resistance index; LV, left ventricular.

†Mode of exercise is a categorical variable set to 1 for treadmill and to 0 for bicycle detesting.

*Gender is a categorical variable set to 1 for male and 0 for female.

method.[27,37–43] Given that these limit of agreement included data at peak exercise, the results signify a clinically acceptable degree of agreement between these 2 noninvasive methods.

In comparison to metabolic and CO measurements obtained through assessment of gas exchange, the bioreactance technique is not associated with patient discomfort and requires neither patient cooperation nor patient training. Accordingly, the bioreactance system can also easily be used in patients with severe heart failure, and even unstable patients, which is not generally possible with methods requiring measurement of expired gases.

There are several potential limitations of the present study that should be acknowledged. First, we relied on NYHA for grading severity of heart failure for purposes of grouping patients. The NYHA classification system is subjective and not ideal. The large standard deviations in all the parameters measured (Tables 1, 2) means that there is significant overlap in their respective values between the different NYHA classes, indicating that NYHA does not sharply discriminate between patients with different degrees of hemodynamic compromise. Despite its limitations, use of NYHA in clinical practice and in most observational and interventional clinical trials remains the standard and, for the present purposes, was successful in segregating patients into groups in which average values of hemodynamic, clinical, and functional parameters varied in proportion. Nevertheless, the interpretation of the present results should be considered within the context of the inherent limitations of the NYHA classification system. Second, although measurement of CO by the NICOM is continuous during exercise, measurement by the inert gas technique is made at the end of exercise; therefore, the 2 measurements are not strictly simultaneous but were typically less than 1 minute apart. Because CO decreases fairly rapidly after exercise is terminated (eg, as illustrated in the curves in Fig. 2A), this can contribute to the +0.4 L/min bias noted between NICOM and the inert gas techniques. Although this bias was not statistically significant ($P = .10$), this could have reached statistical significance had more patients been included. Further, although the limits of agreement between NICOM and the inert gas technique ($\sim \pm 2$ L/min) is similar to those obtained when other CO measurement techniques are compared, caution is still warranted concerning the level of agreement between the 2 methods.

Finally, we included a group of patients with normal ejection fraction and no history of heart failure per se. These patients were primarily those with coronary artery disease and hypertension (explaining the high β-blocker, vasodilator, and statin use). Thus, although this group cannot serve as true normal control patients, they did have the highest resting values of CO and attained the greatest values of CO and CO-derived hemodynamic parameters in response to exercise. Nevertheless, in the future, it may be important to obtain data from a group of age-matched truly normal controls.

## Summary and Conclusions

In summary, using the bioreactance-based noninvasive measurements of CO at rest and at peak exertion, we identified NYHA class-dependent pathophysiologic abnormalities of cardiovascular function consistent with those identified in prior studies using invasive methods of CO measurement.[4,5] These consisted of NYHA class-dependent limitations in ability to increase CO because of both chronotropic incompetence and inability in increase SV during symptom-limited exercise as well as class-dependent limitations in vasodilatory capacity. In addition to confirming correlations between CO and $VO_2$ over a very wide range of values, we have also identified strong NYHA class-dependent reductions in peak LV power, an index of cardiovascular reserve (peak/resting $VO_2$), and an index of cardiac reserve (peak/resting CO). Collectively, these data highlight the utility of exercise CO measurements and suggest that such measurements might be useful clinically for indexing disease severity, for prognostication, and for tracking specific hemodynamic responses during disease progress or in response to treatment. This is significant because these parameters can be measured more easily than $VO_2$ and may provide the same prognostic information; future studies will have to validate this hypothesis. The present results demonstrate, however, that important hemodynamic parameters can be obtained in any clinic with a treadmill or stationary bicycle without the need for a metabolic cart or specially trained technicians. Significantly, in settings where a metabolic cart is available, measurement of exercise CO provides information that is complementary to that provided by gas exchange. These same features indicate the likely feasibility of using the bioreactance-based measurement of CO in large, multicenter studies.

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