Cardiac output estimated noninvasively from oxygen uptake during exercise

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Stringer, William W., James E. Hansen, and K. Wasserman. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J. Appl. Physiol.* 82(3): 908–912, 1997.—Because gas-exchange measurements during cardiopulmonary exercise testing allow noninvasive measurement of oxygen uptake ($\dot{V}O_2$), which is equal to cardiac output (CO) × arteriovenous oxygen content difference [C(a-vD_{O_2})], CO and stroke volume could theoretically be estimated if the C(a-vD_{O_2}) increased in a predictable fashion as a function of %maximum $\dot{V}O_2$ ($\dot{V}O_{2max}$) during exercise. To investigate the behavior of C(a-vD_{O_2}) during progressively increasing ramp pattern cycle ergometry exercise, 5 healthy subjects performed 10 studies to exhaustion while arterial and mixed venous blood were sampled. Samples were analyzed for blood gases (pH, P_{CO_2}, P_{O_2}) and oxyhemoglobin and hemoglobin concentration with a CO-oximeter. The C(a-vD_{O_2}) (ml/100 ml) could be estimated with a linear regression [C(a-vD_{O_2}) = 5.72 + 0.105 × %$\dot{V}O_{2max}$; r = 0.94]. The CO estimated from the C(a-vD_{O_2}) by using the above linear regression was well correlated with the CO determined by the direct Fick method (r = 0.96). The coefficient of variation of the estimated CO was small (7–9%) between the lactic acidosis threshold and peak $\dot{V}O_2$. The behavior of C(a-vD_{O_2}), as related to peak $\dot{V}O_2$, was similar regardless of cardiac function compared with similar measurements from studies in the literature performed in normal and congestive heart failure patients. In summary, CO and stroke volume can be estimated during progressive work rate exercise testing from measured $\dot{V}O_2$ (in normal subjects and patients with congestive heart failure), and the resultant linear regression equation provides a good estimate of C(a-vD_{O_2}).

ramp pattern cycle ergometer exercise; arterial oxygen content; mixed venous oxygen content; direct Fick cardiac output

TO AVOID ARTERIAL and mixed venous blood sampling, a noninvasive method for estimating cardiac output (CO) during exercise has been sought for over 100 years. Prior noninvasive methods of estimating CO have relied on the rate of solution of inert gases or the estimation of CO_2 contents of mixed venous and arterial blood by analyzing expired gases (indirect Fick method) (1, 3, 4). These methods require sophisticated equipment, considerable technical expertise, and subject cooperation during the required breath-holding maneuvers. These measurements are likely to be invalid during exercise in patients with heart and lung disease with varying degrees of ventilation-perfusion mismatching and lactic acidemia. The end-tidal concentration will not reflect the arterial concentration, and in the case of the indirect Fick method, the assumption of mixed venous pH cannot be used during heavy exercise.

Cardiac output or stroke volume (SV) can be expressed as CO = SV × heart rate (HR) and as CO = O_2 uptake ($\dot{V}O_2$)/arteriovenous content difference [C(a-vD_{O_2})]. Because both HR and $\dot{V}O_2$ can be easily measured during standard incremental cardiopulmonary exercise testing (12, 13), both CO and SV could be accurately quantitated if the simultaneous C(a-vD_{O_2}) could be estimated.

In two previously published studies (11, 14) involving both normal and heart failure subjects, C(a-vD_{O_2}) and CO were measured as a function of $\dot{V}O_2$. In both studies, the C(a-vD_{O_2}) increased linearly as a function of %peak $\dot{V}O_2$ ($\dot{V}O_{2peak}$). Furthermore, in normal subjects as well as in patients with heart failure [ranging from patients with little or no impairment in aerobic capacity [maximum $\dot{V}O_2$ ($\dot{V}O_{2max}$) > 20 ml·kg^{-1}·min^{-1}] to severe impairment ($\dot{V}O_{2max}$ < 10 ml·kg^{-1}·min^{-1})], the maximum C(a-vD_{O_2}) was ~13–14 ml/dl or an extraction ratio [C(a-vD_{O_2})/arterial O_2 content] of 75% at peak exercise.

We therefore hypothesized that if C(a-vD_{O_2}) as a function of exercise intensity (%$\dot{V}O_{2max}$) increased in a predictable fashion, it would be possible to estimate CO noninvasively throughout exercise. To test this hypothesis, we measured C(a-vD_{O_2}) during progressive ramp pattern cycle ergometer exercise while continuously measuring $\dot{V}O_2$ and generated a regression of C(a-vD_{O_2}) as a function of %$\dot{V}O_{2max}$. From these estimates, we calculated CO and compared these estimates with CO determinations by the direct Fick method.

METHODS

Subjects. After informed consent was obtained, five healthy nonsmoking male subjects performed a preliminary noninvasive increasing work rate exercise test on an electromagnetically braked cycle ergometer (type 18070, Gould-Godart, Bilthoven, The Netherlands). Exercise capacity was quantified by determining their maximum work rate, lactic acidosis threshold (LAT) by the V-slope method (2, 10), and $\dot{V}O_{2max}$, defined as the $\dot{V}O_2$ averaged over the last 30 s of exercise.

Catheter placement. On the morning of testing, the subjects reported to the cardiac catheterization laboratory, and the right groin was shaved, cleaned, and anesthetized with lidocaine. Under sterile conditions, an 8-cm 10-Fr sheath (Cordis, Miami, FL) was inserted percutaneously into the right femoral vein 2 cm below the inguinal ligament by using the Seldinger technique (8). The sheath was secured with a single suture, and the catheter tip was positioned ~4 cm above the inguinal ligament. A flow-directed pulmonary arterial catheter (Arrow International, Reading, PA) was then introduced via the femoral vein sheath and positioned in the main pulmonary artery under direct fluoroscopic guidance. After catheter placement, the subject returned to the exercise physiology laboratory where a left brachial arterial catheter was placed percutaneously under local anesthesia. All catheters were attached to an infusion apparatus (Continu-Flo, Baxter Health Care, Deerfield, IL) that provided a slow

continuous flow (15 ml/h) of heparinized normal saline (1,000 U heparin/l) as well as periodic bolus flushing of the catheter.

Exercise protocols. Two progressive exercise tests to exhaustion were performed in each of the five subjects, with work rate increased at 25–40 W/min, depending on fitness. At least 1 h of rest separated the two exercise bouts.

Respired gas analysis. The subjects respired through a mouthpiece during each exercise period. Expired air was directed to a Fleisch no. 3 pneumotachograph via a breathing valve (100 ml dead space). Respired P_{O_2}, P_{CO_2}, and N_2 partial pressure at the mouthpiece were continuously measured by mass spectrometry (MGA-1100, Perkin Elmer, Pomona, CA). Minute ventilation (BTPS) and $\dot{V}_{O_2}$ and CO_2 output ($\dot{V}_{CO_2}$) (both STPD) were calculated as whole breath averages for each 30-s exercise period, as previously reported (9). The LAT was determined from a plot of millimoles $\dot{V}_{CO_2}$ vs. millimoles $\dot{V}_{O_2}$ (V-slope plot) as described by Beaver et al. (2).

Blood samples. Blood was sampled simultaneously from the pulmonary artery and brachial artery during rest, unloaded cycling, and at each minute of increasing work rate exercise.

Blood analysis. The blood samples were agitated and immediately chilled in an ice slurry. Blood-gas analysis was performed with an Instrumentation Laboratories 1306 blood-gas machine for pH, P_{CO_2}, P_{O_2}, and on a 482 CO-oximeter for total hemoglobin (Hb) and oxyhemoglobin saturation (Lexington, MA).

Data analysis and statistics. Data from the first and second tests from each subject were treated separately. The following standard equations were utilized in the data analysis

$$CO = \dot{V}_{O_2}/C(a\text{-}vD_{O_2}) \quad \text{(direct Fick method)} \qquad (1)$$

$$SV = CO/HR \qquad (2)$$

$$O_2 \text{ pulse} = \dot{V}_{O_2}/HR \qquad (3)$$

$$O_2 \text{ content} = 1.34 \cdot [Hb] \cdot O_2 \text{ saturation} \qquad (4)$$

$$C(a\text{-}vD_{O_2}) = \text{arterial } O_2 \text{ content} - \text{mixed venous } O_2 \text{ content} \qquad (5)$$

$$\text{Extraction ratio} = [C(a\text{-}vD_{O_2})/\text{arterial } O_2 \text{ content}] \qquad (6)$$

where [Hb] is Hb concentration.

Group mean values for mixed venous and arterial P_{O_2}, O_2 Hb saturation, O_2 content, and $C(a\text{-}vD_{O_2})$ were analyzed by repeated-measures analysis of variance. $C(a\text{-}vD_{O_2})$ was correlated with $\%\dot{V}_{O_{2max}}$ by the use of linear regression analysis. A $P < 0.05$ was considered significant. All values are expressed as means ± SE, unless otherwise specified.

RESULTS

The subject's physical characteristics and aerobic parameters were age 25 ± 6 (SD) yr, height 179 ± 4 cm, weight 72 ± 5 kg, resting arterial Hb 15.4 ± 0.21 g/dl, maximum work rate 296 ± 50 W, $\dot{V}_{O_{2max}}$ 3.77 ± 0.61 l/min, and LAT 1.84 ± 0.36 l/min (49% of $\dot{V}_{O_{2max}}$; see Table 1).

In Fig. 1, the group mean direct Fick CO, HR, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, lactate, SV, O_2 content, and O_2 pulse responses are displayed as a function of $\%\dot{V}_{O_{2max}}$ during exercise for the 10 exercise studies in the 5 study subjects (means ± SE). In Fig. 1*A*, the group mean CO (each minute during exercise) increases to ~80% of the maximal value at the LAT $\dot{V}_{O_2}$ (which is 48% of $\dot{V}_{O_{2max}}$, on average) and then increases more gradually for the remainder of exercise. HR (Fig. 1*B*), in contrast, continues to increase at the same rate throughout exercise. This results in a peak in SV at approximately the LAT (Fig. 1*D*), with a subsequent small but statistically significant fall as exercise progresses (final value differs from LAT value, $P < 0.05$). The absolute values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are plotted against $\%\dot{V}_{O_{2max}}$ (Fig. 1*C*). $\dot{V}_{CO_2}$ exceeds $\dot{V}_{O_2}$ after the LAT (respiratory exchange

Table 1. *$\dot{V}_{O_2}$ measured by gas exchange at LAT and maximum exercise and C(a-vDO_2) and extraction ratios at rest, LAT, and maximum exercise*

	$\dot{V}_{O_2}$		$C(a\text{-}vD_{O_2})$			LAT $C(a\text{-}vD_{O_2})$	Extraction Ratio		
Subject No.	LAT	Max	Rest	LAT	Max	$\%\dot{V}_{O_{2max}}$	Rest	LAT	Max
1									
A	2.10	4.37	5.33	11.70	17.47	52%	0.25	0.54	0.76
B	2.25	4.17	6.00	11.75	16.00	52%	0.27	0.51	0.73
2									
A	1.55	2.80	6.57	11.80	16.19	43%	0.30	0.54	0.70
B	1.30	2.80	9.32	10.95	14.64	50%	0.46	0.59	0.67
3									
A	2.38	4.45	5.38	11.80	18.23	52%	0.26	0.55	0.85
B	2.08	4.40	5.32	12.10	17.61	51%	0.28	0.53	0.85
4									
A	1.55	3.65	3.35	9.60	15.69	38%	0.16	0.46	0.67
B	1.53	3.64	4.84	10.40	14.86	42%	0.24	0.49	0.66
5									
A	1.85	3.65	7.91	12.20	15.70	47%	0.38	0.57	0.74
B	1.80	3.75	7.35	10.50	15.93	48%	0.39	0.54	0.78
Mean ± SD	1.84 ± 0.36	3.77 ± 0.61	6.14 ± 1.71	11.28 ± 0.87	16.23 ± 1.18	48% ± 5%	0.30 ± 0.09	0.53 ± 0.04	0.74 ± 0.07

Values are for 10 studies. Max, maximum exercise; $\dot{V}_{O_2}$, O_2 uptake; $C(a\text{-}vD_{O_2})$, arteriovenous O_2 content difference; LAT, lactate acidosis threshold; $\dot{V}_{O_{2max}}$, maximum $\dot{V}_{O_2}$. A, *test 1;* B, *test 2.*

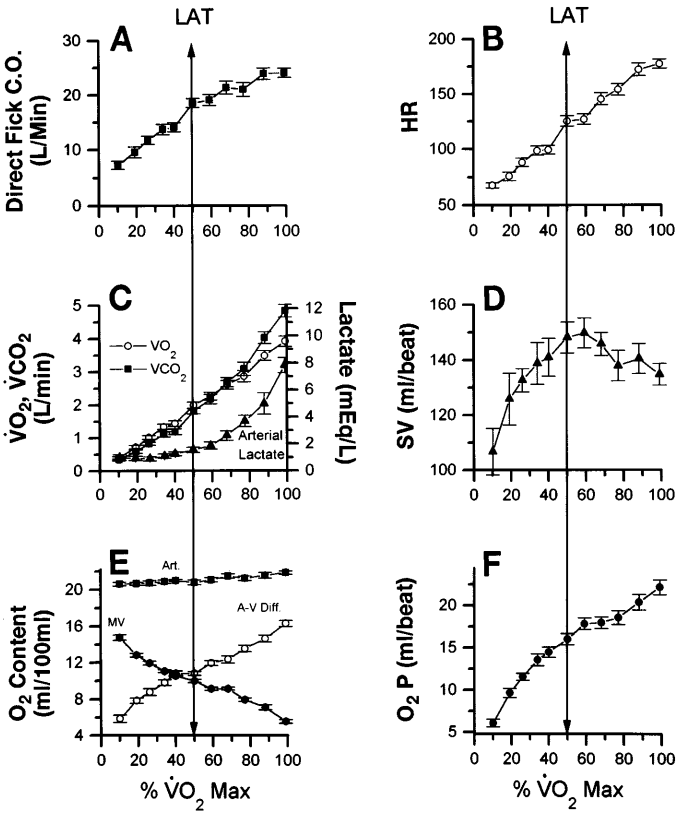

Fig. 1. Group data in normal subjects during ramp exercise. Values are means ± SD; n = 10 studies. Cardiac output (CO), heart rate (HR; beats/min), O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), lactate, stroke volume (SV), O_2 content, and O_2 pulse (O_2-P) responses are shown as functions of %maximum $\dot{V}O_2$ ($\dot{V}O_{2max}$) during ramp pattern cycle ergometer exercise. LAT, lactic acidosis threshold; Art, arterial; MV, mixed venous; A-V Diff, arteriovenous difference.

ratio >1.0) as would be expected. Figure 1*E* presents the arterial and mixed venous O_2 content and $C(a\text{-}vD_{O_2})$ during exercise. Arterial O_2 content increases slightly due to the increase in [Hb] (~1 g/dl) and to a lesser degree to an increase in arterial P_{O_2} above the LAT. Mixed venous O_2 content progressively decreases during exercise, resulting in a continuous increase in $C(a\text{-}vD_{O_2})$. Importantly, the increase in $C(a\text{-}vD_{O_2})$ as a function of $\%\dot{V}O_{2max}$ appears to be linear, increasing 51% to the LAT (49% of $\dot{V}O_{2max}$) and 49% between the LAT and $\dot{V}O_{2max}$. Finally, O_2 pulse (Fig. 1*F*) increases throughout exercise, with the majority of this increase occurring before the LAT (~66%). All of the increase in O_2 pulse above ~48% of $\dot{V}O_{2max}$ is attributable to the increase in $C(a\text{-}vD_{O_2})$.

The individual values of $C(a\text{-}vD_{O_2})$ (in ml/100 ml) as a function of $\%\dot{V}O_{2max}$ (10 studies in 5 subjects) are displayed in Fig. 2. The linear regression applied to the data reveals that the slope is ~0.10 ml·100 ml^{-1} ·$\%\dot{V}O_{2max}{}^{-1}$, and the intercept is 5.7 ml/100 ml. The even distribution (or scatter) of $C(a\text{-}vD_{O_2})$ over the entire range of $\%\dot{V}O_{2max}$ values is evident as well as the close approximation by a linear regression.

In Fig. 3, the group mean $C(a\text{-}vD_{O_2})$ values are plotted as a function of measured CO (±SE) with $\dot{V}O_2$ isopleths generated from the equation $\dot{V}O_2 = CO \times C(a\text{-}vD_{O_2})$

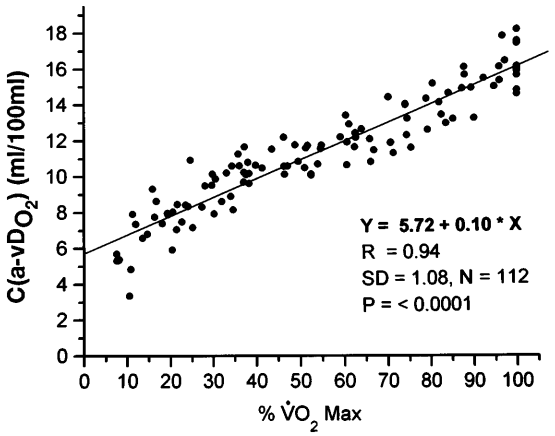

Fig. 2. Arteriovenous O_2 content differnce [$C(a\text{-}vD_{O_2})$] as a function of $\%\dot{V}O_{2max}$. Data were determined from systemic arterial and pulmonary arterial blood that was simultaneously sampled each minute during 10 progressively increasing work rate exercise tests in 5 subjects.

overlaid on the data. Graphing of CO as a function of $C(a\text{-}vD_{O_2})$ results in a rectangular hyperbole for each $\dot{V}O_2$. This display demonstrates three points: *1*) the importance of concurrent increases in both CO and $C(a\text{-}vD_{O_2})$ to obtain the highest $\dot{V}O_2$ during exercise; *2*) as the LAT is exceeded, CO increase plays a lesser role and $C(a\text{-}vD_{O_2})$ plays a greater role in the increase in $\dot{V}O_2$ (as illustrated in Fig. 1, *A* and *E*); and *3*) $C(a\text{-}vD_{O_2})$ becomes less important in estimating CO as the maximal $C(a\text{-}vD_{O_2})$ is approached because the slope of the hyperbola becomes proportionately more shallow.

In Fig. 4, the COs estimated from $\dot{V}O_2$ and $C(a\text{-}vD_{O_2})$ from the equation established from the data in Fig. 2 are plotted against the directly measured COs (calculated by the Fick principle for O_2). Each point is

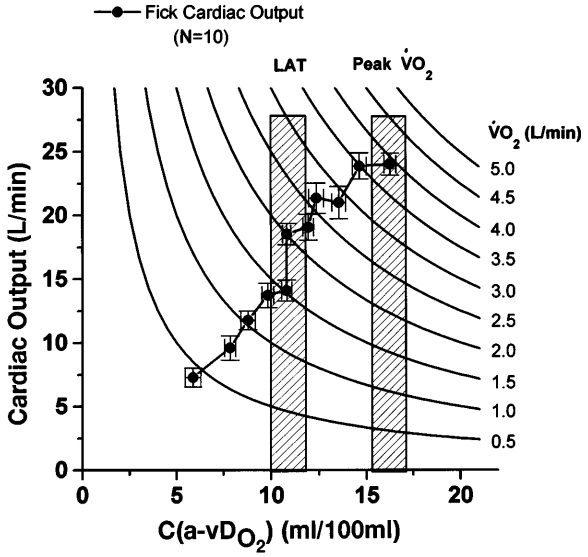

Fig. 3. CO as a function of $C(a\text{-}vD_{O_2})$ with superimposed $\dot{V}O_2$ isopleths. Group mean is ±SE. Isopleths are those calculated from following equation: $\dot{V}O_2 = CO \times C(a\text{-}vD_{O_2})$ for various $\dot{V}O_2$ values. Vertical hatched bars are means ± SD taken from Table 1. $\dot{V}O_{2peak}$, peak $\dot{V}O_2$.

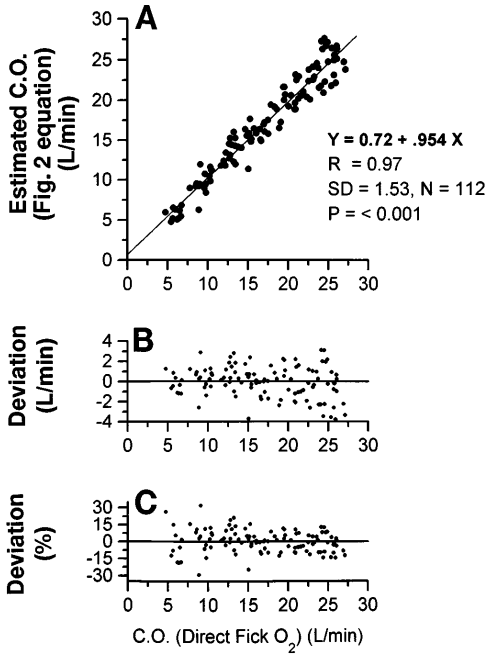

Fig. 4. Estimated CO (Fig. 2 equation) as a function of measured CO (direct Fick method). CO was estimated from $\dot{V}O_2$ and $C(a\text{-}vD_{O_2})$ by using the equation [$C(a\text{-}vD_{O_2}) = 5.721 + (0.1047 \times \%\dot{V}O_{2\,max})$; Fig. 4*A*]. Absolute (Fig. 4*B*) and relative deviations (Fig. 4*C*) plotted against measured COs (calculated by Fick principle for O_2).

determined from the data set of simultaneously measured arterial and mixed venous O_2 content and $\dot{V}O_2$. Estimated CO = measured $\dot{V}O_2$/[5.721 + (0.1047 × $\%\dot{V}O_{2\,max}$)]. As can be seen, the directly measured and estimated COs are highly correlated, and the slope and intercept do not differ statistically from one and zero, respectively. In Fig.4*B*, the absolute deviation of the estimated CO and the measured (Fick) COs are displayed. In Fig. 4*C*, the %deviation from the measured value across the range of COs is displayed. The deviation from the directly measured values was almost always 15% or less across the entire range of COs (5–28 l/min). This is comparable to the variability of estimating CO by any of the methods currently available (6, 7).

Table 1 displays the mean $\dot{V}O_2$ values measured by gas exchange at LAT and maximum exercise and the $C(a\text{-}vD_{O_2})$ and the extraction ratios at rest, LAT, and maximum exercise. There is considerably less variation in $C(a\text{-}vD_{O_2})$ and the extraction ratio at LAT and at $\dot{V}O_{2\,max}$ [coefficient of variation (CV) = SD/mean ≅7–9%] than at rest (CV = 20–30%).

Figure 5 shows the data of Weber and Janicki (14), Sullivan et al. (11), and the present study for the values of CO and $C(a\text{-}vD_{O_2})$ plotted on a graph showing the $\dot{V}O_2$ isopleths. The Sullivan et al. study contained normal study subjects as well as patients with CHF; the Weber and Janicki (14) study contained only CHF patients with a range of disease severity. The reduction in measured $\dot{V}O_2$ (and the subsequent decreased ability to perform external work) during exercise in the patients with cardiac disease was primarily related to a reduced ability to increase CO rather than a reduced ability to increase $C(a\text{-}vD_{O_2})$. Regardless of the level of maximally measured $\dot{V}O_2$ [normal subjects (>54 ml·kg^{-1}·min^{-1}) to CHF patients (<10 ml·kg^{-1}·min^{-1})], the maximal $C(a\text{-}vD_{O_2})$ at end exercise were all 12.5–16.5 ml/100 ml. [Note the Hb values used to calculate the $C(a\text{-}vD_{O_2})$ were not detailed in either study, and anemia in the patients would result in a reduced maximal $C(a\text{-}vD_{O_2})$]. If the $C(a\text{-}vD_{O_2})$ of the studies by Weber and Janicki (14) and Sullivan et al. (11) (both CHF patients and normal subjects) are plotted with the present study as a function of $\%\dot{V}O_{2\,max}$ (Fig. 6), a similar regression, intercept, and slope comparable to Fig. 2 are obtained, despite a wide variation in cardiac function.

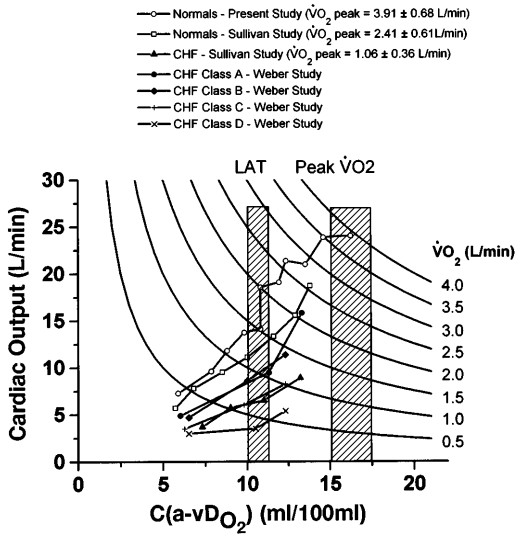

Fig. 5. CO in normal and congestive heart failure patients (CHF). Data are shown from Sullivan [Sullivan et al. (11)] and Weber [Weber and Janicki (14)] studies and from present study for values of CO and measured $C(a\text{-}vD_{O_2})$ plotted on a graph showing $\dot{V}O_2$ isopleths. Normals, normal subjects.

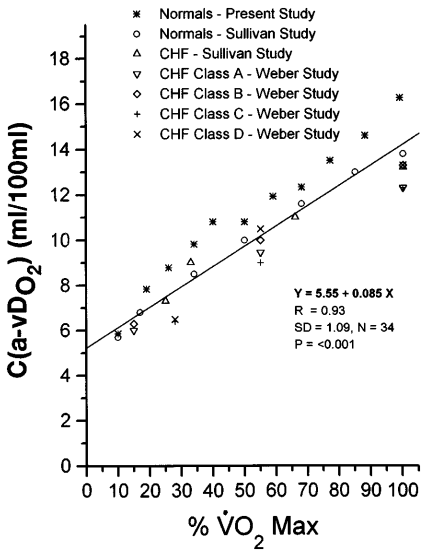

Fig. 6. Regression of $C(a\text{-}vD_{O_2})$ values. If $C(a\text{-}vD_{O_2})$ from studies of Weber and Janicki (14) and Sullivan et al. (11) (both congestive heart failure and normal subjects) are plotted with present study as a function of $\%\dot{V}O_{2\,max}$, a similar regression with a similar intercept and slope to those in Fig. 2 is obtained, despite a wide variation in cardiac function.

DISCUSSION

The recognition by Fick (5) that virtually all of the heart's output passed through the lungs and, therefore, that the law of conservation of mass could be applied to measure CO from measured $\dot{V}O_2$ and the O_2 content differences across the lung sets the foundation for the present study. A totally noninvasive determination of CO and SV during exercise would be very useful in normal subjects as well as in patients with various degrees of cardiac insufficiency. Both CO and SV could be estimated from $\dot{V}O_2$ and HR if the behavior of $C(a\text{-}vD_{O_2})$ were known. Because $C(a\text{-}vD_{O_2})$ behaves in a consistent pattern in response to upright cycle exercise in the present study (and in other reports) (11, 14), we believe that CO can be estimated from $\dot{V}O_2$ alone at the LAT and $\dot{V}O_{2max}$ on the basis of the predictability and reduced variability of $C(a\text{-}vD_{O_2})$ at these points.

We found that in normal subjects, the majority of the CO increase occurred before the LAT (Fig. 1*A*), although $\dot{V}O_2$ continued to increase throughout exercise (Fig. 1*C*). $C(a\text{-}vD_{O_2})$ increased in a relatively linear fashion throughout exercise (Figs. 1*E* and 2). Additionally, the predicted CO with the use of the linear regression equation from Fig. 2 resulted in small, nonsystematic deviations from the actual CO measurements (Fig. 4). If $\dot{V}O_{2max}$ were not reached during exercise, the CO could be estimated from a $C(a\text{-}vD_{O_2})$ of 11.3 ml/100 ml (see Fig. 5) at the LAT because this level of exercise is reached in normal subjects and in most patients with cardiovascular and lung diseases during exercise testing. Finally, we found the highest SV is reached at the LAT (Fig. 1*D*) in normal subjects; SV is unlikely to rise much farther with increasing exercise intensity either in patients or in normal subjects. In a comparison of the results from the present study to prior studies in which CO and $C(a\text{-}vD_{O_2})$ were determined in normal subjects and in patients with CHF (11, 14), the $C(a\text{-}vD_{O_2})$ values were quite similar when compared at $\dot{V}O_{2peak}$ (Fig. 6), despite a very large range of CO responses.

Therefore, in a consideration of the interrelationships among CO, $C(a\text{-}vD_{O_2})$, and $\dot{V}O_2$, as plotted in Figs. 3 and 5, and the relatively narrow ranges of $C(a\text{-}vD_{O_2})$ at the LAT and $\dot{V}O_{2peak}$, three major points become apparent. *1*) In normal subjects, both CO and $C(a\text{-}vD_{O_2})$ increase severalfold from rest to $\dot{V}O_{2peak}$. *2*) In patients with cardiovascular disease resulting in a reduced $\dot{V}O_{2peak}$, the CO can be validly estimated because it is much more dependent on the $\dot{V}O_{2peak}$ reached than the absolute level of $C(a\text{-}vD_{O_2})$ estimated [note the shallow slope of the isopleths as maximal $C(a\text{-}vD_{O_2})$ is approached]. *3*) In CHF patients and normal subjects, CO (and peak SV) can be well estimated from the $\dot{V}O_2$ at the subject's LAT. Although patients with primary lung disease would be expected to manifest a similarly low $\dot{V}O_{2peak}$ (see above), the present results must be evaluated and validated in this particular subject group.

We conclude that CO can be accurately estimated from $\dot{V}O_2$ during exercise in normal subjects and patients with heart failure by measuring the LAT or $\dot{V}O_{2peak}$. From these data and HR, SV can be calculated. This can provide a simple and low-cost assessment of cardiac function (CO and SV) in response to exercise that is independent of disturbed lung physiology and acid-base changes during exercise.

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