

## Estimating exercise stroke volume from asymptotic oxygen pulse in humans

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**Whipp, Brian J., Michael B. Higgenbotham, and Frederick C. Cobb.** Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *J. Appl. Physiol.* 81(6): 2674–2679, 1996.—Noninvasive techniques have been devised to estimate cardiac output ( $\dot{Q}$ ) during exercise to obviate vascular cannulation. However, although these techniques are noninvasive, they are commonly not noninvasive to subjects' spontaneous ventilation and gas-exchange responses. We hypothesized that the exercise stroke volume (SV) and, hence,  $\dot{Q}$  might be accurately estimated simply from the response pattern of two standardly determined variables:  $\text{O}_2$  uptake ( $\dot{V}\text{O}_2$ ) and heart rate (HR). Central to the theory is the demonstration that the product of  $\dot{Q}$  and mixed venous  $\text{O}_2$  content is virtually constant ( $k$ ) during steady-state exercise. Thus from the Fick equation,  $\dot{V}\text{O}_2 = \dot{Q} \cdot \text{Ca}_{\text{CO}_2} - k$ , where  $\text{Ca}_{\text{CO}_2}$  is the arterial  $\text{CO}_2$  content, the  $\text{O}_2$  pulse ( $\text{O}_2\text{-P}$ ) equals  $\text{SV} \cdot \text{Ca}_{\text{CO}_2} - (k/\text{HR})$ . Because the arterial  $\text{O}_2$  content ( $\text{Ca}_{\text{O}_2}$ ) is usually relatively constant in normal subjects during exercise,  $\text{O}_2\text{-P}$  should change hyperbolically with HR, asymptoting at  $\text{SV} \cdot \text{Ca}_{\text{O}_2}$ . In addition, because the asymptotic  $\text{O}_2\text{-P}$  equals the slope ( $S$ ) of the linear  $\text{O}_2\text{-HR}$  relationship, exercise SV may be predicted as  $S/\text{Ca}_{\text{O}_2}$ . We tested this prediction in 23 normal subjects who underwent a 3-min incremental cycle-ergometer test with direct determination of  $\text{Ca}_{\text{O}_2}$  and mixed venous  $\text{O}_2$  content from indwelling catheters. The predicted SV closely reflected the measured value ( $r = 0.80$ ). We therefore conclude that, in normal subjects, exercise SV may be estimated simply as five times  $S$  of the linear  $\dot{V}\text{O}_2\text{-HR}$  relationship (where 5 is approximately  $1/\text{Ca}_{\text{O}_2}$ ).

cardiac output; oxygen uptake; heart rate

THE EXERCISE STROKE VOLUME ( $\text{SV}_{\text{ex}}$ ) is one of the most important indexes of both the functional state of the heart and the propensity for achieving a high level of physical activity. Consequently, several noninvasive estimators have been developed that obviate the requirements for intravascular catheterization. Noninvasive methods such as Doppler (5) and impedance (23) techniques require technical acumen for accurate determination and also are not commonly available to most laboratories. Estimation procedures such as  $\text{CO}_2$  re-breathing (12) or acetylene uptake (10), on the other hand, temporarily disrupt the determination of other ventilatory and gas-exchange variables that may also be of interest during the exercise test. They do, how-

ever, all allow the stroke volume (SV) profile to be estimated.

We describe in this paper a method of estimating a single average value for  $\text{SV}_{\text{ex}}$  in normal subjects that uses only standardly computed variables and, consequently, does not disrupt the temporal profile of any other variable of interest during the investigation.

### METHODS

*Theory.* We hypothesize that a single average value for  $\text{SV}_{\text{ex}}$  can be accurately estimated from the response profiles of  $\text{O}_2$  uptake ( $\dot{V}\text{O}_2$ ) and heart rate (HR) in normal healthy subjects. The ratio of  $\dot{V}\text{O}_2$  and HR represents the  $\text{O}_2$  pulse ( $\text{O}_2\text{-P}$ ); this simply is derived from the Fick equation

$$\frac{\dot{V}\text{O}_2}{\text{HR}} = \frac{\dot{Q} \times \text{Ca}_{\text{O}_2}}{\text{HR}} - \frac{\dot{Q} \times \text{C}\bar{\text{v}}_{\text{O}_2}}{\text{HR}} \quad (1)$$

or

$$\text{O}_2\text{-P} = \text{SV}_{\text{ex}} \times \text{Ca}_{\text{O}_2} - \frac{\dot{Q} \times \text{C}\bar{\text{v}}_{\text{O}_2}}{\text{HR}} \quad (2)$$

where  $\text{Ca}_{\text{O}_2}$  and  $\text{C}\bar{\text{v}}_{\text{O}_2}$  are the arterial and mixed venous  $\text{O}_2$  contents, respectively, and  $\dot{Q}$  is cardiac output.

Central to this theory is the demonstration (6) that the product of  $\dot{Q}$  and  $\text{C}\bar{\text{v}}_{\text{O}_2}$  is virtually constant over a wide range of steady-state work rates. Therefore, Eq. 2 can be rewritten as

$$\text{O}_2\text{-P} = \text{SV}_{\text{ex}} \times \text{Ca}_{\text{O}_2} - \frac{k}{\text{HR}} \quad (3)$$

where  $k$  is the constant.

Because  $\text{Ca}_{\text{O}_2}$  is normally relatively constant during exercise,  $\text{O}_2\text{-P}$  should therefore change hyperbolically with respect to HR (as shown in Fig. 1A), with an asymptote on the  $\text{O}_2\text{-P}$  axis at a value of  $\text{SV}_{\text{ex}} \times \text{Ca}_{\text{O}_2}$ . That is, as shown in Eq. 3, as HR becomes large,  $k/\text{HR}$  tends at zero, at which time  $\text{O}_2\text{-P}$  equals  $\text{SV}_{\text{ex}} \times \text{Ca}_{\text{O}_2}$ . Therefore, when  $\text{O}_2\text{-P}$  is plotted as a function of  $1/\text{HR}$ , it results in a linear relationship (Fig. 1B) that extrapolates to the asymptotic  $\text{O}_2\text{-P}$ . In the region in which  $\dot{V}\text{O}_2$  changes as a linear function of HR, the asymptotic  $\text{O}_2\text{-P}$  is nothing more than the slope of the  $\dot{V}\text{O}_2\text{-HR}$  relationship, i.e.,  $\Delta\dot{V}\text{O}_2/\Delta\text{HR}$ , as shown in Fig. 1C. Hence

$$\frac{\Delta\dot{V}\text{O}_2}{\Delta\text{HR}} = \text{SV}_{\text{ex}} \times \text{Ca}_{\text{O}_2} \quad (4)$$

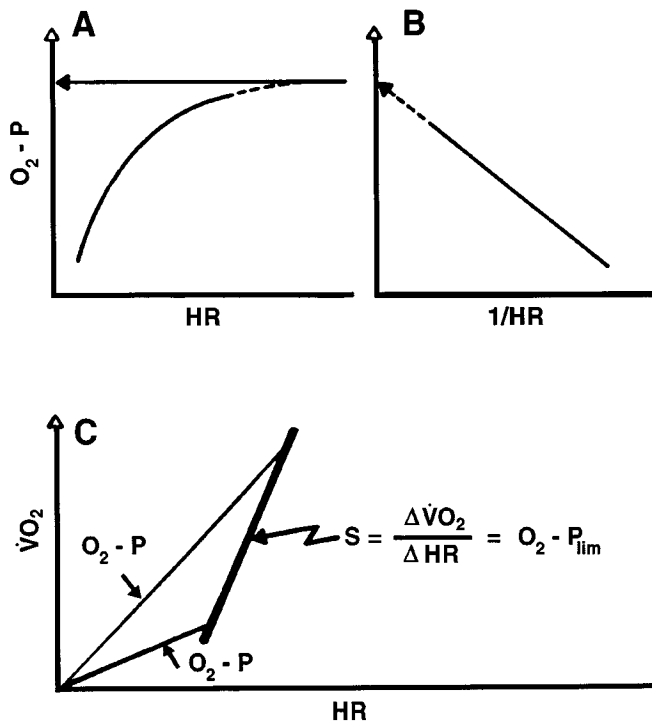


Fig. 1. A: schematic representation of time course of  $O_2$  pulse ( $O_2$ -P) as function of heart rate (HR) in response to progressively increasing work rates. Solid arrow, asymptotic value for  $O_2$ -P, i.e., not maximally attained value. B: profile of  $O_2$ -P as function of  $1/HR$ . C: relationship between  $O_2$  uptake ( $\dot{V}O_2$ ) and HR for progressively increasing exercise. Note that linear  $\dot{V}O_2$ -HR relationship results in progressive increase in  $O_2$ -P, such that in the limit slope (S) of  $O_2$  as function of HR is equivalent to asymptotic  $O_2$ -P (i.e.,  $O_2$ -P<sub>lim</sub>).

or

$$SV_{ex} = \frac{\frac{\Delta \dot{V}O_2}{\Delta HR}}{Ca_{O_2}} \quad (5)$$

By using a somewhat different approach, Cole and Miller (4) have also theorized that this relationship should hold true.<sup>1</sup> That is, if  $Ca_{O_2}$  has been determined before or during the exercise (the exercise-induced hemoconcentration produces only a small error term), then SV may be calculated. If not, it may be closely estimated, i.e., as  $Ca_{O_2}$  (in l/l) approximately equals 0.2 in normal subjects, then

$$SV_{ex} = 5 \times \frac{\Delta \dot{V}O_2}{\Delta HR} \quad (6)$$

**Experiments.** We tested this prediction in 23 healthy men aged between 20 and 50 yr who had a normal medical history and physical examination and were not receiving medications. The subjects' heights ranged from 173 to 185 cm, weights from 63 to 103 kg, and hemoglobin concentrations from 13.2 to 16.7 g/100 ml. The subjects gave informed consent for the study, which was approved by the Institutional Ethical Review Board.

The subjects each performed an incremental exercise test on an electromagnetically braked cycle ergometer (Fitron,

Lumes) with the work rate increased in 25-W steps, each lasting 3 min, up to 125 W. The pedaling frequency was maintained between 60 and 70 revolutions/min. This profile is widely used in exercise testing, since in normal subjects it allows steady states of  $\dot{Q}$  and  $\dot{V}O_2$  to be attained. One hour before the test, a 2-in. cannula was inserted percutaneously into the brachial artery, and a 7-Fr Swan-Ganz catheter was positioned in the pulmonary artery via an antecubital vein. At rest, and in the last 30 s of each work rate, arterial and mixed venous blood (2–3 ml) was drawn for measurement of  $O_2$  content (model 282, Instrumentation Laboratory). HR was monitored by standard electrocardiographic leads.

Expired volume was measured with a turbine volume sensor (Alpha Technologies) calibrated with known volumes of room air at mean flows and flow profiles spanning the exercise range. Respired air was sampled continuously at the mouthpiece for continuous measurement of  $PO_2$  (Fuel Cell analyzer) and  $PCO_2$  (Infrared analyzer). Precision-analyzed mixtures were used for calibration. The time delay between the volume and gas-concentration signals was measured by passing a bolus of gas through the system (2). Electrical signals from these devices underwent analog-to-digital conversion and were processed (model 2000, Sensorsmedics) for breath-to-breath determination of pulmonary gas-exchange variables but with particular reference to  $\dot{V}O_2$  ( $\dot{V}O_2$  STPD).

**RESULTS**

The typical response profiles for the gas-exchange and cardiovascular variables of interest are shown in Figs. 2 and 3.  $\dot{V}O_2$  increased as a linear function of work rate with a slope of  $\sim 10 \text{ ml} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ , as previously demonstrated (9, 21), and  $\dot{Q}$  increased linearly with respect to  $\dot{V}O_2$  with a slope of  $\sim 5$ . The mean slope of this relationship (Fig. 3) was actually 5.6, with an SE of estimate of 0.29 and an intercept on the  $\dot{Q}$  axis of 5.2 l/min with an SE of 0.41. The dashed lines in Fig. 3 represent a 95% confidence interval, ranging from 5.00

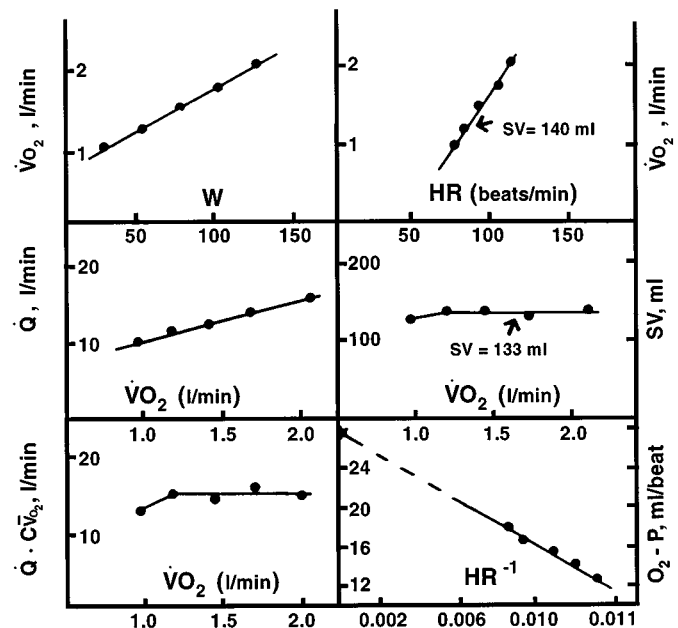


Fig. 2. Representative example of profile of changes of variables of interest in response to incremental exercise in normal subject.  $\dot{Q}$ , cardiac output;  $C\bar{v}O_2$ , mixed venous  $O_2$  content; SV, stroke volume; W, work rate.

<sup>1</sup>We thank Dr. James Reed for drawing this abstract to our attention.

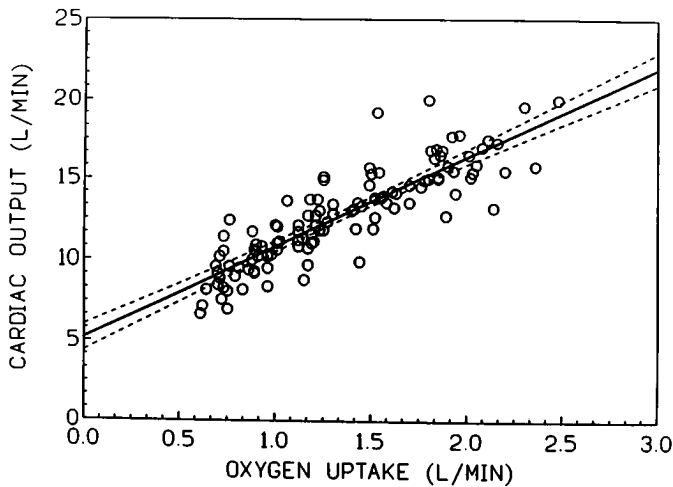


Fig. 3.  $\dot{Q}$ , determined by direct Fick measurements as function of  $\dot{V}O_2$  in 23 normal subjects performing incremental exercise. Solid line through data points, regression line; dashed lines, 95% confidence limits on slope.

to 6.17 for the slope and from 4.38 to 6.02 for the intercept on the  $\dot{Q}$  axis. This resulted in an  $r$  of 0.87 and an  $r^2$  of 0.76.

The product of  $\dot{Q}$  and  $C\bar{v}O_2$  (the returning  $O_2$  delivery to the lung), however, was not constant in our studies but increased initially before becoming stable over the higher work-rate range. This was a consistent pattern in all of our subjects. However, the increase of  $\dot{V}O_2$  as a function of HR was linear over this work-rate range. The linearity of this response predicts that  $O_2$ -P as a function of  $1/HR$  will consequently be linear. This is depicted in Fig. 2, *bottom right*. SV, estimated noninvasively from the slope of the  $\dot{V}O_2$ -HR relationship, was shown to be 140 ml in this subject. This compares well with the measured SV of 133 ml. It is important to point out that the actual SV was not constant over this work-rate range; rather, it increased from an average of  $108 \pm 17$  (SD) ml at 25 W to  $115 \pm 16$  ml at 125 W.

Figure 4 depicts the relationship between the SV estimated, as described in METHODS, as a function of the SV determined from the direct Fick computation of  $\dot{Q}$  and the measured HR and also the difference between the measured and estimated value as a function of the average of the two values, as proposed by Bland and Altman (3). This demonstrated a good relationship between the variables. The estimated SV correlated highly with the directly measured SV ( $r = 0.78$ ,  $r^2 = 0.61$ ). The slope of this relationship was 0.77, with 95% confidence limits from 0.49 to 1.05. The SV intercept was 24.1 ml; this was not significantly different from zero, since the 95% confidence limited extended from  $-7.4$  to 57.0 ml. The mean difference between the measured and the estimated SV values, however, was only 0.9 ml ( $\pm 2$  SD = 18 ml) (i.e., there was no significant difference between them), and only three of the points were not within 10% of the measured value.

In Fig. 5, the SV was estimated by using the inverse of the measured  $Ca_{O_2}$  as the multiplier of the  $\dot{V}O_2$ -HR slope. This differs from the method used in Fig. 4, in which we used the value 0.2 as the  $Ca_{O_2}$ . This

changed the relationship somewhat but not statistically significantly. The slope increased to 0.85, with 95% confidence limits from 0.60 to 1.09 and an SV intercept of 12.5 ml, which again was not significantly different from zero (the 95% confidence intervals extend from  $-14.5$  to 39.6 ml). Similarly, the correlation coefficient for this relationship increased somewhat to an  $r$  of 0.85 and an  $r^2$  of 0.73. The difference between these two values averages 3 ml ( $\pm 2$  SD = 19 ml). The use of the directly measured  $Ca_{O_2}$  in the estimation algorithm corrected one of the two noticeably errant points in Fig. 4. The other point, however, remained noticeably low even with this correction.

Consequently, although it does not allow the profile of SV change to be determined, the simple algorithm for estimating the exercise SV noninvasively, as described in METHODS, may be considered to have resulted in acceptable estimations (Fig. 4) with respect to the values actually measured for 21 of the 23 subjects.

## DISCUSSION

The value of a noninvasive estimator of a cardiovascular variable such as SV depends on the constructs

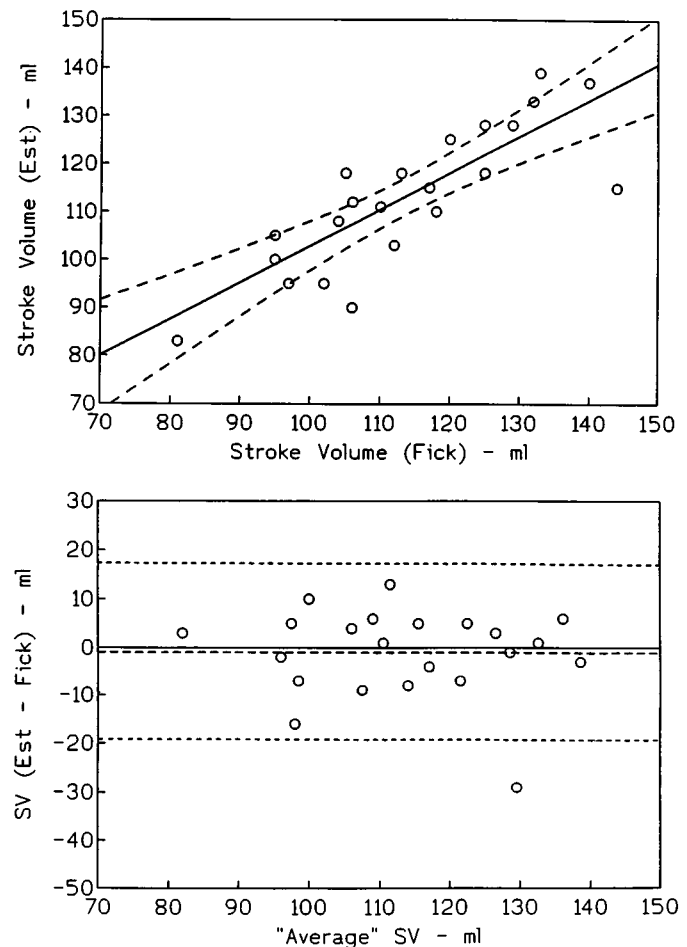


Fig. 4. *Top*: estimated SV (assuming  $Ca_{O_2}$  to equal 0.2 l/l) plotted as function of SV determined directly from Fick measurements. Dashed lines, 95% confidence limits on slope. *Bottom*: difference between measured and estimated value as function of average of 2 values, as proposed by Bland and Altman (3).

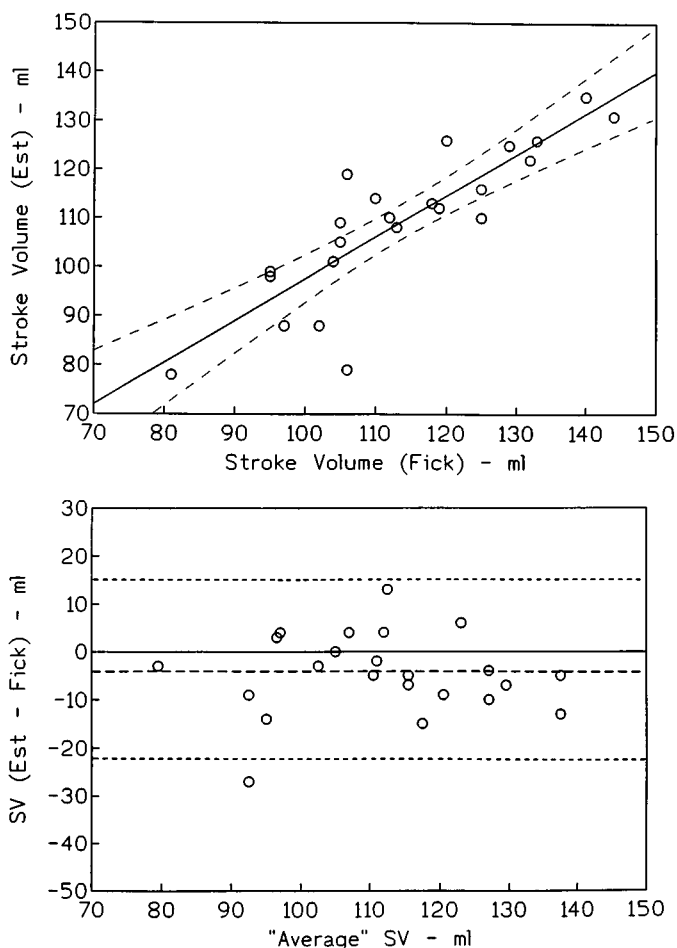


Fig. 5. *Top*: SV estimated (Est) as in Fig. 4 but in this case using measured value for  $Ca_{O_2}$ . Dashed lines, 95% confidence limits on slope. *Bottom*: difference between measured and estimated value as function of average of 2 values, as proposed by Bland and Altman (3).

that underlie the estimation procedure having a sound basis in physiology and on it providing useful information with an appropriate degree of accuracy. The physiological basis of this estimation lies in the implication of the widely reported linear relationship between  $\dot{V}O_2$  and HR during exercise in healthy subjects. This relationship has, as a necessary consequence, a hyperbolic increase in  $O_2$ -P in this range. It is important to recognize, however, that although our technique for estimating SV depends on the asymptotic  $O_2$ -P, it is not necessary that  $O_2$ -P actually attains, or even closely approaches, this asymptotic value. It is only necessary that, over the range in which it is measured, it changes as though it would attain this asymptotic value were the response to continue. This means that even if nonlinearities in the  $\dot{V}O_2$ -HR rate relationships were to occur at very high work rates (i.e., resulting in distortions in the hyperbolic increase in  $O_2$ -P), the projection derived from the appropriate regions remains valid. That is, the variables of interest must have an appropriate pattern of response to meet the criteria for the estimation; without this, the estimation should not be attempted. Because the pattern of the  $\dot{V}O_2$ -HR response was typically linear, the simple estimation procedure

of multiplying the slope of the  $\dot{V}O_2$ -HR relationship by five (i.e., the inverse of the  $Ca_{O_2}$ ) consequently provided a highly acceptable estimation of the directly measured SV, as shown in Fig. 4. In fact, the difference between the measured and estimated values was not significantly different.

We also tested our estimation algorithm on data available in the literature (1, 7-9, 11, 16-20) that 1) allowed the asymptotic  $O_2$ -P to be determined from an adequate number of data points and 2) provided SV measurements or both Q and HR. Data included subjects of varying fitness levels and included effects of physical training. However, the tests were all sufficiently long that steady states of  $\dot{V}O_2$  and Q would have likely been attained. As shown in Fig. 6, the results cohered well with our experimental findings despite the fact that the Q values in these studies were determined by a variety of techniques, including  $CO_2$  and acetylene rebreathing, dye dilution, and direct Fick.

In 2 of the 23 subjects in our study, the values were noticeably and unacceptably low. In one subject, this proved to be a consequence of an unexpectedly low

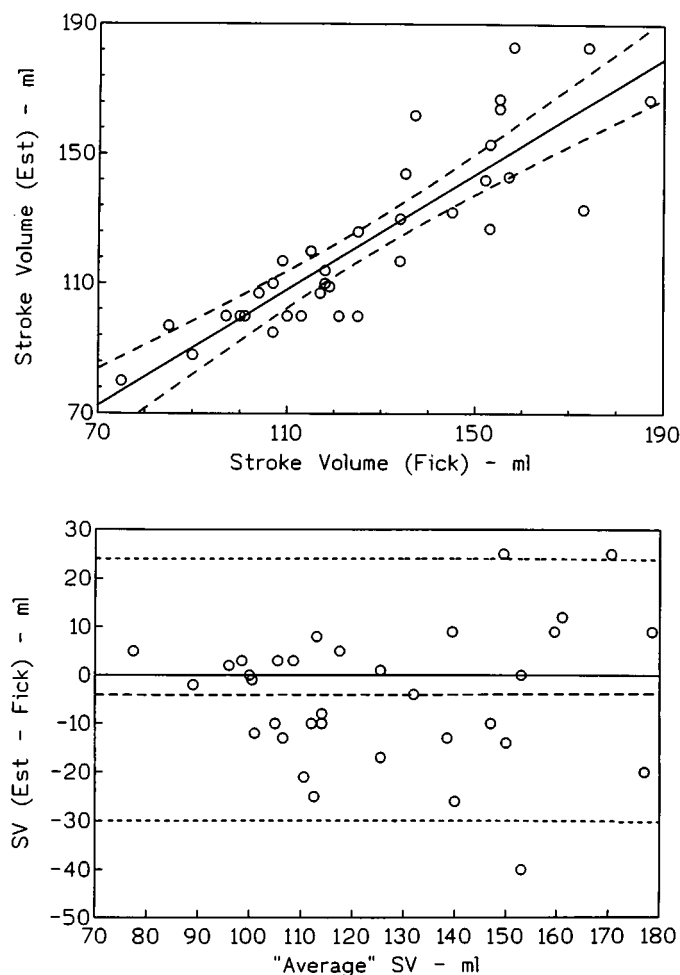


Fig. 6. *Top*: SV estimated as described in text plotted as function of measured SV available in literature. Dashed lines, 95% confidence limits on slope. See text for further elaboration. *Bottom*: difference between measured and estimated value as function of average of 2 values, as proposed by Bland and Altman (3).

Ca<sub>O<sub>2</sub></sub> of 175 ml/l rather than the 200 ml/l that forms the basis of the simple estimation technique. When the correct value for the Ca<sub>O<sub>2</sub></sub> was included in the estimation, this increased the estimated SV from 115 to 131 ml compared with a measured value of 145 ml. This disparity, however, was not the cause of the other errantly low value. It may be a consequence of the assumption that a steady state of  $\dot{V}O_2$  is attained in all normal subjects within 3 min. If the time constant or mean response time (14, 22) for  $\dot{V}O_2$  were ~45 s, then  $\dot{V}O_2$  for the exponential increase would only be just attaining 98% of the expected steady-state value at 3 min. In addition, as our sample for  $\dot{V}O_2$  was averaged over the last 30 s of the work rate, the average would be appreciably less than this value. Of course, when sampling over the last 30 s of a 3-min increment, a subject with an even longer time constant for  $\dot{V}O_2$  would be even further from the presumed steady-state value.

$\dot{Q}$ , however, has been consistently demonstrated to increase with a time constant that is appreciably faster than that for  $\dot{V}O_2$  (5, 15). It is possible, therefore, that a subject may attain a steady state for  $\dot{Q}$  with  $\dot{V}O_2$  still being in its transient phase of response. We do not know whether this is the case, since we did not establish the kinetics of the  $\dot{V}O_2$  response in these studies. This does, however, point to the fact that, although 3 min is a popular duration for work-rate increments, it will not be of sufficient duration for some subjects to attain a steady state of  $\dot{V}O_2$ ; a 4-min increment would be much more inclusive. However, 6 min may be necessary for such steady-state requirements if other gas-exchange indexes such as ventilation or CO<sub>2</sub> output are required, since their response time constants are appreciably longer (22).

It is especially important that care is taken to ensure high confidence on the  $\dot{V}O_2$ -HR regression in highly fit subjects, since the slope increases tangentially toward infinity at high values. Small errors in the slope can therefore produce large errors in SV estimation. This is of less concern at low slope values. By the same token, a group mean response of a range of individual slopes is also prone to error and should be avoided.

There is another important caveat, however. Although we have demonstrated that the estimation procedure appears to provide an adequate characterization for such a steady-state incremental test, we do not know whether the same relationship will hold true for the now-popular non-steady-state (ramp-type) incremental exercise tests. The main concern is the disparity of the time constants of  $\dot{Q}$  and  $\dot{V}O_2$ . If, however, it can be demonstrated that the slope of the  $\dot{V}O_2$ -HR relationship during a rapid incremental test is the same as that for the steady-state test (after the appropriate number of time constants have elapsed), then the consequent parallel displacement of the  $\dot{V}O_2$ -HR relationship will not affect the value for the asymptotic O<sub>2</sub>-P, although it will affect the rate at which this is achieved.

In conclusion, we have demonstrated that an acceptably linear relationship between  $\dot{V}O_2$  and HR during steady-state incremental exercise can be used to estimate a value for the exercise SV in normal subjects.

Naturally, if SV changes during the exercise, the estimator can only provide a single value reflective of the average SV over that work-rate interval. In normal subjects, therefore, the exercise SV may be estimated simply as

$$SV_{\text{ex}} = \frac{\text{asymptotic } O_2\text{-P}}{Ca_{O_2}} \quad (7)$$

or

$$SV_{\text{ex}} = 5 \times \frac{\Delta \dot{V}O_2}{\Delta \text{HR}} \quad (8)$$

This relationship is not valid, however, in patients with lung disease, anemia, or hyperemia; normal subjects at high altitude or breathing hypoxic inspirates; or subjects who desaturate during exercise, such as some highly trained athletes. Further studies are needed, however, to determine to what extent the relationship holds for the now-popular non-steady-state incremental exercise testing in normal subjects.

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