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Estimating stroke volume from oxygen pulse during exercise

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Abstract

This investigation aimed at verifying whether it was possible to reliably assess stroke volume (SV) during exercise from oxygen pulse (OP) and from a model of arterio-venous oxygen difference (a-vO_2D) estimation. The model was tested in 15 amateur male cyclists performing an exercise test on a cycle-ergometer consisting of a linear increase of workload up to exhaustion. Starting from the analysis of previous published data, we constructed a model of a-vO_2D estimation (a-vO_2D_{est}) which predicted that the a-vO_2D at rest was 30% of the total arterial O_2 content (CaO_2) and that it increased linearly during exercise reaching a value of 80% of CaO_2 at the peak workload (W_{max}) of cycle exercise. Then, the SV was calculated by applying the following equation, SV = OP/a-vO_2D_{est}, where the OP was assessed as the oxygen uptake/heart rate. Data calculated by our model were compared with those obtained by impedance cardiography. The main result was that the limits of agreement between the SV assessed by impedance cardiography and the SV estimated were between 22.4 and −27.9 ml (+18.8 and −24% in terms of per cent difference between the two SV measures). It was concluded that our model for estimating SV during effort may be reasonably applicable, at least in a healthy population.

Keywords: arterio-venous oxygen difference, impedance cardiography, cardiac output, oxygen uptake, heart rate

Introduction

In normal individuals the cardiovascular response to dynamic exercise involves an interaction of changes in heart rate (HR) and stroke volume (SV) which aim at increasing cardiac output

(CO). However, there are marked differences between sedentary and trained subjects in the strategy to raise CO. In fact, while both groups have a similar capacity to increase HR, which only depends on the subject's age, trained persons show a greater ability to augment SV than untrained ones (Concu and Marcello 1993, Gledhill *et al* 1994, Zhou *et al* 2001). Moreover, the SV response to exercise is markedly different between normals and subjects suffering from heart diseases. For example, in heart failure patients SV tends to fall during dynamic effort, whereas in healthy persons it increases (Cohen-Solal *et al* 1999, Crisafulli *et al* 2006a, Higginbotham *et al* 1986). Hence, from the SV behaviour during effort it is possible to discriminate between sedentary and fit subjects as well as to identify and follow patients with heart disease. Therefore, knowledge of SV response during dynamic exercise is very useful and this parameter can be considered to be one of the most important markers of the functional state of the circulation.

Unfortunately, SV during effort is not easily assessed. The direct measure of this parameter can be made by means of invasive techniques such as thermodilution and dye-dilution, which, however, need the placement of catheters and are uncomfortable and potentially dangerous. For these reasons several non-invasive methods have been developed, such as Doppler echocardiography (Rowland and Obert 2002), CO_2 and acetylene rebreathing (Johnson *et al* 2000, Warburton *et al* 1999a, Warburton *et al* 1999b) and impedance cardiography (Bogaard *et al* 1997, Charloux *et al* 2000, Miles and Gotshall 1989, Warburton *et al* 1999b).

Besides, there is the possibility of assessing SV from HR and oxygen uptake ($V'O_2$). In fact, according to the Fick principle, cardiac output can be expressed as CO = $V'O_2$/arterio-venous oxygen difference (a-vO_2D). Since CO can be also expressed as CO = SV × HR, it is possible to derive SV from the following equation:

$$SV = (V'O_2/HR)/\text{a-v}O_2D.$$

The quantity $V'O_2$/HR is also known as oxygen pulse (OP) and represents the quantity of oxygen being consumed by the body for each single cardiac beat. Given that HR and $V'O_2$ can be nowadays gathered even during hard efforts, the OP can be easily measured. In contrast, the a-vO_2D assessment, which is necessary for calculating SV from OP, requires the placement of catheters, is potentially dangerous and causes discomfort. Thus, the direct measure of a-vO_2D is not advisable in subjects who do not require invasive manoeuvres for therapeutic and/or diagnostic purposes. However, several clues suggest that this parameter increases almost linearly and in a predictable way with respect to workload (Crisafulli *et al* 2005, 2006a, Proctor *et al* 1998, Stringer *et al* 1996). If this concept was correct, then it would be possible to predict a-vO_2D and consequently SV with sufficient precision during an incremental progressive exercise test.

In the present study conducted on a group of healthy people we sought to validate a non-invasive procedure for estimating SV from oxygen pulse by assuming a linear behaviour of a-vO_2D during incremental exercise. This method was compared with the results obtained by an accepted non-invasive technology to assess haemodynamics during exercise, i.e., impedance cardiography.

Methods

Subjects

Fifteen amateur male cyclists, who trained 8 to 12 h per week and free of any known cardiovascular or pulmonary disease, agreed to take part in this study which was conducted according to the declaration of Helsinki and approved by the local ethics committee. The

subjects' mean ± standard deviations (SD) of age, height and body mass were 26.8 ± 9.7 years, 175.2 ± 8.8 cm and 70.4 ± 8.8 kg, respectively. Each subject gave written informed consent.

Experimental design

The subjects underwent an incremental test on an electromagnetically braked cycle-ergometer (Tunturi EL 400, Finland). This test consisted of a warm-up period of 3 min pedalling against 20 W followed by a linear increase of work load of 50 W every 3 min, starting from 50 W, at a pedalling frequency of 60 rpm, up to exhaustion, which was taken as the point when the subject was no longer able to maintain the pedalling rate. The workload achieved during the latest minute of exercise was taken as the maximum workload (W_{max}).

Metabolic and haemodynamic measurements

The oxygen uptake was measured throughout exercise by a breath-by-breath metabolic measurement chart (MedGraphics Breeze, St Paul, MN) calibrated immediately before each test.

During exercise the subjects were connected to an impedance cardiograph (NCCOM 3, BoMed Inc., Irvine, CA), which allows non-invasive haemodynamic measurements (Belardinelli *et al* 1996, Concu and Marcello 1993, Charloux *et al* 2000, Richard *et al* 2001). This technique assumes that when an electrical current circulates through the thorax, the pulsatile aortic blood flow induces a proportional fluctuation in electrical conductivity. Thus, changes in thoracic electrical impedance during systole are representative of SV (Bernstein 1986, Woltjer *et al* 1997). We previously used the impedance method in order to evaluate haemodynamics during exercise and recovery and detailed descriptions of its rationale and application can be found in these reports (Crisafulli *et al* 2003, 2004, 2005, 2006a, 2006b).

Briefly, the device was connected to the subject by means of eight electrodes: two pairs were thoracic and cervical injecting electrodes, while two other pairs were sensing electrodes placed above the cervical and below the thoracic pairs. Thorax impedance (Z_0), its first derivative (dZ/dt) and electrocardiogram traces were recorded by means of a digital chart recorder (ADInstruments, PowerLab 8 sp, Castle Hill, Australia). Afterwards, traces were cleaned of signals affected by movement and respiratory artefacts and analysed taking special care to calculate variables only from traces not affected by impedance artefacts. We already used this signal processing procedure, which though time-consuming, allows one to obtain reliable and reproducible haemodynamic data during exercise and recovery (Crisafulli *et al* 2003, 2004, 2005, 2006a, 2006b).

The stroke volume was assessed by applying the Sramek–Bernstein equation (Bernstein 1986):

$$SV = \left(VEPT \times Z_0^{-1}\right) \times dZ/dt_{max} \times VET$$

where VEPT is the volume of electrical participating tissue and was derived using a nomogram of sex, height and weight of the subject, Z_0 is the thorax impedance measured at the end of cardiac diastole, dZ/dt_{max} is the maximal Z_0 first derivative during cardiac systole and VET is the left ventricular ejection time measured as the interval between the beginning and the minimum of the deflection in the dZ/dt trace during systole (Crisafulli *et al* 2001, Woltjer *et al* 1997).

The heart rate was obtained as the reciprocal of the electrocardiogram R–R interval and the CO was calculated as SV × HR. We obtained a-vO_2D by dividing $V'O_2$ values by CO. As previously stated, the OP was calculated as $V'O_2$/HR.

Model for a-vO_2D and SV estimation

Starting from the analysis of previous published data, our model was constructed assuming that in healthy subjects the a-vO_2D at rest is on average 30% of the total arterial O_2 content (CaO_2) and that it reaches a value of 80% of CaO_2 at W_{max} of cycle exercise (Beck *et al* 2006, Crisafulli *et al* 2005, 2006a, Higginbotham *et al* 1986, Lewis *et al* 1983, Proctor *et al* 1998, Stringer *et al* 1997). Moreover, we assumed that this parameter increases linearly with workload (Crisafulli *et al* 2005, 2006a, Proctor *et al* 1998, Stringer *et al* 1997). Thus, a-vO_2D expressed as % with respect to CaO_2 can be estimated by applying the following equation:

$$\text{a-v}O_2\text{D (\% of } CaO_2) = 30\% + [(80\% - 30\%)/100 \times \%W_{max}],$$

where $\%W_{max}$ is the workload percentage with respect to the peak workload reached. Hence, the only unknown term in this equation is W_{max}, which can be easily gathered from an incremental exercise test such as that employed in our study.

Then, in order to transform a-vO_2D into absolute value it is necessary to know the quantity CaO_2, which for the most part results from the oxygen carried by haemoglobin, according to the following formula:

$$CaO_2 = \text{Hb} \times 1.34 \times \text{Hb}O_2\text{Sat (Stringer } \textit{et al} \text{ 1997)},$$

where Hb is the haemoglobin concentration in the blood expressed in g dl^{-1} and HbO_2Sat is the percentage of Hb being saturated with O_2. For example, for a Hb concentration of 15 g and a HbO_2Sat of 99%, the CaO_2 is equal to 19.8 ml for every 100 ml of blood. To this amount of CaO_2 is to be summed a further little quantity of O_2 (about 0.3 ml for every 100 ml of blood) which is loose, physically dissolved in the plasma (Shaskey and Green 2000). The result is that for an individual with a Hb concentration of 15 g and a HbO_2Sat of 99% the total CaO_2 is 20.1 ml/100 ml. In order to obtain the mean group value of HbO_2Sat during exercise we measured this parameter in five of the 15 subjects during the incremental test by employing a pulse oximetry (Biox 3740 Pulse Oximeter, Ohmeda). At rest HbO_2Sat was 99.2 $\pm$ 0.3%, while at W_{max} it was 98.1 $\pm$ 0.2%. This result was in good agreement with previous findings reporting that in healthy persons, during dynamic exercise, the HbO_2Sat remains stable around a value of 96–99%, with a mean value close to 98% (Saltin *et al* 1986, Stringer *et al* 1994, 1997). Therefore, in our model we assumed a group mean HbO_2Sat value of 98% throughout exercise and we calculated the CaO_2 (ml) as

$$(\text{Hb} \times 1.34) \times 98\% + 0.3.$$

The Hb concentration was measured by employing a portable photometer (B-Hemoglobin, HemoCue, Ängelholm, Sweden), which allows reliable haemoglobin measurement from a single blood drop (10 μl) obtained with a finger prick (Bridges *et al* 1987). The device calibration was verified before making measurements by using a control cuvette provided with the photometer. The calibration was considered reliable if the photometer provided a Hb value within $\pm$0.3 g dl^{-1} with respect to what is expected from the control cuvette. Inasmuch as heavy-prolonged exercise can induce liquid loss and blood Hb increment, for each subject we made two Hb measurements: one at rest before exercise and one just at the end of effort (within 1 min after exercise termination) in order to verify whether exercise induced significant Hb increase. The mean $\pm$ SD of Hb at rest and at the end of exercise were 14.5 $\pm$ 1.2 and 15 $\pm$ 1.3 mg dl^{-1} respectively, which did not differ statistically ($p = 0.31$). To calculate the CaO_2 we utilized the average of the two measurements.

In summarizing, our model for a-vO_2D estimation was built assuming a linear increase of this parameter from 30% of CaO_2 at rest to 80% at W_{max} and further assuming a HbO_2Sat

of 98% throughout exercise. Thus, this model only needed knowledge of Hb concentration at rest and at the end of exercise. Then, from the estimated a-vO_2D (a-vO_2D_{est}) for each exercise step we could also assess SV (SV_{est}) from OP by applying this simple equation:

$$SV_{est} = OP/\text{a-v}O_2D_{est}.$$

Statistics

The mean ± SD of variables are shown. Data are displayed as a function of % of W_{max}. The suffixes 'est' and 'ic' added to each acronym denote estimated or measured data, where 'est' stands for estimated and 'ic' for impedance cardiography, respectively. Bland and Altman statistics (1986) to assess agreement between two methods of measurement were carried out in order to evaluate the agreement between a-vO_2D, SV and CO estimated by our model and measured with impedance cardiography. Comparison of data sets with the Bland and Altman statistics was performed for both absolute values and for per cent difference between methods of measurements. A paired *t* test was also applied in order to find out differences between measured and estimated variables at each workload. The statistical significance was set at a *P* value of <0.05.

Results

All subjects completed the exercise protocol. The mean ± SD of W_{max}, maximum HR and maximum $V'O_2$ reached were 249.3 ± 34.9 W, 172.4 ± 11.8 bpm and 3.35 ± 0.51 l min^{-1}, respectively.

Figure 1 shows time courses of HR (top panel) and $V'O_2$ (middle panel), which rise almost linearly with respect to workload. Accordingly with previous published data (Stringer *et al* 1997, Whipp *et al* 1996), the OP (bottom panel) increased hyperbolically, reaching an average maximum value of 19.4 ± 2.8 ml bpm^{-1}.

Figure 2 (top panel) depicts the group mean responses of a-vO_2D derived from impedance cardiography and estimated from our model. A total of 165 couple of measurements were made for the 15 subjects enrolled. In detail, a-vO_2D_{ic} and a-vO_2D_{est} appeared quite similar and almost superimposed. Linear regression applied to a-vO_2D_{ic} reveals that this parameter increased linearly throughout exercise, with a slope of (0.86 ± 0.03 ml/100 ml)%W_{max} and an intercept of 6.8 ± 0.2 ml/100 ml ($r^2 = 0.98$ and $p < 0.01$). The increase in CO_{ic} per litre increase in $V'O_2$ was on average 5.1 ± 0.3 l min^{-1}, in good agreement with previous published data (Berry *et al* 1993, Crisafulli *et al* 2005, 2006a, Lewis *et al* 1983, Proctor *et al* 1998). Obviously, a-vO_2D_{est} showed a perfect linear increase, with a slope of (0.89 ml/100 ml)%W_{max}. The increase in CO_{est} per litre increase in $V'O_2$ was on average 4.9 ± 0.4 l min^{-1}. A paired *t* test did not find significant differences between a-vO_2D_{ic} and a-vO_2D_{est} data sets at each workload. The middle and bottom panels exhibit the results of the Bland and Altman statistics applied to this variable. The limits of agreement of the a-vO_2D_{ic} − a-vO_2D_{est} difference were between +2.6 and −2.1 ml 100 ml^{-1}. In terms of per cent difference between the two a-vO_2D data sets these limits lay between +24 and −18.8%.

Figure 3 (top panel) illustrates stroke volume behaviour. Both SV_{ic} and SV_{est} showed a first increasing phase, and then levelled off at a workload of about 40% of W_{max}. However, while SV_{ic} remained stable till the end of exercise, SV_{est} tended to slightly decrease. Nevertheless, the *t* test did not find significant differences between the two data sets. The Bland and Altman statistics revealed the limits of agreement of the SV_{ic} − SV_{est} difference between 22.4 and −27.9 ml (middle panel), and +18.8 and −24% in terms of per cent difference between the two SV measures (bottom panel).

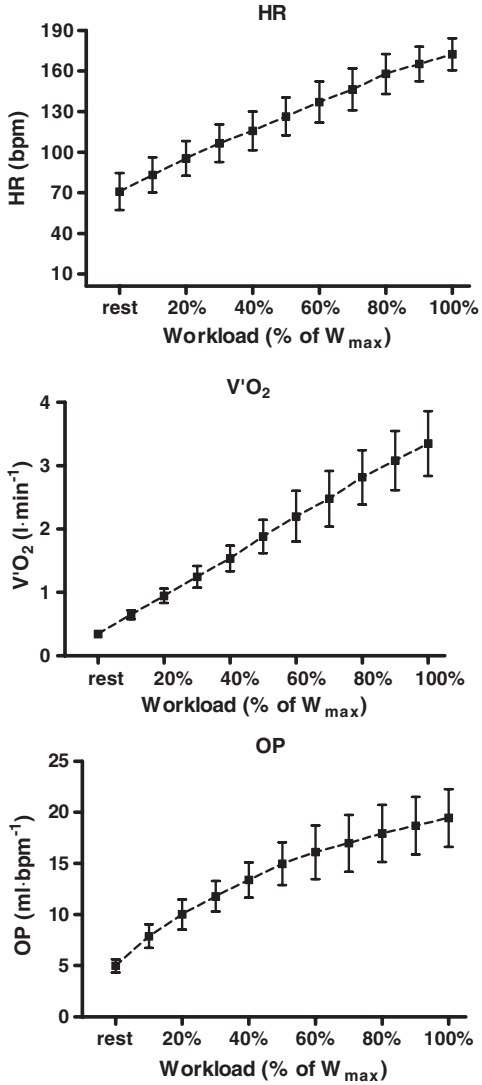

Figure 1. Time courses of heart rate (HR, top panel), oxygen uptake ($V'O_2$, middle panel) and oxygen pulse (OP, bottom panel) plotted as a function of maximum workload achieved (% of W_{max}) during incremental cycle-ergometer exercise. Values are mean ± SD.

Finally, figure 4 shows that both CO_{ic} and CO_{est} rise almost linearly throughout exercise (top panel). The two data sets were quite similar and statistics did not detect any significant difference. The limits of agreement of the $CO_{ic} - CO_{est}$ difference were between 3.05 and 3.40 l min^{-1}. In terms of % difference between the two methods of measurements these limits were between +18.8 and −24%.

Discussion

Stroke volume response to exercise represents one of the most important markers of the functional state of the circulation since the capacity of increasing this parameter allows

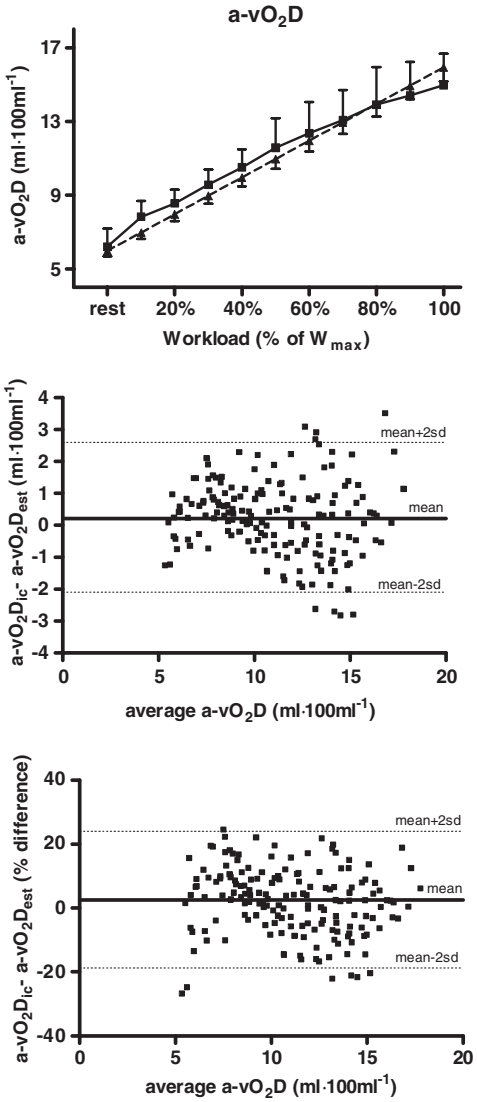

Figure 2. The top panel shows time courses of arterious-venous oxygen difference (a-vO_2D) obtained by impedance cardiography (a-vO_2D_{ic}, squares-continuous line) and estimated by our model (a-vO_2D_{est}, triangles-dotted lines) plotted as a function of maximum workload achieved (% of W_{max}). Values are mean ± SD. The middle panel shows the results of the Bland and Altman statistics applied to the measured and estimated a-vO_2D, while the bottom panel is relative to per cent difference between the two methods of measurements.

discriminating between sedentary and fit subjects as well as identifying and characterizing patients suffering from various kinds of cardiovascular diseases. Thus, a totally non-invasive and simple assessment of SV during exercise would be very useful since it would allow sequential SV measurements through time. This investigation aimed at verifying whether it was possible to reliably assess stroke volume during exercise from oxygen pulse and from a model of a-vO_2D estimation which predicted a linear increase of this variable.

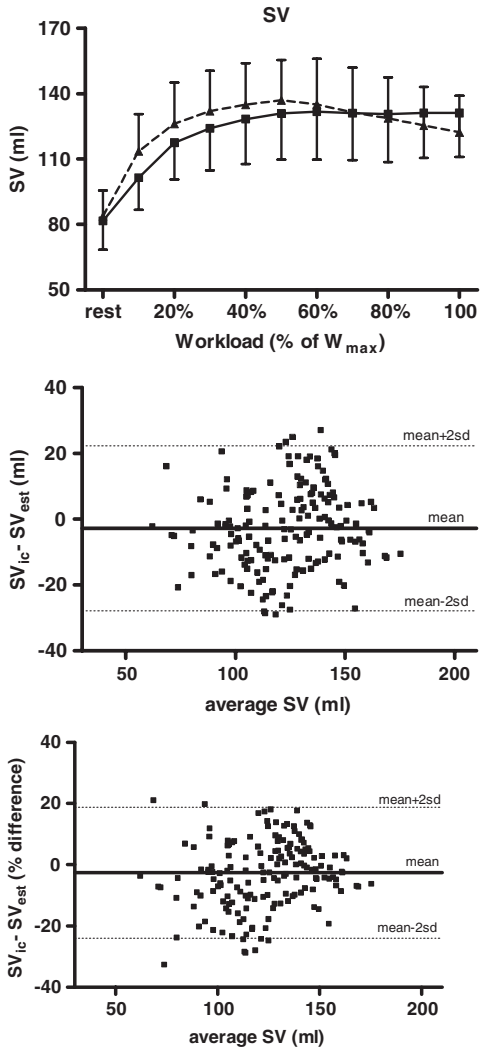

Figure 3. The top panel shows time courses of stroke volume (SV) obtained by impedance cardiography (SV_{ic}, squares-continuous line) and estimated by our model (SV_{est}, triangles-dotted lines) plotted as a function of the maximum workload achieved (% of W_{max}). Values are mean ± SD. The middle panel shows the results of the Bland and Altman statistics applied to the measured and estimated SV, while the bottom panel is relative to per cent difference between the two methods of measurements.

From our results it appears that our model for estimating SV may be reasonably applicable, at least in healthy subjects, such as those enrolled in the present study. Our comparison provided limits of agreement of the $SV_{ic} - SV_{est}$ difference between 22.4 and −27.9 ml and +18.8% and −24% in terms of per cent difference between the measured and the estimated variables. It has been suggested that for clinical purposes techniques that yield haemodynamic data which are within ±22% of the reference method are acceptable (LaMantia *et al* 1990, Stetz *et al* 1982). In our experiment the agreement between the estimated and measured SV was hardly beyond this value (−24% in the lower level of limit of agreement between

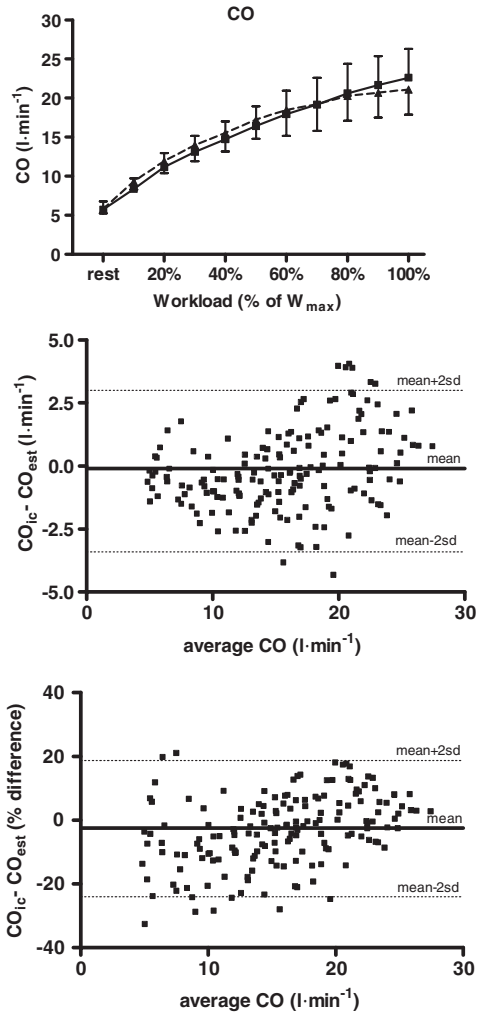

Figure 4. The top panel shows time courses of cardiac output (CO) obtained by impedance cardiography (CO_{ic}, squares-continuous line) and estimated by our model (CO_{est}, triangles-dotted lines) plotted as a function of maximum workload achieved (% of W_{max}). Values are mean ± SD. The middle panel shows the results of the Bland and Altman statistics applied to the measured and estimated CO, while the bottom panel is relative to per cent difference between the two methods of measurements.

methods). In detail, of the total of 165 measurements we made only 11 (i.e. the 6.6%) were out of the ±22% limit suggested, while 154 (i.e. 93.4%) were within this limit.

To the best of our knowledge, in the past only one attempt has been made to measure SV from OP during exercise (Whipp *et al* 1996). In the quoted work the average SV response to exercise was estimated from the asymptotic $HR/V'O_2$ ratio and the authors concluded that the method was reliable. Our results seem to confirm this finding, that OP can be usefully utilized for calculating SV during exercise. However, it should be considered that our model has some limitations that can preclude its application in some situations. Firstly, we hypothesized that the $V'O_2/CO$ ratio (i.e. the a-vO_2D) increased linearly throughout exercise. Nevertheless, the a-vO_2D has been sometimes reported to increase nonlinearly with respect to workload (Beck

et al 2006, Yamaguchi *et al* 1986). In particular, Beck and co-workers have recently found a significantly nonlinear relationship in the $V'O_2/CO$ ratio in 38% of 72 healthy subjects they studied. They also found that the degree of nonlinearity may depend on the fitness level of the subjects, with high fit individuals showing a higher degree of curvature. Thus, we cannot exclude that our method may be inadequate in high fit athletes who have significant non-linearity in the $V'O_2/CO$ ratio during incremental exercise. Therefore, our model should be tested in high fit athletes in order to evaluate its readability in this kind of subjects.

A second limitation arises from the observations that subjects suffering from any kind of pathology that induces early fatigue, such as chronic obstructive pulmonary disease and/or muscular abnormalities, often show reduced a-vO_2D value at peak exercise compared to normals (Oelberg *et al* 1998, Lewis and Haller 1989). Moreover, chronic heart failure patients and subjects with anaemia may have an enhanced peak of a-vO_2D expressed as % CaO_2 with respect to healthy individuals (Katz *et al* 2000, Tocco *et al* 2006). These facts clearly do not allow applying our method of a-vO_2D estimation in these patients since it was constructed assuming that the peak a-vO_2D was 80% of CaO_2. Hence there is the need to construct dedicated models of a-vO_2D behaviour during exercise adapted to the special conditions that occur in these pathologies, taking into account both kind and degree of the disease. Finally, it should be considered that some endurance athletes may show variable degrees of arterial desaturation at maximal workload (Dempsey *et al* 1984, Grassi *et al* 1999). This must be taken into account when applying our model in these subjects and measurement of HbO_2Sat should be performed at least at the exhausting workload in order to verify whether this parameter is lower than the 98% predicted by our model.

We conclude that in normal physically active subjects it is possible to reasonably estimate non-invasively SV during exercise from oxygen pulse and by assuming a linear increase of a-vO_2D from 30% of the total arterial oxygen content at rest to 80% at the maximum workload achieved. This method only needs the measurements of oxygen uptake and heart rate and knowledge of Hb concentration at rest and at the end of exercise. The estimated stroke volume shows a reasonable level of accuracy compared with that of impedance cardiography.

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