Non-invasive measurement of stroke volume during exercise in heart failure patients

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ABSTRACT

The objective of the present study was to determine the variability of the arterio-venous O₂ concentration difference [C(a–v)O₂] at anaerobic threshold and at peak oxygen uptake (VO₂) during a progressively increasing cycle ergometer exercise test, with the purpose of assessing the possible error in estimating stroke volume from measurements of VO₂ alone. We sampled mixed venous and systemic arterial blood every 1 min during a progressively increasing cycle ergometer exercise test and measured, in each blood sample, haemoglobin concentration and blood gas data. Ventilation, VO₂ and CO₂ uptake were also measured continuously. We studied 40 patients with normal haemoglobin concentrations and with stable heart failure due to ischaemic or idiopathic cardiomyopathy. Mean values (+S.D.) for C(a–v)O₂ were 7.8 ± 2.6, 13.0 ± 2.4 and 15.0 ± 2.7 ml/100 ml at rest, anaerobic threshold and peak VO₂ respectively. The patients with heart failure were divided into classes according to their peak VO₂. Classes A, B and C contained patients with peak VO₂ values of > 20, 15–20 and 10–15 ml min⁻¹ kg⁻¹ respectively. At anaerobic threshold, C(a–v)O₂ was 12.3 ± 1.3, 13.1 ± 2.7 and 13.5 ± 2.6 ml/100 ml for classes A, B and C respectively (class A significantly different from classes B and C; P < 0.05). At peak exercise C(a–v)O₂ was 13.6 ± 1.4, 15.6 ± 2.5 and 15.4 ± 3.2 ml/100 ml for classes A, B and C respectively (class A significantly different from classes B and C; P < 0.05). Stroke volume was estimated for each subject using the mean values of the measured C(a–v)O₂ in each functional class and individual values of VO₂ and heart rate using the Fick formulation. The average difference between the stroke volume estimated from mean C(a–v)O₂ and that obtained using the patient’s actual C(a–v)O₂ value was 9.2 ± 9.7, 1.0 ± 8.8 and −0.2 ± 6.1 ml at anaerobic threshold, and −1.9 ± 11.3, 0.9 ± 10.0 and −2.3 ± 8.5 ml at peak exercise, in classes A, B and C respectively. Among the various classes, the most precise estimation of stroke volume was observed for class C patients. We conclude that stroke volume during exercise can be estimated with the accuracy needed for most purposes from measurement of VO₂ at the anaerobic threshold and at peak exercise, and from population-estimated mean values for C(a–v)O₂ in heart failure patients.

INTRODUCTION

Because of a reduced stroke volume (SV), heart failure patients cannot increase cardiac output adequately during exercise to meet metabolic needs. To evaluate the clinical course of disease and the effects of therapy, non-invasive and repeatable estimation of cardiac output during exercise is desirable. The arterio-venous oxygen con-

Key words: cardiac output, heart failure, oxygen consumption, oxygen extraction.

Abbreviations: AT, anaerobic threshold; C(a–v)O₂, arterio-venous O₂ concentration difference; HR, heart rate; O₂Hb, oxyhaemoglobin; PO₂, partial pressure of oxygen; SV, stroke volume; VCO₂, carbon dioxide uptake; VO₂, oxygen uptake.

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centration difference \([C(a\text{--}v)O_2]\) progressively increases as work rate increases to the subject’s maximum exercise level in both healthy subjects and cardiac patients [1–3]. The increase in \([C(a\text{--}v)O_2]\) is due primarily to a decrease in capillary partial pressure of oxygen \((P_{O_2})\), a right-ward shift in the oxyhaemoglobin \((O_2\text{Hb})\) dissociation curve at the venous side of the capillary bed [4–7] and a haemoconcentration which takes place at high work intensities [3,8]. Stringer et al. [3] reported good agreement in direct Fick cardiac output measurements and calculated cardiac output from the Fick formulation with average \([C(a\text{--}v)O_2]\) values in normal subjects during exercise. The major goal of the present study was to evaluate whether it is possible to estimate SV in heart failure patients during exercise from population-averaged values of \([C(a\text{--}v)O_2]\) along with measured oxygen uptake \((\dot{V}O_2)\) and heart rate (HR) values.

**METHODS**

A total of 40 patients (56.5 ±10 years; seven females and 33 males) with chronic congestive heart failure due to ischaemic \((n = 7)\) or idiopathic \((n = 33)\) cardiomyopathy [New York Heart Association class II \((n = 15)\) and III \((n = 25)\)] participated in the study. According to the Weber and Janicki ranking criteria [1,9], 11 were in class A \((\dot{V}O_2\text{ at peak exercise} > 20 \text{ mI\text{·}min}^{-1}\text{·kg}^{-1})\), 12 in class B \((\dot{V}O_2\text{ at peak exercise ranging between 15 and } 20 \text{ mI\text{·}min}^{-1}\text{·kg}^{-1})\) and 17 in class C \((\dot{V}O_2\text{ at peak exercise ranging between 10 and } 15 \text{ mI\text{·}min}^{-1}\text{·kg}^{-1})\). All were in a stable clinical condition and were taking an optimized drug regimen (Table 1). Patients were free from angina pectoris, intermittent claudication, primary valvular heart disease, systemic hypertension, pericardial effusion, primary lung diseases (forced expiratory volume in 1 s and vital capacity > 70% of predicted), artificial pacemakers, severe arrhythmias, and sinus or atrio-ventricular node dysfunction. Patients unable to pedal for at least 6 min were excluded from the study.

**Table 1** Drug treatment of the various subjects

<table>
<thead>
<tr>
<th>Abbreviation: ACE, angiotensin-converting enzyme.</th>
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<tr>
<td><strong>Patients (no.)</strong></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Digitalis</td>
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<tr>
<td>Diuretics</td>
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<td>ACE inhibitors</td>
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<td>Amiodarone</td>
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<td>Nitrates</td>
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<tr>
<td>Calcium channel blockers</td>
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<td>(\beta)-Blockers</td>
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The investigation was approved by the Institutional Ethics Committee and has been carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Patients gave written informed consent to the study. The invasive study is a part of our pre-heart-transplant clinical evaluation; during the study patients were hospitalized. All patients had previous experience with a non-invasive cardio-pulmonary exercise test in our laboratory. All patients who participated in our pre-heart-transplantation evaluation programme who fulfilled the study inclusion/exclusion entry criteria and who provided informed consent to the research trial between January 1, 1995 and December 30, 1997 were enrolled in the study. Data obtained from the same test in 27 and 10 patients were included in two previous reports [5,10].

A 7 French Swan-Ganz catheter was introduced into the right internal jugular vein and advanced into the pulmonary artery. A 3 French catheter was positioned into the brachial or radial artery. After haemodynamic stabilization, patients were seated on a cycle ergometer (Ergometrics 800 S; SensorMedics, Anaheim, CA, U.S.A.) and breath-by-breath monitoring of gas exchange was started (SensorMedics 2900). The exercise evaluation utilized either a protocol with a 25 W increment every 3 min \((n = 20)\) or a personalized ramp pattern increasing work rate protocol, with the work rate increase set so that patients would fatigue in 8–12 min \((n = 20)\). Both protocols were preceded by a brief warm-up (unloaded pedalling). Regardless of the exercise protocol, at rest, every 1 min during exercise and at peak exercise blood samples were withdrawn simultaneously from the pulmonary and the systemic arteries for blood gas analysis \((P_{O_2}; O_2\text{Hb} \text{ saturation and haemoglobin were measured directly; IL}142 \text{ and IL}1306 \text{ instruments; Instrumentation Laboratories, Lexington, MA, U.S.A.)}. \text{ Lactate concentration was measured (PCP} 6121; \text{ Eppendorf, Hamburg, Germany) in the pulmonary artery. Cardiac output was measured by the direct Fick method. In the 20 patients who performed the 25 W increment protocol, cardiac output was also measured by thermodilution (duplicate) during the 2nd minute of each exercise step. Anaerobic threshold (AT) was obtained from ‘V-slope’ analysis, in which carbon dioxide production \((\dot{V}CO_2)\) was plotted as a function of \(\dot{V}O_2\). \(\dot{V}O_2\) values at AT and at peak exercise were 30-s averages. The arterial and pulmonary artery blood gas data obtained from the blood sample closest to the measured \(\dot{V}O_2\) were utilized to estimate cardiac output and SV. The SV was calculated as:

\[
SV = \dot{V}O_2/[C(a\text{--}v)O_2 \times HR]
\]

\(C(a\text{--}v)O_2\) was the mean measured \(C(a\text{--}v)O_2\) for the population, whereas \(\dot{V}O_2\) and HR were measured in individual subjects.

Data are reported as means ± S.D. Correlations and differences between measured and estimated SV were
evaluated by linear regression analysis and by Bland and Altman plots respectively [12]. The Student–Newman–Keuls post hoc test was used for comparison among heart failure classes [13].

RESULTS

Exercise tests to a symptom-limited maximum were performed by all patients without untoward effects. The duration of exercise ranged between 6 and 14 min and between 8 and 11 min for the incremental (25 W increase every 3 min) and the ramp exercise protocols respectively. Results were not influenced by the exercise protocol used. AT was identified by ‘V-slope’ analysis in all subjects [11]. Table 2 shows the actual average percentage increase in VO₂ from rest to peak exercise, at the time of blood sampling. The difference between the actual percentage increase in VO₂ and that selected as the point of measurement in the column headings in Table 2 (20%, 40%, etc.) is due to the variability in VO₂ at the time of blood sampling (every 1 min) and to the fact that, by necessity, calculations of percentage VO₂ increase were done a posteriori. Lactic acid concentration, C(a–v)O₂, arterial and venous O₂Hb saturation, and arterial and venous oxygen content at rest, at 20, 40, 60 and 80% increases in VO₂ at AT and at peak exercise are also reported in Table 2. C(a–v)O₂ increased progressively during the exercise, with the lowest variability (as inferred from the S.D.) being at AT (Table 2). The average

<table>
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<th>Table 2</th>
<th>Blood gas and lactate data during exercise</th>
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<td>Tot.</td>
<td>(n = 40); A, class A patients (n = 11); B, class B patients (n = 12); C, class C patients (n = 17). Significance of differences: *P &lt; 0.05 versus B and C; †P &lt; 0.05 versus C.</td>
</tr>
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Anaerobic Threshold

Peak exercise

Figure 1  \( C(a-v)O_2 \) against cardiac output at the AT and at peak \( VO_2 \) for all subjects

Data are reported on a graph showing \( VO_2 \) isopleths. ●, Class A; ■, class B; ▲, class C. The ◆ symbol shows the normal-subject data of Stringer et al. [3] (mean ± S.D.).

Figure 2 Estimated and measured SV values at the AT

Upper panels: SV estimated from measured \( VO_2 \) and HR and average \( C(a-v)O_2 \) against directly measured (actual) SV at the AT for each functional class. \( C(a-v)O_2 \) values of 12.3, 13.1 and 13.5 ml/100 ml were used for classes A, B and C respectively. Lines show the correlation ± 95% confidence intervals for the measured SV. Lower panels: Bland and Altman plots of the same data. Horizontal lines are means ± 1 S.D. The precision of estimation was greatest in class C subjects.

\( C(a-v)O_2 \) was 13.0 ± 2.4 and 15.0 ± 2.7 ml/100 ml at AT and at peak exercise respectively. At AT, \( C(a-v)O_2 \) was lower (12.3 ± 1.3 ml/100 ml) in class A than in classes B and C (13.1 ± 2.7 and 13.5 ± 2.6 ml/100 ml respectively) (Table 2). Similarly, at peak exercise \( C(a-v)O_2 \) was lower (13.6 ± 1.4 ml/100 ml) in class A than in classes B and C (15.6 ± 2.5 and 15.4 ± 3.2 ml/100 ml respectively) \((P < 0.05)\).

Figure 1 is a plot of the measured \( C(a-v)O_2 \) on the isopleth of measured \( VO_2 \). Each symbol indicates one patient. A line parallel to the x-axis from each individual \( C(a-v)O_2/VO_2 \) point identifies the subject’s cardiac output at AT (left panel) and at peak exercise (right panel). The \( C(a-v)O_2 \) values measured at AT by Stringer et al. [3] are also reported in Figure 1. These data show relatively low variability in \( C(a-v)O_2 \) at AT. Because of the \( VO_2 \)
isopleth shape [they become more shallow as \( \text{C(a–v)}O_2 \) increases], variability in \( \text{C(a–v)}O_2 \) has a relatively small effect on cardiac output. This is particularly true when peak \( \dot{V}O_2 \) and AT are low and \( \text{C(a–v)}O_2 \) is high.

At AT, an interclass difference was observed in the venous \( O_2 \)Hb saturation (Table 2). A weak correlation between \( \dot{V}O_2 \) at peak exercise and venous \( O_2 \)Hb saturation at AT was found \((r = 0.37; P < 0.02)\). The arterio–venous \( O_2 \)Hb saturation differences at AT were 58.1 ± 11.1, 64.8 ± 10.8 and 68.6 ± 8.1% in classes A, B and C respectively (a statistically relevant difference at \( P < 0.05 \) between classes A and C was observed).

At peak exercise, no correlation was found between \( \dot{V}O_2 \) and \( \text{C(a–v)}O_2 \). Measured arterial \( O_2 \)Hb saturation at peak exercise was similar among functional classes (Table 2). Mixed venous (pulmonary artery) \( O_2 \)Hb saturation was the lowest in class C (Table 2). A weak inverse correlation between peak \( \dot{V}O_2 \) and mixed venous \( O_2 \)Hb saturation at peak exercise was found \((r = -0.46; P < 0.02)\). The arterio–venous \( O_2 \)Hb saturation difference at peak exercise was 71.3 ± 7.7, 74.8 ± 5.7 and 78.9 ± 6.1% in classes A, B and C respectively (significant differences between classes A and C; \( P < 0.05 \)). In the 20 patients in whom cardiac output was measured by thermodilution a small difference between measured and estimated SV was observed \((3.1 ± 7.6 \) and \( 3.9 ± 7.6 \) ml at AT and peak exercise respectively).

Correlation analysis and Bland and Altman plots of the differences between estimated and measured values of SV at AT and at peak \( \dot{V}O_2 \) are reported in Figures 2 and 3 respectively. Because \( \text{C(a–v)}O_2 \) was different among the functional classes, SV was estimated using the mean \( \text{C(a–v)}O_2 \) measured for the specific functional class (Table 2). At AT the mean differences between estimated and measured SV values were \( 9.2 ± 9.7, 1.0 ± 8.8 \) and \( -0.2 ± 6.1 \) ml for classes A, B and C respectively. The correlations between measured and estimated SV were \( r = 0.88 \) \((P < 0.001)\), \( r = 0.88 \) \((P < 0.001)\) and \( r = 0.90 \) \((P < 0.001)\) for classes A, B and C respectively.

Similarly, at peak exercise the mean differences between estimated and measured SV values were \( -1.9 ± 11.3, 0.9 ± 10.0 \) and \( -2.3 ± 8.5 \) ml for classes A, B and C respectively. The correlations between measured and estimated SV were \( r = 0.71 \) \((P < 0.01)\), \( r = 0.80 \) \((P < 0.01)\) and \( r = 0.83 \) \((P < 0.001)\) for classes A, B and C respectively.

**DISCUSSION**

The present work takes advantage of predictable changes in \( \text{C(a–v)}O_2 \) during exercise to estimate, non-invasively, cardiac output and SV during exercise from \( \dot{V}O_2 \) and HR measurements alone. SV estimations were found to be least different from the directly measured SV values at AT, because \( \text{C(a–v)}O_2 \) had the lowest variability at AT. We felt justified in selecting AT for the comparison of cardiac output and SV estimated from the mean value of \( \text{C(a–v)}O_2 \) and from the directly measured \( \text{C(a–v)}O_2 \) using the Fick formulation, for two reasons; (1) \( \text{C(a–v)}O_2 \) is relatively uniform at the AT, and (2) variability in

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*Figure 3  Estimated and actual SV values at peak exercise*

Upper panels: SV estimated from measured \( \dot{V}O_2 \) and HR and average \( \text{C(a–v)}O_2 \) against directly measured (actual) SV at peak \( \dot{V}O_2 \) for each functional class \( \text{C(a–v)}O_2 \) values of 13.6, 15.6 and 15.4 ml/100 ml were used for classes A, B and C respectively. Lines show the correlation ± 95% confidence intervals for the measured SV. Lower panels: Bland and Altman plots of the same data. Horizontal lines are means ± 1 S.D. The precision of estimation was greatest in class C.
C(a–v)O₂ has a relatively small effect on estimation of cardiac output when the latter is high, such as during exercise (Figure 1). This is even more true when AT is low, such as in the case of patients with severe heart failure (Figure 2). However, because of the invasive nature of the study, no patient repeated the test, so that no information is available regarding SV variability for both the actual measured and the estimated SV values.

We obtained our best estimation of SV at AT. Indeed, the S.D. of the difference between the measured and estimated values was 8.5 ml using the specific mean C(a–v)O₂ of the three functional classes. These findings are in line with our assumption that the decrease in mixed venous O₂Hb concentration is more predictable at AT than at other work levels, as suggested by the critical capillary PO₂ concept [4,7]. This concept hypothesizes that there is a minimal capillary PO₂ needed to sustain O₂ flow from capillary to muscle mitochondria [4], and that this is reached at the AT. This concept has been demonstrated in normal subjects [7] and in patients with heart failure [6,8] during progressive and constant work-rate exercise. It has been shown that the end-capillary PO₂ has reached its nadir value at the lactate threshold in heart failure, and increased O₂ extraction depends on the Bohr effect above the lactate threshold [6,10]. Indeed, Weber and Janicki [1] reported that mixed venous lactate increases at a relatively uniform O₂ extraction (~ 60%) regardless of the heart failure class. The C(a–v)O₂ values obtained at AT in normal subjects by Stringer et al. [3] also showed a small variation (Figure 1).

To calculate cardiac output and SV, the O₂ content in the arterial and mixed venous blood needs to be estimated. Because blood flow redistribution is influenced by severity of heart failure [8,10,14], a fixed relationship between muscular and non-muscular blood flow cannot be assumed. Therefore we determined C(a–v)O₂ at the AT, peak VO₂ and at 40 and 80% of peak VO₂ for the different classes of heart failure. We found, at the same relative exercise level, a lower venous O₂Hb saturation in the group with more severe heart failure (Table 2). At AT, the mean C(a–v)O₂ value was slightly greater than that reported for normal subjects [1,15], and became greater with increased degree of heart failure (Table 2). Accordingly, an interclass difference in mixed venous blood O₂Hb saturation at AT was found. To estimate SV from VO₂, we utilized the mean value obtained in each functional class of our population (Table 2). Because the difference between classes and the variation in C(a–v)O₂ values within a class were small, we found that estimates based on the class average C(a–v)O₂ and on measured values of VO₂ and HR for each subject, provided good non-invasive estimates of SV.

Cardiac output measurements by thermodilution were done only in the 20 patients who performed the 25 W increment protocol. This is due to the fact that, for cardiac output determinations by thermodilution, a steady-state condition is required, particularly if several levels of exercise are to be compared. Estimated SV values at AT and at peak exercise correlated well with data obtained by thermodilution.

It should be noted that, among the three heart failure functional classes considered, the difference between the estimated and measured SV values at AT was least in class C patients (S.D. 7.1 ml) (Figure 2). This is probably due to two reasons: (1) the absolute SV is lower for this class of patients compared with classes A and B; and (2) class C patients have the greater capability to divert blood from tissue not actively involved in exercise to exercising muscle when the AT is reached [10]. In other words, leg blood flow as a percentage of total cardiac output is greatest in class C patients, as suggested, in the present study, by C(a–v)O₂ values (Table 2). Accordingly, Stringer et al. [3] reported a C(a–v)O₂ value at AT lower than that observed by us in heart failure patients. The ability to estimate SV in the class C patients with a high degree of reliability is especially relevant because these are the patients who are most sick and in whom sequential cardiac output and SV measurements are most often needed in the evaluation of therapeutic efficacy and prognosis. Indeed haemodynamic exercise testing has been considered a valuable tool in the selection of cardiac transplant candidates [16].

No patient had arterial O₂Hb desaturation at rest or during exercise [17]. Presumably, if there was sufficient arterial O₂Hb desaturation, C(a–v)O₂ would not increase during exercise to the same level as found in the normoxic state. A similar problem would arise with anaemia or poliglobulic. Since the arterial oxygen content is decreased in anaemia and arterial hypoxaemia, from the critical capillary PO₂ concept we would anticipate that C(a–v)O₂ at the AT would be systematically reduced. However, at the present time it is not feasible to apply the Fick formulation for estimating from mean C(a–v)O₂ in hypoxaemic (such as heavy smokers and chronic pulmonary patients), anaemic or poliglobulic subjects.

We conclude that cardiac output and SV can be estimated, non-invasively, during exercise from VO₂ at the AT and/or peak exercise, by substituting the C(a–v)O₂ in the Fick formulation for cardiac output with the mean average C(a–v)O₂ found in a relevant heart failure population. The calculated values have a practical level of accuracy which is similar to that of invasive methods. Apart from being non-invasive, this method has the advantage of being easily repeatable, cheaper and simpler than any other non-invasive technique such as electrical bioimpedance, continuous-wave Doppler, pulsed-wave Doppler, carbon dioxide rebreathing, etc., and therefore has important application in studies requiring sequential measurements. However, further studies are needed to confirm the clinical applicability and usefulness of this method for estimating SV. Furthermore, the effects of decreased or increased arterial O₂ content caused by
Exercise stroke volume in heart failure

hypoxaemia, anaemia and polyglobulia need to be assessed.

ACKNOWLEDGMENTS

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