Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients

Harel M. C. Kemps,1,2 Eric J. M. Thijssen,2 Goof Schep,1 Boudewijn T. H. M. Sleutjes,3 Wouter De Vries,4 Adwin R. Hoogeveen,1 Pieter F. F. Wijn,5,6 and Pieter A. F. M. Doevendans7

Departments of 1Sports Medicine and of 2Cardiology, Máxima Medical Centre, Veldhoven; 3Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven; 4Rudolf Magnus Institute of Neuroscience, Section of Rehabilitation and Sports Medicine, University Medical Centre Utrecht, Utrecht; 5Department of Medical Physics, Máxima Medical Centre, Veldhoven; 6Department of Applied Physics, Eindhoven University of Technology, Eindhoven; and 7Department of Cardiology, University Medical Centre Utrecht, Utrecht, The Netherlands

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Kemps HM, Thijssen EJ, Sleutjes BT, De Vries WR, Hoogeveen AR, Wijn PF, Doevendans PA. Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients. J Appl Physiol 105: 1822–1829, 2008. First published October 23, 2008; doi:10.1152/japplphysiol.90430.2008.—The purpose of this study was to evaluate the accuracy of two techniques for the continuous assessment of cardiac output in patients with chronic heart failure (CHF): a radial artery pulse contour analysis method that uses an indicator dilution method for calibration (LiDCO) and an impedance cardiography technique (Physioflow), using the Fick method as a reference. Ten male CHF patients (New York Heart Association class II–III) were included. At rest, cardiac output values obtained by LiDCO and Physioflow were compared with those of the direct Fick method. During exercise, the continuous Fick method was used as a reference. Exercise, performed on a cycle ergometer in upright position, consisted of two constant-load tests at 30% and 80% of the ventilatory threshold and a symptom-limited maximal test. Both at rest and during exercise LiDCO showed good agreement with reference values [bias ± limits of agreement (LOA), −1% ± 28% and 2% ± 28%, respectively]. In contrast, Physioflow overestimated reference values both at rest and during exercise (bias ± LOA, 48% ± 60% and 48% ± 52%, respectively). Exercise-related within-patient changes of cardiac output, expressed as a percent change, showed for both techniques clinically acceptable agreement with reference values (bias ± LOA: 2% ± 26% for LiDCO, and −2% ± 36% for Physioflow, respectively). In conclusion, although the limits of agreement with the Fick method are pretty broad, LiDCO provides accurate measurements of cardiac output during rest and exercise in CHF patients. Although Physioflow overestimates cardiac output, this method may still be useful to estimate relative changes during exercise.

cycle ergometry; circulatory dysfunction; hemodynamic response

COMMONLY ACCEPTED METHODS to accurately assess cardiac output in patients with chronic heart failure (CHF) include the direct Fick method and thermodilution (27, 36). However, because these methods require cardiac catheterization they are unsuitable for daily clinical use. Therefore, numerous studies have investigated the clinical utility of less invasive measures, such as radionuclide methods, Doppler cardiology, gas rebreathing techniques, and impedance cardiology (40, 41). Because radionuclide methods require steady-state conditions, they are unsuitable for measurements during maximal exercise (41). The widespread use of Doppler cardiology is limited because its accuracy (i.e., agreement with the gold standard) highly depends on the skills of the operator (41). Studies evaluating the accuracy of impedance cardiology in the heart failure population yielded conflicting results (3, 23). Although foreign gas rebreathing techniques have shown promising results in CHF patients (1, 20), these methods do not provide continuous cardiac output measurements. We aimed to evaluate techniques for continuous estimation of the cardiac output, because of its merit for studying the pathophysiological mechanisms underlying exercise intolerance in CHF (17, 18, 29). Two methods have recently been introduced for real-time continuous cardiac output measurement. One method is based on radial artery pulse contour analysis, using an indicator dilution method to calibrate the system (LiDCO, London, UK). Up to the present, the accuracy of this method for the assessment of cardiac output during exercise has not been evaluated. The other method is an impedance technique (Physioflow, Manatec Biomedical, Petit Ebersviller, France). This method is different from previously used impedance methods. The algorithm that is used does not require basal thoracic impedance measurement or the estimation of blood resistivity and the position of the electrodes is not critical for the accuracy of the measurements. Previous studies showed that Physioflow provides accurate cardiac output measurements during steady-state and maximal exercise in healthy subjects (8, 34). However, in patients with chronic obstructive pulmonary disease (COPD), cardiac output was systematically overestimated (7). The authors of the latter study hypothesized that this might be due to specific characteristics of COPD patients, such as hyperinflation and changes in the distribution of lung volumes. The sensitivity of Physioflow to detect changes in cardiac output was not addressed in this study. Currently, no studies have evaluated the accuracy and sensitivity of this technique in CHF patients.

The purpose of this study was to evaluate the accuracy of LiDCO and Physioflow at rest and during exercise, using the Fick method as reference. In addition, we investigated the sensitivity of both techniques by evaluating within-patient changes in cardiac output.

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METHODS

The study was conducted at the Department of Cardiology of the Máxima Medical Centre. The research protocol was approved by the local Research Ethics Committee, and all patients provided written informed consent.

Subjects

Ten male patients with stable CHF were recruited to participate in the study. Criteria for eligibility were CHF secondary to ischemic or dilated cardiomyopathy, New York Heart Association class II–III, left ventricular ejection fraction of 40% or less (assessed by echocardiography or radionuclide ventriculography), and sinus rhythm. Exclusion criteria were recent myocardial infarction (<3 mo prior), angina pectoris at rest, hemodynamically significant valvular heart disease, significant COPD and peripheral, vascular, neurological, or orthopedic disease limiting the ability to exercise. Subject characteristics are listed in Table 1. During the study period, there were no changes in medication use.

Exercise Protocol

All patients performed exercise tests on two occasions using an electromagnetically braked cycle ergometer in an upright position (Corival, Lode, Groningen, The Netherlands). In both tests ventilatory parameters were measured breath-by-breath (Zan 680 USB, Oberthulba, Germany). Volume and gas analyzers were calibrated before each test. A 12-lead electrocardiogram was registered continuously. The mean duration between both occasions was 7.8 ± 4.9 days.

During the first session, patients underwent a symptom-limited incremental exercise test, using an individualized ramp protocol, with a duration of 8–12 min (42). The test was ended when a patient was not able to maintain the required pedaling frequency of 70 per minute. Peak oxygen uptake (V\(\text{O}_2\)) and peak workload were defined as the average values of the last 30 s of the test. The V\(\text{O}_2\) at the ventilatory threshold was determined by the V-slope method, using the average value obtained by two independent observers (2). From this test the individual workload for the two constant-load tests was calculated (see below).

The second session was performed to evaluate the accuracy of the cardiac output assessment methods under different conditions: at rest, during light and moderate steady-state exercise, and maximal exercise. The session started with a resting period, in which cardiac output measurements were performed (see later). Thereafter, patients started exercising with 2 min of cycling at the lowest intensity of the ergometer (7 W), followed by two subsequent 5-min bouts at a light and moderate constant load of 30% and 80% of the workload of the ventilatory threshold (VT), respectively. Based on our previous experience with CHF patients, a workload of 30% of VT is the lowest workload at which significant changes in V\(\text{O}_2\) and cardiac output (Q\(\text{O}_2\)) occur, and a workload higher than 80% of VT does not ensure a steady state for all patients. Steady state was defined as a stable heart rate (increase <5%) during the last 2 min of exercise. Finally, a symptom-limited incremental exercise test was performed after a resting period of at least 15 min (average duration between tests: 81 ± 47 min) to assess cardiac output at maximal exercise.

Cardiac Output Assessment

**Fick method.** First, a 7.5-F fiber-optic catheter (CCOmb, Edwards Lifesciences, Irvine, CA) was positioned in the right pulmonary artery under fluoroscopic guidance through the antecubital vein and connected to a hemodynamic monitor (Vigilance II, Edwards Lifesciences, Erlangen, Germany), using a disposable pressure transducer (Safedraw, Becton-Dickinson, Franklin Lakes, NJ). In addition, a pulse oximeter (Onyx 9500, Nonin Medical, Plymouth, MN) was attached to the index or middle finger to monitor arterial oxygen saturation (S\(\text{aO}_2\)) continuously.

Cardiac output (Q\(\text{O}_2\)) was calculated using the Fick equation:

\[
Q(\text{l/min}) = \frac{\text{VO}_2 (\text{ml/min})/(\text{CaO}_2 - \text{CvO}_2)(\text{ml/l})}{\text{arterial oxygen content}}
\]

where CaO\(_2\) is arterial oxygen content and CvO\(_2\) is mixed venous oxygen content. Stroke volume (SV) was calculated by dividing Q by heart rate.

For cardiac output assessments at rest, the direct Fick method (Q\(_D\)) was applied as reference, using Hb and oxygen saturation (S\(\text{O}_2\)) obtained from blood samples drawn from the radial and pulmonary artery that were analyzed by an in vitro oximeter (ABL800 Flex, Radiometer America, Copenhagen, Denmark). These measurements were performed twice in an upright position before the start of the constant-load exercise tests (time interval ~5 min) and repeated during the preceding resting period of the symptom-limited maximal test.

During exercise, the continuous Fick method was applied as a reference method, using continuously measured V\(\text{O}_2\), S\(\text{aO}_2\), and mixed venous oxygen saturation (S\(\text{Vo}_2\)) data. After the tests, these data were resampled into 0.5-s intervals and synchronized by using event markers. The second resting Hb measurement was used to calculate cardiac output (Q\(_\text{exp}\)). The continuous Fick method was used because it allows multiple paired comparisons with the other methods. Previous studies demonstrated that this method is feasible and accurate during exercise in patients with left ventricular dysfunction (31, 43).

**Pulse contour analysis (LiDCO).** The pulse contour analysis method (LiDCCO, London, UK) provides beat-to-beat changes in stroke volume, by calculating nominal stroke volume from a pressure-volume transform of the radial artery pressure waveform. Heart rate is calculated by the duration between subsequent pressure waveforms. To convert nominal stroke volume to absolute stroke volume, the system needs to be calibrated. An advantage of this method is that a calibration method (indicator dilution) is already incorporated. The indicator, lithium chloride, can be administered through a central or peripheral vein (13). The indicator dilution curve is generated by a flow-through cell containing a lithium-selective electrode, which is attached to the arterial line (16). Cardiac output is calculated from the dilution curve, using the following equation:

**Table 1. Clinical characteristics of the study population (n = 10)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63±8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177±12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89±14</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>28±3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33±7</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td>9</td>
</tr>
<tr>
<td>DCM</td>
<td>1</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>9</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>10</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>9</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>2</td>
</tr>
</tbody>
</table>

Values mean ± SD or n. LVEF, left ventricular ejection fraction; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
Q(1/min) = LiCl dose (mmol) × 60/area under the curve

where PCV is packed cell volume (Hb (g/dl)/34). After the patient was properly positioned on the ergometer, the calibration procedure started. First, the LiDCO plus monitor was connected to the SC9000 pressure monitor, which, in its turn, was connected to the radial artery catheter. Subsequently, 2 ml lithium chloride (30 mM LiCl) was injected into the right atrium through the pulmonary artery catheter. This measurement was repeated after 5 min and during the resting period preceding the symptom-limited exercise test. These resting measurements were used for comparison with the other cardiac output measurement methods. Immediately after each lithium dilution measurement, blood samples were drawn for determination of the reference Q_{dy}. Therefore, the direct Fick method and lithium dilution were not performed simultaneously (delay: 10–15 s). Normally, only one lithium dilution measurement is required for calibration. We used the second lithium dilution measurement for this purpose, because this was the last measurement before the start of the exercise protocol. After the calibration procedure, uncalibrated cardiac output values were automatically corrected to calibrated values.

During the exercise protocol, cardiac output (Q_{cF}) and stroke volume values (SV_{Li}) were stored beat-to-beat for offline analysis. Physioflow is an impedance technique based on the principle that variations in the impedance to a high-frequency (75 kHz) low-magnitude (1.8 mA) alternating current across the thorax during cardiac ejection result in a waveform from which SV can be calculated. Initially, stroke volume index is calculated at rest by evaluating 24 consecutive heart beats (autocalibration procedure), using measurements of the largest impedance difference during systole, the largest variation of the impedance signal (contractility index), the thoracic fluid inversion time, heart rate, and the pulse pressure (= difference between systolic and diastolic arterial pressure) (8). Cardiac output is then calculated by multiplying the stroke volume index with body surface area and heart rate, which is obtained from the R-R interval determined on the ECG first derivative (8). Compared with the commonly used Sramek-Bernstein approach (5), Physioflow does not require estimations of baseline thoracic impedance or blood resistivity. Furthermore, as already stated, the position of the electrodes is not critical for the accuracy of the measurements.

After cleaning the skin, two pairs of electrodes (FS50, Skintact, Innsbruck, Austria) were positioned at the left base of the neck and along the xiphoid for transmitting and receiving electrical currents. Two electrodes were also placed on the chest (V1/V6 position) to obtain the ECG signal. The autocalibration procedure was started after a period of at least 5 min, in which patients were sitting immobile on the cycling ergometer. The SV (SV_{Ph}) and cardiac output (Q_{Ph}) values were stored beat-to-beat.

Data Analysis

All cardiac output data were imported into MATLAB (Mathworks, Natick, MA). After removal of outliers (30), data were synchronized by cross-correlating the heart rate data of the different assessment methods. Subsequently, data were averaged into 30-s intervals. Resting cardiac output and SV values obtained by LiDCO and Physioflow were compared with the direct Fick method at three different time moments, resulting in 30 measurements (10 patients × 3 measurements). During exercise, comparisons of simultaneous measurements were made during the last 2 min of constant-load exercise, resulting in four comparisons at both exercise intensities (i.e., a total of 80 measurements: 10 patients × 8 measurements), and during the last minute of the symptom-limited maximal test, resulting in two comparisons (i.e., a total of 20 measurements).

As outlined by Linton and Linton (25), the between-patient variability in cardiac output can have a substantial influence on the agreement between different assessment methods of absolute cardiac output values. One may expect that the presence of within-patient changes in cardiac output may be of even greater relevance for the clinical utility of a cardiac output assessment method. Therefore, as in other studies (23, 24), we evaluated within-patient changes in cardiac output by calculating relative rather than absolute changes (i.e., % increase relative to the second resting cardiac output value). An advantage of this approach is that relative changes are not influenced by the absolute resting cardiac output values.

Statistical Analysis

All data were analyzed using SPSS 12.0 statistical software (SPSS, Chicago, IL). Differences between continuous data were evaluated by the paired Student’s t-test. Pearson’s correlation coefficient (r) was calculated to quantify relations between variables. Differences between the assessment methods at rest and during exercise were evaluated by one-way ANOVA with Bonferroni post hoc analyses. The variation between measurements at rest and during steady-state exercise (repeatability) was evaluated by the coefficient of variation (SD of difference as a percentage of the mean). Agreement between methods was assessed by the approach described by Bland and Altman (6). The bias and limits of agreement (= bias ± 1.96 SD) among the methods are presented as a percentage of the mean values rather than as absolute values. This was done because it allows for a better evaluation of the relationship between cardiac output values and the size of the error (10). Because there was no difference in heart rate among the different methods, bias and limits of agreement are equal for cardiac output and SV and therefore are only provided for cardiac output. Data are presented as means ± SD. P values of <0.05 were considered significant.

RESULTS

At rest, 5 of 30 Q_{dF} measurements could not be analyzed because of blood clot formation in the syringe (n = 3) or technical problems (n = 2). The indicator dilution measurements were not performed in two patients owing to logistic reasons. Because of aberrant shapes of the dilution curves, 4 of the remaining 24 measurements could not be used for further analysis, with at least 1 valid measurement in each of the remaining eight patients. A total of 6 of 30 Q_{Ph} measurements could not be analyzed because of an insufficient quality of the impedance signal. The mean coefficients of variation of the measurements at rest were 12.1% for the direct Fick method, 9.0% for lithium dilution, and 7.4% for Physioflow.

All subjects completed the exercise tests. During exercise, 8 of 100 Q_{dF} measurements could not be used because of an unstable SO_{2} signal from the fiber-optic catheter. As stated before, indicator dilution measurements could not be performed in two patients, resulting in a total of 80 available calibrated LiDCO measurements (Q_{Li}). Of these measurements, 13 had to be excluded from further analysis due to damping or motion artifacts of the radial artery pressure tracing, with at least two remaining valid measurements per exercise intensity level in each patient. An insufficient quality of the impedance signal was observed in 24 of 100 Q_{Ph} measurements. The mean coefficients of variation of consecutive measurements at light steady-state exercise were 4.5% for the continuous Fick method, 1.8% for LiDCO, and 2.4% for Physioflow. At moderate steady-state exercise these coefficients of variations were 5.9%, 2.3%, and 3.6%, respectively.

Table 2 summarizes cardiac output and SV values of the different methods at rest, during light and moderate constant-load exercise, and at peak exercise with corresponding VO_{2} and workload values. Considering the constant-load exercise tests,
Comparison of Methods at Rest

ANOVA revealed overall differences in Q and SV values at rest between the three assessment methods (P < 0.001); post hoc testing showed only significant differences in Q and SV values between Physioflow and both other methods (P < 0.001). Table 3 summarizes the bias and limits of agreement among the different methods. Both Q_{Li} and SV_{Li} were positively correlated with Q_{df} and SV_{df} (r = 0.50, P = 0.04; and r = 0.71, P = 0.001, respectively). Neither Q_{Ph} nor SV_{Ph} was significantly correlated with values obtained by the other methods.

Comparison of Methods During Exercise

ANOVA revealed overall differences in Q and SV values among the methods (P < 0.001); post hoc testing revealed that only Q_{Ph} and SV_{Ph} were significantly different from values obtained from LiDCO or the continuous Fick method (P < 0.001). The bias and limits of agreement between the methods at different exercise levels are summarized in Table 3, and Fig. 1 provides a graphic representation. A positive correlation was found between Q_{Ph} and Q_{df} during exercise (r = 0.73, P < 0.001, Fig. 1B); however, SV values of these methods were not significantly correlated. There were highly significant positive correlations between Q_{Li} and Q_{df} (r = 0.90, P < 0.001, Fig. 1A) and also between SV_{Li} and SV_{df} (r = 0.76, P < 0.001). The lowest bias and narrowest limits of agreement were observed between Q_{Li} and Q_{df} (0% ± 27%, Fig. 1A). Bias and limits of agreement between Q_{Ph} and both other methods were from the same order of magnitude (48% ± 52% for Q_{Ph} vs. Q_{df} and 52% ± 50% for Q_{Ph} vs. Q_{Li}, Fig. 1, B and C).

Comparison of Changes of Cardiac Output During Exercise

When comparing relative within-patient changes in Q, ANOVA showed no significant overall differences between the methods. However, significant differences between changes in SV values were observed (P = 0.02), with only a significant difference between Physioflow and LiDCO in post hoc analysis (P = 0.03). Correlations and Bland-Altman plots comparing within-patient changes of cardiac output are depicted in Fig. 2. The limits of agreement between changes of Q_{df} and Q_{Li} (± 26%) were somewhat narrower than in the other comparisons (Q_{df} vs. Q_{Ph}: ± 36%; and Q_{Li} vs. Q_{Ph}: ± 31%). In all comparisons the bias was close to zero (2%, −2%, and −3%, respectively). Significant correlations were observed among the different methods (Fig. 2, A–C). In addition, changes of both SV_{Li} and SV_{Ph} showed positive correlations with changes of the reference SV_{df} (r = 0.67, P < 0.001; and r = 0.41, P < 0.001, respectively), as well as with each other (r = 0.51, P < 0.001). Considering the transition from “rest” to light steady-state exercise (i.e., the smallest increase in exercise intensity), there were no significant differences between relative changes among the methods. Bias and limits of agreement for changes at this transition were 2% ± 27% for Q_{df} vs. Q_{Li}, −4% ± 42% for Q_{df} vs. Q_{Ph}, and −4% ± 25% for Q_{Li} vs. Q_{Ph}.

Table 2. Workload, oxygen uptake, cardiac output, and stroke volume values at rest, light and moderate constant-load exercise, and peak exercise in 10 CHF patients

<table>
<thead>
<tr>
<th></th>
<th>Workload, W</th>
<th>Oxygen uptake, ml/min</th>
<th>Oxygen uptake, ml·min⁻¹·kg⁻¹</th>
<th>Cardiac output, l·min⁻¹</th>
<th>Stroke volume, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>26 ± 9</td>
<td>302 ± 62</td>
<td>3.5 ± 0.9</td>
<td>6.3 ± 1.6</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>Light</td>
<td>73 ± 23</td>
<td>790 ± 142</td>
<td>9.2 ± 2.5</td>
<td>10.5 ± 2.6</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>Moderate</td>
<td>108 ± 46</td>
<td>1,274 ± 330</td>
<td>14.8 ± 5.8</td>
<td>13.7 ± 4.2</td>
<td>88 ± 13</td>
</tr>
<tr>
<td>Peak</td>
<td>100 ± 46</td>
<td>1,415 ± 496</td>
<td>16.4 ± 5.1</td>
<td>15.6 ± 5.4</td>
<td>87 ± 18</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Light, constant-load exercise at 30% of the ventilatory threshold; Moderate, constant-load exercise at 80% of the ventilatory threshold; Peak, peak exercise. *The direct Fick method was used at rest and the continuous Fick method during exercise.

Table 3. Comparison of different methods for assessing cardiac output in CHF patients

<table>
<thead>
<tr>
<th></th>
<th>LiDCO vs. Fick*</th>
<th>Physioflow vs. Fick*</th>
<th>Physioflow vs. LiDCO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Bias, %</td>
<td>LOA, %</td>
</tr>
<tr>
<td>Rest</td>
<td>17</td>
<td>−1</td>
<td>−29</td>
</tr>
<tr>
<td>Light</td>
<td>22</td>
<td>−1</td>
<td>−30</td>
</tr>
<tr>
<td>Moderate</td>
<td>26</td>
<td>−1</td>
<td>−28</td>
</tr>
<tr>
<td>Peak</td>
<td>15</td>
<td>3</td>
<td>−22</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; Light, constant-load exercise at 30% of the ventilatory threshold; Moderate, constant-load exercise at 80% of the ventilatory threshold; Peak, peak exercise; Bias, mean difference between methods expressed as percentage of their mean values; LOA, limits of agreement (bias ±1.96 SD), expressed as percentage. *The direct Fick method was used at rest and the continuous Fick method during exercise.
DISCUSSION

To decide whether a cardiac output measurement technique is useful in clinical practice, it is crucial to know the accuracy of the used reference method (10). In the present study, we used the Fick method as the gold standard. Although this method is generally considered to be reliable in healthy individuals (40) and in CHF patients (27, 36), its accuracy during exercise is not well established. Theoretically, the Fick principle only applies to steady-state conditions in which the time lag in the response of $\dot{V}O_2$ with respect to $\text{SaO}_2$ and $\text{SvO}_2$ (14) can be compensated. Therefore, it is questionable whether the Fick principle can be applied during peak exercise. Yamabe et al. (43), however, reported that cardiac output obtained by the continuous Fick method during ramp exercise showed good agreement with values during steady-state exercise at the same intensity in CHF patients, suggesting that the Fick principle can also be applied during peak exercise in these patients.

The accuracy of the continuous Fick method mainly depends on operator-related factors and the summed inaccuracies of the measurements of $\dot{V}O_2$, $\text{SaO}_2$, $\text{SvO}_2$, and $\text{Hb}$. According to the manufacturer’s specifications, the gas exchange monitor for assessment of $\dot{V}O_2$ had a precision error of 1.5% (defined as 1 SD of the difference with the actual value). The used fiber-optic catheter had a precision error of 4% (37). Assuming precision errors of 3% for $\text{SaO}_2$ (39) and 2% for $\text{Hb}$ (11), we calculated a theoretical precision error of 11% for the continuous Fick method, with corresponding limits of error of 22% (28). Because we considered a measuring method clinically useful when its limits of error approximated the continuous Fick method, limits of agreement up to 31% were accepted (10). It should be recognized that these limits only apply to the comparison of absolute values and not to the changes of cardiac output, because the precision error of the continuous Fick method to detect these changes is not exactly known.

Although LiDCO has been shown to be useful to assess cardiac output in patients undergoing major surgery (15, 24), its accuracy during exercise conditions has not been evaluated previously. In a study using a different pulse contour analysis method, it was shown that this method is not suitable for measuring absolute cardiac output values during exercise in healthy individuals (33). However, it was also demonstrated that initial calibration with another method improved the accuracy substantially (38). As already stated, an advantage of our method is that an indicator dilution method as calibration is already incorporated. Although not all calibration measurements were successful in our study (failure of 17%), at least one valid measurement could be obtained in all patients. As only one calibration is required, this failure percentage does not have any impact on the potency of this technique in clinical practice. In agreement with other studies (19, 26), we observed an acceptable level of agreement with the reference method, and the repeatability of measurements was higher than the reference method (coefficient of variations: 9.0% and 12.1%, respectively). However, despite the high accuracy of the lith-

Fig. 1. Scatter diagrams (left) and corresponding Bland-Altman plots (right) for cardiac output measurements during constant-load (CL) and peak exercise (Peak), comparing LiDCO ($Q_L$) with the continuous Fick method ($Q_c$) (A), Physioflow ($Q_P$) with $Q_c$ (B), and $Q_P$ with $Q_L$ (C). In the scatter diagrams the lines of identity are shown. The solid lines in the Bland-Altman plots represent the mean difference between the tests, and the dashed lines indicate the 95% confidence intervals of the difference, expressed as a percentage of their mean values.
ium dilution technique, there are some drawbacks to its clinical use. First, it is relatively time-consuming and expensive. Second, it requires an additional peripheral intravenous access for administration of lithium chloride (13). Therefore, it is valuable to consider the use of noninvasive methods for calibration of this technique, such as Doppler cardiography (35) or open-circuit inert gas techniques (4).

A major advantage of using LiDCO is that, once calibrated, it provides real-time beat-to-beat cardiac output data at rest and during exercise. However, an essential prerequisite remains a good quality of the radial artery pressure waveform. In our study, 16% of the calibrated measurements could not be used for further analysis because of the influence of damping or motion artifacts on the waveform during exercise. Yet, we could obtain two or more valid measurements at each exercise intensity level in all subjects, indicating that this technique is feasible during exercise in CHF patients. Considering the accuracy, we observed a low bias and acceptable limits of agreement between this technique and the continuous Fick method, both for the assessment of absolute values as well as for changes in cardiac output. However, this technique may somewhat overestimate cardiac output values exceeding 10 l/min (Fig. 1A), possibly due to an overestimation of resting cardiac output during the calibration procedure. This view is supported by the observation that an obvious overestimation of changes in cardiac output in the higher range is lacking (Fig. 2A). Another explanation for the possible overestimation of higher cardiac output values may be related to the fact that the algorithm that is used to transfer changes in arterial pressure to changes in volume is based on data obtained from healthy individuals. Yet, it was shown previously that exercise-induced changes in the relation between arterial pressure and flow (arterial input impedance) in CHF patients were not different from changes in healthy individuals (21, 22), suggesting that the algorithm is also suitable for CHF patients.

Despite the possible overestimation of cardiac output values exceeding 10 l/min, this study showed that LiDCO is accurate for assessment of absolute cardiac output values in a range that is normally obtained in CHF patients. Importantly, this technique was also able to detect accurately relatively small changes in cardiac output. Therefore, we postulate that pulse contour analysis is potentially useful for clinical purposes, such as assessment of prognosis or selection of candidates for heart transplantation (9), and for research purposes such as investigating the physiological determinants of exercise tolerance in CHF patients (17, 18, 29).

Impedance cardiography is a simple, inexpensive, and completely noninvasive method to assess cardiac output. The
accuracy of impedance cardiography during exercise has been an issue of debate for many years, despite advancements in technology. Common problems that may compromise the quality of the impedance signal are movement and respiration artifacts (41), as well as the presence of pulmonary congestion (32). In the present study, 24% of the measurements obtained during exercise could not be analyzed because of insufficient quality of the signal. This relatively high percentage of failure may have been caused mainly by an irregular or oscillatory breathing pattern (12). As none of our CHF patients showed any clinical signs of pulmonary congestion, we believe that this did not significantly affect our study results. Moreover, pulmonary congestion has been shown to cause an underestimation of cardiac output by impedance cardiography (32), rather than an overestimation, which we observed. Despite the relatively high failure rate of Physioflow in our study, we obtained successful measurements at all exercise intensity levels in eight patients.

Considering the accuracy of Physioflow during exercise, previous studies in healthy individuals demonstrated a high level of agreement between Physioflow and the direct Fick method (8, 34). In contrast, the results of our study showed poor agreement with the reference method, with a systemic overestimation of SV by Physioflow. However, as shown by Bland-Altman analysis, the relative bias (i.e., expressed as a percentage of the mean value) between Physioflow and the reference method was almost similar under rest and exercise conditions (Table 3). This suggests that the discrepancy between both methods during exercise is mainly caused by an overestimation of SV during the calibration procedure. This notion is supported by the fact that the bias between Physioflow and the reference method for estimating relative changes is negligible (Fig. 2B). In a recent study with COPD patients, SV assessed by the Fick method was also overestimated by Physioflow (7). It is striking that the mean resting SV value in these COPD patients was comparable with the CHF patients in our study (60 and 57 ml, respectively). As no significant bias between Physioflow and the Fick method was observed in healthy individuals with higher SV values (8, 34), we postulate that the autocalibration algorithm of Physioflow is less suited for patients with relatively low SV values.

Despite the low accuracy of Physioflow for the assessment of absolute cardiac output values, we demonstrated a reasonable overall agreement between Physioflow and the reference method for the assessment of relative changes in cardiac output and SV. However, as shown by the Bland-Altman plot (Fig. 2B) and the relative wide limits of agreement between both methods for cardiac output changes from rest to light constant-load exercise (±42%), the accuracy of Physioflow to detect subtle changes in cardiac output is limited. Yet, as greater changes in cardiac output (i.e., >200%) can be assessed with reasonable accuracy (Fig. 2B), Physioflow may still be useful for clinical purposes such as the evaluation of the cardiac output response to maximal exercise in mild to moderate heart failure, or the evaluation of exertional dyspnea during cardiopulmonary exercise testing.

To our knowledge, there are no studies that have evaluated reproducibility of LiDCO and Physioflow during exercise in CHF patients, and also our study design did not permit an assessment of day-to-day reproducibility of these methods. However, we evaluated the variation of subsequent measurements of the different methods. Both at rest and during constant-load exercise, the mean coefficients of variation of LiDCO and Physioflow were lower than those obtained from the reference method. Another limitation of this study is that only moderately impaired male patients were included. Consequently, our observations cannot be generalized to women or more severely impaired patients.

In conclusion, although the limits of agreement with the Fick method are pretty broad, the accuracy of LiDCO is clinically acceptable for the assessment of absolute values of cardiac output as well as within-patient changes during exercise in a range that is normally obtained by CHF patients. There may, however, be a slight overestimation by values exceeding 10 l/min. Whereas Physioflow offers the advantage of being completely noninvasive, relatively inexpensive, and easy to use, it strictly overestimates cardiac output during exercise, due to an overestimation of stroke volume at rest. However, provided that changes in cardiac output are not too small (i.e., <200%), this method may still be used to assess the relative increase in cardiac output during exercise in CHF patients. Although the failure rates of both LiDCO and Physioflow during exercise were relatively high (16% and 24%, respectively), the number of valid measurements was sufficient for these methods to be feasible in clinical practice.

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REFERENCES
