Non-invasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique

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ABSTRACT

Values of effective pulmonary blood flow (QEP) and cardiac output, determined by a non-invasive foreign gas rebreathing method (CORB) using a new infrared photoacoustic gas analysing system, were compared with measurements of cardiac output obtained by the direct Fick (COFICK) and thermodilution (COTD) methods in patients with heart failure or pulmonary hypertension. In 11 patients, of which three had shunt flow through areas without significant gas exchange, the mean difference (bias) and limits of agreement (±2 S.D.) were 0.6 ± 1.2 litre·min⁻¹ when comparing COFICK and QEP, and −0.8 ± 1.3 litre·min⁻¹ when comparing COFICK and COTD. When correction for intrapulmonary shunt flow was applied (i.e. calculation of CORB) in all 11 patients, the bias between COFICK and CORB was 0.1 ± 0.9 litre·min⁻¹, primarily because agreement improved in the three patients with significant shunt flow. In the eight patients without significant shunt flow, the agreement between QEP and COFICK was 0.3 ± 0.9 litre·min⁻¹. In conclusion, a foreign gas rebreathing method with a new infrared photoacoustic gas analyser provided at least as reliable a measure of cardiac output as did thermodilution. In the absence of significant shunt flow, measurement of QEP itself provides a reliable estimate of cardiac output in heart failure patients. The infrared photoacoustic gas analyser markedly facilitates clinical use of the rebreathing method in general, which makes the method available to a larger group of clinicians working with patients with cardiovascular diseases.

INTRODUCTION

Measurements of cardiac output by standard methods, such as the direct Fick method (COFICK) or the thermodilution method (COTD), are time consuming and require cardiac catheterization, which is associated with a potential risk of adverse events. Therefore these methods are not feasible for routine patient monitoring in larger population groups.

Key words: cardiac output, foreign gas rebreathing, heart failure.
Abbreviations: COFICK, cardiac output measured by the direct Fick method; COTD, cardiac output measured by the thermodilution method; COORB, cardiac output determined by a non-invasive rebreathing method; QEP, effective pulmonary blood flow; RQ, respiratory quotient; S\textsubscript{a}O\textsubscript{2}, O\textsubscript{2} saturation; PO\textsubscript{2}, partial pressure of O\textsubscript{2}; CO\textsubscript{a}, O\textsubscript{2} content; note that arterial, mixed venous, capillary and alveolar values are denoted by a, v, cap and A respectively, e.g. S\textsubscript{a}O\textsubscript{2} is arterial O\textsubscript{2} saturation, C\textsubscript{cap}O\textsubscript{2} is capillary O\textsubscript{2} content, etc.
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and require frequent calibration and maintenance. These factors have significantly limited the clinical application of measurements of CO_{RB}.

More recently, an accurate infrared photoacoustic gas analyser has been introduced for the continuous analysis of ventilatory gas concentrations [2]. Compared with conventional mass spectrometers, this analyser weighs less, and is less expensive, more user friendly and stable, which markedly facilitates clinical use. Therefore we compared measurements of Q_{EP} and CO_{RB} obtained using the new infrared photoacoustic gas analyser with measurements of CO_{FICK} (gold standard) and CO_{TD} in patients undergoing cardiac catheterization.

**METHODS**

**Subjects**

Study subjects were recruited from a group of patients undergoing cardiac catheterization with measurement of cardiac output for diagnostic or follow-up purposes. The investigation was approved by the Ethics Committee of Copenhagen (KF 11-097/99 and KF 11-075/00), and was performed in agreement with institutional guidelines and the principles set forth in the Declaration of Helsinki. Informed consent was obtained from all participants following a full explanation of the purpose and nature of the study and the potential risks and discomforts associated with participation.

**Experimental protocol**

Two different experimental protocols were applied in patients diagnosed with heart disease or primary pulmonary hypertension (see Table 1).

**Protocol 1**

In the first protocol (10 patients), values of CO_{TD} were compared with estimates of CO_{RB} obtained by measuring Q_{EP} by foreign gas rebreathing. CO_{TD} was monitored continuously (see below) during 3–5 min, and immediately thereafter rebreathing (see below) was performed. In most of the patients these measurements were repeated, so that a total of 20 comparisons were obtained. The protocol was repeated three times in one patient

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Diagnosis</th>
<th>NYHA</th>
<th>MPAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>LVEF</th>
<th>RVEF</th>
<th>FEV1/FVC</th>
<th>TLCO (mmol [min^{-1} · kPa^{-1}])</th>
<th>SaO2</th>
<th>Shunt fraction</th>
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<tbody>
<tr>
<td>Protocol 1</td>
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<tr>
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<td>42</td>
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<td>–</td>
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<td>30</td>
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<td>–</td>
<td>0.70 (94%)</td>
<td>6.9 (72%)</td>
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</tr>
<tr>
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<td>0.82 (104%)</td>
<td>5.6 (64%)</td>
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<tr>
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<td>10.0 (86%)</td>
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<td>0.99</td>
<td>–</td>
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<tr>
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<td>–</td>
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<td>–</td>
<td>0.96</td>
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<tr>
<td>Protocol 2</td>
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<td>7.9 (75%)</td>
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<td>0.88 (107%)</td>
<td>4.8 (62%)</td>
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<td>12</td>
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<td>–</td>
<td>0.80 (104%)</td>
<td>11.0 (99%)</td>
<td>0.96</td>
<td>0.10</td>
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<tr>
<td>15</td>
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<td>52</td>
<td>7</td>
<td>0.27</td>
<td>–</td>
<td>0.87 (108%)</td>
<td>6.0 (66%)</td>
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<td>0.78 (96%)</td>
<td>10.0 (73%)</td>
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<td>0.30</td>
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<td>–</td>
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<td>0.97</td>
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<td>18</td>
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<td>III</td>
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<td>12</td>
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<td>4.7 (50%)</td>
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<td>6.2 (75%)</td>
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<tr>
<td>20</td>
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<td>26</td>
<td>0.17</td>
<td>–</td>
<td>0.77 (102%)</td>
<td>4.6 (59%)</td>
<td>0.95</td>
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<tr>
<td>21</td>
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<td>22</td>
<td>0.20</td>
<td>–</td>
<td>0.79 (100%)</td>
<td>6.5 (54%)</td>
<td>0.97</td>
<td>0.05</td>
</tr>
</tbody>
</table>
receiving infusion of incremental doses of a nitrate vasodilator.

Protocol 2
Acknowledging that the thermodilution technique is not the ‘gold standard’ for measurement of cardiac output, a second protocol was performed where measurement of CO\textsubscript{FICK} (gold standard) was included. Another 11 patients participated in this experiment. In the resting patients, O\textsubscript{2} uptake was measured over 7 min, and CO\textsubscript{FICK} was determined (see below). CO\textsubscript{TD} was measured simultaneously. In one patient, a thermodilution catheter could not be positioned in the pulmonary artery, so that thermodilution measurements were performed in 10 patients only. Immediately after measuring O\textsubscript{2} uptake, measurement of Q\textsubscript{EP} by rebreathing was performed in duplicate (3–5 min apart) and subsequently averaged.

Measurement of CO\textsubscript{TD}
In both protocols, cardiac output was measured via a thermodilution catheter placed in the pulmonary artery and connected to a Baxter Vigilance® CCO computer. Automated CO\textsubscript{TD} measurements were generated by the computer approx. every 50 s. Averages of the automated readings over the time interval of interest were used in the comparisons.

Measurement of CO\textsubscript{FICK} (protocol 2)
CO\textsubscript{FICK} was determined by factoring O\textsubscript{2} uptake with the arteriovenous O\textsubscript{2} content difference determined from systemic arterial and mixed venous (pulmonary artery) blood samples. For each of the blood samples, haemoglobin concentration ([Hb]), O\textsubscript{2} saturation of haemoglobin (\text{Sa}O\textsubscript{2}, \text{Sv}O\textsubscript{2}), and O\textsubscript{2} (\text{Pa}O\textsubscript{2}, \text{Pv}O\textsubscript{2}) and CO\textsubscript{2} (\text{Pa}CO\textsubscript{2}, \text{Pv}CO\textsubscript{2}) partial pressures were measured (ABL-500 and OSM-3; Radiometer, Copenhagen, Denmark) (a and v denote arterial and mixed venous blood respectively). O\textsubscript{2} content (C\textsubscript{xO\textsubscript{2}} = 1.34[Hb] \cdot S\text{x}O\textsubscript{2} + P\text{x}O\textsubscript{2} \cdot 0.003, where x denotes arterial or mixed venous blood) and the arteriovenous O\textsubscript{2} content differences (C\textsubscript{a}O\textsubscript{2} − C\textsubscript{v}O\textsubscript{2}) were determined using standard formulae. In the one patient in whom a thermodilution catheter could not be positioned in the pulmonary artery, a multi-purpose catheter was placed in the pulmonary artery so that a mixed venous blood sample could be obtained. Oxygen uptake was measured using a mouthpiece connected to a breathing system with unidirectional flow (ventilation through the nose was prevented by a nose-clip) and an inspiratory differential pressure flowmeter. Concentrations of O\textsubscript{2} and CO\textsubscript{2} were measured at the inlet and in the mixed expired air (AMIS 2001; Innovision A/S, Odense, Denmark). From the ventilatory flow and the inspiratory and expiratory gas concentrations, O\textsubscript{2} uptake was calculated by a computer connected to the gas analyser system, with a specific software program using standard formulae. Furthermore, CO\textsubscript{2} excretion and the respiratory quotient (RQ) were determined.

Measurement of Q\textsubscript{EP} and CO\textsubscript{RB}
The rebreathing system used for measurement of Q\textsubscript{EP} has been described in detail previously [2]. The system consists of a three-way respiratory valve with a mouth-piece and a rebreathing bag connected to an infrared photoacoustic gas analyser (AMIS 2001; Innovision A/S) interfaced with a computer equipped with a specific software program. The software program functions as a user interface and controls the respiratory valve and gas analyser system settings, and stores retrieved gas concentration data on the computer for subsequent calculations.

Q\textsubscript{EP} was measured by rebreathing in a closed system (ventilation through the nose was prevented by a nose-clip), which contained a gas mixture of 1% SF\textsubscript{6}, 5% N\textsubscript{2}O and 50% O\textsubscript{2} in N\textsubscript{2} in a 4 litre antistatic rubber bag. Rebreathing was performed over 34 s with a gas volume of 30% of the estimated vital capacity [3] and a breathing rate of 14 min\textsuperscript{-1}. Gas was sampled continuously from the mouthpiece for analysis by the infrared photoacoustic gas analyser. A constant ventilation rate was ensured by having the subject breathe in synchrony with a graphical tachymeter on the computer screen (set at 14 min\textsuperscript{-1}) and a constant ventilation volume was ensured by requesting that the subject completely emptied the rebreathing bag with each breath. The rebreathing system software calculated Q\textsubscript{EP} from the rate of uptake of N\textsubscript{2}O into the blood [slope of the regression line through logarithmically transformed expiratory (i.e. alveolar) N\textsubscript{2}O concentrations plotted against time] after correction for system volume changes using the SF\textsubscript{6} (blood-insoluble gas) concentrations. The first two or three breaths were excluded from the analysis due to initial incomplete gas mixing.

Because rebreathing determines Q\textsubscript{EP} (i.e. the non-shunted fraction of cardiac output) and not total cardiac output, we also evaluated the importance of correcting for shunted blood flow. Therefore in protocol 2 the measured Q\textsubscript{EP} was corrected for the fraction of cardiac output shunted through areas without significant gas exchange (shunt fraction). From the shunt fraction, shunt flow was calculated, and CO\textsubscript{RB} was determined as CO\textsubscript{RB} = Q\textsubscript{EP} + shunt flow. The shunt fraction was determined in each patient from the O\textsubscript{2} content of arterial and mixed venous blood samples and the calculated pulmonary capillary oxygen content (C\text{cap}O\textsubscript{2}) using the standard formula:

\[
\text{Shunt fraction} = \frac{(C\text{cap}O\textsubscript{2} - \text{Ca}O\textsubscript{2})}{(C\text{cap}O\textsubscript{2} - \text{Cv}O\textsubscript{2})}
\]
CcapO₂ was calculated using the standard formula:

\[ C_{\text{capO}_2} = 1.34[Hb] \cdot ScapO_2 + P_{\text{capO}_2} \cdot 0.003 \]

where ScapO₂ was set to 1 and PcapO₂ was estimated as the alveolar oxygen tension (PAO₂). PAO₂ was calculated from the formula:

\[ PAO_2 = \left[ FiO_2 \cdot (P_h - 47) \right] - \left[ P_{aCO_2} \cdot (FiO_2 + (1 - FiO_2/RQ)) \right] \]

where \( P_h \) is the barometric pressure, \( FiO_2 \) is O₂ fraction in inspired air and \( P_{aCO_2} \) is the measured arterial CO₂ tension.

**Statistical analysis**

The agreement between values of COICK, QEP, CORB, and COTD was evaluated as suggested by Bland and Altman [4]. To improve clarity, however, ordinary scatterplots of the paired measurements are also presented.

**RESULTS**

In protocol 1, where only QEP and COTD were compared, QEP tended to underestimate COTD (Figure 1), with a mean difference (bias) of 1.0 litre \( \cdot \) min\(^{-1}\) and limits of agreement (±2 S.D.) of ±0.8 litre \( \cdot \) min\(^{-1}\). Our further investigations in protocol 2 disclosed that the difference occurred because QEP tended to underestimate and COTD tended to overestimate cardiac output as compared with values of COICK (gold standard).

In protocol 2, the mean difference (bias) and limits of agreement (±2 S.D.) between COICK and QEP were 0.6 ± 1.2 litre \( \cdot \) min\(^{-1}\); when COICK and CORB were compared this value was −0.8 ± 1.3 litre \( \cdot \) min\(^{-1}\). Therefore rebreathing provided at least as reliable an estimate of cardiac output as the thermodilution method (Figure 2A compared with Figure 2C).

In three patients with low \( SaO_2 \) (Figure 2; patients denoted by open circles), indicating intrapulmonary shunting of blood through areas without significant gas exchange, QEP tended to underestimate COICK. When
correction for intrapulmonary shunt flow was applied (i.e. calculation of $Q_{RB}$) in all 11 patients, the bias between $CO_{Fick}$ and $CO_{RB}$ was $0.1 \pm 0.9$ litre \cdot min$^{-1}$, primarily because agreement improved in the three patients with significant shunt flow (compare Figures 2A and 2B). If these three patients were not included in the analysis and correction for shunt flow was not applied, the bias and limit of agreement between $CO_{Fick}$ and $Q_{RB}$ was $0.3 \pm 0.9$ litre \cdot min$^{-1}$. Thus measurement of $Q_{RB}$ provided a reliable estimate of cardiac output in heart failure patients in the absence of significant intrapulmonary shunt flow (indicated as $S\alpha O_2 > 0.95$).

DISCUSSION

The results of the present study demonstrate that rebreathing using an infrared photoacoustic gas analyser is a promising non-invasive method for the measurement of cardiac output in patients with heart failure. The method is safe and easy, which makes it suitable for more frequent monitoring of cardiac performance and systemic vascular resistance at rest or during exercise testing.

Foreign gas rebreathing is an established method for the measurement of $Q_{EP}$ and cardiac output [1]. Although the method has been applied extensively in basic cardiovascular research, the clinical application of rebreathing has been more modest. Previous [5] and more recent [6,7] investigations indicate, however, that the rebreathing method possesses potential for clinical use. Until recently, accurate continuous measurement of gas concentrations during rebreathing was carried out mainly by the use of mass spectrometers. These instruments, however, are difficult to operate and require frequent calibration and maintenance, which has limited the clinical application of the rebreathing method. Thus the infrared photoacoustic gas analyser, which is easier to operate in a clinical setting, can make the rebreathing method available to a larger group of clinicians working with patients with cardiovascular diseases, and contribute to further clinical use and evaluation of the rebreathing method.

The results of the present investigation demonstrate that, in patients with heart failure, measurement of $Q_{EP}$ provides an estimate of cardiac output that are at least as reliable as the estimate obtained with a thermodilution method when compared with the direct Fick method. Another recent study in patients with pulmonary hypertension, where a mass spectrometer was used during rebreathing, also reported that measurement of $Q_{EP}$ by rebreathing provided reliable estimates of cardiac output [7]. Thus rebreathing measurements represent a promising technique for clinical monitoring of cardiac output in these groups of patients. However, clinical experience with the rebreathing method is modest, and further evaluation is needed.

Limitations of the rebreathing method for estimation of cardiac output may be divided into two principal categories (which may both be present in the same patient); (1) factors that cause errors in the measurement of $Q_{EP}$ itself, and (2) factors that result in discrepancies between $Q_{EP}$ and cardiac output. Theoretical simulation models have suggested that uneven distribution between ventilation, lung tissue volume, alveolar volume and pulmonary blood flow, similar to that observed in more severe forms of lung disease, may cause errors in the measurement of $Q_{EP}$ by rebreathing [8]. Thus the presence of pulmonary disease might present one obstacle to the use of the rebreathing method. The results of the present investigation indicate that moderate decreases in diffusing capacity (see Table 1) do not significantly invalidate the rebreathing method in patients with heart failure. Because ventilatory function was relatively well preserved in our patient population, we were not able to evaluate the effect of reduced ventilatory function on measurements of cardiac output using rebreathing.

Kallay and co-workers [5], using a mass spectrometer, observed good agreement between $Q_{EP}$ determined by rebreathing and cardiac output determined by indicator-dilution methods in a group of patients with various cardiopulmonary diseases with preserved pulmonary function. However, the agreement was weakened when patients exhibited either restrictive or combined restrictive and obstructive pulmonary disease. These authors concluded that the measured dead space during rebreathing expressed as a fraction of the inspired volume provided the best index with which to identify discrepancies between $Q_{EP}$ and cardiac output of more than 20%. However, the same criterion resulted in false-positive rates and positive predictive values of 6% and 60% respectively. Thus a generally useful and accepted criterion for discarding rebreathing measurements in patients with pulmonary disease has not yet been established. Further investigations will be needed to clarify the impact of reduced pulmonary function on rebreathing measurements in more detail.

Important information is, however, obtained from the insoluble (in our case $S_{F_{6}}$) gas concentration curve obtained during rebreathing. Complete mixing of gases within the alveoli is an important assumption of the rebreathing method. The $S_{F_{6}}$ gas concentration curve provides direct information in this regard, and is obtained automatically during each rebreathing measurement. Thus the rebreathing measurement contains an inherent evaluation of the degree of gas mixing. If the $S_{F_{6}}$ curve indicates incomplete mixing, e.g. by continuously exhibiting large breath-to-breath variations in inspiratory and end-expiratory (alveolar) concentrations, the measurement must be discarded. Because incomplete mixing invalidates the measurement of $Q_{EP}$ regardless of the type and severity of lung disease, the $S_{F_{6}}$ curve may provide more useful information in regard to the validity.
of the measurement than other measures of pulmonary function.

Another potential source of error in the determination of cardiac output by rebreathing is the presence of shunted blood flow through areas without gas exchange, which will cause the measured \( Q_{EP} \) to underestimate the true cardiac output. Kallay et al. [5] did not observe a significant correlation between venous admixture (shunt fraction) and the discrepancy between \( Q_{EP} \) and cardiac output. However, it is shunt flow, not shunt fraction, that will be the more important determinant of the discrepancy between \( Q_{EP} \) and cardiac output. A lower shunt fraction at a higher cardiac output may cause a larger shunt flow (and thus a larger discrepancy between \( Q_{EP} \) and cardiac output) than a higher shunt fraction at a lower cardiac output. Our observations indicate that, when \( S_aO_2 \) is normal (i.e. 0.95 or above), the error is small and \( Q_{EP} \) provides a good estimate of cardiac output in patients with heart failure. Thus, from a practical clinical perspective, a normal \( S_aO_2 \) confirmed by non-invasive measurements (pulse oximeter) combined with adequate gas mixing during rebreathing (confirmed by the SF\(_n\) concentration curve) would indicate that a reliable estimate of cardiac output can be obtained. If shunt flow is significant, however, correction for this might be needed, as indicated from our observations in three patients with pulmonary hypertension and low \( S_aO_2 \). Theoretically, such a correction can be made from non-invasive measurements of \( S_aO_2 \) if \( O_2 \) uptake and haemoglobin concentration are known, but further studies are needed to validate such a non-invasive correction for shunt flow.

Finally, it should be pointed out that the rebreathing method also possesses potential for clinical application in a number of other diseases (e.g. essential hypertension, liver cirrhosis, diabetes, renal failure, and thyroid or adrenal dysfunction), where non-invasive evaluation of cardiovascular function might be preferred over invasive techniques.

In conclusion, the results of the present investigation demonstrate that a rebreathing method using an infrared photoacoustic gas analyser represents a promising non-invasive method for the measurement of cardiac output in patients with heart failure. The method could be useful for more frequent monitoring of cardiac performance and systemic vascular resistance at rest or during exercise testing. Compared with the mass spectrometer, the use of the infrared photoacoustic gas analyser markedly facilitates the clinical use of the rebreathing method in general, which makes the method available to a larger group of clinicians working with patients with cardiovascular diseases.

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**REFERENCES**