Validation of Noninvasive Measurement of Cardiac Output Using Inert Gas Rebreathing in a Cohort of Patients With Heart Failure and Reduced Ejection Fraction

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Background—Cardiac output (CO) is a key indicator of cardiac function in patients with heart failure. No completely accurate method is available for measuring CO in all patients. The objective of this study was to validate CO measurement using the inert gas rebreathing (IGR) method against other noninvasive and invasive methods of CO quantification in a cohort of patients with heart failure and reduced ejection fraction.

Methods and Results—The study included 97 patients with heart failure and reduced ejection fraction (age 42±15.5 years; 64 patients (65.9%) had idiopathic dilated cardiomyopathy and 21 patients (21.6%) had ischemic heart disease). Median left ventricle ejection fraction was 24% (10%–36%). Patients with atrial fibrillation were excluded. CO was measured using 4 methods (IGR, cardiac magnetic resonance imaging, cardiac catheterization, and echocardiography) and indexed to body surface area (cardiac index [CI]). All studies were performed within 48 hours. Median CI measured by IGR was 1.75, by cardiac magnetic resonance imaging was 1.82, by cardiac catheterization was 1.65, and by echo was 1.7 L·min⁻¹·m⁻². There were significant modest linear correlations between IGR-derived CI and cardiac magnetic resonance imaging–derived CI (r=0.7; P<0.001), as well as cardiac catheterization–derived CI (r=0.6; P<0.001). Using Bland–Altman analysis, the agreement between the IGR method and the other methods was as good as the agreement between any 2 other methods with each other.

Conclusions—The IGR method is a simple, accurate, and reproducible noninvasive method for quantification of CO in patients with advanced heart failure. The prognostic value of this simple measurement needs to be studied prospectively.

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Key Words: cardiac output ■ catheterization ■ echocardiography ■ heart failure ■ magnetic resonance imaging

Cardiac output (CO) is arguably the best measure of overall cardiac function, which carries strong prognostic implications.¹ To date, there is no universal agreement on what constitutes the best noninvasive method for measuring this parameter.²

See Clinical Perspective

CO measurement using the Fick method—which is considered the gold-standard method—is limited primarily by the need for invasive catheterization, the difficulty in obtaining accurate oxygen consumption (Vo₂) measurements, and the inability to achieve a steady state under certain conditions.³,⁴ This has stimulated the development and use of several noninvasive approaches—such as echocardiography, cardiac magnetic resonance (CMR), and inert gas rebreathing (IGR).³,⁵,⁶ However, each of these methods relies on various assumptions and has its own limitations.⁴,⁷,⁸

Measurement of CO by Doppler echocardiography has large inter- and intraobserver variability, and it is hampered by improper alignment of ultrasound beam and the geometric assumption of the left ventricle (LV) outflow tract (LVOT).⁴ In addition, CO quantification with CMR is relatively expensive and requires long image-acquisition time.⁵

IGR has emerged as an alternative noninvasive method to evaluate CO in patients with heart failure (HF), especially during exercise.⁹ However, the application of this method is still limited to a small number of patients and had not been validated in a large cohort of HF patients.¹⁰–¹²

The current study aimed to validate CO measurement using the IGR method in a cohort of patients with HF and reduced ejection fraction (HFrEF).

Methods

Patients

This was a prospective study conducted in Aswan Heart Center in the interval between September 2014 and February 2016. Among 264 consecutive patients presented to HF clinic, all 97 patients with...
HFrEF (ejection fraction <40%)—who were judged to need right heart catheterization to optimize therapy—were enrolled. Patients with poor echocardiographic window or contraindications to CMR (implantable pacemakers or resynchronization devices, claustrophobia) were excluded from this study. Three patients were not able to perform the rebreathing maneuver were also excluded. In addition, patients with atrial fibrillation were excluded because irregular rhythm hinders the retrospective ECG-gated CMR acquisitions because of incorrect combination of data, which causes significant image corruption and measurement errors. Moreover, the beat-to-beat variation in stroke volume might affect the accuracy of CO measurement by echocardiography.

A written informed consent was obtained from all patients. The study complies with the Declaration of Helsinki, and the protocol was approved by the Institutional Research Ethics Committee.

Clinical Data
Detailed history and clinical examination was performed with special emphasis on the cause of underlying heart disease, severity of symptoms, New York Heart Association class, and family history. Body surface area was calculated using Mosteller formula. All patients had 6-minute walk test. NT-proBNP (N-terminal probrain natriuretic peptide) was measured for all patients. CO was measured by cardiac catheterization (cath; Fick method) and 3 noninvasive (IGR, CMR, and transthoracic echocardiography) methods. All CO measurements were obtained within no more than 48 hours in a blinded manner and then indexed to body surface area (cardiac index [CI]).

IGR Method
This was performed during cardiopulmonary exercise testing using an Innocor device (Inninion, Denmark) equipped with an infrared photoacoustic gas analyzer. During the test, the patient rebreathes an oxygen-enriched mixture containing small amounts of 2 physiologically inert gases—one is blood soluble (0.5% nitrous oxide, N₂O) and the other is insoluble (0.1% sulfur hexafluoride, SF₆)—from a closed rebreathing system for 5 breaths or 15 seconds. During this time, the N₂O gas is dissolved in the blood perfusing the ventilated parts of the lungs. The concentration curve of the N₂O gas was then obtained, by the heart rate to obtain the CO in liters per minute (Figure 2).

\[
\text{CO} = \frac{\text{VO}_2}{\text{VE}} \times \left(\text{Aortic SO}_2 - \text{mixed venous SO}_2\right) \times 1.36 \times \text{Hb} \times 10
\]

where \(\text{VO}_2\) is the assumed O₂ consumption (3 mL/kg), Hb is the hemoglobin concentration (g/dL), and the constant 1.36 is the oxygen-carrying capacity of hemoglobin (expressed in mL O₂/g Hb).

Cardiac Catheterization
Right heart catheterization was performed to obtain mixed venous (pulmonary artery) and arterial (aorta) oxygen saturation (SO₂). Then, CO is calculated using the Fick principle as follows:

\[
\text{CO} = \frac{\text{VO}_2 \times \left(\text{Aortic SO}_2 - \text{mixed venous SO}_2\right)}{\text{VO} \times \text{O}_2 \times \text{Aortic SO}_2}
\]

where \(\text{VO}_2\) is the assumed O₂ consumption (3 mL/kg), Hb is the hemoglobin concentration (g/dL), and the constant 1.36 is the oxygen-carrying capacity of hemoglobin (expressed in mL O₂/g Hb).

Cardiac Magnetic Resonance
All studies were performed with a 1.5-T MRI scanner (Aera; Siemens) and a 48-channel cardiac coil. Initially, localizers were obtained in 3 orthogonal slices for orientation of anatomy of the heart and the great vessels, to plan the different cardiac views. A steady-state free precession sequence was performed to measure the ventricular volumes. LV and right ventricular volumes were scanned in short-axis views. Contours were drawn manually at the boundary between the blood pool and the myocardium. Trabeculae and papillary muscles were excluded from the myocardium.

Blood flow of the ascending aorta was quantified at the level of the pulmonary artery bifurcation using standard 2-dimensional phase-contrast velocity-encoding imaging of the ascending aorta. Imaging parameters were free breathing (acquisition time: around 1 minute), retrospective ECG gating, the velocity encoding set to 200 cm/s, slice thickness: 8 mm, time of repetition: 47 ms, and time of echo: 2.6 ms. Thirty images were obtained per cardiac cycle. Careful screening of the ECG along the whole sequence was made in order to view the triggering. After the acquisition is finished, images were checked for any possible aliasing. Postprocessing was done by manual contour using the same workstation used for the volumes assessment (Argus software tool). Forward stroke volume was multiplied by the heart rate to obtain the CO in liters per minute (Figure 2).

Transthoracic Echocardiography
Images were obtained via a Philips EPIQ 7 ultrasound system with 2 and 2.5 MHz sector transducers, while the patient in the left lateral...
decubitus position. The studies were done according to criteria provided by the American Society of Echocardiography.20 ECG was connected to define the timing of cardiac cycle events. Measurement of the LVOT diameter was done in a zoomed LVOT-focused view from the parasternal long axis. The LVOT diameter was then measured during early systole from the junction of the aortic leaflets with the septal endocardium to the junction of the leaflet with the mitral valve posteriorly, using inner edge to inner edge. The largest of 3 to 5 measurements was taken to avoid underestimation of the diameter, which is an inherent error of the tomographic plane imaging. The LV outflow velocity is recorded using pulsed-wave Doppler from the apical 5-chamber view, with the sample volume positioned ≈5 mm proximal to the aortic valve. The LVOT velocity time integral was obtained by tracing the envelope. CO was then calculated using the formula CO=(LVOT diameter)²×0.785×LVOT velocity time integral×heart rate.

Statistical Analysis
Statistical analysis was performed using Statistical Package for Social Sciences, version 16 (SPSS 16). First, all variables were tested for normality using Kolmogrov–Smirnov test.21 Most of the quantitative variables in this study were not normally distributed and accordingly are presented as median (min–max). Quantitative data are presented as mean±SD when normality assumptions were satisfied. Qualitative data are presented as number (percentage).21 Bivariate correlations (2-sided tests) were performed using Spearman correlation coefficient.22 Probability value <0.05 was considered statistically significant. Agreement among the 4 methods was performed using Bland–Altman analysis.23

Results
The demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. Sixty-four patients (65.9%) had idiopathic dilated cardiomyopathy, whereas 21 patients (21.6%) had HF of ischemic cause. Median LV ejection fraction was 24% (10%–36%). Despite optimal medical treatment, 73 patients (75.3%) have severe HF symptoms (New York Heart Association class III or IV). Median 6-minute walk test was 280 m. The majority of patients were on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (96.6%), β-blockers (74.2%), or mineralocorticoid antagonist (83.5%). NT-proBNP was significantly high (median NT-proBNP was 1114 pg/mL).

Echocardiographic and CMR measurements are shown in Table 2. Two thirds of patients had severe LV dysfunction (defined as LV ejection fraction <30%), whereas 52 patients (53.6%) had right ventricular systolic dysfunction (defined as right ventricular ejection fraction <50%).24 Severe mitral regurgitation was detected in 17 patients (17.5%).

During cardiopulmonary exercise testing, patients achieved a median workload of 4.6 metabolic equivalents. Median peak VO₂ was 15.5 mL·kg⁻¹·min⁻¹, and 60.8% of patients had peak VO₂ <12 mL·kg⁻¹·min⁻¹. VE/VCO₂ slope was 36.7. Median CI was 1.75 L·min⁻¹·m⁻², whereas cardiac power output at peak exercise was 1.3 W (Table 3).

Hemodynamic data obtained during right heart catheterization were shown in Table 4. LV end-diastolic pressure was significantly high (23 mmHg). Pulmonary hypertension (defined as mean pulmonary artery pressure > 25 mmHg) was detected in 68 patients (70%). Thirty patients (31%) had severe pulmonary hypertension (defined as pulmonary artery systolic pressure >60 mmHg).

Intraobserver Variability of IGR-Derived CI
Intraobserver variability of CI measurements using the IGR method was judged by calculating the mean difference between the repeated measurements performed in 30 patients, then intraclass correlation coefficient was calculated.25 The intraobserver mean absolute difference for IGR-derived CI was 0.03 L·min⁻¹·m⁻² (1.8%), and the intraclass correlation coefficient was 0.94 (P<0.001).
No significant difference was detected between IGR-derived CI and cath-derived CI (1.75 versus 1.65 L·min⁻¹·m⁻², respectively; P=0.65). A moderately strong positive linear correlation was demonstrated between IGR-derived CI and CMR-derived CI (r=0.70; P<0.001; R²=0.49) as well as cath-derived CI (r=0.61; P<0.001; R²=0.37). However, IGR-derived CI showed fair positive linear correlation with echo-derived CI (r=0.44; P<0.001; R²=0.19; Figure 3).

CMR-derived CI showed significant linear correlation with cath-derived CI (r=0.52; P<0.001; R²=0.27) and relatively weak correlation with echo-derived CI (r=0.36; P=0.001; R²=0.13). Echo-derived CI showed fair significant linear correlation with cath-derived CI (r=0.51; P<0.001; R²=0.27; Figure 3).

Bland–Altman analysis revealed good and relatively narrow limits of agreement between IGR-derived CI and cath-derived CI (upper and lower limits of agreement were 0.6 and -0.6, respectively; difference: 0.03 L·min⁻¹·m⁻²), as well as CMR-derived CI (upper and lower limits of agreement were 0.5 and -0.8, respectively; difference: 0.1 L·min⁻¹·m⁻²). The upper and lower limits of agreement between IGR-detected CI and echo-derived CI were 1.03 and -1.2 L·min⁻¹·m⁻², respectively, whereas those between CMR-detected CI and cath-derived CI were 1.02 and -0.6 L·min⁻¹·m⁻², respectively (Figure 4).
Table 3. CPX Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>METs achieved</td>
<td>4.6 (2.0–13)</td>
</tr>
<tr>
<td>Peak VO₂, ml/kg/min</td>
<td>15.5 (6.5–25)</td>
</tr>
<tr>
<td>Peak VO₂ &lt;12 ml/kg/min</td>
<td>59 (60.8)</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>36.7 (17.8–117)</td>
</tr>
<tr>
<td>VE/VCO₂ slope ≥36</td>
<td>49 (50.5)</td>
</tr>
<tr>
<td>Pₐ CO₂ at rest, mmHg</td>
<td>41 (24–49.2)</td>
</tr>
<tr>
<td>Pₚ CO₂ at peak exercise, mmHg</td>
<td>42.6 (25.6–63)</td>
</tr>
<tr>
<td>CI at rest, L/min/m²</td>
<td>1.75 (1.0–3.4)</td>
</tr>
<tr>
<td>Peak CI, L/min/m²</td>
<td>3.1 (1.4–6.9)</td>
</tr>
<tr>
<td>Cardiac power output at rest, W</td>
<td>0.7 (0.2–1.4)</td>
</tr>
<tr>
<td>Peak cardiac power output, W</td>
<td>1.3 (0.3–2.4)</td>
</tr>
</tbody>
</table>

Data are presented as median (min–max) and n (%). CPX indicates cardiopulmonary exercise; and METs, metabolic equivalents.

Discussion

The present study demonstrated good reproducibility and intraobserver variability for CO measurements using the IGR method in patients with HFrEF. Moreover, significant modest linear correlations and good agreement were detected between CO measured using the IGR method and invasive catheterization (the gold-standard invasive method) as well as CMR (the gold-standard noninvasive method). To the best of our knowledge, this is the first study to validate CO measurement using IGR against cath and CMR in a large cohort of HF patients.

Patients included in this study were severely symptomatic despite optimal guideline-directed medical therapy. Most of the patients were Weber class C (64% of patients had peak VO₂ <16) and ventilatory class III (50.5% of patients have VE/VCO₂ slope ≥36). Half of patients had low peak exercise cardiac power output (<1.5 W). Low CO is a key element of HF, and its measurement is recommended in patients with advanced HF being evaluated for heart transplantation or ventricular assist devices (class I recommendation; level of evidence C). CI is an independent predictor of all-cause mortality and heart transplantation in ambulatory patients with advanced HF. In addition, peak exercise cardiac power output has been identified as an independent predictor of outcome in HF patients. Although the role of periodic measurement of CO has not been established, it could reveal occult deterioration of cardiac function that may give a rationale for intensification of pharmacological therapy or for more advanced therapy (heart transplantation or mechanical assist devices).

In reality, measurement of flow is much more difficult than measurement of pressure, and CO quantification is hampered by the need for invasive catheterization and the low precision and accuracy of measurements. The Fick method is still the gold standard for CO quantification; however, it is time consuming and requires invasive pulmonary artery catheters to obtain mixed venous oxygen saturation, which is associated with a potential risk of adverse events. In addition, large errors can be obtained when assumed—rather than measured—VO₂ is used.

Flow quantification with CMR using phase contrast flow velocity mapping has also been extensively validated with high accuracy; however, it is a relatively expensive imaging modality that requires long image-acquisition time. Furthermore, CO quantification by CMR may be affected by several factors. The first is the isocenter offset, which affects the homogeneity of the magnetic field; however, in our study, it was always at the center of the vessel of interest (aorta). Another important factor is perpendicular planning of the through plane measurements to the aorta. The through plane in our study was performed from 2 orthogonal views. Lastly, studies with segmented sequences in modern scanners with shorter bore have shown problems with phase offsets that may cause errors in CO measurements.

The IGR method is a simple, easy, and cost-effective method for noninvasive measurements of effective pulmonary blood flow, which is equivalent to CO as long as no significant intrapulmonary or intracardiac shunts exist. It provides important additional information to that obtained from VO₂ and VE/VCO₂, which are appreciated as strong independent prognostic predictors in patients with HFrEF. Furthermore, it helps to differentiate whether reduced VO₂ is because of cardiac or noncardiac (pulmonary or musculoskeletal) diseases.

In the present study, IGR-derived CI showed modest correlations with CI measured by CMR (r=0.7; P<0.001) and cath (r=0.6; P<0.001) and correlated less with CI measured by echocardiography (r=0.36; P=0.001). The agreement between the IGR method and the other tested methods was as good as the agreement between any 2 other methods with each other. Given the apparent excellent reproducibility of this simple and noninvasive IGR method, as well as the low and acceptable percentage error (95% limits of agreement/mean CI) for IGR-derived CI measurements, which is close to 30%, the commonly quoted criterion for acceptability of agreement with a reference standard method when assessing the accuracy and precision of a new technique for CO measurement, the IGR method lends itself to serial evaluation of CO in HF patients in daily clinical practice.

Several previous small studies have shown acceptable agreement between CO measured by IGR with those obtained by thermodilution. Sobanski et al demonstrated significant correlation between IGR-derived CO and Fick-derived CO (r=0.75; P<0.001) and mean difference 0.006 L/min in 21 patients. The mean difference in the latter study was smaller than our study (0.03 L/min/m²); however, the

Table 4. Hemodynamic (Catheterization) Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP, mm Hg</td>
<td>23 (11–34)</td>
</tr>
<tr>
<td>PAPsystolic, mm Hg</td>
<td>46 (16–95)</td>
</tr>
<tr>
<td>PAPmean, mm Hg</td>
<td>34.5 (11–64)</td>
</tr>
<tr>
<td>RAPmean, mm Hg</td>
<td>11 (4–26)</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>1.65 (0.9–2.6)</td>
</tr>
</tbody>
</table>

Data are presented as median (min–max).

CI indicates cardiac index; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressure; and RAP, right atrial pressure.
Validation of Inert Gas Rebreathing

limits of agreement were wider (±1.3 L/min versus ±0.7 L·min⁻¹·m⁻²). Similar results were obtained by Gabrielsen et al., who evaluated an older model of the device in 21 patients; the difference and limits of agreement (±2 SD) between IGR-derived CO and Fick-derived CO was 0.6±1.2 L/min (11 patients), whereas the difference between IGR-derived CO and thermodilution-derived CO was 1.0±0.8 L/min (10 patients). Furthermore, Agostoni et al. demonstrated a strong and significant correlation between IGR-derived CO and Fick-derived CO (r=0.94) in 20 patients with HFrEF (mean cardiopulmonary exercise–derived CO exceeded Fick-derived CO by 0.1 L/min).

On the contrary, Saur et al. have compared IGR-derived CO with CMR-derived CO in 264 patients (43% of participants had HF). They showed a good correlation between the 2 methods with a mean difference of 0.2±1.0 L/min; however, the accuracy of measurements was low in extreme CO ranges, and the percentage error has exceeded the proposed error limit developed by Critchley and Critchley. The current study demonstrated higher IGR-derived CI than cath-derived CO (1.75 versus 1.65 L·min⁻¹·m⁻², respectively); however, it did not reach statistical significance (P=0.65). This could be explained in two ways. The first of these is the influence of lung congestion on gas diffusion and IGR-derived CO measurements. N₂O dissolves not only in the circulating blood but also in the congested blood in the lungs, which could overestimate CO calculations in advanced HF patients included in our study. According to the ESCAPE trial, patients in lower New York Heart Association classes (classes I and II) are less likely to have substantial pulmonary congestion than those with more advanced HF (classes III and IV). This is supported by the significant, although not strong,
linear correlation that was detected between LV end-diastolic pressure and the difference between IGR-derived CI and catheter-derived CI (r=0.32, P=0.008) in our study patients. Second, the utility of assumed—rather than measured—VO₂ may lead to a systematic error in CO measurement using Fick method.

IGR method showed very good precision and reproducibility using the Innocor machine in the current study. However, with regard to accuracy, there are reports that demonstrated significant differences between gas exchange variables measured by metabolic systems made by different manufacturers, for example, Innocor and CardiO2.35 This might also apply to the IGR-derived CO measurements, despite the fact that Innocore is the only instrument on the market that can noninvasively measure CO using IGR.

Limitations

One limitation of the current study is that it is mainly concerned with validation of a snapshot measurement of CO at rest using the IGR method against the other currently available methods, which could subsequently prove the reliability of such measurement at peak exercise. In addition, the presence of lung disease may cause errors in CO measurement using IGR because of ventilation perfusion mismatch36; however, moderate decreases in diffusing capacity do not significantly invalidate the IGR method in patients with HF.31 Finally, the presence of significant intrapulmonary shunt may underestimate CO measurement using the IGR method.

Conclusions

Inert gas rebreathing method is a simple, accurate, and reproducible noninvasive method for measurement of CO in patients with advanced heart failure. The prognostic value of this simple measurement needs to be studied prospectively.

Acknowledgments

We would like to acknowledge the two heart failure specialist nurses (Hader Abdelmennaem and Saber Mostafa) for their great contribution in conducting the study and data collection.

Disclosures

None.

References

Validation of Inert Gas Rebreathing


**CLINICAL PERSPECTIVE**

To date, there is no universal agreement on what constitutes the best noninvasive method for measuring cardiac output (CO). All available methods—even the gold-standard Fick method—rely on various assumptions and hence are subject to low accuracy and precision. Inert gas rebreathing method is a simple, accurate, nonintrusive, reproducible, and cost-effective method for noninvasive measurement of CO, which showed good correlation and relatively narrow limits of agreement with CO measured using the gold-standard invasive (cardiac catheterization) and noninvasive (magnetic resonance imaging) methods. Inert gas rebreathing may allow periodic measurement of CO, which could reveal occult deterioration of cardiac function and, thus, provide a rationale for the intensification of pharmacological therapy or for more intensive therapy (heart transplantation or mechanical assist devices). The findings of our study may act to spur several other studies; this could include, for example, sequential CO measurement in follow-up of heart failure patients during ventricular assist device support (which may be a criterion for explantation and detecting changes after explantation) and studying the prognostic value of inert gas rebreathing—derived CO in patients with heart failure and preserved ejection fraction or any other group.
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