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ORIGINAL RESEARCH

Noninvasive Assessment of Cardiac Output: Accuracy and Precision of the Closed-Circuit Acetylene Rebreathing Technique for Cardiac Output Measurement

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BACKGROUND: Accurate assessment of cardiac output is critical to the diagnosis and management of various cardiac disease states; however, clinical standards of direct Fick and thermodilution are invasive. Noninvasive alternatives, such as closed-circuit acetylene (C_2H_2) rebreathing, warrant validation.

METHODS AND RESULTS: We analyzed 10 clinical studies and all available cardiopulmonary stress tests performed in our laboratory that included a rebreathing method and direct Fick or thermodilution. Studies included healthy individuals and patients with clinical disease. Simultaneous cardiac output measurements were obtained under normovolemic, hypovolemic, and hypervolemic conditions, along with submaximal and maximal exercise. A total of 3198 measurements in 519 patients were analyzed (mean age, 59 years; 48% women). The C_2H_2 method was more precise than thermodilution in healthy individuals with half the typical error (TE; 0.34 L/min [r=0.92] and coefficient of variation, 7.2%) versus thermodilution (TE=0.67 [r=0.70] and coefficient of variation, 13.2%). In healthy individuals during supine rest and upright exercise, C_2H_2 correlated well with thermodilution (supine: r=0.84, TE=1.02; exercise: r=0.82, TE=2.36). In patients with clinical disease during supine rest, C_2H_2 correlated with thermodilution (r=0.85, TE=1.43). C_2H_2 was similar to thermodilution and nitrous oxide (N_2O) rebreathing technique compared with Fick in healthy adults (C_2H_2 rest: r=0.85, TE=0.84; C_2H_2 exercise: r=0.87, TE=2.39; thermodilution rest: r=0.72, TE=1.11; thermodilution exercise: r=0.73, TE=2.87; N_2O rest: r=0.82, TE=0.94; N_2O exercise: r=0.84, TE=2.18). The accuracy of the C_2H_2 and N_2O methods was excellent (r=0.99, TE=0.58).

CONCLUSIONS: The C_2H_2 rebreathing method is more precise than, and as accurate as, the thermodilution method in a variety of patients, with accuracy similar to an N_2O rebreathing method approved by the US Food and Drug Administration.

Key Words: acetylene ■ cardiac output ■ exercise ■ Fick ■ noninvasive diagnostics ■ heart failure ■ thermodilution

The accurate assessment of cardiac output (Qc) is critical for the appropriate diagnosis and management of a variety of cardiac diseases. The gold standard for measuring Qc, the direct Fick method, is not routinely performed in clinical settings as it requires specific equipment and expertise that are not readily available. Thus, the thermodilution technique is often used for decision making. Both the direct Fick and thermodilution methods are invasive techniques that require pulmonary artery catheter placement with associated risks including pneumothorax, infection, bleeding, or damage to the vasculature including pulmonary artery rupture.[1,2] Additionally, invasive techniques are expensive, time consuming, and require specialized personnel. Importantly, even “gold-standard” invasive estimates of Qc, which rely on various

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CLINICAL PERSPECTIVE

What Is New?

- Noninvasive assessment of cardiac output (Qc) by means of inert gas rebreathing techniques, used in physiology laboratories for nearly 100 years, has broad applications for use in clinical patient populations.
- In contrast to standard methods of assessing Qc, which are invasive, this technique is safe and easy for patients and staff to use.
- Our data demonstrate that assessment of Qc using the inert gas rebreathing technique is as accurate and precise as current clinical gold standards in a wide population of patients.

What Are the Clinical Implications?

- The ability to accurately and noninvasively measure Qc represents a major advancement for the field of cardiology, and can be helpful in patients with dyspnea of unclear cause, pulmonary hypertension, valvular heart disease, heart failure, and cardiogenic shock for confirmation and treatment.
- The inert gas rebreathing technique allows for the ability to obtain measurements in a variety of locations (clinic and hospital) using a portable device without the risks associated with invasive procedures.
- We encourage other investigators and clinicians to consider this technique in studies and patient populations where accurate and precise measurement of Qc would be important.

Nonstandard Abbreviations and Acronyms

C_2H_2	acetylene
FDA	Food and Drug Administration
HF	heart failure
N_2O	nitrous oxide
Qc	cardiac output
r	Pearson correlation coefficient
TE	typical error
$\dot{V}O_2$	oxygen uptake

equations to estimate rather than measure oxygen uptake ($\dot{V}O_2$), have proven inaccurate.[3] Therefore, an accurate and reliable noninvasive alternative to assess Qc is appealing.

Acetylene (C_2H_2) is one of several gases used for Qc measurement by the foreign gas rebreathing technique (C_2H_2 rebreathing).[4–6] C_2H_2 is an inert, soluble gas that enters the blood stream via pulmonary diffusion but, importantly, does not bind to hemoglobin and thus its concentration decreases during rebreathing at a rate proportional to Qc. In patients without significant lung disease, intracardiac, or intrapulmonary shunting, the estimated pulmonary blood flow to ventilated lung obtained from the closed-circuit C_2H_2 rebreathing method is proportional to systemic blood flow.[5]

The initial use of C_2H_2 for measuring Qc was first described by Grollman in the 1920s.[4–6] Since then, inert gas rebreathing methods have been validated against gold standards of dye dilution and the direct Fick method in animal models and healthy patients at rest and during exercise.[7–9] Additionally, the accuracy and feasibility of noninvasive rebreathing methods have been shown in patients with pulmonary hypertension, valvular heart disease, cardiomyopathy (including low Qc states), and pulmonary disease.[10–17] Importantly, the ease of using commercially available foreign gas rebreathing systems has been demonstrated with exercise stress testing and supports its use in predicting outcomes in patients with heart failure (HF).[18–20] The nitrous oxide (N_2O) rebreathing technique is currently approved by the US Food and Drug Administration (FDA) for commercial use and is marketed as the Innocor device (Innovision). This approval was granted given “substantial clinical evidence” for its equivalence to both the thermodilution and direct Fick methods.[21] While these previous investigations provide compelling evidence for the accuracy and feasibility of the inert gas rebreathing technique, most studies relied on small sample sizes and limited age ranges. Additionally, no studies have evaluated the precision and accuracy of the inert gas rebreathing technique in patients over a large range of defined cardiac preload conditions. Therefore, the goals of this study are to assess the precision and accuracy of the closed-circuit C_2H_2 rebreathing technique for estimating Qc at rest, over a range of cardiac hemodynamic conditions, and during exercise in a large number of healthy volunteers and clinical patients compared with current clinical standards.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The studies included in this analysis were approved by an institutional review committee and the participants gave informed consent.

We retrospectively analyzed 10 clinical research studies and all available invasive cardiopulmonary exercise tests performed in our laboratory using standard measurement protocols (including patient conditions), and using the same equipment, the same techniques, and mostly the same staff over the past decade. These studies included a mixture of healthy individuals and patients with clinical disease recruited from the surrounding community,[4,22–26] as well as patients referred for evaluation of dyspnea. All study participants underwent invasive hemodynamic assessment with right heart catheterization. The majority of healthy participants were middle-aged, sedentary adults, and those with clinical disease had HF with preserved ejection fraction as determined by Framingham HF diagnostic criteria and at least 1 prior hospitalization for HF.[10] Patients who were referred for invasive cardiopulmonary exercise testing had a variety of indications including unexplained dyspnea and HF. Studies involving healthy individuals had similar exclusion criteria to those involving patients who had HF with preserved ejection fraction and included inducible coronary artery disease, active or recent tobacco use, significant renal dysfunction (creatinine >2 mg/dL), obesity with a body mass index >35 kg/m^2, and poorly controlled diabetes mellitus or hypertension.

The majority of studies were performed with participants at rest in the supine position. Baseline measurements were obtained after 30 minutes of quiet rest. Lower body negative pressure was then used to decrease cardiac filling, as previously published.[25,26] Qc measurements were performed after 5 minutes each of −15 and −30 mm Hg lower body negative pressure, which lowered both right atrial (≈−2 and −4 mm Hg) and pulmonary capillary wedge pressure (≈−3 and −6 mm Hg). After a 20-minute break, repeat measurements were used to confirm a return to steady state. Cardiac filling was then increased by rapid infusion (100–200 mL/min) of warm normal saline. Measurements were repeated after 10 to 15 mL/kg and 20 to 30 mL/kg of saline infusion, which increased right atrial (≈+2 and +4 mm Hg) and pulmonary capillary wedge (≈+3 and +6 mm Hg) pressure, respectively. This protocol provided a large physiological range of pulmonary capillary wedge pressure from ≈4 to 18 mm Hg. For patients who underwent exercise testing, baseline measurements were obtained at rest in the upright position on a cycle ergometer and again during upright exercise under submaximal steady-state conditions with at least 5 minutes spent at each workload to ensure hemodynamic stability, followed by a maximal effort.

Qc Comparison Methods

Closed-Circuit C_2H_2 Rebreathing Technique

The modified closed-circuit C_2H_2 rebreathing method, with C_2H_2 as the soluble gas and helium as the insoluble gas, was used for noninvasive Qc assessment and has been previously described.[4,6,25,27] This method assumes that Qc is equal to effective pulmonary blood flow to ventilated lung, which can be assessed by the rate of decay of C_2H_2 concentration during rebreathing. Adequate mixing of the rebreathing gas in the lung was confirmed by a constant level of helium in all cases. The inspired fraction of C_2H_2 was calculated from the volume-weighted integral of C_2H_2 concentration measured during the first inspiration of a known mixture. The rate of C_2H_2 absorption into blood was computed from the regression slope of the logarithm of regressed end-tidal C_2H_2 fractions. The end-tidal points were selected by the software based on Sackner criterion, only for breaths where a stable helium concentration had been established.[28] As per the usual laboratory practice in the studies used for this analysis, after a change in posture or prolonged break, the first 2 or 3 C_2H_2 rebreathing measures are discarded to allow for stabilization of posture-related distribution of intrathoracic blood volume. No thermodilution measurements are obtained at this time to avoid excessive infusion of saline, and none of these measures were used for accuracy or precision analysis. Occasionally during the course of study, and at the discretion of the study cardiologist, measurements thought to be erroneous at the time of each individual study were excluded from analysis. These values were excluded immediately, in real time, and their exclusion was unrelated to the current comparison study. Common reasons for exclusion included poor inspiratory effort, evidence of inadequate gas mixing, or values obtained that were clearly outside of the achievable physiologic range. After the initial stabilization period (generally ≈15 minutes, and encompassing 2 or 3 measurements) this exclusion occurred rarely, involving no more than 1% to 2% of all measurements.

Thermodilution Technique

Determinations of Qc from thermodilution were based on the temperature changes recorded at the pulmonary artery thermistor after 10 mL of room temperature isotonic saline was injected into the right atrium. All curves were inspected visually, and only curves consistent with the required exponential decay were used for data analysis. Similar to the C_2H_2 rebreathing technique, <2% of thermodilution measurements were excluded from analysis based on poor temperature/time curves or values that were clearly outside of the achievable physiologic range. As with the C_2H_2 rebreathing measurements, the decision to exclude values was made at the time of study performance and unrelated to the current analysis.

Direct Fick Technique

Samples of pulmonary artery blood were drawn for determination of mixed venous oxygen content ($C\bar{v}_{O_2}$) in the middle of a 3-minute Douglas bag collection (at rest) and 1-minute Douglas bag collection (during exercise) for calculation of $\dot{V}O_2$. Gas concentrations were determined from mass spectrometry and ventilatory volumes from a Tissot spirometer. Hemoglobin concentration and oxyhemoglobin saturation were determined using co-oximetry (IL 482, Instrument Laboratories).

N_2O Technique

This technique has been previously described by Jarvis and colleagues[4] and is essentially the same technique on which the clinically approved Innocor device was based.[29] Qc measurements were determined using the Sackner algorithm.[28]

Statistical Analysis

For assessment of reliability (precision), individual measurements over a short period (on average 5 minutes between measurements) under the same condition were used for analysis. The reliability of all 3 methods was quantified by calculating the typical error (TE) of the measurement, retest correlation coefficients, and coefficients of variation (TE expressed as a percentage) for each method.[30]

For assessment of accuracy (sensitivity), all patients underwent simultaneous Qc measurements with at least 2 different methods at each time point while either resting or exercising. The average of at least 2 (and up to 4) simultaneous measurements was used for analysis. These measurements were obtained ≈5 minutes apart. The accuracy of the rebreathing method was compared with the direct Fick, thermodilution, and N_2O measurements (when available) using Pearson correlation coefficients (*r*), coefficients of variation, TE of the estimate, and visual presentation of the residuals (*y* axis) versus the predicted Qc (*x* axis). The predicted Qc is the practical measure (ie, C_2H_2, thermodilution or N_2O) adjusted for random bias in the sample population using the Hopkins regression method.[30] The resulting plots allow for inspection of possible heteroscedasticity of error in the measurement.

RESULTS

Our study consisted of 3198 measurements in 519 individual encounters (including 34 encounters for patients referred for clinical assessment). Some patients were studied before and after at least a year of intervention or volunteered for a second research protocol. These patients were considered individual encounters as long as there was at least a year between studies. The mean age of the cohort was 59 years (range, 19–89 years) and 48% were women.

Assessment of Precision

The test-retest reliability for the C_2H_2 rebreathing method was more precise than thermodilution in healthy patients with nearly half the TE: C_2H_2 rebreathing *r*=0.92 and TE 0.34 L/min (0.33–0.36) versus thermodilution *r*=0.70 and TE 0.67 L/min (0.64–0.71) (Figure 1). For comparison, precision analyses performed in a subset of healthy patients with repeated measurements of direct Fick yielded an excellent correlation (*r*=1.00) and a low TE of only 0.19 L/min (0.16–0.25).

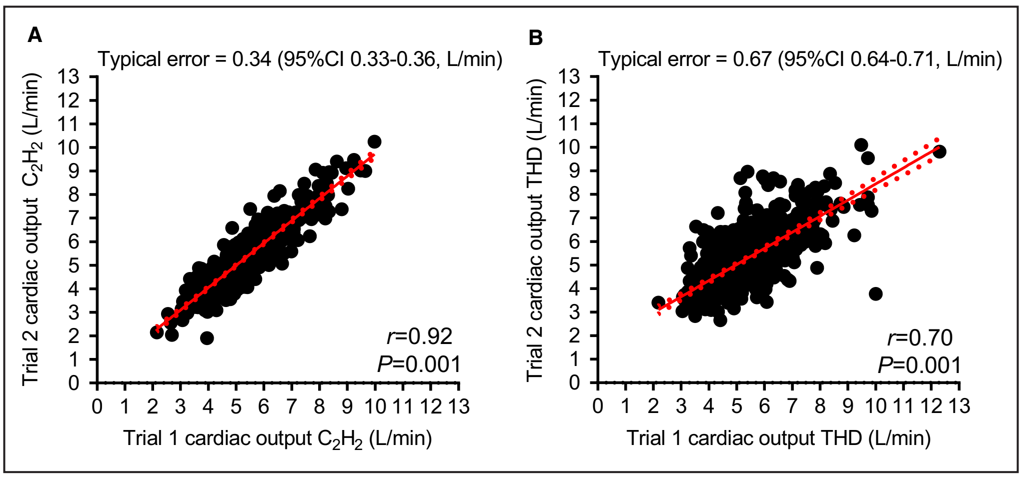

Figure 1. Reliability of the acetylene (C_2H_2) rebreathing technique vs thermodilution method for assessment of Qc.
A, Reliability of C_2H_2 rebreathing for estimation of Qc; (**B**) Reliability of thermodilution for estimation of Qc. Qc indicates cardiac output.

Assessment of Accuracy

Comparison of Rebreathing and Thermodilution in the Supine Position at Rest

At rest in the supine position, the C_2H_2 rebreathing method showed excellent agreement with thermodilution (*r*=0.84) and a clinically acceptable TE of 1.02 L/min (1.00–1.050) (Figure 2). When patients were stratified by loading condition, the TE was lower at normal loading conditions (0.79 L/min [0.76–0.83] versus low (1.0 L/min [0.96–1.05] and high (1.21 L/min [1.16–1.27] preload states) (Table 1). Similarly, the C_2H_2 rebreathing method showed excellent agreement with thermodilution in patients with clinical disease at rest in the supine condition (*r*=0.85); however, there was a larger TE of 1.43 L/min (1.24–1.69) as compared with healthy controls.

Comparison of Rebreathing and Thermodilution in the Upright Position at Rest and With Exercise

In healthy individuals during upright exercise, the agreement between the C_2H_2 rebreathing and thermodilution methods remained excellent (*r*=0.82). As expected, there was a larger TE at higher Qc of 2.36 L/min (2.13–2.98). However, when expressed as a percentage, the variation in TE was similar to that observed for direct Fick versus C_2H_2 rebreathing. We did not have a significant number of patients who had simultaneous rebreathing and thermodilution measured with upright exercise in our cohort of patients with clinical disease for comparison.

Comparison of Rebreathing and Thermodilution Versus Direct Fick During Supine Rest, Upright Rest, and Upright Exercise: Sensitivity Analyses

We studied a subset of patients who underwent simultaneous measurement of direct Fick and either the C_2H_2 rebreathing or thermodilution method (Figures 3 and 4). In healthy patients at rest in the supine position, the C_2H_2 rebreathing method had better agreement than thermodilution when compared with direct Fick (C_2H_2 rebreathing *r*=0.85 versus thermodilution *r*=0.72) with a lower TE (C_2H_2 rebreathing TE=0.84 L/min [0.51–0.86] versus thermodilution TE=1.11 L/min [0.93–1.39]). In healthy patients at rest in the upright position, the C_2H_2 rebreathing method had a similar

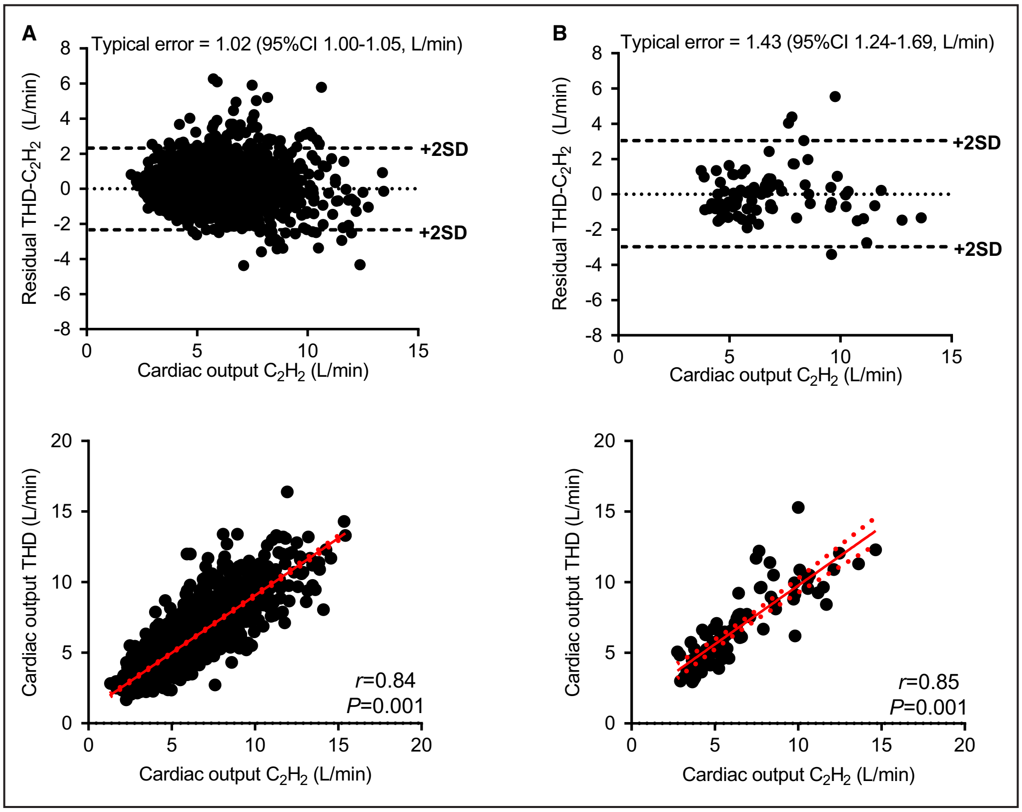

Figure 2. Comparison of the accuracy of the acetylene (C_2H_2) rebreathing technique vs thermodilution method for the assessment of Qc in both healthy patients and those with clinical disease in the supine position at rest.
A, Accuracy of C_2H_2 rebreathing for estimation of Qc vs thermodilution in healthy patients; (**B**) Accuracy of C_2H_2 rebreathing for estimation of Qc vs thermodilution in a clinical population. Qc indicates cardiac output.

Table 1. Assessment of Accuracy Between Various Methods of Qc Measurements

Patients	Condition	Qc Comparison	No. of Data Points	Qc, Mean (SD)	*r*	TE	CV
Healthy, supine							
	Rest, all loading conditions	Thermodilution vs C_2H_2	2793	Thermodilution 5.5 (1.9) C_2H_2 5.7 (2.0)	0.84 (0.83–0.85)	1.02 (1.00–1.05)	19.5% (18.9–20.0)
	Rest, normal loading/baseline	Thermodilution vs C_2H_2	989	Thermodilution 5.4 (1.2) C_2H_2 5.5 (1.3)	0.76 (0.73–0.78)	0.79 (0.76–0.83)	15.7% (15.0–16.5)
	Rest, lower body negative pressure	Thermodilution vs C_2H_2	849	Thermodilution 4.8 (1.8) C_2H_2 4.8 (1.7)	0.84 (0.82–0.86)	1.00 (0.96–1.05)	22.4% (21.3–23.7)
	Rest, rapid saline infusion	Thermodilution vs C_2H_2	900	Thermodilution 6.5 (2.2) C_2H_2 6.7 (2.4)	0.84 (0.82–0.85)	1.21 (1.16–1.27)	19.5% (18.6–20.6)
Clinical disease, supine							
	Rest, all loading conditions	Thermodilution vs C_2H_2	86	Thermodilution 6.8 (2.7) C_2H_2 6.4 (2.7)	0.85 (0.78–0.90)	1.43 (1.24–1.69)	21.7% (18.6–26.0)
Healthy, upright							
	Rest	Fick vs C_2H_2	117	Fick 5.3 (1.5) C_2H_2 5.6 (1.6)	0.77 (0.69–0.84)	0.94 (0.83–1.08)	20.2% (17.7–23.5)
	Exercise	Fick vs C_2H_2	114	Fick 15.4 (4.8) C_2H_2 13.5 (3.7)	0.87 (0.81–0.91)	2.39 (2.12–2.75)	16.5% (14.5–19.2)
	Rest	Fick vs Thermodilution	109	Fick 5.3 (1.5) Thermodilution 5.6 (1.5)	0.81 (0.74–0.87)	0.88 (0.78–1.02)	17.6% (15.3–20.5)
	Exercise	Fick vs Thermodilution	87	Fick 14.7 (4.2) Thermodilution 14.0 (3.3)	0.73 (0.61–0.82)	2.87 (2.50–3.38)	20.5% (17.6–24.5)
	Exercise	Thermodilution vs C_2H_2	98	Thermodilution 15.0 (4.1) C_2H_2 13.3 (3.2)	0.82 (0.75–0.88)	2.36 (2.06–2.74)	16.5% (14.3–19.4)
Clinical disease, upright							
	Exercise	Fick vs C_2H_2	44	Fick 8.2 (2.5) C_2H_2 8.2 (2.5)	0.89 (0.81–0.94)	1.14 (0.94–1.45)	13.4% (11.0–17.4)

C_2H_2 indicates acetylene; CV, coefficient of variation; Qc, cardiac output; *r*, Pearson correlation coefficient; and TE, typical error.

correlation (C_2H_2 rebreathing *r*=0.77 versus thermodilution *r*=0.81) and TE (C_2H_2 rebreathing TE=0.94 L/min (0.83–1.08) versus thermodilution TE=0.88 L/min [0.78–1.02]) as thermodilution when compared with the direct Fick method.

During exercise, the C_2H_2 rebreathing method correlated better with a lower TE when compared with the direct Fick than the thermodilution method (C_2H_2 rebreathing *r*=0.87 versus thermodilution *r*=0.73; C_2H_2 rebreathing TE=2.39 L/min [2.12–2.75] versus thermodilution TE=2.87 L/min [2.50–3.38]). In our clinical cohort of patients during exercise, the C_2H_2 rebreathing method correlated significantly with the direct Fick method (*r*=0.89) and had a very good TE of only 1.14 L/min (0.94–1.45).

Comparison of Direct Fick and Thermodilution to the C_2H_2 and N_2O Rebreathing Techniques

Direct Fick and thermodilution Qc measurements, along with both C_2H_2 rebreathing and N_2O rebreathing estimates of Qc, were obtained in 14 young, healthy patients in the supine and upright resting positions as well as during upright exercise. When compared with both the direct Fick and thermodilution methods, the C_2H_2 rebreathing technique appeared at least as good as, if not better than, the N_2O rebreathing technique with respect to the degree of correlation and TE (Table 2 and Figure 5).

Comparison of C_2H_2 to N_2O Rebreathing Technique

The C_2H_2 rebreathing and N_2O rebreathing methods from the cohort of 14 young, healthy patients in the supine and upright resting positions, as well as during upright exercise, were directly compared. There was excellent agreement between the 2 with an *r* of 0.99 and a low TE of only 0.58 L/min (0.52–0.65) under all conditions (Table 2 and Figure 6).

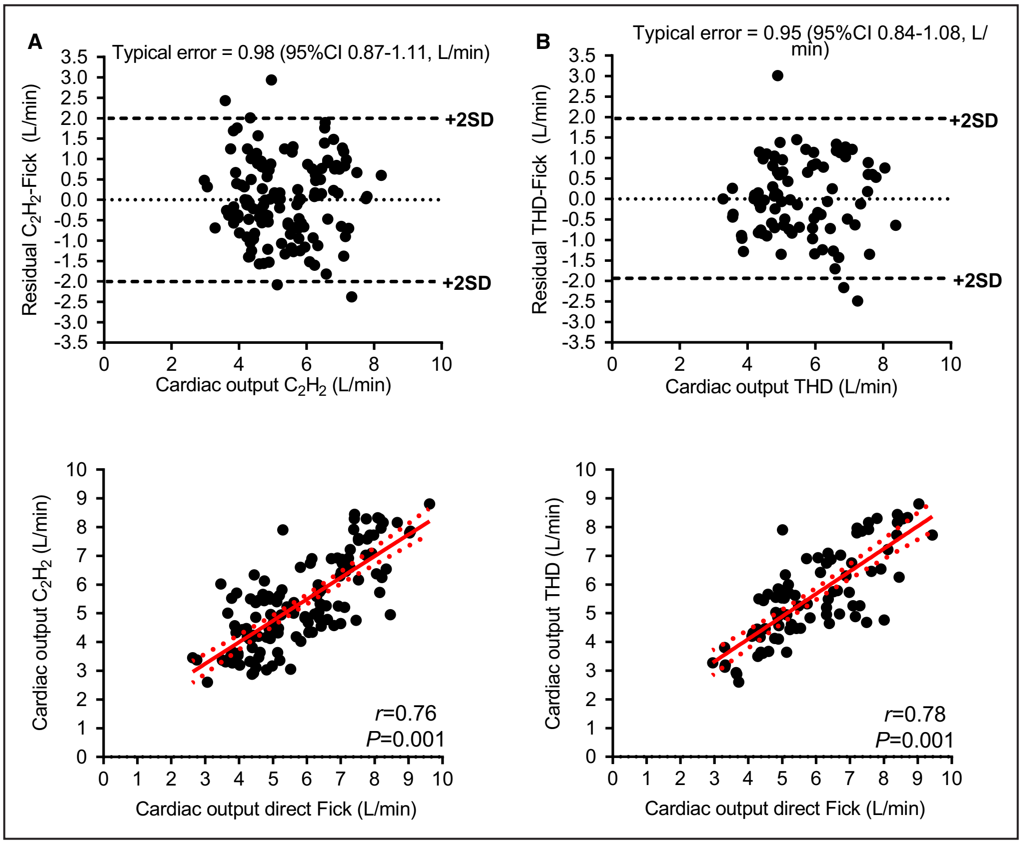

Figure 3. Comparison of the accuracy of the acetylene (C_2H_2) rebreathing technique and thermodilution method vs the direct Fick method for assessment of Qc in healthy patients in both the supine and upright positions at rest.

A, Accuracy of C_2H_2 rebreathing for estimation of Qc at rest; (**B**) Accuracy of thermodilution for estimation of Qc at rest. Qc indicates cardiac output.

DISCUSSION

In this study, we assessed the precision and accuracy of the C_2H_2 rebreathing method for estimation of Qc in a large cohort of individuals and found it to be much more precise than, and at least as accurate as, thermodilution—the most commonly used invasive method. To the best of our knowledge, this is the largest reported study to analyze methods for Qc comparison both simultaneously and under a variety of hemodynamic conditions, including both men and women across a wide age range.

Patients are referred for Qc assessment at rest and with exercise for a variety of indications (shock, dyspnea, pulmonary hypertension, HF), and important clinical decisions, including when to refer for heart transplant evaluation, rely heavily on the correct assessment of Qc.[31] The noninvasive method of assessment of Qc in our laboratory using the C_2H_2 rebreathing technique has a number of advantages over other available techniques that could facilitate its use: (1) the ease of use for both patients and staff (patients need to simply breathe through a mouthpiece, at a regular pace, for several breaths as instructed by easily trained staff); (2) the ability to obtain measurements in a variety of locations (ie, in a regular clinic setting or anywhere in the hospital) using a portable device without the risks associated with invasive procedures; and (3) substantially reduced overall cost compared with other available foreign gas rebreathing techniques (C_2H_2 gas is less expensive than other inert gasses such as N_2O and sulfur hexafluoride). Moreover, the technical modification to allow the patient to determine their own inspiratory volume, which is measured at the mouthpiece, ensures a smooth and patient-specific bag volume allowing improved rebreathing technique. Disadvantages to this technique include the need for patients to cooperate with rebreathing including the ability to tolerate a mouthpiece and additional limitations in use with patients who have *significant* underlying lung disease or shunt physiology.

Our data show that the C_2H_2 rebreathing method is much more precise than thermodilution and is comparable to the precision of the direct Fick measurement. This is likely a result of less susceptibility of the

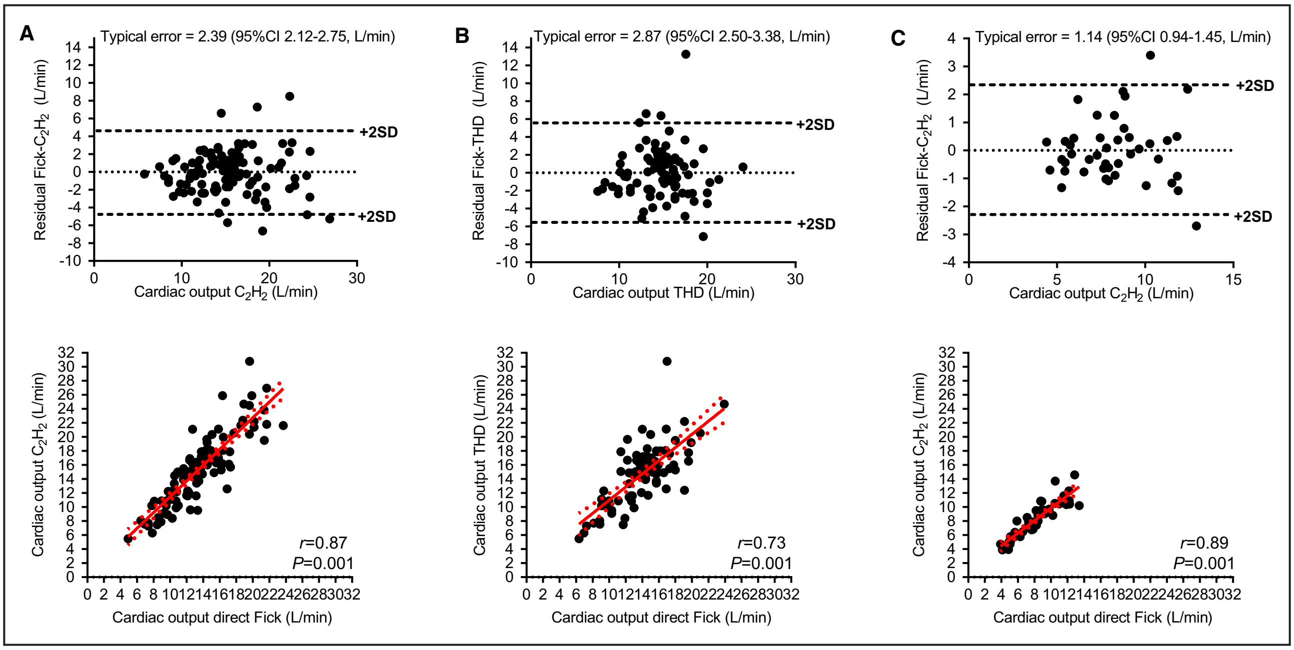

Figure 4. Comparison of the accuracy of the acetylene (C_2H_2) rebreathing technique and thermodilution method vs the direct Fick method for assessment of Qc during upright exercise in healthy patients and those with clinical disease.
A, Accuracy of C_2H_2 rebreathing for estimation of Qc during exercise in healthy patients; (**B**) Accuracy of thermodilution for estimation of Qc during exercise in healthy patients; and (**C**) Accuracy of C_2H_2 rebreathing for estimation of Qc during exercise in clinical populations. Qc indicates cardiac output.

rebreathing method to measurement errors inherent to thermodilution including operator inconsistency in the rate of injection of saline, variability in the temperature of saline used, and the presence of underlying cardiac pathology (such as tricuspid regurgitation) in the patients.

Our results also demonstrate that the C_2H_2 rebreathing method is at least as accurate as the thermodilution method under a variety of preload and exercise conditions as evidenced by excellent correlation when the C_2H_2 rebreathing method is compared directly with the thermodilution method. There is a larger TE with exercise, related to higher Qc, as compared with measurements in the resting position without a significant difference in the coefficients of variation when comparing the true gold standard of the direct Fick method with the rebreathing method. In clinical practice, Qc measurements are most often assessed at rest and the variability in the rebreathing method of ≈1 L/min is acceptable. Importantly, sensitivity analyses performed in healthy patients at rest and with exercise in the upright position show that the C_2H_2 rebreathing method, as compared with the direct Fick method, was at least comparable to that of thermodilution. Notably, with exercise, the C_2H_2 rebreathing method is more accurate than thermodilution when compared with the direct Fick method, as demonstrated by a higher correlation coefficient, lower TE (nearly 10%), and smaller coefficients of variation. Additionally, we analyzed a subset of patients with clinical disease undergoing exercise in the upright position. The C_2H_2 rebreathing method was highly correlated with the direct Fick method with a clinically acceptable TE of just over 1 L/min (similar to that found in healthy patients at rest) even though the average Qc with exercise in our cohort of HF with preserved ejection fraction was >8 L/min.

The overall agreement between the C_2H_2 rebreathing method and the current clinical standards based on linear correlation is excellent, although the variability in measurements between the 2 methods ranges from 13.4% to 22.9%. This variation is multifactorial and caused by both technical sources of error inherent to each method and biologic variability of the patients based on age, sex, and medical comorbidities. Importantly, the variability of measurements between the rebreathing method and current clinical standards is not larger than those reported in prior studies involving healthy individuals and patients with clinical disease, which was up to 30%.[16] Notably, the C_2H_2 rebreathing technique is as accurate as the FDA-approved N_2O rebreathing technique both at rest and during exercise in our cohort of healthy patients when compared with direct Fick, thermodilution, and N_2O rebreathing techniques. This close relationship should be no surprise since they are essentially the same biological technique, just using different soluble and insoluble gases. Our data suggesting similarity in accuracy and precision between various inert gasses

Table 2. Assessment of Accuracy Between 2 Inert Gas Rebreathing Methods

Patients	Condition	Qc Comparison	No. of Data Points	Qc, Mean (SD)	*r*	TE	CV
Healthy, supine							
	Rest	Fick vs N_2O	52	Fick 6.4 (1.6) N_2O 6.6 (1.0)	0.82 (0.71–0.89)	0.94 (0.79–1.17)	16.5 (13.9–20.9)
	Rest	Fick vs C_2H_2	51	Fick 6.3 (1.6) Rebreathing 7.2 (1.0)	0.85 (0.76–0.91)	0.84 (0.70–1.05)	14.5% (12.0–18.3)
	Rest	Thermodilution vs N_2O	56	Thermodilution 7.2 (1.2) N_2O 6.6 (1.0)	0.65 (0.46–0.78)	0.90 (0.76–1.11)	14.1 (11.8–17.7)
	Rest, all loading conditions	Thermodilution vs C_2H_2	2793	Thermodilution 5.5 (1.9) Rebreathing 5.7 (2.0)	0.84 (0.83–0.85)	1.02 (1.00–1.05)	19.5% (18.9–20.0)
Healthy, upright							
	Rest	Fick vs N_2O	54	Fick 4.5 (0.9) N_2O 4.1 (1.0)	0.44 (0.19–0.63)	0.82 (0.69–1.01)	19.8 (16.3–25.0)
	Exercise	Fick vs N_2O	57	Fick 16.9 (3.9) N_2O 11.8 (2.4)	0.84 (0.74–0.90)	2.18 (1.84–2.68)	13.9 (11.6–17.3)
	Rest	Fick vs C_2H_2	117	Fick 5.3 (1.5) Rebreathing 5.6 (1.5)	0.77 (0.69–0.84)	0.94 (0.83–1.08)	20.2% (17.7–23.5)
	Exercise	Fick vs C_2H_2	114	Fick 15.4 (4.8) Rebreathing 13.5 (3.7)	0.87 (0.81–0.91)	2.39 (2.12–2.75)	16.5% (14.5–19.2)
	Rest	Thermodilution vs N_2O	54	Thermodilution 4.8 (0.9) N_2O 4.1 (1.0)	0.73 (0.57–0.83)	0.64 (0.54–0.80)	14.5 (12.0–18.2)
	Exercise	Thermodilution vs N_2O	62	Thermodilution 15.8 (3.9) N_2O 12.1 (2.3)	0.82 (0.72–0.89)	2.21 (1.88–2.69)	15.0 (12.6–18.6)
	Exercise	Thermodilution vs C_2H_2	98	Thermodilution 15.0 (4.1) Rebreathing 13.3 (3.2)	0.82 (0.75–0.88)	2.36 (2.06–2.74)	16.5% (14.3–19.4)
Healthy, supine/upright rest and upright exercise		N_2O vs C_2H_2	172	N_2O 7.9 (3.8) Rebreathing 8.9 (4.2)	0.99 (0.98–0.99)	0.58 (0.52–0.65)	89 (8.1–10.1)

C_2H_2 indicates acetylene; CV, coefficient of variation; N_2O, nitrous oxide; Qc, cardiac output; *r*, Pearson correlation coefficient; and TE, typical error.

should encourage other investigators, clinicians, and perhaps industry to consider noninvasive rebreathing techniques for assessment of Qc.

Several strengths of our study include the assessment of an ample number of men and women under a variety of loading conditions, the evaluation of patients with clinical cardiac or pulmonary disease at rest and with exercise, and the inclusion of simultaneously derived Qc data for optimal comparison with current clinical standards as well as an inert gas rebreathing method that is approved for clinical use.[13,17] There are also pertinent limitations to our study. The surrogate "clinical" gold standard of thermodilution was used for the majority of comparisons with the rebreathing method as the majority of our patients did not have simultaneous direct Fick measurements for analysis. Although not considered the true gold standard of the direct Fick method, the thermodilution method showed clinical utility in predicting mortality in 2 large clinical cohorts.[32]

As previously noted, there are several technical sources of error inherent to the thermodilution method. However, in the subset of patients for whom we did have direct Fick measurement for comparison, there remains good correlation with thermodilution. Given this information, and the fact that thermodilution is used routinely in clinical practice, we felt that this was a valuable comparison to make. Room-temperature saline was used as the injectate for thermodilution, which could have contributed to less precision when comparing sequential trials.[33,34] However, this approach mimics the technique that is used most frequently in clinical settings such as the cardiac catheterization laboratory or intensive care unit. As a matter of policy and good experimental technique, we often excluded the first few C_2H_2 rebreathing measurements obtained during baseline assessments in our studies as previously discussed. Importantly, this was performed at the time of each individual study as a part of the study protocol and not for the purposes of this analysis. The initial measurements were often discarded because of patient factors (inadequate breath size) and technical considerations (saturation of the mass spectrometer C_2H_2) and were similar to the ≈1% to 2% of the thermodilution values that were excluded from analysis for reasons such as inadequate thermodilution curves. Additionally, patients had generally practiced C_2H_2 rebreathing measurements for various other components

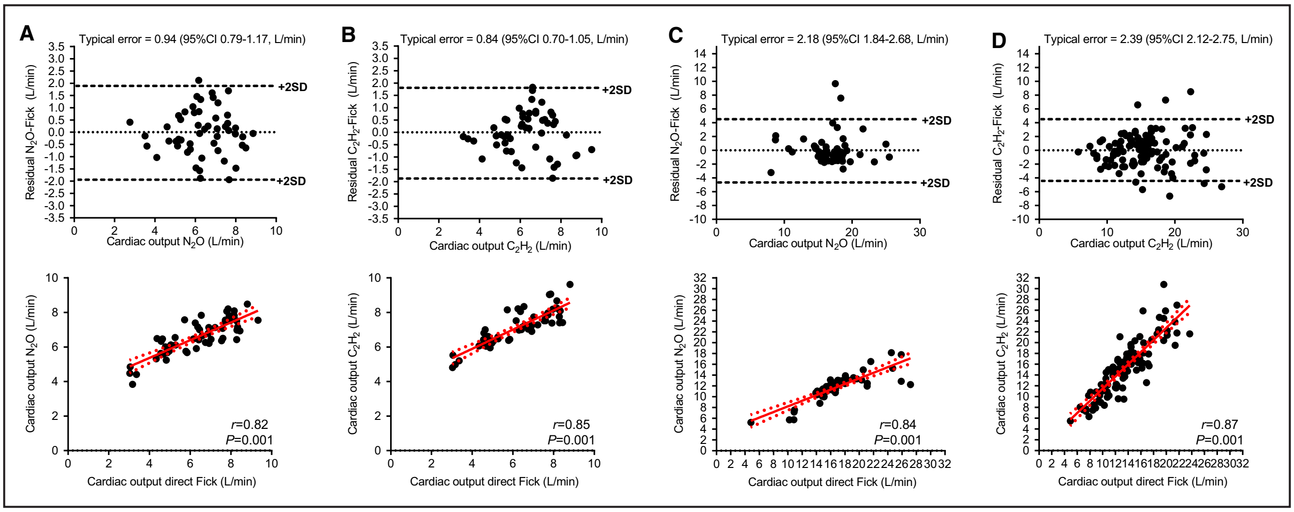

Figure 5. Comparison of the accuracy of the acetylene (C_2H_2) and nitrous oxide (N_2O) rebreathing techniques vs the direct Fick method for assessment of Qc in healthy patients during supine rest and upright exercise.
A, Accuracy of N_2O rebreathing for estimation of Qc during supine rest in healthy patients; (**B**) Accuracy of C_2H_2 rebreathing for estimation of Qc during supine rest in healthy patients; (**C**) Accuracy of N_2O rebreathing for estimation of Qc during exercise in healthy patients; and (**D**) Accuracy of C_2H_2 rebreathing for estimation of Qc during exercise in healthy patients. Qc indicates cardiac output.

of our studies before undergoing the measurements used in this analysis, which could have improved the precision of this technique under laboratory conditions.

Currently, there is not universal use of inert gas rebreathing techniques for Qc assessment. Previous, smaller studies have supported the use of inert gas rebreathing techniques in predicting clinical outcomes.[18–21] Given our data, we encourage other investigators and clinicians to consider this technique in studies and patient populations where accurate and precise measurement of Qc would be important (such as in patients with dyspnea of unclear cause, pulmonary hypertension, valvular heart disease, HF for risk stratification, and cardiogenic shock for confirmation and treatment). Increased use and standardization of inert gas rebreathing techniques is important as it would allow for analysis of data from larger and broader patient populations and could have strong implications for assessing prognosis in health outcomes studies.

CONCLUSIONS

The C_2H_2 rebreathing method is much more precise than, and at least as accurate as, the thermodilution method under a variety of conditions in healthy patients and those with clinical disease. It has an accuracy that parallels that of a commercially available, FDA-approved N_2O rebreathing technique that

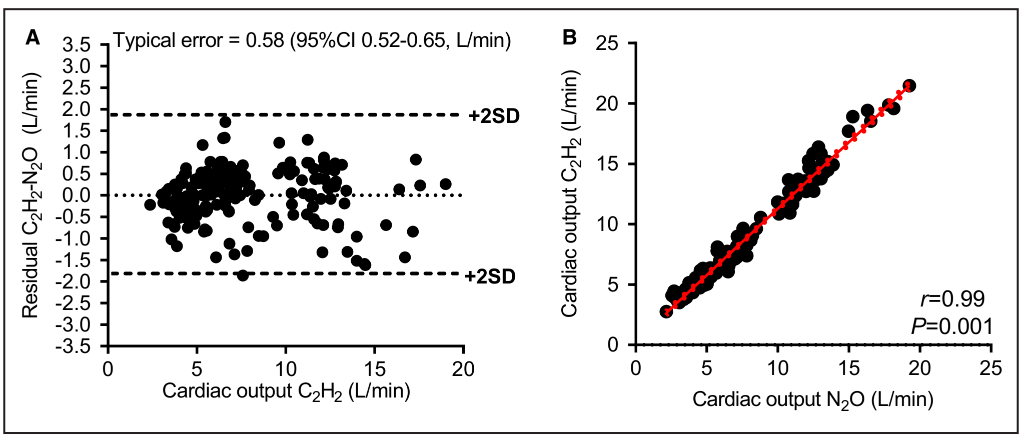

Figure 6. Agreement between the (A) acetylene (C_2H_2) rebreathing and (B) nitrous oxide (N_2O) techniques for assessment of Qc.
Qc indicates cardiac output.

is currently in clinical use. Our data suggest that inert gas rebreathing techniques can be employed in Qc assessment with similar diagnostic accuracy as compared with current clinical standards. Although this study is retrospective in nature, it has allowed us to demonstrate the utility of this technique in a large number of healthy individuals and a variety of patient populations, across a broad range of age and sex, and under diverse conditions. By means of presenting these robust validation data, we hope to inspire increased confidence from the scientific community that the inert gas rebreathing technique used by our laboratory and others is reliable and valid. Our data support the use of the C_2H_2 rebreathing method as a precise and accurate way to noninvasively measure Qc in healthy individuals and patients with clinical disease at rest and during exercise.

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Disclosures

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