Measurement of Cardiac Output by Automated Single-Breath Technique, and Comparison with Thermodilution and Fick Methods in Patients with Cardiac Disease

Mark R. Zenger, MD, Matthew Brenner, MD, Malcolm Haruno, MD, Donald Mahon, MD, and Archie F. Wilson, MD, PhD

Accurate noninvasive methods are needed for determination of cardiac output. Current methods are generally complex or may be unreliable. A previously described method, based on absorption of acetylene gas during a constant exhalation that enables calculation of cardiac output by estimating pulmonary capillary circulation, is incorporated in a new, automated commercial product (SensorMedics 2200). In this study, cardiac output by single-breath acetylene blood flow measured with this device was compared with the standard thermodilution and direct Fick methods in 20 patients undergoing cardiac or pulmonary artery catheterization. Patients inhaled test gas mixture to total lung capacity and exhaled at a constant rate through an adjustable resistor. Lung volumes and noninvasive acetylene blood flow value were calculated automatically. Correlation between the automated single-breath technique and both thermodilution and Fick cardiac output determinations was very high (correlation coefficients were 0.90 and 0.92, respectively), regression slopes were close to identity (0.98 and 0.90), and bias (–0.39 and –0.79 liter/min) and precision (0.94 and 1.02) were good; when shunt correction was applied, bias was reduced to 0.06 and 0.35 liter/min, respectively. Rapid, accurate, noninvasive measurement of cardiac output was easily obtained using the automated device. This technique may have a wide applicability for noninvasive evaluation of patients with cardiac disease and for monitoring effects of therapeutic interventions.

(Am J Cardiol 1993;71:105–109)

From the Pulmonary and Critical Care, and Cardiology Divisions, Department of Medicine, University of California Irvine Medical Center, Orange, California. Manuscript received May 4, 1992; revised manuscript received and accepted July 30, 1992.

Address for reprints: Matthew Brenner, MD, Pulmonary and Critical Care Division, University of California Irvine Medical Center, 101 City Drive South, Orange, California 92668.

Simple, accurate, noninvasive methods for measuring cardiac output are needed. Currently available methods for noninvasive estimation of cardiac output are frequently inconvenient, complex or unreliable. Acetylene gas uptake from alveoli is proportional to pulmonary capillary blood flow and has been extensively demonstrated to accurately estimate cardiac output noninvasively in patients with preserved pulmonary function.[1–5] In this study, we present noninvasive, cardiac output data obtained using a new, automated device that is simple, rapid, and convenient. This approach is based on measurement of acetylene blood flow during 1 slow, constant exhalation using a previously described, clinically validated, mathematical model.[6] Measurements are obtained using a mobile, integrated system. We compared automated, single-breath, noninvasive, acetylene blood flow measurements with pulmonary artery catheter thermodilution cardiac outputs and standard direct Fick measurements.

METHODS

Patients: We studied 20 patients (mean age 43 years, range 17 to 75), 15 undergoing elective cardiac catheterization and 5 who had indwelling pulmonary artery catheters for monitoring. The investigative protocol was approved by the local institutional review board, and signed informed consent was obtained from all patients. Ten patients had valvular heart disease, 3 had coronary artery disease, 3 had cardiomyopathy (2 ischemic and 1 idiopathic), 3 had undergone heart transplantation and 1 had experienced blunt trauma.

Acetylene uptake cardiac output measurement theory: The rate of alveolar absorption of gas that is soluble in tissue and blood (such as acetylene) is proportional to pulmonary capillary blood flow during a single-breath, constant exhalation maneuver.[4,6] A standard factor (height 3.5 g/cm) is applied to account for tissue effect.[7]

Mathematically, the relation between gas absorption and pulmonary capillary blood flow is expressed as follows[6]:

$$\dot{Q}_C = \frac{\ln (F_A/F_{A_0})}{\ln [(V_A + \alpha_t V_t)/(V_{A_0} + \alpha_t V_t)]} * \frac{\dot{V}_E}{\alpha_b} * \frac{60*1{,}000}{760}$$

where F = fraction of gas; V = volume of gas; $\dot{V}$ = flow rate; α = bunsen coefficient for solubility of acetylene in tissue (t) or blood (b); A = alveolar; A_o = at full inspi-

ration; IF = inspiratory flow; I = inspiratory; E = expiratory; and DS = dead space.

During constant flow exhalation, alveolar (as reflected by expired) concentrations of acetylene and carbon monoxide decrease exponentially (Figure 1A). The test gas mixture comprises 0.3% methane, 0.3% acetylene, 0.3% carbon monoxide, 21% oxygen, and balance nitrogen.

Automated single-breath device: The SensorMedics 2200 (Yorba Linda, California) is a pulmonary function test cart that integrates pneumatic, electronic, computer and analyzer components of a pulmonary function test system into a portable unit. The device configuration used in this study includes a mass flow sensor (accuracy ± 3%; 0.1 liter/s) that measures inspiratory and expiratory flows directly, a breath-by-breath nitrogen analyzer (accuracy ± 2%, resolution 0.1% and range 0 to 95% nitrogen), and a rapid-response, multigas, nondispersive, infrared analyzer (accuracy ± 0.006%, resolution 0.0005% and range 0.00 to 0.33%) measuring carbon monoxide, methane and acetylene.

Single-breath procedure: Patients were connected to the mouthpiece of the SensorMedics 2200 machine. A nose clip was used. Patients inhaled to total lung capacity. This was followed by breath-holding of approximately 2 seconds to enable acetylene tissue absorption and gas distribution equilibration. Patients then passively exhaled most of the vital capacity at a constant flow rate of 200 to 500 ml/s (facilitated by positioning an adjustable resistor at the expiratory port).

Two or more trials of automated acetylene blood flow measurement were performed ≥10 minutes apart to ensure residual acetylene washout from blood and tissues. Acetylene blood flow was measured within 15 to 20 minutes of the Fick and thermodilution cardiac output determinations.

Acetylene blood flow: Acetylene blood flow was determined using Equation 1 by obtaining the slope of $\ln (F_A/F_{Ao})$ vs $\ln[(V_A + \alpha_t V_t)/(V_{Ao} + \alpha_t V_t)]$ in the linear region of the constant exhalation phase between dead space washout and closing volume (Figure 1, A and B). Marks delineating the linear phase were positioned automatically at 20 and 80% of exhaled vital capacity. Manual marker adjustments were made to linear portions of the exhalation curves by 2 independent observers unaware of the Fick and thermodilution blood flow measurements.

Thermodilution cardiac output: All patients had pulmonary artery catheters in place. Thermodilution cardiac output measurement was determined using standard techniques on a Marquette Cardiac Output computer. Three to 5 trials were performed, requiring a variability of <20%, and averaged. Thermodilution cardiac output measurements were obtained within 15 minutes of acetylene blood flow determinations.

Fick cardiac output: Cardiac output was also calculated by the standard Fick equation:

$$\text{Cardiac output} = \frac{VO_2}{(ArtO_2Sat\text{-}VenO_2Sat)(Hgb)(13.9)}$$

where VO_2 = oxygen consumption; $ArtO_2Sat$ = arterial oxygen saturation; $VenO_2Sat$ = venous oxygen saturation; and Hgb = hemoglobin.

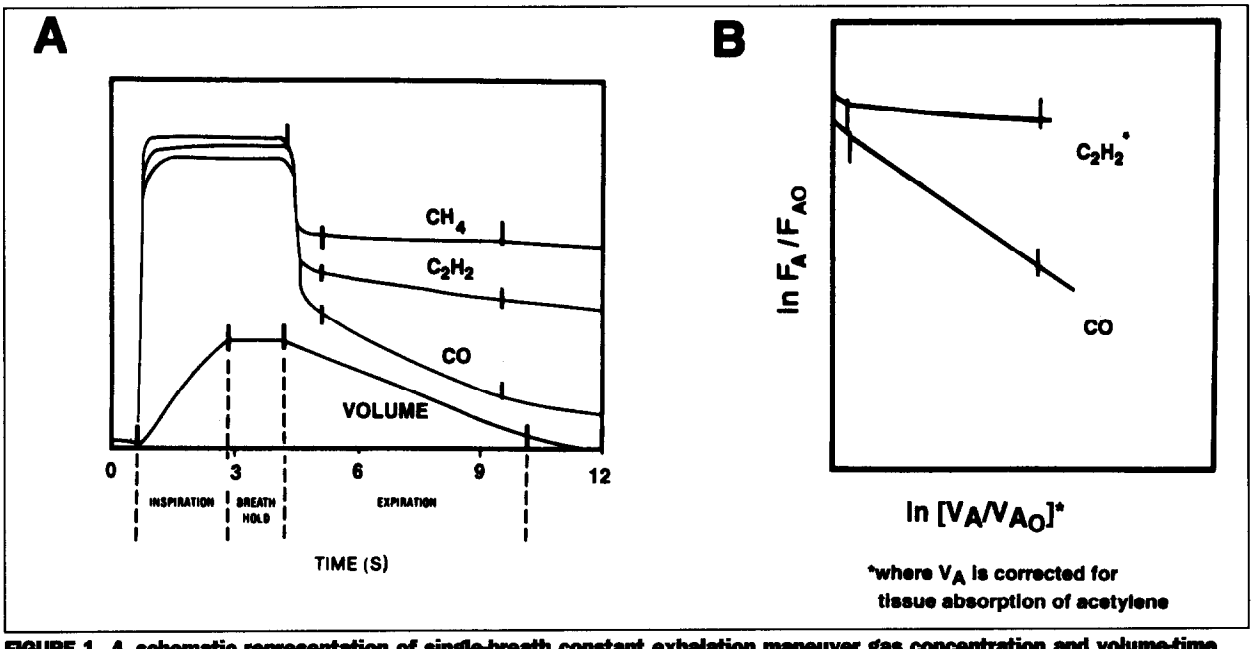

FIGURE 1. ***A,*** **schematic representation of single-breath constant exhalation maneuver gas concentration and volume-time curves used for determination of pulmonary capillary blood flow. Time in seconds is displayed on** ***abscissa.*** **Methane (CH_4) concentration used as inert reference gas. Acetylene (C_2H_2) concentration used as absorbable gas. Carbon monoxide (CO) is administered concurrently to measure pulmonary diffusing capacity and is displayed on screen, but is not used in determination of pulmonary capillary blood flow with this device. Volume-time curve for maneuver is displayed with individual inspiratory, breath- holding and expiratory components as labeled.** ***B,*** **schematic representation of linear region of log acetylene (corrected for inert gas dilution and initial concentration as $\ln F_A/F_{Ao}$) and natural log alveolar volume relation (corrected for tissue volume as $\ln [(V_A + \alpha_t V_t)/(V_{Ao} + \alpha_t V_t)]$) used in calculating pulmonary capillary blood flow (see Equation 1).** ***Markers*** **delineating measurement segment are positioned in linear portion of curve. Again, carbon monoxide curve is displayed for calculation of diffusing capacity, but is not used in pulmonary capillary blood flow determination with this device.**

Oxygen consumption was calculated from analyses of exhaled gases. All patients breathed room air. All expired gases were obtained for a measured period of time (3 to 8 minutes were needed to fill the bag) in a 60 liter, non-diffusing bag (#6030, Cal Med, Brea, California). Expired gas was analyzed on a Perkin-Elmer 1100 mass spectrometer (Norwalk, Connecticut). Inspired oxygen values were determined by analysis of room air. The mass spectrometer was calibrated daily before each trial. The volume of exhaled gas was measured on a Tissot Spirometer. All samples were corrected for temperature and humidity. Mixed venous oxygen saturation samples were obtained from the pulmonary artery catheter distal port. Arterial oxygen saturation was determined by aortic blood sampling in patients undergoing cardiac catheterization or by peripheral arterial blood gas in those with an indwelling pulmonary artery catheter. Oxygen saturations were determined on either a Corning model 178 (Medfield, Massachusetts) blood gas machine or an Oxicom 2000 (Waters Inst. Inc.). Hemoglobin was obtained from the Corning model 2500 co-oximeter or from concurrent laboratory complete blood count analysis.

Shunt functions were determined using the Fick cardiac output, arterial and mixed venous oxygen contents with standard formulas[8]: $Qs/Qt = (CiO_2 - CaO_2)/(CiO_2 - C\text{–}\bar{v}O_2)$; where Qs/Qt = shunt fraction; CiO_2 = ideal inspired oxygen content; CaO_2 = arterial oxygen content; and $C\text{–}\bar{v}O_2$ = venous oxygen content.

Statistics: Linear regression was analyzed with the least-squares method (Systat, Inc., Evanston, Illinois). Bias and precision were determined from the mean and standard deviation of the difference between the methods using standard analytical methods.[9–12]

RESULTS

Cardiac output values: Mean acetylene blood flow was 4.77 ± 2.18 liters/min. Mean cardiac outputs for Fick and thermodilution were 5.59 ± 2.13 and 5.16 ± 2.01 liters/min, respectively. When acetylene blood flow was corrected for shunt, average cardiac output was 5.50 ± 2.34 liters/min.

Acetylene blood flow and thermodilution cardiac output correlation: The relation between acetylene blood flow and thermodilution cardiac output is shown in Figure 2A: Slope of regression line was 0.98, correlation 0.9, bias –0.39 liter/min and precision 0.938 liter/min. When acetylene blood flow was corrected for shunt, slope of best fit line was 1.05, correlation 0.9, bias 0.347 liter/min and precision 1.015 liter/min (Figure 2B).

Acetylene blood flow and Fick cardiac output correlation: When acetylene blood flow was compared with Fick cardiac output, slope of regression line was 0.90, correlation coefficient 0.92, bias –0.793 liter/min and precision 0.904 liter/min (Figure 2C). For shunt-corrected acetylene blood flow, correlation coefficient was 0.91, slope 0.97, bias –0.056 liter/min and precision 0.953 liter/min (Figure 2D).

Thermodilution and Fick cardiac output correlation: When Fick and thermodilution cardiac outputs were compared, similar results were obtained; slope of regression line was 0.99, with an r value of 0.98 (Figure 3).

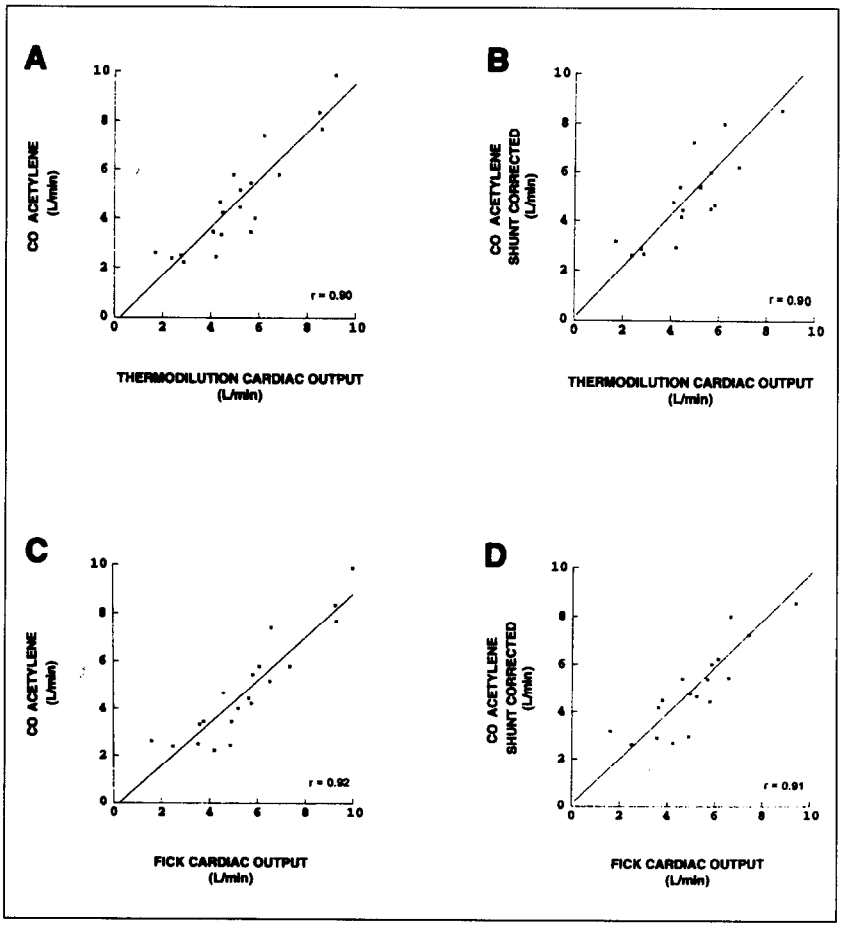

FIGURE 2. Relation between pulmonary capillary blood flow and cardiac output as determined by thermodilution and Fick methods in 20 patients. *A*, correlation between pulmonary capillary blood flow acetylene and thermodilution cardiac output. *B*, correlation between acetylene blood flow and cardiac output by thermodilution after correcting acetylene blood flow by shunt fraction. *C*, correlation between acetylene blood flow and direct Fick cardiac output. *D*, correlation between acetylene blood flow and cardiac output by direct Fick after correcting acetylene blood flow by shunt fraction.

Variability of acetylene blood flow: Mean coefficient of variation between the 2 observers for each acetylene blood flow trial was 6.43%; mean coefficient of variation between acetylene blood flow trials was 13%.

DISCUSSION

There are several methods for clinical measurement of cardiac output. The dye dilution, thermodilution and Fick methods require intravenous lines with attendant complications. Repeat measurements, particularly over extended periods of time, are limited with these invasive methods. Several noninvasive techniques have been developed for estimating cardiac output. Doppler echocardiographic determination of cardiac output has been evaluated in numerous studies.[13] Some problems found with cardiac output measurements by Doppler echocardiography include left ventricular asymmetry,[13] inadequate ultrasound windows and operator variability.[14] In approximately 10 to 20% of patients, Doppler echocardiography cannot be performed.[14,15] Radionuclide scanning requires injection of radiolabeled albumin, expensive scintillation monitors and computer equipment. Repeat measurements of cardiac output are impractical and prohibitively expensive with radionuclide scanning.[16] Impedance cardiography has shown considerable variability in assessing cardiac output.[13]

Numerous studies validating acetylene gas uptake have been published, some using rebreathing techniques. Studies of normal subjects show good correlation with cardiac output.[3,5,17] Rebreathing methods require patients to perform rapid, deep breathing maneuvers. Theoretical and technical problems including changes in alveolar volume and cardiac output during rebreathing maneuvers occur with this method, and can produce errors in the measurement of cardiac output. These difficulties have led to the development of the constant exhalation, single-breath maneuver.[4,6]

The constant exhalation technique involves continuous rapid analysis of gases exhaled at a constant rate after 1 full inhalation of a mixture of absorbable and inert gases. Several studies have validated the constant exhalation, single-breath technique. Elkayam et al[2] compared the single-breath, acetylene technique with thermodilution in 20 cardiac patients and found good correlation.[2] Ramage et al[4] compared the single-breath, acetylene technique with cardiac output estimated by radionuclide scanning and found close correlation.

This study determined cardiac output using an automated SensorMedics 2200 pulmonary function machine. This portable device has rapid infrared sensors for tracking acetylene and carbon monoxide uptake and inert gas concentration, in addition to volume analysis and standard pulmonary function testing. Correlation of the acetylene blood flow technique with the thermodilution and Fick cardiac output methods was high; correlation coefficients were >0.9. Bias and precision were also closely correlated. Correlation of the Fick and thermodilution methods with acetylene blood flow was as strong as that between thermodilution and Fick itself in this study. Accuracy of the acetylene blood flow technique with the mobile SensorMedics 2200 cart was also similar to that of prior studies estimating cardiac output using the mass spectrometer for measurement of single-breath, acetylene gas absorption blood flow.[4,18]

The acetylene method slightly underestimates cardiac output compared with the Fick or thermodilution methods in normal subjects. This is because the acetylene blood flow method reflects pulmonary capillary blood flow and does not measure blood flow shunted by physiologic,

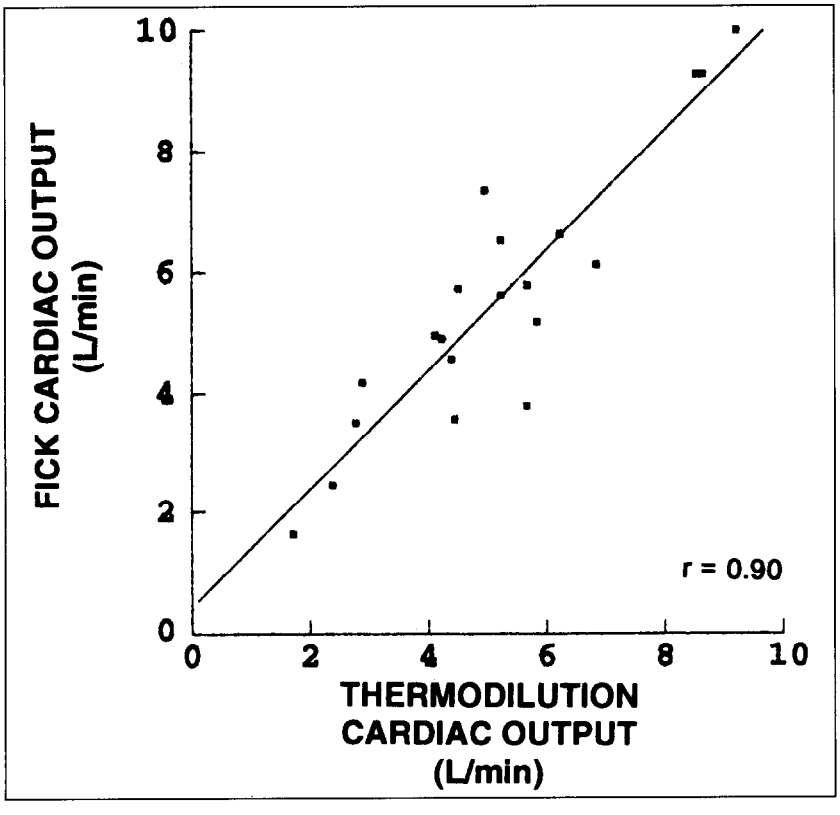

FIGURE 3. Correlation between cardiac output by thermodilution and direct Fick methods.

intracardiac or pulmonary shunts. When physiologic shunt correction was applied to evaluate this effect, all 3 methods showed similar cardiac outputs, and bias was reduced. No patient in this study had significant anatomic shunts. In patients with substantial intracardiac or intrapulmonary shunts, significant underestimation of cardiac output would be expected. In such cases, combining the acetylene blood flow technique with methods for determination of cardiac output not affected by shunting may be helpful in more accurately assessing shunt fractions and evaluating patients with complex shunts.

Whereas the accuracy of acetylene blood flow methods is well-established in patients with preserved lung function,[1–5] it is not known in those with obstructive lung disease, but may be inaccurate due to ventilation-perfusion inhomogeneity. One study suggests that the acetylene blood flow technique may be inaccurate in patients with an $FEV_1/FVC < 60\%$,[2] although Pierce et al[19] found a good correlation when they evaluated 8 patients with ob-structive lung disease.

The accuracy of some maneuvers was limited by the ability of patients to passively exhale at a constant flow rate. This potential problem may be overcome by the placement of a variable resistor designed to cause exhalation that lasts from 4 to 8 seconds. However, Valsalva maneuvers and increased intrathoracic pressures during exhalation should be avoided because of effects on cardiac output and gas concentration measurements. Another potential problem found with this device is the inability to measure residual acetylene concentrations in the lungs before performing maneuvers to verify adequate acetylene washout from the preceding maneuver.

This study confirms the accuracy of an automated, cardiac output measurement method based on well-established principles of acetylene absorption by pulmonary blood flow in patients undergoing cardiac catheterization compared with those of the thermodilution and Fick methods. Incorporation of this method in an automated device has made the technique rapid and easy to perform. In the future, this technology should enable repeated, noninvasive, clinical measurements of cardiac output with attendant clinical and research applications in patients with normal and near normal lung function.

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