MEASUREMENT

Automated non-invasive measurement of cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution and thermodilution

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Abstract

The accuracy and reproducibility of indirect measurement of cardiac output at rest by the carbon dioxide rebreathing (indirect Fick) method with an automated respiratory analysis system (Gould 9000IV) were compared with simultaneous measurements made in duplicate by dye dilution and thermodilution in 25 patients having cardiac catheterisation studies. Measurements of cardiac output by the carbon dioxide rebreathing method were not significantly different from those obtained with dye dilution (mean difference -0.3 l/min, SD 0.76 , 95% confidence interval -0.7 to 0.1). Thermodilution significantly overestimated cardiac output by a mean of 2.2 l/min or 39% (SD 1.5 , 95% confidence interval 1.6 to 2.8) compared with the carbon dioxide rebreathing method and significantly overestimated cardiac output by 1.9 l/min or 31% (SD 1.2 , 95% confidence interval 1.2 to 2.5) compared with dye dilution. The reproducibility of measurements of cardiac output in individual patients was satisfactory with the dye dilution method but was poor with carbon dioxide rebreathing and thermodilution.

Indirect measurement of resting cardiac output by the Gould 9000IV automated carbon dioxide rebreathing method is more accurate but the variability inherent with this method requires that multiple measurements be taken for each determination. Measurement of cardiac output by the thermodilution method by a commercially available cardiac output computer was not satisfactory because not only was there considerable variability between repeat measurements but the method also consistently overestimated cardiac output compared with the dye dilution method.

Although cardiac output is a haemodynamic variable of considerable interest in clinical cardiology and cardiovascular research, simple and accurate non-invasive methods for its measurement have not been readily available.

In current practice the indicator dilution methods, dye dilution and thermodilution, have replaced the direct Fick method because of their relative ease and suitability for automation.^{1,2} The invasive nature of these techniques limits their application and accordingly non-invasive methods including electrical bioimpedance cardiography,³ echocardiography,^{4,5} radionuclide angiography,⁶ and the indirect Fick method⁷ have been developed. These methods can be used for serial estimations but are limited by technical difficulty or doubts about their accuracy.^{8,9}

The indirect Fick or carbon dioxide rebreathing method has been available for many years and in general has an accuracy for measurement of cardiac output similar to that of other methods.¹⁰⁻¹² The Gould 9000IV cardiopulmonary exercise system (Gould, Dayton, Ohio) is an automated system for respiratory analysis that has removed much of the technical difficulty in performing indirect Fick measurements. It is relatively easy to use and is ideal for performing repeated estimates of cardiac output in ambulatory individuals.¹³

We compared indirect Fick measurements of cardiac output made by the Gould 9000IV with simultaneous measurements of cardiac output made by dye dilution and thermodilution and we obtained a measure of the reproducibility of each method. Previous studies have largely relied upon correlation to compare methods.¹⁰⁻¹⁴ While two estimates may be highly correlated the estimates may still show poor agreement in individual subjects.^{15,16} We used the method of Bland and Altman¹⁵ to examine the agreement between and the reproducibility of different methods for estimating cardiac output.

Patients and methods

PATIENTS

We studied 25 patients undergoing diagnostic right and left heart catheterisation for valvar heart disease or cardiomyopathy. There were 17 men and eight women (aged 28-80 years (median = 67)). In all but one a multiple lumen thermistor tipped catheter (Swan-Ganz) was placed into the pulmonary artery via the right femoral vein. The left heart catheter was inserted via the right femoral artery. All patients were fully informed of the study

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details and then gave written consent to participation. The study was approved by the committee on clinical investigation of the Flinders Medical Centre.

CARBON DIOXIDE REBREATHING MEASUREMENTS (INDIRECT FICK)

The Gould 9000IV consists of an infrared absorption analyser for carbon dioxide, a paramagnetic oxygen analyser, a dry rolling seal spirometer, and a microcomputer with an analogue to digital converter and a printer. It provides measurements of the concentration of expired carbon dioxide with resolution to 0.01% and an accuracy of $\pm 0.1\%$ when measuring concentrations from 0 to 10%. Minute volume is measured with resolution to 0.01 l/min and an accuracy of ± 0.025 l/min. These variables have been independently validated.¹⁷ The analysers and the spirometer were calibrated before each study according to the manufacturer's instructions.

With this method the cardiac output is calculated by the equation:

$$\text{Cardiac output} = V_{CO_2} / (Cv_{CO_2} - Ca_{CO_2})$$

where V_{CO_2} is the rate of production of carbon dioxide per minute calculated from continuous measurements of expired minute volume and the concentration of carbon dioxide in expired gas. Cv_{CO_2} is the concentration of carbon dioxide in mixed venous blood and Ca_{CO_2} is the concentration of carbon dioxide in arterial blood. The arteriovenous difference in the concentration of carbon dioxide is calculated by the formula:

$$Cv_{CO_2} - Ca_{CO_2} = 11.02(Pv_{CO_2}^{0.396} - Pa_{CO_2}^{0.396})$$

where Pv_{CO_2} and Pa_{CO_2} are the partial pressure of carbon dioxide in venous and arterial blood respectively.¹⁸⁻²⁰ A haemoglobin concentration of 150 g/l and oxygen saturation of 95% was assumed. The partial pressure of carbon dioxide in arterial blood was estimated from the concentration of carbon dioxide in expired gas at the end of expiration. The carbon dioxide tension of mixed venous blood was estimated in a similar way by using the equilibrium rebreathing procedure described by Collier.²¹ The individual respired from an anaesthetic bag filled with a mixture of approximately 10% carbon dioxide in oxygen. The volume in the bag was fixed at 1.5 times the mean tidal volume of the preceding respirations. During the rebreathing procedure the end tidal concentration of carbon dioxide was displayed on the computer screen so that the operator could signal to the computer that a satisfactory equilibrium had been achieved. The equilibrium value was used to estimate the mixed venous carbon dioxide tension. No correction was made for differences between blood and alveolar tensions.^{10 18 22} The computer performed all the calculations and displayed the estimated cardiac output.

THERMODILUTION MEASUREMENTS

Measurements of cardiac output were taken using the 7 French pulmonary arterial catheter (Swan-Ganz, 93A-151-7F, American Edwards Laboratories, Anasco, Puerto Rico) linked to a

9520A cardiac output computer (Edwards Laboratories, Santa Ana, California). Ten ml of iced 5% dextrose drawn into a 10 ml plastic syringe was hand injected into the right atrium via the proximal lumen of the Swan-Ganz catheter. The thermodilution cardiac output was taken as the value for the second of two or three injections.

DYE DILUTION MEASUREMENTS

Dye dilution measurements were made with 5 or 10 mg of indocyanine green (Cardio-green, HW&D, Baltimore, Maryland) (the larger dose was used for those with mitral valve disease) injected by hand into the right atrium via the proximal lumen of the Swan-Ganz pulmonary artery catheter. Arterial blood was drawn from the proximal aorta through a DC-410 photoelectric detector with a SW-367 pump (Waters Instruments, Rochester, Minnesota). Cardiac output was calculated with a CO-10 cardiac output computer (Waters Instruments).

EXPERIMENTAL PROTOCOL

All measurements of cardiac output were taken at the end of the diagnostic study. The patients remained supine and breathed room air via a respiratory valve connected by a flexible hose to the spirometer of the Gould 9000IV so that all expired gas could be collected and analysed. Indocyanine green was injected at the onset of carbon dioxide rebreathing and this injection was immediately followed by the two or three injections of thermodilution indicator. This sequence was repeated within approximately 10 minutes. In the patients who were not given indocyanine green, the thermodilution indicator was injected at the start of the rebreathing procedure. From the 25 subjects we obtained 24 duplicate indirect Fick measurements with 24 paired thermodilution readings, and 19 pairs of measurements for dye dilution. This gave 23 comparisons between the carbon dioxide rebreathing and thermodilution methods and 18 comparisons between the indirect Fick and dye dilution methods and between thermodilution and dye dilution. In 17 of the patients cardiac output was estimated using all three methods.

ANALYSIS

For each patient the cardiac output by each of the three methods was taken as the mean of the two measurements with each method. The values of cardiac output in each subject obtained by the three methods were compared by analysis of variance in a repeated measures two factor design. Individual comparisons were made by the Newman-Keuls multiple range test. Differences between cardiac output values obtained by the three methods were examined by the method of Bland and Altman in which the individual differences between the two methods in each individual are plotted against the average value obtained from both methods in that individual.¹⁵ The mean, standard deviation, and 95% confidence interval of the differences were calculated. We also compared mean values for each method with one

Table 1 Reproducibility of different methods for estimating cardiac output

Comparison (n)	Dye ₁ /Dye ₂ (19)	Fick ₁ /Fick ₂ (24)	Thermal ₁ /Thermal ₂ (24)
Mean difference (l/min) between duplicates	0.22	-0.31	-0.39
Standard deviation of difference	0.44	1.35	1.11
Coefficient of repeatability (2 × SD)	0.88	2.7	2.2

another using scatter plots.

The accuracy of both the carbon dioxide rebreathing and thermodilution methods was assessed from the mean differences between each of these methods and dye dilution. The “limits of agreement”¹⁵ were calculated from the mean difference plus and minus twice the standard deviation of the difference such that 95% of differences were within that range. The differences between the values obtained in each individual for the carbon dioxide rebreathing and thermodilution methods were examined in a similar fashion.

The reproducibility (repeatability) of each method was examined by plotting the differences between duplicate measurements against the average of the two measurements.¹⁵ The mean and standard deviation of the differences between the two readings were calculated so that the “coefficient of repeatability”¹⁵ (twice the standard deviation of the differences) could be calculated.

Results

REPRODUCIBILITY OF DIFFERENT METHODS FOR CARDIAC OUTPUT

For each method there was no significant difference between the duplicate measurements (table 1). For dye dilution all of the differences were less than 16% of the mean value (fig 1a). For the indirect Fick method the reproducibility was low with only 50% of the

differences being within 20% of the mean value (fig 1c). For thermodilution reproducibility was such that 70% of the differences were within 20% of the mean value (fig 1b).

DIFFERENCES BETWEEN METHODS

The mean values with the indirect Fick method and the dye dilution method were not significantly different, although the limits of agreement were wide (table 2) with 28% of the differences being > 20% of the mean value (fig 2a). The mean thermodilution value was 31% greater than the dye dilution value (*p* < 0.001) and 39% greater than that by the indirect Fick method (*p* < 0.001) (table 2). For both comparisons with thermodilution the range of differences was wide (fig 2).

Discussion

In this study we found no systematic difference between estimates of cardiac output made by the indirect Fick and dye dilution methods but measurements obtained by the thermodilution method consistently overestimated the cardiac output compared with measurements obtained by the other two methods. The reproducibility of estimates of cardiac output within an individual was significantly worse for measurements obtained by carbon dioxide rebreathing or by thermodilution than it was for those obtained by dye dilution. The poor reproducibility of these two methods contributed to the wide range of differences seen between methods.

Several factors contribute to the considerable variation seen between repeated measurements of cardiac output with any one method. One important factor is that the cardiac output is not a tightly regulated haemodynamic variable such as blood pressure²³ and biological variability between measurements is considerable.^{24 25} In addition, both thermodilution and dye dilution are subject to random errors owing to variation in the dose of indicator and its rate of injection, to the pulsatile nature of blood flow, and to variation in the calculation of the area under the indicator dilution curve.^{1 24 26} Thermodilution is also subject to variation from the placement of the thermistor in the pulmonary artery and from physiological variations in the temperature of pulmonary arterial blood with respiration.^{1 24 26} For indirect Fick measurements of cardiac output small random errors in the estimation of the arterial and mixed venous carbon dioxide concentrations from the end tidal and the rebreathing equilibrium concentrations of carbon dioxide can result in relatively large errors in the estimate of the arteriovenous difference for carbon dioxide concentration.^{27 28} This problem seems to be less important when the arteriovenous difference is large such as during exercise, when the carbon dioxide rebreathing method has been found to be more reliable.^{7 27 29} Another important source of variation is that small deviations in ventilation and alveolar carbon dioxide tension can result in large changes in carbon dioxide transfer and thus carbon dioxide production.²⁸

Figure 1 Differences between the first and second estimate of cardiac output with each method plotted against the mean of those two measurements by dye dilution (a), thermodilution (b), and indirect Fick (c).

Table 2 Comparisons of different methods for cardiac output

Comparison (n)	Fick-Dye (18)	Thermal-Dye (18)	Thermal-Fick (23)
Mean difference (l/min) (95% CI)	-0.28 (-0.66 to 0.07)	1.85* (1.24 to 2.47)	2.16* (1.52 to 2.79)
Standard deviation of difference	0.76	1.24	1.49
Lower limit of agreement (95% CI)	-1.80 (-2.45 to -1.15)	-0.63 (-1.18 to -0.08)	-0.82 (-4.09 to 6.19)
Upper limit of agreement (95% CI)	1.24 (0.59 to 1.89)	4.33 (3.78 to 4.87)	5.14 (-1.87 to 0.23)

*p < 0.001.

Apparent differences between estimates of cardiac output by any two methods may stem both from random variation within each individual method (poor reproducibility) or from systematic differences between one method and another. The dye dilution method has been accepted as a "gold standard" because no systematic bias has been found between direct (oxygen) Fick and dye dilution estimates of cardiac output.^{30,31} Our results for the comparison of indirect Fick and dye dilution estimates of cardiac output are consistent with such previous observations and with comparisons of the indirect Fick method with dye dilution^{7,12} or with the direct Fick method.^{11,24} The thermodilution method is well established in clinical practice and is capable of providing accurate estimates of cardiac output provided that appropriate corrections are made for several potential errors.^{10,26} The method is subject to overestimation of cardiac output, such as that observed in this study, owing to loss of indicator before and after injection.^{1,26} Loss of indicator can be reduced by injection at ambient temperature at the expense of a reduction in the thermistor signal to noise ratio and thus greater variability in the estimate of car-

diac output.¹ The thermodilution cardiac output computer used in this study uses a computation constant to adjust for loss of indicator with different Swan-Ganz catheters that is derived from an "in vitro study" (product literature). The recommended constant may not be correct for catheters inserted from the femoral vein where the longer intravascular course could result in greater loss of indicator. None the less, an in vitro study using thermodilution cardiac output computers (including the model used in this study) obtained similar overestimates of cardiac output under conditions of cold injection and pulsatile flow.¹ The computer used in the present study also overestimated cardiac output when compared with invasive Fick measurements in another study.³² Further evaluation of such devices is needed before they can be used as a standard for comparison with other methods.^{1,33}

In previous studies comparing different methods for estimating cardiac output the range of differences between estimates has been wide and a considerable number of differences were >25% of the mean value.^{7,12,22} The range of differences seen in the present study is similar to that reported between direct Fick and indirect Fick^{11,22,29} or dye dilution^{7,31} estimates. Such observations are consistent with the inherent variability of cardiac output and of the methods available for its estimation.

We found that indirect Fick estimates of resting cardiac output measured by the Gould 9000IV are accurate but that the variability of estimates is large. Averaging of repeated measurements is required to achieve a reliable estimate of cardiac output in individual subjects.

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Figure 2 Differences between cardiac output estimates by two different methods plotted against the mean of those two estimates; indirect Fick and dye dilution (a); thermodilution and dye dilution (b); indirect Fick and thermodilution (c).

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