Journal of Clinical Monitoring and Computing (2008) 22:113–119
DOI: 10.1007/s10877-008-9112-5

MULTICENTER EVALUATION OF NONINVASIVE CARDIAC OUTPUT MEASUREMENT BY BIOREACTANCE TECHNIQUE

Nirav Y. Raval, MD[1], Pierre Squara, MD[2], Michael Cleman, MD[3], Kishore Yalamanchili, MD[4], Michael Winklmaier, MD[5] and Daniel Burkhoff, MD PhD[6]

Raval NY, Squara P, Cleman M, Yalamanchili K, Winklmaier M, Burkhoff D. Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique.
J Clin Monit Comput 2008; 22:113–119

ABSTRACT. Objectives. Bioreactance, the analysis of intrabeat variations in phase of a transthoracic voltage in response to an applied high frequency transthoracic current, was recently introduced for noninvasive cardiac output measurement (NICOM). We evaluated NICOM compared to thermodilution (TD) in several clinical settings. **Methods.** 111 patients with a clinical indication for TD cardiac output (CO) measurement were recruited at five centers, including patients in cardiac catheterization laboratories, cardiac care units and intensive care units. CO measurements were made simultaneously with TD and the bioreactance method and compared by regression analysis. **Results.** For studies in the intensive care units, TD-based CO and NICOM were highly correlated ($r = 0.78$, $P < 0.0001$) and did not differ significantly from each other ($P = 0.55$). Results in the cardiac catheterization laboratory were similar ($r = 0.71$, $P < 0.001$; $P = 0.28$ NICOM versus TD). In subsets of patients, NICOM was shown to be better correlated with TD-CO than CO obtained with the Fick method or with standard bioimpedance-based measurements of CO. **Conclusions.** On average, compared to TD, bioreactance-based NICOM has acceptable accuracy in challenging clinical environments. Availability of such a tool may allow clinicians to have information about CO in patients where this information is not currently available to help diagnosis and guide therapy.

KEY WORDS. non-invasive monitoring, cardiac output, bioimpedance, bioreactance.

INTRODUCTION

Cardiac output (CO) is a fundamental measure used for diagnosis and guiding therapy in many clinical conditions. The most widely trusted and used method for CO measurement is thermodilution (TD) [1–3]. However, this technique is invasive since it requires that a catheter be placed in the pulmonary artery. Consequently, use of TD is restricted to intensive care and other specialized units in the hospital. Thus, there are many situations where information about CO could be helpful but is not available. As a result of this unmet need, there have been many efforts to develop noninvasive methods of CO measurement. The most widely investigated, noninvasive technique is based on *bioimpedance*, which involves the analysis of intrabeat variations in transthoracic voltage in response to applied high frequency transthoracic currents [4]. However, this method has had limited success in monitoring patients over long time periods and particularly in settings where patients may not be totally still

From the [1]Atlanta Cardiology Group, 5665 Peachtree Dunwoody Road, Suite 172, Atlanta, GA, 30342, USA; [2]Clinique Ambroise Pare, Neuilly, Paris, France; [3]Yale University, New Haven, CT, USA; [4]Northwest Texas Hospital, Amarillo, TX, USA; [5]Klinikum Traunstein, Traunstein, Germany; [6]Columbia University, New York, NY, USA.

Received 12 December 2007. Accepted for publication 11 February 2008.

Address correspondence to N. Y. Raval, Atlanta Cardiology Group, 5665 Peachtree Dunwoody Road, Suite 172, Atlanta, GA, 30342, USA.
E-mail: nraval@acgmd.com

[5, 6]. To overcome these limitations, an alternate method based on *bioreactance* has been developed. Bioreactance involves the analysis of intrabeat variations in voltage phase shifts in response to applied high frequency transthoracic currents. Prior studies have detailed the underlying principles and basic validation of this technique both in preclinical and clinical studies [7–9]. A rather extensive clinical study investigating the accuracy of this approach was performed in the surgical intensive care unit on sedated (frequently intubated) post-cardiac surgical patients [8]. CO from this device was shown to correlate with CO derived from continuous TD with a correlation coefficient of 0.82 and bias of only 0.18 l/minute. Furthermore, relative to continuous TD, NICOM had >90% sensitivity and specificity for detecting clinically relevant changes in CO from a baseline value. However, whether these findings are transferable to other clinical settings or to the more standard bolus TD method is currently unknown.

The specific purpose of this multicenter study was to test the accuracy of bioreactance-based noninvasive CO measurement in several clinical settings compared to TD. Measurements were obtained in the cardiac catheterization laboratory and in medical and cardiac intensive care units in which patients were awake or only slightly sedated. Measurements were also made in another cohort of patients in the original setting of the surgical intensive care. Finally, in selected studies, measurements of CO by Fick and standard bioimpedance methods where also performed for additional comparisons.

METHODS

Methods

Bioreactance measurement

Bioreactance CO monitoring was performed using the NICOM® system (Cheetah Medical Inc., Indianapolis, IN). As detailed previously, the system is based on an analysis of relative phase shifts of an oscillating current that occur when traversing the thoracic cavity [7–9]. In brief, the NICOM system is comprised of a radiofrequency generator for creating a high frequency current that is injected across the thorax, four dual surface electrodes (placed at the four corners of the thoracic body surface) that are used to establish electrical contact with the skin, a receiving amplifier for recording the transthoracic voltage in response to the injected current and circuitry for determining the relative phase shift between the injected current and the recorded voltage. Signals are applied to and recorded from the left and right sides of the thorax and these signals are processed separately and averaged after digital processing.

The system's signal processing unit determines the relative phase shift (Φ) between the input and output signals (which is actually detected by electronic circuitry as modulations in signal frequency). Changes in Φ, in turn, are considered to be related to changes in blood volume in the thorax, so that the peak rate of change of Φ ($d\Phi/dt_{max}$) is proportional to peak aortic flow during the beat. It has been shown that stroke volume (SV) can be estimated by: $SV = C \cdot VET \cdot d\Phi/dt_{max}$, where C is a constant of proportionality and VET is ventricular ejection time which is determined from the NICOM and ECG signals. The value of C has been optimized in prior studies and accounts for patient age, gender and body size [7–9]. CO is then calculated using the relation: $CO = SV \cdot HR$, where HR is the heart rate.

Patients and data recording

Data were obtained at five centers from a total of 111 patients who had a clinical indication for hemodynamic monitoring with a pulmonary artery catheter (PAC) and measurement of CO by TD. At two of the sites, short term measurements were made with either continuous cardiac output (CCO) TD (Yale University) or bolus TD (Klinikum Trauntstein) in the cardiac catheterization laboratory in patients undergoing diagnostic or interventional procedures. In the three other sites, longer term measurements were made with CCO TD in the cardiac care unit (St Joseph's Hospital), the medical intensive care unit (Northwest Texas Hospital) and in the post cardiac surgical intensive care unit (Clinique Ambroise Pare). The study was approved by the Institutional Review Board or Ethics Committee at each center and all patients provided informed consent to participate in this study. This was a monitoring study only; therapeutic decisions were made freely as decided by the primary physicians on the basis of standard practice without any modifications due to study participation.

For the studies performed on patients in an intensive care unit, CCO monitoring was performed using a Vigilance monitor (Edwards Life Sciences, Irvine, CA) and data were automatically recorded using a data logger that generates a table with minute-by-minute time-averaged CO and heart rate. Data from the NICOM (SV, CO, HR) were recorded simultaneously at the same 1 minute intervals. In the catheterization laboratory studies, measurements were made with repeated bolus saline injections. In these cases, at least three readings were obtained and the results averaged.

At one site (St Joseph's Hospital) continuous measurements were also made in a subset of patients with a standard bioimpedance system (BioZ ICG Monitor with

ZMarc© Algorithm for calculations of CO, Cardiodynamics, San Diego) in addition to the NICOM and PAC measurements. Preliminary studies in normal volunteers showed that these devices can operate at the same time without any interference. At another site (Klinikum Traunstein), CO was also estimated by the Fick method (CO_{Fick}), where CO_{Fick} = (O_2 consumption)/($AVO_{2,diff} \times 10$). O_2 consumption (in ml/minute) was estimated as BSA (138.1 − 17.04 ln(age) + 0.38.HR)] for females and BSA (138.1–11.49 ln(age) + 0.38.HR)] for males and $AVO_{2,diff}$ is based on measurement of arterial and mixed venous O_2 saturations (O_2Sat_A, O_2Sat_V) and partial pressures of oxygen ($pO_{2,A}$, $pO_{2,V}$):

$$AVO_{2,diff} = [(O_2Sat_A - O_2Sat_V)/100]\ Hb\ 1.36 + 0.03\left(pO_{2,A} - pO_{2,V}\right).$$

Data analysis

Summary data are presented as mean ± SD. Linear regression and Bland-Altman analyses were used to quantify correlations and degrees of agreement between different methods of CO measurement. The coefficient of variation, a measure of signal fluctuation around the linear trend line, was also determined; this is calculated as 2 times the square root of the average squared difference between the measured signal and the trend line over the entire recording period.

RESULTS

The basic demographics of the patients at each site are summarized in Table 1. There was a very wide range of ages and body sizes among each of the study cohorts. Typical original data obtained with the NICOM system are shown in Figure 1. Following the QRS complex, the phase shift measured by the system (Φ) increases indicating increase in aortic blood volume. The first portion of the dΦ/dt signal resembles the contour of a typical aortic flow pulse; in addition to tracking peak dΦ/dt on each beat, ventricular ejection time (VET) is also determined by the zero crossings of the dΦ/dt signal.

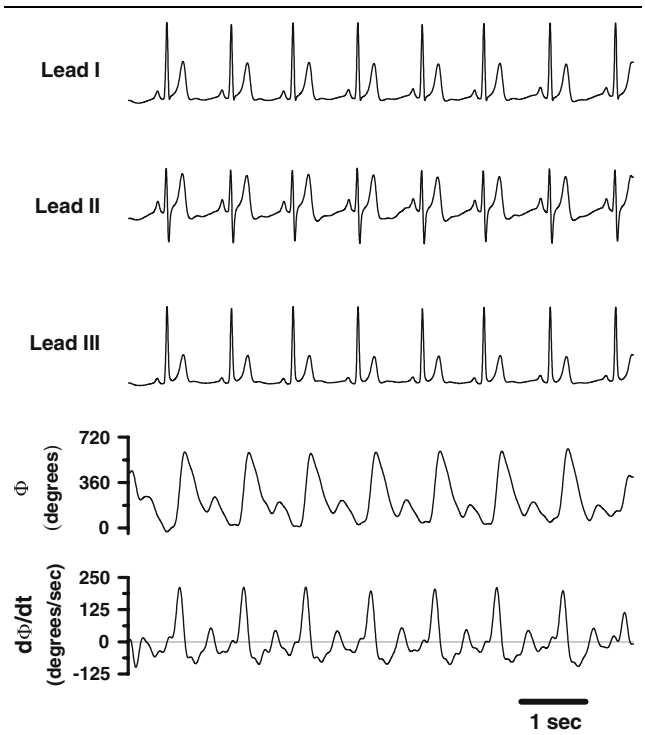

Fig. 1. Example of signals recorded from NICOM, including three leads of ECG, the phase shift (Φ) and the first derivative of phase shift (dΦ/dt).

Figure 2 shows an example of the minute-by-minute continuous cardiac output by TD (CCO) and by NICOM from an awake patient in the medical intensive care unit over approximately 400 minutes. The two measurements track each other throughout the recoding period. In this example, the average CO during the entire recording period was 7.2 for CCO versus 7.9 for

Table 1. Summary of patient characteristics at each investigational site

Site	Clinical setting	*N*	Recording					
			Duration	Age	Gender	Height	Weight	BSA
Yale Hospital	Cardiac Catheterization Lab	16	NA	62 ± 15	9M/7F	172 ± 11	91 ± 26	2.03 ± 0.31
Traunstein	Cardiac Catheterization Lab	25	NA	70 ± 9	13M/12F	170 ± 8	84 ± 14	1.95 ± 0.16
St. Joseph's Hospital	Cardiac Care Unit	20	261 ± 120	54 ± 14	16M/4F	177 ± 17	89 ± 27	2.03 ± 0.38
Ambroise Pare	Surgical ICU	35	778 ± 448	71 ± 11	29M/6F	171 ± 9	73 ± 16	1.85 ± 0.21
Amarillo	Medical ICU	15	307 ± 130	57 ± 19	7M/8F	174 ± 11	104 ± 38	2.15 ± 0.34

NA, not applicable.

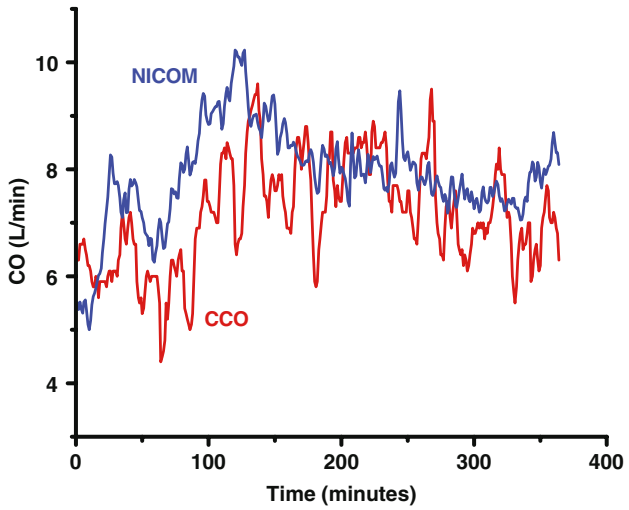

Fig. 2. Minute-by-minute values of cardiac output measured by continuous thermodilution from a pulmonary artery catheter and NICOM in an awake patient in the medical intensive care unit.

NICOM. As identified in prior studies, it can be seen in these tracings that changes in NICOM signal precede those in CCO (i.e., NICOM is more responsive than CCO) which is simply a result of the different time averaging performed by the two systems; the CCO system provides 5-minutes running averages of CO, while NICOM provides 1-minute running averages. Despite the more heavily filtered CCO signal, there were numerous moments where CCO indicated rather large, abrupt (clinically unrealistic) fluctuations in CO; in comparison, the minute-by-minute variations were smaller for the NICOM. For the example shown in Figure 2, the coefficient of variation was 0.31 l/minute for CCO and only 0.23 l/minute for NICOM.

The results from the three intensive care settings are summarized in Figure 3. The mean values of CCO and NICOM were highly correlated ($r = 0.78$, $P < 0.0001$) and did not differ significantly from the line of identity ($P = 0.55$). As seen in the Bland-Altman plots (Figure 3B) there was very little bias between CCO and NICOM (−0.09 l/minute). The coefficients of variation were very consistent among the three centers and were consistently and significantly lower for NICOM than for CCO (Table 2).

Bioimpedance-based CO was measured in a subset of 7 patients along with CCO and NICOM. Figure 4 shows continuous recordings over an approximately 200 minutes period from a typical, awake, cardiac care unit patient. As seen, while CCO and NICOM generally tracked each other (with changes appearing first in NICOM as discussed above), bioimpedance generally underestimated CCO for long periods of time and also showed higher

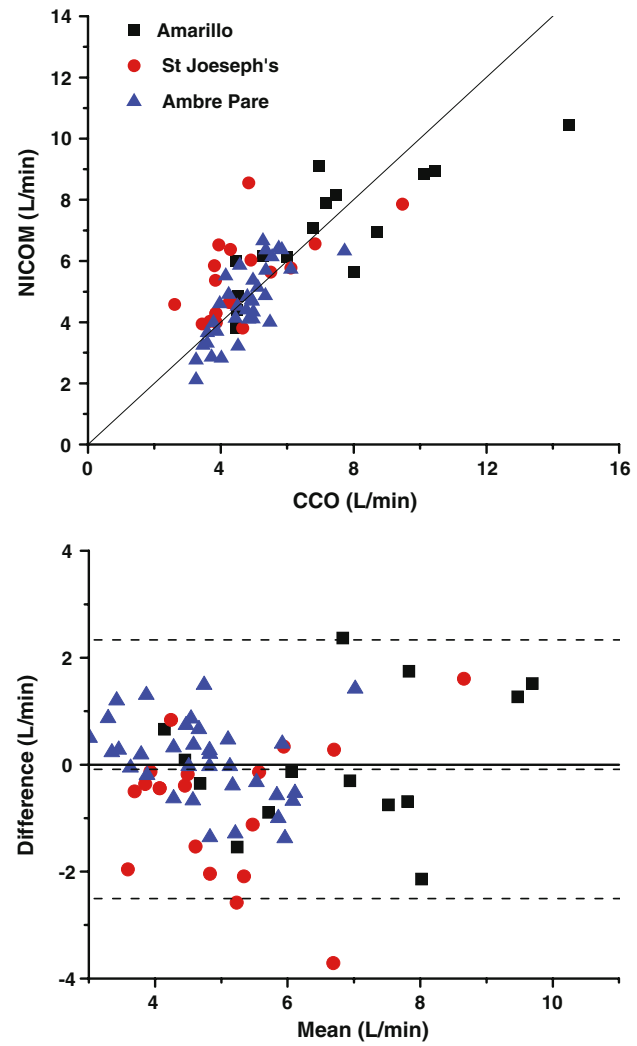

Fig. 3. Relationship between mean values of cardiac output from continuous cardiac output from thermodilution (TD) versus bioreactance-based NICOM in three different clinical setting in three separate hospitals as indicated (top, solid line is line of identity) with corresponding Bland and Altman plot. The correlation between the two values is r = 0.79. From the Bland Altman plot it is seen that the mean value of the difference between TD and NICOM (termed bias) is −0.09 l/minute, with the confidence band extending between −2.5 l/minute and +2.3 l/minute. See text for further explanation.

degree of variability. For these 7 patients, CO averaged 5.4 ± 2.1 by CCO, 5.5 ± 1.4 by NICOM ($P = 0.78$ vs. CCO by paired t-test) and 2.7 ± 0.80 by bioimpedance ($P = 0.01$ vs. CCO by paired t-test).

Measurements made in the cardiac catheterization laboratory showed similar correlations with TD-based CO measurements (Figure 5A, B). Overall bias was −0.18 l/minute, the correlation was significant ($P < 0.001$) with correlation coefficient 0.71; the correlation did not differ from the line of identity ($P = 0.28$). The Fick method was

Table 2. Coefficient of variation

	CCO	NICOM
St. Joseph's Hospital	0.61 ± 0.2	0.34 ± 0.15★
Ambroise Pare	0.64 ± 0.21	0.32 ± 0.16★
Amarillo	0.58 ± 0.2	0.24 ± 0.14★

★ $P < 0.001$.

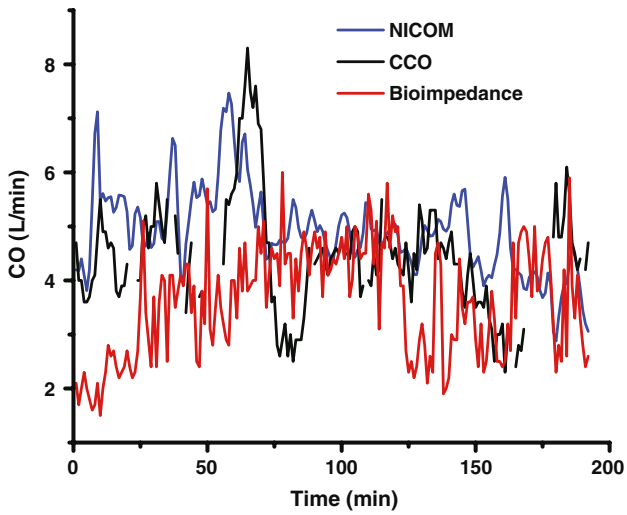

Fig. 4. Minute-by-minute cardiac output from NICOM, continuous thermodilution and standard bioimpedance from an awake patient in the cardiac care unit. While NICOM and TD results track each other reasonably well throughout the recording period, bioimpedance-based measurements deviated for large periods of time.

used in a subset of 20 of these patients (Figure 5C, D). As an interesting comparison, although Fick and bolus TD CO values correlated well ($r = 0.67$, $P = 0.001$), the Fick method generally provided a significantly lower estimate than TD (4.5 ± 1.2 vs. 5.4 ± 1.4, $P < 0.001$ by paired t-test) with a mean bias of −0.87 l/minute.

DISCUSSION

Because of the invasive nature of TD-derived CO, many investigators have questioned the risk-benefit ratio of routine hemodynamic monitoring using a PAC even in critically ill patients in intensive care units [10, 11]. Indeed, PAC use is on the decline over the past several years. Consequently, even in intensive care units, many patients are managed without a PAC, though there can be situations where such information can be useful. In addition, availability of CO measurements could be helpful in many settings where it has typically not been available, such as outpatient clinics, emergency rooms, general medical wards and during most surgical procedures. As a result, there have been many efforts to develop approaches to measuring CO less invasively. Techniques based on arterial pulse contour analysis [12, 13], transesophageal Doppler echocardiography [14, 15], impedance cardiography, and carbon dioxide breath analysis [16] are among the techniques that are available. Aside from arterial pulse contour analysis, these other techniques are completely noninvasive; of these, only impedance cardiography is suitable for continuous monitoring.

Recently, the feasibility and accuracy of a completely noninvasive technique of CO estimation based on *bioreactance* has been demonstrated in sedated patients in the surgical intensive care unit [9]. We now demonstrate that a similar degree of accuracy can be obtained in multiple hospital settings, including catheterization laboratories and medical, surgical and cardiac intensive care units. Patients in the cardiac and medical care units were awake and although the patients were in bed during the measurements, movements were not restricted. In this setting, the degree of concordance identified between NICOM and TD CCO was comparable to that reported in the prior study and also between TD CCO and other noninvasive techniques. In particular, the bias between these two techniques was <0.2 l/minute in all settings. Also as in the prior studies, the responsiveness of NICOM was quicker than for TD CCO, perhaps because of the differences in time averaging algorithms used in the two systems. Also notable in this patient cohort was the finding that the coefficient of variation (an index of fluctuation of the reading about the mean) for NICOM was consistently about half that of the TD CCO; this is despite the more aggressive time averaging of the TD CCO monitor.

For cases when comparing two measurement techniques that are each subject to variability, Bland-Altman analysis is the preferred method for comparison. Strictly speaking, this approach is used to evaluate the equivalence of two methods of measurement [17]. With this approach, the difference between the two measurements is plotted as a function of the average value of the two methods. The mean value of all the differences is defined as the "bias" between the two measurement techniques. The limits of agreement (LOA), defined by the boundaries set between the mean ± 1.96SD, give a measure of the variability between the two measurements. In the case of our comparison between PAC and NICOM, there was very little bias and the variability was within approximately ±2 l/minute. These LOAs are similar to those observed in prior studies of PAC vs. NICOM, between continuous TD and bolus TD [18] and between PAC and other methods [14]. To put the present results with NICOM

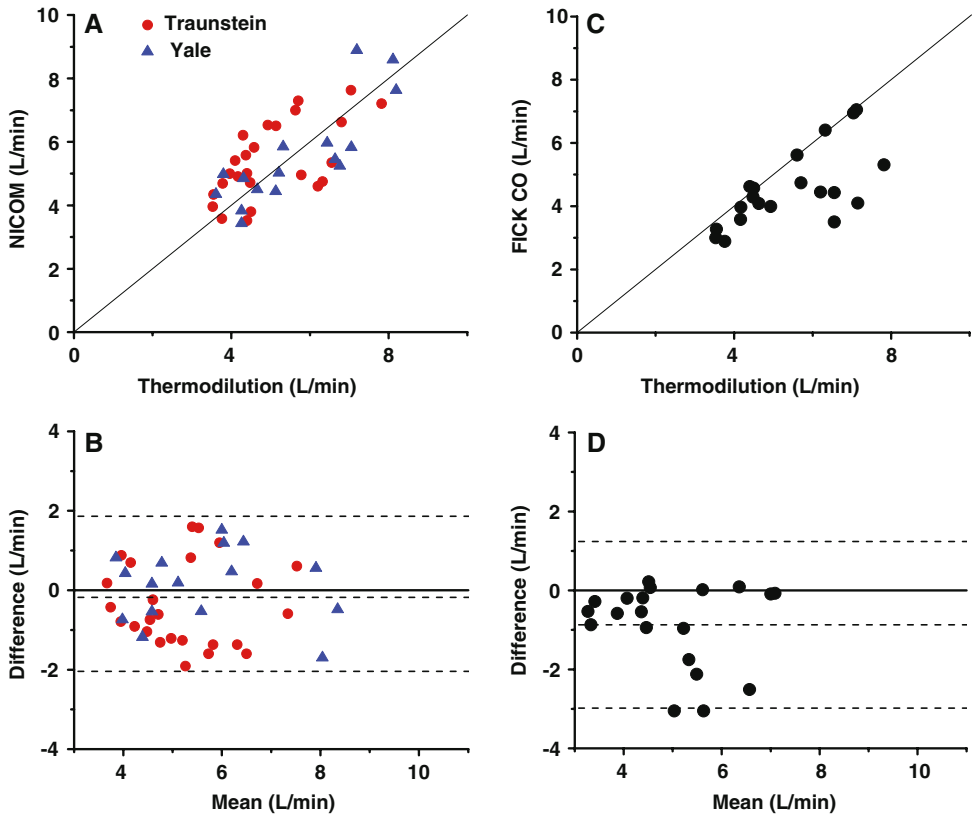

Fig. 5. Regression between TD and NICOM based cardiac output from patients in two separate cardiac catheterization laboratories (A, solid line is line of identity) with corresponding Bland Altman plot (B). The correlation between the measurements is r = 0.71. The mean value of the difference between these two measurements (termed bias), as seen in panel b is −0.17 l/minute with confidence bands spanning from −2.21 l/minute to 1.87 l/minute. Similar plots for the comparison between bolus thermodilution and Fick method of cardiac output determination are shown in panels C and D. As seen, there is a lower degree of correlation (r = 0.66), the bias is greater (−0.87 l/minute) and the confidence band is broader (spanning from −2.98 l/minute to 1.24 l/minute). See text for further explanation.

into perspective, we also investigated the correlation between TD and Fick-estimated CO. In our series, the correlation between TD and Fick was lower, the bias was greater and the LOA were about the same as between TD and NICOM. There are several factors that contribute to this quite consistently observed variability of bias and LOA between different modalities of CO measurements. First, there is the precision of each individual method, which refers to the intrinsic variability of measurement that is due to random errors of measurement. Second is potential difference in time responsiveness of the two modalities of measurements associated with the natural intra-patient CO variability. Finally, there is real discordance between the two modalities (i.e., the true bias). In practice, it is not possible to determine the relative contributions of these factors to the results, only their net effect. This highlights the difficulties inherent in evaluating a new technology for CO determination; even techniques that are considered to be gold standards don't always yield the same results. It must be recognized that no technique currently available for measuring CO in the clinical setting (including TD, which is typically used as the method of comparison) is accurate all the time.

In a recent study, NICOM has been used in the setting of exercise testing and shown to correlate with oxygen consumption (VO_2) at rest and at peak exercise, which obviously involves measurements made during significant body motion [19]. Furthermore, the correlation between CO and VO_2 at peak exercise was similar to that reported in prior studies in which CO was measured by other techniques. The present study posed further challenges to the NICOM by operating in intensive care units and cardiac catheterization laboratories, environments rich in electrical noise from other equipment. NICOM performed well compared with a standard bioimpedance-based system which may be more influenced by ambient electrical noise and not necessarily designed to be used for CCO monitoring. Still, the bioimpedance system has

been used successfully with patient movement during exercise testing [20] and in challenging settings such as in obese patients with trauma in the intensive care unit [21].

In summary, the present study shows that on average, compared to TD, the bioreactance-based NICOM system for noninvasive CO measurement has acceptable accuracy in challenging clinical environments. Availability of such a tool will allow clinicians to have information about CO in patients in whom this information is not currently available to help diagnosis and to guide therapy.

This research was funded by Cheetach Medical. P. Squara and D. Burkhoff are consultants to Cheetah Medical.

REFERENCES

1. Boldt J, Kling D, Thiel A, Hempelmann G. Non-invasive versus invasive cardiovascular monitoring. Determination of stroke volume and pulmonary hydration using a new bioimpedance monitor. Anaesthesist 1988; 37: 218–223.
2. Rubini A, Del MD, Catena V, et al. Cardiac output measurement by the thermodilution method: an in vitro test of accuracy of three commercially available automatic cardiac output computers. Intensive Care Med 1995; 21: 154–158.
3. Zollner C, Polasek J, Kilger E, et al. Evaluation of a new continuous thermodilution cardiac output monitor in cardiac surgical patients: a prospective criterion standard study. Crit Care Med 1999; 27: 293–298.
4. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp Med 1966; 37: 1208–1212.
5. Engoren M, Barbee D. Comparison of cardiac output determined by bioimpedance, thermodilution, and the Fick method. Am J Crit Care 2005; 14: 40–45.
6. Leslie SJ, McKee S, Newby DE, Webb DJ, Denvir MA. Noninvasive measurement of cardiac output in patients with chronic heart failure. Blood Press Monit 2004; 9: 277–280.
7. Keren H, Burkhoff D, Squara P. Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance. Am J Physiol Heart Circ Physiol 2007; 293: H583–H589.
8. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, Dubois C. Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med 2007; 33: 1191–1194.
9. Squara P, Marque S, Cariou A, Chiche J. Non invasive cardiac output monitoring (NICOM) compared to minimally invasive monitoring (VIGILEO) (abstr). Anesthesiology 2007; 107: A1527 .
10. Frezza EE, Mezghebe H. Indications and complications of arterial catheter use in surgical or medical intensive care units: analysis of 4932 patients. Am Surg 1998; 64: 127–131.
11. Kac G, Durain E, Amrein C, Herisson E, Fiemeyer A, Buu-Hoi A. Colonization and infection of pulmonary artery catheter in cardiac surgery patients: epidemiology and multivariate analysis of risk factors. Crit Care Med 2001; 29: 971–975.
12. Gratz I, Kraidin J, Jacobi AG, deCastro NG, Spagna P, Larijani GE. Continuous noninvasive cardiac output as estimated from the pulse contour curve. J Clin Monit 1992; 8: 20–27.
13. Combes A, Berneau JB, Luyt CE, Trouillet JL. Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intensive Care Med 2004; 30: 1377–1383.
14. Su NY, Huang CJ, Tsai P, Hsu YW, Hung YC, Cheng CR. Cardiac output measurement during cardiac surgery: esophageal Doppler versus pulmonary artery catheter. Acta Anaesthesiol Sin 2002; 40: 127–133.
15. Dark PM, Singer M. The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. Intensive Care Med 2004; 30: 2060–2066.
16. Rocco M, Spadetta G, Morelli A, et al. A comparative evaluation of thermodilution and partial CO_2 rebreathing techniques for cardiac output assessment in critically ill patients during assisted ventilation. Intensive Care Med 2004; 30: 82–87.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307–310.
18. Medin DL, Brown DT, Wesley R, Cunnion RE, Ognibene FP. Validation of continuous thermodilution cardiac output in critically ill patients with analysis of systematic errors. J Crit Care 1998; 13: 184–189.
19. Myers J, Gujja P, Neelagaru S, Burkhoff D. Cardiac output and cardiopulmonary responses to exercise in heart failure: application of a new bio-reactance device. J Card Fail 2007; 13: 629–636.
20. Ziegeler S, Grundmann U, Fuerst O, Raddatz A, Kreuer S. Hemodynamic response to exercise as measured by the solar IKG impedance cardiography module and correlation with metabolic variables. J Clin Monit Comput 2007; 21: 13–20.
21. Brown CV, Martin MJ, Shoemaker WC, et al. The effect of obesity on bioimpedance cardiac index. Am J Surg 2005; 189: 547–550.