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Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance

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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* 293: H583–H589, 2007. First published March 23, 2007; doi:10.1152/ajpheart.00195.2007.—Noninvasive cardiac output (CO) measurement can be useful in many clinical settings where invasive monitoring is not desired. Bioimpedance (intrabeat measurement of changes in transthoracic voltage amplitude in response to an injected high-frequency current) has been explored for this purpose but is limited in some clinical settings because of inherently low signal-to-noise ratio. Since changes in fluid content also induce changes in thoracic capacitive and inductive properties, we tested whether a noninvasive CO measurement could be obtained through measurement of the relative phase shift of an injected current (i.e., bioreactance). We constructed a prototype device that applies a 75-kHz current and determines the relative phase shift ($d\Phi/dt$) of the recorded transthoracic voltage. CO was related to the product of peak $d\Phi/dt$, heart rate, and ventricular ejection time. The preclinical study was done in nine open-chest pigs put on right heart bypass so that CO could be varied at known values. This was followed by a feasibility study in 27 postoperative patients who had a Swan-Ganz catheter (SGC). The measurements of noninvasive CO measurement and cardiopulmonary bypass pump correlated to each other ($r = 0.84$) despite the large variation in CO and temperatures. Similarly, in patients, mean CO values were 5.18 and 5.17 l/min as measured by SGC and the noninvasive CO measurement system, respectively, and were highly correlated over the range of values studied ($r = 0.90$). Preclinical and clinical data demonstrate the feasibility of using blood flow-related phase shifts of transthoracic electric signals to perform noninvasive continuous CO monitoring.

noninvasive monitoring

THE DEVELOPMENT of an accurate, simple, cost-effective, noninvasive technique of measuring cardiac output (CO) can be important for clinical decision making and research in many inpatient and outpatient clinical settings. The recent emphasis on the uncertain risk-benefit ratio of invasive CO monitoring by pulmonary artery catheterization (PAC) with a Swan-Ganz catheter (SGC) further highlights the clinical imperative of developing noninvasive alternatives (15). A number of noninvasive methods of assessing CO have been studied in the past, with transesophageal Doppler echocardiography, impedance cardiography, and carbon dioxide breath analysis currently available (11).

Thoracic bioimpedance was the first and currently the most widely used noninvasive method for CO monitoring (2, 3, 17). Standard bioimpedance systems apply a high-frequency electrical current of known amplitude and frequency across the thorax and measure changes in voltage. The ratio between voltage and current amplitudes is a measure of transthoracic direct current resistance (more generically referred to as impedance, Z_o) and this varies in proportion to the amount of fluid in the thorax. The instantaneous rate of change of Z_o therefore relates to instantaneous blood flow in the aorta. Since the aortic blood flow pulse contour is roughly triangular in time (Fig. 1), stroke volume (SV, the integral of flow over time) is proportional to the product of peak flow and the ventricular ejection time (VET). Thus SV is also proportional to the product of maximal rate of change of Z_o (dZ_o/dt_{max}) and VET.

Although clinical utility has been increasingly recognized in some clinical settings (13, 14), bioimpedance has been found to be inaccurate in intensive care units (ICUs) and other settings where significant electrical noise and body motion exist (5, 9). Also, the technique is sensitive to placement of the electrodes on the body, variations in patient body size, and other physical factors that impact on electrical conductivity between the electrodes and skin (e.g., temperature and humidity).

In addition to changing resistance to blood flow (Z_o), changes in intrathoracic volume also produce changes in electrical capacitive and inductive (i.e., bioreactance) properties that result in phase shifts of the received signal relative to the applied signal. Techniques for detecting relative phase shifts are inherently more robust and less susceptible to noise (e.g., the comparison between AM and FM radio). We therefore hypothesized that, in contrast to analysis of changes in transthoracic voltage used in standard bioimpedance-based systems, analysis of relative phase shifts would yield a system with improved accuracy and less susceptibility to ambient conditions.

To test this hypothesis, we developed a bioreactance-based system of noninvasive CO measurement and tested its accuracy in two settings: *1*) an animal model in which CO can be controlled and measured accurately and *2*) in preliminary clinical studies by comparing its performance to that of thermodilution.

METHODS

Bioreactance-based noninvasive CO measurement: principle of operation. The bioreactance-based noninvasive CO measurement system is based on an analysis of relative phase shifts of an oscillating current that occur when this current traverses the thoracic cavity, as opposed to traditional bioimpedance-based systems, which rely only on measured changes in signal amplitude. This noninvasive CO measurement system [NICOM, Cheetah Medical (US)] is comprised

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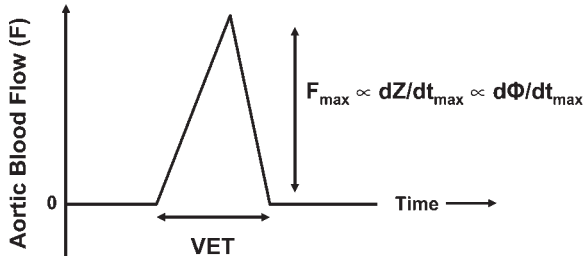

Fig. 1. Schematic representation of aortic flow as a function of time underlying the basic principle for estimation of stroke volume (SV) from changes in bioimpedance (dZ_{max}/dt) or changes in relative phase shifts ($d\Phi/dt_{max}$, bioreactance). Since the aortic flow pulse is relatively triangular in time, SV is proportional to the product of peak flow (F_{max}) and ventricular ejection time (VET).

of a high-frequency (75 kHz) sine wave generator and four dual-electrode "stickers" that are used to establish electrical contact with the body (Fig. 2). Within each sticker, one electrode is used by the high-frequency current generator to inject the high-frequency sine wave into the body, while the other electrode is used by the voltage input amplifier. Two stickers are placed on the right side of the body, and two stickers are placed on the left side of the body. The stickers on a given side of the body are paired, so that the currents are passed between the outer electrodes of the pair and voltages are recorded from between the inner electrodes. A noninvasive CO measurement signal is thus determined separately from each side of the body, and the final noninvasive CO measurement signal is obtained by averaging these two signals.

The system's signal processing unit detects the relative phase shift ($\Delta\Phi$) of the input signal (picked up by the receiving electrodes) relative to the injected signal. As discussed above, the phase shift between the injected current and output signal received from the thorax is due to changes in blood volume in the aorta. With standard bioimpedance, $SV \propto (L/Z_o)^2 \cdot VET \cdot dZ_o/dt_{max}$, where L is the distance between the electrodes on the body surface (Fig. 1) (18). Similarly, we found that there is also a tight correlation between the blood flow rate and the rate of change in the relative phase shift ($d\Phi/dt$). Thus SV can also be expressed as

$$SV = C \cdot VET \cdot d\Phi/dt_{max} \quad (1)$$

where C is a constant of proportionality. CO is then calculated with the relation

$$CO = SV \cdot HR \quad (2)$$

where HR is heart rate. Unlike bioimpedance, bioreactance-based noninvasive CO measurement does not use the static impedance Z_o and does not depend on the distance between the electrodes L for the calculations of SV and CO, which significantly reduces the uncertainty in the result.

The signal processing unit is comprised of a limiter that eliminates amplitude variations in the input signal with an amplitude saturation technique but maintains the information contained in its frequency and phase modulation. The saturated amplitude reference input signal and the output signal are both sent to a mixer-multiplier that subtracts these two high-frequency signals to allow determination of the relative phase shift variation, $d\Phi/dt$. To enhance signal-to-noise ratio, a low-pass filter is applied to the mixed-output signal. The resulting signal is used to calculate $d\Phi/dt$, which is converted from the original analog signal to digital data for processing at a sampling frequency of 500 Hz. The device also records and digitizes a three-lead electrocardiogram (ECG). This is used to identify the start and end of each beat for determination of HR. Within each beat defined by these start and end time marks, the system determines $d\Phi/dt_{max}$, which is used in *Eq. 1*. Finally, the ECG is also used in determination of VET, which is determined with a standard algorithm that uses information from the ECG and the $d\Phi/dt$ signal. Specifically, the peak of the QRS complex of the ECG is used as the timing mark of the start of each beat. VET is then calculated as the time interval between the start of ejection, defined by the first zero crossing of the $d\Phi/dt$ signal, and the end of ejection, defined as the second zero crossing of the $d\Phi/dt$ signal. These zero crossings are readily identified on the $d\Phi/dt$ tracings shown in Fig. 3.

Animal studies. Nine pigs were used in the preclinical phase of the validation study. In each case, the chest was opened by midline thoracotomy after establishment of deep anesthesia with ketamine (10 mg/kg iv) and azaperon (2 mg/kg iv). Each animal was put on right heart bypass as follows. The inferior and superior vena cava were cannulated, and connection to the atrium was completely blocked by bicaval ligation. These cannulas were connected to a cardiopulmonary bypass (CPB) pump that was used to regulate blood flow. After oxygenation, blood was reinfused into the right atrium via a third cannula. In this manner, flow in the pulmonary artery and aorta were pulsatile and with a mean value that was controlled. Four NICOM electrodes were placed on the thorax (2 on the upper thorax, 2 on the lower thorax), and these were connected to the NICOM signal processor. A Transonic flow probe was held in place over the pulmonary artery in some of the experiments in order to record the blood flow velocity profile. After completion of the surgery and stabilization of the preparation, CO was varied in small increments by adjusting the speed of the CPB pump. In a second sequence, CO was varied in large increments and temperature of the blood was varied between 38 and 36°C. Changes in temperature induce significant changes in electrical conductivity and thus impose a relatively rigorous test on the independence of system performance of physical factors.

A single calibration factor was determined retrospectively for each animal by dividing the value obtained with the NICOM system and the known value of CPB pump flow at each pump setting and then taking the average of all measurements; this average value was then applied to all data for that individual experiment. Standard correlation analysis was performed between the readings obtained from preset CPB output and the NICOM system.

The study conformed to the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH Pub. No. 85-23, revised 1996), and the protocol was approved by the Institutional Animal Care and Use Committee of the IMM Recherche Institut Mutualiste Montsouris, Paris.

Clinical study. Twenty-seven patients admitted into the ICU after valve replacement or coronary artery bypass graft surgery were included from two centers, Clinique Ambroise Pare and IMM Recher-

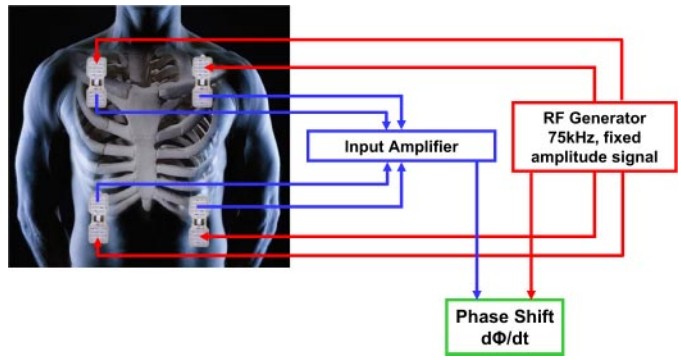

Fig. 2. The NICOM system and its connection to the body. Four double electrode stickers are placed around the thorax. A high-frequency current is passed between the 2 outer electrodes, and the resulting voltages are recorded between the 2 inner electrodes. The relative phase shift (Φ) and rate of change of phase ($d\Phi/dt$) between these signals are determined and used in the calculations of SV. RF, radio frequency.

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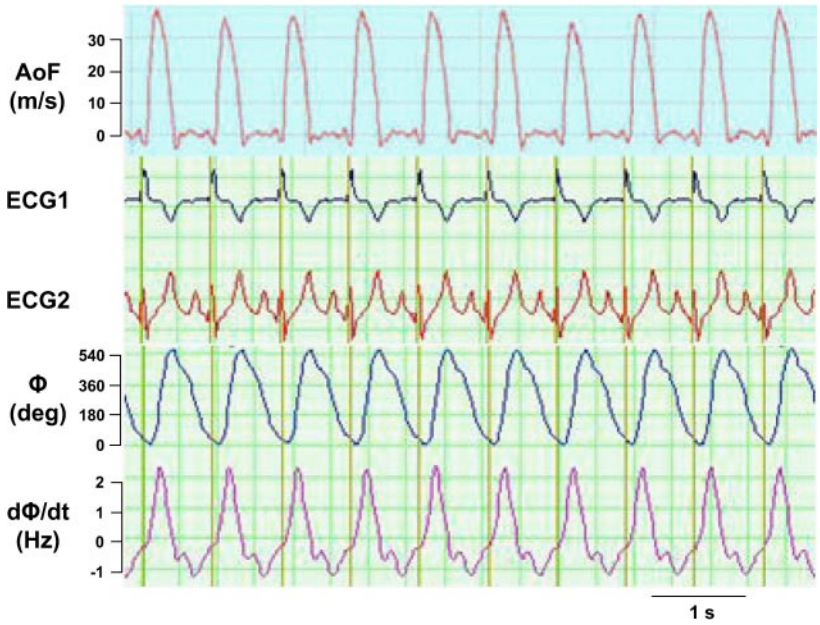

Fig. 3. Original recordings of aortic flow (AoF), 2 electrocardiograms (ECGs), the signal of relative phase (Φ), and its first derivative (dΦ/d*t*). See text for further details.

che Hôpital, Paris. All patients underwent CO measurement invasively by the continuous thermodilution technology with the SGC and noninvasively by the NICOM system. This study was approved by the ethics committees of the hospitals, and each patient provided written informed consent before participation.

After the induction of anesthesia in the operating room, a SGC (Arrow 7.5 Fr) was inserted via the jugular or subclavian vein, as is routine during cardiac surgery. This pulmonary artery catheter provided CO measurements that were time averaged over the preceding 5 min. On admission to the ICU after cardiac surgery, the pulmonary arterial catheter was connected to a continuous thermodilution CO device (Baxter Medical) and proper positioning of the catheter was confirmed on a chest X-ray. NICOM electrodes were placed on the patient's chest and connected to the NICOM controller. No special attention was given to sticker location except that the upper electrodes were to be positioned in the subclavian region and the lower stickers were placed in the lower costal margin. The clock times of the NICOM controller and the continuous thermodilution device were synchronized immediately before the acquisition of the measurements started. Thus timing of data acquisition by both devices was synchronized so as to obtain simultaneous reading by the two devices from each patient. For purposes of analysis, data obtained from each individual patient were averaged over the entire recording, which ranged from 1 to 2 h. Selected patients underwent evaluation of the NICOM system in response to positive end-expiratory pressure (PEEP) tests in which the lungs are inflated by increased air pressure (typically to the equivalent of 15–20 cmH_2O), which in turn reduces venous return and CO.

Statistical analysis was carried out with SPSS statistical software. The null hypothesis was that there was no statistically significant difference between CO determined by thermodilution and NICOM measurements. For each pair of measurements, Pearson's correlation coefficient was calculated.

RESULTS

Animal studies. Examples of the original pulmonary blood flow velocity signals, two electrocardiograms, the NICOM relative phase signal (Φ), and its first derivative (dΦ/d*t*) are shown in Fig. 3. The NICOM relative phase signal shows a periodic signal in synchrony with the QRS complexes. Note the approximately triangular contour of the dΦ/d*t* signal that is in phase with the pulmonary blood flow velocity signal.

Results from one animal in which CPB flow was varied gradually are shown in Fig. 4*A*. As seen, NICOM closely tracked the cardiac output imposed by CPB. Figure 4*B* summarizes the correlation between individual measurements from all the measurements, confirming the consistency of this finding. Figure 5 shows the overall results from all animals in this series. On the whole, there was a strong correlation between the cardiac output set by the CPB pump and that detected by the NICOM ($y = 0.85 + 0.81x$; $r = 0.87$). As noted, there is a relatively large offset in the regression equation, which may suggest that at very low values of CO the assumptions underlying the NICOM estimation of CO may not be fully valid. Nevertheless, if the regression line is forced through the origin (line not shown on the graph), the correlation coefficient remains at 0.87 and the slope increases to 1.09.

An example in which large variations of CO were imposed by the CPB flow with superimposed changes in blood temperature is shown in Fig. 6*A*. As shown in the example, the close match between NICOM and imposed CPB flow was retained, despite abrupt, large changes in flow and despite changes in temperature (Fig. 6*B*). The overall correlation between CPB flow and NICOM for all points measured in all animals is summarized in Fig. 7*A*. Overall, the correlation between CPB flow and NICOM measurement was not impacted by temperature. When data from both temperatures were pooled, the overall correlation between CPB flow and NICOM measurement was $y = 0.13 + 0.95x$ ($r = 0.84$), which was not significantly different from the line of identity.

Within this last protocol, imposed changes in CO ranged from approximately −1.5 to +2.0 l/min in 0.5 l/min increments. The correlation between imposed changes in CO and changes detected by NICOM are summarized in Fig. 7*B* (data from both temperatures and all animals included). The regression between imposed and measured CO changes was not different from the line of identity ($y = 1.06x - 0.03$, $r = 0.88$).

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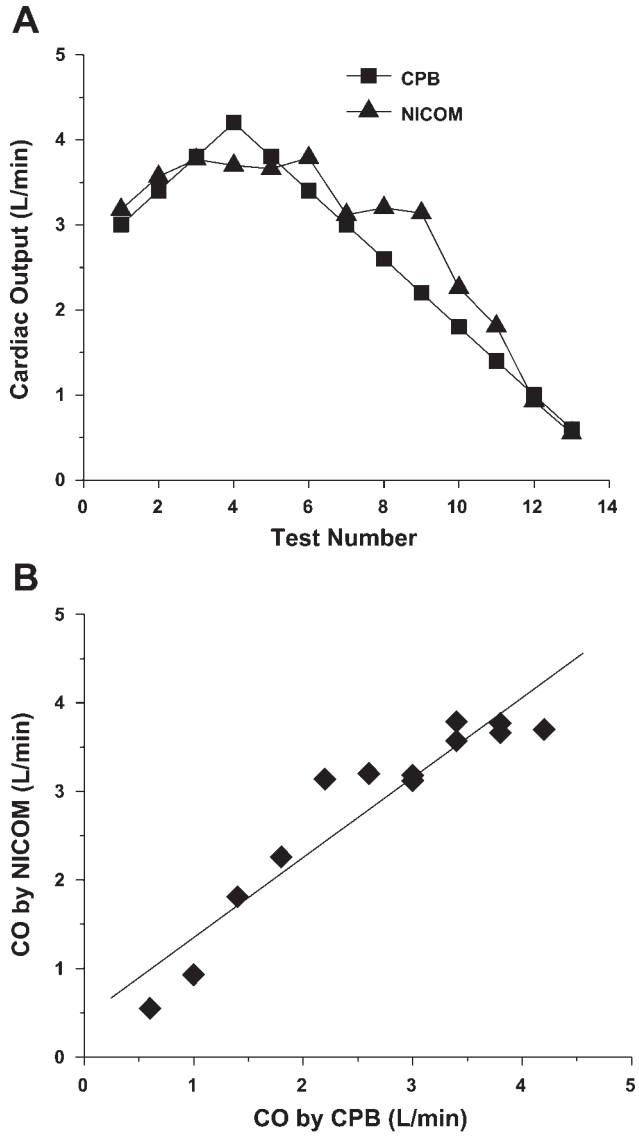

Fig. 4. Cardiac output (CO) measurements in animals on cardiopulmonary bypass (CPB) by the NICOM system during gradual changes in CPB pump flow. *A*: comparison between CPB flow and NICOM measurements from a typical experiment. *B*: data from *A* plotted to show the correlation between the CO measurements by NICOM and CPB.

Clinical data. The baseline characteristics of the patients are summarized in Table 1. No adverse events were noted in any patients, and monitoring with the NICOM system was found to be safe. The mean CO for the group was 5.17 and 5.18 l/min as measured by the NICOM system and by the SGC, respectively. An example of 1.5 h of simultaneously recorded NICOM and SGC data is shown in Fig. 8. There is generally good agreement between the techniques, both of which show a gradual increase in CO from ~4.5 to ~5.5 l/min. These recordings are typical in that because of the difference in time averaging (1 min for NICOM vs. 5 min for SGC) there was slightly more variability in the NICOM signals. The regression plot of mean CO measured from the NICOM system versus mean CO measured from the SGC system for all patients showed a good correlation ($r = 0.90$) that did not differ statistically from the line of identity ($y = 0.59 + 0.89x$; Fig. 9).

Data showing the responsiveness of the SGC and NICOM systems to episodes of PEEP are shown in Fig. 10. As shown, the NICOM system was found to be highly reactive to variations in PEEP. In this example, NICOM indicated an initial CO of ~6.6 l/min. On application of 15-cmH_2O PEEP, the NICOM signal decreased within the first 1 min to ~4.1 l/min, with an additional small amount of reduction over the ensuing 4 min. PEEP was then reduced stepwise (in steps of 5 cmH_2O) back to 0 cmH_2O, during which time the NICOM signal returned toward normal. With abrupt reintroduction of 15-cmH_2O PEEP, the NICOM signal immediately reduced back toward 4.0 l/min with even an additional small reduction. When PEEP was removed 10 min later, the NICOM signal returned to the original starting level. It is noteworthy that compared with the NICOM signal, the SGC signal (data not shown) was significantly less responsive (a consequence of the 5-min running averaging done by that system). So there was high concordance between the NICOM and SGC during the hemodynamically stable periods, but differences emerged during these rapid periods because of the differences in filtering. NICOM proved to be similarly responsive in other patients subjected to PEEP test.

DISCUSSION

Preclinical and clinical data from this pilot study validate the safety and feasibility of using a bioreactance-based system for tracking CO in animals and humans. The study also established that the device can work even in the experimental laboratory and the intensive care setting, environments that are rich in ambient electrical noise. It is in such settings that traditional bioimpedance-based systems are known to exhibit poor performance (1, 5, 9). Nevertheless, NICOM performed well compared with the SGC, which is currently considered to be the gold standard for CO determination in the clinical setting.

Measurement of CO and, sometimes more importantly, changes in CO can be extremely useful when assessing circulatory function. A simple and reliable method of measuring CO is frequently required both clinically and for research purposes. However, the thermodilution technique using PAC is invasive,

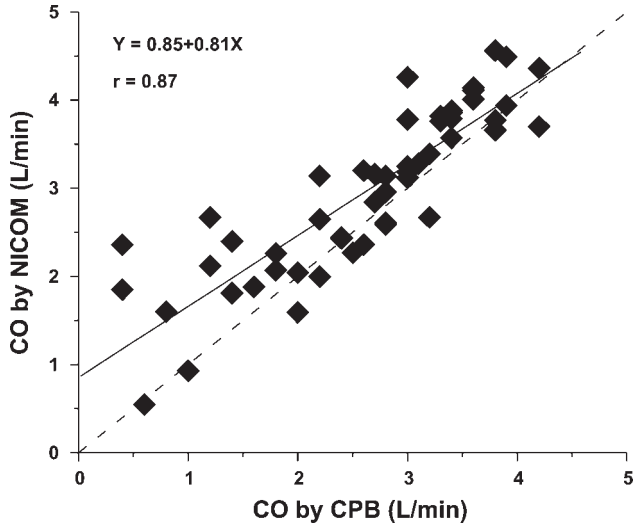

Fig. 5. CO measurements in animals on CPB by the NICOM system during gradual changes in CPB pump flow: summary data from all animals studied.

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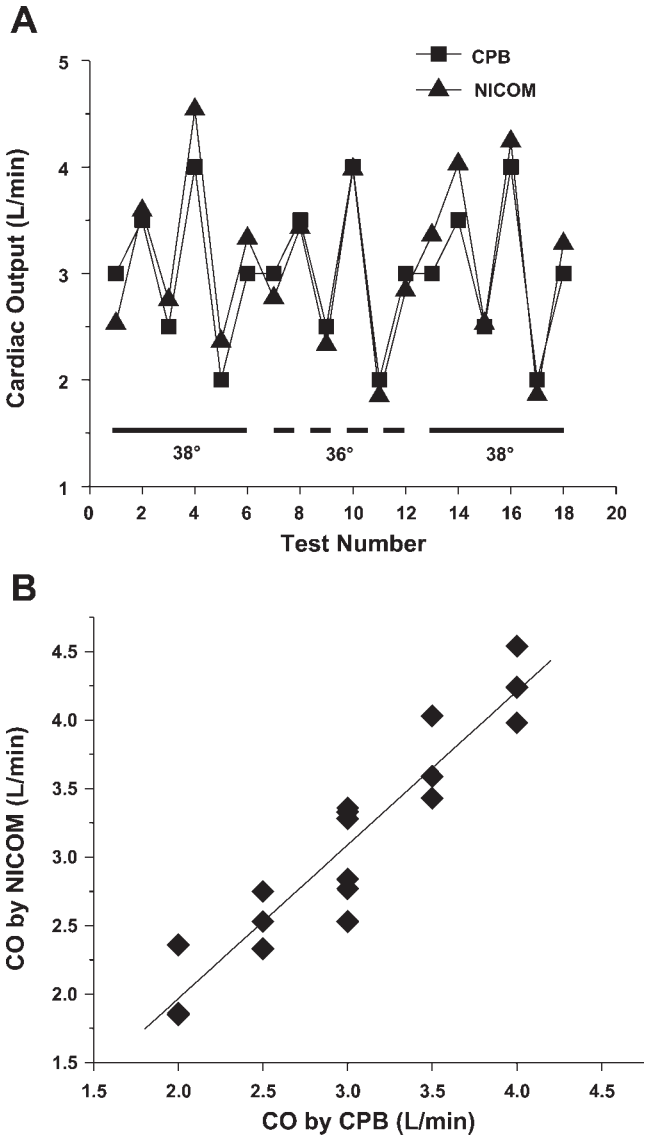

Fig. 6. *A*: CO measurements by NICOM with large variation imposed by CPB and superimposed temperature variation in a typical animal experiment. *B*: data from *A* plotted to show the correlation between the CO measurements by NICOM and CPB.

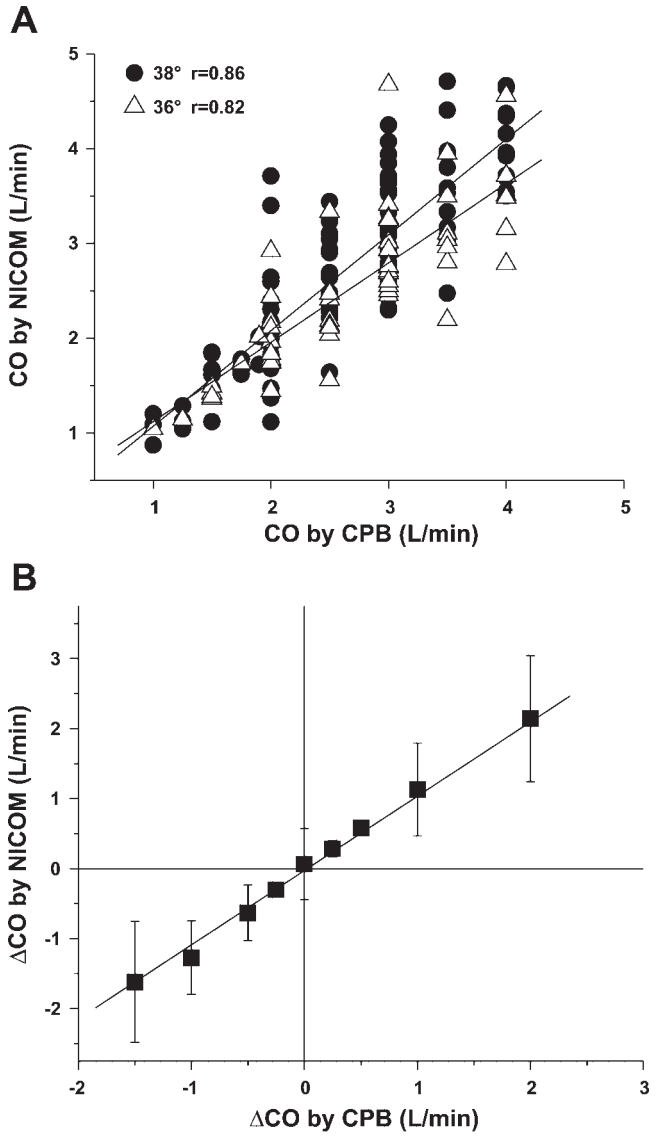

Fig. 7. *A*: overall correlation between CO measurements by NICOM and CPB pump with large variation imposed in all animals at 2 different blood temperatures. *B*: correlation between changes (Δ) in CO imposed by CPB and those measured by NICOM. Points are means ± SD derived from data at both blood temperatures and all animals. Line of regression: $y = 1.06x - 0.03$ ($r = 0.88$).

and recently the use for hemodynamic monitoring has been increasingly criticized because of its uncertain risk-benefit ratio and cost (15). As a result, there is a continuing search for a method of CO measurement that is less invasive than its predecessors. In this respect, impedance cardiography, which calculates SV and CO from changes in the instantaneous mean resistance (i.e., impedance) of a small electrical current transferred through the body, has received much attention in the last four decades because it is noninvasive, easy to use, and adapted for continuous monitoring of CO and related parameters (16).

To investigate the validity of thoracic bioimpedance, numerous studies have compared the results obtained from thoracic bioimpedance with values obtained from reference methods in different research settings. Some studies have reported very good correlations (6), while others have reported relatively poor correlations (8). In contrast, the NICOM system uses an approach based on bioreactance to estimate CO. This bioreactance approach is based on an analysis of relative phase shifts of oscillating currents that occur when this current traverses the thoracic cavity as opposed to the traditional bioimpedance, which relies only on the measured changes in signal amplitude. Use of amplitude is theoretically a suboptimal approach com-

Table 1. *Patient characteristics*

Parameters	Mean ± SD	Maximum Value	Minimum Value
Age, yr	65±13	82	38
Weight, kg	78±12	99	53
Height, cm	169±8	180	153
CO from NICOM, l/min	5.17±1.14	7.83	2.36
CO from SGC, l/min	5.18±1.15	7.83	2.52

Number of patients = 21 men, 6 women. CO, cardiac output; SGC, Swan-Ganz catheter.

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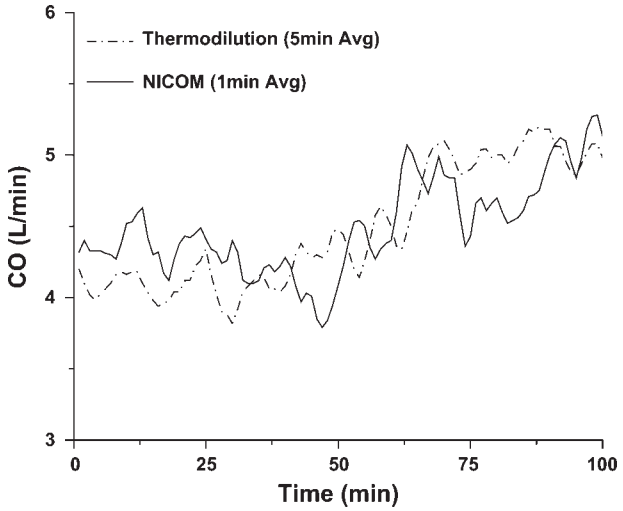

Fig. 8. Simultaneous CO monitoring from the NICOM system (1-min running time average) and continuous thermodilution from the Swan-Ganz catheter (5-min running time average) from a patient during a 100-min period of time when there was ~1 l/min increase in mean CO. Trends in NICOM nicely track those of the thermodilution technique.

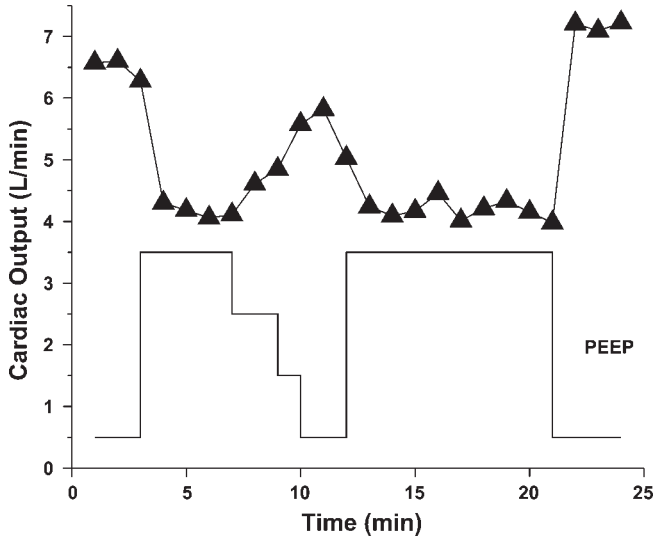

Fig. 10. Recording of NICOM in an intubated patient during an episode of positive end-expiratory pressure (PEEP) showing the responsiveness of the NICOM system to an intervention that reduces CO. The results of the continuous-output thermodilution system showed much less variation, owing to the long filtering time (5 min) used in that system (data not shown).

pared with phase shift-related changes because it is impacted more by patient movement, variable environment, humidity, and sticker location and is patient dependent. Unlike bioimpedance technologies, NICOM offers the theoretical advantages of little to no performance variability related to interpatient body variance and electrode positioning.

No major adverse events were observed in the animals or human subjects throughout the course of the study when the NICOM system was used. This can be expected, because the system is noninvasive in nature. The event-free experiments thus point to the safety of the NICOM device. The preliminary right heart bypass study in animals provided consistent results, allowing comparison tests to be performed. The NICOM system provided very good correlation with the preset CPB pump. Moreover, the NICOM system showed comparable performance with both small and large abrupt increments in CO.

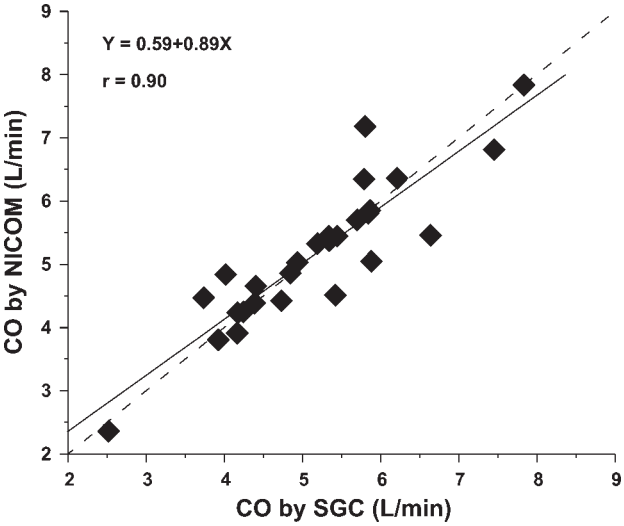

Fig. 9. Correlation between mean values of CO measured from the NICOM system and thermodilution in 27 postoperative patients.

Importantly, there was no variation in the correlation of the NICOM system with the preset CPB at either temperature.

Limitations. Like several other noninvasive techniques, noninvasive CO measurement is based on the assumption that the area under the flow pulse is proportional to the product of peak flow and VET. However, there may be situations, especially during periods of low flow, in which this assumption may not be valid. A second limitation is that in the animal studies using right heart bypass, great cardiac vein and azygous vein flows are left intact. The flow through these structures are not controlled, so that the correlation between pump flow and NICOM estimates of CO do not account for these, which combined amount to a small percentage of the total flow. Finally, for the clinical studies, SGC was taken as a gold standard in the clinical study because it is the best available reference for continuous CO monitoring (4, 7, 10, 12). Our interest was comparing the NICOM system with an automatic and continuous monitoring tool. In this regard, the data show that there is good correlation between NICOM- and SGC-derived measurements of CO. However, thermodilution technique may not actually provide an accurate value for comparison.

Conclusions. The results of this study show the feasibility of using a bioreactance-based system for noninvasive measurement of CO. The system is safe and can work in challenging environments where there is a lot of electrical noise. Further testing and validation of this approach is required to support use of the system in the clinic. In particular, the theoretical claims of improved accuracy and less susceptibility to ambient factors and patient physical characteristics require testing in a relatively large number of patients. In addition, derivation and validation of an algorithm for assigning a patient-specific proportionality constant (for *Eq. 1*) will be important for broad clinical applicability. If this is not possible, this technique might only be useful as a qualitative index of changes in CO. The current feasibility study shows that the first-generation

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device can perform well in open-chest animals in a laboratory setting and in humans in the ICU, which is very encouraging.

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DISCLOSURES

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