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Minimally Invasive Determination of Cardiac Output by Transthoracic Bioimpedance, Partial Carbon Dioxide Rebreathing, and Transesophageal Doppler Echocardiography in Beagle Dogs

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(Received 9 May 2006/Accepted 28 September 2006)

ABSTRACT. Minimally invasive cardiac output was determined using transthoracic bioimpedance (BICO), partial carbon dioxide rebreathing (NICO) and transesophageal Doppler echocardiography (TEECO) and compared to thermodilution (TDCO) in 6 beagle dogs. The dogs were 2 years old, weigh between 9.1–13.0 kg and were anesthetized with nitrous oxide-oxygen-sevoflurane. All dogs were administered a neuromuscular blocking drug and artificially ventilated during anesthesia. Thirty paired measurements of TDCO and each non-invasive method were collected during low, intermediate, and high values of cardiac output achieved by varying the depth of anesthesia and the administration of dobutamine. Cardiac output values ranged from 1.10–2.50 L/min for BICO compared to 0.81–4.88 L/min for TDCO; 0.70–2.60 L/min for NICO compared to 0.89–4.45 L/min for TDCO; and 0.59–4.37 L/min for TEECO compared to 0.57–4.15 L/min for TDCO. The limits of agreement and percentage error were –0.58 ± 1.56 L/min and ± 75.4% for BICO, –1.04 ± 1.08 L/min and ± 56.0% for NICO, and 0.03 ± 0.26 L/min and ± 12.3% for TEECO compared to TDCO. In conclusion, TEECO provided the best agreement to TDCO in sevoflurane anesthetized beagle dogs.

KEY WORDS: beagle dog, cardiac output, minimally invasive measurement.

J. Vet. Med. Sci. 69(1): 43–47, 2007

Maintaining optimal cardiac output (CO) during general anesthesia is an important goal for intraoperative hemodynamic management and therefore for favorable patient outcome. However, most methods for determining CO have limited application in veterinary clinical practice due to the invasive techniques required. The development of non-invasive or minimally invasive measuring methods may provide a potential solution to this problem.

Recently, transthoracic bioimpedance, partial carbon dioxide (CO_2) rebreathing and transesophageal Doppler echocardiography methods, which are non-invasive or minimally invasive techniques, have been used for determining CO in humans [11,15,20]. In addition, transthoracic bioimpedance and partial CO_2 rebreathing methods have a technical advantage because they do not rely on operator skill [12, 18]. These three non-invasive or minimally invasive measuring methods have been also reported in dogs [8, 21, 22]. However, the accuracy of these techniques has not been evaluated in middle size dogs.

We designed a study to compare CO values obtained by the transthoracic bioimpedance method (BICO), partial CO_2 rebreathing method (NICO) or transesophageal Doppler echocardiography (TEECO) method and standard thermodilution method (TDCO) in anesthetized beagle dogs.

MATERIALS AND METHODS

Experimental animals: Six beagle dogs aged 2 years, weighing 9.1–13.0 kg were used for the study and cared for according to the principles of the "Guide for the Care and Use of Laboratory Animals" prepared by Rakuno Gakuen University. The dogs were judged to be in good to excellent health based upon physical examination, hemogram and an electrocardiogram. Food and water were withheld from dogs for 12 hr before the experiment. The dogs were anesthetized for comparison of CO measurements between one of the three non-invasive or minimally invasive measuring methods (BICO, NICO or TEECO) and the standard thermodilution method (TDCO). Each dog was anesthetized three times at 28 days intervals for the comparisons.

Anesthesia and instrumentation: All dogs were intravenously (IV) administered 0.3 mg/kg of midazolam (Midazolam Injection 0.5% [F], Fuji Pharmaceutical Co., Tokyo, Japan) and 0.1 mg/kg of butorphanol (Vetorphale, Meiji Seika Co., Tokyo, Japan) through a 22-gauge catheter (Happycath Z, Medikit Co., Tokyo, Japan) placed in the left cephalic vein. All dogs were anesthetized with ketamine (Ketalar 50, Sankyo Co., Tokyo, Japan; 5 mg/kg, IV), orotracheally intubated, and connected to an anesthetic machine (ACOMA BLANDA-STD, Acoma Medical Industry Co., Tokyo, Japan), which delivered sevoflurane (Sevofrane, Maruishi Pharmaceutical Co., Tokyo, Japan) in nitrous oxide (1 L/min) and oxygen (1 L/min). The dogs were paralyzed with pancuronium (Mioblock, Sankyo Co.; 0.06 mg/kg IV and repeated as needed) and mechanically ventilated. Respiratory rate and inspiratory and expiratory ratio were set at 12 breaths/min and 1:2, respectively. Tidal volume was adjusted to maintain end-tidal carbon dioxide tension

($PETCO_2$) between 35–38 mmHg. All dogs received lactated Ringer's solution (Solulact, Terumo, Tokyo, Japan) at a rate of 10 m*l*/kg/hr intravenously during anesthesia.

Each dog was positioned in the right lateral recumbency. A 6-french catheter introducer (Catheter Introducer, Medikit Co.) was transcutaneously placed in the left jugular vein. A 5-french thermodilution catheter (TC-504, Nihon Koden Co., Tokyo, Japan) was advanced into the pulmonary artery through the introducer. Respiratory gases were continuously sampled from the endtracheal tube to determine the end-tidal concentration of sevoflurane (ETSEV) and $PETCO_2$ with an anesthetic gas monitor (Capnomac Ultima, Datex, Helsinki, Finland). Anesthesia was maintained with sevoflurane at 2.2 % of ETSEV during instrumentation.

Experimental protocol: After the animals were stabilized, CO was measured by BICO, NICO or TEECO as base line values. CO was also measured by TDCO just after the measurements by BICO, NICO or TEECO to compare with those obtained by minimally invasive methods. After the collection of baseline data, high value of CO was obtained by administration of dobutamine (Dobutrex, Shionogi, Osaka, Japan) at doses of 3 and 10 μg/kg/min. Fifteen min after the start of dubutamine infusion at 3 μg/kg/min, CO measurements by BICO, NICO, or TEECO and TDCO were repeated and then the dose of dobutamine was increased to 10 μg/kg/min. CO measurements were repeated in a same manner as described above. After the cessation of dobutamine infusion and the anesthesia was maintained at 2.2% ETSEV for 1 hr, ETSEV was maintained at 3.3% to obtain intermediate value of CO. Anesthesia was maintained for 15 min and then CO measurements were repeated in a same manner. Low value of CO was also obtained during anesthesia maintained at 5.0% of ETSEV. Thirty data sets were obtained from 6 dogs to compare each minimally invasive technique (BICO, NICO, TEECO) and TDCO.

CO measuring techniques: BICO was obtained by an impedance cardiography (ICG) using a monitoring system (Solar 8000M, GE Marquette Medical Systems Japan, Ltd., Tokyo, Japan) and an ICG module (BioZ ICG Module, GE Marquette Medical Systems Japan) during controlled ventilation. A tetrapolar system of electrodes placed on the ventral midline at the level of 6th cervical vertebrae, upper abdomen caudal to the xiphoid process, the dorsal midline at the level of 6th cervical vertebrae and on the back at the level of 13th thoracic vertebrae, was adopted in this system and outer electrodes inject a constant high-frequency, very-low-magnitude current while inner electrodes sense the voltage and measure electrical resistance. BICO (L/min) was calculated using an algorithm (ZMARC algorism, GE Marquette Medical Systems Japan) specifically designed for bioimpendence determination of CO in human.

NICO was obtained using a NICO monitor ($NICO_2$, Novametrix Medical Systems Inc., Walling-ford, U.S.A.). NICO sensor (Novametrix Medical Systems Inc.) for tidal volume 150–450 m*l* was connected between the endotracheal tube and Y-piece. The CO_2 elimination rate (VCO_2) and end-tidal CO_2 ($ETCO_2$) were measured during normal controlled ventilation for 60 sec. Then, VCO_2 and $ETCO_2$ during rebreathing for 50 sec were measured and changes in VCO_2 (ΔVCO_2) and $ETCO_2$ ($\Delta ETCO_2$) were obtained. NICO (L/min) was calculated as: $NICO=\Delta VCO_2 / \Delta ETCO_2$.

TEECO was obtained with a 5.0 Hz multiplane transesophageal probe (PEF-510MA, Toshiba Medical Supply Co., Tokyo, Japan) and a digital echo system (Nemio 35, Toshiba Medical Supply Co.). The transesophageal probe was advanced into the esophagus through the mouth to the level of the left ventricle. Two-dimensional echocardiogram of the left ventriclar (LV) out flow tract was imaged through the esophagus. The time-velocity integral (TVI) at the ascending aorta was estimated by pulsed-wave Doppler echocardiography during expiration. The cross sectional area of the ascending aorta (Flow Area) was estimated on the two-dimensional LV out flow tract view and TEECO (L/min) calculated as: TEECO= Flow Area × TVI × Heart Rate.

TDCO was obtained by injection of 3 m*l* iced 5% dextrose (Terumo) into the right atrium through the thermodilution catheter. Temperature change was detected by the thermo-sensor placed in the pumonary artery and CO value was calculated using an anesthetic monitoring system (DS-5300, Fukuda Denshi Co., Tokyo, Japan). CO was measured three times during controlled ventilation and the mean value was used as TDCO (L/min).

Statistical analysis: Data are expressed as the mean ± standard deviation (SD). Differences in overall data, base line data and high, intermediate and low CO data between BICO, NICO or TEECO and TDCO were analyzed by a Wilcoxon signed rank test. Bland-Altman analysis [3] was also used to determine bias and precision between BICO, NICO or TEECO and TDCO. This bias and precision statistics involved plotting the differences between comparative measurements (bias) against the mean values of each pair. The SD of all the individual bias measurements (precision) was calculated and 95% confidence limits drawn (limits of agreement). Using these limits, judgments were made regarding the precision and acceptability of BICO, NICO or TEECO to TDCO. Limits of agreement were defined as bias ± 2 × precision. The ratio of the limits of agreement to mean CO value (percentage error; expressed in %) were calculated as 100 × (± 2 × precision) ÷ overall mean CO between BICO, NICO or TEECO and TDCO [5]. Differences in the limits of agreement and percentage error among BICO, NICO and TEECO were analyzed by a Kruskal-Wallis test. A value of $p<0.05$ was considered significant.

RESULTS

CO values in each comparison ranged from 1.10 to 2.50 L/min for BICO versus 0.81 to 4.88 L/min for TDCO, 0.70 to 2.60 L/min for NICO versus 0.89 to 4.45 L/min for TDCO, and 0.59 to 4.37 L/min for TEECO versus 0.57 to 4.15 L/min for TDCO (Table 1). There were significant differences between TDCO and BICO ($p<0.001$) and between TDCO and NICO ($p<0.001$). BICO was significantly lower

Table 1. Cardiac output values determined by thermodilution (TDCO), transthoracic bioimpedance (BICO), partial CO_2 rebreathing (NICO) and transesophageal echocardiography (TEECO)

	BICO	NICO	TEECO
Overall data (L/min)	1.78 ± 0.36**	1.41 ± 0.47**	2.14 ± 0.92
	(2.36 ± 0.98)	(2.44 ± 0.92)	(2.11 ± 0.89)
Baseline value (L/min)			
2.2% of ETSEV	1.84 ± 0.36	1.27 ± 0.16*	2.08 ± 0.45
	(2.20 ± 0.31)	(2.13 ± 0.30)	(2.09 ± 0.41)
High value (L/min)			
Dobutamine 3 μg/kg/min	1.90 ± 0.34*	1.65 ± 0.23*	2.33 ± 0.45
	(2.51 ± 0.34)	(2.92 ± 0.26)	(2.30 ± 0.50)
Dobutamine 10 μg/kg/min	2.03 ± 0.24*	2.07 ± 0.35*	3.45 ± 0.50
	(3.83 ± 0.74)	(3.69 ± 0.59)	(3.35 ± 0.46)
Intermediate value (L/min)			
3.3% of ETSEV	1.76 ± 0.28*	1.17 ± 0.18*	1.97 ± 0.36
	(2.21 ± 0.26)	(2.28 ± 0.33)	(1.91 ± 0.32)
Low value (L/min)			
5.0% of ETSEV	1.35 ± 0.22*	0.88 ± 0.18*	0.89 ± 0.27
	(1.03 ± 0.14)	(1.20 ± 0.35)	(0.88 ± 0.28)

Data are obtained from 6 dogs and expressed as mean ± standard deviation. Data in the parentheses are TDCO measured simultaneously with each minimally invasive method. Significant difference against TDCO: * $p<0.05$. ** $p<0.01$. ETSEV: end-tidal concentration of sevoflurane.

than TDCO at high and intermediate values of CO ($p=0.028$). On the other hand, BICO was significantly higher than TDCO at low value of CO ($p=0.028$). NICO was significantly lower than TDCO over the entire range of CO ($p=0.027$ or 0.028). TEECO showed no statistical difference from TDCO.

Bland-Altman analysis of BICO, NICO and TEECO compared to TDCO produced differences that ranged from –0.69 to 2.58 L/min for BICO, 0.19 to 2.42 L/min for NICO and –0.38 to 0.35 L/min for TEECO (Fig. 1). The limits of agreement were –0.58 ± 1.56 L/min between BICO and TDCO, –1.04 ± 1.08 L/min between NICO and TDCO and 0.03 ± 0.26 L/min between TEECO and TDCO. The overall mean CO and percentage error were 2.07 L/min and ± 75.4% between BICO and TDCO, 1.93 L/min and ± 56.0% between NICO and TDCO and 2.12 L/min and ± 12.3% between TEECO and TDCO. There were significant differences ($p<0.001$) in limits of agreement and percentage error among BICO, NICO and TEECO.

DISCUSSION

In this study, Bland and Altman analysis was used to determine bias and precision for comparison of BICO, NICO or TEECO to TDCO. This bias and precision statistics has now replaced correlation and regression as the accepted statistical analysis for comparing two techniques measuring the same physiological variable, such as CO [5]. It is recommended that the percentage error between the new and reference technique is less than ± 30 % [5]. In the present study, the percentage error was less than ± 30 % only in TEECO (± 12.3 %). In addition, the comparison of CO values between BICO, NICO or TEECO and TDCO using the Wilcoxon singed rank test showed that CO was underestimated at the intermediate and high values and overestimated at the low value by BICO, and underestimated at all range of values by NICO. Therefore, TEECO is acceptable for determining CO but BICO and NICO are not acceptable in anesthetized beagle dogs.

Transesophageal Doppler echocardiography is increasingly being used as an intraoperative method for assessing cardiac function in humans [4, 6, 14, 16] and horses [24]. In this study, TEECO provided the closest values to TDCO with the narrow limits of agreement and percentage error. TEECO also provides a good agreement with TDCO in horses [24]. On the other hand, the poorer correlation and wider limits of agreement between TEECO and TDCO were reported in humans [4, 6, 14, 16]. Studies conducted in humans usually determine CO using trans-mitral and pulmonary blood flows because of superior alignment with the ultrasound beam from a transesophageal probe. In biped species including humans, the descending aorta runs parallel to the esophagus, therefore it is difficult to align aortic flow and ultrasound from an esophageal transducer. In dogs and other quadrupeds, the anatomical relationship of aorta and esophagus differs from that of humans, and a transducer within the esophagus can be aligned with blood flow in the ascending aorta. Generally, it is accepted that the accuracy in the determination of flow area is major source of error in the determination of CO with the Doppler echocardiography method [9]. The product of TVI and heart rate has been proposed as an accurate and repeatable indicator of CO [13]. It is possible that failure to detect flow area may reflect the poor sensitivity of TEECO determined in humans. This probably explains the reason for obtaining better agreement between TEECO and TDCO in dogs and horses [24]. It is

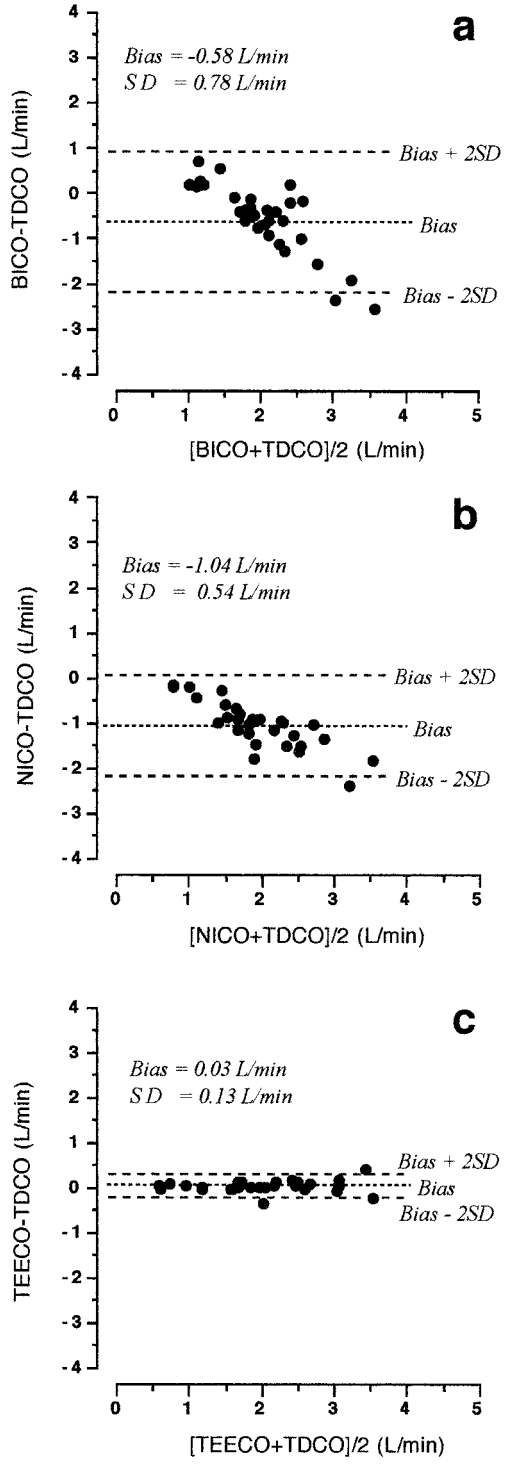

Fig. 1. Bland-Altman analysis. The differences between measurements of cardiac output by thermodilution technique (TDCO) and transthoracic bioimpedance (BICO), partial CO_2 rebreathing (NICO), or transesophageal echocardiography (TEECO) plotted against the average of TDCO and BICO (**a**), TDCO and NICO (**b**), or TDCO and TEECO (**c**).

thought that TEECO is a viable method for monitoring CO in anesthetized dogs. However, further studies are required to determine the effects of diseases, heart diseases, breeds or body size on the accuracy of TEECO in dogs. Unfortunately, it still relies on operator skill to determine CO. In addition, it was reported that the pressure produced by contact between the transesophageal probe and the esophagus was sufficient to cause esophageal damage [23]. Care should be taken to prevent esophageal damage by an experienced operator during TEECO determination.

In our study, the limits of agreement between BICO and TDCO were much larger than acceptable level. BICO uses a low-amplitude, high-frequency alternating signal to calculate electrical impedance through the chest wall [19]. BICO correlated strongly with TDCO in human patients [1, 7, 17, 18]. The limits of agreement between BICO and TDCO were small in human patients suggesting clinical utility [1, 17, 18]. Accurate determination of BICO depends on accurate measurement of left ventricular injection time and instantaneous changes in impedance as a function of time [10]. In the present study, BICO was calculated using an algorithm designed for human. The electrical impedance of thoracic cavity changes with blood flow. This is due to the increase in arterial vessel size with pulsation and the alignment of the red blood cells with blood velocity. Both of these changes increase the electrical conductance of the thoracic cavity and cause a bioimpedance waveform. From this impedance waveform an estimate of cardiac stroke volume can be determined if a thoracic geometrical constant is available [22]. Accurate CO values also depend upon assumptions regarding the patient's shape and ideal body weight [2]. Clearly these and potentially other factors are responsible for the poor limits of agreement in our studies. Further studies are needed to develop an accurate bioimpedance based algorithm for determining CO in dogs.

In the present study, the limits of agreement between NICO and TDCO were large in beagle dogs weighing from 9.1 to 13.0 kg. NICO utilizes a differential CO_2 Fick partial rebreathing method to measure capillary blood flow noninvasively and continuously in mechanically ventilated patients. The device requires minimal operator experience and is not subjected to electromagnetic interference during surgery. Others have suggested that the percentage limits of agreement NICO compared to TDCO was small enough (± 27.4%) to be clinically acceptable in large breed dogs weighing from 18.2 to 39.5 kg [8]. The partial CO_2 rebreathing method underestimated CO over the whole range of CO values compared to TDCO. The CO values were calculated from equation: $NICO=\Delta VCO_2/\Delta ETCO_2$. The underestimation of ΔVCO_2 and/or overestimation of $\Delta ETCO_2$ may provide a potential explanation in our dogs. The NICO sensor assembly consists of a rebreathing valve with large bore tubing (rebreathing loop) and a combination CO_2/flow sensor. The flow through the valve during rebreathing is diverted through the rebreathing loop. The rebreathing valve has a dead space of 32 m*l* in normal ventilation (non-rebreathing) [11]. This dead space is low

enough to achieve accurate CO estimation in large breed dogs with big tidal volume. On the other hand, it might be responsible for lowered VCO_2 and $PETCO_2$ determined during normal controlled ventilation in our dogs with smaller tidal volume. As a result, underestimation of ΔVCO_2 and overestimated $\Delta ETCO_2$ might be induced. Our data show that NICO does not provide an accurate determination of CO in smaller dogs. The application of NICO to anesthetic monitoring should be limited to large breed dogs with big tidal volume to obtain accurate information of CO.

In conclusion, TEECO is a viable minimally invasive method for determining CO in sevoflurane anesthetized beagle dogs, while BICO and NICO do not provide accurate determination of CO in these dogs.

ACKNOWLEDGEMENTS. This research was partially supported by a Grant-in-Aid for Cooperative Research 2004-9 from Rakuno Gakuen University 2004 and Grants-in-Aid for Scientific Research 16580267 from the Japan Society for the Promotion of Science to K.Y.

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