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Impedance Cardiography for Cardiac Output Estimation

— Reliability of Wrist-to-Ankle Electrode Configuration —

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Background Non-invasive measurement of cardiac output (CO) may become an important modality for the treatment of heart failure. Among the several methods proposed, impedance cardiography (ICG) has gained particular attention. There are 2 basic technologies of ICG: thoracic and whole-body ICG whereby the electrodes are applied either to the chest or to the limbs. The present study is aimed to test the effectiveness of the Non-Invasive Cardiac System (NICaS), a new ICG device working with a wrist-to-ankle configuration.
Methods and Results To evaluate the reliability of NICaS derived CO (NI-CO), 50 CO measurements were taken simultaneously with thermodilution (TD-CO) and modified Fick (Fick-CO) in 35 cardiac patients, with the TD-CO serving as the gold-standard for the evaluation. Overall, 2-tailed Pearson's correlation and Bland-Altman limits of agreement between NI-CO and TD-CO were r=0.91 and –1.06 and 0.68 L/min and between Fick-CO and TD-CO, r=0.80 and –1.52 and 0.88 L/min, respectively. Good correlation was observed in patients with loading conditions altered by nitroglycerin and also in patients with moderate valvular diseases.
Conclusion Agreement between NI-CO and TD-CO is within the boundaries of the FDA guidelines of bio-equivalence. NI-CO is applicable for non-invasive assessment of cardiac function. (*Circ J* 2006; **70:** 1164 – 1168)

Key Words: Cardiac output; Impedance cardiography; Thermodilution method

Several studies suggest the importance of cardiac power output calculation, which is derived from cardiac output (CO) and mean blood pressure, to predict the prognosis in heart failure patients not only in hospital but also in the outpatient setting[1–3] CO measured by the thermodilution method with a Swan-Ganz catheter placed in the pulmonary artery has become one of the most widely accepted and used methods of monitor cardiac function, despite its certain limitations[1,3,4] A noninvasive and low cost method for measuring CO would be relevant for the widespread clinical use of cardiac power output.

Some noninvasive techniques of measuring CO have been proposed over the past years. The indirect Fick method of re-breathing carbon dioxide[5,6] and Doppler flow measurement of the left ventricular outflow tract have been shown to be accurate;[7] however, their applications require expensive equipments and trained operators. Other promising results have been observed with devices based on electrical bioimpedance technology[8] and 2 basic technologies of impedance cardiography (ICG) are currently in use. The first is called whole-body ICG[9,10] (ICGWB), which was introduced in 1948;[11] in which the electrodes are placed on the distal portion of the limbs. The second one is thoracic ICG (ICGT), which was introduced in 1964, and the electrodes are placed on the root of the neck and on the lower chest. When the CO is measured in subjects with healthy hearts, the results from both these technologies are usually reliable, but the reliability of CO measurements taken by ICGT is compromised in patients with cardiac diseases[12–16] According to the Food and Drug Administration (FDA) standard of bio-equivalence,[17] the disparity between 2 tech-

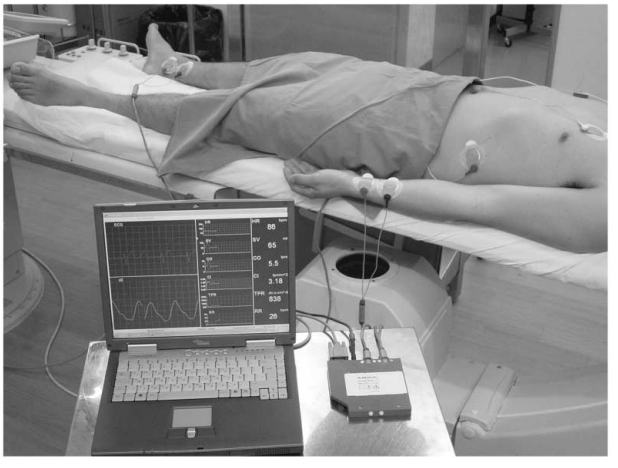

Fig 1. Schema of Non-Invasive Cardiac System, showing the impedance box, which is connected to the patient via proprietary electrodes and the computer that interprets the collected data. Three electrodes are applied to patient's chest for the ECG monitor. One pair of impedance electrodes is applied to the left wrist and another pair to the right ankle (tetra polar mode).

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Table 1 Statistical Analysis of CO Measurements Performed by NI-CO and Indirect Fick-CO Compared With TD-CO

	All measurements in 35 patients (n=50)					*Measurements after NTG injection (n=15)*				
	NI-CO vs TD-CO	*Fick-CO vs TD-CO*	*TD-CO*	*NI-CO*	*Fick-CO*	*NI-CO vs TD-CO*	*Fick-CO vs TD-CO*	*TD-CO*	*NI-CO*	*Fick-CO*
Correlation	*0.91*[1a]	*0.80*[1b]				*0.96*[2a]	*0.82*[2b]			
Bias (L/min)	*–0.18*	*–0.32*				*–0.15*	*–0.34*			
SD (L/min)	*0.43*	*0.60*				*0.50*	*0.69*			
Lower level of agreement (L/min)	*–1.06*	*–1.52*				*–1.16*	*–1.73*			
Upper level of agreement (L/min)	*0.68*	*0.88*				*0.85*	*1.04*			
Average CO±SD (L/min)			*4.18±1.01*	*4.36±1.03*	*4.05±0.89*			*3.59±0.76*	*3.85±0.85*	*3.67±0.79*

Values are mean±SD. Correlation was calculated using Pearson's 2-tailed test.
[1a]p<0.0001, [1b]p<0.0001, [2a]p<0.0001, [2b]p=0.0001.
CO, cardiac output; NI-CO, Non-Invasive Cardiac System derived CO; Fick-CO, modified Fick derived CO; TD-CO, thermodilution-derived CO; NTG, nitroglycerine.

nologies should not exceed the range of 20%. The purpose of this study was to evaluate the reliability and feasibility of the new Non-Invasive Cardiac System (NICaS: NI Medical, Hod-Hasharon, Israel), which calculates the CO by measuring ICG in a tetra polar mode, derived from electrodes placed on one wrist and the contra-lateral ankle (Fig 1).

Methods

The Trial

This study prospectively enrolled 35 patients. The thermodilution-derived CO (TD-CO) was measured using a Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA), followed immediately by the modified Fick (Fick-CO) and with the NICaS (NI-CO). In 15 subjects, a second round of CO measurements was carried out using the 3 technologies after 2–4 mg nitroglycerin injection into the arteries. Thus, a total of 50 comparative CO measurements were performed. The Institutional Ethics Committee of the Kobe University Hospital approved the study protocol and all patients gave their consent.

Patient Selection and Exclusion Criteria

All cardiac disease patients who were scheduled for routine right heart catheterization or emergency procedures that required the deployment of a Swan Ganz catheter for continuous cardiac function monitoring were eligible for the study, unless they fulfilled one of the exclusion criteria.

The exclusion criteria for the NI-CO measurements included: restlessness and/or chaotic patient condition, severe aortic valve regurgitation and/or aortic stenosis, aortic aneurysm, heart rate above 130 beats/min, intra- and extracardiac shunts, severe peripheral vascular disease, severe pitting edema, sepsis and dialysis, all of which interfere with the proper measurements of impedance derived stroke volume[4]

The study population comprised 35 patients (17 men, 18 women, mean age 65.5±13.7 years). In most patients there was coexistence of multiple underlying heart diseases, including hypertension (n=15), diabetes mellitus (n=13), coronary artery disease (n=21) and idiopathic dilated cardiomyopathy (n=3). Twelve patients presented with congestive heart failure (CHF) and 4 patients had atrial fibrillation when CO was measured. In addition, our study subjects included 7 cases of moderate degree of valve regurgitation (aortic regurgitation 2 cases, mitral regurgitation 4 cases, mild tricuspid regurgitation 1 case) and 7 cases of moderate aortic valve stenosis.

Measuring CO

All operators were unaware of the CO results obtained by the various measuring techniques.

TD-CO Right heart catheterization using a 6 or 8Fr Swan-Ganz catheter was performed according to the standard institutional protocol. The catheter was advanced to the pulmonary artery under fluoroscopic guidance and verified with the pressure waveforms registered on the polygraph. TD-CO was measured 5 times by injecting 5 ml bolus of iced 9% saline solution at the same rate. Thereafter, the 3 results of the saline injections that were within 15% of their extreme disparity were averaged for the TD-CO result.

Fick-CO For arterial oxygen saturation, blood samples were obtained from the arterial access sheath, and for venous oxygen saturation, blood samples were withdrawn using the distal edge lumen of the Swan-Ganz catheter placed in the pulmonary artery. All samples were immediately measured for oxygen saturation using the same device (Radiometer ABL 715, Copenhagen, Denmark).

NI-CO To measure the CO with the NICaS apparatus, an alternating electrical current of 1.4 mA with a 30 kHz frequency is passed through the patient via 2 pairs of tetrapolar electrodes, one pair placed on the wrist above the radial pulse, and the other pair on the contralateral ankle above the posterior tibialis arterial pulse. If the arterial pulses in the legs are either absent or of poor quality, the second pair of electrodes is placed on the contralateral wrist. The NICaS apparatus calculates the stroke volume by Frinerman's formula:[18]

$$\text{Stroke volume} = dR/R \times \rho \times L^2/Ri \times (\alpha+\beta)/\beta \times KW \times HF$$

where dR is the impedance change, R is the basal resistance, ρ is the blood electrical resistivity, L is the patient's height, Ri is the corrected basal resistance according to gender and age;[18–23] KW is a correction of weight according to ideal values;[19–24] HF is the hydration factor, which takes into account the body water composition;[21] and $\alpha+\beta$ is equal to the ECG R–R wave interval, and β is the diastolic time interval.

Because the NI-CO results are calculated every 20 s, the average of 3 measurements obtained consecutively during 60 s of monitoring was considered to be the NI-CO value for each individual case.

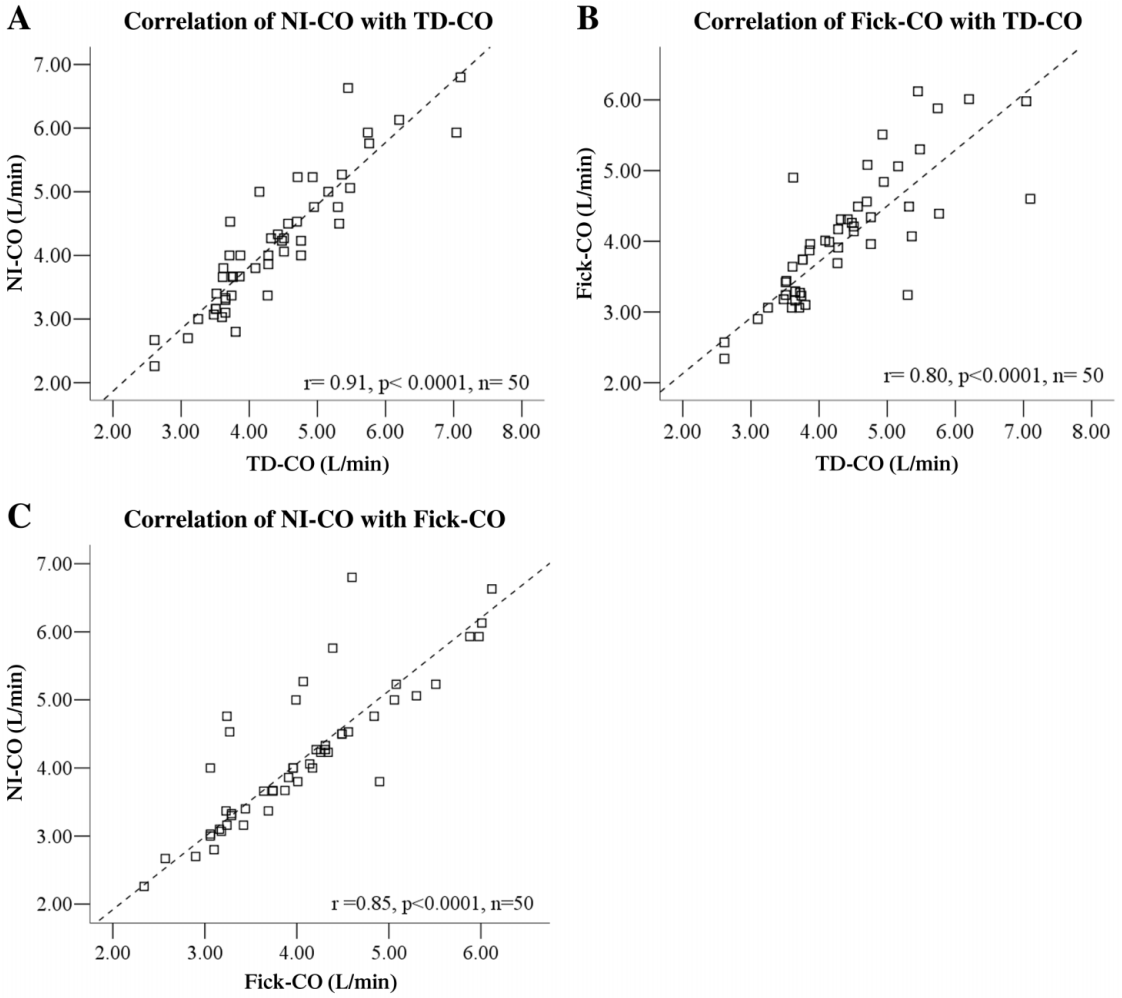

Fig 2. Scatter plots of cardiac output (CO) showing the correlation between Non-Invasive Cardiac System (NICaS) derived CO (NI-CO) with thermodilution-derived CO (TD-CO) [A]; modified Fick derived CO (Fick-CO) with TD-CO [B] and NI-CO with Fick-CO [C]. The 2-tailed Pearson's correlation test (r) was used for the analyses.

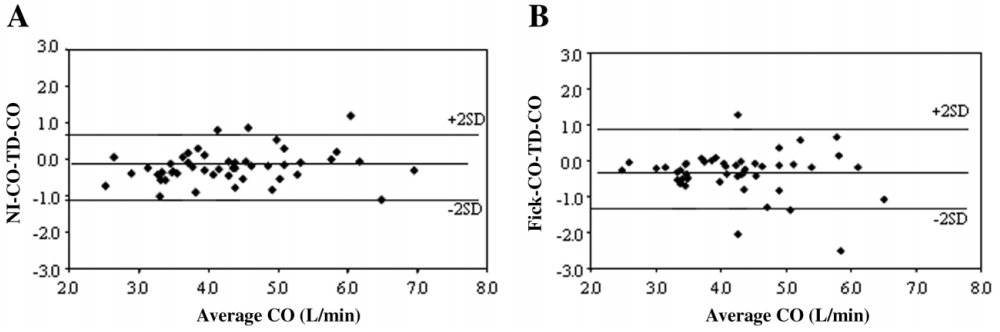

Fig 3. [A] Bland-Altman scatter plot of difference against average of cardiac output (CO) results measured by Non-Invasive Cardiac System (NICaS) and thermodilution method. [B] Bland-Altman scatter plot of difference against average of CO results measured by the modified Fick and thermodilution methods. NI-CO, NICaS derived CO; TD-CO, thermodilution-derived CO; Fick-CO, modified Fick derived CO.

Statistical Analysis

The quantitative data are expressed as mean ± SD. For descriptive statistic, Student's t-test was used. To compare the results of NI-CO, Fick-CO and TD-CO, 2-tailed Pearson's correlation and the Bland-Altman[25] limits of agreement were used. The gold-standard for determining accuracy of the results was the TD-CO. Values of $p<0.05$ were considered to be significant.

Results

The average values of CO in the study subjects for TD-CO, NI-CO and Fick-CO were 4.18±1.01 L/min, 4.36±1.03 L/min, and 4.05±0.89 L/min, respectively. There were

no significant differences between the 3 groups (Table 1). The overall results of the Pearson correlation analysis were as follows: NI-CO vs TD-CO: r=0.91, p<0.0001; Fick-CO vs TD-CO: r=0.80, p<0.0001 and NI-CO vs Fick-CO: r=0.85, p<0.0001 (Fig 2). The Bland-Altman 2-standard deviation limit of agreement between the NI-CO and TD-CO was ±0.87 (–1.06 and 0.68) L/min, and the agreement between the Fick-CO and TD-CO was ±1.20 (–1.52 and 0.88) L/min (Fig 3). The calculated percentage of disparity between the NI-CO and TD-CO would thus be 19.95% (0.87 L/min ÷ 4.36 L/min), which was less than that between Fick-CO and TD-CO (29.63% [1.20 L/min ÷ 4.05 L/min]). Nevertheless, there are 3 cases in this series in which the disparity between the NI-CO and TD-CO was greater than 20%, indicating that the disparity here is not equal, but close to FDA bio-equivalence (Note that the mathematical model of the FDA for determining bio-equivalence was not used here. Yet the simple model of limits of agreement, which was used, offers an acceptable appraisal of the good interrelationships between the 2 statistical approaches).

When we analyzed the subgroup of measurements before and after nitroglycerine injection to alter vascular resistance, identical changes in CO were observed with the NI-CO and TD-CO (TD-CO: 4.42±1.00 L/min → 3.59±0.76 L/min, NI-CO: 4.07±1.07 L/min → 3.85±0.85 L/min (Fig 4)). The relation between NI-CO and TD-CO after nitroglycerine injection was r=0.96, p<0.0001, n=15. All other statistical details are summarized in Table 1.

In the other subgroups of moderate degree of valvular regurgitation (n=7) and aortic valve stenosis (n=7), the correlation of NI-CO with TD-CO was r=0.92, p<0.0001, with a lower limit of agreement of –0.97 L/min and upper limit of agreement of 0.73 L/min.

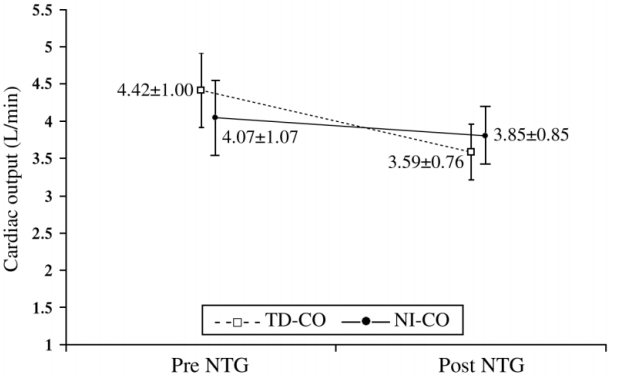

Fig 4. Changes in cardiac output in 15 patients with repeated measurements, pre and post nitroglycerine (NTG) administration. The graph compares the results obtained by Non-Invasive Cardiac System derived cardiac output (NI-CO) and thermodilution-derived cardiac output (TD-CO). Values are mean ± SD.

Discussion

According to Bland and Altman[26] and Raaijmakers et al,[15] when averages of repeated measurement results are used to compare the performance of a new medical device with a gold-standard, there is an overestimation of the correlation coefficient. In the present investigation the preferable single measurement design was used; namely, each test consisted of a TD-CO measurement, followed immediately by a NI-CO and a Fick-CO measurement. In 20 patients, only 1 study was performed, whereas in the remaining 15 patients 2 studies were done: before and after nitroglycerine injection. However, each of the second tests was conducted in the manner of an independent comparative measurement.

According to the definition of the FDA, if there is bio-equivalence between the gold-standard and a new technology, all the comparative results should be within a range of 20% disparity. Previous studies reported limits of agreement between ICG$_T$-CO vs TD-CO of –2.2 to 2.2 L/min at best;[27–29] ICG$_{WB}$-CO (JR Medical-Tallinn, Estonia) vs TD-CO of –1.37 to 1.87 L/min;[10] and bipolar NI-CO vs TD-CO of –1.25 to 1.30 L/min (Table 2).[4] Based on these reports, it can be calculated that the disparity between ICG$_T$-CO, ICG$_{WB}$-CO, bipolar NI-CO vs TD-CO is 40%, 32.4% and 26%, respectively. Our result for tetra polar NI-CO vs TD-CO (–1.06 to 0.68 L/min, disparity 20%) is better than those results. The reason for the better result with NICaS may be related to the most upgraded calculation formula.

An important fringe benefit of this trial is the data produced by the Fick-CO technology. This method, which enjoys increasing popularity among practical cardiologists, is still considered controversial.[30] According to the present results, the limits of agreement between Fick-CO and TD-CO are –1.52 and 0.88 L/min (average ±1.20 L/min). In the presence of a mean Fick-CO of 4.05 L/min, the disparity between the 2 technologies is 30%, better than that of ICG$_T$ but inferior to that of NI-CO.

Among the established exclusion criteria related to the use of the NICaS are: severe aortic stenosis, in which the NI-CO is usually underestimated, and significant aortic regurgitation, in which the NI-CO tends to be overestimated. In the present trial, however, 7 cases of moderate aortic stenosis and 2 with mild–moderate aortic regurgitation were involved, indicating that NICaS is applicable in cases of mild to moderate aortic valve disease.

From the 15 measurements that were obtained after nitroglycerine injection, we observed a decrease in the mean CO

Table 2 Summary of Previous Reports of the Accuracy of CO Measurements by ICG (ICG$_T$-CO, ICG$_{WB}$-CO, and NI-CO vs TD-CO)

Authors	*Method*	*Condition*	*Year published*	*Limits of agreement between ICG and TD (L/min)*
Drazner M, et al[27]	*ICG$_T$*	*CHF*	*2002*	*–2.2 to 2.2*
Van De Water JM, et al[28]	*ICG$_T$*	*CABG*	*2003*	*–2.36 to 1.99*
Leslie S J, et al[29]	*ICG$_T$*	*CHF*	*2004*	*–2.2 to 2.2*
Koobi T, et al[10]	*ICG$_{WB}$*	*CABG*	*1997*	*–1.37 to 1.87*
Cotter G, et al[4]	*ICG$_{NICaS}$ Bipolar*	*CABG, CHF*	*2004*	*1.25 to 1.30*

Values are mean. ICG, impedance cardiography; ICG$_T$, thoracic ICG; ICG$_{WB}$, whole-body ICG; TD, thermodilution; CHF, congestive heart failure; CABG, coronary artery bypass graft; ICG$_{NICaS}$, Non-Invasive Cardiac System ICG. Other abbreviations as in Table 1.

levels. However, the accuracy of the results remained unaltered in NI-CO, which suggests that NICaS is also applicable even when the arterial resistance has changed.

Clinical Implications

Recent studies have shown that the calculation of cardiac power output (CO×mean arterial pressure) and systemic vascular resistance are important for the management of various cardiac diseases[1–3] Cardiac power output was found to be the strongest independent predictor of in-hospital mortality in patients admitted with cardiogenic shock[2] and is an important tool for assessing the clinical response to drug therapy. In addition, there is enough evidence that ambulatory monitoring of cardiac power would benefit patients with CHF, resulting in better titration of medication and possibly less readmission to hospital. By introducing NICaS apparatus, wide-spread clinical use of cardiac power calculation would become feasible.

Conclusion and Limitations of NICaS

The present study indicates that NICaS performs at least as accurately as the thermodilution method. However, the reliability of the NICaS method depends on an alignment with exclusion criteria. This allows for the use of NICaS in approximately 80–85% of patients needing the examination.

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