

Whole Body Bioimpedance Monitoring for Outpatient Chronic Heart Failure Follow up

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Background: Although cardiac output index (CI), stroke volume index (SVI), and total systemic vascular resistance (TSVR) are important hemodynamic parameters for the prognosis of chronic heart failure (CHF), they are difficult to measure in an outpatient setting. Whole body bioimpedance monitoring using a Non-Invasive Cardiac System (NICaS) allows for easy, non-invasive estimation of these parameters. Here, whether NICaS-derived hemodynamic parameters are clinically significant was investigated by relating them to other conventional cardiovascular functional indices, and by evaluating their predictive accuracy for CHF readmission.

Methods and Results: Study subjects of 68 patients with CHF were enrolled in the study immediately upon discharge from the hospital. NICaS-derived CI, -SVI, and -TSVR values obtained at an outpatient clinic were significantly related with left ventricular ejection fraction (LVEF) measured by echocardiography, serum B-type natriuretic peptide (BNP), and exercise tolerance. During the 100±98 days follow-up, 15 patients were readmitted to our hospital for CHF recurrence. Multivariate analysis indicated that LVEF, NICaS-derived CI, NICaS-derived SVI, and plasma BNP were significant indicators (receiver operating characteristic curve cut-off point, LVEF: 37%, NICaS-derived CI: 2.49L·min⁻¹·m⁻², NICaS-derived SVI: 27.2 ml/m², plasma BNP: 344 pg/ml) for readmission.

Conclusions: Hemodynamic parameters derived by NICaS are applicable for the non-invasive assessment of cardiac function in outpatient CHF follow up. (Circ J 2009; 73: 1074–1079)

Key Words: Bioimpedance; Cardiac output; Congestive heart failure; Non-invasive cardiac monitoring system; Prediction of readmission

The growing geriatric population and increased number of survivors of acute heart failure have dramatically increased the number of outpatients with chronic heart failure (CHF)^{1–2} Hemodynamic parameters, such as stroke volume (SV), cardiac output (CO), total systemic vascular resistance (TSVR), and plasma level of B-type natriuretic peptide (BNP) are thought to be important for predicting the long-term prognosis and guiding the optimal treatment of CHF^{3–5} Until recently, hemodynamic parameters could only be obtained using the invasive thermodilution method with a Swan–Ganz catheter placed in the pulmonary artery. A non-invasive and low-cost method for measuring hemodynamic parameters would be useful for the clinical assessment of CHF in an outpatient setting.

Several non-invasive technologies for measuring hemodynamics are now available. Non-Invasive Cardiac System (NICaS) (NI Medical; Hod-Hasharon, Israel) is a new device for calculating SV, CO, and TSVR utilizing whole body bioimpedance cardiography with electrodes placed on one wrist and on the contralateral ankle. We previously

established that NICaS-derived CO (NI-CO) is a reliable parameter when compared with thermodilution CO or modified Fick CO⁶

The purpose of the present study was to evaluate the feasibility of using NICaS in outpatients with CHF and to assess whether NICaS-derived hemodynamic parameters in CHF are clinically significant by relating them to other conventional cardiovascular functional indices, and to assess the predictive accuracy of NICaS-derived parameters for CHF-related readmission.

Methods

Patient Selection and Exclusion Criteria

In the present study, patients who met the following criteria were enrolled: (1) hospitalized because of acute CHF; (2) had a stable condition after optimal medical therapy including diuretics, vasodilators, ACE-inhibitors; (3) had no renal dysfunction (defined as a creatinine value >2.0 mg/dl); and (4) had no significant severe valve diseases. The cardinal manifestations of heart failure were dyspnea and fatigue caused by cardiac dysfunction.

The study population comprised 68 CHF patients (56 men, 12 women, mean age 64.9±10.8 years); 20 patients were classified as New York Heart Association (NYHA) class I and 48 were NYHA class II patients (Table 1). The Institutional Ethics Committee of the Kobe University Hospital approved the study protocol and all patients provided informed consent to participate in the study.

In most patients, CHF coexisted with multiple underlying heart diseases, as shown in Table 1. Three patients

(Received September 8, 2008; revised manuscript received January 4, 2009; accepted January 20, 2009; released online April 16, 2009)

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Conflict of Interest: none declared.

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had atrial fibrillation when CO was measured. In addition, 20 cases (29.4%) had a moderate degree of mitral valve regurgitation, 7 cases (10.3%) had a moderate degree of aortic valve regurgitation, and 1 case (1.5%) had moderate aortic valve stenosis. The cardiovascular medicines taken by the patients comprised: diuretics (n=44, 68.7%), digitalis (n=7, 10.9%), angiotensin-converting enzyme inhibitors (n=28, 43.7%), angiotensin receptor blockers (n=42, 65.6%), beta blockers (n=53, 82.8%), nitrates (n=8, 12.5%), calcium channel blockers (n=13, 20.3%), and oral inotropic agents (n=10, 15.6%).

The exclusion criteria for the NICaS measurements included restlessness and/or unstable patient condition, severe aortic valve regurgitation and/or aortic stenosis, aortic aneurysm, heart rate above 130 beats/min, intra- and extra-cardiac shunts, severe peripheral vascular disease, severe pitting edema, sepsis, and dialysis, all of which interfere with the accurate measurement of impedance-derived SV⁷ as previously described.

All patients were followed up at the outpatient clinic of the Cardiovascular Division of Kobe University hospital and had no walking disability. We measured the cardiac parameters once the patients' attended the outpatient department, which was the first routine visit to our hospital 1 month after discharge from the hospital for the first heart failure admission. At the same visit, serum BNP levels were measured and a questionnaire about exercise tolerance was administered.

Cardiac Indicators Derived by NICaS

To measure NI-CO, an alternating electrical current of 1.4 mA with a 30 kHz frequency was passed through the patient via 2 pairs of tetrapolar electrodes, 1 pair placed on the wrist above the radial artery, and the other pair placed on the contralateral side above the posterior tibialis artery. If the arterial pulses were either absent or of poor quality, a second pair of electrodes was placed on the contralateral site. The NICaS apparatus calculated the SV using Tsoglin and Frinerman's formula:⁸

$$SV = dR/R \times \rho \times L^2/Ri \times (\alpha + \beta)/\beta \times KW \times HF$$

where dR is the change in impedance, R is the basal resistance, ρ is the blood electrical resistivity, L is the patient height, Ri is the corrected basal resistance according to gender and age,⁸⁻¹² KW is a correction of weight according to ideal values,⁹⁻¹³ HF is a hydration factor that takes into account body water composition,¹¹ $\alpha + \beta$ 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. By using the NI-CO value, the following parameters were calculated: NI-CO index (NI-CI = NI-CO/body surface area), SV index (NI-SVI = NI-CI/heart rate), and TSVR (NI-TSVR = Mean arterial pressure/CO*80 [dyne·s⁻¹·cm⁻⁵]).

Plasma BNP Measurements

Blood samples were obtained from the patient in a resting condition after NICaS measurement. The samples were drawn into plastic syringes, transferred to chilled siliconized disposable tubes containing aprotinin (1,000 kallikrein inactivator in units/ml; Ohkura Pharmaceutical, Kyoto, Japan) and ethylenediaminetetraacetic acid (1 mg/ml), immediately placed on ice, and then centrifuged at -48°C. An aliquot of

Table 1. Patient Characteristics

No. of patients	68
Men	56 (82.4%)
Women	12 (17.6%)
Age (years)	64.9±10.8
NYHA I	20 (29.4%)
NYHA II	48 (70.6%)
Hypertension	8 (11.8%)
Diabetes mellitus	17 (25.0%)
Ischemic heart disease	18 (26.5%)
Dilated cardiomyopathy	28 (41.2%)

NYHA, New York Heart Association classification.

the plasma was immediately frozen at -80°C and thawed only once at the time of the assay, which was performed within 1 week. The plasma BNP concentration was measured using a specific immunoradiometric assay kit (Shionogi Co, Osaka, Japan), as previously reported.¹⁴

Echocardiography Measurement of the Ejection Fraction (EF) and the Ratio of Early-to-Atrial Filling of Transmitral Flow (E/A)

B-mode recordings were obtained with a commercially available instrument (SONOS 5500™; Agilent Technologies Inc, Palo Alto, CA, USA) operating at 2.5 MHz. Two-dimensional imaging examinations were performed in the standard manner from apical 4 and 2 chamber views, and the left ventricular (LV) EFs were measured from B-mode images according to the modified Simpson's method. Also, pulsed-Doppler findings of transmitral flow were obtained to calculate the E/A.

Exercise Tolerance Estimation

Each patient underwent a questionnaire-based interview for the estimation of the exercise tolerance threshold (ET) according to a specific activity scale.⁵

Statistical Analysis

MedCalc version 9.6 (MedCalc Software, Mariakerke, Belgium) was used for data analysis. The quantitative data are expressed as mean ± SD. A Student's t-test was used for descriptive statistics. The Mann-Whitney U-test was used for non-parametric data sets. A two-tailed Pearson's correlation was used to compare the relationship between LVEF, log BNP, and NI-CI, NI-SVI, and NI-TSVR. Spearman's coefficient of rank correlation (rho) was used to estimate the probability of correlations with ET. We used the multiple regression analysis in order to detect the predictors for CHF readmission, and also used receiver operating characteristic curve (ROC) analysis for BNP, NI-CI, NI-SVI, NI-TSVR, LVEF and ET to determine the thresholds between the readmission group and the non-readmission group. A two-tailed P-value of less than 0.05 was considered to be significant.

Results

Relationship Between NICaS-Derived Hemodynamic Parameters and LVEF, Plasma logBNP and ET

There were significant but weak correlations between LVEF and NI-CI (LVEF = 22.70 + 5.21 * NI-CI, r = 0.3148, P = 0.0089), NI-SVI (LVEF = 22.80 + 0.38 * NI-SVI, r = 0.3257, P = 0.0067), NI-TSVR (LVEF = 46.02 - 0.003 * NI-TSVR, r = 0.2636, P = 0.0298; **Figure 1**). There were significant moderate correlations between log BNP and NI-CI (log BNP =

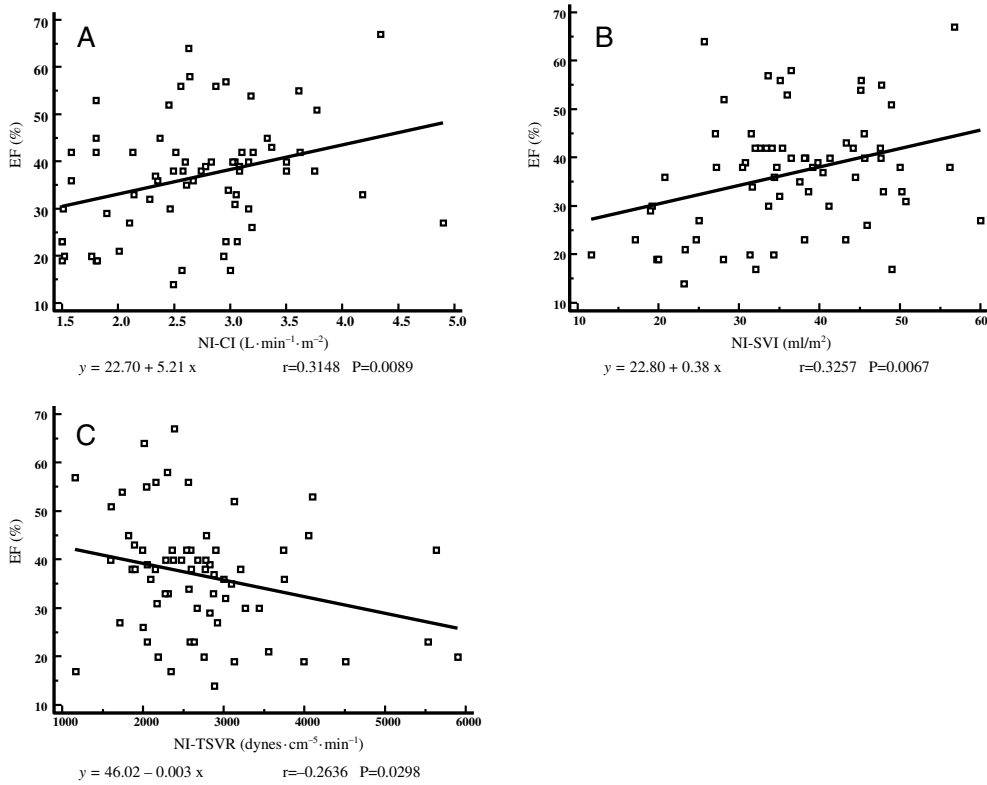


Figure 1. Scatter plots showing the correlation between left ventricular ejection fraction (EF) and Non-Invasive Cardiac System (NICaS) derived cardiac output index (NI-CI) [A]; EF and NICaS derived stroke volume index (NI-SVI) [B], EF and NICaS derived total systemic vascular resistance (NI-TSVR) [C]. The 2-tailed Pearson's correlation test (r) was used for the analyses.

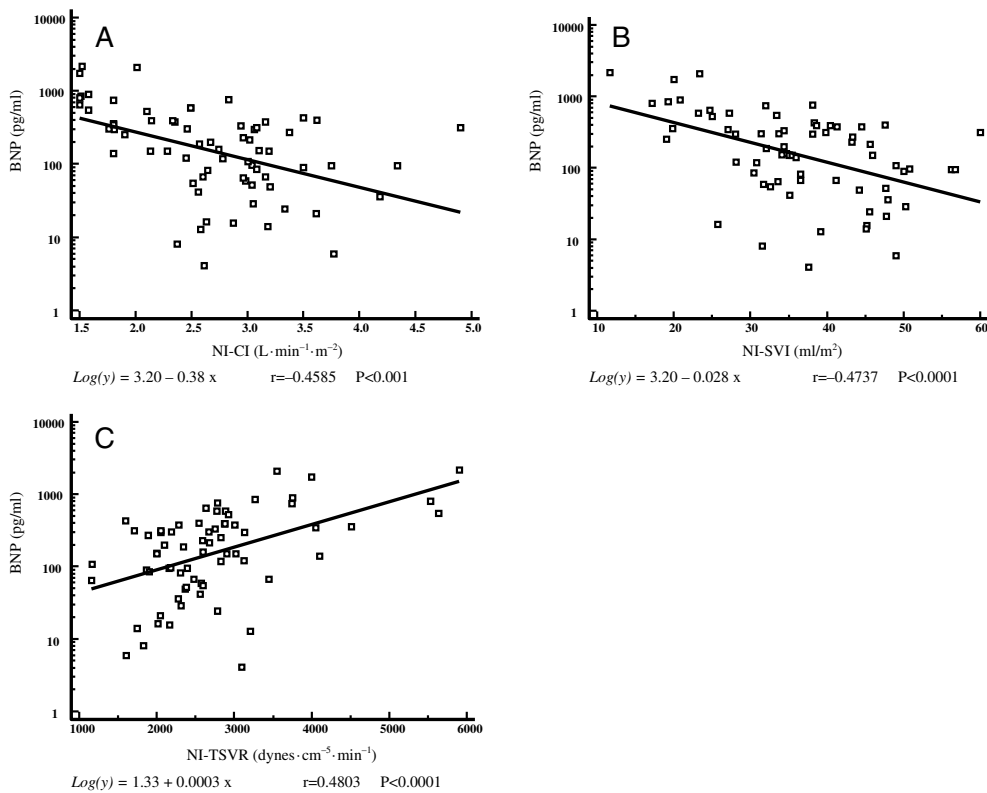


Figure 2. Scatter plots showing the correlation between the logarithmic serum B-type natriuretic peptide (BNP) levels with NI-CI [A]; BNP and NI-SVI [B], BNP and NI-TSVR [C]. The 2-tailed Pearson's correlation test (r) was used for the analyses. NI, non-invasive; CI, cardiac output index; SVI, stroke volume index; TSVR, total systemic vascular resistance.

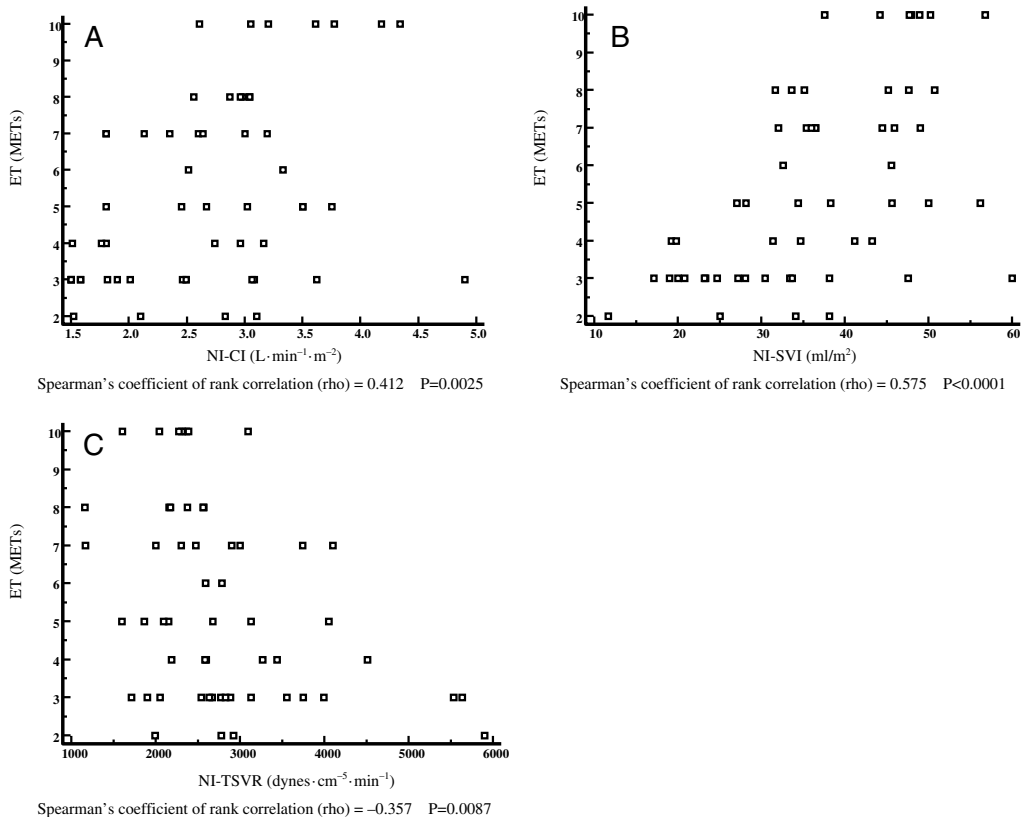


Figure 3. Scatter plots showing the correlation between exercise tolerance threshold (ET) and NI-CI [A]; ET and NI-SVI [B], and ET and NI-TSVR [C]. Spearman’s coefficient of rank correlation test (ρ) was used for analysis. NI, non-invasive; CI, cardiac output index; SVI, stroke volume index; TSVR, total systemic vascular resistance.

3.20–0.38*NI-CI, $r = -0.4585$, $P = 0.0001$), NI-SVI ($\log \text{BNP} = 3.20 - 0.028 * \text{NI-SVI}$, $r = -0.4737$, $P < 0.0001$), and NI-TSVR ($\log \text{BNP} = 1.33 + 0.0003 * \text{NI-TSVR}$, $r = 0.4803$, $P < 0.0001$; **Figure 2**). There was a significant correlation between ET and NI-CI ($\rho = 0.412$, $P = 0.0025$), NI-SVI ($\rho = 0.575$, $P < 0.0001$), and NI-TSVR ($\rho = -0.357$, $P = 0.0087$; **Figure 3**). There was no significant relationship between ET and E/A (**Figure 4**).

Predictive Factors for CHF Readmission

During the 100 ± 98 days (95%CI for the mean: 46–154) follow-up, 15 patients were readmitted to our hospital because of CHF recurrence (readmission group) whereas 53 patients were not readmitted because of CHF recurrence (no-readmission group). There was a significant difference in NI-CI between the readmission and non-readmission groups ($1.86 \pm 0.37 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ vs $2.92 \pm 0.63 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, $P < 0.0001$). Similarly, there were significant differences between groups in NI-SVI ($24.2 \pm 7.9 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ vs $40.4 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, $P < 0.0001$), NI-TSVR ($3,786 \pm 1,162 \text{ dynes} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ vs $2,420 \pm 583 \text{ dynes} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$, $P = 0.0007$), LVEF ($27.4 \pm 8.4\%$ vs $39.3 \pm 11.7\%$, $P = 0.0005$), ET (2.89–3.11 metabolic equivalents vs 5.00–7.00 metabolic equivalents in 95%CI for median, $P < 0.0001$), and BNP (696.5 pg/ml [95%CI: 487.5–995.1] vs 98.1 pg/ml [95%CI: 69.8–138.1], $P < 0.0001$). Receiver operator characteristic curves for sensitivity, specificity, positive predictive value, and negative predictive value for readmission for each parameter are shown in **Table 2**. Multivariate analysis for readmission showed that LVEF measured by echocardiography, NI-CI, NI-SVI, and

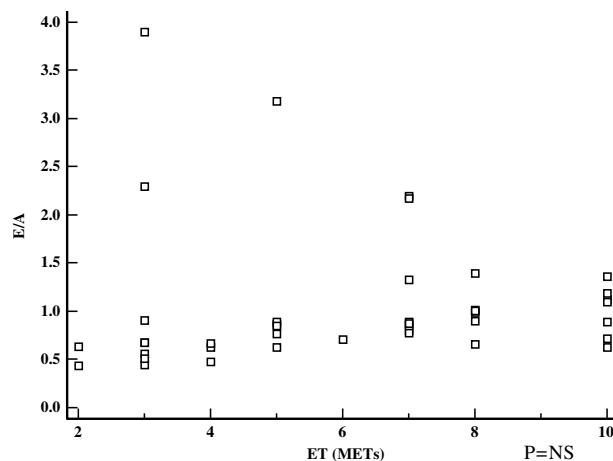


Figure 4. Scatter plots showing the correlation between exercise tolerance threshold (ET) with E/A of transmitral flow derived by Doppler echocardiogram. Spearman’s coefficient of rank correlation test (ρ) was used for analysis.

plasma BNP were significant predictors of readmission (**Table 3**).

Discussion

We have previously reported the reliability of NICaS-derived hemodynamic parameters when compared with those obtained by the Swan-Ganz catheter. Overall, 2-tailed

Table 2. Receiver Operating Curve Analysis for Readmission

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Cut-off
BNP	93.3	88.7	70.0	97.9	0.95	344 pg/ml
NI-CI	100	79.3	57.7	100	0.93	2.49 L · min ⁻¹ · m ⁻²
NI-SVI	80	98.1	92.3	94.4	0.91	27.2 ml/m ²
NI-TSVR	100	68.6	46.7	100	0.89	2,597 dyne · cm ⁻⁵ · min ⁻¹
LVEF	86.6	64.2	40.6	94.4	0.80	37%
ET	100	71.4	52.0	100	0.88	4 METs

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; BNP, B-type natriuretic peptide; NI-CI, NICaS derived cardiac index; NI-SVI, NICaS derived stroke volume index; NI-TSVR, NICaS derived total systemic vascular resistance; LVEF, left ventricular ejection fraction; ET, exercise tolerance threshold.

Table 3. Multivariate Analysis for Factors of Readmission

	OR (95% confidence interval)	P value
Age	1.0429 (0.9530–1.1414)	0.3611
Gender	0.3235 (0.0593–1.7647)	0.1923
LVEF	0.8918 (0.8205–0.9693)	0.007069
NI-CI	0.0318 (0.0023–0.4421)	0.01023
NI-SVI	0.8121 (0.6914–0.9540)	0.01129
BNP	1.0068 (1.0019–1.0117)	0.006053
Heart rate	1.0456 (0.9905–1.1038)	0.1064
SBP	1.0118 (0.9711–1.0542)	0.5750

OR, odds ratio; SBP, systolic blood pressure. Other abbreviations as in Table 2.

Pearson's correlation and Bland–Altman limits of agreement between NI-CO and thermodilution CO were $r=0.91$ and -1.06 and 0.68 L/min in 2SD and between NI-CO and Fick CO, $r=0.80$ and -1.52 and 0.88 L/min in 2SD, respectively.⁶ In the present study, NICaS-derived hemodynamic parameters were significantly correlated with LVEF, plasma log BNP, and ET. Furthermore, NICaS-derived CI and SVI were significant parameters for predicting the future recurrence of heart failure. An NICaS-derived CI of less than 2.49 L · min⁻¹ · m⁻² had 100.0% sensitivity and 79.3% specificity, and an NICaS-derived SVI of less than 27.2 ml · min⁻¹ · m⁻² had 80.0% sensitivity and 98.1% specificity. In the readmission group, no cases of a preserved EF greater than 55% were observed. ET was significantly worse in the readmission group than in the non-readmission group. The overall average EF was 36.68%, and the average EF was 27.40% in the readmission group and 39.30% in the non-readmission group. In this study, the NICaS-derived indices seem to be good predictors of readmission with CHF second to BNP.

Serum BNP levels can be a good surrogate indicator for the long-term prognosis of CHF patients.¹⁶ Logeart et al. reported that a serum BNP of more than 350 ng/L at pre-discharge predicted a worse prognosis in outpatients with CHF.¹⁷ According to our data, BNP had 93.3% sensitivity and 88.7% specificity for readmission when its cut-off value was 344 pg/ml, indicating that BNP had good predictive power. Thus, in the present study, NICaS did not have a decisive advantage over serum plasma BNP levels for predicting readmission. In clinical use, however, NICaS has sufficient predictive power. BNP measurement requires a peripheral venous blood sample, but some patients might consider repeated blood sample collection an invasive procedure. NICaS has the advantage of not being invasive because it only requires some electrodes to be placed on the patient's skin, similar to an electrocardiogram. It is also

important that NICaS is compatible with the conventional hemodynamic indicators derived by the Swan–Ganz catheter. Other hemodynamic indices including CI, SV are used when patients are in the intensive care unit. Once the patients are moved to the general ward, however, these indices are not readily available, although there are some limited modalities similar to echocardiography. Even when the patients are in the general ward or an outpatient department, the hemodynamic indices derived by NICaS can be easily taken and linked directly with the hemodynamic data derived by conventional methods. Therefore, another advantage of NICaS is that patient hemodynamic data obtained inside and outside the intensive care unit can be reported using the same scale, allowing for easy comparison.

According to the Ministry of Health, Labour, and Welfare in Japan, the number of outpatients with CHF has been increasing over the past several years.^{1–2} Recent studies have been initiated to better determine the actual prevalence of CHF in Japanese communities.^{18,19} Therefore, a less invasive method that is easier to use, sufficiently accurate, and inexpensive is needed to categorize CHF patients according to their disease severity or probability of readmission. The exercise tolerance test is a major index for estimating a patient's practical cardiovascular performance, but there are a number of patients who cannot perform an exercise test because of their age, disability, or poor muscle conditioning. In such cases, an alternative evaluation standard of cardiovascular performance, such as NICaS, should be utilized.

Study Limitations

It is widely believed that exercise capacity is related to LV diastolic function²⁰ but not to the LVEF, which in the present study was closely correlated to CI and SVI. We did not, however, find a significant relationship between E/A and ET. Also, in our study subjects, 3 patients were thought to have a purely diastolic dysfunction because they had a preserved EF of more than 55% and an E/A with the transmitral Doppler echocardiogram of less than 1 during their first visit to the outpatient department, and were not in the readmission group. Thus, in our study subjects, diastolic dysfunction did not have a significant effect, probably because of the small number of subjects used.

Although NICaS might be useful for estimating cardiac performance in patients who are not exercise tolerant or who have difficulty walking, it might not be reliable when applied to patients who match the exclusion criteria described above, including those with arteriosclerosis obliterans and severe pitting edema of the limbs.

Conclusions

NICaS-derived hemodynamic parameters obtained by monitoring whole body bioimpedance are applicable for the non-invasive assessment of cardiac function for the follow up of outpatients with CHF.

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