# Non-invasive measurement of cardiac output by whole-body bio-impedance during dobutamine stress echocardiography: Clinical implications in patients with left ventricular dysfunction and ischaemia

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## Abstract

*Objectives:* To compare non-invasive determination of cardiac index (CI) by whole body electrical bioimpedance using the NICaS apparatus and Doppler echocardiography, and the role of cardiac power index (Cpi) and total peripheral resistance index (TPRi) calculation during dobutamine stress echocardiography (DSE).

*Subjects and methods:* We enrolled 60 consecutive patients undergoing DSE. Patients were prospectively divided into 3 groups: Group 1 ($n=20$): normal DSE (control). Group 2 ($n=20$): EF$<$40% without significant ischaemia. Group 3 ($n=20$): patients with significant ischaemia on DSE. Measurements of CI were performed at the end of each stage of DSE by both echocardiographic left ventricular outflow track flow and the NICaS apparatus, using whole-body bio-impedance. MAP was measured simultaneously and TPRi and Cpi were calculated.

*Results:* The correlation between non-invasive CI as determined by NICaS and echocardiography was 0.81, although Echocardiographic readings of CI were higher during administration of higher doses of dobutamine. Lower EF correlated with lower Cpi, especially stress induced Cpi. Hence, patients with reduced EF (group 2) had a blunted increase in Cpi during stress. Patients with ischaemia (group 3) had a blunted increase in Cpi as well as a decrease in Cpi and increase in TPRi during the last stages of DSE.

*Conclusion:* Measurement of CI by NICaS correlated well with Doppler derived CI. The calculation of Cpi and TPRi changes during dobutamine stress may provide important clinical information.

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*Keywords:* Cardiac index; Cardiac power; Bioimpedance

## 1. Background and aims

Cardiac power index (Cpi) is the product of simultaneously measured cardiac index (CI) and mean arterial blood pressure (MAP). Cpi increases — cardiac power reserve during stress [1,2] or dobutamine administration [3] was shown in previous studies to be an important measure of systolic cardiac contractile reserve, better than $VO_2$ and echocardiographic ejection fraction (EF). Recently, Samejima et al. [4] demonstrated that CO increase during stress using non-invasive CO determination with bioimpedance was correlated with stress induced dyspnea.

The use of hemodynamic measures such as increase in vascular resistance for the detection of ischaemia was suggested almost a decade ago [5]. However, this research avenue has not been pursued due to the lack of simple non-invasive devices for CO measurement. Recently Weiss et al.

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Table 1
Baseline characteristics of patients in the three groups

|  | Normal DSE | Ischaemia by DSE | EF<40% | *P* value |
|---|---|---|---|---|
| *N* | 20 | 20 | 20 |  |
| Age (years) | 59±10 | 59±17 | 54±20 | 0.6 |
| Prior MI | 25% | 55% | 90% | 0.003 |
| Hypertension | 50% | 75% | 80% | 0.12 |
| Diabetes mellitus | 25% | 45% | 50% | 0.46 |
| Hyperlipidaemia | 35% | 55% | 40% | 0.6 |
| Prior smoking | 30% | 35% | 30% | 0.7 |
| Family history of ischaemic heart disease | 30% | 10% | 10% | 0.3 |
| *Medical therapy* |  |  |  |  |
| Aspirin | 75% | 95% | 85% | 0.17 |
| Beta-blockers | 45% | 75% | 80% | 0.03 |
| ACEi/AT II antagonists | 30% | 55% | 90% | 0.04 |
| Diuretics | 10% | 45% | 90% | 0.03 |
| Statins | 45% | 80% | 75% | 0.1 |
| *Echocardiographic findings* |  |  |  |  |
| Left ventricular EF (%) | 57±6 | 50±11 | 28±7 | <0.001 |
| LVH | 40% | 50% | 45% | 0.78 |

EF: Ejection fraction, MI: Myocardial infarction, ACEi: Angiotensin converting enzyme inhibitors, ATII antagonists — angiotensin II antagonists, LVH: Left ventricular hypertrophy.

[6] demonstrated that in patients with significant ischaemia during stress, CO increase by bio-impedance is lower than in patients without ischaemia.

The NICaS apparatus uses whole body bio-impedance and the Tsoglin–Frinerman formula for non-invasive determination of CI [7]. In short, a small electrical current is transferred from the left wrist to the right foot, and the impedance to its transit is detected (termed whole-body bio-impedance). The instantaneous change in bio-impedance has previously been shown to be related to the pulsatile changes in the volume of the great arteries. The Tsoglin–Frinerman formula uses this change in bio-impedance ($\Delta R$) as well as population based constants correcting for age, sex, weight and body composition (electrolytes, haematocrit and changes in baseline bio-impedance) to calculate the stroke volume (SV). Thereafter by electrocardiographically measuring the pulse rate it calculates cardiac output and CI. In a few recently published studies [7–9], NICaS measurements of CI in patients with various cardiac conditions showed good reproducibility and correlated well with thermodilution ($R=0.8$–$0.9$), with no bias and precision of approximately 0.6 L/min/M$^2$.

The aim of the present study was two fold: first, to compare CI measurements by NICaS and Doppler echocardiography over a wide range of values during dobutamine stimulation and, secondly, to determine whether the non-invasive continuous measurement of CI and MAP and calculation of Cpi and TPRi changes during dobutamine stress could be used for diagnosis of significant left ventricular (LV) dysfunction or myocardial ischaemia as determined by dobutamine stress echocardiography (DSE).

## 2. Patients and methods

We enrolled 60 consecutive patients undergoing standard DSE using incremental dobutamine infusion from 10 to 40 μg/min and atropine up to 1 mg as required to reach the pre-determined target heart rate. Patients were recruited in our outpatient clinic during a once weekly session. All consecutive patients attending the clinic during that day for the purpose of DSE were considered for the study. Patients were divided into 3 groups: Group 1: *Control*. Normal DSE, including baseline EF >40% and no significant ischaemia, Group 2: *LV systolic dysfunction* as determined by baseline echocardiographic EF <40% without significant ischaemia and Group 3: *Significant ischaemia* as determined by improvement of contractility during low-dose dobutamine infusion followed by decreased contractility during high dose dobutamine infusion in at least one non-infarcted myocardial segment.

Exclusion criteria were inability to achieve good echocardiographic visualization, significant hypotensive or hypertensive reactions or tachy or bradyarrhythmias during dobutamine infusion and inability to reach the pre-determined heart rate.

### 2.1. Study protocol

DSE was performed according to a standard protocol by 2 DSE teams. NICaS CI was measured by one NICaS operator. CI was determined by both echocardiographic left ventricular outflow track (LVOT) diameter and flow velocity as well as the NICaS apparatus. Operators measuring CI by one method were blinded to the result of the other method throughout the examination. Thereafter, based on NICaS determined CI, we calculated Cpi and total peripheral vascular resistance (TPRi) for each of the above mentioned time-points. NICaS and Doppler determined CI were not calculated during dobutamine administration in 3 patients (5%) in whom it was judged by
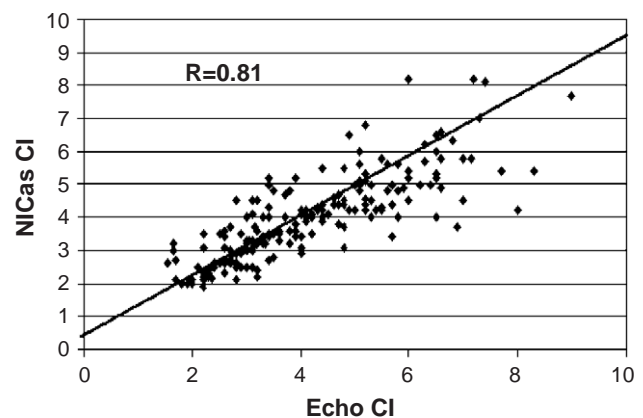


Fig. 1. Correlation between Doppler echocardiography CI and NICaS CI measurements. Horizontal axis — CI measured by echocardiography, L/min/M$^2$, Vertical axis: CI measured by NICaS, L/min/M$^2$.
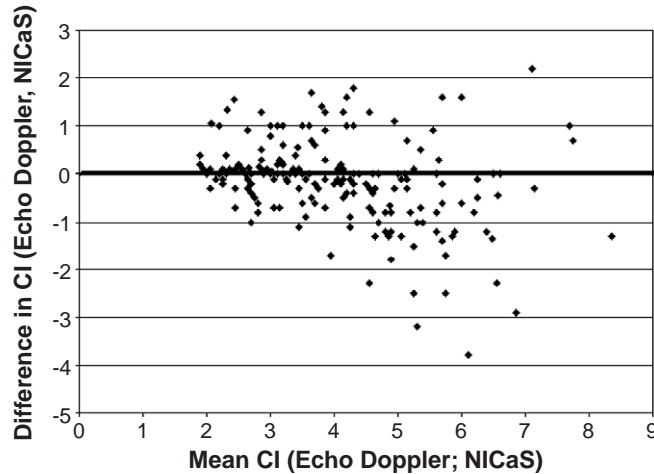
Fig. 2. Difference of CI measurements by Doppler echocardiography and NICaS vs. their mean (Bland and Altman analysis).

the operator that LVOT obstruction occurred due to dobutamine administration.

### 2.2. Study end-points

(1) The correlation between NICaS and Doppler echocardiography derived CI and (2) the absolute and relative changes in NICaS determined Cpi and TPRi during dobutamine stress in the 3 groups.

### 2.3. Statistical methods

All data is reported based on pre-determined group allocations. To compare the baseline characteristics of the groups we used the Student's *t*-test to compare continuous variables and the chi-square test to compare categorical variables. Since the cardiac index and cardiac power measurements were not normally distributed we used the Spearman-rank test for comparison of NICaS and echocardiographically determined CI and for comparison of resting EF and Cpi during the different stages of DSE. Since both NICaS and Doppler echocardiography are not regarded as gold standard for CI determination, when comparing the two methods we used the Bland and Altman [10] recommendations and for each dobutamine stage, as well as for the whole cohort, we determined *bias* (mean difference between the 2 methods) and the limits of agreement (*precision*) calculated as 2 SD of the bias.

Analysis of variance with repeated measurements (time * group) was used to compare changes in Cpi and TPRi over time in the different groups. All *P* values <0.05 were considered significant.

### 3. Results

Sixty consecutive patients where enrolled in the 3 prospectively defined groups. The baseline characteristics of the three groups are presented in Table 1. As expected, patients differed with respect to baseline echocardiographic EF, age and severity of background diseases.

The correlation between CI as determined by echocardiographic LVOT area and mean flow velocity and the NICaS apparatus was $R=0.81$ (Fig. 1). The Bland–Altman distribution of CI measurements is depicted in Fig. 2. The correlation was better for CI measurements at baseline and during the infusion of dobutamine at doses of up to 20 μg/min than for CI determinations during administration of dobutamine at a rate of 30 and 40 μg/min (Table 2, Fig. 2), due to increasing bias (i.e., CI measurements by Doppler echocardiography tending to be higher) and lower precision. Therefore, the CI increase in the different stages of DSE was similar by both techniques (Fig. 3). Again, a slight tendency was observed for higher increase in the Doppler echocardiography determined CI during the last phase of dobutamine infusion.

Table 2
CI measurements obtained by Doppler echocardiography and NICaS during the different DSE stages

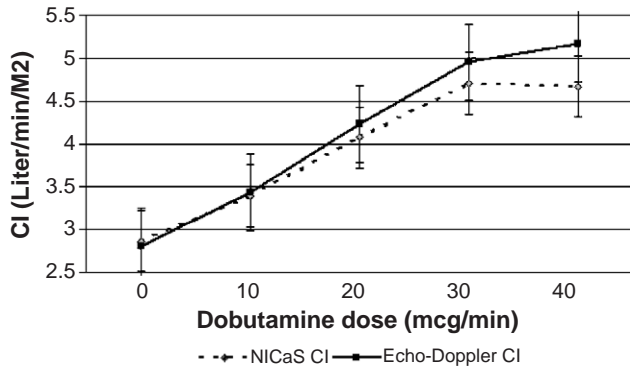| Dobutamine infusion rate | Mean NICaS-CI | Mean echo-Doppler CI | Spearman Rank Correlation | Bias | Precision |
|---|---|---|---|---|---|
| Baseline | 2.9±0.6 | 2.8±0.6 | 0.77 | −0.06 | 0.39 |
| 10 μg/min | 3.4±0.9 | 3.4±1.1 | 0.81 | 0.04 | 0.71 |
| 20 μg/min | 4.1±1.1 | 4.2±1.5 | 0.87 | 0.16 | 0.8 |
| 30 μg/min | 4.7±1.4 | 4.9±1.5 | 0.81 | 0.24 | 1.16 |
| 40 μg/min | 4.7±1.2 | 5.2±1.4 | 0.62 | 0.49 | 1.18 |
| All measurements | 3.9±1.3 | 4.1±1.5 | 0.81 | 0.17 | 0.9 |

Fig. 3. Trend changes in CI during dobutamine infusion: Doppler echocardiography vs. NICaS CI.

We have observed a significant correlation between EF and Cpi based both on echocardiographically determined CI and on NICAS-CI (Table 3). Interestingly, and consistent with previous studies [11], this correlation was better for stress Cpi than for rest Cpi.

During dobutamine infusion, NICaS determined Cpi increase was significantly different in the three groups (Fig. 4). Cpi increase was smallest in the group of patients with LV dysfunction followed by the group of patients with significant ischaemia and highest in patients with normal DSE ($p = 0.002$ comparing LV dysfunction with normal DSE, $p = 0.03$ comparing patients with ischaemia with patients with normal DSE and $p = 0.02$ comparing patients with ischaemia to patients with LV dysfunction).

Baseline TPRi was significantly higher at baseline in the LV systolic dysfunction group as compared to patients with normal DSE ($3120 \pm 1020$ vs. $2450 \pm 940$ dynes s $M^2$, $p = 0.04$) however, during dobutamine stress it decreased steeply in all 3 groups, to a similar degree.

A significant difference was observed in Cpi and TPRi changes during the last phase of dobutamine infusion in patients in the significant ischaemia group. As compared to patients in the control as well as the systolic LV dysfunction group, patients who were found by DSE to have significant ischaemia had during the last phase of DES a significant decrease in Cpi ($-0.16 \pm 0.15$ vs. $+0.1 \pm 0.15$ W/M$^2$,
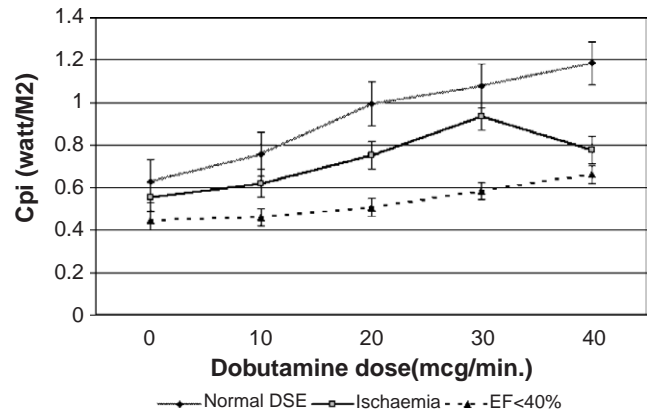


Fig. 4. Changes in Cpi during dobutamine infusion in the 3 groups.

$p = 0.0002$) and increase in TPRi. ($+279 \pm 636$ vs. $-59 \pm 169$ dynes s $M^2$, $P = 0.022$).

No significant adverse events were recorded during the dobutamine stress test.

## 4. Discussion

The results of the present study demonstrate that CI determination by whole-body bio-impedance using the NICaS device is correlated well with CI determination by Doppler echocardiography. However, during infusion of higher doses of dobutamine ($\geq 30$ μg/min), the correlation became less accurate, mainly due to significant bias, i.e. Doppler echocardiography CI measurements tended to be significantly higher than NICaS readings.

In the overall cohort we found a correlation between severity of LV dysfunction by resting EF and Cpi at rest and especially Cpi during the dobutamine stress; i.e., the lower the EF the lower the rest and peak DSE Cpi. Hence, in the group of patients with reduced baseline EF (group 2), Cpi increase during exercise was significantly blunted. This finding is substantiated by the results of previous studies showing that lower Cpi increase during stress (lower cardiac power reserve) is correlated with poor outcome — although this correlation was superior to the correlation of EF and outcome. In the present study, the small number of patients enrolled did not allow for outcome analysis, however, it is possible that accurate non-invasive CI determination and calculation of Cpi reserve by whole body bio-impedance during stress may become a useful predictor of outcome in patients with reduced left ventricular function.

The results of the present cohort, in concordance with previous studies [5,6] show that during significant ischaemia, cardiac power tends to decrease and vascular resistance increases. Again, such non invasive calculation may enable an additional important indication for significant ischaemia in addition to conventional signs on DSE.

Importantly, all haemodynamic data was obtained in the present study using a simple non-invasive device. Although

Table 3
Correlations between resting EF and Cpi by NICaS and echocardiography during the different DSE stages

| Dobutamine infusion rate | Spearman Rank Correlation between resting EF and echo-Doppler Cpi at different DSE stages | Spearman Rank Correlation between resting EF and NICaS-Cpi at different DSE stages |
|---|---|---|
| Baseline | 0.44 | 0.44 |
| 10 μg/min | 0.56 | 0.39 |
| 20 μg/min | 0.61 | 0.54 |
| 30 μg/min | 0.58 | 0.53 |
| 40 μg/min | 0.59 | 0.45 |
| All measurements | 0.57 | 0.52 |

the size of the present cohort does not allow for far-reaching conclusions, if these results are reproduced by additional, larger studies, cardiac power and vascular resistance changes could be used for non-invasive detection of left ventricular dysfunction and ischaemia during simple stress tests such as electrocardiographic exercise stress test or mental stress test. Moreover, serial changes in these measures may be useful for improving detection of ischaemia in patients at home using telemedicine.

### 4.1. Study limitations

The study included a small, select group of patients referred for DSE due to various symptoms. Hence, the results require further confirmation in a larger study including a non-selected group of outpatients.

## 5. Conclusion

The results of the present study suggest that a simple stress test using dobutamine infusion and non-invasive determination of CI by the NICaS™ 2001 apparatus and calculation of Cpi and TPRi can be used for easy out-patient screening of patients for systolic LV dysfunction and myocardial ischaemia.

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