HF and Intensive Care: Research Article

cardiology

Cardiology
DOI: 10.1159/000505809

Received: September 27, 2019
Accepted after revision: January 8, 2020
Published online: February 7, 2020

Non-Invasive Hemodynamic Whole-Body Bioimpedance Indices for the Early Detection of Cancer Treatment-Related Cardiotoxicity: A Retrospective Observational Study

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Keywords
Cardiotoxicity · Chemotherapy · Detection · Heart failure · Whole-body bioimpedance

Abstract
Introduction: Patients undergoing chemotherapy are extremely vulnerable to cardiotoxicity. Early detection of cardiac dysfunction is of vital importance to optimize the management of these patients. ***Objective:*** The aim of this study was to test the effectiveness of non-invasive hemodynamic whole-body bioimpedance (WBI) technology as a modality to detect heart failure in patients undergoing chemotherapy treatment. ***Methods:*** This retrospective observational trial included 84 patients treated at the cardio-oncology outpatient clinic of the Rabin Medical Center. Clinical assessments were performed including biomarker testing and measurement of hemodynamic and volume status parameters as measured by WBI. ***Results:*** We included 84 patients with a median age of 64.8 years, and 40.5% were males. Clinical heart failure was detected in 43% of the whole group. Patients were divided into two groups according to baseline NT-proBNP levels with a cut-off of 900 pg/mL. Left ventricular ejection fraction did not differ between the groups. Those with NT-proBNP >900 pg/mL had lower levels of stroke index, cardiac index, and Granov-Goor index (GGI; 25.9 vs. 34.0, 2.0 vs. 2.3, 8.3 vs. 11.4, respectively, with $p < 0.001$ for all comparisons). The optimal cut-off value for the GGI to detect NT-proBNP >900 pg/mL was 8.3. The area under the curve of a GGI cut-off <8.3 to detect NT-proBNP >900 pg/mL was 0.81 (positive predictive value 95% and negative predictive value 72%), with a 51% sensitivity and 98% specificity. ***Conclusion:*** GGI, a parameter measured by WBI, can reliably correlate to biomarker evidence of heart failure in patients after chemotherapy. Its use as a screening tool for cardiotoxicity in patients with ongoing anticancer therapy is promising.

Introduction

Cancer therapeutics related cardiac dysfunction is a concerning and potentially debilitating complication of chemotherapy defined as a decrease of left ventricular ejection fraction (LVEF) of 10% to a value below the lower limit of normal (<53%) [1]. Up to 5–10% of patients who undergo chemotherapy will have some degree of cardiac injury, which mostly will manifest as left ventricular

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systolic dysfunction and clinical heart failure [2]. It is highly important to screen for and identify cardiotoxicity in its early stages in order to adjust the different treatment modalities and prevent further cardiac injury. Clinical monitoring, imaging, and cardiac biomarkers have been the main methods of detecting cardiac injury during chemotherapy. Specifically, NT-proBNP has been repeatedly demonstrated as a predictive marker of cardiac dysfunction in the population of cancer patients undergoing chemotherapy [3].

Whole-body bioimpedance (WBI) measures the ability of tissue to impede electric currents and has the ability to provide multiple physiological cardiac parameters [4]. This modality is non-invasive, quick, safe, reproducible, and low cost. One parameter is the Granov-Goor index (GGI), which is designed to assess the systolic contractile function of the left ventricle by calculating the sum of the heart rate and changes in impedance. Evidence has shown a good correlation between the GGI and LVEF (GGI <10 predicts LVEF <55%) [5]. Multiple studies have found that cardiac biomarkers and WBI parameters, alone and in combination, can predict subsequent heart failure decompensation in patients with chronic heart failure [6], and that these parameters could prognosticate a heart failure-related event in stable patients with or without left ventricular dysfunction [7]. In view of the above evidence, the aim of this study was to test the effectiveness of WBI technology as a modality to detect early-stage heart failure in patients undergoing chemotherapy.

Table 1. Baseline demographic and clinical characteristics

Demographics	
Patients	84
Age, years	64.8±17.6
Male	34 (40.5)
Weight, kg	73.2±20.1
BMI	26.7±6.2
Comorbidities	
Active solid cancer	36/76 (47.4)
Active hematologic cancer	42/76 (55.3)
Heart failure	43 (51.2)
NYHA class	2.3±0.6
Hypertension	42 (50.0)
Hyperlipidemia	28 (33.3)
Diabetes mellitus	21 (25.0)
Peripheral vascular disease	8 (9.5)
Atrial fibrillation	6 (7.1)
Ejection fraction, %	53 (42–60)
Systolic BP, mm Hg	118±23
Diastolic BP, mm Hg	69±11
Mean arterial pressure, mm Hg	85±14
NICaS parameters	
GGI	10.0±2.8
Heart rate, beats/min	71±12
Stroke index, mL/m^2	30.4±8.4
Stroke work index, J/m^2	0.34±0.11
Cardiac index, L/min/m^2	2.2±0.6
Cardiac power index, w/m^2	0.41±0.13
Total peripheral resistance index, dyn × S/cm^5 × m^2	3,391±1,147
Total body water, % of body weight	46.7±10.1

Data are presented as the mean ± SD, median (25th–75th quartiles), or *n* (%).

Methods

This retrospective observational trial included patients with ongoing active cancer therapy, age 18 years or older, treated at the cardio-oncology outpatient clinic of Rabin Medical Centre between January 1, 2017 and December 30, 2018. Patients were excluded if they had prominent grade 3–4 pitting edema (total body water percentage more than 80% by WBI).

All demographic, clinical, laboratory, and echocardiographic data were collected from patients' electronic records. The clinical diagnosis of heart failure was based on several parameters: pulmonary congestion by lung auscultation, elevated jugular venous pressure, and peripheral edema, with one point being attributed for each finding. When the total score was 0, patients were considered to be without heart failure; those scoring ≥1 were considered to have heart failure [8]. Functional class was assessed using the New York Heart Association (NYHA) classification.

NT-proBNP levels were measured. Patients with an NT-proBNP >900 pg/mL were considered to have biomarker evidence of heart failure. This cut-off level of NT-proBNP was chosen as it has been demonstrated as a reliable tool for diagnosing heart failure in the age group of 50–75 years [9, 10]. While considering various strategies that incorporated age, sex, kidney function, and other comorbidities, the optimal approach to NT-proBNP appears to be an age-stratified approach [11]. LVEF was estimated by trans-thoracic echocardiography.

The WBI of patients was measured using a Non-Invasive Cardiac System (NICaS®, NI Medical, Petach Tikva, Israel). This device is registered with the Food and Drug Administration (FDA) for statistical bioequivalence to thermodilution cardiac output [12, 13]. The WBI device works by transmitting a small electric signal between two electrodes that are placed on the wrist and on the ankle. Changes in arterial blood volume throughout the cardiovascular cycle alter the body's electrical resistance. These changes are measured by the device and stroke volume, cardiac output, cardiac power, total peripheral resistance, and GGI are calculated by proprietary algorithms. The GGI is designed to assess the systolic contractile function of the left ventricle by calculating the sum of the heart rate and changes in impedance. The hemodynamic data obtained by NiCAS was correlated with the most recent echocardiographic examination.

Table 2. Comparison of demographics, comorbidities, and hemodynamic parameters in patients presenting with NT-proBNP <900 and those with NT-proBNP ≥900 ng/mL

	NT-proBNP <900 ng/mL (n = 47)	NT-proBNP >900 ng/mL (n = 37)	p value
Demographics			
Male, %	35.6	48.5	0.257
Age, years	60.0 (55.5–64.6)	70.8 (64.7–76.9)	0.003
BMI	26.2 (24.5–27.8)	27.4 (25.1–29.6)	0.743
Comorbidities			
Hypertension	33.3	72.7	<0.001
Hyperlipidemia	17.0	54.5	<0.001
Diabetes mellitus	17.0	36.4	0.065
Hemodynamics			
LVEF (by Echo)	51.6 (48.1–55.0)	46.8 (41.9–51.7)	0.120
Systolic blood pressure, mm Hg	116 (109–122)	121 (113–129)	0.294
Mean arterial pressure, mm Hg	84 (80–88)	86 (81–91)	0.551
NICaS parameters			
GGI	11.4 (10.7–12.0)	8.3 (7.5–9.2)	<0.001
Heart rate, beats/min	68 (65–71)	75 (71–80)	0.004
Stroke index, mL/m^2	34.0 (31.7–36.2)	25.9 (23.6–28.2)	<0.001
Stroke work index, J/m^2	0.38 (0.35–0.41)	0.30 (0.27–0.33)	<0.001
Cardiac index, L/min/m^2	2.3 (2.1–2.5)	2.0 (1.8–2.1)	0.006
Cardiac power index, w/m^2	0.43 (0.39–0.47)	0.37 (0.33–0.41)	0.046
Total peripheral resistance index, dyn × S/cm^5 × m^2	3,067 (2,827–3,307)	3,807 (3,354–4,259)	0.004
Total body water, %	45.6 (42.6–48.7)	48.1 (44.9–51.3)	0.280
High-sensitivity cardiac troponin T, ng/mL	26.1 (10.3–30.0)	54.0 (25.6–78.2)	<0.001
NT-proBNP, ng/mL	359 (292–426)	6,057 (3,361–8,754)	<0.001

Data are presented as the medians (25th–75th quartiles) or as percentages.

Statistical Analysis

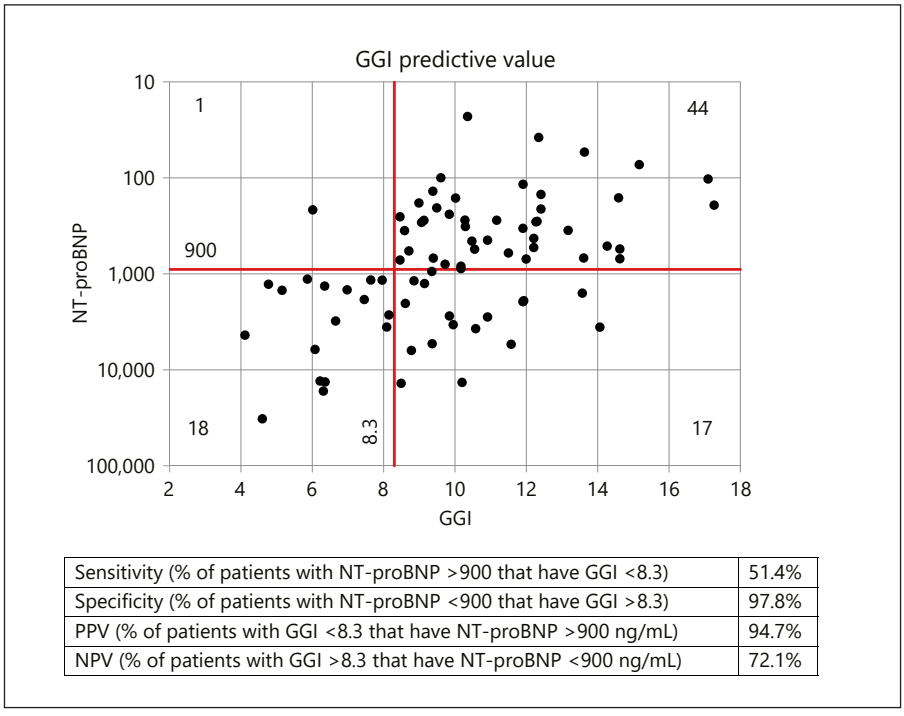
Continuous variables are presented as medians with 25th–75th percentile, and categorical variables are presented as percentages. We used the Mann-Whitney test to compare continuous variables and the χ^2 test and Fisher's exact test for categorical variables. The discriminatory power for heart failure detection for GGI was analyzed by receiver operating characteristic (ROC) curves. The cut-off, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve were calculated to assess the overall diagnostic accuracy of the GGI in heart failure prediction. Statistical analysis was performed using the IBM SPSS package version 24 (IBM Corp., Armonk, NY, USA).

Results

We included 84 cancer patients undergoing active oncology treatment. Most patients were females and most had hematological malignancies (Table 1). Most patients received heart failure-targeted therapy (69% beta-blockers, 53% angiotensin-converting enzyme inhibitor / angiotensin receptor blocker, and 45% were using diuretic therapy).

Patients were divided into two groups according to their baseline NT-proBNP levels (Table 2). Patients with lower NT-proBNP levels were younger, while patients with elevated NT-proBNP levels were more likely to have clinical heart failure and other comorbidities, such as hypertension, diabetes mellitus, and dyslipidemia. Moreover, high-sensitivity cardiac troponin T levels were significantly elevated in those with NT-proBNP >900 pg/mL.

In terms of the WBI parameters, the GGI was significantly higher in the group with NT-proBNP <900 pg/mL. The mean GGI was 8.3 in those with NT-proBNP >900 pg/mL. The patients with lower NT-proBNP also had a higher stroke index, cardiac index, and lower total peripheral resistance index.



Sensitivity (% of patients with NT-proBNP >900 that have GGI <8.3)	51.4%
Specificity (% of patients with NT-proBNP <900 that have GGI >8.3)	97.8%
PPV (% of patients with GGI <8.3 that have NT-proBNP >900 ng/mL)	94.7%
NPV (% of patients with GGI >8.3 that have NT-proBNP <900 ng/mL)	72.1%

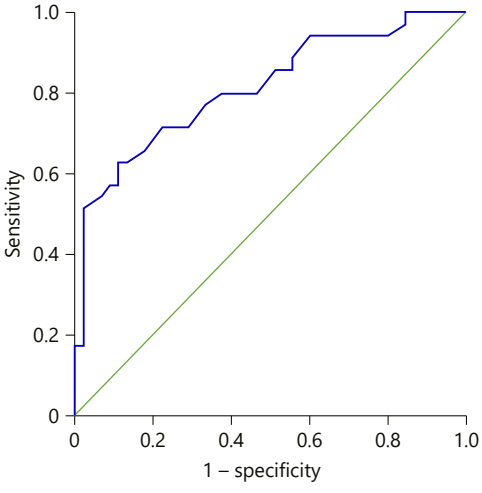
Color version available online

Fig. 1. Scatter plot of NT-proBNP versus GGI demonstrating the predictive value of a GGI cut-off of 8.3 to detect NT-proBNP >900.

The optimal GGI cut-off value for the detection of NT-proBNP >900 pg/mL was 8.3. Figure 1 shows a scatter plot of NT-proBNP versus GGI demonstrating the predictive value of a GGI cut-off of 8.3 to detect NT-proBNP >900. The ROC curve of GGI as a diagnostic test for heart failure is shown in Figure 2. The area under the curve with a GGI cut-off <8.3 to detect NT-proBNP >900 pg/mL was 0.81 (PPV 95% and NPV 72%), with a 51% sensitivity and 98% specificity. In our cohort, few patients had a history of atrial fibrillation and only 1 patient with atrial fibrillation had an NT-proBNP value higher than 900 pg/mL. Overall results did not differ after a sensitivity analysis was performed to exclude patients with a history of atrial fibrillation.

Discussion

In this study, we were able to demonstrate that the GGI, a parameter measured by WBI, can reliably correlate to biomarker evidence of heart failure in patients after chemotherapy. Previous evidence has shown that GGI can accurately determine whether the LVEF is normal or abnormal [5]. In this study we found that GGI values lower than 8.3 were associated with higher values of NT-proBNP, which corresponds to LV dysfunction and heart failure.



Area under the curve	0.81 (95% CI 0.72, 0.91)
GGI cut-off	8.3
Sensitivity	51%
Specificity	98%
PPV	95%
NPV	72%

Color version available online

Fig. 2. ROC curve of GGI as a diagnostic test for heart failure (NT-proBNP >900 ng/mL).

Natriuretic peptides in general and NT-proBNP in particular have been a cornerstone of heart failure diagnosis [14]; however, they require a blood test to be done, there is a waiting period for the result, and this test is not routinely available in many settings. NT-proBNP is also affected by various conditions. It can be elevated in older patients, those with renal dysfunction and non-heart failure conditions such as sepsis, and it can be decreased in obese patients [15–18]. This often makes NT-proBNP difficult to interpret in specified conditions. On the other hand, GGI can be carried out in a matter of minutes, is non-invasive, is simple to interpret, and can be conducted even when the patient is fully clothed. As it is a physiological marker, it is less influenced by other conditions (such as those mentioned above).

The early detection of cancer treatment-related cardiotoxicity in patients after chemotherapy is extremely important. The onset of this cardiotoxicity in these patients is often insidious and difficult to predict and can occur years after the cessation of therapy [19]. Our results show that this marker could be used as a surrogate to detect subclinical cardiac injury in these patients instead of an invasive blood test. This has important clinical implications in enabling clinicians to promptly decide on management issues such as downgrading chemotherapy and/or initiating cardiopreventative measures.

There is no consensus on the appropriate screening for cardiotoxicity after chemotherapy. Echocardiography is a relatively expensive and time-consuming modality, and biomarker blood tests are costly and inconvenient for frequent follow-up. WBI is an inexpensive, quick, non-invasive, and reproducible test based on physiological parameters. Our study shows promising results of WBI as a modality to detect heart failure. Indeed, GGI could be used for screening purposes to enable early intervention of cardiac complications of chemotherapy.

Our results are promising; however, additional trials are required to prove the efficacy of this device in the target population of asymptomatic patients at risk. The limitations of our trial include the small cohort of patients, heterogeneity of the cohort, and that WBI and echocardiography were not always performed on the same day. Our cohort included both patients with solid and hematological malignancies with different treatment protocols. Our definition of heart failure was subjective and based on clinical examination. Further studies are needed to evaluate WBI in more homogenous patient populations where cohorts are focused according to specific malignancies.

Conclusion

GGI can be used as a non-invasive and readily available parameter to identify heart failure as defined by an NT-proBNP level of more than 900 ng/mL in patients after chemotherapy. Its use may be considered as a screening tool for cardiotoxicity in patients with ongoing anticancer therapy.

Statement of Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

N.S.P. made a substantial contribution to the acquisition, analysis, and interpretation of data. S.L. made a substantial contribution to the conception and design of the work. O.I.B.Z. made a substantial contribution to the analysis and interpretation of data for the work. R.K. made a substantial contribution to the conception and acquisition of the data for the work. Z.I. made a substantial contribution to the conception, design, acquisition, and analysis of the data. All authors were involved in the drafting of the work and revising if for important intellectual content. All authors approved the final version for publication.

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