Relationship between Serum NT-ProBNP Level and Electrical Cardiometry in Monitoring Heart Failure Therapy

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ABSTRACT
Background: Heart failure (HF) is a complex condition with a high death and hospitalization rate worldwide. Monitoring hospitalized patients receiving HF therapy is usually done by either invasive or non-invasive techniques. Nowadays more studies are focused on non-invasive techniques as they are easier and have fewer side effects.
Objective: This study aimed to prove the relationship between electrical cardiometry fluid status measurements and serum NT-pro BNP levels in patients hospitalized for heart failure treatment.
Methods: Fifty patients with chronic heart failure of both sexes over the age of 18 years participated in this prospective trial. Complete history taking, physical examination that included a general, cardiac, and chest examination, routine laboratory investigations and echocardiography evaluation were done for every patient. Assessment of congestion status based on the Everest congestion score, assessment of electrical cardiometry fluid status measurements (TFC and SVV) and NT-proBNP were evaluated for every patient twice, on time on admission and another before discharge after receiving optimal antifailure decongestion therapy.
Results: The Everest congestion score, Thoracic fluid content (TFC) measured by electrical cardiometry (EC), and the serum NT-proBNP level were all significantly lower upon discharge than upon admission ($P < 0.001$). The discharge results had a considerably larger stroke volume variation (SVV) than the admission ($P < 0.05$). Serum NT-proBNP level and TFC at admission and discharge showed a positive correlation, while serum NT-proBNP level and SVV at admission and discharge showed a negative correlation (P value<0.05). **Conclusions:** EC can play a key role in monitoring the response to heart failure therapy via providing real time non-invasive objective assessment of fluid status through TFC and SVV measurements, which showed strong correlation with NT proBNP levels and Everest congestion score.
Keywords: Electrical cardiometry, Everest congestion score, Fluid status assessment, Monitoring heart failure, Serum NT-proBNP level.

INTRODUCTION
Heart failure (HF) is a complex medical disease that affects medical practice worldwide. The prevalence of HF is estimated to be between 1% and 2% in developed nations, with a higher percentage of individuals over the age of 70–80% having this diagnosis. Approximately 5% of hospital hospitalizations are due to heart failure (HF), and the total death rate for HF patients within a year of hospitalization is 17–45% [(1)]. Global interest has been generated by the assessment of hemodynamic indices and their alterations in acute decompensated heart failure. Hemodynamic examinations were previously almost exclusively conducted using invasive examination techniques that had limited applicability. However, in addition to the use of established techniques like echocardiography, ECG, brain natriuretic peptide test, or chest X-ray, a lot of researches have recently begun for alternative non-invasive techniques. These methods should ideally be simple to use in both inpatient and outpatient settings [(2)].

A straightforward diagnostic technique that is simple to use and doesn't require any specialized staff training is electrical cardiometry. This technique is based on measuring the variations in thoracic electrical conductivity that the circulatory system creates during diastole or systole. It also measures cardiac function and contractility parameters including cardiac output (CO), stroke volume (SV), and other hemodynamic fluid status parameters including TFC and SVV. The parameters identified during electrical cardiometry analysis are used to diagnose heart failure (HF), assess risk, regulate therapy effectiveness, and distinguish between acute dyspnea caused by cardiac and non-cardiac etiology [(3)]. In the setting of asymptomatic ventricular dysfunction and clinical heart failure, the clinical usefulness of BNP has been demonstrated in a variety of clinical scenarios. The European Guidelines for Heart Failure Diagnosis and Therapy include brain natriuretic peptide in the diagnostic algorithm for HF along with other initial tests, such as the electrocardiogram, chest X-ray and echocardiogram. So, low BNP values "rule out" HF and very high values would strongly support the diagnosis and be useful in follow up [(4)]. The biological differences between BNP and NT-proBNP mostly stem from the fact that BNP is a hormone that is biologically active, but NT-proBNP is eliminated from the body passively. As a result, antifailure drugs have less of an impact on NT-proBNP [(5)]. The purpose of this study was to prove the relationship between electrical cardiometry fluid status measurements and serum NT-pro BNP levels in patients hospitalized for heart failure treatment.

METHODS
This prospective study was carried out on 50 patients (72% males and 28% females).

Inclusion criteria: Age over 18 years old diagnosed as chronic HF of ischemic or non-ischemic etiology for at

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least 3 months before starting the study and admitted to hospital for acute decompensated HF, congestion status must be evaluated for all patients and all patients must have stable sinus ECG rhythm on admission.

Exclusion criteria: Sepsis, atrial fibrillation, renal failure, severe arterial hypertension, valvular prosthesis, rheumatic heart disease, liver cirrhosis, morbid obesity, chemotherapy, tachyarrhythmia, recent myocardial infarction and pace maker.

Every patient underwent a thorough history taking and a full general examination, which included taking their vital signs, body mass index (BMI), cardiac examination and chest examination. Everest congestion score including peripheral oedema score, dyspnea score, orthopnoea score, rale score, jugular venous pressure score and fatigue score were evaluated for every patient twice, one time on admission and another before discharge after receiving optimal anti-failure therapy. Everest congestion score evaluation according to signs and symptoms shown in (Table 1).

Table (1): Clinical Everest congestion score [6]

Signs and symptoms	Score points	0	1	2	3
Dyspnea	(0-3) points	None	Seldom	Frequent	continuous
Orthopnea	(0-3) points	None	2 pillows	3 pillows	>30 angel degree
Fatigue	(0-3) points	None	Seldom	Frequent	Continuous
LL oedema	(0-3) points	Absent	Slight	moderate	Marked
Rales	(0-3) points	None	Bases	Less than 50%	More than 50%
Jugular venous pressure (cm h2o) (0-3)points		<6	9-Jun	15-Oct	>15
Total Everest score		From 0 -18 according to signs and symptoms			

Other diagnostic investigations including (Echocardiography, ECG) were done for all patients on admission. All patients had Echocardiographic evaluation of left ventricular systolic function. The left ventricular ejection fraction was determined by utilizing pulsed wave Doppler echocardiography to evaluate the left ventricular diastolic function and calculate the E/A ratio. Aortic valve Doppler echocardiography was used to assess the peak gradient. The evaluation of right ventricular function was conducted by assessing the tricuspid annular plane systolic excursion (TAPSE) and the inferior vena cava (IVC). Every patient underwent biochemical tests, including a complete blood count, C-reactive protein, serum creatinine, urea, and troponin level. Nt-proBNP serum level was evaluated for each patient. The patient does not have to be fasting in order to have a spot blood sample taken for the Nt-proBNP test [7]. For people under the age of 75, the normal range for NT-proBNP was less than 125 pg/ml, while for those over 75, it was less than 450 pg/ml [8]. Every patient was admitted for acute decompensated HF was evaluated for serum NT-proBNP level twice, one time on admission and another before discharge after receiving optimal anti-failure decongestion therapy.

Electrical cardiometry (EC): It depends on measuring the resistance that the electrical current encountered while passing a high frequency, passing a little electrical current across the chest. The EC employs sophisticated filtering methods to detect alterations in conductivity resulting from the circulatory system. Four skin sensors were attached to patient's body two sensors are positioned on the patient's neck and the others on the left side of the thorax. This enabled for continuous monitoring of changes in the thoracic electrical conductivity for at least 30 seconds while the patient was in the laying position. To make sure taking accurate measurements, EC should detect stable ECG sinus rhythm and stable electrical signal before start. During diastole, the RBCs in the aorta take on a random configuration that increases resistance to the electrical current and lowers its conductivity. A greater conductivity state results from the RBCs aligned parallel to the blood flow and electrical current during systole by pulsatile flow. EC technology measures the rate of conductivity change before and after the aortic valve opens to estimate the peak acceleration of blood in the aorta and the time it takes for the left ventricle to evacuate blood (flow time) and so on, evaluating stroke volume and cardiac contractility. Also fluids provide a faster media for transferring EC electrical current and so a greater conductivity. By identifying the changes in conductivity, EC can estimate thoracic fluid content (TFC) [9]. Every patient was evaluated for EC fluid status measurements (TFC and SVV) twice, one time on admission and another before discharge after receiving optimal anti-failure therapy.

Ethical approval: The patient or the patient's family members signed written informed consent. The study was carried out with permission from Menoufia University Hospital's Ethical Committee Cardiac Intensive Care Unit and Cardiology Department. Helsinki declaration was followed through conduction of the study.

Statistical analysis

IBM Inc., Armonk, NY, USA SPSS version 26 for statistical analysis was used. Using the unpaired the Student's t-test was used to compare quantitative variables between the two groups. The results were reported as the mean ± standard deviation (SD). Qualitative factors were displayed as percentages (%) and frequencies. To determine the level of correlation between two quantitative variables, Pearson correlation analysis was performed. A P-value with two tails ≤ 0.05 was deemed statistically significant.

RESULTS

Our study showed that the age of the studied patients was 60.8 ± 4.3 years. There were 36 (72%) males and 14 (28%) females. BMI was 27.7 ± 2.67 Kg/m^2. Comorbidities were DM in 34 (68%) patients, HTN in 30 (60%) patients, dyslipidemia in 37 (74%) patients, IHD in 44 (88%) patients and CVS in 8 (16%) patients. The LVESD was 49.63 ± 5.02 mm. LVEDD was 61 ± 5.07 mm. LVEF was 36.16 ± 7.97 %. Regarding diastolic dysfunction, 8 (16%) patients were grade I, 19 (38%) patients were grade II and 23 (46%) patients were grade III. TAPSE was 17.13 ± 3.83 mm. IVC was 25.24 ± 2.67 mm (Table 2).

Table (2): Demographic data, BMI, comorbidities distribution, and echocardiography evaluation of left ventricular function, diastolic function and right ventricular functions of the studied patients (n = 50)

		Patients (n = 50)
Age (years)		60.8 ± 4.3
Sex	**Male**	36 (72%)
	Female	14 (28%)
BMI (kg/m^2)		27.7 ± 2.67
Comorbidities	**DM**	34 (68%)
	HTN	30 (60%)
	Dyslipidemia	37 (37%)
	IHD	44 (88%)
	CVS	8 (16%)
LVEDD (mm)		61 ± 5.07
LVESD (mm)		49.6 ± 5.02
LVEF (%)		36.2 ± 7.97
Diastolic dysfunction	**Grade I (E/A <0.8)**	8 (16%)
	Grade II (E/A >0.8)	19 (38%)
	Grade III E/A (>1.5)	23 (46%)
TAPSE (mm)		17.1 ± 3.83
IVC (mm)		25.2 ± 2.67

The data are reported as the mean ± SD), or as a frequency expressed as a percentage (%). BMI: Body Mass Index. DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic Heart Disease, CVS: Cardiovascular Stroke, LVEDD: Diameter of the left ventricle of the heart at the end of diastole, LVESD: Diameter of the left ventricle at the end of systole, LVEF: Left ventricular ejection fraction, TAPSE: Tricuspid Annular Plane Systolic Excursion, IVC: Inferior vena cava.

Peripheral oedema, orthopnoea, rales, dyspnea, jugular venous pressure, and fatigue scores were among the Everest congestion scores that were considerably lower at discharge than at admission (P <0.001). The level of serum NT-proBNP was considerably lower upon discharge compared to admission (P <0.001). Regarding EC fluid status measurements, SVV of patients showed a considerable improvement at the time of release compared to that at admission, with a substantial increase in one parameter (P<0.001) and a significant decrease in another parameter (P<0.001) (Table 3).

Table (3): Everest congestion score, electrical cardiometry fluid status parameters, and serum NT-proBNP level of the studied patients at admission and discharge

Variable		Admission (n=50)	Discharge (n=50)	P-value
Everest congestion score	**Peripheral oedema score**	1.88 ± 0.8	0.18 ± 0.39	**<0.001***
	Orthopnea score	2.1 ± 0.71	1.1 ± 0.71	**<0.001***
	Rale score	2 ± 0.7	0.3 ± 0.46	**<0.001***
	Dyspnea score	2.2 ± 0.53	0.74 ± 0.66	**<0.001***
	JVP score	1.98 ± 0.51	1.08 ± 0.67	**<0.001***
	Fatigue score	0.94 ± 0.51	0.38 ± 0.49	**<0.001***
	Everest score	11.1 ± 2.82	3.6 ± 2.42	**<0.001***
EC parameters	**TFC (kOhm-1)**	53.41 ± 8.19	31.62 ± 5.25	**<0.001***
	SVV (%)	5.66 ± 3.86	14.34 ± 4.06	**<0.001***
Serum NT-proBNP level (pg/mL)		2288.1 ± 131.77	1353.8 ± 70.21	**<0.001***

Data are presented as mean ± SD, JVP: Jugular venous pressure, EC: Electrical cardiometry, SVV: Stroke volume variation, TFC: Thoracic fluid content, BNP: B-Type Natriuretic Peptide, *: Significant as P value ≤ 0.05.

According to our findings, a strong positive connection was seen between serum NT-proBNP level and TFC at admission (R-value:0.702; P-value: < 0.001) and at discharge (R-value:0.758; P-value: < 0.001), while there was a negative correlation between serum NT-proBNP level and SVV at admission (R-value: -0.301; P-value: < 0.05) and at discharge (R-value: -0.741; P-value: < 0.001) as shown in table (4).

Table (4): Correlation between serum NT-proBNP level and electrical cardiometry fluid status parameters (TFC and SVV) at admission and discharge.

		Admission (n=50)		Discharge (n=50)	
		R	**P**	**r**	**P**
Serum NT-proBNP level (pg/mL)	**TFC (kOhm-1)**	0.702	**< 0.001***	0.758	**< 0.001***
	SVV (%)	-0.301	**0.033***	-0.741	**< 0.001***

TFC: Thoracic fluid content, SVV: Stroke volume variation, SV: Stroke volume, *: Significant as P value ≤0.05

According to our results, the Everest congestion score and TFC showed positive correlation at admission (R-value:0.797; P-value < 0.001) and at discharge (R-value:0.755; P-value < 0.001). Additionally, Everest congestion score and Nt-proBNP were correlated positively at admission (R-value:0.791; P-value < 0.001) and at discharge (R-value:0.806; P-value < 0.001) as shown in table (5).

Table 5: Correlation between Everest congestion score and both of thoracic fluid content (TFC) measured by electrical cardiometry and Nt-proBNP

		Admission (n=50)		Discharge (n=50)	
		R	P	R	P
Everest score	TFC (kOhm-1)	0.797	< **0.001***	0.755	< **0.001***
	Nt-proBNP	0.791	< **0.001***	0.806	< **0.001***

TFC: Thoracic fluid content, *: Significant as P value ≤ 0.05

DISCUSSION

HF is a complicated syndrome characterized by several cardiac and non-cardiac disorders, with a high death and hospitalization rate. Traditionally, treatment has been tailored on medical history and physical examination. However, because cardiac biomarkers reflect the pathogenesis of HF, they supplement clinical assessment, diagnosis and follow up HF patients [10].

We utilized the Everest congestion score, which includes ratings for peripheral oedema, orthopnea, dyspnea, rales, JVP, and fatigue to assess the clinical status of congestion. Upon release, the scores exhibited a notable decrease compared to the scores recorded upon admission.

Serum NT-proBNP levels were significantly lower at discharge than at admission, according to our study. This is because receiving optimal anti-failure decongestion therapy led to a decrease in intraventricular blood volume, which in turn decreased the level of Nt-proBNP as brain natriuretic peptide is a hormone released by cardiac ventricles' cardiomyocytes in response to stretching of the left ventricle due to an increase in blood volume within the ventricle. Furthermore, According to **Ambrosy *et al.*** [6], the Everest trial which consisted of patients admitted for worsening heart failure symptoms and signs with an EF ≤ 40% their Everest score was improved at discharge compared to admission. These findings are consistent with our hypothesis. Additionally, the mean values of the levels of B-type natriuretic peptide and NT-proBNP decreased from 734 pg/mL and 4857 pg/mL at the beginning to 477 pg/mL and 2834 pg/mL at the time of discharge or on day 7.

Similar to this, **Yu *et al.*** [11] study found that NT-proBNP levels decreased 1 month following cardiac resynchronization therapy (CRT) (2655 ± 2242 pg/mL vs. 2149 ± 2033 pg/mL; P =.03), and they decreased even more at 3 months (1473 ± 1786 pg/mL; P < 0.001 vs. baseline). **Knebel *et al.*** [12] in their study that focused on chronic heart failure patients who were admitted to the hospital due to acute decompensation, namely those classified as New York Heart Association class III-IV. These patients were given the most effective drugs for treating heart failure such as diuretics, vasodilators, and inotropes. Hemodynamic measurements were taken using a balloon-tipped pulmonary artery catheter. The results showed that after eight hours, the average decrease in NT-proBNP was 91.0% ± 21.3% compared to the initial value. After sixteen hours, the average decrease was 73.0% ± 16.0% of the initial value. After twenty-four hours, the average decrease was 62.4% ± 20.3% of the initial value. Finally, after thirty-two hours, the average decrease in NT-proBNP was 42.3% ± 12.3% of the initial value. Additionally, there was a decrease in pulmonary capillary wedge pressure.

Parameters measured by electrical cardiometry including TFC (representing intravascular and extravascular thoracic fluid volume) was significantly lower at discharge than at admission. Another parameter, SVV which can represent the status of intravascular circulatory volume and cardiac preload was significantly higher at discharge than at admission. And this is attributed to the effect of diuretic therapy through increasing salt and water urinary excretion leading to reduction in intravascular circulatory fluid volume, pulmonary congestion and thoracic fluid content [13].

According to our research, a strong positive connection was seen between serum NT-proBNP level and TFC at both admission and discharge. According to a research conducted by **Sadauskas *et al.*** [14], 60 patients (24 women and 36 men) who had acute decompensated heart failure and were hospitalized to intensive care units were assessed using the impedance cardiography (ICG). The results of the assessment were correlated with BNP levels and other HF diagnostic methods. There was a noteworthy positive correlation discovered between BNP and TFC.

According to **Fathy *et al.*** [15], there was a substantial difference in TFC measured by EC between the successful and failed weaning groups. It has also been found that the predictive accuracy of TFC in identifying weaning failure is particularly pronounced in patients with impaired systolic function. Stroke volume fluctuation refers to the changes in the volume of blood pumped out of the heart with each heartbeat (SVV) is one of naturally occurring hemodynamics in which changes in intra-thoracic pressure occurring during negative pressure ventilation lead the arterial pulse pressure to fall at inspiration and rise at expiration. The results of our research showed a negative correlation between SVV and serum NT-proBNP at admission and at discharge.

El-Ghonimy *et al.* [16] conducted a study, which examined the effectiveness of using the inferior vena cava (IVC) collapsibility index to assess fluid responsiveness in critically sick hypotensive patients. The study also investigated the correlation between the IVC collapsibility index and stroke volume fluctuation (SVV). The study found that fluid responsiveness may be predicted using the caval index, which has a substantial correlation with SVV. A total of 568 patients from 23 studies were included in **Zhang *et al.*** [17] comprehensive evaluation of a systematic review and meta-analysis of clinical studies investigating the diagnostic effectiveness of SVV in predicting fluid responsiveness. Fluid responsiveness and baseline SVV were correlated. Having a pooled correlation value of 0.718. Our observations indicated that SVV had a diagnostic odds ratio of 18.4, allowing it to accurately predict fluid responsiveness in all situations. It demonstrated a sensitivity of 0.81 and a specificity of 0.80. The SVV was found to be valuable for diagnostic reasons. SO, we can depend on SVV in evaluation of intravascular fluid volume status and make the best decision regarding management and follow up heart failure decongestion therapy.

LIMITATIONS

EC requires correct electrodes placement, good electrical signal & stable ECG sinus rhythm should be considered. The study focused on patients with reduced systolic function, and further research is required to assess individuals with maintained systolic function. The findings of this single-center study cannot be extrapolated to the entire country due to its limited scope. The small sample size had an impact on the outcomes and the study's validity needs to be confirmed.

CONCLUSION

EC can play a key role in monitoring the response to heart failure therapy via providing real time non-invasive objective assessment of fluid status through TFC and SVV measurements, which showed strong correlation with NT proBNP levels and Everest congestion score.

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