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Complex assessment of patients with decompensated heart failure: The clinical value of impedance cardiography and N-terminal pro-brain natriuretic peptide

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ABSTRACT

Background: Acute decompensated heart failure (ADHF) is a serious clinical problem and a condition requiring immediate diagnostics, supporting the therapeutic decision adequate to the specific ADHF mechanism. N-terminal pro-brain natriuretic peptide (NT-proBNP) is an established biochemical marker of heart failure, strongly related to hemodynamic status. Impedance cardiography (ICG) provides non-invasive hemodynamic assessment that can be performed immediately at the bedside and revealed to be useful diagnostic tool in some clinical settings in cardiology.

Objectives: The aim of this study was to evaluate the usefulness of ICG in the admission diagnostics and monitoring the effects of treatment in patients hospitalized due to ADHF, with special emphasis on its relation to NT-proBNP.

Methods: This study enrolled 102 patients, aged over 18 years, hospitalized due to ADHF. The subjects underwent detailed clinical assessment, including ICG and NT-proBNP at admission and at discharge day.

Results: Among all analyzed ICG parameters thoracic fluid content (TFC), a marker of chest overload, was the most significantly correlated with NT-proBNP level ($R = 0.46$; $p = 0.000001$). In comparison with patients with low thoracic fluid content (TFC $\leq$ 35/kΩ), those with higher TFC values (>35/kΩ) exhibited a greater severity of symptoms (NYHA functional class); higher NT-proBNP levels; lower left ventricular ejection fraction (LVEF), stroke index (SI), and cardiac index (CI); as well as significantly higher systemic vascular resistance index (SVRI). These TFC-based subgroups showed no significant differences in terms of heart rate (HR), systolic blood pressure (SBP), or diastolic blood pressure (DBP).

Conclusions: The evaluation of hemodynamic parameters, especially TFC, seems to be a worthwhile addition to standard diagnostics, both at the stage of hospital admission and while monitoring the effects of treatment. Impedance cardiography is a useful method in evaluating individual hemodynamic profiles in patients with ADHF.

Introduction

Acute decompensated heart failure (ADHF) is a serious clinical problem and a condition requiring immediate diagnostics, supporting the therapeutic decision adequate to the specific ADHF mechanism[1]. The presence of comorbidities, such as arrhythmias, coronary artery disease, chronic kidney disease, and lung conditions makes it more difficult to establish a definitive diagnosis.[2–4]

Medical history and physical examination findings remain key in differentiating ADHF etiology. They are usually supplemented by additional assessments, including electrocardiography, echocardiography, chest X-ray, and lung ultrasound.[1,5–9] Among laboratory tests, N-terminal pro-brain natriuretic peptide (NT-proBNP) is an

Abbreviations: ADHF, acute decompensated heart failure; BMI, body mass index; CI, cardiac index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICG, impedance cardiography; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; SI, stroke index; SVRI, systemic vascular resistance index; TFC, thoracic fluid content

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established biochemical marker in diagnosis of heart failure (HF), strongly related to cardiac hemodynamics,[10,11] useful in monitoring the effects of treatment,[12,13] as well as determining the prognosis.[14–18] However, its diagnostic accuracy is lower in patients with obesity and renal dysfunction. Additionally, the relatively high cost of NT-proBNP testing considerably limits its use in routine practice.[19–23] The necessity to take a blood sample and waiting for a laboratory test result is also not indifferent in life-threatening situations. Therefore, it is reasonable to searching for new methods identifying the causes of ADHF and monitoring the effects of its treatment.

Impedance cardiography (ICG) is a simple, low-cost, non-invasive assessment, which can be performed at the bedside (urgently, if needed). This method not only evaluates thoracic fluid content (TFC), but also other hemodynamic parameters, such as cardiac function (cardiac index, CI) and vasoconstriction (systemic vascular resistance index, SVR). Impedance cardiography was demonstrated to be of practical use in differentiating the causes of dyspnea in emergency settings,[24] predicting HF decompensation,[25] and identifying HF patients with high defibrillation threshold.[26] In a study conducted in 142 patients with HF and low left-ventricular ejection fraction (LVEF = 30.6 ± 6.1%), Malfatto et al.[27] demonstrated the combination of brain natriuretic peptide (BNP) levels of >450 pg/mL and TFC of >40/kΩ to be the strongest indicator of mortality within a 12-month follow-up.

Therefore, the purpose of this study was to evaluate the usefulness of ICG in the admission diagnostics and monitoring the effects of treatment in patients hospitalized due to ADHF, with special emphasis on its relation to NT-proBNP.

Methods

This prospective, observational study enrolled 102 patients of both sexes, aged >18 years, hospitalized at the Department of Cardiology and Internal Diseases in the period between November 2014 and March 2017, whose cause of hospitalization was ADHF (defined according to the European Society of Cardiology guidelines[1]) and who required intravenous diuretic therapy.

The exclusion criteria were: (1) unstable angina; (2) history of acute coronary syndrome and/or coronary artery bypass grafting surgery within the last 12 weeks; (3) cardiac resynchronization therapy introduced within the last year (or planned implantation within the next 24 months); (4) non-cardiogenic shock; (5) valvular disease or other acquired heart defects requiring surgical intervention; (6) hypertrophic cardiomyopathy; (7) severe pulmonary hypertension or other severe lung condition (severe form of chronic obstructive pulmonary disease or bronchial asthma); (8) poorly controlled hypertension; (9) anemia (hemoglobin <10.0 g/dL); (10) acute and/or decompensated non-cardiovascular disease; (11) pulmonary embolism; (12) end-stage chronic kidney disease and/or ongoing hemodialysis therapy; (13) severe or chronic inflammatory disease, severe infection (including febrile conditions, radiologically-confirmed pneumonia, suspected septic shock); (14) neoplastic disease; (15) severe psychiatric disorder; (16) the lack of informed consent.

The study protocol was approved by the Military Institute of Medicine Institutional Review Board (approval no. 14/WIM/2012), and all study participants provided their written informed consent. The study was registered at ClinicalTrials.gov (NCT 02355769). The patients were treated according to current guidelines and there were no limitation or delay in the treatment because of performing below mentioned clinical tests.

Clinical examinations were conducted with a particular emphasis on the history of symptoms (graded according to New York Heart Association (NYHA) functional class), concomitant diseases, and current medication. The following were measured on physical examination: heart rate (HR) office systolic blood pressure (SBP), office diastolic blood pressure (DBP), and body parameters (including body mass index (BMI)).

Laboratory tests were conducted on peripheral venous blood samples collected twice: within 2 h from admission and in the morning at discharge day (7:00–8:30 a.m.). The measured parameters included: the levels of NTproBNP ($n = 102$ at admission, $n = 75$ at discharge) high-sensitivity troponin T, creatinine and estimated glomerular filtration rate (eGFR), calculated with the Modification of Diet in Renal Disease (MDRD) study equation.[28]

Echocardiographic examinations ($n = 97$) were conducted with Vivid S6 (GE-Healthcare, USA) and Vivid 7 (GE-Healthcare, USA) ultrasound systems and the assessment included cardiac chamber dimensions, left ventricular wall thickness and contractility, ejection fraction, as well as valvular structure and function. Echocardiography reports included any moderate-to-severe mitral, tricuspid, and/or aortic regurgitation; severe aortic stenosis; as well as the numerical values of the following parameters: left ventriclular end-diastolic diameter, right ventriclular end-diastolic diameter, interventricular septum thickness, and left atrial diameter, measured in the parasternal long-axis view. There were no time limit for echocardiography defined (the median of time delay from admission to echocardiography was 3 days).

Impedance cardiography (ICG). All ICG measurements were performed with the Niccomo™ device (Medis, Germany) within 24 h of admission, after 10 min of rest in a sitting position. Data was recorded during a 10 min assessment and exported to the dedicated software (Niccomo Software). The measurement was also performed at discharge day.

The final analysis included mean values of hemodynamic parameters, such as: HR [bpm], SBP [mmHg], DBP [mmHg], TFC [1/kΩ], calculated from basic impedance (Z0) as its reciprocal: TFC = 1000/Z0; SI, calculated using the Sramek and Bernstein formula for stroke volume (SV) and indexed to body surface area to yield SI [mL/m^2]; CI [(mL/min)/m^2], calculated as SI × HR; SVRI [(dyn × s)/cm^5/m^2)], calculated as 80 × (MBP− central venous pressure)/CI, where central venous pressure is assumed 6 mm Hg.

Statistical analysis

The statistical analysis was performed using Statistica 12.0 (StatSoft, Inc., Tulsa, USA). The distribution and normality of the data were assessed via visual inspection and the Kolmogorov–Smirnov test. Continuous variables were presented as means ± standard deviation (SD) and categorical variables were presented as absolute and relative frequencies (percentages). The associations between selected variables were analyzed with Pearson's/Spearman's correlation coefficients. The change in selected variables was calculated as: d_X (delta) = [absolute value at discharge] − [absolute value at admission]. For comparative analysis, the study group was stratified (basing on previous studies[25,26]) by the admission TFC values (>35/kΩ vs. ≤35/kΩ; $n = 48$ vs. $n = 54$). These subgroups were compared in terms of clinical, echocardiographic, and hemodynamic parameters with the use of ANOVA/Mann–Whitney *U* test for continuous variables and chi2 test/Fisher's exact test for categorical variables. The p value of <0.05 was considered statistically significant.

Results

Study group baseline characteristics

The majority of the study group ($n = 66$ 64.7%) were patients with NYHA class III symptoms, whereas the remaining 36 patients (35.3%) reported symptoms at rest (class IV). The most commonly reported symptoms were dyspnea on exertion, orthopnea, and edema (Table 1). Auscultation revealed evidence of pulmonary congestion in nearly all patients (98.1%), three-fourths of patients presented with peripheral edema. History-taking most commonly revealed ischemic heart

Table 1
Basic characteristics ($n = 102$)

	Study group $n = 102$
Age, mean ± SD	71.4 ± 12.5
Males, *n* (%)	78 (76.5%)
HR [bpm], mean ± SD	87.4 ± 24.2
SBP [mmHg], mean ± SD	135.4 ± 26.8
DBP [mmHg], mean ± SD	81.8 ± 13.5
Symptoms	
Dyspnea at rest, *n* (%)	41 (40.2)
Dyspnea on effort, *n* (%)	100 (98.1)
Ortophnoe, *n* (%)	78 (77.2)
Paroxysmal nocturnal dyspnoea, *n* (%)	44 (43.1)
Tachypnoe, *n* (%)	21 (20.6)
Pulmonary rales, *n* (%)	100 (98.1)
Oedema, *n* (%)	77 (75.5)
Concomitant disease	
Prior MI, *n* (%)	42 (41.1)
Hypertension, *n* (%)	68 (66.6)
Atrial fibilation, *n* (%)	54 (52.9)
Moderate-to-severe valvular disease *n* (%)	60 (58.8)
Diabetes mellitus, *n* (%)	50 (49.0)
Chronic obstructive pulmonary disease, *n* (%)	15 (14.7)
Chronic kidney disease (stadium ≥3), *n* (%)	30 (29.4)
Laboratory data on admission	
NT-proBNP [pg/ml], mean ± SD	6197 ± 7057
Creatinine [mg/dl], mean ± SD	1.31 ± 0.51
eGFR [ml/min/1,73 m^2], mean ± SD	62.2 ± 23.9
Hemoglobin [g/dl], mean ± SD	12.6 ± 2.6

DBP, diastolic blood pressure; eGFR, estimated glomeruar filtration rate; HR, heart rate, NTproBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.

disease, hypertension, atrial fibrillation, valvular disease, and diabetes mellitus (Table 1). The mean LVEF was 37.3 ± 14.1%, left ventriclular end-diastolic diameter 59.2 ± 10.2 mm, right ventriclular end-diastolic diameter 35.3 ± 5.7 mm, left atrial diameter 47.3 ± 0.60 mm.

Table 2
Correlations between NT-proBNP and hemodynamic parameters at admission ($n = 102$)

vs NT-proBNP [pg/ml]	*R*	*p*
HR [1/min]	0.08	0.461
SBP [mmHg]	0.01	0.885
DBP [mmHg]	0.15	0.146
SI [ml m^{-2}]	−0.22	0.036
CI [ml m^{-2} min^{-1}]	−0.10	0.347
SVRI [dyn s cm^{-5} m^2]	0.16	0.138
TFC [1/kΩ]	0.46	0.000001

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SI, stroke index; CI, cardiac index; SVRI, systemic vascular resistance index; TFC, thoracic fluid content.

The following proportions of patients had moderate-to-severe valvular disease: mitral regurgitation 48.4% ($n = 47$), tricuspid regurgitation 36.1% ($n = 35$), aortic regurgitation 2.1% ($n = 2$), and aortic stenosis 10.3% ($n = 10$).

Correlations between hemodynamic parameters and NT-proBNP levels in the study group

The analysis of baseline values of the evaluated parameters revealed a significant correlation between TFC values and NT-proBNP levels (Table 2, Fig. 1). The only other hemodynamic parameter that showed a correlation with NT-proBNP levels was SI.

Analysis of subgroups stratified by TFC

Study group stratification based on TFC values demonstrated that, in comparison with patients with lower TFC values (≤35/kΩ), those with higher baseline TFC values (>35/kΩ) had more pronounced

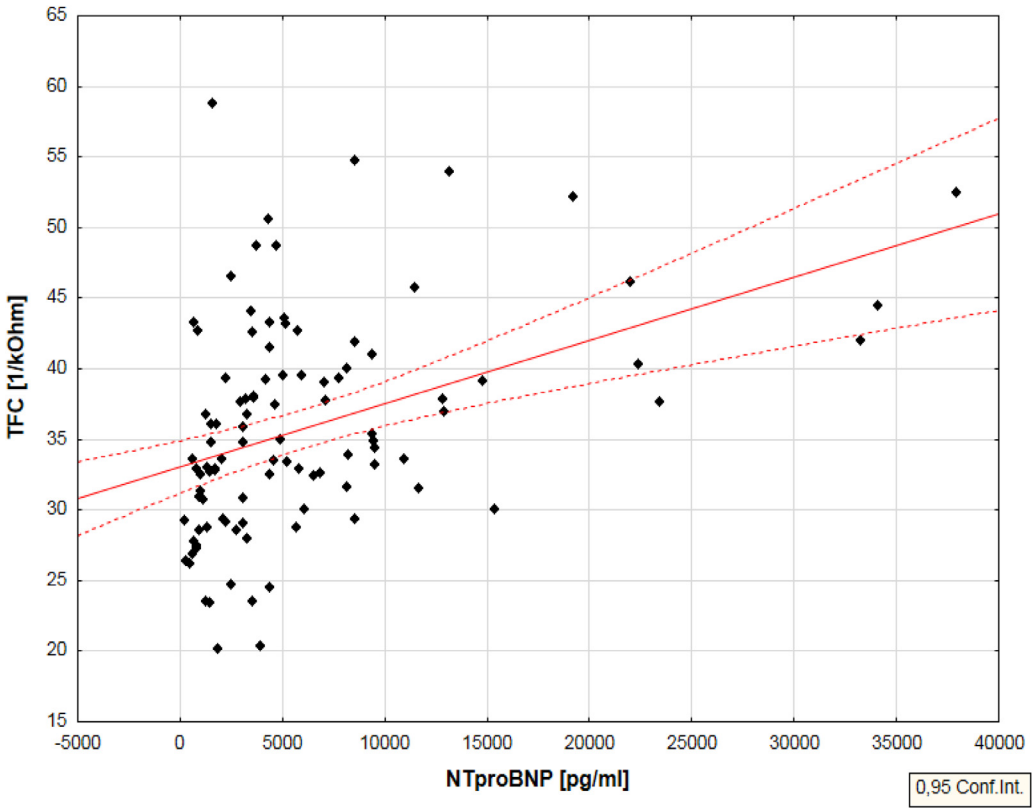

Fig. 1. Correlation plots: NTproBNP ($n = 75$).

Table 3
The comparison between subgroups with higher (>35 1/kΩ) and lower TFC (≤35 1/kΩ) at admission (n = 102)

	Subgroup with TFC > 35 1/kΩ n = 48	Subgroup with TFC ≤ 35 1/kΩ n = 54	p
Age, mean ± SD	70.9 ± 14.1	71.9 ± 10.9	0.981
BMI [kg/m^2], mean ± SD	28.6 ± 6.6	31.4 ± 6.1	0.007
NYHA class [-], mean ± SD	3.48 ± 0.58	3.17 ± 0.47	0.009
Creatinine [mg/dl], mean ± SD	1.33 ± 0.51	1.30 ± 0.51	0.178
eGFR, [ml/min/1,73 m^2], mean ± SD	63.1 ± 24.2	61.4 ± 23.9	0.424
NTproBNP [pg/ml], mean ± SD	8793 ± 8911	3846 ± 3484	0.0002
High-sensitivity troponin T [ng/l], mean ± SD	167.9 ± 358.5	45.6 ± 72.9	0.009
Hemodynamics			
HR [1/min], mean ± SD	83.2 ± 23.1	79.9 ± 20.7	0.522
SBP [mmHg], mean ± SD	120.4 ± 22.8	125.5 ± 25.8	0.249
DBP [mmHg], mean ± SD	73.6 ± 11.6	73.1 ± 11.8	0.339
SI [ml*m^{-2}], mean ± SD	36.5 ± 13.7	42.8 ± 12.0	0.013
CI [ml*m^{-2}*min^{-1}], mean ± SD	2.71 ± 0.76	3.27 ± 0.87	0.005
SVRI [dyn s cm^{-5} m^2], mean ± SD	2611 ± 761	2128 ± 697	0.0008
TFC [1/kΩ], mean ± SD	42.2 ± 5.6	30.0 ± 3.8	<0.0001

BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SI, stroke index; CI, cardiac index; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Assocation; SVRI, systemic vascular resistance index; TFC, thoracic fluid content.

symptoms (higher NYHA class) and higher NT-proBNP levels, along with lower hemodynamic parameters of left ventricular systolic function (i.e. LVEF, SI, and CI) and a significantly higher SVRI. There were no significant differences in terms of HR, SBP, or DBP (Table 3).

The effect of treatment on NT-proBNP levels and TFC values

Both parameters decreased significantly as a result of treatment: NT-proBNP levels (from 5,213 ± 5,238 to 2,752 ± 3,924 pg/L;

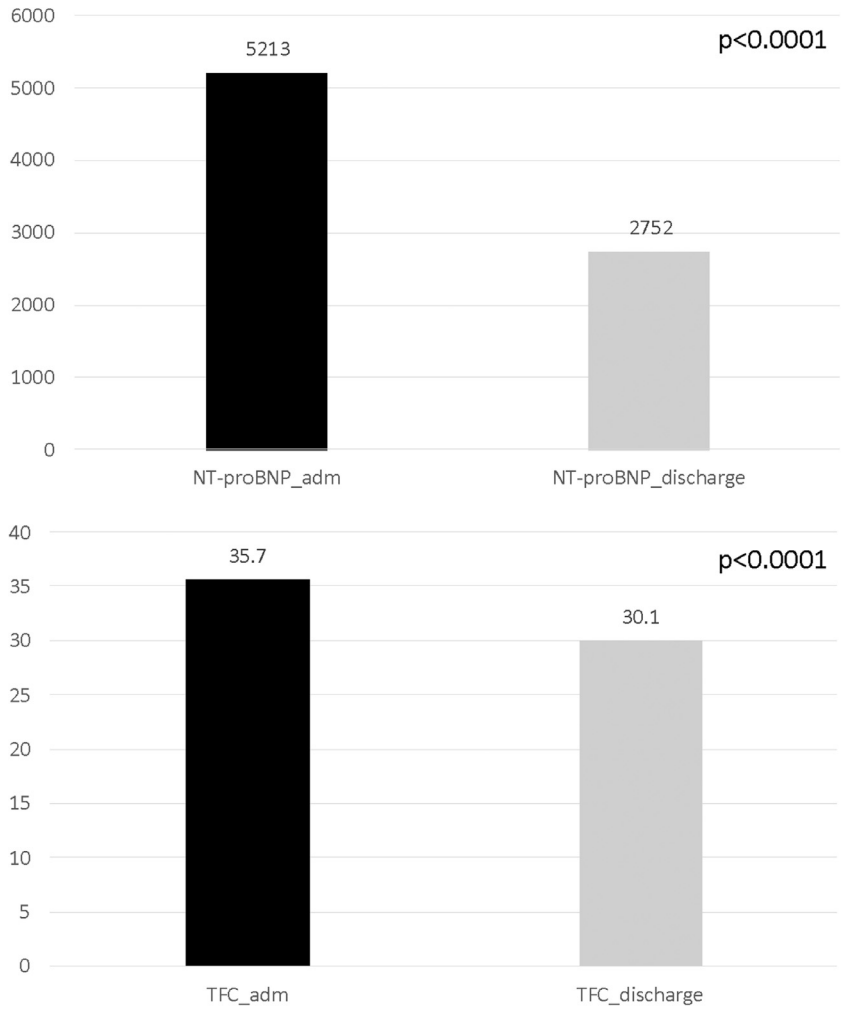

Fig. 2. The effect of in-hospital therapy on NT-proBNP [pg/l; n = 75] and TFC [1/kΩ; n = 102].

$p < 0.0001$) and TFC (from 35.6 ± 7.6 to 30.1 ± 6.1/kΩ; $p < 0.0001$) (Fig. 2). Assessment of the mean changes in these parameters demonstrated a more pronounced decrease in TFC in the subgroup with higher baseline TFC (> 35 /kΩ) versus the other subgroup (≤35/kΩ): -9.5 ± 7.3/kΩ vs. -2.0 ± 5.5/kΩ ($p < 0.000001$), with a similar (though less pronounced) tendency in NTproBNP levels: $-2{,}997 \pm 3{,}771$ vs. $-1{,}938 \pm 2{,}580$ pg/L, respectively ($p = 0.160$).

The direction of TFC changes in the subgroup with higher baseline TFC (>35/kΩ) was more uniform, with most patients achieving a reduced TFC value (Fig. 3). The opposite was true in the subgroup with lower baseline TFC (≤35/kΩ), where TFC changes varied widely and showed no consistent direction.

Analysis revealed a correlation between the treatment-induced changes in NT-proBNP levels and changes in some hemodynamic parameters evaluated via ICG (Table 4, Fig. 3). Changes in TFC and SI values were the only variables that correlated with a change in NT-proBNP levels, and (according to analyses in subgroups stratified by baseline TFC) this correlation was shown only in the subgroup with higher baseline TFC values (Fig. 4).

Discussion

ICG assessments conducted in patients hospitalized due to ADHF demonstrated significant heterogeneity in individual hemodynamic profiles. Impedance cardiography showed that pulmonary congestion was not the main underlying cause of HF exacerbation in a non-inconsequential proportion of patients. The reliability of ICG assessments seems to be supported by a correlation between TFC values and NT-proBNP levels as well as the concurrent changes in these parameters, reflecting the clinical improvement in response to treatment.

The characteristics of our study group were comparable with the relevant data from large registries and other studies on ADHF.[29–32] The majority of our patients had at least moderate left ventricular dysfunction (mean LVEF = 37.3%) and a typical clinical presentation, including predominantly dyspnea, evidence of pulmonary congestion, and peripheral edema. The comorbidity profile of our patients was also consistent with that of other ADHF populations.

Our findings suggest that ADHF may be due to pathomechanisms other than fluid overload in a much greater proportion of patients than conventional diagnostic assessments would indicate.[1] However, patients whose ICG assessment showed high TFC (>35/kΩ) exhibited more severe symptoms (graded by NYHA class), higher NT-proBNP levels, and a more pronounced impairment of cardiac function (i.e. lower LVEF, SI, CI). This is consistent with the generally established belief that pulmonary congestion is the most typical ADHF manifestation in patients with severe myocardial injury.[1,33] In such cases even a slight increase in left ventricular filling pressure leads to HF decompensation and increased release of natriuretic peptides (as a result of increased cardiac wall stress).[34–37] The hemodynamic consequence of this (due to an impaired Frank-Starling mechanism) is impaired cardiac function as a pump and pulmonary congestion.[38–40]

To our knowledge, it is the first study in patients with ADHF that included ICG assessment at admission and discharge. Earlier studies on the use of ICG in HF focused mainly on identifying the cause of dyspnea[41,42] or were conducted in patients with stable clinical state.[26,27,43–47] The results of those studies were not definitive. Drawing any comparisons between those findings and the findings of our

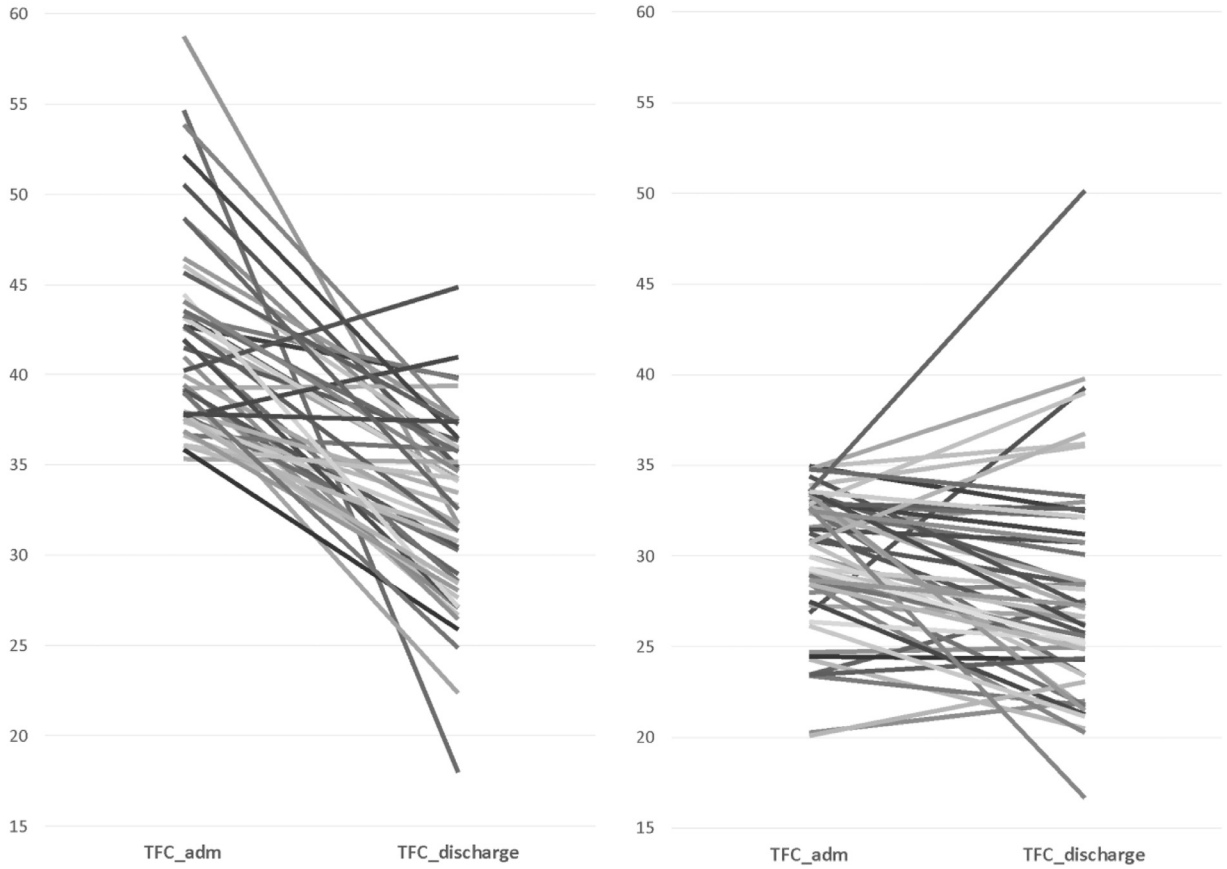

Fig. 3. The effect of in-hospital therapy on TFC [1/kΩ] in individual subjects of group with higher (>35 1/kΩ, left chart; $n = 48$) and lower admission TFC (≤35 1/kΩ, right chart; $n = 54$).

Table. 4
Correlations between changes in NT-proBNP and hemodynamic parameters related to in-hospital therapy ($n = 75$)

vs d_NT-proBNP	Whole group		TFC > 35 /kΩ		TFC < 35 1/kΩ	
	R	*p*	*R*	*p*	*R*	*p*
d_HR	−0.02	0.851	−0.07	0.697	0.07	0.686
d_SBP	0.09	0.468	0.11	0.534	0.06	0.722
d_DBP	0.14	0.246	0.15	0.394	0.10	0.545
d_SI	0.32	0.006	0.36	0.029	−0.03	0.844
d_CI	0.01	0.978	0.02	0.894	−0.04	0.830
d_SVRI	0.19	0.123	0.14	0.473	0.18	0.297
d_TFC	0.28	0.015	0.41	0.011	−0.01	0.962

d_ ,change in; CI, cardiac index; DBP, diastolic blood pressure; HR, heart rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; SI, stroke index; SVRI, systemic vascular resistance index; TFC, thoracic fluid content.

study would not be free from limitations. This is due to different methodologies, especially in terms of baseline characteristics and overall condition of the evaluated patients.

A study by Feliciano et al.,[48] conducted in a group of 55 patients with dilated cardiomyopathy (mean LVEF 24.7 ± 8.2%), demonstrated a correlation between TFC and NT-proBNP levels. Also, Havelka et al.[49] reported a moderate correlation between BNP levels and TFC values in patients with HF presenting to an emergency department with dyspnea (Spearman's $\rho = 0.32$, $p = 0.02$). They observed no relationship between BNP levels and CI ($\rho = -0.07$, $p = 0.64$). Our study also showed no correlation between CI and NT-proBNP levels, however, there were correlations between the absolute values and changes in SI on one hand and NT-proBNP levels on the other ($R = -0.22$; $p = 0.036$ and $R = 0.32$; $p = 0.0006$, respectively). Conversely, Balak et al.,[50] in patients with stable systolic HF, reported no correlation between TFC and natriuretic peptide levels. Also Täger et al.,[19] showed no significant correlation between either the abnormal clinical assessment findings or ICG-measured changes in hemodynamic parameters and the changes in NTproBNP levels in patients with stable HF. Thus, both our findings and those reported by others indicate that the relationship between hemodynamic parameters and natriuretic peptide levels is higher in patients with severe myocardial injury and clinically decompensated HF. In view of the fact that decrease in natriuretic peptide levels in patients hospitalized for ADHF may indicate their better prognosis,[51–54] the clinical importance of reducing TFC seems to be worth further investigation.

Clinical implications

Our findings confirm ADHF pathomechanisms diversity, especially in patients with less impaired cardiac function. This suggests the necessity of individualized diagnostic and therapeutic management, with ICG apparently being a useful method. In a substantial proportion of cases, dyspnea and other manifestations of cardiovascular decompensation are due to factors other than high TFC. Abnormal fluid distribution, concomitant arrhythmia, ischemic heart disease of atypical clinical presentation, poorly controlled hypertension and chronic kidney disease are common HF comorbidities in which a diuretic therapy, universally used in ADHF, may be not only ineffective but even harmful. In such cases, quantification of hemodynamic disturbances can help to select the most suitable treatment.

Study limitations

The main limitation of our study is the small size of the evaluated subgroups. Another important limitation was the 24 h window in which ICG assessments were performed, as the hemodynamic profile may change even within less than an hour of initiating effective treatment. It may influence (overestimate) the number of subjects in TFC ≤ 35/kΩ subgroup. There was also no time limit to perform echocardiography that excluded more advanced analysis of echocardiographic parameters. Our study did not evaluate in detail the

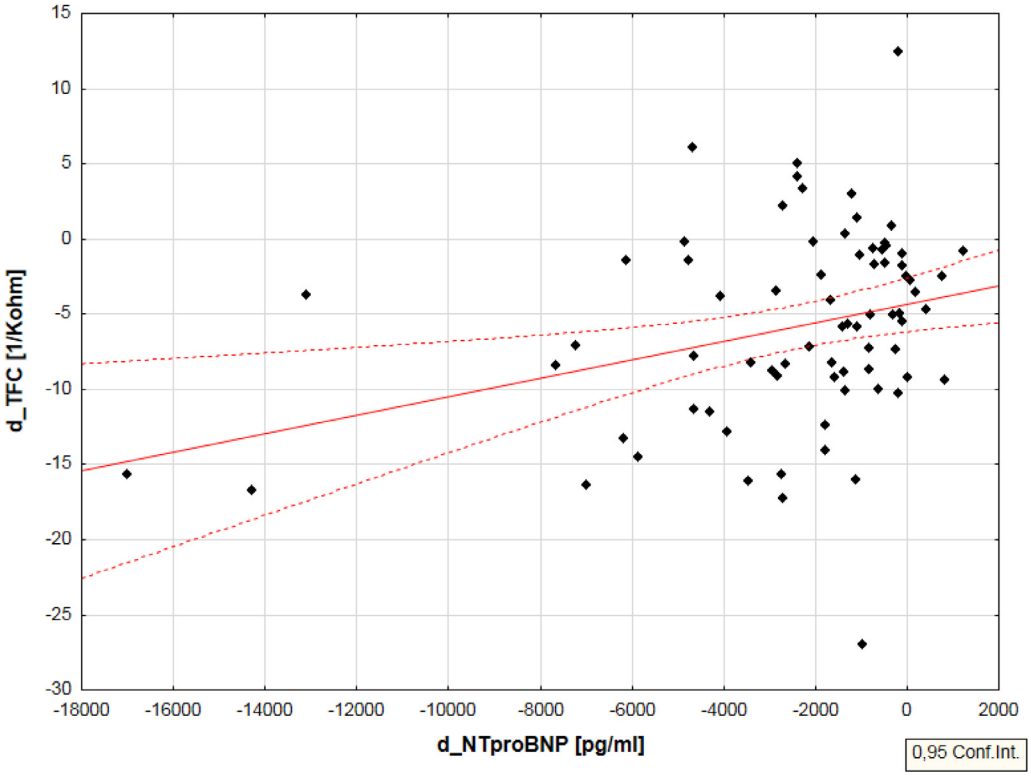

Fig. 4. Correlation plot between changes in NTproBNP [pg/ml] and TFC [1/kΩ] ($n = 75$).

relationship between the type of treatment used and its hemodynamic effect, nor did we analyze the correlation between hemodynamic parameters and variables other than NT-proBNP levels. We would also like to emphasize the fact that it is only the fluid content within the thorax that can be measured via ICG, which significantly restricts any possible conclusions as to the overall body fluid content. This is particularly important in patients with right-dominant HF, in whom whole-body bioimpedance techniques may be a valuable adjunct in evaluating total body fluid content.

Conclusions

Impedance cardiography is a useful method in evaluating individual hemodynamic profiles in patients with ADHF. The option of evaluating hemodynamic parameters, including TFC, seems to be a worthwhile addition to standard diagnostics, both at the stage of hospital admission and while monitoring the effects of treatment. The relationship between TFC and NT-proBNP levels indicates that TFC is a reliable parameter in assessing patients with ADHF. Nonetheless, this aspect of ICG use requires further studies in larger groups of patients.

Conflict of interest

None declared

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