MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 6573-6578
DOI: 10.12659/MSM.910754

Received: 2018.04.23
Accepted: 2018.05.21
Published: 2018.09.18

Diagnostic and Outcome Prediction Value of Transthoracic Impedance Cardiography in Heart Failure Patients During Heart Failure Flare-Ups

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: This study aimed at evaluating the diagnostic and outcome prediction value of transthoracic impedance cardiography (ICG) in heart failure (HF) patients admitted for in-hospital treatment due to flare-ups of their condition.

Material/Methods: In total, 120 patients of intensive care units who were admitted due to HF flare-ups were involved to the study. The findings of ICG were compared to data obtained by other methods used for diagnosing HF.

Results: Statistically significant ($p<0.001$) results were obtained when evaluating differences in ICG data between admission and discharge from the intensive care unit. In addition, a correlation was detected between brain natriuretic peptide (BNP) and thoracic fluid content index ($r=0.4$, $p<0.001$). Differences in ICG values, and BNP data emerged after the participants were grouped according to NYHA classes ($p<0.05$). The evaluation of lethal outcome during 6 months after the discharge yielded statistically significant results: BNP ≥350 pg/mL (Odds Ratio (OR) 4.4), thoracic fluid content ≥34 1/kOhm (OR 4.3), and systolic time ratio ≥0.55 (OR 2.9), $p<0.05$.

Conclusions: ICG data might be applied for the diagnosis and prognosis of HF, although the links between ICG and HF need further evaluation.

MeSH Keywords: **Cardiography, Impedance • Heart Failure • Natriuretic Peptide, Brain**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/910754

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Background

Heart failure (HF) is a common syndrome that affects approximately 1–2% of the adult population in developed countries and over 10% of the elderly (over >70–80 years of age) [1]. About 17% of patients hospitalized for HF die within 1 year from the admission, and mortality among outpatients (those with stable HF) reaches 7%. The rate of re-hospitalization within one year is 44%, whereas the frequency of hospitalization among outpatients (those with stable HF) within one year is 32%. The main causes of death include sudden cardiac death and worsening HF [2].

In 2016, the proportion of HF in Lithuania was 32.12/1000 population (in total, 92,115 cases), the proportion of patients hospitalized for HF was 5.83/1000 population (in total, 16,721), and mortality – 164.64/1000 hospitalized patients [3].

Acute HF refers to a rapid worsening of symptoms and signs of HF. This is a condition that requires urgent evaluation and treatment. The diagnostic process needs to be initiated on admission/in the outpatient department and should be continued in the emergency department in order to make the diagnosis and to prescribe treatment. The diagnostics methods include echocardiography, ECG, natriuretic peptide tests, cardiac magnetic resonance, chest X-ray, etc., and other non-invasive diagnostic techniques are continuously being developed [1]. Finding examination techniques that would be inexpensive, effective, and, ideally, would not involve invasive procedures is of relevance for the optimization of HF diagnostics.

Transthoracic impedance cardiography (ICG) is a non-invasive technique that may be performed without any special training. Its additional advantage is that it is inexpensive – the cost of the procedure is about 8 euro, or 9 US dollars. In impedance cardiography, synchronous pulse variations of blood volume in the thorax – and especially in the thoracic aorta – are evaluated and used for calculating the stroke volume and different hemodynamic parameters. The parameters evaluated during ICG may be used in various fields of medicine, including HF diagnostics, the evaluation of the risk, and the effectiveness of the therapy applied. In addition, these parameters may help in distinguishing between causes of dyspnea and may be useful in perioperative patient monitoring.

Numerous studies have analyzed the possibilities for the application of ICG in the diagnostics and monitoring of HF [4]. The obtained results revealed a correlation between ICG and echocardiography (EC) and brain natriuretic peptide (BNP). For instance, when monitoring patients with HF, ICG data (cardiac output (CO), systolic time ratio (STR)) were found to correlate (r=0.85) with the ejection fraction (EF) [5]. A correlation (r=0.65–0.8) was also detected between ICG data and CO calculated via the application of thermodilution (TD) [6]. In addition, a study that recruited 54 patients revealed a correlation (r=–0.54) between EF and STR [7]. Another study showed a correlation (r=0.69, with 86% sensitivity and 94% specificity) between the thoracic fluid content (TFC) and an elevated pulmonary capillary wedge pressure [8]. In addition, good correlations were observed between TFC and other examinations in the evaluation of pulmonary congestion in heart failure patients both during the acute phase of HF and over a long term [9–11]. However, there were several studies where no good correlation was detected: only a weak correlation (r=0.29) was found between ICG and cardiac indices (CI) when applying TD [12]. Another study showed a correlation (r=0.35) between CO calculated by applying ICG and TD [13]. The results of studies with BNP revealed high sensitivity (95%) and specificity (96%) of the combination of TFC >35 1/kOhm in the diagnosis of diastolic HF; STR could be used as indicator of early HF flare-ups [14,15]. However, the results of other studies did not show a good correlation between ICG data and BNP [16,17]. According to research data, ICG parameters might be useful in differentiating between causes of dyspnea [18,19].

As the research findings are controversial, we decided to investigate the diagnostic and outcome prediction value of ICG data in individuals who were admitted to intensive care units because of HF flare-ups, continuing and supplementing the previous studies conducted by our team [20].

Material and Methods

The studied sample

The study was conducted at the Departments of Intensive Cardiology and Cardiology of the Hospital of the Lithuanian University of Health Sciences, and the Intensive Care Unit and Department of Cardiology of Kaunas Clinical Hospital (Lithuania), after the approval of the Bioethics Committee. All participants gave their informed consent. The study was conducted on a sample of 120 patients (60 women and 60 men) who were admitted for treatment in intensive care units due to HF flare-ups without signs of myocardial infarction (MI). The characteristics of the subjects are presented in Table 1. Universally accepted techniques were applied for the verification of the diagnosis of HF [1]. Following the ICG examination guidelines, the following main conditions were used as exclusion criteria: severe aortic regurgitation, severe aortic sclerosis, and HR >200 bpm [21,22].

Methods of examination

The verification of HF diagnosis was performed by using an interview (for example, the NYHA class of HF), objective

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Table 1. Characteristics of the studied population.

Parameters	Mean ±95% Cl
Sex (M/F)	60/60
Age (years)	68.9±2.2
Systolic blood pressure (mmHg)	126.3±3.6
Diastolic blood pressure (mmHg)	77.8±3.6
Respiratory rate (breaths/minute)	27.3±0.9
Heart Failure NYHA class	3.3±0.1
Intravenous dose of diuretics (mg/day)	98.5±4.8
Parameters	**%**
Coronary artery disease (relevant diagnosis)	86.0
Arterial hypertension (relevant diagnosis)	68.7
Cardiomyopathy (relevant diagnosis)	91.0
Chest X-ray: pulmonary congestion/edema	92.3

examination (for example, respiratory sounds, edemas, and blood pressure), ECG, chest X-ray, BNP, and two-dimensional EC. To predict mortality, we collected information about the subjects' medical status over the period of 6 months.

In this study, ICG was performed after EC, using a Niccomo™ transthoracic ICG monitor produced by Medis Medizinische Messtechnik GmbH, Germany [22]. The evaluation was performed by using ICG parameters that, in our opinion, were most suitable for the diagnostics and prognosis of HF: Stroke Index (SI), TFC, CO, Thoracic Fluid Content Index (TFCI), STR, Left Cardiac Work (LCW), and Left Cardiac Work Index (LCWI).

Statistical data analysis

Statistical data were analyzed by using Statistical Package for Social Sciences (SPSS) v. 25 software. In descriptive statistics, the evaluation of mean values was carried out, multiple distributions were compared using the Kruskal-Wallis test, and the evaluation of the relationships between the attributes was performed by applying Spearman's correlation coefficient. Differences between two dependent variables were analyzed using the Wilcoxon signed ranks test. The influence of confounding factors on the results was evaluated by applying multivariate regression analysis. Pairwise comparisons between the groups were carried out by using post-hoc tests (LSD and Tukey). The Kaplan-Meier method with the Log-rank test and Cox proportional hazards model, Odds ratio (OR), and Mantel-Haenszel Common Odds Ratio were used to calculate survival rates and differences in survival curves and to estimate the risk of death. The results were considered to be statistically significant when $p<0.05$.

Results

In total, the study included 120 patients, 60 of which were women (50%) and 60 were men (50%). The subjects' mean age was 68.9 years (95% CI 66.7–71.1).

The results of the differences in ICG data between admission to and discharge from the intensive care unit evaluated by using the Wilcoxon signed ranks test are presented in Table 2. Statistically significant ($p<0.001$) results were obtained when evaluating all ICG parameters, and no statistically significant ($p=0.69$) results were obtained when evaluating EF.

The mean EF evaluated during EC was 36.9% (95% CI 34.1–39.7), the correlation between EF and ICG STR being moderately strong

Table 2. Results of differences in ICG data between admission to and discharge from the intensive care unit evaluated by using the Wilcoxon signed ranks test.

ICG parameter	Admission (intensive care unit) mean (95% CI)	Discharge (intensive care unit) mean (95% CI)	Wilcoxon test p-value
TFC (1/kOhm)	47.5 (44.6–50.4)	43.8 (41.0–46.6)	<0.001
TFCI (1/kOhm/m²)	25.2 (23.4–27.0)	23.4 (21.6–25.2)	<0.001
SI (mL/m²)	30.9 (28.7–33.1)	33.9 (31.8–36.0)	<0.001
CO (L/min)	5.0 (4.7–5.3)	5.3 (5.0–5.6)	<0.001
STR	0.43 (0.38–0.48)	0.35 (0.32–0.38)	<0.001
LCW (kg*m)	6.0 (5.6–6.4)	6.3 (5.9–6.7)	<0.001
LCWI (kg*m/m²)	3.1 (2.9–3.3)	3.2 (3.0–3.4)	<0.001

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Table 3. Correlation of BNP and ICG data.

ICG parameter	Spearman's r	p-Value
TFC	0.32	<0.001
TFCI	0.4	<0.001
SI	–0.15	0.093
CO	–0.23	0.012
STR	0.18	0.05
LCW	–0.29	0.002
LCWI	–0.25	0.006

(r=–0.31) (p=0.001), but the evaluation of the relationships of other ICG data revealed no statistically significant correlations (p>0.05). The results of the multivariate regression analysis showed that when evaluating EF by applying ICG parameters only TFC and TFCI showed significant (p<0.05) standardized coefficients.

The subjects' mean BNP level was 769.0 pg/mL (95% CI 659.0–879.0). The analysis revealed a moderately strong correlation of BNP with TFC and TFCI, whereas the correlations between BNP and CO, STR, LCW, and LCWI were weak (Table 3). The results of the multivariate regression analysis showed that when evaluating BNP by applying ICG parameters using ICG, the standardized coefficients of TFC, TFCI, LCW, and LCWI were significant (p<0.05).

The subjects' distribution by the HF NYHA classes was the following: NYHA class II – 17 subjects (14%), NYHA class III – 55 subjects (46%), and NYHA class IV – 48 subjects (40%). The analysis of the data by NYHA classes showed differences in the evaluation of BNP, TFC, and TFCI as well as in the evaluation of CO and LCW. No differences (p>0.05) were detected in other ICG data and EF by HF NYHA classes. During post-hoc tests, differences (p<0.05) were detected when evaluating BNP, and ICG data during the comparison of the group of NYHA class II subjects with those who had HF NYHA class III and IV.

To evaluate the relationship of ICG and other parameters with lethal outcome within 6 months after discharge, we calculated the odds ratio (Table 4) and survival curves (Kaplan-Meier test, see Figures 1–3). The evaluation of the following admission parameters yielded statistically significant (p<0.05) results: BNP ≥350 pg/mL (OR 4.4), TFC ≥34 1/kOhm (OR 4.3), and STR ≥0.55 (OR 2.9), while no statistically significant results were obtained when evaluating sex (Men), NYHA class III-IV, TFCI ≥18 1/kOhm/m^2, SI ≤40 mL/m^2, CO ≤3.0 L/min, or LCWI ≤3.0 kg*m/m^2. In the evaluation of BNP ≥350 pg/mL, TFC ≥34 1/kOhm consistently increased the risk of mortality within 6 months, whereas during the evaluation of STR ≥0.55, a more significant increase in mortality was only observed at the 6-month margin.

Discussion

The study was conducted with the aim of investigating the diagnostic and outcome prediction value of ICG in patients hospitalized because of HF flare-ups. The majority of studies on the value of ICG involved small samples, while data of larger-scale studies are controversial [23,24]. However, overall, the diagnostic value of ICG tended to be poorer in patients who had severe HF, compared to that in patients with milder forms [5,12–15]. For this reason, our study included patients admitted to intensive care units (i.e. those with clinically severe HF),

Table 4. Relationship of ICG and other parameters with lethal outcome.

Parameter	Odds ratio (95% CI)	Mantel-Haenszel common odds ratio estimate p-value	Log-rank test p-value
Sex (Men)	2.1 (0.9–5.1)	0.09	0.105
NYHA class III–IV	2.5 (0.5–11.8)	0.24	0.241
BNP ≥350 pg/ml	4.4 (1.3–15.7)	0.02	0.017
TFC ≥34 1/kOhm	4.3 (1.0–19.7)	0.05	0.049
TFCI ≥18 1/kOhm/m^2	2.8 (0.9–8.7)	0.08	0.078
SI ≤40 mL/m^2)	0.8 (0.3–2.4)	0.73	0.758
CO ≤3.0 L/min)	1.1 (0.3–3.8)	0.87	0.765
STR ≥0.55	2.9 (1.1–7.7)	0.04	0.05
LCWI ≤3.0 kg*m/m^2	0.9 (0.4–2.1)	0.81	0.93

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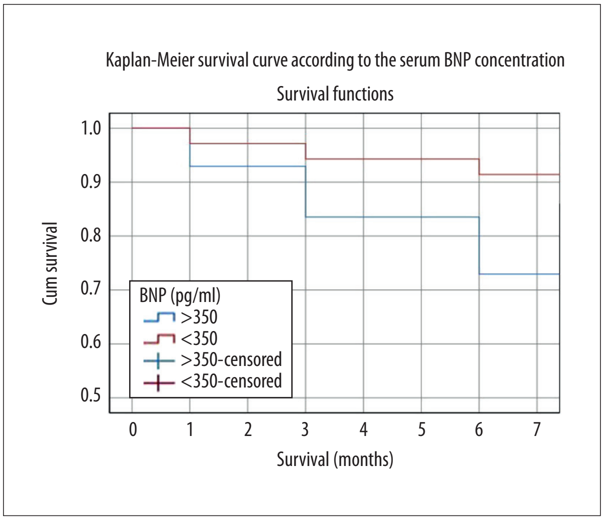

Figure 1. Kaplan-Meier 6-month survival curve according to the serum BNP concentration.

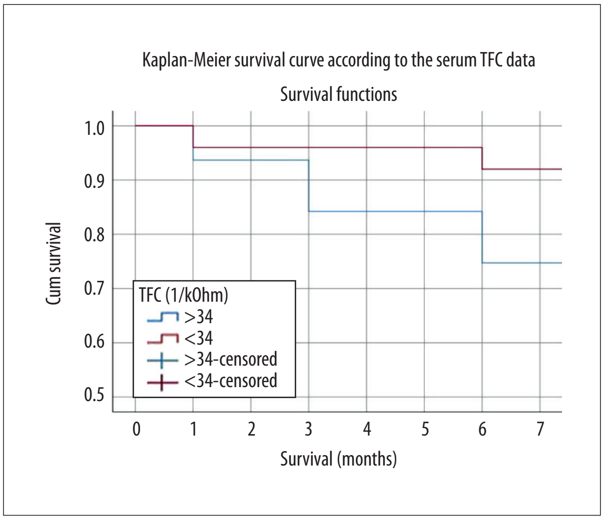

Figure 2. Kaplan-Meier 6-month survival curve according to the TFC ICG data.

and the usefulness of ICG during HF flare-ups was evaluated because this is relevant in clinical practice. Patients with HF flare-ups secondary to MI were excluded from the study because in such cases, ICG would be of little use for HF evaluation, as MI usually requires invasive diagnostic and therapeutic procedures.

The evaluation of the usefulness of ICG included its parameters that reflect the systolic (SI and CO) and contractile functions (STR) of the heart, cardiac work, and fluid content. Our team expected that ICG data would correlate with other diagnostic criteria of HF. In addition, we evaluated how ICG parameters could be useful in predicting the probability of death within 6 months and whether they could help in decision making concerning the transfer of the patients from the intensive care unit to the department of cardiology.

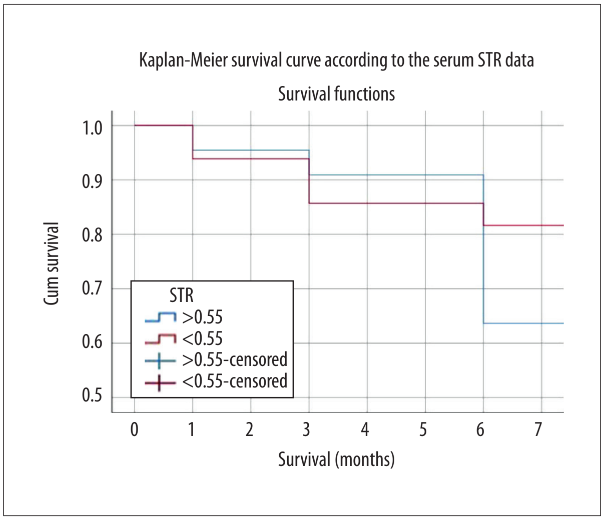

Figure 3. Kaplan-Meier 6-month survival curve according to the STR ICG data.

The results of the study revealed that EF correlated with STR (which is in line with the results of other studies [7]). However, contrary to medical logic, EF did not correlate with other ICG parameters. Moreover, these findings contradict the results of some other studies [5]. While we failed to find a clear explanation, we tend to think that the cause might have been the relatively small sample size, the fact that the subjects had severe HF (which might have caused measurement errors), and that HF with reduced ejection fraction and HF with preserved fraction were examined together. In addition, thoracic fluid content may increase because of pulmonary rather than cardiac conditions – e.g. pneumonia or traumatic hydrothorax [25].

In this study, BNP was found to correlate with ICG data, which is in line with findings published by other researchers [14,15]. Following the distribution of the subjects into groups by the NYHA class, differences were detected when evaluating ICG data and BNP. The comparison of the subject group with the NYHA class II to patients with NYHA class IV revealed especially significant differences. However, we failed to detect any correlations of EF with the NYHA class– contrary to what could have been expected. This could probably be attributed to the causes mentioned above.

The obtained results showed that the dynamics of ICG parameters could help in deciding whether to transfer the patients from the intensive care unit to the department of cardiology. The results also showed that in the prediction of the lethal outcome during 6 months after the discharge, the following parameters could be useful: BNP ≥350 pg/mL (OR 4.4), TFC ≥34 1/kOhm (OR 4.3), and STR ≥0.55 (OR 2.9). These findings are in line with the results of other studies [14,15].

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Practical clinical implementation of ICG

To date, there are no uniform recommendations for the adaptation of ICG parameters in the evaluation of HF. The reason for this is that most studies involved small samples of subjects, while larger studies yielded controversial results. All in all, transthoracic ICG is a diagnostic technique that is simple and inexpensive and can be employed in the evaluation of numerous important cardiological parameters, which might help in the diagnostics and monitoring of HF as well as in the prognostication of its outcomes.

There is an ongoing research in other impedance analysis systems such as intrathoracic ICG [21] or Multifrequency Bioimpedance Analysis (BIA) [26].

Limitations

A total of 120 subjects were selected for this pilot study. No distribution of the subjects by the cause of HF was performed, and HF with reduced ejection fraction and HF with preserved fraction were examined together, and thus other studies are needed to evaluate the links between ICG data and HF.

Conclusions

ICG data might be applied for the diagnosis and prognosis of HF, although the links between ICG and HF necessitate further evaluation.

Conflict of interest

None.

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