Relationship between thoracic fluid content and natriuretic peptide type B in patients with systolic heart failure

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Abstract

Background: Thoracic fluid content (TFC) is one of the basic parameters measured by impedance cardiography (ICG). The B-type natriuretic peptide (BNP) is a neuroendocrine mediator produced in the ventricular myocardium and released in response to the increase of wall tension.

Aim: To determine the relationship between TFC measured by ICG and BNP serum level in patients with systolic heart failure (HF).

Methods: The study population included 50 patients: a group of 30 patients with systolic HF in functional NYHA class II and III [27 males and 3 females, aged 53 ± 6 years, with mean left ventricular ejection fraction (LVEF) 23 ± 6%], and 20 controls without HF symptoms and preserved LVEF. The TFC and BNP serum level were measured on the same day.

Results: Mean BNP serum concentration was 521 ± 882 pg/ml in HF patients and 44 ± 36 pg/ml in healthy controls ($p = 0.02$). The TFC values did not differ significantly between the two groups (27.3 ± 4.5 1/kΩ in the study group versus 26.3 ± 2.8 1/kΩ in control subjects, NS). A significant correlation between TFC and BNP was found in patients with overt HF ($r = 0.57$, $p = 0.001$); however, after excluding one patient with exacerbation of HF symptoms, the correlation was non-significant ($r = 0.24$, $p = 0.22$). No correlation between these parameters was observed in healthy controls ($r = 0.17$, $p = 0.51$).

Conclusions: There was no significant correlation between TFC measured by ICG and BNP serum level in haemodynamically stable patients with HF symptoms. The usefulness of ICG measurements in patients with exacerbated chronic HF needs further investigations.

Key words: thoracic fluid content, natriuretic peptides, heart failure

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Introduction

Impedance cardiography (ICG) is a non-invasive diagnostic method, which in the last years has become an important tool in the assessment of the haemodynamic status in patients with various diseases [1]. One of the basic parameters determined using this method is thoracic fluid content (TFC), which is the reciprocal of the basic thoracic impedance. The B-type natriuretic peptide (BNP) is a neurohormone which is produced in the ventricular myocardium and released in response to increased wall tension [2]. The aim of our study was to assess the relationship between TFC measured by ICG and BNP level in patients with systolic heart failure (HF). Until now only a few studies evaluating the relationship between these parameters in various patient population have been published [3-5].

Methods

Patients and controls

The study included 50 patients hospitalised in our department. The study group consisted of 30 patients with systolic HF (LVEF ≤ 35%, LV end-diastolic diameter ≥ 60 mm) in a stable clinical state (functional class II-III according to NYHA), treated with optimal pharmacotherapy (ACEI and/or ARB and beta-blockers) hospitalised in order to evaluate the results of treatment and to consider the need for invasive diagnostic procedures. The control group consisted of 20 patients matched for gender and age, hospitalised for different causes in the cardiology department with no HF symptoms and normal LVEF.

The exclusion criteria were:

- presence of acute or chronic infectious diseases,

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- symptoms of hypervolaemia determined in the physical examination (pulmonary congestion, peripheral oedema),
- functional NYHA class IV,
- atrial fibrillation/flutter or dominant paced rhythm,
- an acute cerebrovascular incident during the last 30 days or documented stenosis of carotid or vertebral arteries,
- pregnancy or breastfeeding.

The study was accepted by the local ethics committee. A written informed consent was obtained from each patient.

BNP measurement

On the day of ICG, BNP level was measured. Venous blood samples were obtained from patients in a supine position immediately before ICG measurements. Analysis of BNP levels was performed with the AxSYM BNP test (Abbott Diagnostics Division), based on an immunoenzymatic assay using microparticles (microparticle enzyme immunoassay, MEIA).

Impedance cardiography

The first reports about the possibility of using thoracic impedance for measurement of cardiac output come from the 1930s. Atzler and Lehman demonstrated that changes during the heart cycle are reflected in changes in thoracic impedance as the result of changes of fluids contained in the thoracic cavity [6]. In 1966, with the cooperation of Kubička, as part of the Apollo programme, the first devices enabling monitoring of haemodynamic parameters were developed. It was assumed that the thorax has a cylindrical shape and homogeneous blood with constant resistance (ρ) flows inside it. This system is characterised by constant basic impedance (Z_0), pulsatile changes of blood flow inside the thorax cause pulsatile decreases of impedance (dZ), and the blood ejection has a standard curve shape [7]. Changes of impedance are also influenced by changes of volume caused by respiratory movements. Because these changes have different frequency than changes caused by blood flow, it is possible to eliminate them by applying a mathematical algorithm. One of the basic parameters determined using cardioimpedance is thoracic fluid content (TFC). It reflects the water content in both the intravascular and extravascular space. An important characteristic of this method is the simplicity of measurement, which is based on the measurement of basic impedance of the system between registering leads (Z_0), and thereafter its reciprocal is calculated. Owing to this characteristic, it is possible to eliminate errors due to the use of some simplifications and constants, which is the case when other parameters are calculated on the basis of ICG [8].

The ICG measurements were performed in a supine position using the Task Force Monitor (Task Force® Monitor 3040i, CNSystems Medizintechnik GmbH, Graz, Austria), which is a computer monitoring system measuring non-invasively, in a continuous 'beat-to-beat' manner, the following parameters:

- 6 lead ECG (bipolar leads I, II, III and unipolar leads aVR, aVL and aVF),
- cardioimpedance (ICG),
- blood pressure (BP) using photoelectric plethysmography.

The measured parameters were registered in a continuous 5-minute period. The mean value was calculated, and this value was used for further calculations.

Statistical analysis

Results are presented as mean ± SD. For comparison of parametric variables with normal distribution Student's t-test was used. For comparison between nonparametric variables Mann-Whitney U test was used. In order to determine an association between studied parameters Pearson's correlation coefficient was used (r). A p value < 0.05 was considered significant. Statistical analyses were performed using Statistica 6.0 software (StatSoft).

Results

Characteristics of the study group and control group

The study group consisted of 30 patients (27 males, 3 females) aged 37-64 years with systolic heart failure. In 13 patients the aetiology of HF was ischemic heart disease (43% of the study group) and in 17 individuals HF was due to idiopathic dilated cardiomyopathy. The control group consisted of 20 patients (18 males, 2 females) aged 37-63 years with no HF symptoms and normal LVEF. Subjects from the control group were matched for sex and age to the study group. There were significant differences between the two groups in LVEF, results of 6-minute walk test and BNP levels (Table I).

Table I. Comparison between the study group and the control group

	Study group	Control group	p
Gender [f/m]	3/27	2/18	NS
Age [years]	53 ± 6	51 ± 7	NS
Weight [kg]	83 ± 12	88 ± 13	NS
Height [cm]	172 ± 6	175 ± 7	NS
LVEF [%]	23 ± 6	64 ± 7	< 0.0001
6MWT [m]	358 ± 78	489 ± 69	< 0.0001
BNP [pg/ml]	521 ± 882	44 ± 36	0.02
TFC [1/kΩ]	27.3 ± 4.5	26.3 ± 2.8	NS
Hypertension, n (%)	14 (47)	15 (75)	0.049
Diabetes, n (%)	5 (17)	3 (15)	NS
Hyperlipidaemia, n (%)	17 (57)	13 (65)	NS

Abbreviations: f – female, m –male, LVEF – left ventricular ejection fraction, 6MWT – 6-minute walk test, BNP – brain natriuretic peptide, TFC – thoracic fluid content

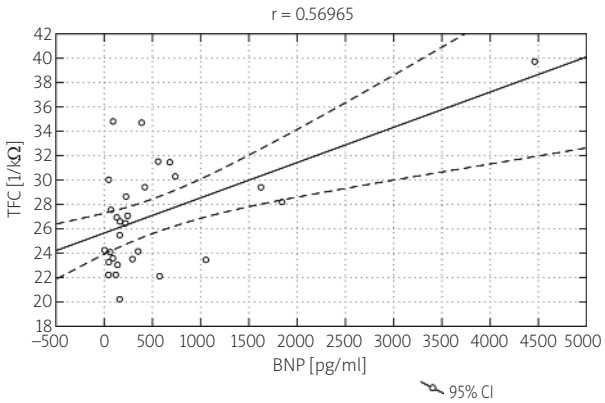

Figure 1. Linear correlation between TFC and BNP in the study group

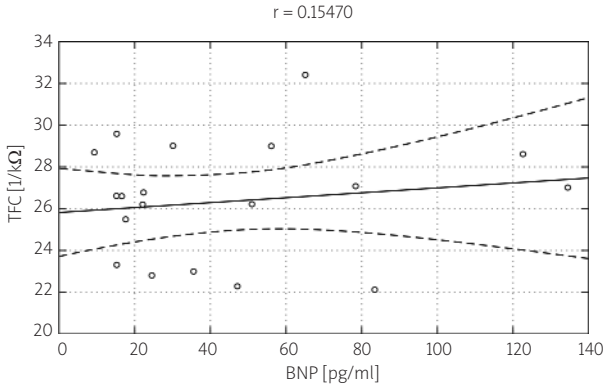

Figure 2. Linear correlation between TFC and BNP in the control group

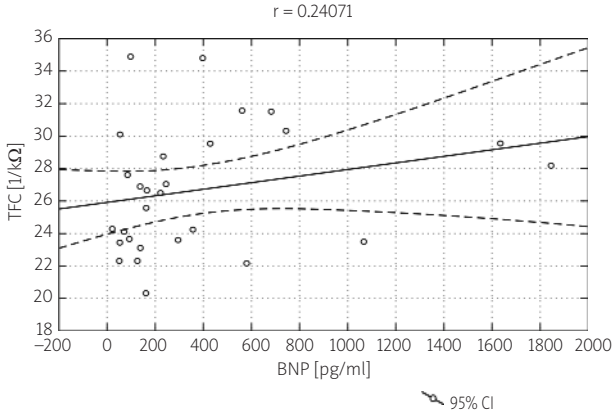

Figure 3. Linear correlation between TFC and BNP in the study group in stable haemodynamic patients

On the basis of symptoms 13 patients from the study group were classified into functional class II according to NYHA, 6 patients into NYHA class III and 11 individuals had intermediate symptoms between NYHA class II and III.

The mean BNP level was 521 ± 882 pg/mL in the study group and 44 ± 36 pg/mL in the control group, (p = 0.02). There was no significant difference in TFC between the two groups (27.3 ± 4.5 1/kΩ in the control group vs. 26.3 ± 2.8 1/kΩ in the study group, NS).

There was a strong correlation between TFC and BNP in patients with clinically overt HF (r = 0.57, p = 0.001). No correlation in patients in the control group was observed (r = 0.17, p = 0.51) (Figures 1 and 2).

However, detailed analysis of the obtained results revealed that the statistical significance of the correlation was based on the results of one of the patients with a TFC value of 39.8 1/kΩ and BNP level of 4464.9 pg/ml. After exclusion of this patient the correlation coefficient became weaker (r = 0.24) and statistically insignificant (p = 0.22) (Figure 3).

Discussion

Thoracic fluid content, the reciprocal of the basic thoracic impedance, reflects fluid content inside the thorax, in both the intravascular and extravascular space. Previous studies confirmed that absolute and relative changes of impedance or TFC are influenced by different clinical events. Congestion in pulmonary circulation can be determined using basic impedance (Z_0) measurement with sensitivity and specificity exceeding routine chest X-ray [9]. Studies by Van de Water and Peterson demonstrated an association between the amount of fluid removed by thoracocentesis or pericardiocentesis and the change of TFC measured using cardioimpedance [10, 11]. Increase of the intravascular fluid content by infusion of saline or by blood transfusion has a substantial influence on impedance (causing its decrease) and TFC (causing its increase). A similar effect is observed when lung lavage is performed during surgical procedures [12, 13]. Other studies have demonstrated high efficacy of TFC measurement in diagnosis of pulmonary oedema, not only in patients with HF but also in pregnant women. It was demonstrated that the sensitivity of this test is comparable with X-ray [14, 15]. Studies by Brodin and Larsen confirmed the impact of treatment with diuretics on fluid content inside the thorax measured by ICG [16, 17].

Wynne et al. performed a study including 41 patients with chronic renal disease undergoing haemodialysis. They analysed the relationship between changes of TFC and the amount of fluid removed from the body during the procedure. They demonstrated a strong correlation between those parameters (r = 0.579, p = 0.0003) [18]. Also the study by Yoshii et al. confirmed a decrease of TFC in patients undergoing haemodialysis [19].

Studies comparing invasive measurements with ICG demonstrated an almost linear relationship between central venous pressure and basic thoracic impedance. The B-type natriuretic peptide as a hormone produced in the myocardium and released in response to increased wall tension should show an association with parameters

of LV preload. It was confirmed in the study by Iwanaga et al., in which an association was demonstrated between values of end-diastolic LV pressure (measured with echocardiography or using invasive methods), end-diastolic wall tension and BNP level. That study showed a strong correlation between those parameters and BNP level [20]. Until now, there are no studies confirming the correlation between TFC and invasively measured pulmonary artery wedge pressure [21-23].

The results of the current study demonstrated a strong correlation between TFC and BNP level ($r = 0.57$, $p = 0.001$) in patients with systolic HF and lack of such an association in patients with no HF symptoms and preserved LV systolic function. However, after exclusion of one patient with extremely high BNP and TFC levels, this association became non-significant. In the remaining patients BNP levels were < 2000 pg/ml and TFC values < 35 1/kΩ (this level was used in the PREDICT study to identify patients at high risk of haemodynamic decompensation [24]).

Thus, it can be stated that in patients with HF, who are haemodynamically stable, no significant correlation between BNP and TFC was observed. The small number of the studied patients is an obvious limitation of the current study. In the future, it would be worth including a group of haemodynamically unstable patients who are in class IV according to NYHA, i.e. those patients whose BNP levels often exceed 2000 pg/ml.

So far only a few studies have been published assessing the relationship between TFC and BNP levels in small groups of patients with HF. Lawless et al. studied 38 patients with chronic systolic HF (mean LVEF was 26 ± 12%). The authors compared haemodynamic parameters measured in the supine position with neurohormone levels (norepinephrine and BNP). They demonstrated a significant correlation between stroke volume (SV) and BNP ($r = 0.920$, $p < 0.05$) as well as between TFC and BNP ($r = 0.453$, $p < 0.01$). Norepinephrine level correlated only with SV ($r = –0.347$, $p < 0.05$) [3].

A similar study was performed by Feliciano et al., who assessed the correlation between NT-proBNP level and haemodynamic parameters measured using ICG in a group of 55 patients with systolic HF (LVEF 24.7 ± 8.2%). Among all studied parameters the strongest correlation was demonstrated for TFC [4].

Havelka et al. assessed the relationship between selected parameters measured using ICG and BNP in patients arriving at the emergency department due to dyspnoea. Out of three analysed parameters (SVR, CI and TFC) only TFC showed a significant correlation with the BNP level ($r = 0.32$, $p = 0.02$). However, the study group was quite inhomogeneous, and only in a subset of patients was chronic HF diagnosed [5].

The study by Velazquez-Cecena et al. may be further evidence of the usefulness of non-invasive haemodynamic measurements using ICG. The authors demonstrated significantly higher BNP levels and LVEDP in patients qualified on the basis of ICG measurements (high TFC and low SVI) into a group at high risk of HF decompensation [25].

The PREDICT study performed in a group of over 200 patients with chronic HF also demonstrated the usefulness of TFC and SVI measurements using ICG in risk stratification of acute HF decompensation in 14- and 30-day follow-up periods [24].

The ICG measurements were the basis for development of new methods of automatic measurement of free water content inside the thoracic cavity, by measurement of impedance between the coil and the pulse generator cover. The first studies performed using the OptiVol system (Medtronic) demonstrated that this method can be useful in diagnosing adverse haemodynamic changes during the asymptomatic or mildly symptomatic period. Introducing adequate therapy at this point usually helps to prevent the patient from being hospitalised due to exacerbation of HF [26-29].

At the end, it is worth mentioning the economic aspect of this study. The overall cost of ICG is associated with a single purchase of the device and leads used for measurements. The study is simple, not time consuming, and not inconvenient even for patients in a serious clinical state. It can be performed by a trained nurse, and the obtained results are not influenced by the subjective judgment of the investigator, as is the case, for instance, of echocardiographic studies. The ICG results are obtained immediately which may be associated with a decrease of costs caused by promp correct diagnosis and introduction of adequate therapy, and therefore shorter hospitalisation time [30].

Conclusions

Thoracic fluid content measured using ICG did not show a significant correlation with BNP level in patients with stable systolic HF. Further studies are needed to assess the usefulness of these measurements in patients at risk of HF aggravation.

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Ocena związku zawartości płynu w klatce piersiowej mierzonej metodą kardiografii impedancyjnej ze stężeniem natriuretycznego peptydu typu B w osoczu u osób ze skurczową niewydolnością serca

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Streszczenie

Wstęp: Jednym z podstawowych parametrów określanych za pomocą kardiografii impedancyjnej jest zawartość płynu w klatce piersiowej (ang. *thoracic fluid content*, TFC). Natriuretyczny peptyd typu B (BNP) jest neurohormonem produkowanym w miokardium komór i uwalnianym w odpowiedzi na wzrost naprężenia ścian.

Cel: Zbadanie zależności pomiędzy TFC zmierzoną metodą kardiografii impedancyjnej a stężeniem BNP w grupie osób ze skurczową niewydolnością serca.

Metody: Badaniem objęto 50 pacjentów – grupę badaną stanowiło 30 osób ze skurczową niewydolnością serca w II–III klasie wg NYHA [27 mężczyzn i 3 kobiety, w wieku 53 ± 6 lat, ze średnią wartością frakcji wyrzutowej lewej komory (LVEF) 23 ± 6%], a grupę kontrolną 20 osób bez objawów niewydolności serca, z prawidłową LVEF. W tym samym dniu oznaczano stężenie BNP oraz przeprowadzano pomiar TFC. Wyniki poddano analizie statystycznej z oceną współczynnika korelacji liniowej Pearsona r (poziom istotności z $p < 0,05$).

Wyniki: Stężenie BNP wynosiło średnio 521 ± 882 pg/ml w grupie badanej oraz 44 ± 36 pg/ml w grupie kontrolnej ($p = 0,02$). Wartości TFC zmierzone w obu grupach pacjentów nie różniły się w sposób istotny statystycznie i wynosiły: 27,3 ± 4,5 1/kΩ w grupie badanej oraz 26,3 ± 2,8 1/kΩ w grupie kontrolnej. Dla całej grupy badanej stwierdzono znamienną korelację między TFC i BNP ($r = 0,57$, $p = 0,001$), jednak po wyłączeniu wyników pacjenta znajdującego się w okresie zaostrzenia niewydolności serca współczynnik korelacji tych parametrów utracił znamienność statystyczną ($r = 0,24$, $p = 22$). Także w grupie kontrolnej nie stwierdzono istotnej korelacji między TFC i BNP ($r = 0,17$, $p = 0,51$).

Wnioski: Uzyskane metodą kardiografii impedancyjnej pomiary TFC nie wykazały istotnej korelacji z poziomem BNP u chorych ze skurczową niewydolnością serca w stabilnym stanie hemodynamicznym. Przydatność tych pomiarów, zwłaszcza u pacjentów zagrożonych zaostrzeniem niewydolności serca, wymaga dalszych badań.

Słowa kluczowe: zawartość płynu w klatce piersiowej, peptydy natriuretyczne, niewydolność serca

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