Original Research

Thoracic Fluid Content and Impedance Cardiography: A Novel and Promising Noninvasive Method for Assessing the Hemodynamic Effects of Diuretics in Hypertensive Patients

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Key words:
Rheocardiography, hypertension, clinical applications.

Manuscript received:
May 23, 2008;
Accepted:
February 23, 2009.

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Introduction: Impedance cardiography (ICG) is a reliable, noninvasive method allowing the assessment of the hemodynamic profile in hypertensive patients. The aim of the study was to evaluate the potential hemodynamic effects of diuretics with ICG and examine whether the empiric administration of diuretics actually has a substantial impact on thoracic fluid content (TFC).

Methods: The study population included 248 hypertensive and 68 healthy subjects (35-87 years old) and was divided into 4 groups: group A comprised hypertensive patients under treatment including diuretic; group B consisted of hypertensive patients under treatment without diuretic; group C included untreated hypertensive patients; and group D included healthy subjects. The measurements were performed using the Cardio Screen® ICG system (Medis, Germany). Men and women were examined separately, since TFC seems to be sex-dependent.

Results: In the men's subgroup, the highest TFC value (41.7 ± 4.9) was found in Group C (untreated hypertensive group), while the lowest TFC (36.4 ± 5.7) was seen in Group A (diuretic hypertensive group). Women treated empirically with diuretics (group A) had a mean TFC of 27.3, while the other no-diuretic groups had a mean TFC of approximately 30. The mean TFC in men was significantly higher than in women in all study groups examined.

Conclusions: Both men and women who were treated empirically with diuretics showed a significantly lower TFC in comparison with patients treated with other antihypertensive drugs, untreated patients and healthy control subjects. TFC is an ICG parameter that is associated with the administration of diuretics and has interesting clinical applications in optimizing and tailoring antihypertensive treatment.

Diuretics are considered to be one of the most widely used drug categories in the management of arterial hypertension. They are used in everyday clinical practice either as monotherapy or in combination with other categories of antihypertensive pharmacological agents. Blood pressure reduction induced by diuretics is mainly attributed to the reduction of the intravascular blood volume.[1-6] It has recently been hypothesized that in hypertensive patients hemodynamic criteria play a significant role in determining and monitoring the appropriate treatment regimen and should be seriously considered in any attempt to individualize antihypertensive treatment.[7-8]

Impedance cardiography (ICG-Rheocardiography) is a reliable, noninvasive and cost-effective method of measuring cardiac output and other hemodynamic parameters, allowing the assessment of the central hemodynamic profile even in non-hospitalized hypertensive patients.[9-11] One of the parameters examined is thoracic fluid content (TFC), which is inversely associated with the patient's transthoracic electrical bioimpedance (Figure 1), as measured with the rheocardiographic system, and reflects the total (intravascular and extravascular) fluid volume contained in the chest cavity.[12]

The fluid content is a pronouncedly variable parameter of a human's chest and this is why the dynamic measurements of chest impedance by means of rheocardiography can reliably and accurately reflect its alterations. Potential changes in thoracic fluid content are directly proportional to total fluid changes; thus, rheocardiographic parameters can prove to be extremely significant for the monitoring of thoracic blood volume changes under the influence of antihypertensive treatment or other agents.[12]

The aim of the present study was to investigate the potential hemodynamic effects of diuretics using ICG and to examine whether the empiric administration of diuretics in hypertensive patients actually has a substantial impact on thoracic fluid content.

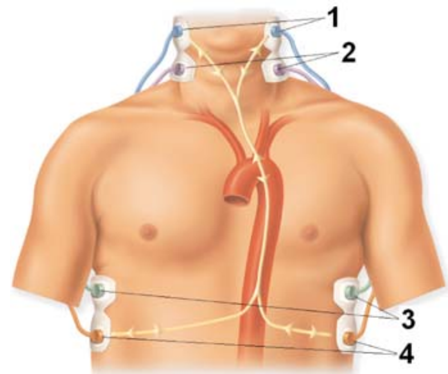

Figure 1. The rheocardiographic measurement of thoracic electrical bioimpedance. The external sensors (1 and 4) provide alternating electrical current of high frequency and low amperage. A current with such properties is totally harmless for the patient. The internal sensors (2 and 3) measure the electrical bioimpedance. The impedance measured is called baseline thoracic bioimpedance (Zo). Because of the pulsatile blood flow, the intra-aortic blood volume and consequently the chest bioimpedance are constantly changing. The impedance is depicted in a waveform and the stroke volume is estimated with mathematical equations. Reproduced with permission from Medis (Medizinische Messtechnik GmbH).

Methods

Study design

This was a retrospective cross-sectional study examining the effect of diverse antihypertensive drugs on TFC in a cohort that included hypertensive patients with and without ongoing treatment.

Participants

The study population included 248 hypertensive and 68 healthy subjects (men and women aged from 35 to 87 years old). The material was retrieved from the database of patients who had visited the outpatient clinic of the "Laiko" General Hospital during the period December 2005 to December 2006.

Group A comprised hypertensive patients whose antihypertensive treatment included a diuretic drug; group B consisted of hypertensive patients whose antihypertensive treatment did not include any diuretic drug; group C was made up of hypertensive patients who did not receive any antihypertensive medication; and finally group D included healthy subjects. Men and women were studied separately, since there seems to be a gender-dependent difference in the normal range values of thoracic electrical bioimpedance.

The main inclusion criteria for the hypertensive patients were as follows: primary or secondary arterial hypertension irrespective of the patient's age; an antihypertensive treatment having been administered without rheocardiographic criteria being taken into account; the antihypertensive treatment should have remained unaltered for at least 3 consecutive months; the patients should not have received any other medication except for antihypertensive and lipid-lowering drugs for at least one month before the first visit; the no-treatment period for patients of group C should have lasted at least one month before the first visit; and finally the study excluded patients suffering from severe health conditions that could have a potential effect on the hemodynamic parameters examined, such as already diagnosed heart failure (NYHA II-IV and ejection fraction <45%), valvulopathy, renal dysfunction (serum creatinine >1.5 mg/dl), or atrial fibrillation. In all the patients enrolled in the study the hemodynamic measurements with ICG were performed during their first visit. Last but not least, subjects in study group D should not have been taking medication for any reason.

Impedance cardiography methodology and basic principles

The thoracic electrical bioimpedance is a complicated parameter. Skin and bones have the highest bioimpedance, while the chest fluid content has the lowest. In order to measure the chest fluid volume, it is essential that the electrical bioimpedance of skin and underlying tissues is somehow eliminated. This elimination can be accomplished in rheocardiography by providing high frequency alternating electrical current. With this method the thoracic bioimpedance measured is directly dependent on the volume of intra- and extravascular fluid. TFC is inversely related with the chest baseline bioimpedance Zo (TFC= 1000/Zo). When the chest fluid content is increased the thoracic baseline bioimpedance is expected to decrease, and when the chest fluid volume is reduced the baseline bioimpedance is respectively expected to increase.

The rheocardiographic examination was carried out with the examinee in a supine position, after five minutes of resting, with the placement of four dual sensors, two of them positioned on the examinee's neck and two on the chest (Figure 1). The measurements were performed using the CardioScreen® rheocardiographic system (Medis, Germany).[13-14] No patient was excluded because of bad record quality.

Statistical analysis

All continuous variables are expressed as mean values plus/minus the standard deviation (mean ± SD). Mean differences in the continuous variables examined between the 4 study groups were tested for statistical significance by the paired Student's t-test and by ANOVA. A p-value <0.05 was considered statistically significant. Data were analyzed using the special statistical software SPSS 15 (SPSS Inc. Chicago, Illinois, USA).

Results

The analysis included 316 subjects in total (248 hypertensive and 68 healthy individuals). The variables examined were age, weight, height, body mass index (BMI, calculated as body weight in kilograms divided by the height in meters squared), cardiac index and finally TFC. The analysis was stratified by gender (separate subgroups of men and women examined), since TFC seems to be sex-dependent. The results of the analysis are therefore presented separately for the male and female subpopulations.

As far as men are concerned (Table 1), there were no statistically significant differences regarding age, height, weight or BMI among the four study groups. In terms of mean arterial pressure, patients under antihypertensive treatment with or without a diuretic (groups A and B) did not differ significantly. However, significant differences were found for all the other group comparisons. Values of TFC were significantly lower ($p<0.001$) in the diuretic group (group A) than in all the other groups, but there were no statistically significant differences between the groups that took no diuretics (groups B, C and D). The highest TFC (41.7 ± 4.9) was demonstrated by Group C (untreated hypertensive group), while the lowest (36.4 ± 5.7) was observed in Group A (diuretic hypertensive group). Cardiac index showed no significant differences among patients of the four study groups.

In the women (Table 2), there were some statistically significant differences between groups in the anthropometric data. Specifically, hypertensive women who were treated with drugs other than diuretics (group B) were older than untreated hypertensive women (group C) and healthy controls (group D). Women in the diuretic group (A) were also found to be taller than women in group B (treated with other than diuretics) and weighed more than women in group D (controls). The clinical significance of these anthropometric differences is, however, minimal as discussed below.

Concerning mean arterial pressure, there was no significant difference between groups A and B (hypertensives with or without diuretics), whereas all other group comparisons found significant differences, as expected. The results for TFC in the women were similar to those in the men. In the diuretic group (A), the values of TFC were significantly lower ($p<0.001$) than in other groups, but comparisons between the no-diuretic groups (B, C, D) found no significant differences. Women treated empirically with diuretics (group A) had a mean thoracic fluid content of 27.3, while the other groups had a mean TFC of approximately 30. It is also noteworthy that the mean TFC in the men was significantly higher than in the women in all 4 study groups examined. Cardiac index, as in the men, showed no significant differences among the four groups in women.

From the information mentioned above, it is obvious that the results were essentially similar in the two subpopulations of men and women examined in our study, in terms of the basic and clinically important parameters of mean arterial pressure, TFC and cardiac index. In both men and women, hypertensive patients who were empirically treated with diuretics showed a significantly lower chest fluid volume in

Table 1. Comparisons among the male subjects of the 4 study groups in terms of 9 variables.

Variables	Groups				p-value					
	A (N=24)	B (N=34)	C (N=67)	D (N=32)	A-B	A-C	A-D	B-C	B-D	C-D
Age (years)	60.3 ± 9.5	62.3 ± 13.0	57.7 ± 12	57.7 ± 12.3	NS	NS	NS	NS	NS	NS
Height (cm)	170.8 ± 7.0	171.4 ± 7.1	173 ± 7.3	171.1 ± 6.2	NS	NS	NS	NS	NS	NS
Weight (kg)	91.2 ± 27.6	83.7 ± 14.4	88.8 ± 15.8	81.6 ± 18.1	NS	NS	NS	NS	NS	NS
BMI (kg/m^2)	31.0 ± 7.8	28.5 ± 4.4	29.6 ± 4.5	27.8 ± 5.7	NS	NS	NS	NS	NS	NS
SAP (mmHg)	151.3 ± 21.6	145.3 ± 18.4	157.8 ± 14.1	127.9 ± 8.3	NS	NS	<0.00001	<0.001	<0.0001	<0.00001
DAP (mmHg)	83.5 ± 10.0	82.7 ± 12.2	93.5 ± 10.7	78.6 ± 5.9	NS	<0.0001	<0.05	<0.001	=0.08	<0.00001
MAP (mmHg)	103.6 ± 10.9	102.4 ± 14.3	114.4 ± 11.4	94.4 ± 5.9	NS	<0.0001	<0.001	<0.0001	<0.01	<0.00001
CI (L/min)	3.33 ± 1.04	3.74 ± 1.19	3.65 ± 1.17	3.78 ± 0.82	NS	NS	NS	NS	NS	NS
TFC (1/kΩ)	36.4 ± 5.7	40.7 ± 6.4	41.7 ± 4.9	39.8 ± 4.8	=0.009	=0.0002	=0.02	NS	NS	NS

BMI – body mass index; SAP – systolic arterial pressure; DAP – diastolic arterial pressure; MAP – mean arterial pressure; CI – cardiac index; TFC – thoracic fluid content; NS – not significant.

Table 2. Comparisons among the female subjects of the 4 study groups in terms of 9 variables.

Variables	Groups				p-value					
	A (N=37)	B (N=38)	C (N=48)	D (N=36)	A-B	A-C	A-D	B-C	B-D	C-D
Age (years)	63.2 ± 8.6	66.8 ± 11.0	61.4 ± 10.2	59.1 ± 10.9	NS	NS	NS	=0.022	=0.0033	NS
Height (cm)	160.4 ± 5.7	157.1 ± 5.4	158.4 ± 6.4	160.3 ± 6.1	=0.014	NS	NS	NS	NS	NS
Weight (kg)	76.8 ± 12.5	72.9 ± 12.7	75.2 ± 11.8	70.0 ± 11.9	NS	NS	=0.019	NS	NS	=0.05
BMI (kg/m^2)	29.9 ± 4.6	29.6 ± 5.3	30.1 ± 5.2	27.3 ± 4.6	NS	NS	=0.02	NS	NS	=0.011
SAP (mmHg)	149.0 ± 22.4	158.1 ± 20.3	161.6 ± 12.7	126.2 ± 9.6	NS	=0.0037	<0.0001	NS	<0.0001	<0.0001
DAP (mmHg)	85.0 ± 8.6	81.8 ± 9.6	90.5 ± 8.9	76.9 ± 7.4	NS	=0.0049	<0.0001	<0.0001	=0.016	<0.0001
MAP (mmHg)	104.5 ± 10.8	104.2 ± 10.2	112.2 ± 8.9	92.1 ± 7.9	NS	<0.0001	<0.0001	<0.001	<0.0001	<0.0001
CI (L/min)	3.55 ± 0.93	3.90 ± 1.27	3.73 ± 1.22	3.65 ± 0.7	NS	NS	NS	NS	NS	NS
TFC (1/kΩ)	27.3 ± 4.5	30.9 ± 6.3	30.1 ± 4.9	30.0 ± 3.6	=0.0056	=0.0081	=0.0062	NS	NS	NS

Abbreviations as in Table 1.

comparison with patients treated with other antihypertensive drugs (angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, calcium channel blockers, b-blockers and other), untreated patients, and healthy control subjects.

Discussion

The reproducibility and accuracy of ICG technology is nowadays well established and has recently been validated in patients with various cardiovascular disorders and emergent medical situations[7] other than hypertension.

Impedance cardiography retains the significant capability of assessing severely hyper-hydrated and dehydrated patients and detecting pulmonary fluid and pleural effusions.[15-16] Petersen et al[17] also found a strong correlation between the volume of pleural fluid extracted and the thoracic baseline bioimpedance (r=0.97). Ebert et al[18] found a significant linear correlation between the alterations of central venous pressure and the alterations of the thoracic baseline bioimpedance. In the large clinical trial, PREDICT,[19] the correlation between stroke volume and the values of TFC appeared to bear substantial prognostic significance for patients with congestive heart failure.

Even though TFC is not associated exclusively with the intravascular blood volume, the well established correlation of this parameter with chest fluid content in general could prove to be a useful tool for assessing the clinical necessity of administering a diuretic drug.

The individualization of antihypertensive treatment based on objective criteria could lead to a more tailored approach in the management of arterial hypertension. Since blood pressure is the effect of interactions between several hemodynamic parameters, the hemodynamic evaluation of the hypertensive patient could lead to a successful and individualized selection of the appropriate antihypertensive drug. Recent trials with rheocardiography technology have shown that treatment based on hemodynamic criteria (ICG-guided treatment) is more effective than empiric treatment.[20-22] Even though in these trials TFC was used in order to select a diuretic or not according to its alterations in standing and supine position, these trials did not finally conclude that there is a correlation between TFC and diuretics. On the other hand, nor can the potential impact of other factors and variables on such a correlation be excluded.

Limitations of the study

A major limitation of the study is that there is no reference to specific antihypertensive drugs utilized in groups A and B of the study population; as a result, no reliable conclusions can be drawn regarding the hemodynamic effect of specific drug categories used in the management of arterial hypertension.

TFC is also a greatly variable hemodynamic parameter that could potentially be influenced by several confounding factors. In order to overcome this limitation, we designed the study in such a way as to eliminate the impact of additional variables on TFC, such as the selective restriction of salt intake, gender, the concomitant use of other drugs, etc. Medical treatment was randomly administered by physicians who were not related to the research group. The participants did not include patients with certain health conditions that could possibly demand a diuretic treatment, such as heart failure or severe renal dysfunction. Finally, the study included only patients who underwent ICG at their first visit.

The present study cannot conclude that a certain drug category is superior to the others in terms of optimal hypertension management and optimal hemodynamic effects. The study focused on patients who were empirically treated with diuretics (the clinical decision was not driven by rheocardiographic criteria) and concludes that in these patients the diuretics taken had significantly reduced their chest fluid volume. Whether these patients actually needed diuretic medication based on their hemodynamic profile, or could be expected to benefit from this treatment option in the long term, cannot be answered from the findings of the present study.

Another important limitation is that our study does not refer to other hemodynamic measurements that can be taken from ICG, such as systemic vascular resistance and cardiac output. The present study was strictly focused on the parameter of chest fluid content. The other hemodynamic parameters will be analytically examined by the same research group in future research protocols currently being conducted and the findings will be discussed in future publications.

Conclusions

The present study concludes that TFC is associated with the administration of diuretics. The fact that TFC values are significantly lower in the diuretic group compared with all the other groups, together with the absence of significant differences between the no-diuretic groups, indicate that the parameter TFC is clearly influenced by the diuretic intake. Anthropometric characteristics such as age, weight and height, which could possibly have an impact on chest fluid content, did not differ among the study groups. The statistically significant difference in terms of age between women's group B and groups C and D does not seem to have had an effect on TFC. The statistically significant difference in terms of height between women's groups A and B cannot be correlated with the difference of TFC, since such a difference was not observed in the other study groups.

The correlation found in this study indicates that TFC is an ICG parameter that could find interesting clinical applications in the decision whether or not to include a diuretic in a patient's antihypertensive treatment, as well as in making the appropriate dosage adaptations and adjustments. The validation of this potential requires well designed trials that will have to assess the impact of diuretics on rheocardiographic parameters in hypertensive patients by comparing their initial hemodynamic profile, the changes of this profile under the influence of diuretic drugs, and their antihypertensive therapeutic efficacy.

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