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Editor's comment: Heart failure is a major health problem that is often difficult to diagnose early. The present paper assesses the feasibility of a technique that combines ECG recording and bio-impedance spectroscopy techniques to extract information about fluid retention/accumulation associated with congestive heart failure. The authors envisage a low-cost adjunct device to conventional ECG as a means to identify patients with heart failure at an early stage, and for subsequent monitoring of those patients and how they respond to treatment.

Richard Black, Editor in Chief

Adding "hemodynamic and fluid leads" to the ECG. Part I: The electrical estimation of BNP, chronic heart failure (CHF) and extracellular fluid (ECF) accumulation

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ABSTRACT

Objectives: In primary care the diagnosis of CHF and ECF accumulation is no triviality. We aimed to predict plasma BNP, CHF and ECF accumulation with segmental impedance spectroscopy while using and extending the electrodes of the conventional electrocardiography.
Methods: Three combined multiple electrodes were added to the 15 lead ECG for segmental impedance spectroscopy and for measuring the maximal rate of segmental fluid volume change with heart action at the thorax and the legs. The obtained signals were analyzed by partial correlation analyses in comparison with plasma BNP, CHF classes, ejection fraction by echocardiography and cardiac index by double gas re-breathing. 119 subjects (34 healthy volunteers, 50 patients with CHF, NYHA classes II to IV and 35 patients without CHF) were investigated.
Results: The maximal rate of volume change with heart action at the thorax and at the legs, as well as the ECF/ICF ratio at the legs contribute equally and independently to the prediction of BNP and heart failure in an unknown test sample of 49 patients (multiple $r = 0.88$, $p < 0.001$). The ROC-curve for the predicted plasma BNP > 400 pg/ml gave an AUC = 0.93. The absence or the presence of heart failure could be predicted correctly by a binomial logistic regression in 92.9 and 87.5% of cases, respectively.
Conclusion: The methodology, which is based on inverse coupling of BNP release and of maximal blood acceleration and on sensitive detection of ECF overload, could enable the diagnosis of CHF with useful sensitivity and specificity while writing a routine-ECG.

1. Introduction

Chronic heart failure (CHF) is recognized as a major and increasing health problem in industrialized nations. The problem is exacerbated by the limited clinical abilities to diagnose this condition [1]. The measurement of plasma natriuretic peptide and related compounds has become a cornerstone in the diagnosis of acute and chronic heart failure [2–5] as it is elevated in systolic [2] and diastolic [2,6] heart failure. BNP measurements may help to reduce morbidity of this condition [7]. BNP release is mediated by "cellular overstretch–BNP-release coupling" [8]. Simultaneously, overstretch of the myocardial fibers also leads to diminished maximal blood acceleration of the right [9] and the left [10,11] ventricle. It was hypothesized that both phenomena may be inversely related (Fig. 1) and clinically detectable by measuring the maximal rate of electrical resistance change and hence the maximal rate of segmental fluid volume change. Lung water can be monitored adequately by electrical impedance tomography [12,13] or internal

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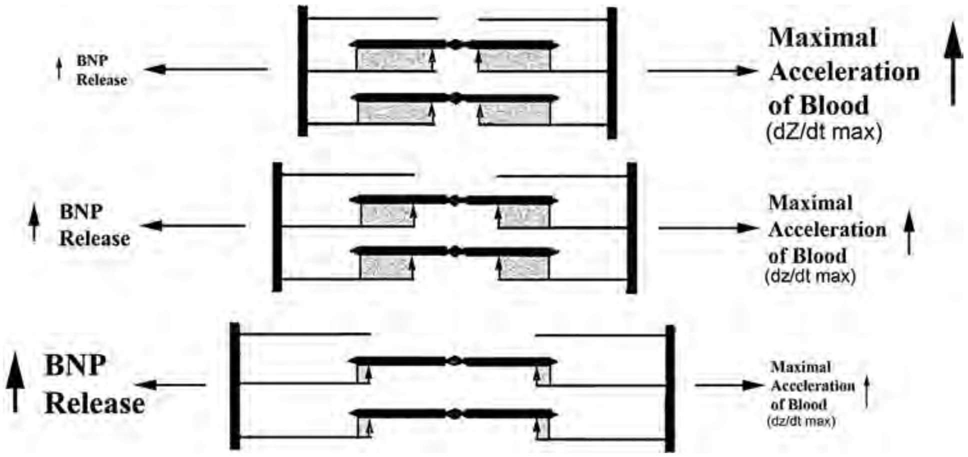

Fig. 1. The disposition of thick (myosin) and thin (primarily actin) filaments within the sarcomere. Overstretch of the myocardial fibers leads to a reduction of actin–myosin interaction sites (shaded area): it is hypothesized that BNP release and maximal acceleration of blood may be inversely related.

devices [14], whether external thoracic impedance measurements correlate with thoracic fluid content or pulmonary wedge pressure is unsettled [15,16]. Also, the ability to detect subclinical peripheral ECF accumulation by whole body [17,18] or segmental impedance spectroscopy [19–28] has not been fully explored in heart failure. It was also hypothesized that the above two technologies in combination help to improve the diagnosis of heart failure and volume overload in primary care. In times of scarce resources even a clinically very useful methodology may be doomed to failure if additional manpower is needed. Therefore, it is presently also being attempted to extract more information about the possible presence of CHF and ECF accumulation from the conventional ECG [29]. In the present work the electrode placement of the conventional 15 lead ECG was used in combination with three additional multiple electrodes for the impedance spectroscopy. Despite being successful, the methodology is not intended to compete with state-of-the-art diagnostic work-up of heart failure according to the guidelines but to raise or confirm the suspicion of heart failure and/or subclinical fluid overload in primary care also in patients where it is not primarily suspected.

2. Materials and methods

2.1. Subjects investigated

119 subjects were investigated: 34 healthy controls were students of the Medical University Graz and healthy members of a gymnastic club. Consecutive patients referred to the Department of Internal Medicine of the hospital were asked to participate in this study voluntarily. Of them, 85 agreed and were studied: The diagnoses were obtained by board-certified physicians responsible for the care of the patients who were not involved in the study and are quite representative for those admitted to a general internal ward. Many patients had more than one diagnoses, therefore, the total number of diagnoses is greater than the number of patients. 50 patients suffered from CHF due to coronary or hypertensive heart disease (NYHA class II (20), class III (17), class IV (13)). 66% of patients had systolic heart failure with an EF < 50%, while the others had evidence of diastolic heart failure according to the European guidelines [30]. The other diagnoses were: essential hypertension (13), coronary heart disease without clinically evident heart failure (12), atherosclerosis (11), chronic kidney disease [31] stage II (24), stage III (22), stage IV (5), Stage VI (1), pleural effusion (6), metastatic cancer (5); breast cancer with bulky disease (1), bronchial carcinoma (1), bile duct carcinoma (1), carcinoma of the ovary (2), epithelial ovarian cancer (1), celiac disease (4), cirrhosis of the liver with ascites (4), ascites due to malignancy (1), deep vein thrombosis (3), type II diabetes (3), previous gastrectomy (2), morbid obesity (2), atelectasis of the left lung (1), one-sided lymphedema of the leg with pelvic lymph node metastasis (2), Milroy disease (1), gastritis (1), chronic pancreatitis (1), type II osteoporosis (1), myositis (1), anorexia nervosa (1), chronic polyarthritis (1), Conn's syndrome (1), Addison's disease (1) and renal transplantation (1). The patients being already on treatment were studied without changing their home medication, which included beta-blockers, ACE inhibitors, AT1 blockers, calcium channel blockers, hydrochlorothiazide, loop diuretics and spironolactone. The study complies with the Declaration of Helsinki. It was approved by the ethical committee of the hospital and all patients gave written informed consent.

Clinical details of the normal subjects and patients are given in Table 1.

Table 1
Clinical details of healthy controls and patients.

	Mean	Range	
		Min	Max
Healthy males ($n = 19$)			
Age (years)	52.7	25	77
Height (cm)	177.8	169	188
Weight (kg)	80.4	67	99
BMI	24.9	21.6	28.9
BNP (pg/ml)	29.6	11	73
Healthy females ($n = 15$)			
Age (years)	34.4	24	63
Height (cm)	166.6	153	175
Weight (kg)	60	48	76
BMI	21.6	18.9	27
BNP (pg/ml)	24.9	15	65
Male patients ($n = 54$)			
Age (years)	70.1	28.1	94.2
Height (cm)	173.2	153	192
Weight (kg)	76.2	33	122
BMI	25.2	12.9	39.9
BNP (pg/ml)	888.3	11	13,476
Female patients ($n = 31$)			
Age (years)	72.6	34.7	92.5
Height (cm)	159.1	141	172
Weight (kg)	72.4	38	155
BMI	28.6	14.8	61.4
BNP (pg/ml)	359.7	21	2403

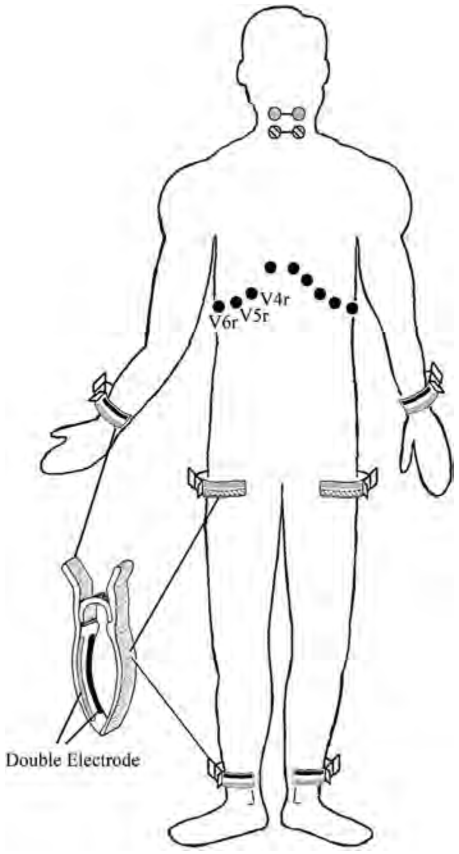

Fig. 2. The electrode placement is shown. At the extremities elastic double clamp electrodes and at the neck adhesive spot electrodes are used. Conventional electrodes necessary for the 15-lead ECG are shown in black, these are used additionally as voltage pick-up electrodes for the impedance measurements. The current injection electrodes are shown in gray. The voltage pick-up electrodes at the neck and the hips, which are not used for the ECG, are shown in black, striped. The body is thereby divided into six segments: thorax, abdomen and the four extremities. Further simplifications of electrode placement are feasible.

2.2. Methods

All the patients were investigated in the fasting state between 8 and 10 am. A blood sample was taken for the measurement of plasma BNP (Architect System, Abbott Laboratories, Diagnostics Division, Abbott Park, IL 60084 USA) and serum creatinine. Echocardiography was performed by two trained observers (GG and AH) using the Vivid 7 of GE (www.gehealthcare.com). EF was evaluated using the biplane Simpson method, through the software given with the instrument [32]. Diastolic function was evaluated by echo Doppler according to the European guidelines [30]. The cardiac output was measured by the double-gas re-breathing method using INNO500 by Innovision^{TM} (www.innovision.dk).

2.3. Impedance measurements

The subjects were supine for at least 10 min with a 30° upward inclination of the upper body. This position was chosen for the convenience of patients with dyspnea and/or heart failure. Electrodes were placed as shown in Fig. 2. The distal leg electrodes of the conventional ECG were replaced by double band clamp electrodes for the impedance measurements and the ECG. Double band-clamp electrodes were also placed at both proximal legs. Four spot adhesive electrodes were placed on the neck. Current was applied between the outer two neck and the outer of the proximal leg electrodes for the measurement of the thoracic and abdominal segments and between the inner of the proximal leg and outer distal leg electrodes for the analysis of the leg segments. The double band electrodes (6 cm × 1 cm) and the spot electrodes (diameter 2 cm) consisted of silver chloride. Edge to edge distances between current injection and voltage pick-up electrodes were 4.5 cm.

Definition of the segments: the thoracic segment was measured between the inner two neck electrodes and V4, V5, V6, V4r, V5r, V6r, respectively. The abdominal segment was measured between V4, V5, V6, V4r, V5r, V6r and both inner proximal leg electrodes, respectively. The placement of the current injection and voltage pick-up electrodes for the impedance measurements is shown in more detail in Fig. 2. The legs were measured in combination and alone between the outer proximal and the inner distal leg electrodes. The analysis of the arms is not subject of the present paper.

Segmental impedance spectroscopy was performed using the Imp^{TM} SFB7 by Impedimed (www.impedimed.com) at the thorax, abdomen and both legs. The instrument supplies Z_{zero} and Z_{∞} from Cole–Cole-plots [33]. In addition, impedance change with heart action ($\mathrm{d}Z/\mathrm{d}t$) was measured at 40 kHz as described previously [34]. A template was constructed by signal averaging the $\mathrm{d}Z/\mathrm{d}t$ of between 40 and 120 heart beats depending on the quality of the signals. Therefore about an equal number of beats were acquired during inspiration and expiration. Representative templates of impedance change with heart action are shown in Fig. 3. All characteristics of the curves (angle of slopes, height of peaks and distances of turning points) were analyzed manually by a blinded technician and the data fed into an Excel sheet. For the thoracic, abdominal and both leg segments the relations of extracellular to intracellular water (ECF/ICF ratios) were calculated using the resistances at Z_{zero} and Z_{∞} and specific resistances of ECF and ICF [35]. In the calculation of this ratio the variable lengths and the diameters of the investigated segments are canceled so that the exact placement of the electrodes and the irregular and unknown cross-sectional areas of the segments are no longer critical. The reproducibility of $\mathrm{d}Z/\mathrm{d}t_{max}$ and ECF/ICF ratio measurements was tested in 20 subjects, 1 h apart: Means and coefficients of variations were 102.4 + 2.5% and 99.6 + 1.2%, and 97 + 3.4% for the measurements of $\mathrm{d}Z/\mathrm{d}t_{max}$ at the thorax and at the leg segments and for the ECF/ICF ratio at the legs, respectively.

2.4. Statistical analysis

Logarithmic transformation of BNP was performed because of its log-normal distribution [36]. NYHA classes, EF, stroke index and log-transformed plasma BNP (logBNP) were analyzed in relation to the particulars of the impedance curves, to impedance spectroscopy outputs and to the ECF/ICF ratios of the measured body segments by single and partial correlation and multiple regression analyses. The calculation of this ratio cancels out the lengths of the investigated segments which varies between the individual subjects. The prediction of the presence or the absence of CHF was evaluated by a binomial logistic regression using the backward exclusion of non-significant parameters. For this analysis the 34 healthy controls and 8 patients in the group with miscellaneous diagnoses but without heart failure (no symptoms, normal EF, normal diastolic function and plasma BNP < 100 pg/ml) were added to the no-heart failure group. Because not all data were available in all subjects, the number of subjects in different correlations and other analyses may vary. The respective numbers are given in the figures and tables. Because of multiple testing only p values <0.01 were considered significant.

2.5. Evaluation in an independent test set and by leave-one-out cross-validation (LOOCV)

For assessing how the results of the statistical analysis will generalize to an independent data set, the collective was approximately

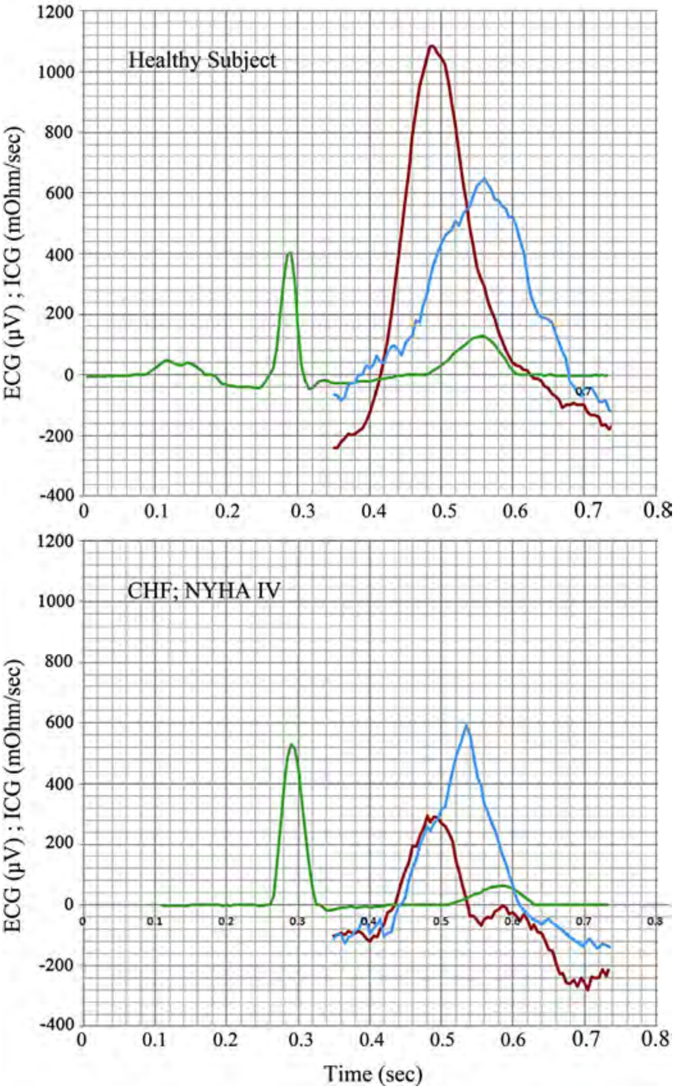

Fig. 3. Representative templates of the impedance signal at the thoracic and the leg segments in a normal subject and a patient with CHF are shown. These were constructed by signal averaging from between 40 and 120 heart beats. ECG, green; ICG thorax, red; ICG legs, blue. Note the time delay of d*Z*/d*t* max between the thorax and the legs which is due to traveling of the volume wave.

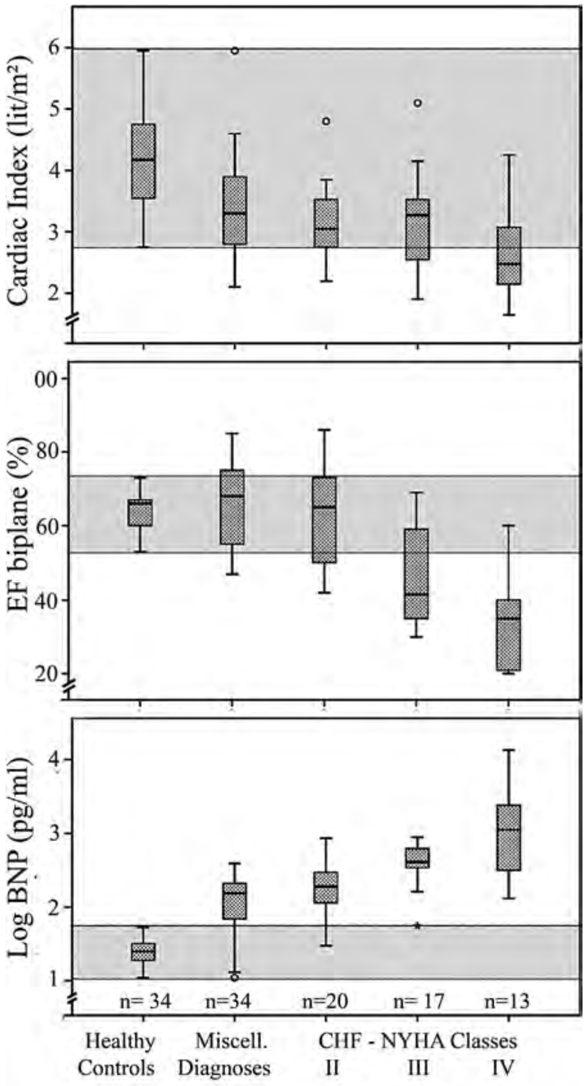

Fig. 4. Box–whisker plot of cardiac index, EF and BNP values in healthy controls and patients. The shaded areas correspond to the respective normal ranges.

halved randomly by SPSS into an evaluation set to obtain the regression equation. Then plasma BNP was predicted in a test set of 49 unknown patients. ROC analyses of the calculated plasma BNP were performed. In addition, LOOCV [37] has been used. Each single observation from the original data set was left out from the training data, and this was repeated so that each observation in the sample was used once as the validation data. All statistical calculations were performed using the SPSS statistic package, version 18.0.

3. Results

Table 2 shows the raw impedance data for healthy subjects and patients with chronic heart failure. Cardiac indices, EF, and measured logBNP in the different NYHA classes are shown in Fig. 4.

Table 2

Impedance values in subjects without heart failure and patients with heart failure.

		Thorax				Abdomen				Beine				Thorax	
		Z_0		Z_{inf}		Z_0		Z_{inf}		Z_0		Z_{inf}		d*Z*/d*t*	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Males without HF	25	38.9#	4.11	21.1	3.21	42.9#	5.61	25.0	3.25	175.8	21.43	112.0	13.96	1.20	0.34
Male patients heart failure	21	34.0	7.36	20.2	4.78	36.5	9.27	23.1	5.77	159.3	44.26	118.4	30.78	0.70	0.29
Females without HF	17	44.8	7.87	26.5	6.34	45.1	5.81	29.1‡	4.97	197.7	37.45	133.3	22.75	1.72	0.61
Female patients heart failure	11	41.5	5.18	24.7	2.48	38.2	8.68	25.1	4.56	193.1	55.23	143.2	35.09	0.77	0.28

Differences between subjects with and without heart failure in the male and female groups are indicated.

§ $p < 0.001$.

\# $p < 0.01$.

‡ $p < 0.05$.

Table 3
Partial correlation analysis predicting logBNP.

Model prediction logBNP; total $r = 0.86$, $p < 0.001$	T	Sig.	Correlations			Collinearity statistics	
			Zero Order	Partial	Part	Tolerance	VIF
Step 1							
Constant	1.606	0.114					
Age	0.118	0.906	0.582	0.016	0.008	0.418	2.394
BMI	−1.656	0.104	0.071	−0.218	−0.113	0.677	1.478
MDRD_Clearence	−1.266	0.211	−0.023	−0.168	−0.086	0.939	1.065
Stroke Index (Innocor)	0.132	0.895	−0.421	0.018	0.009	0.690	1.448
ECF/ICF ratio thorax	0.491	0.626	0.433	0.066	0.033	0.355	2.816
dZ/dt thorax	−4.671	0.000	−0.675	−0.533	−0.318	0.365	2.739
dZ/dt both legs	−4.030	0.000	−0.600	−0.477	−0.274	0.701	1.426
ECF/ICF ratio both legs	2.226	0.030	0.658	0.287	0.152	0.329	3.035
Final step							
Constant	2.567	0.013					
dZ/dt thorax	−5.834	0.000	−0.675	−0.602	−0.395	0.766	1.305
dZ/dt both legs	−5.230	0.000	−0.600	−0.560	−0.354	0.840	1.191
ECF/ICF ratio both legs	3.473	0.001	0.658	0.409	0.235	0.677	1.477

Part, semipartial correlation; collinearity statistics: the tolerance value is higher and VIF (variance inflation factor) is lower than the cut-off point advisable for a logistic regression (0.3 and 3.416, respectively) which suggests that the selected variables are truly independent.

EF and cardiac index in different NYHA classes show much larger variation than logBNP. LogBNP was the parameter that showed the least overlap between healthy subjects and NYHA classes of CHF. Therefore, and according to the original hypothesis for the present work, the paper focuses on the prediction of BNP from the electrical parameters obtained. The logBNP values in patients classified according to the NYHA class resemble also quite closely those reported by Abbott in the BNP Architect package insert Ref 8K2B 260–737 for the respective NYHA classes.

EF was not related to any of the electrical variables in single or partial correlation analysis. Stroke index as measured by double-gas re-breathing correlated with $\mathrm{d}Z/\mathrm{d}t_{\max}$ of the thorax ($r = 0.38$, $p < 0.001$), no other electrical variable contributed to the prediction of stroke index in partial correlation analysis.

The correlation coefficient between the stroke index, obtained by double gas re-breathing and log plasma BNP was $r = -0.33$, $p < 0.001$. Single correlation coefficients of $\mathrm{d}Z/\mathrm{d}t_{\max}$ at the thorax, $\mathrm{d}Z/\mathrm{d}t_{\max}$ at the legs and ECF/ICF ratio at the legs to log plasma BNP were $r = -0.67$, $p < 0.001$, $r = -0.61$, $p < 0.001$, $r = 0.67$, $p < 0.001$, respectively. Only $\mathrm{d}Z/\mathrm{d}t_{\max}$ at the thorax, at the legs and the ECF/ICF ratio of the legs contributed significantly to the prediction of logBNP in the partial correlation analysis. Table 3 shows the partial correlation analysis of the three parameters to the measured logBNP using the backward exclusion of non-significant parameters. The identified parameters correlate with logBNP independently as also proved by collinearity statistics with a combined $r = 0.86$, $p < 0.001$. The regression equation for the prediction was $\log \mathrm{BNP} = C - f_1\left(\frac{\mathrm{d}Z}{\mathrm{d}t_{\max}}\,\mathrm{thorax}\right) - f_2\left(\frac{\mathrm{d}Z}{\mathrm{d}t_{\max}\,\mathrm{legs}}\right) + f_3\left(\frac{\mathrm{ECF}}{\mathrm{ICF}}\,\mathrm{ratio\ legs}\right)$

The values for C, f_1, f_2 and f_3 vary markedly depending on the exact configuration and location of the electrodes. The exact values will have to be determined by any user of the method specifically for the selected equipment.

There was no significant correlation between $\mathrm{d}Z/\mathrm{d}t_{\max}$ at the thorax and at the legs ($r = 0.25$, n.s.). Neither the calculation of $(\mathrm{d}Z/\mathrm{d}t_{\max})/Z_0{}^2$ of the particular segment nor the inclusion of height, weight or electrode distance did improve the obtained multiple r. The multiple regression equation obtained was used to predict logBNP from the three parameters. The correlations between the measured logBNP and the predicted logBNP from the multiple regression equation and the corresponding Bland–Altman plot [38] are shown in Fig. 5. For these analyses, the independent unknown test set of 49 subjects (top of Fig. 5) and LOOCV (bottom of Fig. 5) were used. In this unselected population of patients attending a general internal ward, logBNP could be predicted with an $r = 0.88$, $p < = 0.001$ and $r = 0.86$, $p < 0.001$, respectively. Fig. 6 shows the ROC curves for predicting a plasma BNP higher than 400 pg/ml (>2.602 logBNP) in unknown cases by using the multiple regression (Table 3), which gives an AUC = 0.93.

Table 4 shows the results of the binomial logistic regression for predicting the absence or presence of CHF from the three impedance parameters. For this analysis the 34 healthy controls and 8 patients in the group with miscellaneous diagnoses but without heart failure (no symptoms, normal EF, normal diastolic function and plasma BNP < 100 pg/ml) were added to the no-heart failure group. Only $\mathrm{d}Z/\mathrm{d}t_{\max}$ at the thorax and at the legs contributed significantly to the prediction. 92.9% of the subjects without heart failure and 87.5% with heart failure were allocated correctly to the respective group. In the groups divided by a BMI below or above 25 the prediction of heart failure was comparable: for the group with a range of BMI from 17.8 to 24.4 the correct allocations were 96.0 and 92.3%, for the group with a range of BMI from 25.6 to 51.5, the correct allocations were 93.3 and 95.2%, respectively.

Fig. 7 shows the ECF/ICF ratio of the thoracic and the abdominal segment in healthy male and female subjects and in patients with chronic heart failure. The latter show significantly increased ECF/ICF ratios at both segments. Male subjects exhibit a lower ratio than females in both segments. Out of the eleven patients with fluid accumulation in one of the segments eight are located outside the 95% confidence limits for healthy males and females, respectively. A female patient with atelectasis of the left lung and a raised ECF/ICF ratio is also seen.

Table 4
Binomial logistic regression for predicting heart failure: classification table.

Observed		Predicted		
		No heart failure	Heart failure	Percentage correct
		0.00	1.00	
Step 1				
No heart failure	0.00	39	3	92.9
Heart failure	1.00	4	28	87.5
Overall percentage				90.5
Step 2				
No heart failure	0.00	39	3	92.9
Heart failure	1.00	4	2 8	87.5
Overall percentage				90.5

The cut value is 0.500.
Step 1: dZ/dt thorax, dZ/dt legs, ECF/ICF ratio legs.
Step 2: exclusion ECF/ICF ratio legs.

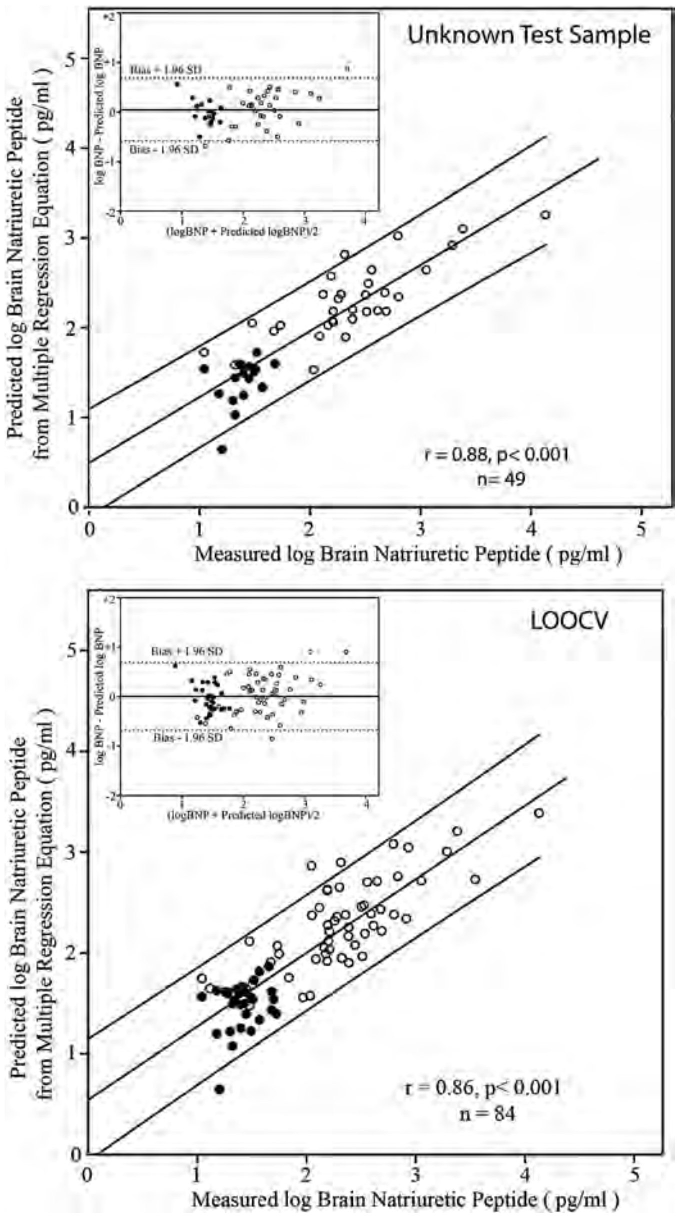

Fig. 5. The correlation of measured to predicted BNP by the multiple regression equation in an unknown test sample (top) and in cases unknown by LOOCV (bottom). The corresponding Bland–Altman plots are also shown.

In contrast, thoracic fluid content, as measured with just one frequency, did not correlate with the plasma BNP ($r = 0.22$, n.s.) which is in agreement with the study of Kamath et al. [15]. A binomial logistic regression was unable to predict the presence or the absence of CHF on the basis of thoracic fluid content measured at just one frequency (51.6% correct overall allocation).

Fig. 8 shows the correlation of the ECF/ICF ratio of the right and the left legs, respectively, in healthy subjects and patients with chronic heart failure NYHA classes II–IV. As expected, the ECF/ICF ratios of the right and the left legs correlate closely in healthy subjects and in patients with CHF. 6 cases of unilateral venous or lymph edema are also shown. These patients lie outside the 95% confidence limits of healthy subjects and patients with CHF. In contrast, a patient with left-sided congenital lymphedema (Milroy's syndrome) exhibited no side difference of the ECF/ICF ratio.

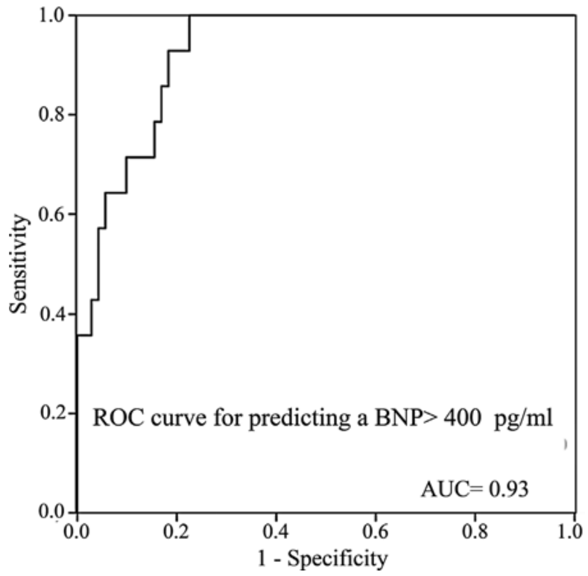

Fig. 6. ROC curves for detecting a BNP > 400 pg/ml in the unknown cases by the multiple regression equation.

4. Discussion

Besides a detailed history and physical examination, assessing the heart function of a patient echocardiography is usually required [2]. In recent years, plasma BNP has become important for diagnosing heart failure [2]. The present study predicted BNP, chronic

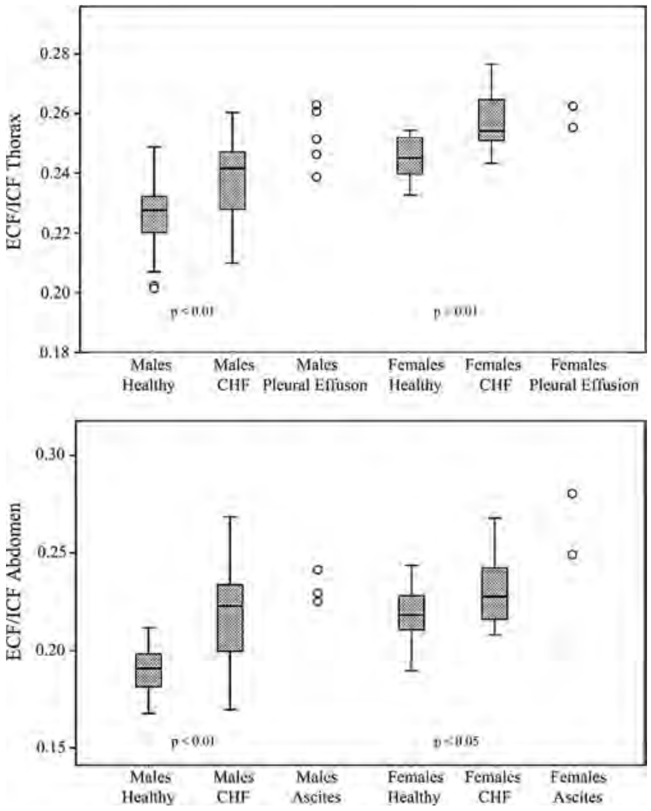

Fig. 7. The ECF/ICF ratio of the thoracic and the abdominal segment in healthy male and female subjects as compared to patients with CHF and to patients with ascites and pleural effusion. Patients with CHF have an increased ECF/ICF ratio at all investigated segments. Still, in the multiple regression analysis the ECF/ICF ratio at the legs is included instead of other segments.

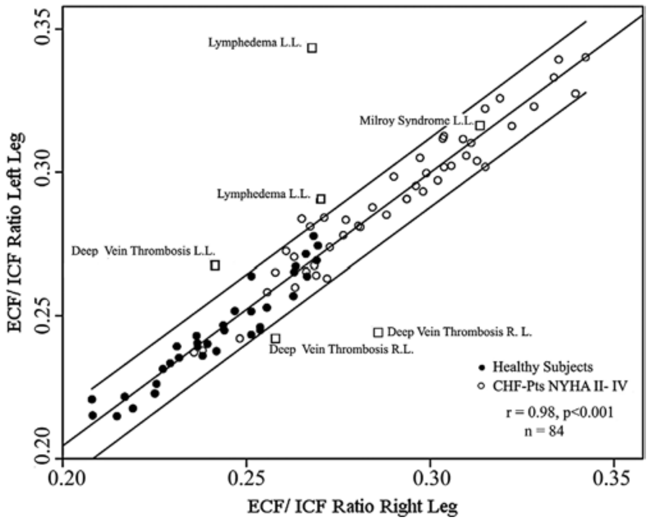

Fig. 8. The ECF/ICF ratio of the right and the left leg respectively in healthy subjects and patients with chronic heart failure NYHA classes II–IV. Regression line and confidence limits from healthy subjects and patients with heart failure. Also shown are the ECF/ICF ratios of 6 patients with unilateral venous edema or lymphedema (R.L. = right leg; L.L. = left leg).

heart failure and/or disorders of fluid homeostasis by electrical means with electrodes placed in addition to the conventional ECG. This was attempted independently of the presence or the absence of other concomitant diseases or of possible prior treatment. In a broad variety of patients admitted consecutively to a general internal ward, this could be achieved with satisfactory sensitivity and specificity.

The electrical resistance of a body segment and its change with heart action can be measured with a high technical reproducibility [39,40] (see also Section 2.2): the present paper rests only on three physical principles, namely that an alternating current of low frequency passes only through the extracellular fluid and does not pass cell membranes [41], that an alternating current of high frequency additionally penetrates the cell membrane [41], and that the maximal rate of change of electrical resistance with heart action in a given body segment is related to the maximal rate of fluid volume change in the investigated segment [40].

4.1. *Assessment of fluid status*

Figs. 7 and 8 suggest that it may be possible to detect the accumulation of extracellular fluid in the thorax, abdomen or the legs, if impedance spectroscopy is performed and an ECF/ICF ratio is calculated. The calculation of this ratio cancels out the lengths of investigated segments which varies between the individual subjects. The discrimination of healthy subjects from patients with heart failure on the basis of the ECF/ICF ratio of the legs is especially impressive, since there is little overlap between the groups (Fig. 8) and since part of the patients was on diuretics and had little or no visible or palpable edema. This parameter alone could become helpful for the diagnosis and management of CHF in the future. It must be emphasized that the accumulation of ECF as measured by the ECF/ICF ratio (Figs. 7 and 8), was not detected by physical examination in many cases. It was not the primary goal of the present study to detect ECF accumulation at localized areas such as the pleural or abdominal cavity, or unilateral leg edema. Those patients were included as they were admitted consecutively to the hospital. Therefore the number of subjects is small and no definite conclusions can be drawn about the sensitivity of the method in these conditions. However, it appears possible that in the above conditions the methodology might be of value (Figs. 7 and 8), especially as impedance spectroscopy has already been shown to be useful for the diagnosis and follow-up of one-sided lymphedema after mastectomy [42].

4.2. *Assessment of heart failure*

Except for the terminal state, heart failure may be associated with low or normal resting cardiac output (Fig. 4) [43]. Measurement of resting cardiac output [44] is therefore not useful for routine assessment of heart failure [2]. Also, thoracic fluid content, as calculated from just a single frequency measurement, was not correlated to the presence or the absence of heart failure in the present study, which confirms the results of Kamath et al. [15]. One characteristic of chronic heart failure is the reduced resting peak pulmonary [9] and aortic blood acceleration [10,11] due to cellular overstretching of heart muscle fibers, which leads to less interaction sites between actin and myosin (Fig. 1). A parameter that can be extracted with certainty from impedance change with heart action, is the maximal rate of fluid volume change within a given body segment [40]: it is proposed and confirmed that there must be an inverse relation between the “cellular overstretch–BNP release coupling” and the “cellular overstretch–reduced maximal rate of segmental fluid volume change” within the thorax or other body segments such as the legs (Fig. 1 and Table 3).

Both maximal rate of the segmental fluid volume change at the thorax and at the legs with heart action contribute independently to the prediction of logBNP in a partial correlation analysis (Table 3) and of the presence or the absence of heart failure by a binomial logistic regression (Table 4). This is not surprising, as peak leg blood acceleration is also reduced in heart failure [45]. The lack of correlation between peak fluid volume change rates within the thorax and the leg segments may imply that the volume change at the thorax may reflect volume change at least partly within the lung induced by the action of the right ventricle (and not predominantly at the aorta as has been proposed [40]), whereas the fluid volume change in the legs reflects volume change induced by the left ventricle. In addition, the ECF/ICF ratio of the legs, indicating the extracellular fluid accumulation, is the third parameter contributing independently to the prediction of logBNP in the partial correlation analysis. Whether the whole body ECF/body water ratio correlates with BNP has been investigated mainly in dialysis patients with conflicting results [46–48]. The bioimpedance vector analysis (BIVA) [49,50] is dependent on sex, race/ethnicity, BMI, and age and further clinical validation studies are needed to establish definite relationships between hydration disorders and vector distribution [51]. From the correlation between the measured logBNP and the predicted logBNP (Fig. 5) and from the ROC curve (showing an AUC = 0.93 for a prediction of BNP > 400 pg/ml), it appears that the method could be of value to diagnose heart failure while writing a conventional ECG. Fig. 2 shows that the electrode placement is still feasible for recording a combined “electrical and hemodynamic” ECG by a nurse at primary care or emergency room settings, if the necessary hardware and software are included in the ECG apparatus.

The validity of the prediction of plasma BNP rests on a test sample of patients who were not used for the prediction: after dividing the patient sample into about equally sized validation – and test samples randomly by SPSS, in the unknown test set of 49 patients log plasma BNP could be predicted with good precision (Fig. 5 top). It additionally rests on the method of leave-one-out cross-validation, whose reliability may be questionable under certain circumstances. As the method was evaluated in unselected patients admitted consecutively to a general internal ward, cross-validation should be nearly unbiased [37].

One can explain the satisfactory power of the three parameters identified to predict heart failure in the following ways: (a) pathophysiology [8,9,11] implies that cellular overstretch- BNP release coupling and overstretch–reduced maximal acceleration of blood of both ventricles must be related closely, (b) the ECF/ICF ratio probably will detect ECF accumulation with a higher sensitivity than even by an experienced clinician by means of traditional clinical examination since edema does not become apparent until the interstitial volume has increased by 2.5–3 l [52], and (c) all three parameters are truly independent and participate equally in the prediction (Table 3). A number of patients not being diagnosed as having CHF by trained physicians had raised BNP levels (Fig. 4) and probably had undiagnosed CHF. Still, the raised BNP could be predicted by the multiple regression equation independent of diagnosis and prior treatment (Fig. 5).

The present study also has limitations: It is not known, how the method would perform in isolated right sided heart failure or in cardiomyopathies in the absence of cellular overstretching. The total number of patients with isolated diastolic heart failure ($n = 12$) and with ECF accumulation in the trunk ($n = 11$) or unilateral leg edema ($n = 5$) is small and the good performance of the methodology in the present study will have to be confirmed prospectively in a large number of patients. Also, it is unexpected that the inclusion of $dZ/dt/Z^2$, height and weight or electrode distance did not improve the prediction equation, since both theoretical and experimental data have shown that the inclusion of Z^2 scales the impedance parameters to volume changes. This will require further study.

From the data presented here it appears that a low-cost device added to the conventional ECG-apparatus possibly could predict plasma BNP levels. It could possibly also warn doctors at primary care about the possible presence of systolic and diastolic heart failure and about the disturbances of body fluid homeostasis such as subclinical edema, venous thrombosis and post-thrombotic syndrome, lymphedema [42], pleural effusion, and ascites (Figs. 7 and 8). This would then warrant further investigation of the body segment under suspicion and referral to the specialist. The method could possibly be also of value for monitoring the response to treatment in CHF. Based on the knowledge and experience gained by the present study, a multicenter study is warranted in primary care and at the emergency room in which the sensitivity and specificity of the method is compared prospectively to standard assessment.

Ethical approval

Ethical approval was given by the Ethical Committee of the Hospital Barmherzige Brüder, Teaching Hospital Medical University Graz, Project: “Body Composition and Heart Function”.

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Conflict of interest

Since submission of the paper patents for the technology presented in this paper (“Function & Spaces-ECG”) have been applied by the authors. The hard- and software necessary for performing the analyses and containing the regression equations have been developed in the research laboratory of the authors and will be supplied on request.

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