ELSEVIER

The European Journal of Heart Failure 7 (2005) 974–983

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Multi-site-frequency electromechanocardiography for the prediction of ejection fraction and stroke volume in heart failure

Falko Skrabal*, Harald Mayer, Elke Hopfgartner, Gerfried Gratze, Gerhard Haitchi, Albert Holler

Department of Internal Medicine, Krankenhaus Barmherzige Brüder, Teaching Hospital, Graz Medical University, Marschallgasse 12, A8020 Graz, Austria

Received 30 April 2004; received in revised form 24 September 2004; accepted 11 November 2004
Available online 9 April 2005

Abstract

Background: Methods for stroke volume (SV) and ejection fraction (EF) measurements require the presence of qualified physicians and are not suited for continuous monitoring.
Aim: To develop an automated non-invasive method for the measurement and continuous monitoring of SV and EF.
Methods: We have designed a method for the measurement of EF and SV using multiple-site-impedance ($z0$) measurements, applying multiple frequencies of 5, 40 and 200 kHz whereby various segments of the human body, including volume changes within these segments, could be defined electrically. The obtained variables were used to train neuronal nets and related by multiple regression analyses to cardiac output (CO) as measured by a partial rebreathing Fick method ($CO_{r\text{-fick}}$) or EF as measured by echocardiography (EF_{echo}), respectively. A total of 129 subjects (48 with normal heart function and 81 with CHF, NYHA I–IV) were investigated.
Results: The multiply derived values of $z0$ and of change of impedance (dz/dt) were shown, by multiple regression analysis, to be significantly related to $CO_{r\text{-fick}}$ and to EF_{echo}, (total r=0.77, n=35, p<0.001, and r=0.81, n=47, p<0.001, respectively.). By training a neuronal net with the electrical data of 67 (out of 94) subjects, EF_{echo} could be predicted in the remaining 27 subjects which were unknown to the neuronal net with a combined r=0.71 (p<0.001,n=27). In contrast, conventional impedance cardiography (ICG) was unable to predict either $CO_{r\text{-fick}}$ or EF_{echo}.
Conclusion: The new method, which we call multi-site-frequency electromechanocardiography (*msf*-ELMC) appears promising for the automated electrical measurement of the mechanical heart action in patients with normal and reduced cardiac function.
© 2004 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

Keywords: Cardiac output; Stroke volume; Ejection fraction; Chronic heart failure; Myocardial contraction; Electromechanocardiography; ELMC; Impedance cardiography

1. Introduction

Accepted current methods for stroke volume (SV) and ejection fraction (EF) measurements require the presence of qualified physicians and are not suited for continuous monitoring. Impedance cardiography (ICG) would not have these draw backs, but despite the use of impedance cardiography (ICG) for the measurement of stroke volume (SV) and cardiac output (CO) since its invention 50 years ago [1], this technique has not gained acceptance among cardiologists. The reason for this is that the performance of this technique deteriorates progressively as the cardiac output deviates from normal [2–4]; therefore, a method reliable with normal and reduced heart function could be useful. In healthy subjects, CO fits very closely to body size. This is the reason why CO can be predicted solely from height, weight, sex and age [5]. All formulas calculating CO from the impedance cardiogram include measurements such as height [6], weight [7] or surface electrode distance [1] (which, again, is related to body height [6]), thereby producing strong bias towards normal values. Therefore, in healthy subjects, CO_{ICG} relates sufficiently well to CO as gauged against the gold standard of the Fick principle. The more CO deviates from normal, as is the case in heart failure

* Corresponding author.
E-mail address: falko.skrabal@meduni-graz.at (F. Skrabal).

1388-9842/$ - see front matter © 2004 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejheart.2004.11.002

or in critically ill patients, the correlation between CO_{ICG} and CO as measured by the Fick principle (CO_{Fick}), due to its bias towards normal values, becomes progressively worse [3,4,8]. In the method presented, we have eliminated all measures of body size and have solely related electrically measured variables, namely impedance ($z0$) and impedance change over time (dz/dt)) derived at different sites and at different frequencies in two different black-box approaches to SV and EF as measured by accepted ("gold standard") methods. Besides using a number of different measurement sites and frequencies, the main difference of the suggested black-box approach to conventional methods of ICG is that no assumptions such as geometrical models are made. In contrast, it is evaluated which electrically measured variables provide independent, statistically significant and meaningful contributions to the prediction of SV and CO as measured by the best available "gold standard" method in patients with normal and reduced cardiac function.

2. Materials and methods

2.1. Patients studied

2.1.1. CO study

Female subjects undergoing gynaecological surgery were chosen because the type of operation enabled undisturbed access to the neck and lower thoracic aperture, where the electrodes had to be placed. There were 35 patients with an age range from 28 to 86 years. Twelve patients had normal heart function as revealed by echocardiography obtained externally, 23 patients had heart failure due to coronary heart disease (clinical NYHA classes I and II). Patients with valvular heart disease were excluded. All patients had normal lung function and none had evidence of pulmonary shunts. Patients with emphysema and chronic obstructive bronchitis were excluded from the study.

2.1.2. EF study

The EF study included 94 subjects (33 female, 61 male) with an age range from 20 to 90 years. 36 had a normal EF (either hospital staff or patients referred for endoscopic evaluation), 58 had chronic heart failure due to coronary heart disease. A total of 29 of these had an EF between 40% and 56%, 14 an EF between 30% and 39% and 15 subjects an EF below 30%. The instrument for whole body impedance measurements only became available at a later stage of the study, so that whole body impedance measurements at different frequencies were obtained in only 47 of the 94 patients. In all 94 patients, measurements of thoracic impedance at 40 kHz and at two different electrode distances (in order to calculate l_{op}, see later) were available.

The ethics committee of the hospital approved both the CO and the EF study and the patients gave informed consent to the experimental protocol. The investigation conforms to the principles outlined in the declaration of Helsinki (Cardiovascular Research 1997; 35:2–4).We relied on a modified Fick principle as the best available "gold standard" method, since the ethical committee did not approve invasive Swan Ganz haemodynamic measurements. This should however not reduce the validity of the conclusions (see Method and Refs. [13–15]).

3. Methods

3.1. Cardiac output study

3.1.1. Experimental protocol during general anaesthesia

Before induction of anaesthesia, short band electrodes [9] were placed on the extensor side of the left foot and at the left hand. Further double band electrodes were placed at the neck and two triple band electrodes were placed at both sides of the lower thoracic aperture [9]. The triple band electrodes of both sides were connected to each other. The placement of the electrodes is shown in Fig. 1. During surgery, the patients were in the supine position and the measurements were started 10 min after the induction of anaesthesia, when absolute haemodynamic stability had been reached.

The application of the currents and the measurement of $z0$ and dz/dt were performed as displayed in Fig. 1. As can be seen, three sites were chosen for the application of the currents (<400 μA effective for all) at frequencies of 5, 40 and 200 kHz, respectively. These frequencies were chosen in order to cover a broad range, whereby the frequency of 5 and 40 kHz predominantly measures the resistance of the extracellular fluid, while the 200 kHz also takes the resistance of the intracellular compartments [10,11] into consideration. The Bodystat Dual Scan 2005 (Bodystat, British Isles, UK) was used for the 5- and 200-kHz measurements, while the Diefenbach (Frankfurt, BRD) device was used for the 40-kHz measurements. Three sites were chosen for the voltage measurements (Fig. 1). Each measurement phase lasted about 60 s while stable values for $z0$ and dz/dt were achieved for each respective period. The hardware and software for measuring and calculating $z0$ and dz/dt at 40 kHz, pre-ejection period (PEP) and left ventricular ejection time (LVET) has been described in detail [12]. It was not necessary to interrupt the ventilation for the $z0$ and dz/dt measurements since a breathing filter was included in the software [9] for the impedance measurements.

The NICO device (Novametrix, USA) was used to monitor CO by a partial rebreathing Fick technique ($CO_{r\text{-}fick}$): the NICO loop was placed into the intraoperative anaesthetic tube system and the system was used as described by the manufacturer. This method is reported to have good precision and reproducibility in patients on fixed ventilation [13,14,15]. All patients investigated were on mechanical ventilation with fixed breathing rate and volume, which is a prerequisite for the CO measurements using the NICO device. There was no significant intra-operative bleeding in any of the patients and all patients

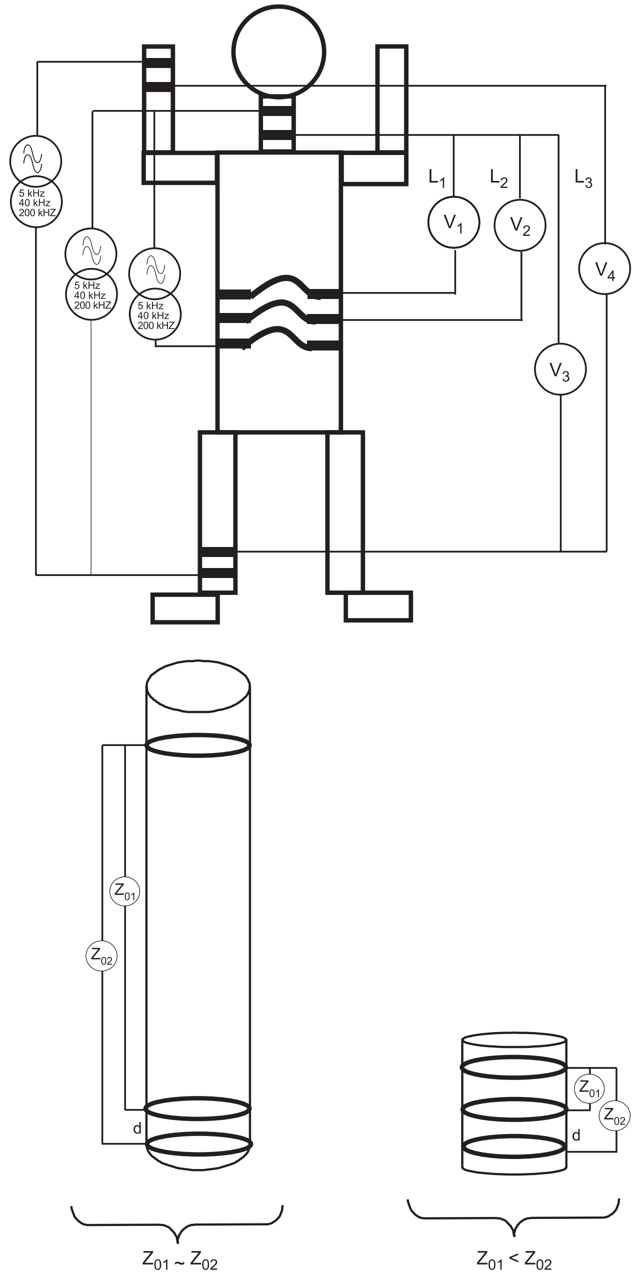

Fig. 1. A scheme of the placement of the electrodes as used in the present study is shown on the top. For explanation see method section. At the bottom of the figure, the principle of measuring essentially the same segment of the body at two different electrode distances in order to derive an "electrically operative" or "virtual " electrode distance is shown. If a small variation of electrode distance does not cause an appreciable change of resistance, the investigated segment must be comparatively very long (bottom left). In contrast, if the same small variation of electrode distance causes a marked change of resistance, the investigated segment must be very short (bottom right).

had very stable CO readings during the entire experimental protocol. The $z0$ and dz/dt readings were matched closely in time to the readings of the NICO instrument and mean values were calculated from the beat-to-beat values of the respective period. SV_{NICO} was calculated from CO_{NICO} divided by the mean heart rate of the respective experimental period.

3.2. Ejection fraction (EF) study

3.2.1. Measurement of EF by echocardiography

One single observer performed all measurements of EF by two-dimensional echocardiography using the modified Simpson's rule technique [16]. The subjects were resting for at least 15 min in the supine position before measurements were begun. The Powervision 6000™ (Toshiba® Medical Systems, Europe), with a 2.5-MHz transducer and the included software as provided by the manufacturer was used. The person responsible for the EF measurements was unaware of any of the electrical measurements.

The electrical measurements were performed on the same day as the echocardiographic study as described above for the CO study. The subjects were rested for at least 15 min in the supine position before measurements were begun during spontaneous breathing. Measurements at the different sites and at the different frequencies were performed for 60 s each, during these periods, very stable $z0$ and dz/dt readings were obtained. Again the mean values of all $z0$ and dz/dt readings of the different periods were used for further evaluation.

3.2.2. Mathematical and statistical methods

3.2.2.1. Calculation of the "electrically derived operative electrode distance". For the calculation of the " electrically operative " electrode distance at the thorax, the following equations were used:

$$z0_1 = \rho * \left(L_{op}/A\right) \tag{1}$$

where $z0_1$=thoracic impedance of segment 1, ρ=the specific resistance, L_{op} is the operative length and A is the area of the first investigated segment.

And where Eq. (2) is:

$$z0_2 = \rho * \left(L_{op_2}/A\right). \tag{2}$$

If d is a constant and defined distance (by the design of the triple band electrode, which is short in comparison with l_{op}), (see Fig. 1) then

$$L_{op_2} = L_{op} + d \tag{3}$$

where ρ=the specific resistance, L_{op_2} is a second length, and A is the area of a second segment under investigation

$$z0_1 = \rho \frac{l_{op}}{A} \tag{4}$$

$$z0_2 = \rho \frac{l_{op} + d}{A} \tag{5}$$

$$\frac{z0_1}{z0_2} = \frac{\frac{\rho * l_{op}}{A}}{\frac{\rho * l_{op} + d}{A}} \tag{6}$$

$$\frac{z0_1}{z0_2} = \frac{l_{op}}{l_{op} + d} \tag{7}$$

$$\frac{z0_2 * l_{op}}{z0_1} = l_{op} + d \tag{8}$$

$$\frac{z0_2 * l_{op}}{z0_1} - l_{op} = d \tag{9}$$

$$\frac{z0_2}{z0_1} - 1 = \frac{d}{l_{op}} \tag{10}$$

The electrically derived operative length L_{op} becomes

$$L_{op} = \frac{d}{\frac{z0_2}{z0_1} - 1} \tag{11}$$

if the area A and ρ are the same for Eqs. (1) and (2) which is fairly safe to assume given the very close distance (d) between the two sections of the body defined by l_{op} and l_{op_2}, which corresponds to the fact that essentially the same part of the body is measured at both l_{op} and l_{op_2}. The electrically derived "operative" electrode distance l_{op} was compared to the mean distance of the electrodes measured at the surface of the body between the inner neck electrode and the inner electrodes at the lower thoracic aperture (see Fig. 1) and this l_{op} was also used for further partial correlation and multiple regression analysis (see below).

Since the resistivity of blood influences all impedance measurements and since the haematocrit (Hk) is the main determinant of its resistivity [17], the haematocrit was measured in all patients of the CO and EF study on the day of the study. The resistivity of blood ρ_{blood} was derived from the formula of Lamberts [18]

$$\rho_{blood} = 71.24e^{0.000358Hk^2}$$

The Hk and the derived value for ρ_{blood} were also included in the mathematical analysis.

Table 1

(a) CO-study raw data

n	NYHA 0		NYHA I–II	
	12		23	
	Mean	S.D.	Mean	S.D.
CO-NICO [ml/min]	5.08	0.38	3.84	0.52
Age [years]	45.83	10.84	53.54	13.04
Height [cm]	166.58	7.59	162.67	6.08
Weight [kg]	69.83	12.96	65.54	10.62
Hkt [%]	40.35	4.24	41.05	3.43
l_{op}	23.74	5.73	25.11	14.65
$z0$ (V1) 5 kHz [Ω]	41.40	5.73	43.71	4.38
$z0$ (V1) 40 kHz [Ω]	33.83	4.55	37.70	6.02
$z0$ (V1) 200 kHz [Ω]	32.80	6.42	35.50	3.92
dz/dt (V1) [Ω]	4.98	11.23	1.38	0.52
dz/dt (V2) [Ω]	4.01	8.69	1.30	0.49
$z0$ (V3) 5 kHz	660.67	37.54	675.32	74.08
$z0$ (V3) 40 kHz	33.46	13.74	32.11	9.21
$z0$ (V3) 200 kHz	511.67	36.72	531.00	64.46

(b) EF-study raw data

n	EF>56		EF>40<56		EF>30<40		EF<30	
	14		13		12		8	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
EF Echo [%]	66.87	5.86	47.86	5.49	34.18	3.31	24.44	3.92
Age [years]	72.50	7.11	65.93	20.95	67.36	13.71	69.00	9.35
Height [cm]	169.00	7.90	168.86	9.52	170.18	6.78	170.88	5.77
Weight [kg]	71.29	13.51	64.74	14.85	78.10	15.03	73.84	13.94
Hkt [%]	39.36	3.69	42.05	3.63	46.02	4.17	43.64	4.70
l_{surf} [cm]	33.00	3.08	31.86	4.30	33.50	3.71	33.56	3.96
l_{op}	22.38	2.80	25.66	4.27	26.83	8.10	24.51	4.20
$z0$ 5 kHz (V1) [Ω]	40.21	9.11	42.07	13.69	40.09	5.74	43.88	8.24
$z0$ 40 kHz (V1) [Ω]	35.53	7.79	34.70	5.06	35.20	4.48	37.95	7.82
dz/dt (V1) [Ω]	1.31	0.53	1.36	0.86	0.95	0.28	1.44	0.49
dz/dt (V2) [Ω]	1.25	0.48	1.25	0.76	0.91	0.28	1.29	0.33
$z0$ (V1) 200 kHz [Ω]	31.36	7.45	30.64	5.62	30.64	4.18	32.50	8.12
$z0$ (V3) 5 kHz [Ω]	613.64	84.84	663.07	155.29	569.73	90.02	700.00	130.94
$z0$ (V3) 40 kHz [Ω]	76.34	2.44	74.34	6.54	76.92	0.88	71.58	7.95
$z0$ (V3) 200 kHz [Ω]	508.57	68.15	549.43	137.66	458.82	84.95	568.50	120.08

3.2.2.2. Partial correlation and multiple regression analysis. SV as derived by the partial rebreathing Fick method and EF measured by echocardiography were related by partial correlation and multiple regression analyses to the multiple values of $z0$ and dz/dt (as obtained at the different sites and frequencies), the pre-ejection period (PEP), left ventricular ejection time (LVET), haematocrit, the mathematically derived ρ and the electrically derived "operative" electrode distance (l_{op}) at the thorax. Partial correlation and multiple regression analyses were performed using the SPSS software package (SPSS, Chicago, USA).

3.2.2.3. Analysis using a neuronal net. In the 95 patients in whom measurements of thoracic impedance at two different electrode distances were available and in whom the electrically operative electrode distance could therefore be calculated, a backward propagation net with two hidden layers (BrainMaker®, California Scientific Software, USA) was trained on 2/3 of the patient samples to predict EF from l_{op}, the multiple $z0$'s, dz/dt, LVET and haematocrit. The derived net structure was used to predict EF in the remaining third of the patients whose values were not used for the training process.

In the current article, the output of the multiple regression equations using different measurement sites and frequencies is called *multiple site-frequency* electromechanocardiography (*msf*-ELMC). The output of the neuronal net from different sites but at only one single frequency is called *ms*-ELMC.

4. Results

The raw data for all impedance measurements are given in Table 1.

4.1. Conventional impedance cardiography

Fig. 2 demonstrates an example of how absolute values of CO are currently derived by commercially available ICG instruments. For this analysis, the healthy subject was under stable bed rest and an FDA approved ICG-instrument produced and currently sold widely in the USA was used to measure stroke volume. While measuring the same person during steady state conditions every 2 min, the manual inputs to the instrument were changed:

(a) to supply the information of a fixed weight of 70 kg and a fictitious body height of the same healthy subject between 140 and 220 cm;
(b) thereafter the body height was kept constant at 180 cm and body weight input of the instrument was changed to supply the fictitious information of a body weight from 40 kg to 140 kg again in the same person. As can be seen from Fig. 2, the CO output of the commercial ICG-instrument in the same person changes linearly and directly with each supplied fictitious step in body weight and height.

Fig. 3 (left) shows the relation and Bland Altman plot of SV derived by conventional impedance cardiography using Sramek's formula [6] and SV_{NICO}. This formula again includes body height (but not body weight), which per se is related to CO in healthy subjects [6]. Surprisingly, only the $z0$ but not dz/dt used in conventional ICG showed a weak relation to SV_{NICO} in the partial correlation or multiple regression analysis (Table 2).

The relation of EF_{Echo} to EF_{ICG} as calculated from conventional formulas [19] is shown in Fig. 3, right. As can be seen, there is no significant correlation of EF_{Echo} to the values determined by conventional ICG. Again, none of the parameters used in conventional ICG showed a significant correlation to EF_{Echo} in the partial correlation or multiple

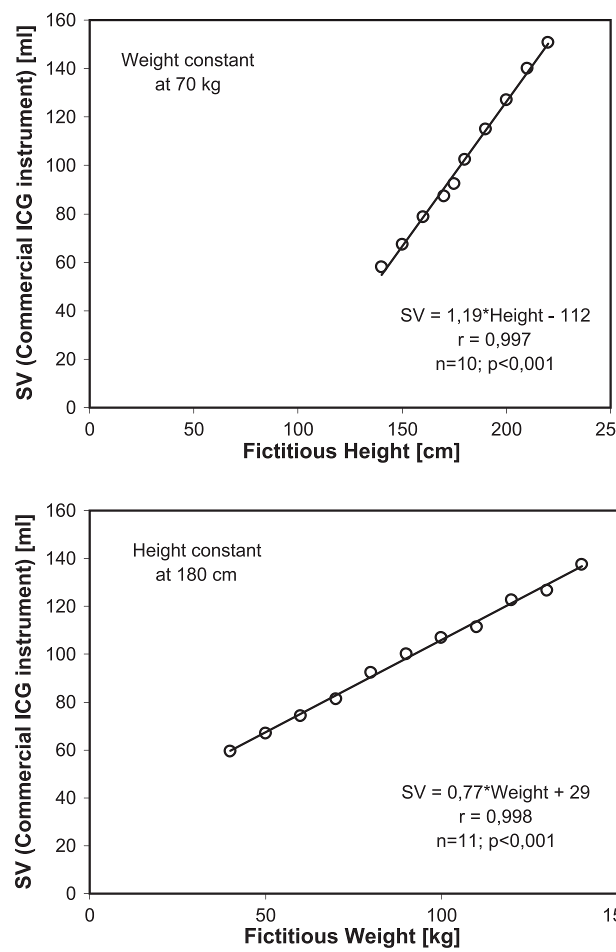

Fig. 2. This figure shows how a widely used commercially available ICG instrument sold widely in the USA, currently calculates stroke volume mainly from body height and body weight in order to derive a nominal value. For these measurements the spot electrodes provided by the manufacturer were used. As can be seen, an input change of weight and/or height for the same investigated subject causes the corresponding change of SV. This measure introduces strong bias towards nominal values and makes the method unsuitable in conditions like heart failure where it is most needed.

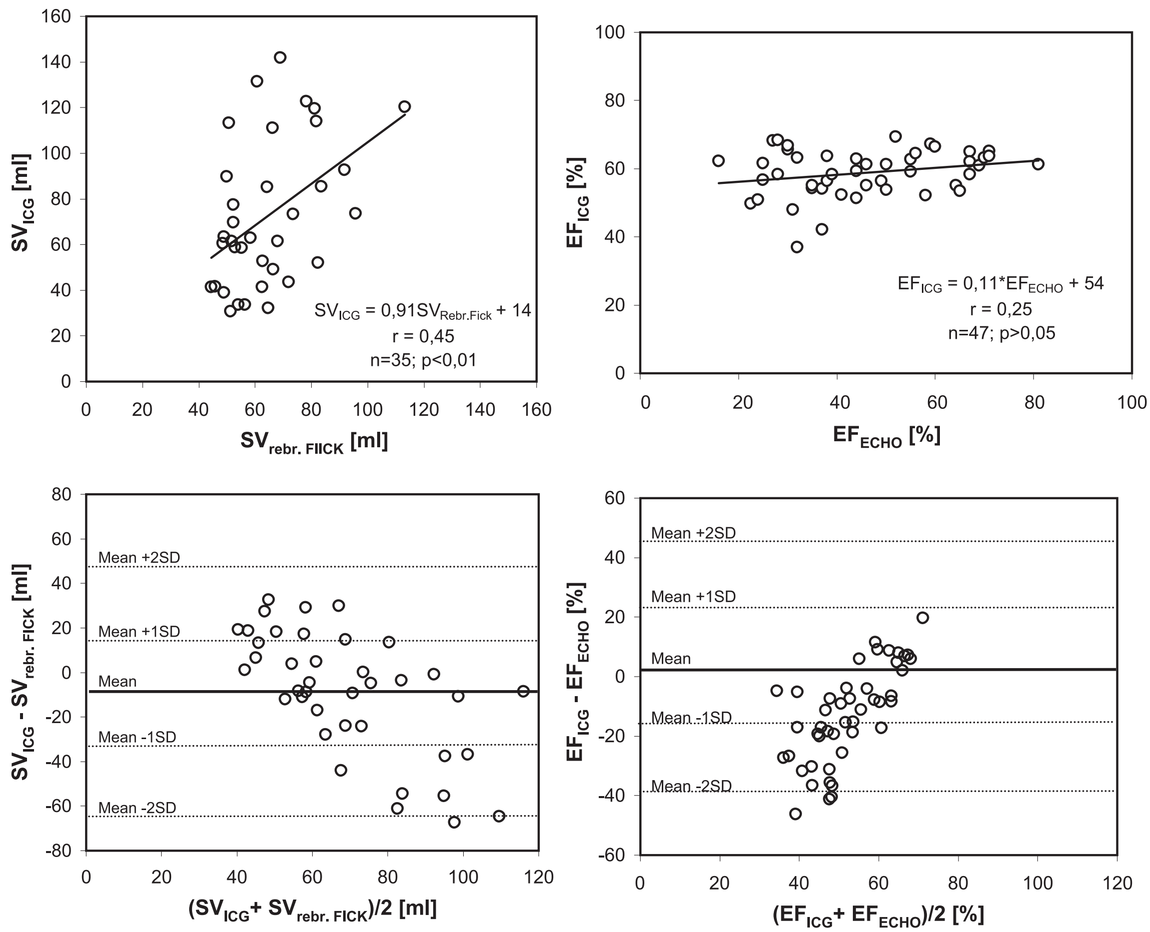

Fig. 3. Left: The correlation and Bland Altman plot of SV as determined by conventional ICG as compared to SV as determined by a partial rebreathing Fick technique (NICO, Novametrix) in 12 normal subjects and 23 patients with heart failure NYHA classes I and II. As can be seen, only a weak and clinically useless correlation was found although weight and height as determinants of CO are included. Right: EF as measured by echocardiography as compared to EF derived from conventional ICG in 47 patients with normal heart function (n=14) and in patients with heart failure NYHA I–IV (n=33). As can be seen, no significant correlation can be found.

regression analyses, nor was it possible to predict EF by neuronal nets.

4.2. New method (msf-ELMC)

The comparison of the electrically operative electrode distance (l_{op}) as calculated from Eq. (4) to the measured surface distance is shown in Fig. 4: As can be seen, the electrically derived operative distance l_{op} is usually much shorter than the measured distance but also very variable so that no significant relation between l_{surf} and l_{op} can be found (r=0.1, n.s.). There was also only a very weak relation between l_{op} and body height (r=0.25, p<0.05,) and no relation to body weight (r=0.11, n.s.) (Fig. 4).

4.2.1. Cardiac output study

The results of the prediction of SV_{Nico} by multiple regression analyses of the parameters provided by *msf*-ELMC are shown in Fig. 5 and in Table 1a (top). As can be seen in the partial correlation and multiple regression analysis l_{op}, dz/dt at the thorax, z0 at the thorax at 40 kHz and whole body z0 at 5 kHz are all highly significantly and independently related to SV_{Nico}. The combined correlation coefficient in the multiple regression analysis is 0.77, p<0.0001, n=35.

4.2.2. EF study

The parameters derived from *msf*-ELMC also show a highly significant relation to EF_{Echo} (Table 1, bottom) if l_{op} is included in the analysis. A multiple regression equation using Hk, LVET, L_{op} and whole body z0 at 40 kHz achieves a combined correlation coefficient of r=0.81, p<0.0001, n=47 (Table 1b).

4.3. Neuronal net to predict EF by ms-ELMC prospectively

The prediction of EF in 27 “unknown” patients with normal EF (n=10) and patients with heart failure NYHA I–IV (n=17) by a neuronal net trained on 67 patients is shown in Fig. 6. As can be seen in this quasi-prospective part of the study, prediction of EF is possible on the basis of electrically measured values if the electrically operative electrode

Table 2

Standardized coefficients

	Beta	t	Sig.
(a) Prediction of $SV_{r\text{-}fick}$ from conventional ICG			
Height [cm]	0.343	2.42	0.021
Weight [kg]			n.s.
$z0$ (V1) 40 kHz [Ω]	−0.346	−2.25	0.031
dz/dt (V1)			n.s.
LVET [ms]			n.s.
(b) Prediction of $SV_{r\text{-}fick}$ from msf-ELMC			
dz/dt (V2) 40 kHz [Ω]	0.260	2.19	0.037
Operative length [cm]	0.524	3.52	0.001
$z0$ (V1) 40 kHz [Ω]	−0.625	−4.13	0.000
$z0$ (V4) 5 kHz [Ω]	−0.331	−2.63	0.013
LVET [ms]			n.s.
$z0$ (V2) 40 kHz [Ω]			n.s.
PEP [ms]			n.s.
$z0$ (V4) 200 kHz [Ω]			n.s.
$z0$ (V3) 40 kHz [Ω]			n.s.
(c) Prediction of EF_{Echo} from msf-ELMC			
Hkt [%]	−0.554	−5.44	0.000
LVET [ms]	0.487	4.84	0.000
Operative length [cm]	−0.373	−3.66	0.001
$z0$ (V3) 5 kHz [Ω]	0.242	2.39	0.022
dz/dt (V2) 40 kHz [Ω]			n.s.
$z0$ (V1) 40 kHz [Ω]			n.s.
$z0$ (V4) 5 kHz [Ω]			n.s.
$z0$ (V2) 40 kHz [Ω]			n.s.
PEP [ms]			n.s.
$z0$ (V4) 200 kHz [Ω]			n.s.
$z0$ (V3) 40 kHz [Ω]			n.s.

distance is included in the analysis. The correlation coefficient (r) between EF_{Echo} and EF_{msELMC} equals 0.71 (n=27, p<0.001).

5. Discussion

There is no doubt that conventional impedance cardiography can be of considerable value for clinical [20,21] and scientific [22] purposes, especially to follow relative changes of SV [20–22]. However, absolute values are often adjusted to plausible values by introducing strong measures of body size into current formulas (as an example, see Fig. 2). The acceptable correlation between CO_{ICG} and the true CO in normal subjects is produced by the simple calculation shown in Fig. 2, but the trade-off is the poor performance of these methods in patients with heart disease. Weight significantly influences Sramek's formula but not Kubicek's method [23]. By using height (and weight), it produces a strong bias towards "normal" values of CO even in patients with heart failure, which makes the method relatively useless where it is needed most [2–4].

One of the many permanent problems with impedance cardiography is that the source of the dz/dt signal is multifactorial and largely unknown [2]. These multiple sources include pulsatile blood volume changes in the lung, atria and the great vessels including the aorta. The present investigation was not designed to address this issue. However, we have addressed another essential and problematic issue of ICG: the fundamental basis of impedance cardiography is the assumption that the volume (i.e. length×area) of the segment, which is used for impedance measurements, is known [1,2]. One important finding of the present study is that the length of the segment cannot be equated to the surface electrode distance, since it bears no relation to the distance the electrical current actually "sees" (Fig. 4); this may be explained partly by distortions of the length caused by hidden electrical bulges and laces. Therefore, very disturbingly for the users of conventional ICG, only $z0$ but not dz/dt shows a weak relation to $SV_{r\text{-fick}}$ by partial correlation analysis (Table 2) and there is also only a weak and clinically useless relation to CO_{Fick}. using Sramek's formula (see Fig. 3 left) and also using formulas of the type shown in Fig. 2. Although we have used short band electrodes [9] instead of the spot electrodes for which Sramek's formula was developed, this is not likely to explain these disappointing results. A multiple regression should, however, identify all "dependent variables" contributing *independently* of each other to the "independent variable" by giving a significant partial correlation coefficient. We have named the distance which the current virtually "sees" (and which we have derived by measuring essentially the same segment of the body at two adjacent measurement sites) "electrically operative length" although we are aware that this electrically operative "length" actually is a combined measure of length divided by area. The importance of this approach is shown by the fact that $z0$ and dz/dt show a highly significant relation to SV as derived from a "gold standard" method in the partial correlation or multiple regression analysis only if the electrode distance is *determined electrically* (l_{op}) (Table 2, mid).

Fig. 1 (bottom) shows the principle of measuring impedance of basically the same segment of the body but at adjacent measurement sites. If a small variation of electrode distance does not cause an appreciable change of the measured impedance, the measured segment can be safely assumed to be very long as compared to the variation in distance (Fig. 1, bottom left). In contrast, a large change of impedance with *the same* small variation of electrode distance can only be explained by a comparatively short segment investigated (Fig. 1, bottom right).

It is interesting to note that the partial correlation and multiple regression analysis *without prior assumptions* (a "black box model" as opposed to a theoretical geometrical model) correctly identifies the direction of the relation of the individual components of the $SV_{msf\text{-}ELMC}$ to SV_{NICO} as predicted from the theoretical model [1] (dz/dt and l_{op} directly and $z0$ inversely, see Table 2). A draw back of the study is that we were unable to recruit patients with very low cardiac outputs during these routine operations, so that our study will have to be extended also to patients with very low CO. Even if CO as measured by the partial rebreathing

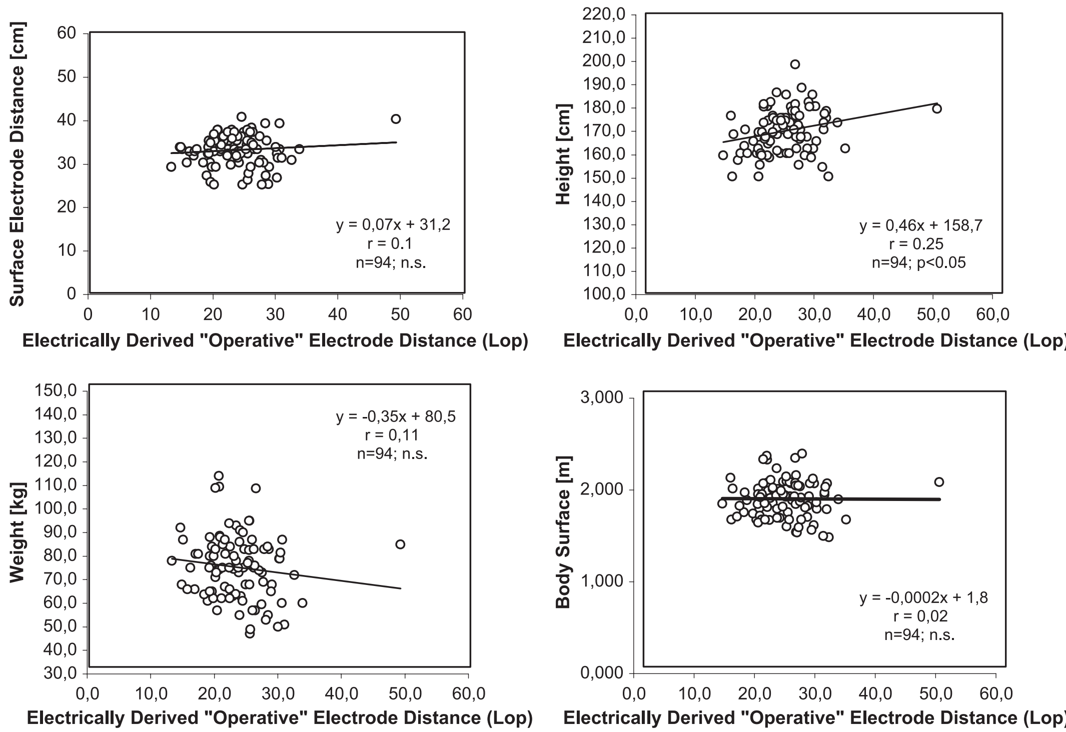

Fig. 4. This figure gives the explanation for the unsatisfactory results of conventional ICG shown in Fig. 3. The fundamental basis of ICG is the knowledge of the length of the investigated thoracic segment. As can be seen, there is no relation between the surface electrode distance of the investigated segment and the “electrically operative” electrode distance as defined in the present paper (see top left). There is also no relation between l_{op} and weight, body surface area and only a very week relation to body height (see top right).

Fick method during general anaesthesia would not show the high precision reported [13–15] (and would, e.g., contain some “noise”), it still gave us the opportunity to show the effectiveness of the newly introduced principles of “*msf*-ELMC”. Fine-tuning of the derived formulas by using the true Fick principle during right-sided heart catheterization will therefore very likely not refute the method of *msf*-ELMC but should contribute further improvement by removing any possible noise of the rebreathing technique.

For physicians interested in heart failure, determination of EF is at present without doubt clinically much more important than CO measurements. Although the most important contribution to the dz/dt signal is probably the volume change in the aorta, impedance cardiography has also been used by many authors to derive ejection fraction (EF) [19,23–26]. In our hands, however, conventional ICG is also unsuited for determining EF (see Fig. 3, top right) which confirms the results of Bowling et al. [27] in heart failure patients. The correlation between EF_{Echo} and EF_{ELMC} shown in Fig. 5 right, especially the Bland Altman plot, gives reason for hope that in the future, it may become possible to measure EF very simply by an inexpensive and automatic electrical method as opposed to the time consuming echocardiographic measurement. The precision of EF predicted by *msf*-ELMC as shown in Fig. 5 would probably satisfy the practicing cardiologist at the present state. Although these measurements will certainly not replace echocardiography, this method could still be of great importance, e.g., for general practice, given the epidemic proportions of heart failure particularly in the elderly population of industrialized countries.

In order to prove that *ms*-ELMC is prospectively able to provide prediction of EF in patients with unknown cardiac performance, we have used two thirds of the 95 subjects in whom multiple site measurements (but not multiple frequency measurements) were available to train a neuronal net with the incomplete data set. This included l_{op}, multiple $z0$’s and dz/dt’s at 40 kHz and the haematocrit. As can be seen in Fig. 6, the principle of *ms*-ELMC is able to provide enough information to predict prospectively EF in the test sample of normal subjects and of patients with severe heart failure, their status being unknown to the neuronal net. Thus, the net was apparently able to generalize and to extract the information needed for the prediction of EF from *ms*-ELMC.

In summary, the present study shows that the introduced technology improves the electrical measurement of the mechanical action of the heart in normal subjects and patients with heart failure. The exclusion of measures of body size from the formulas appears to be mandatory in order to prevent bias towards normal values, especially in heart failure patients. The use of black box models as applied in the present study, whereby all assumptions of geometrical models used for the ICG in the past are avoided, is probably an important step. It has to be mentioned that Mulavara et al. [28] also used neuronal nets to calculate SV from impedance data and our results extend their findings to

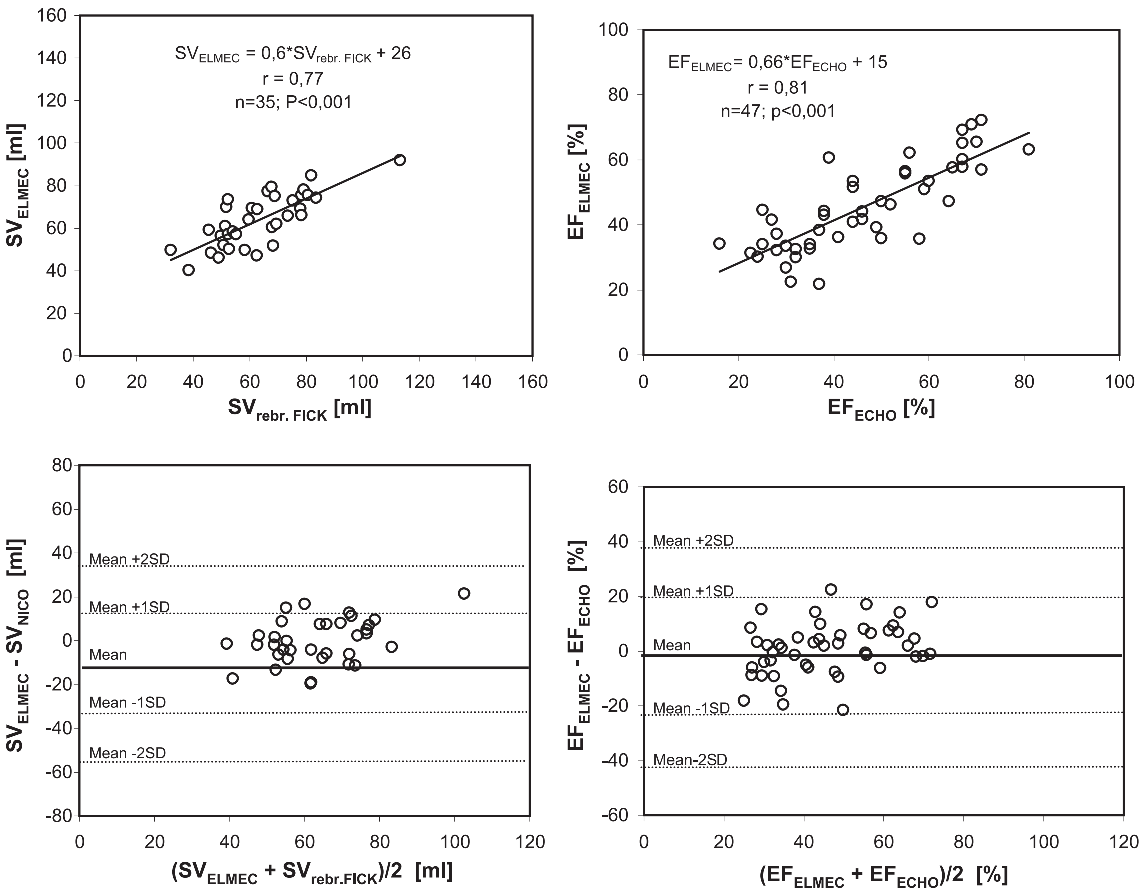

Fig. 5. Left: The correlation and Bland Altman plot of SV as determined by a partial rebreathing Fick technique and SV calculated from a multiple regression equation using *msf*-ELMC (see also Table 1 top). Right: The correlation and Bland Altman plot of EF determined by echocardiography and by multiple regression analysis using *msf*-ELMC. A clinically useful electrical determination of SV and EF can be achieved.

multiple site measurements as well. It will also be interesting to see how the presented method competes against a new version of whole body impedance cardiography [29,30]. Our work differs markedly from the work of Raaimaker et al. [31], who have measured thoracic impedance at two frequencies to differentiate cardiac and non-cardiac edema on the basis of different impedance characteristics of protein-rich and protein-free edema fluid. The method of *msf*-ELMC promoted here appears to be a small but definite step towards cheaper and fully automatic non-invasive measurement and continuous on-line recording of SV, EF and possibly other parameters of heart function. Our mathematical approach is apparently attractive for data too complex and therefore unsuited for the theoretical model approach such as the impedance cardiogram. Further improvements along these lines appear feasible. One such improvement may be to discard the calculation of l_{op} after having shown the effectiveness of it's principle. The calculation of l_{op} is also based on a model, namely that of a conductor with constant diameter. Instead it will be advantageous to feed the raw data from which it is derived into the black box model. Black box models, particularly the hidden layers of neuronal nets are especially suited to detect hidden structures of the input data.

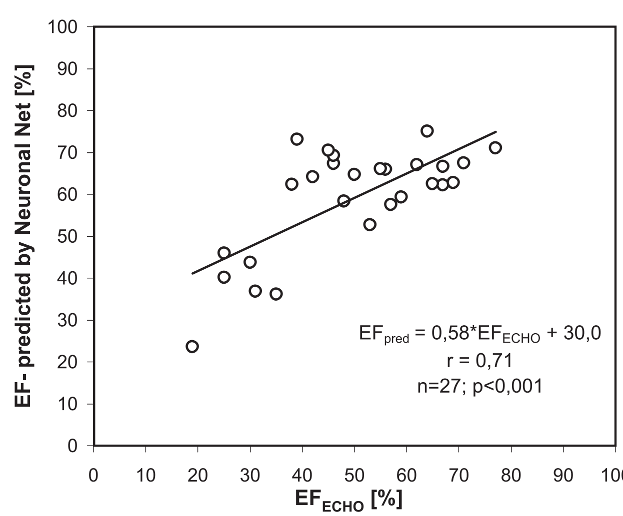

Fig. 6. A "prospective" study of a test sample of 27 patients with normal heart function (n=10) and heart failure NYHA class I to IV (n=17): A neuronal net was trained with a training set of 67 patients with normal heart function (n=26) and heart failure NYHA class I to IV (n=41) to predict EF as measured by echocardiography. Although in this study no multiple frequencies but only multiple measuring sites to determine the l_{op} were available, a highly significant correlation between EF predicted by the neuronal net and EF measured by two-dimensional echocardiography was found.

Acknowledgments

We wish to thank Dr. W. Pluhar for the helpful criticism of the manuscript and D.I. J. Fortin for drawing our attention to a simplified way to derive l_{op}.

References

[1] Kubicek WG, Kargnis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp Med 1966;37:1208–12.
[2] Patterson RP. Fundamentals of impedance cardiography. IEEE Eng Med Biol 1989;8:35–8.
[3] Spinale FG, Smith AC, Crawford FA. Relationship of bio impedance to thermodilution and echocardiographic measurements of cardiac function. Crit Care Med 1999;18:414–8.
[4] Woo MA, Hamilton M, Stevenson LW, Vredevoe DL. Comparison of thermodilution and transthoracic electrical bioimpedance cardiac outputs. Heart Lung J Crit Care 1991;20:357–62.
[5] Cohn JN, Finkelstein S, McVeigh G, Morgan D, LeMay L, Robinson J, et al. Non-invasive pulse wave analysis for the early detection of vascular disease. Hypertension 1995;26:503–8.
[6] Sramek BB, Rose DM, Miyamoto A. Stroke volume equation with a linear base impedance model and its accuracy as compared to thermo dilution and magnetic flow meter techniques in humans and animals. Proc. 6th Int. conference on electrical impedance; 1983. p. 38.
[7] Bernstein DP. A new stroke volume equation for thoracic electrical impedance: theory and rational. Crit Care Med 1986;14:904–9.
[8] Burchell SA, Yu M, Takguchi SA, Ohta RM, Myers SA. Evaluation of continuous cardiac output and mixed venous oxygen catheter in critically ill surgical patients. Crit Care Med 1997;25(3):388–91.
[9] Fortin J, Habenbacher W, Gruellenberger R, Wach P, Skrabal F. Real-time monitor for hemodynamic beat to beat parameters and power spectra analysis of the biosignals. Proc IEEE Eng Med Biol 1998;20:360–3.
[10] Baker LE. Principles of the impedance technique. IEEE Eng Med Biol 1989;8:11–5.
[11] Schoeller DA, Kushner RF. Determination of body fluids by the impedance technique. IEEE Eng Med Biol 1989;8:19–21.
[12] Gratze G, Fortin J, Holler A, Grasenick K, Pfurtscheller G, Wach P, et al. A software package for non-invasive, real time, beat to beat monitoring of stroke volume, blood pressure, total peripheral resistance and for the assessment of autonomic function. Comp Biol Med 1998;28:121–42.
[13] Capek JM, Roy RJ. Noninvasive measurement of cardiac output using partial CO_2 rebreathing. IEEE Trans Biomed Eng 1988;35:653–61.
[14] Hayardi DG, Orr JA, Kück K, McJames S, Westenskow DR. Evaluation of a partial rebreathing Fick technique for measurement of cardiac output. Anesthesiology 1998;89(3A):A543.
[15] Watt RC, Loeb RG, Orr JA. Comparison of a new noninvasive cardiac output technique with invasive bolus and continuous thermodilution. Anesthesiology 1998;89(3A):A536.
[16] Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358.
[17] Geddes LA, Baker LE. The specific resistance of biological material—a compendium of data for the biomedical engineer and physiologist. Med Biol Eng 1967;5:271–93.
[18] Hill DW, Thompson FD. The importance of blood resistivity in the measurement of cardiac output by the thoracic impedance method. Med Biol Eng Comput 1975;3:187–90.
[19] Capan LM, Bernstein DP, Patel KP, Sanger J, Turndorf H. Measurement of ejection fraction by bioimpedance method. Crit Care Med 1987;15:402.
[20] Beitzke M, Pfister B, Fortin J, Skrabal F. Autonomic dysfunction and haemodynamics in vitamin B12 deficiency. Auton Neurosci 2002;97:45–54.
[21] Skrabal F. Editorial: syncope, falls and cobalamin deficiency in the old population. Clin Auton Res 2004;14:60–6.
[22] Gratze G, Fortin J, Labugger R, Binder A, Kotanko P, Timmermann B, et al. β-2 adrenergic receptor variants affect resting blood pressure and agonist-induced vasodilation in young adult Caucasians. Hypertension 1999;33:1425–30.
[23] Woltjer HH, Bogaard HJ, van der Spoel HI, de Vries PMJM. The influence of weight on stroke volume determination by means of impedance cardiography in cardiac surgery patients. Intensive Care Med 1996;22:766–71.
[24] Scherhag AW, Stastny J, Pfleger S, Voelker W, Heene DL. Evaluation of systolic performance by automated impedance cardiography. Ann N Y Acad Sci 1999;873:167–73.
[25] Kerkkamp HJ, Heethaar RM. A comparison of bioimpedance and echocardiography in measuring systolic heart function in cardiac patients. SO: Ann N Y Acad Sci 1999;873:149–54.
[26] Máttar JA, Shoemaker WC, Diament D, Lomar A, Lopes AC, De Freitas E, et al. Systolic and diastolic time intervals in the critically ill patient. Crit Care Med 1991;19:1382–6.
[27] Bowling LS, Sageman WS, O'Connor SM, Cole R, Amundson DE. Lack of agreement between measurement of ejection fraction by impedance cardiography versus radionuclide ventriculography. Crit Care Med 1993;21:1523–7.
[28] Mulavara AP, Timmons WD, Nair MS, Gupta V, Kumar AA, Taylor BC. Electrical impedance cardiography using artificial neural networks. Ann Biomed Eng 1998 (Jul.–Aug.);26(4):577–83.
[29] Cotter G, Moshkovitz Y, Kaluski E, Cohen AJ, Miller H, Goor D, et al. Accurate noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. Chest 2004;125(4):1431–40.
[30] Moshkovitz Y, Kaluski E, Milo O, Vered Z, Cotter G. Recent developments in cardiac output determination by bioimpedance: comparison with invasive cardiac output and potential cardiovascular applications. Curr Opin Cardiol 2004;19(3):229–37.
[31] Raaimaker E, Faes ThJC, Meijer JM, Kunst PW, Bakker J, Goovaerts HG, et al. Estimation of non-cardiagenic oedema using dual-frequency electrical impedance. Med Biol Eng Comput 1998;36:4161–466.