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Effect of postural changes on the reliability of volume estimations from bioimpedance spectroscopy data

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Effect of postural changes on the reliability of volume estimations from bioimpedance spectroscopy data. Bioimpedance spectroscopy (BIS) has been suggested for the assessment of fluid shifts between intracellular (ICV) and extracellular volume (ECV) during dialysis. The electrical tissue parameters are estimated by fitting a Cole-Cole model to the impedance data. Those parameters are used for the calculation of ICV and ECV with a fluid distribution model (FDM). We investigated whether postural changes cause artifacts in the volume data measured with a commercial BIS system. This is of importance at the beginning of dialysis, when the patient lies down for treatment. Volume estimations were performed during tilt table experiments with 11 healthy volunteers. Impedance spectra (5 to 500 kHz) were recorded for the total body as well as for body segments (leg and arm) during three phases: (1) 30 minutes resting in a supine position after standing; (2) 30 minutes 70° head up tilt; and (3) a 30-minute resting period in a supine position. ECV and ICV were estimated with a commercially utilized FDM which is based on Hanai's mixture theory. A monoexponential function was fitted to the data for extracting the time constants and the extrapolated steady state values of the volume changes. The ECV and ICV data changed significantly during all three periods, that is, a steady state could not be reached within 30 minutes. During phase 1 the ECV decreased by 1.8 ± 0.7%, in the tilt phase it increased by 3.8 ± 1.1%, and in phase 3 it decreased again by 2.9 ± 1%. The ICV increased by 3.6 ± 2.4% during phase 1 and decreased by 6.8 ± 5.1% during tilting; in phase 3 it increased by 4.6 ± 1.7%. The time constants were 36.4 ± 12.7 minutes (ECV) and 10.8 ± 5.4 minutes (ICV) during phase 3. Segmental measurements revealed that the legs contribute significantly to the measured volume changes. The absolute volume changes in ICV and ECV differed significantly in all phases, and the same was found for the time constants during phases 1 and 3. From this discrepancy it is concluded that the measured volume changes are artifacts that are caused by extracellular fluid redistribution. Furthermore, it appears unlikely that the measured fluid shifts actually occur between ECV and ICV in the absence of osmotic changes in the body fluids. The validity of the method for a reliable assessment of volume changes during dialysis appears questionable, as dialysis-induced volume changes lie in the same range as the orthostatically-induced spurious volume changes.

Some authors have suggested bioimpedance spectroscopy (BIS) for the assessment of fluid shifts between extra- (ECV) and intracellular volume (ICV) during dialysis [1, 2]. The method is noninvasive, continuous and can be applied easily as a clinical routine procedure. It is based on the fact that cell membranes are virtually nonconducting at low frequencies and become short-circuited at high frequencies due to dielectric currents. This transition is reflected by the β dispersion of tissue impedance. The equivalent resistances of ECV and ICV are usually determined by fitting a Cole-Cole model [1, 3, 4] to the impedance data. From the resistances ECV and ICV are estimated with a fluid distribution model (FDM) that relates body geometry and electrical parameters to the fluid volumes. Until now all published whole-body models were based on the assumption that the body can be subdivided into cylindrical segments with homogeneous tissue structure. The tissue impedance is assumed to be equivalent to that of a suspension of more or less spherical nonconducting particles in a conducting fluid. Theories for the impedance of such emulsions have been published [5–7]. All models require that the following conditions hold: (1) constancy of temperature; (2) constancy of body fluid conductivities; (3) defined body posture during measurements.

However, especially during dialysis these conditions are not fulfilled and the accuracy of the method may be affected adversely by the following effects: changes of the tissue conductivity by ionic shifts [8]; changes of the peripheral temperature and extracellular fluid redistributions due to postural changes. The latter occur especially at the beginning of the dialysis session, when the patient is brought to a supine position. Several authors have investigated the effects of postural changes on the body impedance [9–12]. In a recent study the time course of the impedance during recumbency was investigated at different frequencies [9] and significant changes within several hours were found, especially at low frequencies. Consequently, it might be concluded that also the estimated volumes are influenced by orthostatic processes. If so, spurious volume changes may be reported by the FDM. For practical application it is mandatory that those spurious changes remain significantly below the real changes. The latter can be roughly estimated with a practical example: Assuming an ECV of 15 liters and an UFR of 0.5 liter/hr, an ECV decrease of 3.4% per hour is expected in the case of isotonic dialysis.

Method

Hypotheses

If postural changes do not corrupt the measured data for ECV and ICV, one of the following alternative hypotheses must hold:

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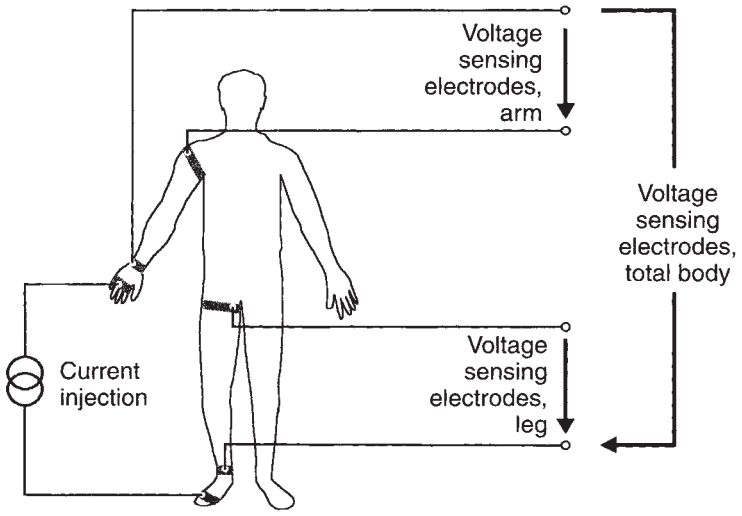

Fig. 1. *Electrode arrangement for impedance measurements of the total body, leg and arm.* The placement of the current injection electrodes remains the same for all three configurations.

Hypothesis 1. ICV-ECV shifts are mainly driven by osmotic forces. Since the osmolalities of body fluids remain constant during postural changes, no significant overall ECV-ICV shifts should be reported by the BIS system.

Hypothesis 2. ICV-ECV shifts can be provoked by postural changes. In this case the following conditions must hold:
(1.) If the total body water (TBW) can be assumed constant within the observation interval, total ECV and ICV changes sum up to zero at any time. Consequently a strict linear correlation between ICV and ECV must exist with a correlation coefficient β of -1. This can easily be seen from equation 1:

$$ECV = -ICV + TBW \qquad \text{(Eq. 1)}$$

(2.) The time constants of ICV and ECV changes must be the same.

Both hypotheses are meaningful only in the case of total body impedance measurements. For testing the hypotheses impedance measurements and subsequent volume modeling have been carried out during tilt table experiments with a commercial BIS system.

Subjects and study design

Eleven healthy people (10 male, 1 female, age 21 to 33 years, 67.8 ± 7.9 kg, 174.9 ± 5.0 cm) without medication participated in the study. They were fully informed about its nature and purpose, and gave their oral consent. They arrived in the lab at 8:00 a.m. and received a standard light breakfast. Investigations were commenced at 8:30 a.m. after the subjects were positioned supine onto a commercial tilt table, which was equipped with a footrest. Electrodes (IS4000, 7.7 × 1.9 cm, self-adhesive; Xitron Technologies Inc., San Diego, CA, USA) were attached and measurements were started within the initial three minutes. The impedance of one pair of electrodes (gel to gel arrangement) does not exceed 50 Ω at frequencis above 1 kHz. Room temperature was kept constant at 24 ± 1°C throughout the experiment.

Measurements were performed on three body segments: (1.) total body impedance between wrist (line between the distal prominences of the radius and the ulna) and ankle joint (line between the lateral malleoli); (2.) arm impedance between wrist (line between the distal prominences of the radius and the ulna) and the proximal end of the biceps; and (3.) leg impedance between ankle joint (line between the lateral malleoli) and trochanter major.

Figure 1 illustrates the electrode configurations for the segmental measurements. The voltage sensing electrodes of the BIS system were selected as required for the respective segment. The current electrodes were attached on the dorsal surfaces of the distal metacarpal and metatarsal joints of the right hand and the right foot. The experiments consisted of three consecutive phases as depicted in Figure 2: (a) phase 1, 30 minutes rest in the supine position; (b) phase 2, 30 minutes in a 70° head up tilt position; (c) phase 3, 30 minutes of recovery in the supine position. Thus, the experiments were finished at 10:00 a.m. The third period was considered to be representative for the situation when an outpatient lies down at the beginning of a dialysis session.

Impedance measurements and volume estimation

A commercially available BIS-system (XITRON 4000B; Xitron Technologies, San Diego, CA, USA) with a tetrapolar electrode arrangement was used. The device provides a sinusoidal current of 200 μA RMS that is injected between the current electrodes and measures the respective voltage drop between the voltage sensing electrodes. Data were acquired every minute at 50 logarithmically spaced frequencies between 5 and 500 kHz. For guaranteeing accurate impedance data throughout the whole frequency range, reference measurements were performed with RC-networks where the impedances were known. Deviations between measured and expected impedance values were stored in lookup tables and used for corrections of the experimental data.

The volume determination required two stages: (1.) fitting of the intra- and extracellular resistances with a Cole-Cole model; and (2.) estimation of the volumes from these resistances with a FDM.

According to [13, 14] the ECV and ICV can be estimated from intra- and extracellular resistances R_{in} and R_{ex} [Ω] and additional anthropometrical data with equations 2 and 3. Those formulae have been derived from Hanai's mixture theory [6] and a simple model of body tissue geometry [15]:

$$V_{ex} = 10^{-3} k_{ex} \left(\frac{H^2 \sqrt{W_b}}{R_{ex}} \right)^{2/3} \qquad \text{(Eq. 2)}$$

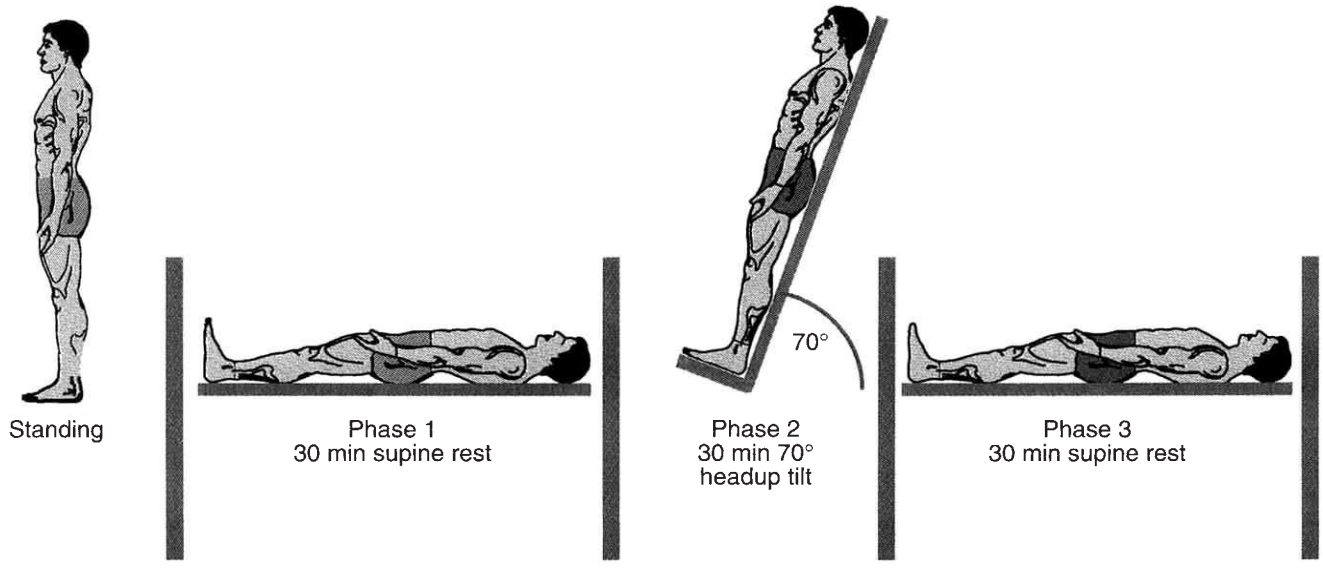

Fig. 2. *Measurement protocol.* The experiment is comprised of three phases: 30 minutes supine rest after standing; 30 minutes 70° headup tilt; 30 minutes recovery in supine position.

$$\left(1+\frac{V_{in}}{V_{ex}}\right)^{5/2}=\left(\frac{R_{ex}+R_{in}}{R_{in}}\right)\left(1+k_{\rho}\frac{V_{in}}{V_{ex}}\right) \qquad \text{(Eq. 3)}$$

$$k_{cx}=\left(\frac{K_B^{\,w}}{\lambda^2_{cx}D_B}\right)^{1/3} k_{\rho}=\frac{\lambda_{cx}}{\lambda_{in}} \qquad \text{(Eq. 4)}$$

Equations 2 and 3 hold for a single equivalent cylinder which is filled with a homogeneous suspension of spherical nonconducting particles. K_B in equation 4 is a dimensionless factor that corrects the simple cylinder model for the true geometrical properties of arms, legs and trunk. Its value can be estimated analytically by assuming the body to consist of five cylindrical elements (legs, arms, trunk). In practice, however, it is determined from tracer dilution experiments and has been reported as 4.3 [4].

A further important assumption is that the conductivities in equation 4 do not change during the measurements. This assumption should hold in our experiments, as no changes of the ion concentrations in body fluids are provoked. The assumption does clearly not hold during dialysis, and a method for correcting the conductivities has been presented in [8]. A recapitulation is beyond the scope of this paper, and for the sake of clarity we will focus on postural changes only.

The resistances R_{in} and R_{ex} [Ω] are calculated by fitting an extended Cole-Cole model (Eq. 5) to the measured impedance data $Z(\omega)$:

$$Z(\omega)=\left(\frac{R_{ex}}{R_{ex}+R_{in}}\right)\left(R_{in}+\frac{R_{ex}}{1+(j\omega C_M(R_{ex}+R_{in}))^{\alpha}}\right)e^{-j\omega T_D} \qquad \text{(Eq. 5)}$$

T_D [s] has been interpreted as propagation time of the electrical signal along the measured segment (**Discussion**) [15, 16]. Equations 2 to 5 and a nonlinear fitting algorithm are implemented in the Xitron software (BIS 4000, ver. 1.0), which was used for this study. The fitted parameters R_{in} and R_{ex} were accepted as reliable only if the correlation coefficient between measured and predicted spectra exceeded 0.996 (the limit above which the fit is classified as good by the Xitron software).

Data processing

After fitting the Cole-Cole model to the measured impedances and calculation of ICV and ECV with the Xitron software, the data of each phase were interpolated with a monoexponential model according to equation 6.

$$V_{ex}(t) = V_{ex,\infty} - (V_{ex,\infty} - V_{ex,0})e^{-t/\tau_{ex}} \qquad \text{(Eq. 6)}$$

$$V_{in}(t) = V_{in,\infty} - (V_{in,\infty} - V_{in,0})e^{-t/\tau_{in}}$$

The subscripts 0 and ∞ denote the values at zero minutes and at theoretically infinite time (steady state). In some cases a nearly linear time course of the volume readings within the 30 minute phases was observed, and a longer measurement period would have been necessary to evaluate the actual time course. In those cases the exponential model was ill conditioned, which resulted in large confidence intervals of the parameters and high residual standard errors. Consequently, the respective parameters were disregarded in the statistics. From the interpolated data the following parameters were calculated:

$\Delta V_{rel}^{ex,30}, \Delta V_{rel}^{in,30}$	relative volume changes at t = 30 minutes for ECV and ICV
$\Delta V_{rel}^{ex,\infty}, \Delta V_{rel}^{in,\infty}$	relative volume changes at t = ∞ for ECV and ICV
τ_{ex}, τ_{in}	time constants for ECV and ICV (min)

The relative volume changes have been calculated according to:

$$\Delta V_{rel}^{k,T} = \frac{V_{k,T} - V_{k,0}}{V_{k,0}} * 100\,[\%] \qquad \text{(Eq. 7)}$$

where k denotes the distribution volume index (ECV = ex, ICV = in) and T denotes the time of evaluation (30 min, ∞). The index 0 denotes the starting value of the respective period.

For all three segments the time constants in the three phases have been mutually compared by using the Wilcoxon U test for paired and unpaired data.

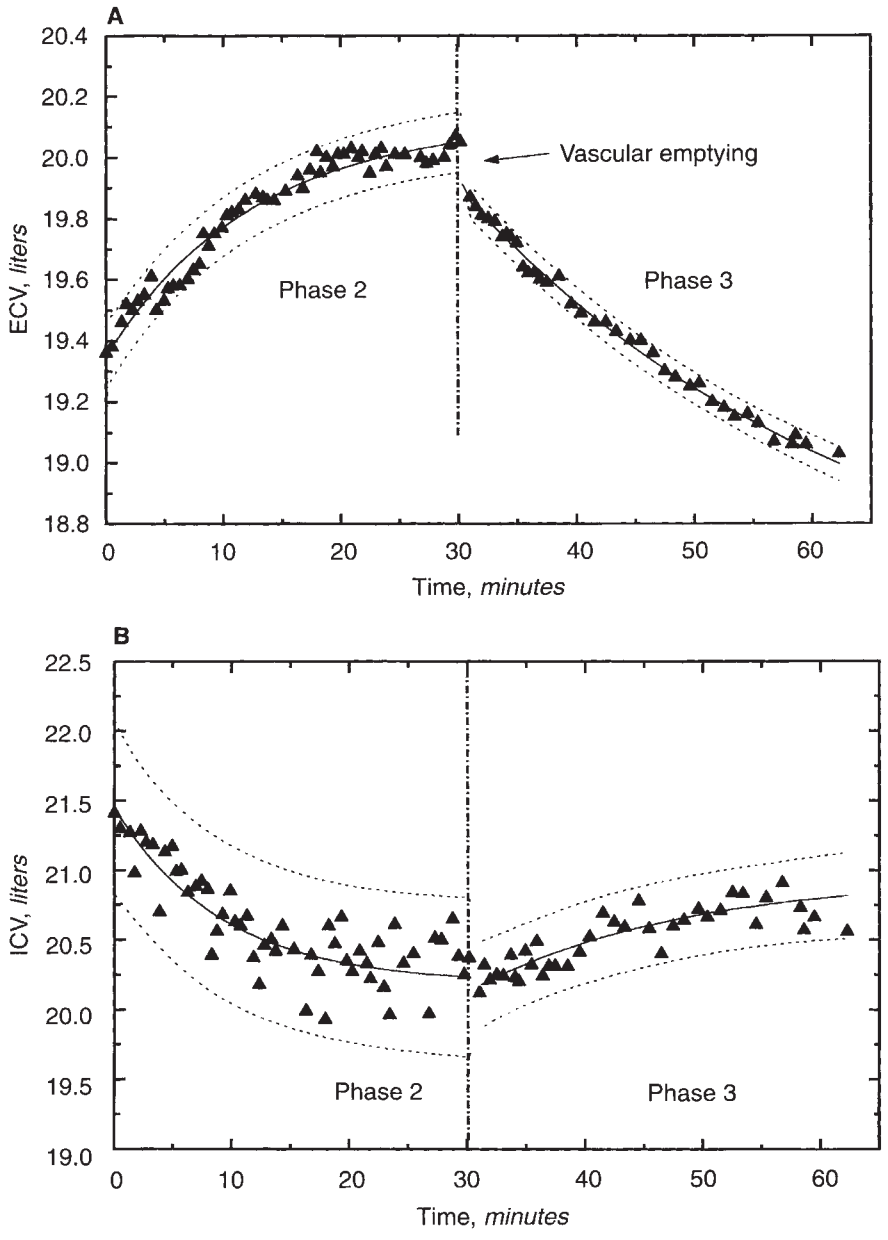

Fig. 3. *Typical time course of the volume readings during phase 2 (70° tilt) and phase 3 (supine).* During phase 3 the ECV decreases (**A**), whereas the ICV (**B**) increases steadily. Symbols are: (▲) measured; (—) interpolation; (----) 95% confidence limits.

Linear regression analysis has been carried out for the absolute ECV and ICV data for each subject and each phase of the total body measurements. We also tested whether or not the 95% confidence interval of the regression coefficient β contained the theoretical value of -1. Curve-fitting and data analysis was performed with ORIGIN 4.0[TM].

Results

Total body impedance

As phase 3 corresponds to the situation when an outpatient lies down at the beginning of dialysis it is documented more detailed than the other phases. Figure 3 illustrates the typical time courses of the computed ECV and ICV during the phases 2 and 3 (subject #9). In phase 2 the ECV increased whereas the ICV decreased. Immediately after tilting back the patient, the ECV decreased very rapidly within two minutes. This transition was followed by a slower, approximately monoexponential decay. As expected the ICV increased in phase 3. Within the measurement period (30 min) no steady state was reached. Figure 4 shows the comparison between $\Delta V_{rel}^{ex,30}$ and $\Delta V_{rel}^{ex,\infty}$ as well as between $\Delta V_{rel}^{in,30}$ and $\Delta V_{rel}^{in,\infty}$ for phase 3. The large differences between $\Delta V_{rel}^{ex,30}$ and $\Delta V_{rel}^{ex,\infty}$ in cases 4 and 6 result from poor fitting of the monoexponential model and are also reflected by large time constants. Both cases have been disregarded in the further evaluation. Figure 5 depicts the time constants τ_{ex} (except cases 4 and 6) and τ_{in} for phase 3. Table 1 summarizes the mean values and standard deviations of the relative volume changes and time constants. Table 2 presents in the form of a matrix the probabilities that the means of two different time constants are not significantly different. The time constants of the ECV in phases 1 and 3 are

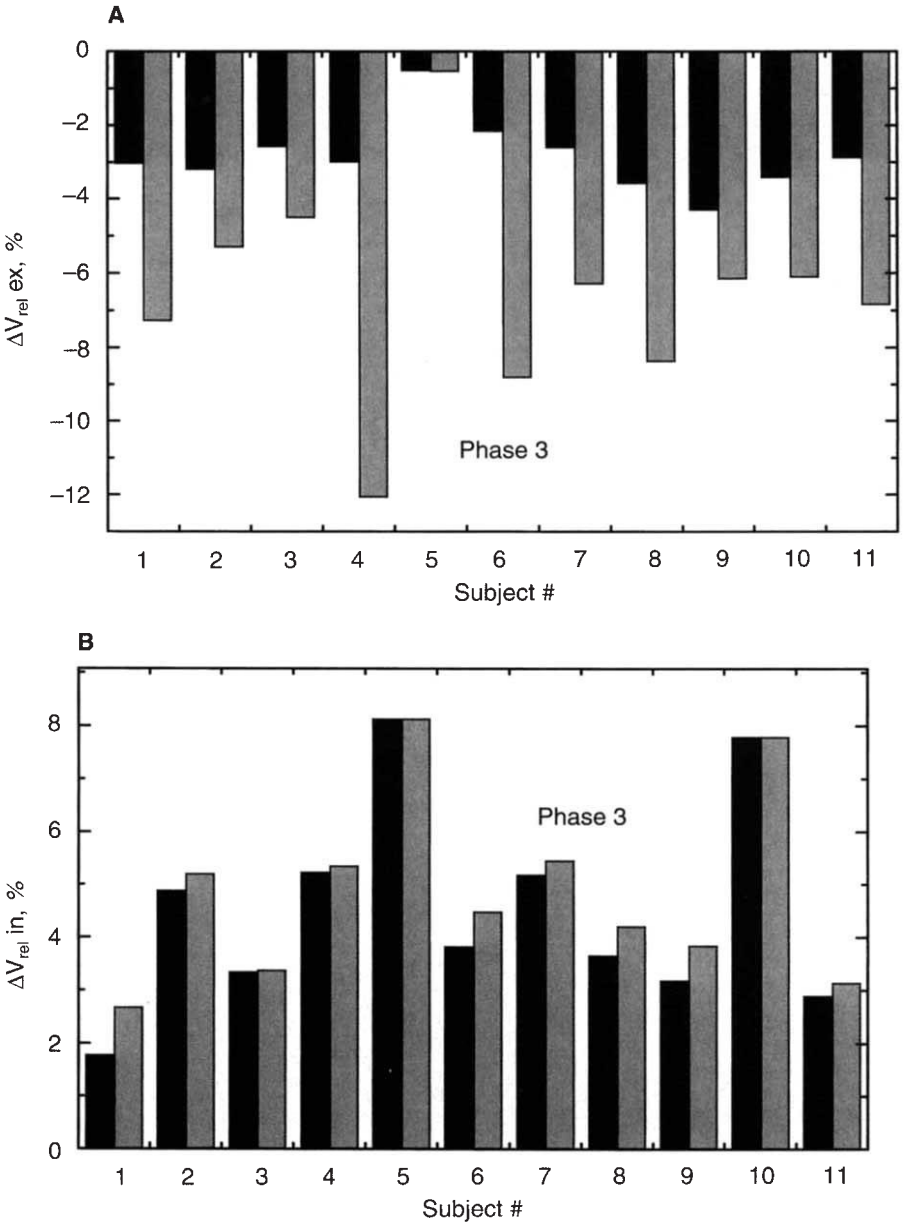

Fig. 4. *Comparison of the relative volume changes at 30 minutes and at theoretically infinite time (extrapolated steady state) for ICV* (**A**) *and ECV* (**B**). The data stem from total body measurements during phase 3. The large differences in cases 4 and 6 (ECV) are due to poor curve fitting and were disregarded in the further analysis. Symbols in A are: (■) $\Delta V_{rel}^{ex,30}$; (▨) $\Delta V_{rel}^{ex,\infty}$. Symbols in B are: (■) $\Delta V_{rel}^{in,30}$; (▨) $\Delta V_{rel}^{in,\infty}$.

significantly higher than those of the ICV ($P < 0.05$). During the tilt phase the extracellular time constants are significantly lower than in the supine position ($P < 0.05$), whereas no significant difference could be found for the phases 1 and 3. No significant differences could be found for the intracellular time constants at the 0.05 level.

Figure 6 shows the results of the regression analysis. In any phase only in four cases the value −1 lay within the 95% confidence interval of the regression coefficient. Those cases for which no linear relationship could be found are marked with an 'X' in Figure 6.

Segmental measurements

The time courses of the volumes in arm and leg were similar to those of the total body measurements. However, volume changes in the arm segment were lower than those in the leg segment. Table 3 summarizes the relevant parameters for the leg and Table 4 for the arm.

Table 5 presents the probabilities that the means of two different time constants in the leg are not significantly different. The time constants of the ECV are significantly higher than those of the ICV ($P < 0.05$) during phases 2 and 3; in phase 1 no significance could be found due to the high variation in the ECV data. In contrast to the total body measurements, the time constants for the ECV changes during phase 3 are higher than in phase 1 and lower than in phase 2 ($P < 0.05$). No significant difference could be found when comparing the intracellular time constants.

Table 6 summarizes the results of the Wilcoxon test for the arm segment. The time constants of the ECV are significantly higher

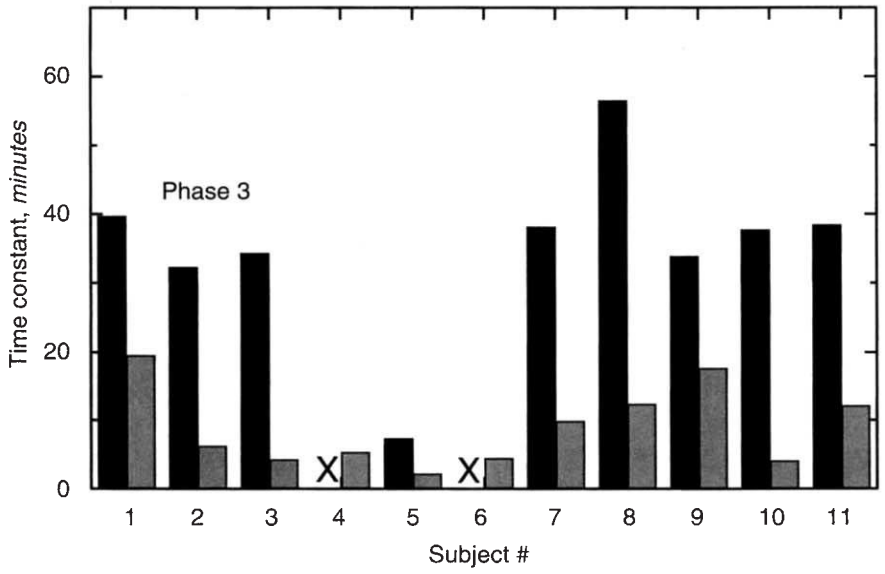

Fig. 5. *Comparison of the time constants of the volume changes in ECV and ICV.* The data stem from total body measurements during phase 3. Data for the ECV in cases 4 and 6 are not shown because of poor curve fitting. Symbols are: (■) τ_{ex}, minutes; (▨) τ_{in}, minutes.

Table 1. Statistical parameters for the results from total body impedance (mean and standard deviation)

	$\Delta V_{rel}^{ex,30}$	$\Delta V_{rel}^{ex,\infty}$		$\Delta V_{rel}^{in,30}$	$\Delta v_{rel}^{in,\infty}$	
	%		τ_{ex} *min*	%		τ_{in} *min*
P1	−1.83 ± 0.70	−3.49 ± 1.56	37.49 ± 15.66	3.64 ± 2.37	3.92 ± 2.41	8.53 ± 7.88
P2	3.77 ± 1.08	4.22 ± 1.40	11.69 ± 4.51	−6.78 ± 5.13	−7.67 ± 7.40	8.54 ± 5.70
P3	−2.85 ± 0.96	−5.72 ± 2.23	35.36 ± 12.67	4.18 ± 1.67	4.56 ± 1.49	10.75 ± 5.34

P1, P2, P3 denote phase 1, phase 2 and phase 3, respectively.

Table 2. Results of the Wilcoxon test for comparison of the time constants of total body measurements

	τ_{ex} (2)	τ_{ex} (3)	τ_{in} (1)	τ_{in} (2)	τ_{in} (3)
τ_{ex} (1)	0.0017	NS	0.0126	—	—
τ_{ex} (2)	—	0.00008	—	NS	—
τ_{ex} (3)	—	—	—	—	0.002
τ_{in} (1)	—	—	—	NS	NS
τ_{in} (2)	—	—	—	—	NS

The entries denote the probability that the corresponding row and column parameters are not significantly different; NS means no significant difference ($P < 0.05$).

than those of the ICV ($P < 0.01$) during phases 1 and 3 but not in phase 2. Similar to the total body measurements the time constants for the ECV changes during the tilt phase are lower than in the supine position ($P < 0.05$), whereas no significant difference could be found for the phases 1 and 3. The intracellular time constants were different between phases 1 and 2 ($P < 0.05$).

Discussion

Discussion of the results

The results clearly show that the calculated ICV and ECV data for the total body change significantly during all three phases. The relative changes range from about 2 to 5% in the ECV and 1.8 to 8% in the ICV.

We did not test whether the extrapolated absolute steady state volumes in phases 1 and 3 were the same. Theoretically this should be the case, however, the monoexponential model is probably not sufficiently valid for a reliable estimation of the steady state, as it does not account for nonlinear properties of the compliance of veins and viscoelastic properties of the tissue. Thus, slow components of the dynamics may depend on the initial filling state of the vessels that is different in phases 1 and 3. Those components cannot be estimated from data measured during a 30 minute period.

The changes of the ICV readings are consistent with the observations of Lozano et al [10], who investigated the time variability of the ratio R_0/R_∞ ('K-factor') during 6° head down tilt (HDT) experiments. The authors found a significant increase of this ratio after the onset of HDT. This increase is assumed to be caused by blood redistribution from the legs to the upper parts of the body. A similar redistribution occurred in our experiments during phases 1 and 3, and thus should also result in an increase of the K factor. Mutual substitution of the identities

$$R_0 = R_{ex}; R_\infty = \frac{R_{in}R_{ex}}{R_{in} + R_{ex}}; K = \frac{R_0}{R_\infty} \qquad \text{(Eq. 8)}$$

yields:

$$\frac{1}{K} = 1 - \frac{R_{ex}}{R_{in} + R_{ex}} \qquad \text{(Eq. 9)}$$

The second term at the right hand side of equation 9 appears in equation 3, which determines the ICV/ECV ratio. Evaluation of equation 3 reveals that an increase of the 'K factor' is equivalent

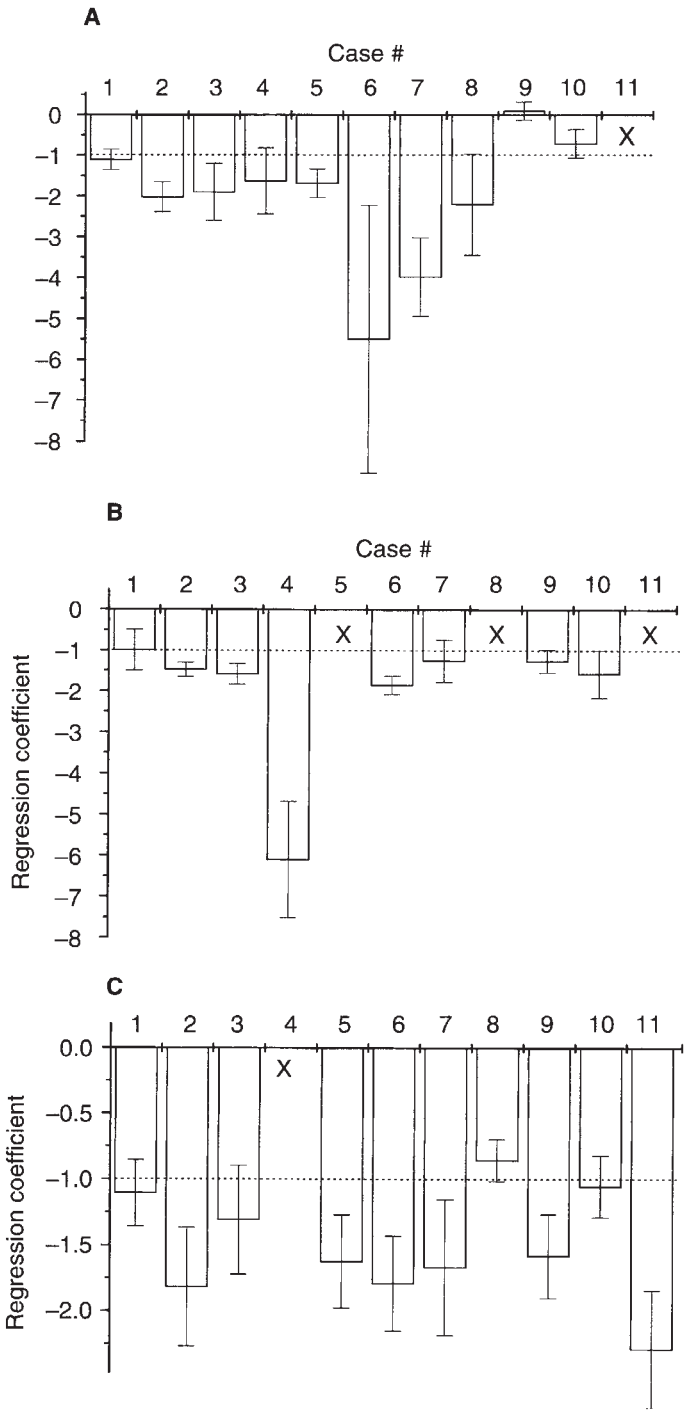

Fig. 6. *Regression coefficients β between ECV and ICV in phase 1 (A), phase 2 (B) and phase 3 (C).* No linear relationship could be found in cases which are marked by 'X'. The error bars denote the 95% confidence intervals of β.

to an increase of the ICV/ECV ratio calculated with equation 3. Thus, during phases 1 and 3 of our experiments an increase of the K-factor can in fact be observed.

Our calculated ECV changes in arm and leg after postural changes are consistent with previous observations. Immediately after tilting back the ECV undergoes a rapid transition, which is most probably associated with redistribution of blood from the extremities towards the trunk ('vascular emptying'). A similar transition has also been observed in the data for the total body (Fig. 3A). After this rapid process microvascular pressure changes after postural changes cause filtration across the capillary walls and alter the interstitial fluid amount. Rapid ECV changes in the extremities must be compensated by opposite changes in the rest of the body, particularly in the trunk, the head and the neck.

Note that a direct comparison of the data for TBW and segmental volumes should be carried out with caution. The Xitron method has been validated with tracer dilution experiments only for total body measurements (D_2O dilution for TBW [17], and NaBr for ECV [13]). To our knowledge the method has not been clearly validated for segmental measurements, however, the assumptions of the FDM are met more closely by the extremities than by the whole body.

The total body measurements show that the FDM predicts total ECV changes up to 3% during phase 3. This has to be interpreted in context with the two initially stated hypotheses.

The conditions of hypothesis 2 are clearly not met according to our total body measurement results. Neither are the time constants of total ICV and ECV equal, nor do the total ICV and ECV changes sum up to zero in most cases. Consequently, hypothesis 1 applies, which is in agreement with physiological reasonings:

- A rapid transfer of water would be aided by the presence of aquaporins [18]. However, such structures have not been identified in myocytes, which represent most of the leg ICV.
- A water shift from the ECV to the ICV should imply an increase of the extracellular Na^+ concentration. Because of the rapid exchange between interstitial and plasma sodium, a pure water shift to the ICV should affect the ionic composition of the blood; an ECV decrease of 5% should result in a Na^+ concentration increase of approximately 3 to 5%. Such an effect has never been observed on experimental grounds. In addition, there is no need for regulatory ion fluxes between ICV and ECV [19] with postural changes. Indeed, it has been confirmed that ECV and ICV remain unaffected by such maneuvers [20].

According to hypothesis 1 no shifts of total ECV and ICV should be observed during postural changes. As the opposite has been demonstrated in our study, it is concluded that changes from the upright to the supine position cause measurement artifacts in the ECV data that may invalidate volume monitoring during dialysis. These artifacts certainly do not stem from insufficient accuracy of the impedance data, as a thorough calibration of the BIS device was performed and no drifts could be detected. More probable reasons for the spurious volume changes are:

(1.) The applied electrode configuration renders the method insensitive to fluid changes in the neck, head and upper thorax. Hence, fluid injection into this fluid reserve region after tilting back may contribute significantly to the observed effects. Even the discrepancies between the intra- and extracellular time constants may be partly explained by this kind of water redistribution. The changes of the ICV, however, cannot be explained in this way.

(2.) The FDM is not sufficiently valid. This assumption is supported by the following arguments:

- The Hanai mixture theory is only valid for a suspension with spherical disperse particles, a model which is approximately valid for blood, but not for different other body tissues.
- The volume estimation equations 2 and 3 have been derived from a model that assumes cylindrical segments with homogenous

Table 3. Statistical parameters for the results from leg impedance (mean and standard deviation)

	$\Delta V_{rel}^{ex,30}$	$\Delta V_{rel}^{ex,\infty}$		$\Delta V_{rel}^{in,30}$	$\Delta V_{rel}^{in,\infty}$	
	%		τ_{ex} *min*	%		τ_{in} *min*
P1	−0.69 ± 0.52	−0.94 ± 0.9	10.77 ± 12.60	3.04 ± 2.02	3.17 ± 2.07	5.88 ± 5.19
P2	3.97 ± 1.54	5.59 ± 2.43	20.91 ± 12.16	−4.62 ± 2.10	−4.94 ± 2.40	7.50 ± 4.91
P3	−2.43 ± 0.94	−6.75 ± 5.88	39.99 ± 28.77	5.03 ± 1.92	5.79 ± 2.55	12.22 ± 14.65

P1, P2, P3 denote phase 1, phase 2 and phase 3, respectively.

Table 4. Statistical parameters for the results from leg impedance (mean and standard deviation)

	$\Delta V_{rel}^{ex,30}$	$\Delta V_{rel}^{ex,\infty}$		$\Delta V_{rel}^{in,30}$	$\Delta V_{rel}^{in,\infty}$	
	%		τ_{ex} *min*	%		τ_{in} *min*
P1	−3.36 ± 1.05	−7.38 ± 3.59	42.29 ± 30.19	4.03 ± 2.14	4.46 ± 2.53	7.69 ± 5.17
P2	5.28 ± 1.72	6.97 ± 3.73	16.59 ± 7.35	−6.11 ± 1.71	−9.02 ± 5.04	19.90 ± 14.50
P3	−5.09 ± 0.49	−13.05 ± 5.70	60.84 ± 37.34	5.44 ± 3.07	7.59 ± 5.99	16.35 ± 10.74

P1, P2, P3 denote phase 1, phase 2 and phase 3, respectively.

Table 5. Results of the Wilcoxon test for comparison of the time constants of leg measurements

	τ_{ex} (2)	τ_{ex} (3)	τ_{in} (1)	τ_{in} (2)	τ_{in} (3)
τ_{ex} (1)	0.046	NS	NS	—	—
τ_{ex} (2)	—	NS	—	0.0128	—
τ_{ex} (3)	—	—	—	—	0.018
τ_{in} (1)	—	—	—	NS	NS
τ_{in} (2)	—	—	—	—	NS

The entries denote the probability that the corresponding row and column parameters are not significantly different; NS means no significant difference ($P < 0.05$).

Table 6. Results of the Wilcoxon test for comparison of the time constants of arm measurements

	τ_{ex} (2)	τ_{ex} (3)	τ_{in} (1)	τ_{in} (2)	τ_{in} (3)
τ_{ex} (1)	NS	NS	0.0036	—	—
τ_{ex} (2)	—	0.00304	—	NS	—
τ_{ex} (3)	—	—	—	—	0.0072
τ_{in} (1)	—	—	—	NS	NS
τ_{in} (2)	—	—	—	—	NS

The entries denote the probability that the corresponding row and column parameters are not significantly different; NS means no significant difference ($P < 0.05$).

electrical tissue properties [15]. This may be an applicable approximation for legs and arms, however, it is certainly invalid for the trunk. For overcoming this difficulty an empirical factor K_B has been introduced which should correct for the real body geometry. This factor must be determined by reference measurements, such as tracer dilution experiments. However, it is only valid for a single defined body position after the achievement of a steady state. Any deviation from the reference position is expected to cause a more or less pronounced volume estimation error due to fluid movements and alterations of the geometrical properties of the tissue.

The volume shifts calculated from total and segmental measurements have the same direction in any phase. This reveals that the calculated total changes are essentially determined by the extremities. This is consistent with the fact that the impedance of the trunk contributes only 5% to the total impedance between the wrist and ankle [21]. As a consequence, the method with the particular electrode configuration used in this study is not very sensitive to fluid changes in the trunk. Moreover, it is completely insensitive to fluid shifts from and to the upper thorax, the neck and the head. Thus, water shifts in the arms and legs dominate the measured impedance signals.

It may be argued that relative volume changes with respect to a defined initial fluid distribution can be measured regardless of the inaccuracies in the absolute volume readings. This should be possible, if the patient is in an approximate steady state before the measurements are started. However, the large time constants imply that more than 30 minutes are required until stable readings are possible. The fact that the time constants of the ICV results are much lower raises the question of whether ICV instead of ECV data should be used for the estimation of fluid shifts. This should be possible after a significantly shorter resting period in the supine position (about 30 min). If so, the ΔV_{ex} could be calculated as the difference between UFR and ΔV_{in}.

Suggestions for further investigations

A tempting idea for overcoming the sensitivity mismatch is to measure the impedances of different body segments separately and to calculate the volumes from an appropriately weighted sum of all impedances in series. Some evidence for this approach can be found [9]. The authors have reported that alternative positioning of the electrodes can decrease the method's sensitivity to postural changes. Lower impedance drifts were obtained when the voltage sensing electrodes were positioned below the knee and at the ellbow. With this configuration some kind of empirical weighting is performed as the contribution of the trunk to the measured impedance is increased at the cost of the contributions of the extremities. Additionally the orthostatically induced effects in the lower legs and forearms are not measured. However, the weighting approach may fail, because the simple cylinder model does not apply for the inhomogeneous trunk, and neither single-frequency plethysmography nor the Hanai model are considered to be reliable methods for volume estimations in this region. A final answer to this question should be given in future experiments with multisegmental measurements.

An alternative is that it appears realistic to develop a valid FDM for an approximately cylindrical segment with a moderate degree of inhomogeneity, such as the thigh. At least the following conductive compartments should be considered: muscle, blood, subcutis and blood. If this FDM renders a correct prediction of the ratio $r_{ex,in}$ between ECV and ICV possible, and if this ratio is assumed to be representative for the whole body, then the entire information on volume changes can be obtained. The initial TBW must be estimated either from anthropometrical formulae or from total body impedance measurements. The absolute changes of TBW is equal to the UFR. Thus, the changes of ECV and ICV can be calculated from the measured $r_{ex,in}$ and the UFR with:

$$\Delta V_{in} = \frac{TBW(t)}{1 + r_{ex,in}(t)} - \frac{TBW(0)}{1 + r_{ex,in}(0)}$$

$$\Delta V_{ex} = \frac{r_{ex,in}(t)TBW(t)}{1 + r_{ex,in}(t)} - \frac{r_{ex,in}(0)TBW(0)}{1 + r_{ex,in}(0)} \qquad \text{(Eq. 10)}$$

$$TBW(t) = TBW(0) - \int_0^t UFR(\tau)d\tau$$

This approach has the advantage that only one segment must be accessed, which significantly facilitates handling in the clinical routine. The method is insensitive to orthostatically induced regional changes of the ECV, as this volume is not calculated directly from impedance data, but from a readily accessible quantity (UFR) and $r_{ex,in}$. A validation criterion that must be met by the FDM is the insensitivity of the calculated ICV to orthostatic changes.

The reason why blood should be included as a separate compartment is that it has been documented that the impedance spectrum does not fit the simple depressed Cole-Cole circle at high frequencies (> 500 kHz). The deviation has been documented in a recent paper [22] and has also been observed in our study (unpublished data). In the Bode plot this effect is reflected by the fact that the S-shaped impedance curve does not reach a plateau at high frequencies, but continues decreasing. This effect gets even more pronounced during segmental measurements if the vascular filling of the segment under investigation is increased. A typical example is shown in Figure 7, where the spectra of the impedance modulus of a human arm are shown for two different positions. The curve approaches the S-shaped ideal curve more closely when the arm is raised, which corresponds to lower vascular filling and, consequently, less influence of the blood on the arm impedance. The manufacturers of the device have explained the deviation from the ideal Cole-Cole circle by phase shifts due to a propagation delay of the signal along the measured tissue segment [15, 16]. A clear model for this propagation delay has not been specified until now. According to the users manual, the deviation can be corrected by multiplying the Cole-Cole equation with a phase factor $e^{-j\omega TD}$. However, this factor influences only the phase angle of the impedance and the modulus remains unchanged. Consequently, the deviation of the impedance from the ideal S-shape as shown in Figure 7 cannot be corrected by such a phase factor. An alternative explanation may be given by considering that the β-dispersion center frequencies of blood and muscle tissue are significantly different [1]. Both compartments lie in parallel within the body. Hence, the conductance-spectra are superimposed and sum up to a spectrum which

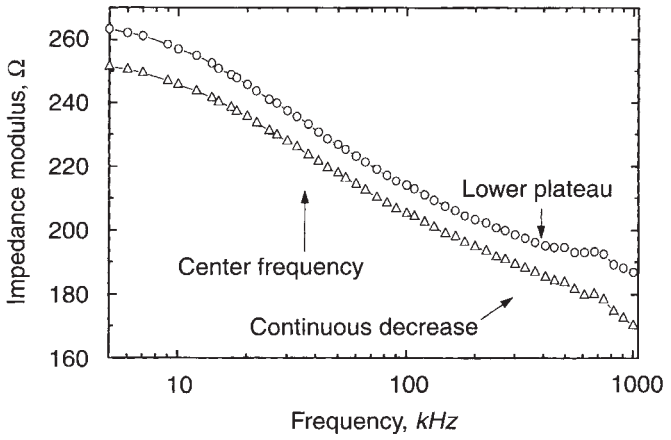

Fig. 7. *Comparison of impedance spectra at different vascular filling of a human arm.* The lower plateau at high frequencies disappears if the vascular filling of the segmant is increased by a position change. Symbols are: (△) arm hanging down; (○) arm raised.

does not fit a single Cole circle. Regional changes of the blood volume result in deformations of the Cole circle and may affect the quality of the fitting with regard to the high frequency resistance. Furthermore, the erythrocytes are essentially nonconducting at frequencies lower than 500 kHz and hence are not identified as a part of the ICV. This aspect has not been considered by other authors.

Conclusion

BIS clearly provides more information about tissue properties (in particular the hydration state) than single frequency methods. It is considered to be a powerful and easily applicable method. However, the potential of BIS can only be exhausted if the data are interpreted with adequate algorithms that include reliable data fitting and a valid FDM. The BIS system by Xitron provides reliable impedance measurements if it is calibrated thoroughly, and the fitting algorithm for the Cole-Cole model performs satisfactorily. The FDM, however, should be improved. We suggest further investigations for the following:

- Development of a more realistic FDM which includes tissue inhomogeneities. A valid model must guarantee that ECV changes do not corrupt the ICV data and vice versa.
- Clarification of how the filling state of blood vessels with high compliance affects the impedance spectra of the extremities and hence the validity of the simple Cole-Cole model. Experiments should be designed for the evaluation of the superposition of the dispersion curves of blood and muscle tissue during postural changes. This may be a key factor for the separation of effects that are caused by local blood shifts. Those experiments could focus on the extremities that are modeled much easier than the highly inhomogeneous thorax. Impedance plethysmography as used in the study by Montgomery [12] at a single low frequency (such as 5 kHz) could be utilized for the estimation of the blood volumes in the extremities and may facilitate the modeling process.

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Appendix

Abbreviations are: BIS, bioimpedance spectroscopy; ECV,extracellular volume (liter); FDM, fluid distribution model; ICV,intracellular volume (liter); TBW, total body water volume (liter); UFR, ultrafiltration rate (liter/min).

Symbols are: α, Cole distribution exponent; β, regression coefficient; C_M, mean cell membrane capacity (F); D_B, mean body density (kg/cm^3); $\Delta V_{rel}^{ex,30}$ and $\Delta V_{rel}^{in,30}$, relative volume changes at t = 30 minutes for ECV and ICV, respectively; $\Delta V_{rel}^{ex,\infty}$ and $\Delta V_{rel}^{in,\infty}$, relative volume changes at t = ∞ for ECV and ICV, respectively; τ_{ex} and τ_{in}, time constants for ECV and ICV (min); H, body height or segment length (cm); K, 'K-factor' according to Lozano et al [10]; K_B, dimensionless correction factor; λ_{ex} and λ_{in} extra- and intracellular conductivities [$(\Omega cm)^{-1}$]; $r_{ex,in}$, ratio between extra- and intracellular volume; R_{ex} and R_{in} extra- and intracellular resistance according to Cole-Cole model (Ω), respectively; R_0 and R_∞ tissue resistance at low and high frequencies (Ω), respectively; t, time (min); T_D, propagation time (seconds); τ_{ex} and τ_{in}, time constants of the monoexponential model for ECV and ICV (min), respectively; V_{ex} and V_{in}, extra- (ECV) and intracellular (ICV) volume, respectively (liter); ω, angular frequency (s^{-1}); W_b, body mass (kg); Z, impedance Ω.

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