Chapter 6

Segmental and whole-body bioimpedance measurements in continuous peritoneal dialysis patients

6.1 Introduction

Cardiovascular disease (CVD) is a leading cause of death in dialysis patients (Foley *et al* 1998, Mallamaci *et al* 2005, McCullough 2005) and fluid overload and arterial hypertension are among the most common risk factors associated with mortality from cardiovascular disease (Kooman *et al* 1998, Kunz *et al* 1998, Nanovic 2005). Arterial Hypertension due to volume overload is especially common in patients on continuous ambulatory peritoneal dialysis (CAPD) and associated with a poor prognosis (Lameire and Biesen 2004). Clearly, there is a clinical demand for a non-invasive, reproducible and inexpensive bed-side method to monitor the hydration status in these patients. Bioelectrical impedance vector analysis (BIVA) is a simple, non-ninvasive, innocuous and repeatable method and does not require the definition of patient dry weight that is being used to determine hydration and nutritional state in HD patients (Kushner 1992, Fisch and Spiegel 1996, Thomas et al 1999, Piccoli et al 1998, Cooper et al 2000) and in PD patients.

The right-side or whole-body method has low sensitivity to changes of fluid content in the trunk (Thomas *et al* 1997, Zhu *et al* 2000 and 2003). In contrast, it has been shown that segmental bioimpedance measured in three body segments (arm, leg, trunk) can be used to monitor changes in regional fluid status (Ellis 2000). Segmental BIA is obtained placing the electrodes at the ends of the superior and inferior limbs, and in the trunk, according to several modalities (Lozano *et al* 1995, Zhu *et al* 1998 and 1999, Chanchairujira *et al* 2001, Cornish *et al* 1999, Ellis 2000, Houtkooper *et al* 1996, Lukaski 1996).

The aim of this work is to analyze the advantages of applying at the same time the BIVA method, (right-side) and segmental, (longitudinal and/or transversal) bioimpedance measurements at 50 kHz in CAPD, and the relationship between bioimpedance parameters, hydration and nutritional state estimated by clinical assessment. Three impedance based estimators were analyzed: Z, Z/H, ZBMI.

6.2 Subject and Methods

6.2.1 Patients

Measurements were taken in the morning, before a fluid exchange, and after complete drainage of the abdominal cavity in all male patients undergoing CAPD at the Service of Nephrology of the Fundaciò Puigvert (Barcelona, Spain). We make three exclusions: one due to death, another due to amputations and the last because the patient changed of dialysis unit. For the first study, 23 male patients were classified taking into account the hydration state as normo-hydrated (group 0) or hyper-hydrated (group 1). Group 0 includes 10 patients (55.6 ± 10.5 yr, BMI 24.0 ± 1.9 kg/m2). Group 1 includes 13 patients (56.6 ± 9.0 yr, BMI 29.5 ± 1.7 kg/m2).

In the second study we incorporated two new male patients. A new classification was performed. Group 0 has normo-hydrated patients and group 1 has varying degrees of hypertension, overhydration, and high score on cardiovascular risk factors (e.g. increased left ventricular mass LVM, increased cholesterol, homocysteine levels, etc). Group 0 includes 10 normo-hydrated patients (52.8 ± 9.6 yr, BMI 24.5 ± 1.9 kg/m^2). Group 1 includes 15 hyper-hydrated leading to hypertension patients (55.3 ± 9.8 yr, BMI 29.1 ± 3.7 kg/m^2). Informed written consent was obtained from all participants prior to the study.

Due to well known gender differences in bioimpedance parameters (Piccoli et al 1998, Nescolarde et al 2004) it was not possible to include the 3 females patients in this dialysis unit in the study.

The following clinical parameters were measured: left ventricular mass (by echocardiography), systolic (SBP) and diastolic blood pressure (DBP), serum levels of homocysteine, cholesterol, triglycerids, total protein (Tprot), albumin, C-reactive protein (CRP) and blood sedimentation rate (BSR).

Blood pressure (BP) measurements were taken by a nurse with a manual sphygmomanometer. The patient was in supine position and the cuff was attached to the left or right arm depending on the Cimino fistula location. SBP and DBP were obtained for each patient. Mean blood pressure was estimated (Cywinski 1980) according to:

$$BP_{mean} = \frac{SBP + 2DBP}{3} \tag{6.1}$$

6.2.2 Bioimpedance measurement protocol

The measures were made with the Analyzer of Biological Impedance, Model STA-BIA (AKERN-RJL System, Italy) (Figure 6.1). Measurement errors of the system are lower than 1 Ω and 1º at 50 kHz using electrical models. Injected current was 800 μA. A frequency of 50 kHz was selected because this is the usual frequency employed for bioimpedance analysis in patients with renal insufficiency (Ellis 2000).

All bioimpedance measurements were taken before the peritoneal dialysis (BPD) sessions by the same investigator who was blinded with respect to the results of the clinical assessment. We used disposable pre-gelled Ag/AgCl electrodes (3M Red Dot, Canada).

Figure 6.1- Bioimpedance analyzer. Model STA-BIA (AKERN-RJL System, Italy)

We used the tetrapolar segmental (longitudinal and transversal) as shown in Figure 6.2. Measurements were taken sequentially connecting manually the 4-leads to the appropriate electrodes. In total, we used 9 configurations (7 longitudinal and 2 transversal) with four electrodes for each bioimpedance measurement: two electrodes for injecting current (I) and two for sensing voltage (V). Note that in the longitudinal configurations, the injecting current are in the same position as in the right-side configuration.

The different electrode configurations are as follow:

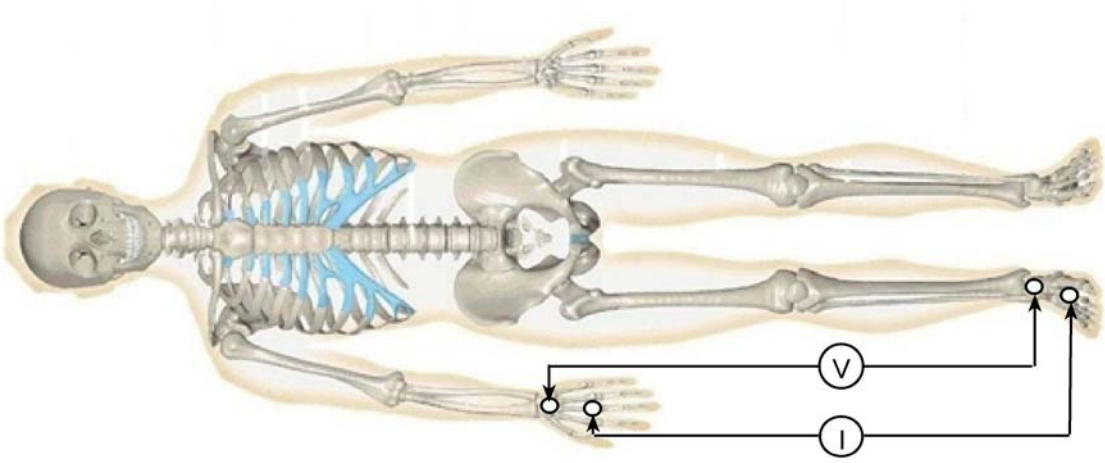
Longitudinal

1) RS: right-side; is the standard whole body impedance measurement

2) RARM: right-arm; electrode for sensing voltage in dorsal-carpal articulation, in right arm and left arm
3) T: thorax; is the segment from left arm (carpo-dorsal articulation) to xiphoid
4) AB: abdomen (RAB); is the segment from left-foot articulation to xiphoid
5) RLEG1: right-leg-1; upper part of right leg, from inguinal region to knee joint
6) RLEG2: right-leg-2; is the lower part of right leg, from knee joint to medial malleolar articulation
7) RLEGTOT: right-leg-total; is the addition of both previous segments from inguinal region to malleolar articulation

Transversal

8) TRABD: transversal-abdomen; at the level of the umbilicus
9) RTRALEG: transversal-right-leg; located in the thigh femoral region



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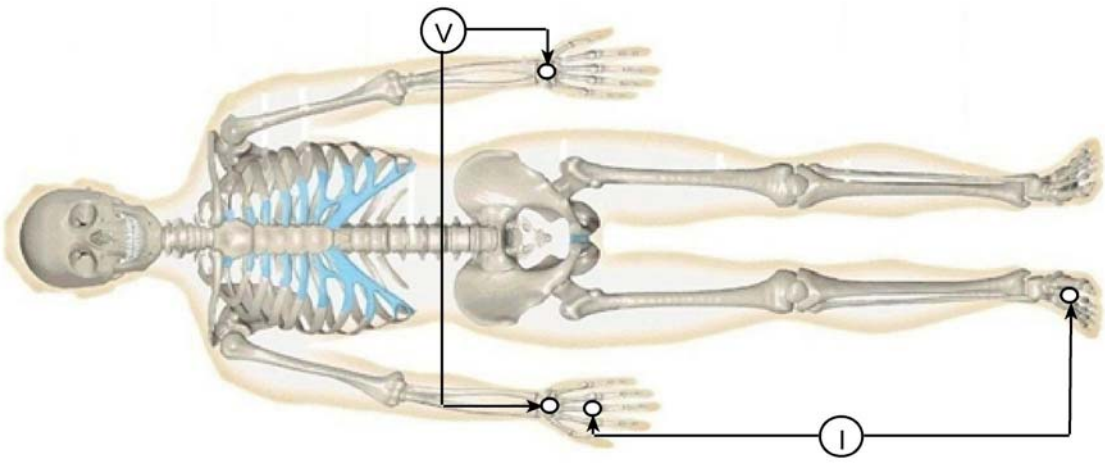

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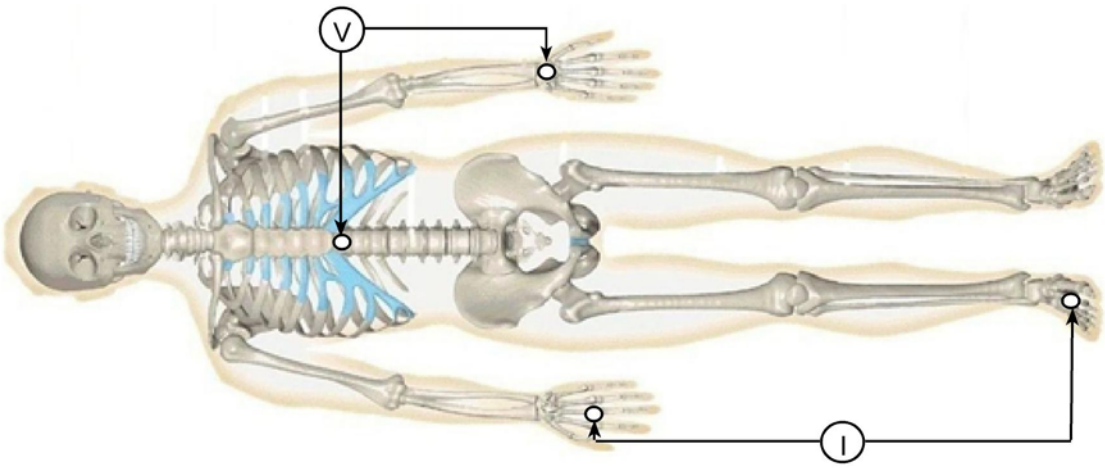

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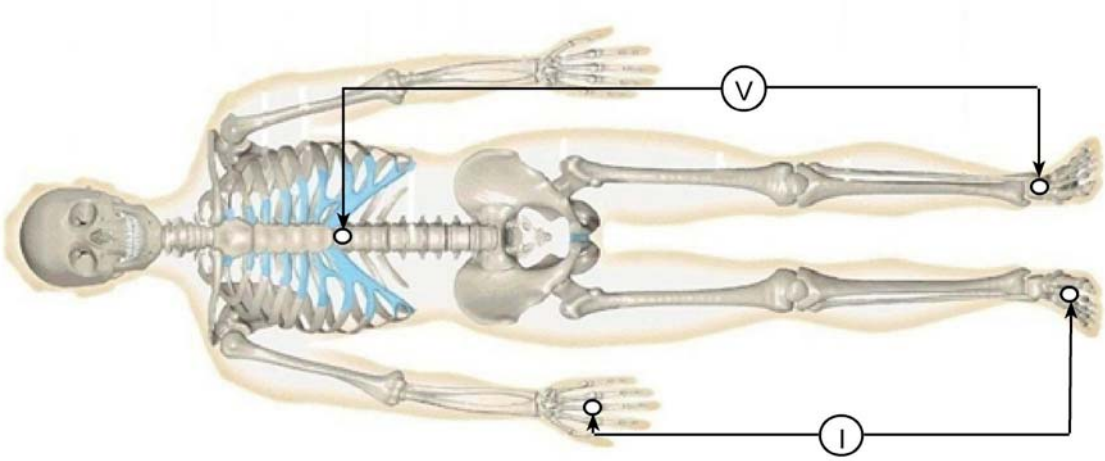

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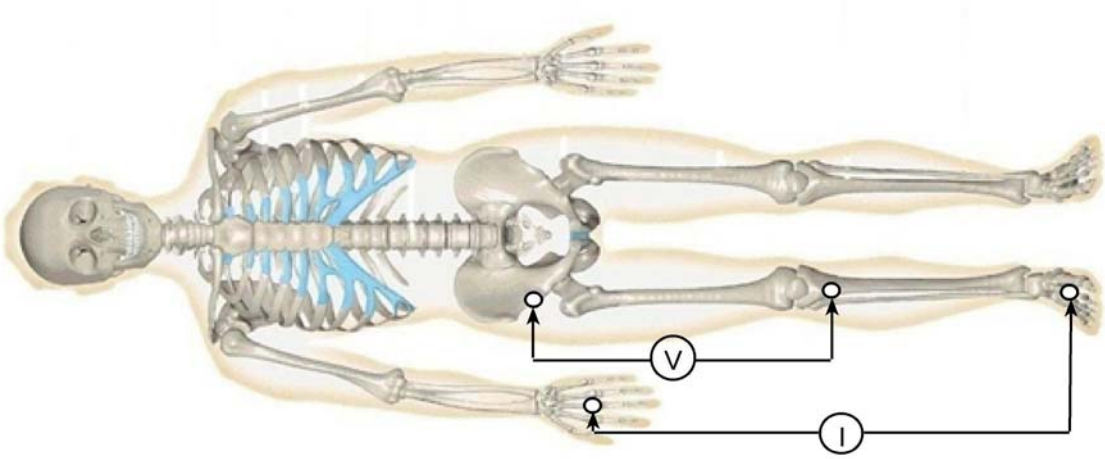

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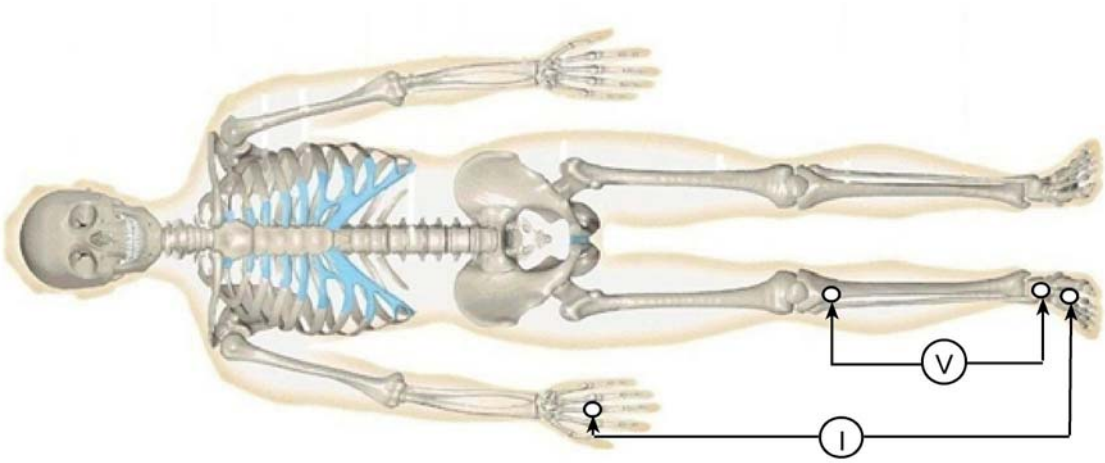

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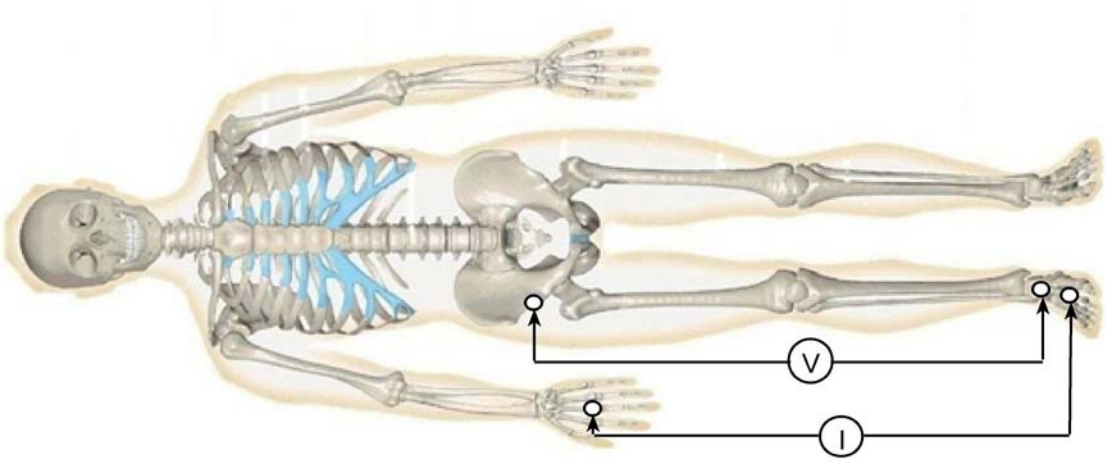

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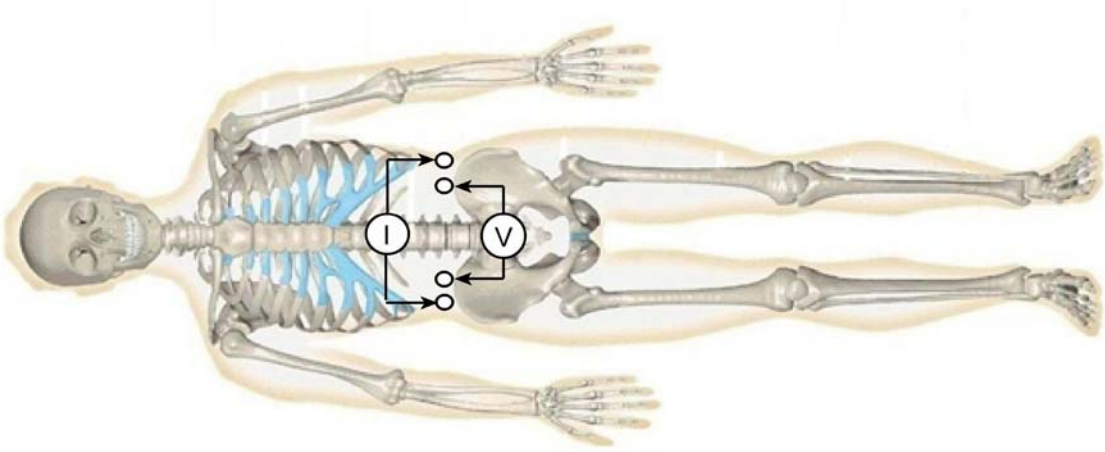

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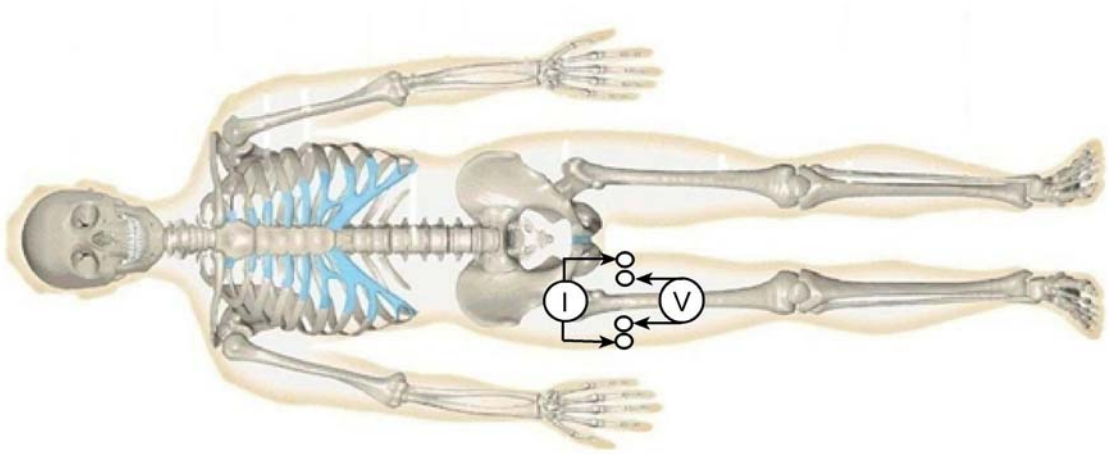

(9)

Figure 6.2- Electrode placement for each measurement configuration (7 longitudinal and 2 transversal)

6.2.3 Resistivity index

The standard method for bioelectrical impedance analysis (BIA) is to measure between the right arm and the right leg (whole body or righ-side impedance method, see figure 1). Based on this measurement body compartments (fat free mass, fat mass, extra and intra-cellular water, etc) is estimated using equations including a term R or H^2/R related to the measured impedance plus additional anthropometric terms (tables 5.1 and 5.2). Most of the literature agrees that BIA equations are only accurate in healthy patients (Ellis 2000). Furthermore, the value of BIA in the dialysis setting has been questioned in several studies (Piccoli 2005, Kuhlmann *et al* 2005). An alternative tool for medical diagnosis in dialysis patients is the bioimpedance vector analysis (BIVA) (Piccoli and Pastori 2002). In this method, the same right-side impedance is measured but the analysis is performed over a probabilistic 2-dimensional space containing the real and the imaginary parts of the impedance normalized by the height of the patient (R/H and Xc/H). Patterns on the RXc-graph relate body impedance to body hydration (Piccoli *et al* 1994, Piccoli 2002). This method does not require the definition of a patient dry weight that is being used to determine hydration and nutritional state in hemodialysis (HD) patients (Cooper *et al* 2000, Kushner 1992, Kyle *et al* 2004, Piccoli *et al* 1998, Spiegel *et al* 2000, Thomas *et al* 1999). In our work we analyze Z, Z/H and we have added a new term, ZBMI.

The basic model behind the majority of bioimpedance techniques applied to Bioelectrical Impedance Analysis (BIA) is the cylindrical model. We have that the impedance between

faces of a cylinder of finite height when a uniform density is applied parallel to its axis is given by

$$Z = \rho^* \frac{h}{S} = \rho^* \frac{2c}{\pi a^2} \tag{6.2}$$

where:

ρ^*: complex resistivity

h: height

S: surface of the base

From this equation, it is clear that the measured impedance will contain information about tissue resistivity ρ, but also from its shape (S, h). One way to standardise the impedance is dividing by the height h as it is done in BIVA. In this case the result could be interpreted as a "sectional" resistivity (we assume that all people must have the same S). Other approximations are the ones used in BIA to calculate body composition using multiple antropometric variables inside the estimation ecuations.

We will introduce a new impedance index based in the following rationale. Using eq. 6.2 and assuming a cylindrical human body once can obtain the resistivity of tissues from the measured impedance

$$\rho^* = Z \frac{S}{h} \tag{6.3}$$

the height in eq. 6.3 can be assimilated to the actual height of the human body, but the surface S cannot be readily estimated.

A usual way to estimate the nutritional state of human beings is the use of the body mass index (BMI), based on the measurement of weight W and height h given by

$$BMI = \frac{W}{h^2}\left(kg/m^2\right) \tag{6.4}$$

which can be calculated easily. Once more, assuming a cylinder human body, eq. 6.4 can be transformed as follows:

$$BMI = \frac{W}{h^2}\left(kg/m^2\right) = \frac{Volume\delta}{h^2} = \frac{Sh\delta}{h^2} = \frac{S\delta}{h} \Rightarrow \frac{S}{h} = \frac{BMI}{\delta} \tag{6.5}$$

where δ is the mean density of the body, that can be considered constant among subjects and equalling that of water.

Substituting eq. 6.5 in eq. 6.3, the resistivity of the tissue can be now obtained:

$$\rho^* = Z\frac{S}{h} = Z\frac{BMI}{\delta} \tag{6.6}$$

We know that the model is very limited but the advantage of this index is its simplicity and the fact that the meaning of the results could be interpreted as tissue conductivity. Our hypothesis is that this index will be less sensitive to racial and anthropometric differences than the standardization used in BIVA.

6.2.4 Statistical methods.

Wilcoxon test was used to analyze the change in impedance (longitudinal and transversal) produced by a session of peritoneal dialysis (BPD against APD). Statistical significance was set at $P < 0.05$. Mann-Whitney U test was used to analyse the separation between groups obtained by means of clinical diagnosis and those obtained by Z, Z/H or ZBMI. Statistical significance was set at $P < 0.05$. We considered as our null hypothesis (H_0) that both groups of patients, normo-hydrated and hyper-hydrated, were extracted from the same population. Spearman correlation was used to study the correlation between Z, Z/H, ZBMI vectors in each segment, with clinical assessment.

In addition, we investigated whether segmental bioimpedance of the thoracic region could improve the prediction of hyper-hydration and cardiovascular risk in CAPD patients compared to the standard right-side whole body measurement. We tested the hypothesis that the use of two non-invasive measurements, i.e. segmental thoracic bioimpedance and BP_{mean} could reliably identify patients with critical volume overload as estimated by clinical assessment. Hotelling's T^2 test was used to analyzed difference between groups (0 and 1) through (R_{TH}/H, BP_{mean}) and (R_{RS}/H, BP_{mean}) vectors.

Mann-Whitney U-test was used to compare the differences in clinical measurements, laboratory test, and bioimpedance measurements (Right-Side (R_{RS}/H) and thorax (R_{TH}/H)) between groups (0 and 1). Statistical significance was set at $P<0.05$.

SPSS software version 12.0 (SPSS, Inc.) was used for data management and statistical analysis.

6.2.5 The Mahalanobis Distance

We used the Mahalanobis Distance for bioimpedance measurements and BP_{mean} to classify the patients with respect to a reference standard (the most critical patient).

The Mahalanobis Distance (Mahalanobis 1930) is a statistical measure between two vectors $\mathbf{x} = (x_1,.....x_p)^T$ and $\mathbf{y} = (y_1,....y_p)^T$ in a p-dimensional space R*p* defined as:

$$dM^2 = \left((\mathbf{x}-\mathbf{y})^T \mathbf{S}^{-1}(\mathbf{x}-\mathbf{y})\right) \tag{6.7}$$

Where $\mathbf{S}^{-1}$ is the covariance matrix computed from the different realisations of **x-y**. It differs from Euclidean distance in that it takes into account the correlations of the data set.

The Mahalanobis Distance is a scale used to distinguish among groups by means of multivariate data set analysis. Some authors suggest that the Mahalanobis Distance can be used to evaluate the progress of treatment of diseases in clinical studies (Kanetaka 1990, Kojima *et al* 1994).

In our work, the Mahalanobis Distance was calculated using a bidimensional space. Each point (P_p) is defined for each patient using the resistance measurement (right-side or thorax segment) divided by the height of the patients and the BP_{mean}. dM^2 was calculated for each patient with respect to a reference point P_{ref} (1.16 Ω/m, 120 mmHg) obtained from the most critical patient (ID=7). This patient had acute lung oedema (determined by electrocardiogram and thorax X-ray), hypertension, high left ventricular mass index LVMI (calculated by LVM), hyperhomocysteinemia, high values of cholesterol, triglycerides, CRP and BSR and low values of albumin**.** So, the Mahalanobis distances were calculated as:

$$dM^2 = \left(\mathbf{P_p} - \mathbf{P_{ref}}\right)^T \cdot \mathbf{S}^{-1} \cdot \left(\mathbf{P_p} - \mathbf{P_{ref}}\right) \tag{6.8}$$

6.3 Results

6.3.1 Z, Z/H and ZBMI in CAPD patients

Tables 6.1 and 6.2 show the mean value ± SD and the Wilcoxon test, in each group (G0 and G1), of each impedance segment, using Z (R and Xc).

The BMI was of 24.0 ± 1.9 kg/m^2 for normo-hydrated group (0) and 29.5 ± 1.7 kg/m^2 for hyper-hydrated group (1). The significance difference within groups of $P<0.0001$.

Table 6.1- The Mean ± SD of R and Xc, and Wilcoxon test in a sample of 10 CAPD patients (G0)

Electrode Configuration	R (Ω) Mean ± SD		*P*(R)	-Xc (Ω) Mean ± SD		*P*(Xc)
	BPD	APD		BPD	APD	
RS	515.7± 46.4	529.0 ± 46.1	0.009*	56.6 ± 10.7	57.1 ± 13.1	-
RARM	273.6 ± 23.6	275.8 ± 25.4	-	21.7 ± 5.1	21.8 ± 5.0	-
T	7.1 ± 2.1	7.1 ± 2.5	-	LS	LS	LS
AB	25.9 ± 3.4	28.9 ± 3.8	0.005**	LS	LS	LS
RLEG1	87.9 ± 8.7	91.7 ± 8.2	0.028*	5.1 ± 2.1	5.2 ± 3.0	-
RLEG2	140.0± 20.0	146.2 ± 12.5	-	11.4 ± 3.1	11.9 ± 5.2	-
RLEGTOT	223.9 ± 31.0	229.0 ± 25.5	0.028*	23.4 ± 12.8	22.8 ± 11.8	-
TRABD	33.9 ± 9.9	40.3 ± 11.5	0.003**	3.4 ± 1.1	3.4 ± 1.0	-
RTRALEG	28.1 ± 6.2	28.4 ± 6.2	-	4.1 ± 1.7	4.2 ± 1.4	-

LS=value no show, for low sensibility of bioimpedance analyzer
*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.2- The Mean ± SD of R and Xc, and Wilcoxon test in a sample of 13 CAPD patients (G1)

Electrode Configuration	R(Ω) Mean ± SD		*P*(R)	-Xc(Ω) Mean ± SD		*P*(Xc)
	BPD	APD		BPD	APD	
RS	409.4 ± 48.7	415.3 ± 48.7	0.007**	39.6 ± 12.1	39.8 ± 12.4	-
RARM	223.3 ± 18.7	224.3 ± 17.8	-	15.8 ± 5.6	16.3 ± 5.6	-
T	3.4 ± 1.7	3.8 ± 1.3	-	LS	LS	LS
AB	21.3 ± 3.8	22.8 ± 4.1	0.003**	LS	LS	LS
RLEG1	68.8 ± 13.5	69.9 ± 13.7	0.023*	3.6 ± 2.2	3.9 ± 2.3	-
RLEG2	109.3 ± 26.5	109.7 ± 26.8	-	8.4 ± 4.5	8.4 ± 5.1	-
RLEGTOT	171.8 ± 37.1	175.6 ± 37.7	0.022*	13.4 ± 6.0	14.3 ± 7.1	-
TRABD	33.0 ± 10.2	39.2 ± 10.3	0.002**	2.7 ± 1.1	2.9 ± 1.4	-
RTRALEG	24.3 ± 6.7	24.6 ± 6.7	-	4.1 ± 1.9	4.1 ± 1.3	-

LS=value no show, for low sensibility to measure Xc, of bioimpedance analyzer
*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.3 shows the Mann-Whitney U test result between group 0 and group 1, in each segment, of the parameters R and Xc.

Table 6.3- Mann-Whitney U test in a sample of 23 patients (G0:10 and G1:13) undergoing CAPD after fluid exchange (BPD)

Electrode Configuration	*P*(R)	*P* (Xc)
RS	0.000**	0.006**
RARM	0.000**	0.025*
T	0.002**	LS
AB	0.006**	LS
RLEG1	0.001**	-
RLEG2	0.008**	-
RLEGTOT	0.006**	-
TRABD	-	-
RTRALEG	-	-

The tables 6.4 and 6.5 show the mean value ± SD, and the Wilcoxon test in each group (G0 and G1), of each impedance segment. In these case, using the normalized impedance Z/H (R/H and Xc/H).

Table 6.4- The Mean ± SD of R/H and Xc/H, and Wilcoxon test in a sample of 10 CAPD patients (G0)

Electrode Configuration	R/H (Ω/cm) Mean ± SD		*P*(R/H)	-Xc/H (Ω/cm) Mean ± SD		*P*(Xc/H)
	BPD	APD		BPD	APD	
RS	309.4 ± 29.9	323.5 ± 26.0	-	31.0 ± 6.2	32.8 ± 6.0	-
RARM	165.2 ± 15.0	169.6 ± 15.9	-	13.1 ± 3.1	11.8 ± 3.0	-
T	4.1 ± 1.1	4.3 ± 1.2	-	LS	LS	LS
AB	14.5 ± 2.3	17.7 ± 1.5	0.005**	LS	LS	LS
RLEG1	52.8 ± 6.4	55.4 ± 5.0	-	3.1 ± 1.2	3.2 ± 1.8	-
RLEG2	84.2 ± 12.7	88.8 ± 8.2	-	6.8 ± 1.8	8.0 ± 3.1	-
RLEGTOT	129.1 ± 26.3	137.6 ± 16.6	-	14.6 ± 7.4	14.3 ± 6.8	-
TRABD	19.4 ± 5.6	25.6 ± 4.3	0.009**	2.0 ± 0.6	2.1 ± 0.6	-
RTRALEG	16.8 ± 3.5	17.7 ± 3.5	-	2.5 ± 1.0	2.5 ± 0.8	-

LS=value no show, for low sensibility to measure Xc, of bioimpedance analyzer
*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.5- The Mean ± SD of R/H and Xc/H, and Wilcoxon test in a sample of 13 CAPD patients (G1)

Electrode Configuration	R/H (Ω/cm) Mean ± SD		*P*(R/H)	-Xc/H (Ω/cm) Mean ± SD		*P*(Xc/H)
	BPD	APD		BPD	APD	
RS	240.4 ± 31.4	255.2 ± 26.0	-	23.7 ± 6.6	25.3 ± 6.0	-
RARM	131 ± 12.9	135.8 ± 11.7	-	9.5 ± 3.3	9.7± 3.1	-
T	2.0± 1.3	2.2 ± 1.2	-	LS	LS	LS
AB	12.7 ± 2.5	14.4 ± 3.4	0.003**	LS	LS	LS
RLEG1	40.7 ± 8.6	43.7 ± 6.4	-	2.1 ± 1.4	2.2 ± 1.3	-
RLEG2	63.9 ± 14.4	70.0 ± 15.4	-	5.1 ± 3.1	5.8 ± 3.7	-
RLEGTOT	102.2 ± 22.6	111.0 ± 19.3	-	8.6 ± 3.9	9.2 ± 5.1	-
TRABD	19.8 ± 6.2	23.5 ± 7.2	0.006**	1.4 ± 0.6	1.6 ± 0.7	-
RTRALEG	15.3 ± 5.4	15.5 ± 4.8	-	2.3 ± 1.1	2.5 ± 0.9	-

LS=value no show, for low sensibility to measure Xc, of bioimpedance analyzer
*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.6 shows the Mann-Whitney U test result between group 0 and group 1, in each segment, of the parameters R/H and Xc/H.

Table 6.6- Mann-Whitney U test in a sample of 23 patients (10: normo-hydrated and 13: hyper-hydrated) undergoing CAPD after fluid exchange (BPD)

Electrode Configuration	*P*(R/H)	*P* (Xc/H)
RS	0.000**	0.010**
RARM	0.000**	-
T	0.000**	LS
AB	-	LS
RLEG1	0.001**	-

RLEG2	0.005**	-
RLEGTOT	0.036**	-
TRABD	-	-
RTRALEG	-	-

*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

The tables 6.7 and 6.8 show the mean value ± SD, and the Wilcoxon test in each group (G0 and G1), of each impedance segment. In these case using ZBMI (RBMI and XcBMI).

Table 6.7- The Mean ± SD of RBMI(ρ_1) and XcBMI(ρ_2), and Wilcoxon test in a sample of 10 CAPD patients (G0)

Electrode Configuration	**RBMI (Ωkg/m²) Mean ± SD**		***P*(ρ_1)**	**-XcBMI (Ωkg/m²) Mean ± SD**		***P*(ρ_2)**
	BPD	**APD**		**BPD**	**APD**	
RS	12499.3 ± 1275.3	12483.2 ± 1197.8	-	1381.3 ± 303.6	1365.5 ± 375.2	-
RARM	6670.9 ± 649.7	6555.1 ± 731.4	-	532.8 ± 139.4	449.8 ± 145.8	-
T	173.7 ± 57.1	169.4 ± 67.1	-	LS	LS	LS
AB	630.3 ± 96.4	685.5 ± 111.1	0.008**	LS	LS	LS
RLEG1	2182.1 ± 238.8	2160.2 ± 174.8	-	120.9 ± 74.4	126.3 ± 51.8	-
RLEG2	3475.2 ± 564.7	3462.0 ± 430.8	-	307.3 ± 133.4	279.5 ± 86.3	-
RLEGTOT	5421.5 ± 751.6	5404.3 ± 648.1	-	595.5 ± 313.9	546.0 ± 292.6	-
TRABD	831.0 ± 264.7	961.9 ± 296.3	0.005**	82.5 ± 25.8	80.4 ± 24.9	-
RTRALEG	685.7 ± 170.5	675.9 ± 170.6	-	102.2 ± 45.2	98.0 ± 36.1	-

LS=value no show, for low sensibility to measure Xc, of bioimpedance analyzer

*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.8- The Mean ± SD of RBMI(ρ_1) and XcBMI(ρ_2), and Wilcoxon test in a sample of 13 CAPD patients (G1)

Electrode Configuration	**RBMI (Ωkg/m²) Mean ± SD**		***P*(ρ_1)**	**-XcBMI (Ωkg/m²) Mean ± SD**		***P*(ρ_2)**
	BPD	**APD**		**BPD**	**APD**	
RS	11626.8 ± 1337.2	11479.2 ± 1351.8	-	1136.6± 397.2	1114.0 ± 405.7	-
RARM	6332.2 ± 570.6	6187.7 ± 575.3	-	462.8± 167.8	440.0 ± 177.5	-
T	106.8 ± 47.9	93.7 ± 37.1	-	LS	LS	LS
AB	611.1 ± 105.9	635.7 ± 154.9	0.001**	LS	LS	LS
RLEG1	1951.0 ± 265.9	1936.1 ± 287.0	-	105.1± 60.2	101.9 ± 60.4	-
RLEG2	3109.8 ± 786.3	3049.7 ± 805.2	-	231.5± 142.2	234.9 ± 153.3	-
RLEGTOT	4935.8 ± 932.2	4861.0 ± 948.8	-	408.8± 188.8	378.9 ± 212.9	-
TRABD	958.7 ± 370.6	1104.6 ± 382.7	0.003**	76.4± 33.3	81.4 ± 39.6	-
RTRALEG	698.7 ± 233.1	698.7 ± 233.1	-	122.2± 56.5	122.4 ± 53.6	-

LS=value no show, for low sensibility to measure Xc, of bioimpedance analyzer
*Statistical significance for $P<0.05$ (bilateral)
** Statistical significance for $P<0.01$(bilateral)

Table 6.9 shows the Mann-Whitney U test result between group 0 and group 1, in each segment, of the parameters RBMI and XcBMI.

Table 6.9- Mann-Whitney U test in a sample of 23 patients (G0:10 and G1:13) undergoing CAPD after fluid exchange (BPD)

Electrode Configuration	*P*(RBMI)	*P*(XcBMI)
RS	-	-
RARM	-	-
T	0.010**	LS
AB	-	LS
RLEG1	-	-
RLEG2	-	-
RLEGTOT	-	-
TRABD	-	-
RTRALEG	-	-

6.3.2 BIVA in CAPD patients

Table 6.10 shows the BIVA parameters BPD and APD in a sample of 10 normo-hydrated and 13 hyper-hydrated patients undergoing CAPD.

Table 6.10-BIVA parameters BPD and APD in a sample of 10 (G0) and 13 (G1) patients undergoing CAPD

	Male-BPD		**Male-APD**	
	Normo-hydrated 22 ≤ BMI < 26 age 30-65	**Hyper-hydrated 26 ≤ BMI < 32 age 30-65**	**Normo-hydrated 22 ≤ BMI < 26 age 30-65**	**Hyper-hydrated 26 ≤ BMI < 32 age 30-65**
Size, N	**10**	**13**	**10**	**13**
BMI, kg/m^2				
Men	24.0	29.5	23.4	28.7
SD	1.9	1.7	1.9	1.7
R/H, Ω/m				
Mean	309.9	240.4	323.5	255.2
SD	29.9	31.4	26.0	26.0
Xc/H, Ω/m				
Mean	31.0	23.7	32.8	25.3
SD	6.2	6.6	6.0	6.0
r(R/H, Xc/H)	0.5	0.5	0.5	0.5
PA, °				
Mean	5.9	5.6	6.2	5.7
SD	1.2	1.6	1.5	1.7

Figure 6.3 shows the confidence ellipses (95 %) for 23 patients in CAPD: 10 normo-hydrated (G0) and 13 hyper-hydated (G1) patients undergoing CAPD, before peritoneal dialysis (BPD) and after peritoneal dialysis (APD).

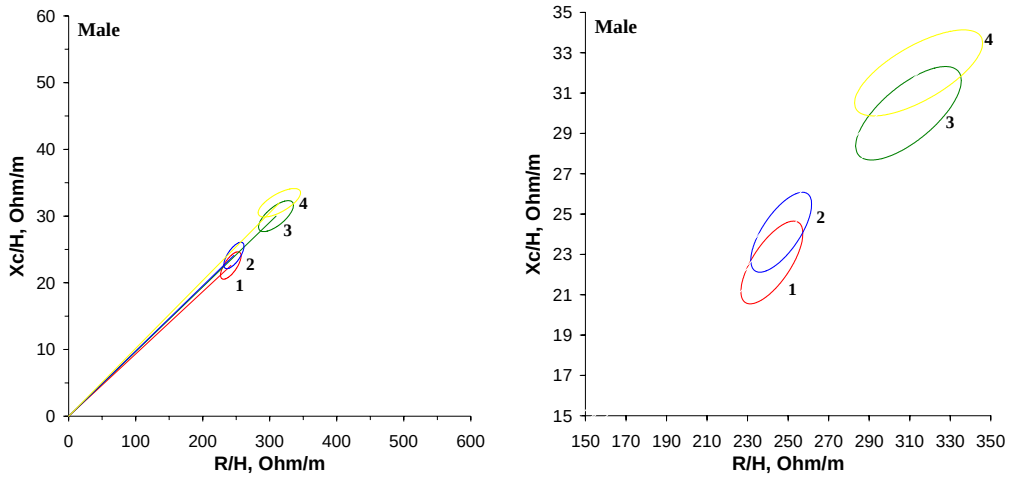

Figure 6.3- Confidence ellipses (95%) for CAPD patients sample: 1= Hyper-hydrtaed BPD, 2= Hyper-hydrated APD, 3= Normo-hydrated BPD, 4= Normo-hydrated APD

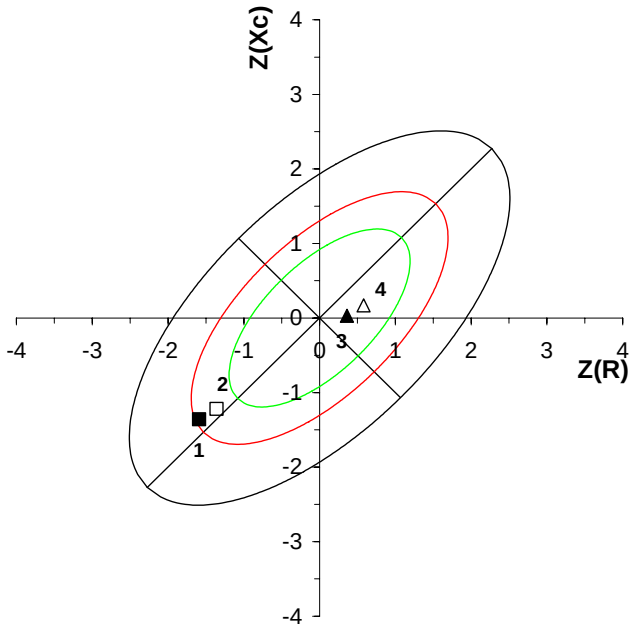

Figure 6.4- Z-score of the standard, reference RXc-score graph (95% confidence interval): 1= Hyper-hydrated BPD, 2= Hyper-hydrated APD, 3=Normo-Hydrated BPD, 4= Normo-hydrated APD

6.3.3 Correlation between Z, Z/H, ZBMI and clinical parameters

Table 6.11 shows the Spearman correlation results between the bioimpedance terms, which have a significative correlation, with clinical assessment (albumin and CRP). All other impedance parameters show a non-significant correlation.

Table 6.11- The Spearman correlation between Z, Z/H and ZBMI (ρ) with clinical parameters in a sample of 23 patients BPD

	RS	**T**	**T/H**	ρ_T	**AB**	**RLEGTOT**	$\rho_{RLEGTOT}$	**RTRALEG**	$\rho_{RTRALEG}$
Albumin (g/L) Rho P	-	0.571* 0.013	0.564* 0.018	0.609** 0.007	0.534* 0.022	-	-	0.633** 0.005	0.498* 0.035
CRP (mg/L) Rho P	0.493* 0.038	-	-	-	0.499* 0.035	-0.520* 0.027	-0.541* 0.020	-	

*Statistical significance for P<0.05 (bilateral)
** Statistical significance for P<0.01(bilateral)
(-): negative correlation

6.3.4 R_{TH}/H vs R_{RS}/H; relation to hydration status and hypertension in CAPD patients through to dM^2

In the second study, the objective is to find out whether segmental bioimpedance of the thoracic region could improve the prediction of overhydration in the thorax region and cardiovascular risk in CAPD patients compared to the standard right-side measurement. Furthermore, we hypothesized that the use of two non-invasive measurements, i.e. segmental thoracic bioimpedance and BP_{mean} could reliably identify patients with overhydrated leading to hypertension volume overload as estimated by clinical assessment. Therefore, we used the Mahalanobis Distance for both of them to classify the patients with respect to a reference standard (the most critical patient).

Clinical parameters of stable and unstable patients are listed in table 6.12 (mean ± SD). All were significantly different by groups of patients (P<0.05). Differences between groups were significant (P<0.01) for R_{TH}/H and less significant (P<0.05) for R_{RS}/H.

We have only considered the real part of the impedance measurement R because the imaginary part X_c showed values below the resolution of the impedance analyzer when measuring the thorax region (<2 Ω).

Table 6.12- Clinical laboratory results, bioimpedance parameters, and Mann-Whitney U test for group 0 (normo-hydrated) and group 1 (hyper-hydrated leading to hypetension) patients

Clinical Status	**SBP (mmHg)**	**DBP (mmHg)**	**BP_{mean} (mmHg)**	**LVMI (gr/m^2)**	**Homoc (umol/L)**	**Cholest. (mmol/L)**	**Triglyc. (mmol/L)**	**Tprot (g/L)**	**Album. (g/L)**	**CRP (mg/L**	**BSR (m/min)**	**BMI (kg/m^2)**	**R_{TH}/H (Ω/m)**	**R_{RS}/H (Ω/m)**
G 0 (n= 10)														
Mean	131.4	76.4	94.7	84.9	12.2	3.9	1.2	64.4	38.3	3.4	12.1	24.5	4.2	306.1
SD	5.3	5.8	3.6	2.7	2.9	0.9	0.6	3.6	3.0	1.9	3.4	1.9	1.1	34.4

G 1 (n = 15)														
Mean	153.3	95.0	110.9	135.3	22.1	5.4	2.0	58.6	31.8	8.3	23.7	29.1	2.1	265.2
SD	6.5	5.0	10.0	3.8	3.2	0.4	0.1	4.1	3.8	1.2	3.4	3.7	0.8	35.9
P	0.002**	0.001**	0.000**	0.001**	0.001**	0.014*	0.016*	0.019*	0.008**	0.017*	0.001**	0.012*	0.000**	0.016*

Differences between groups were tested for statistical significance (P) by Mann-Whitney U-test: ** significant P<0.01; * significant P < 0.05

Table 6.13 shows the individual results for the 25 male patients undergoing CAPD for R_{TH}/H, R_{RS}/H, BP_{mean}, $dM^2(R_{TH}/H, BP_{mean})$, $dM^2(R_{RS}/H, BP_{mean})$ and clinical state (G0: normo-hydrated, G1: hyper-hydrated leading to hypetension).

Table 6.13- Mahalanobis Distance dM^2 calculated through impedance component R_{TH}/H and R_{RS}/H with BP_{mean} for group 0 and group 1

ID	Group #	R_{TH}/H (Ω/m)	R_{RS}/H (Ω/m)	BP_{mean} (mmHg)	$dM^2(R_{TH}/H, BP_{mean})$	$dM^2(R_{RS}/H, BP_{mean})$
7	1	1.16	296.10	120.00	0.00	0.00
3	1	2.42	324.90	110.00	1.14	0.82
14	1	3.05	272.60	110.00	2.01	2.87
10	1	2.91	243.00	106.67	2.12	8.25
13	1	2.89	238.90	133.33	5.12	2.16
16	1	1.14	292.00	96.67	5.14	7.32
23	1	2.87	236.21	110.00	1.71	7.56
27	1	1.39	324.11	96.67	4.80	4.76
24	1	1.18	315.17	96.67	5.08	5.26
26	1	2.48	246.58	106.97	1.59	7.50
30	1	2.25	234.83	120.00	0.77	3.80
33	1	2.07	257.67	120.00	0.54	1.49
31	1	0.59	224.12	113.30	0.88	7.96
2	1	2.25	234.83	110.00	0.99	7.79
18	1	2.37	236.21	113.30	0.84	5.98
12	0	2.52	369.20	90.00	6.97	7.01
6	0	4.14	266.90	96.67	6.29	10.77
11	0	3.75	301.30	93.33	6.49	8.39
9	0	4.73	262.70	100.00	7.31	9.16
1	0	4.60	293.10	93.33	8.31	9.35
8	0	5.20	360.10	100.00	9.01	3.50
15	0	6.25	296.30	90.00	15.18	11.34
21	0	3.07	301.84	93.33	5.70	8.34
28	0	3.53	307.65	93.33	6.17	7.75
17	0	3.68	301.84	96.70	5.35	6.30

Figures 6.6 and 6.7 show the individual R_{TH}/H parameter vs BP_{mean} and R_{RS}/H parameter vs BP_{mean} separated in normo-hydrated (G0) and hyper-hydrated leading to hypertension (G1) groups, respectively. The reference patient used for the Mahalanobis Distance

calculation is also displayed.

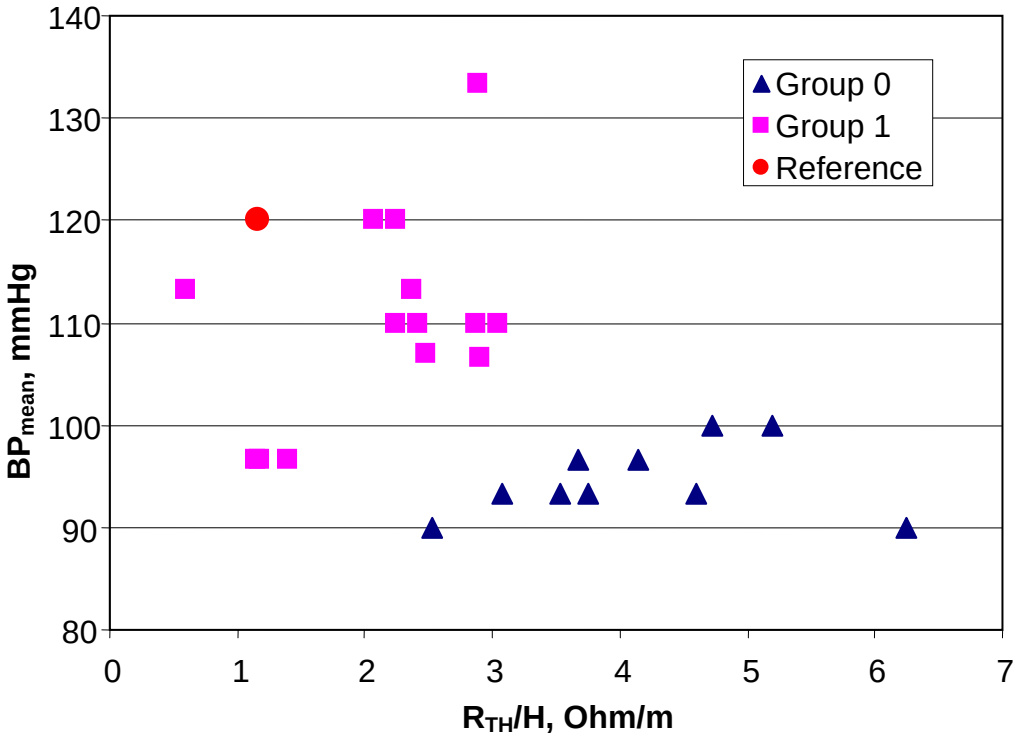

Figure 6.6- Individual R_{TH}/H vs mean blood pressure BPmean

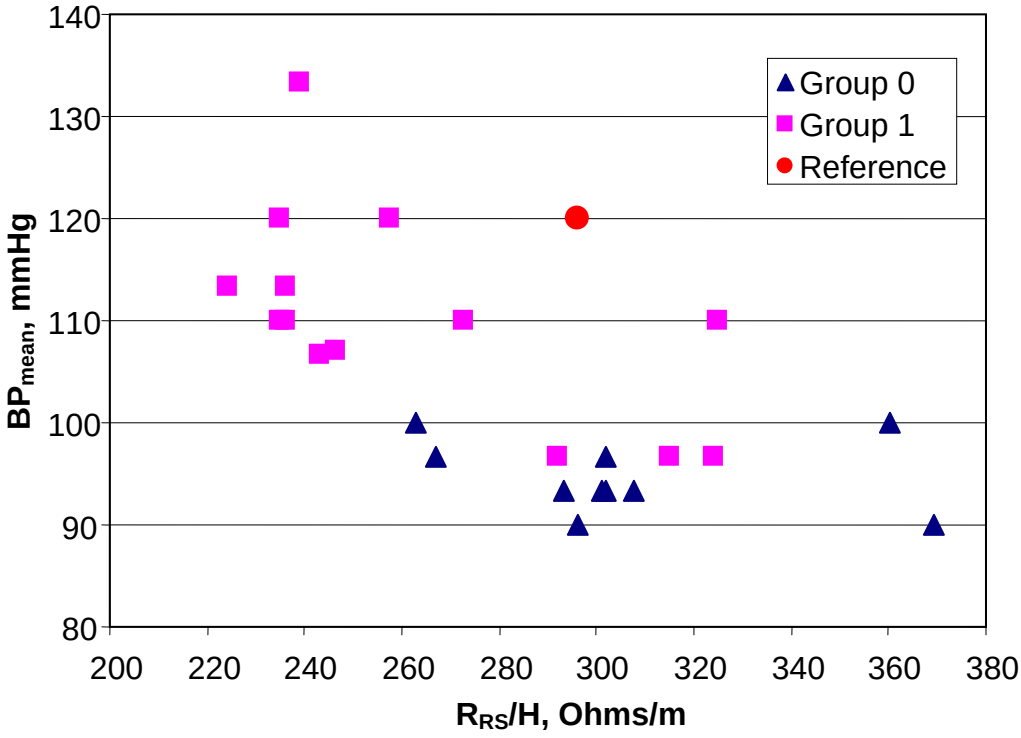

Figure 6.7 Individual R_{RS}/H vs mean blood pressure BP_{mean}

Figure 6.8 shows individual Mahalanobis Distance dM^2 arranged by group. The mean values ± standard deviation of dM^2 using R_{TH}/H and BP_{mean} for hyper-hydrated leading to hypetension (group 1) and normo-hydrated (group 0) patients were 2.18±1.87 and 7.67±2.86, respectively, and significantly different within groups (P<0.0001). Using R_{RS}/H and BP_{Mean} the mean±SD for unstable and stable patients were 4.90±2.87 and 8.19±2.26, respectively. In this case the significance of the difference between groups was lower (P=0.009). Figure 6.9 show all the parameters analyzed in the second study.

Table 6.14 shows a statistically significant difference (P<0.05) of mean vectors (R_{TH}/H, BP_{mean}) and (R_{RS}/H, BP_{mean}) between groups (0 and 1) through Hotelling's T^2 test.

Table 6.14- Hotelling's T^2 test in a sample of 25 male patients before CAPD (G0: 10 normo-hydrated, G1: 15 hyper-hydrated leading to hypertension patients)

G1 vs G0 (R_{RS}/H, BP_{mean})			**G1 vs G0** (R_{TH}/H, BP_{mean})		
R_{RS}/H SDx	**BP_{mean} SDy**	**r(YX)**	**R_{TH}/H SDx**	**BP_{mean} SDy**	**r(YX)**
35.3	8.1	-0.5	0.9	8.1	-0.5
P < 0.05			**P < 0.05**		

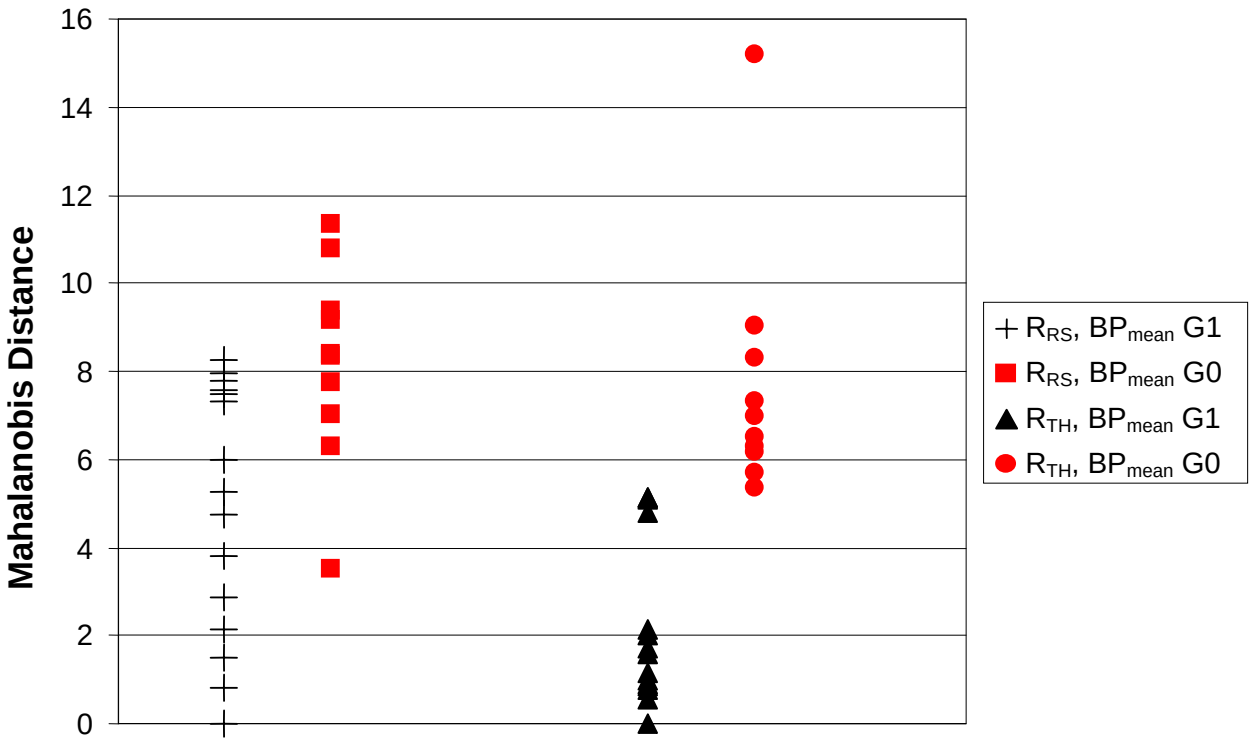

Figure 6.8- Individual Mahalanobis Distance dM^2 by group (G0 and G1) for whole body $dM^2(R_{RS},BP_{mean})$ and for thorax segment $dM^2(R_{TH},BP_{mean})$

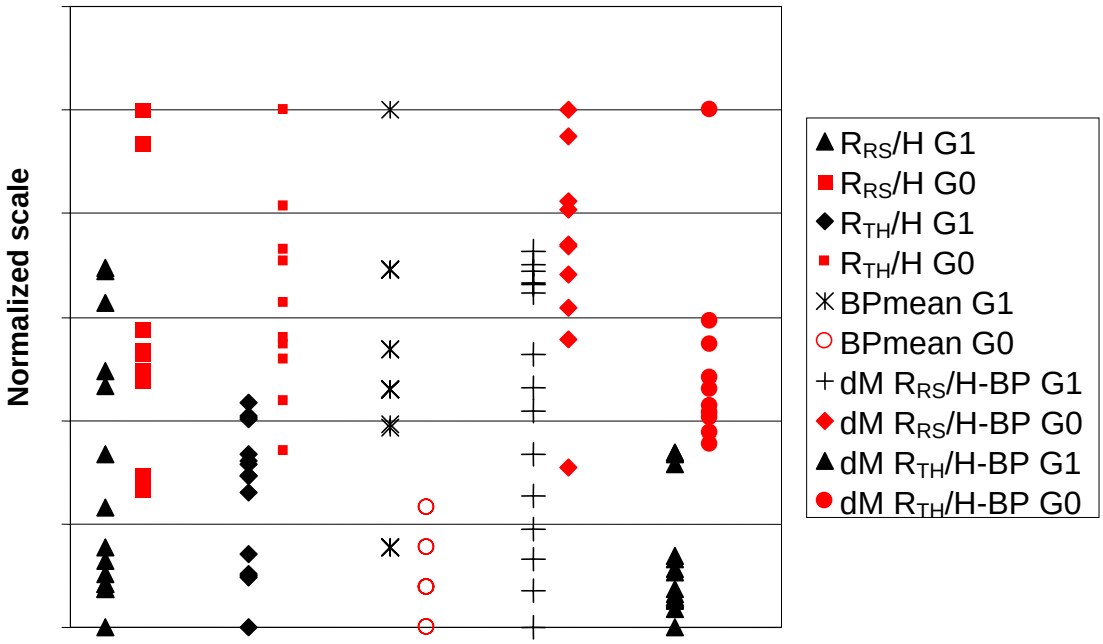

Figure 6.9- R_{RS}/H, R_{TH}/H, BPmean and Mahalanobis Distance dM^2 by groups (G0: normo-hydrated, G1:hyper-hydrated leading to hypertension)

6.4 Discussion

The real part of impedance R (table 6.1 and 6.2) is more sensible to detect fluid change (APD-BPD) than R/H or RMBI. R has detected statistical significant diferences in the segments: RS, AB, RLEG1, RLEG2, RLEGTOT and TRABD. Nevertheless, R/H (table 6.4 and 6.5), or RBMI (table 6.7 and 6.8) show statistical significant diferences only in abdomen segments (AB and TRABD). However, for Z/H measured in the right-side the confidence ellipses for BPD and APD overlap, showing a non significative difference in fluid change, see figure 6.3.

Piccoli et al (2004) offer a new operative definition for the optimal hydration in continuous ambulatory peritoneal dialysis (CAPD) patients. The Z/H vector in CAPD patients with hyperhydration are into the 75 % reference ellipse (overhydration across the lower pole). In Figure 6.4 the hyper-hydrated patients (group 1) are located into the 75 % reference ellipse of Z-Score (Piccoli et al 2002-c). As we can see in Table 6.3 and 6.6 respectively, only R and R/H are capable to identify correctly both groups of patients (table 6.9).

Segmental impedances differentiate both patients groups better than transversal measurements (tables 6.3 and 6.6). Using ZBMI only the real part in the thorax region could differentiate both groups (table 6.9).

In a previous work, we have shown that there is a strong correlation between mortality and volume overload as detected by BIVA in patients undergoing maintenance HD (Nescolarde et al 2002, 2004-a, 2004-b). Some segments such as: RS, T, T/H, ρ_T, AB, RLEGTOT, $\rho_{RLEGTOT}$, RTRALEG and $\rho_{RTRALEG}$ show significant correlations with clinical assessment of nutrition (albumin) and inflammation (CRP) as we show in table 6.11. The parameters ρ_T, $\rho_{RLEGTOT}$ and $\rho_{RTRALEG}$ show a statistical significant correlation. The transversal measurement in the right-leg (RTRALEG) offer the best statistically significant correlation with Albumin, and only in this case the use of $\rho_{RTRALEG}$. does not improve the correlation. This could be explained because the resistivity factor is defined for a cylindrical geometry and not for tranversal measures.

Overt or more frequently, subclinical volume overload is a frequent complication of PD, associated with hypertension and increased cardiovascular morbidity and mortality (Khandelwal *et al* 2003). The present study was performed to find out whether segmental bioimpedance of the thoracic region could correctly predict a hyperhydration in the thorax region and, consequently, cardiovascular risk in CAPD patients.

PD represents an ideal model for studying isolated, localized changes in body fluid. Song *et al* (1999) analyzed the characteristics of fluid shift of each body segment in CAPD and showed that each body segment of the CAPD patient has its own characteristic pattern of fluid shift in response to PD fluid exchange. It has been proposed that more relevant information of the fluid changes in PD might be obtained with segmental bioimpedance measurements rather than using right-side or "whole-body" configurations which are commonly used in HD patients (Ellis 2000). It could indeed be demonstrated that the changes in fluid volume in the trunk cannot be adequately monitored with conventional right-side BIA, but are correctly estimated by segmental bioimpedance (Zhu *et al* 2000). We provide here preliminary evidence that segmental bioimpedance of the thoracic region has better agreement than right-side with the clinical assessment of high-risk patients.

Table 6.12 shows that mean values between both groups are significantly different for R_{TH}/H ($P<0.0001$) and for R_{RS}/H ($P=0.016$). Table 6.14 shows a statistically significant

difference ($P<0.05$) of mean vectors (R_{TH}/H, BP_{mean}) and (R_{RS}/H, BP_{mean}) between groups (0 and 1) through Hotelling's T^2 test. However, comparing the individual values in table 6.13 (or figure 6.6 and 6.7) could be seen that the overlap between groups is bigger for R_{RS}/H than for R_{TH}/H. This reveals that the difference between groups in the hydration state in the thorax region is bigger than the difference in whole-body hydration state measured using R_{RS}/H.

Figures 6.6 and 6.7 show that the addition of another non-invasive parameter BP_{mean} makes possible a better separation of both patient groups. Figure 6.6 gives the impression that BPmean could separate both groups, but looking at figure 6.7, it is clear that there is an overlap of both groups if you only use the BPmean. Figure 6.8 shows that using dM^2 both groups are separated using the thorax or the right-side measurement. Nevertheless, the mean difference between groups is greater using R_{TH}/H than using R_{RS}/H.

Hyper-hydrated patients with an increased risk for CVD (group 1) by medical criteria showed smaller Mahalanobis Distance (dM^2) than normo-hydrated patients (group 0), table 2. Patients with the smallest Mahalanobis distances showed similar clinical characteristics as the reference patient, (see table 1). Piccoli *et al* (1998) showed that subjects with hyperhydrated states have a low R_{RS}/H while subjects with dehydration states have a higher R_{RS}/H. In this study, we have shown that the use of R_{TH}/H improves the identification of patients with hyper-hydration in the thorax region compared with the right-side measurements. Furthermore, the use of R_{TH}/H and BP_{mean} allowed the correct identification of all clinically unstable patients. A close examination of table 2 shows that BP_{mean} is higher in these subjects but the two groups are not completely separated. For example, the subjects 16, 27 and 24 have a lower BP_{mean} than subjects 8 and 9. On the other side, the mean value of R_{TH}/H is lower in group 1 than in normo-hydrated patients. This suggests a higher hydration in the thorax region for these subjects. The two groups could be completely separated using the Mahalanobis Distance between R_{TH}/H and BP_{mean}.

6.5 Conclusion

The first study show that the term R has more sensibility to detect the changes produced by a dialysis session (APD - BPD) that if we used other terms such as R/H or RBMI. The use of ZBMI is not a good index for the detection of fluid changes because it gives information about the specific resistivity of tissues and not to fluid and fat mass changes, this is only true for a cylindrical geometry. We confirm that the BIVA method (Z/H, righ-side

measurements) in CAPD patients could be useful to separate hyper-hydrated patient (in whole body) and normo-hydrated patients, as we can see in Piccoli et al (2004). Also, the segmental impedance of the thorax shows good ability to separate both patients groups.

Taking into account the correlation with clinical parameters, we could see that the transversal impedance measurement in the right leg (RTRALEG) offer the best statistically significant correlation with Albumin. Also, the use of ZBMI increases the correlation with clinical assessment of nutrition (albumin) for the thorax segment and with inflammation (CRP) for the right leg.

In consequence, to apply at the same time BIVA and segmental measures, could be an alternative method to know the hydric and nutritional state in CAPD patients.

The second study indicates that the resistance of the segmental impedance of the thoracic region can identify overhydrated patients with an increased risk for CVD more accurately than right-side measurements. Using the resistance of the thorax region in conjunction with calculated mean blood pressure allows a complete separation between hyper-hydrated leading to hypertension and normo-hydrated groups. Further studies are needed to establish the confidence levels of agreement between the value obtained by segmental measures of electrical resistance at 50 kHz and BP_{mean} and the clinical state of the patients.

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