

## Usefulness of bioelectrical impedance analysis for monitoring patients with refractory ascites

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### ABSTRACT

**Background:** bioelectrical impedance analysis is a technique for the determination of the hydropic component. The hydropic component, determined by blood volume, could be a reflection of the hemodynamic situation. This study aimed to evaluate the usefulness of peripheral bioelectrical impedance analysis (BIA) for the prediction of hemodynamic changes in large-volume paracentesis and prognosis.

**Methods:** this was a proof-of-concept prospective study of 14 patients with liver cirrhosis and refractory ascites. Peripheral bioimpedance was measured three times using a portable device, IVOL<sup>®</sup>, before and after large-volume paracentesis, at different frequencies (5, 10, 20, 50, 100 and 200 kHz). Consequently, resistance, reactance and phase angle were obtained, both pre- and post-paracentesis (the difference between them was defined as  $\Delta$ ).

**Results:** the mean age of patients was  $62.2 \pm 9.6$  years, the Child-Pugh was  $8.4 \pm 1.3$  and the MELD score was  $15.2 \pm 3.9$ . A direct correlation between the extraction of ascitic fluid and  $\Delta$ resistance (10 kHz [ $r = 0.722$ ;  $n = 12$ ;  $p = 0.008$ ], 20 kHz [ $r = 0.658$ ;  $n = 12$ ;  $p = 0.020$ ] and 50 kHz [ $r = 0.519$ ;  $n = 14$ ;  $p = 0.057$ ]) was observed. The presence of edema was related to lower values of both pre-paracentesis resistance (10 Hz [ $23.9 \pm 8$  vs  $32.2 \pm 4$ ;  $p = 0.043$ ]) and phase angle (5 kHz [ $-1.9 \pm 2.8$  vs  $5.9 \pm 7.3$ ;  $p = 0.032$ ]). Pre-paracentesis phase angle was directly correlated with the decline in blood pressure after paracentesis at lower frequencies (5 kHz [ $r = 0.694$ ;  $n = 13$ ;  $p = 0.008$ ] and 10 kHz [ $r = 0.661$ ;  $n = 13$ ;  $p = 0.014$ ]). Lower frequencies of  $\Delta$ phase-angle impacted on patient prognosis (5 kHz [ $-8.6 \pm 5$  vs  $-2.5 \pm 2.7$ ;  $p = 0.021$ ]), patients with  $\Delta$ phase-angle 5 kHz  $> -4$  had a higher rate of mortality (83.3% [5/6] vs 0% [0/6]; logRank 7.306,  $p = 0.007$ ).  $\Delta$ resistance values were associated with overt HE at six months (10 kHz [ $4.9 \pm 2.5$  vs  $-0.4 \pm 4.7$ ;  $p = 0.046$ ]).

**Conclusions:** in conclusion, a significant correlation between peripheral impedance and hemodynamic changes was found. Impedance was also significantly related to prognosis and overt hepatic encephalopathy.

**Key words:** Cirrhosis. Refractory ascites. Bioelectrical analysis. Bioimpedance. Paracentesis.

### INTRODUCTION

Patients with liver cirrhosis frequently develop a hyperdynamic circulation (1), which is characterized by a fall in peripheral vascular resistance and a compensatory increase in cardiac output (2). Hemodynamic alterations may eventually result in acute (hepatorenal syndrome) or chronic complications (refractory ascites) (3,4). In addition, paracentesis-induced circulatory dysfunction (PICD) is a well-documented risk for hemodynamic dysbalance in cirrhotic patients, especially those that require periodically large volume paracentesis (4). Different methods are used to evaluate hemodynamic parameters in cirrhotic patients, from invasive (based on transpulmonary thermodilution that is reserved for critical patients) to non-invasive techniques (such as transthoracic echocardiography) (5,6).

Bioelectrical impedance analysis (BIA) is a simple technique for the determination of body water and body composition (7). This technique obtains measurements such as resistance (R) and reactance (Xc). The combination of these parameters is used to calculate the phase angle (PA), which is directly related to the composition of the tissues and the presence of intra and extracellular water (8,9). These values can be determined at a single frequency (SF-BIA) or multiple frequency (MF-BIA). MF-BIA has been shown to be more accurate for the determination of total body water (TBW) and extracellular fluid (ECF) (10). The hydropic component is determined by blood volume and could therefore be a reflection of the hemodynamic situation. In fact, it has been demonstrated that patients with decompensated have

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a greater amount of extracellular water in the limbs compared to compensated cirrhotics (11). PA, which is the most established BIA parameter for the diagnosis of malnutrition and clinical prognosis, is based on changes in cellular membrane integrity and alterations in fluid balance. For instance, PA has been associated with mortality in cirrhotic patients by a whole-body BIA at 50 kHz (12-14).

Due to the marked alteration in the intra- and extravascular hydropic component in patients with cirrhosis and refractory ascites, this study aimed to evaluate the usefulness of peripheral BIA for the prediction of hemodynamic changes in large-volume paracentesis. Furthermore, its relation to the incidence of cirrhosis complications and survival was also assessed.

## METHODS

### Study design

This was a prospective proof-of-concept study of 14 patients with liver cirrhosis and refractory ascites. Patients were enrolled in 2016, at the time of the first BIA and followed over a twelve month period. Refractory ascites were defined as ascites that cannot be mobilized with diuretics or early recurrence which cannot be satisfactorily prevented by medical therapy due to side effects, as established by the International Club of Ascites. Therefore, all patients were on a periodic large-volume paracentesis program followed by an intravenous infusion of albumin (6-8 g/l of ascites removed) from 5 l extracted (4). None of the patients were candidates for a liver transplantation and no other causes of ascites, such as cardiac or renal insufficiency, were found in these patients.

Demographic and anthropometric characteristics, as well as salt and alcohol consumption, were analyzed. The etiology of cirrhosis and treatment with diuretics and beta-blockers were also recorded. Furthermore, the presence of peripheral edema or venous insufficiency in the lower limbs were recorded, discarding the presence of spontaneous bacterial peritonitis in all patients. Liver function was assessed using the Child-Pugh scale and the MELD score. The time from the first documented episode of ascites and the time that large-volume paracentesis was required were also taken into account.

All patients provided written informed consent and all data (including clinical, demographic and test results) were coded and deposited in the original clinical database. The Ethics Committee of the Hospital Universitario Virgen del Rocío approved the protocol and it was extended to the rest of participating centers. The study was conducted according to the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

### BIA assessment

Peripheral bioimpedance was measured using a portable device, IVOL<sup>®</sup> (Talemology S.L., San Juan de Aznalfarache, Sevilla, Spain). Measurements were obtained in a supine position by applying a low-intensity electric current be-

tween two pairs of electrodes, which were placed vertically on the outer side of the right lower limb, 2 cm above the external epicondyle of the ankle. Three measurements were performed, before and after paracentesis, at different frequencies (5, 10, 20, 50, 100 and 200 kHz). The mean value was used as the definitive result. Consequently, resistance (R), reactance (Xc) and phase angle (PA) were obtained, both pre- and post-paracentesis (the difference between them was defined as  $\Delta$ ).

### Assessment of outcome

All the results were divided into two groups, those related to paracentesis and those related to cirrhosis complications. Blood pressure (including systolic, diastolic and mean arterial pressure) and heart rate were determined three times, before and four hours after the paracentesis (the difference between them was defined as  $\Delta$ ) in order to establish the potential impact of the magnitude of the changes in body homeostasis. The mean values of pre and post-paracentesis measures were taken into account for the analysis. The volume of fluid extracted and replacement with albumin were recorded; the presence of spontaneous bacterial peritonitis (SBP) was routinely ruled out. The following laboratory parameters were collected the day of paracentesis: total bilirubin, international normalized ratio (INR), creatinine, alanine transaminase (ALT), cholinesterase, albumin, platelets and sodium.

Furthermore, cirrhosis outcome was collected during follow-up, including hepatic encephalopathy (HE), variceal bleeding, SBP, kidney failure and hepatocellular carcinoma. All events were classified as short- (occurring within six months) or long-term (occurring within twelve months) depending on the time of appearance. Thus, patients were followed-up for a period of twelve months or until death.

### Statistical analysis

Statistical analysis was performed by a biomedical statistician using SPSS (version 21.0; SPSS, Inc., Chicago, IL). The Chi-square test and the Fisher's exact test (F) when necessary were used for qualitative variables. The Student's t-test (t) was used when the distribution was normal for quantitative variables and the Mann-Whitney U test was used when the distribution was non-normal. The association between different quantitative variables was evaluated using the Pearson's or Spearman's correlation. The area under the ROC curve (AUROC) was computed in order to determine the diagnostic accuracy of the BIA measurements for predicting mortality. Survival curves were compared using the Kaplan-Meier method (log-rank test), as time-to-mortality and time-to-event are crucial for interpreting the results. Statistical significance was set at  $p < 0.05$ . The statistical methods of this study were reviewed by the corresponding author.

## RESULTS

### Baseline features of the overall cohort

Ninety percent (13/14) of the patients were male, with a mean age of  $62.2 \pm 9.6$  years. Child-Pugh was  $8.4 \pm 1.3$  and

the MELD score was  $15.2 \pm 3.9$ . The main etiology was alcoholic cirrhosis (78% [11/14]) and 14% (2/14) and 7% (1/14) of patients suffered from chronic HCV and HBV infection, respectively. With regard to cirrhosis-related complications, all patients had esophageal varices, 64% (9/14) had experienced a prior episode of variceal bleeding and one patient had a previous history of SBP and hepatorenal syndrome; 42% (6/14) of the overall cohort had hepatocellular carcinoma. With regard to treatment, half of the patients consumed diuretics (57% [8/14]) and 35% (5/14) used beta-blockers. Alcohol consumption was unusual (7% [1/14]), although salt intake was common (85% [12/14]). At enrollment, patients had required large-volume paracentesis for ten months (1-56), with a median interval of time between treatments of  $13.4 \pm 4.9$  days. The mean volume of ascites fluid extracted was  $8.4 \pm 4$  liters.

### The role of peripheral BIA during the paracentesis

In the overall population, significant differences were found between pre- and post-paracentesis measurements according to PA at lower frequencies (Table 1). Furthermore, a direct correlation was observed between the extraction of ascitic fluid and  $\Delta R$  (10 kHz [ $r = 0.722$ ;  $n = 12$ ;  $p = 0.008$ ], 20 kHz [ $r = 0.658$ ;  $n = 12$ ;  $p = 0.020$ ] and 50 kHz [ $r = 0.519$ ;  $n = 14$ ;  $p = 0.057$ ]). The presence of edema was related to lower values of both pre-paracentesis R (10 kHz [ $23.9 \pm 8$  vs  $32.2 \pm 4$ ;  $p = 0.043$ ]) and PA (5 kHz [ $-1.9 \pm 2.8$  vs  $5.9 \pm 7.3$ ;  $p = 0.032$ ]) (Fig. 1). However, neither  $\Delta R$  nor  $\Delta PA$  were influenced by the presence of edema. On the other hand, both salt consumption and diuretic use did not impact on the BIA measurements. Post-paracentesis R values at all frequencies were related with the number of days since the previous paracentesis. However, all of these measurements were not associated with the time interval to the subsequent paracentesis requirement.

### The role of peripheral BIA and hemodynamic changes

The mean arterial pressure before paracentesis was  $91 \pm 12$  mmHg and the final value after was  $81 \pm 10$  mmHg ( $-10 \pm 9$  mmHg;  $p = 0.001$ ). In contrast, the heart rate did not show significant differences; pre-paracentesis  $82 \pm 14$  vs  $83 \pm 12$  bpm ( $p = 0.807$ ). Pre-paracentesis PA was directly correlated with a decline of blood pressure after paracentesis at lower frequencies (5 kHz [ $r = 0.694$ ;  $n = 13$ ;  $p = 0.008$ ] and 10 kHz [ $r = 0.661$ ;  $n = 13$ ;  $p = 0.014$ ]). In fact, 88.9% (8/9) of patients

with a pre-paracentesis PA 5 kHz of  $< 5$  suffered from a significant drop of at least 7 mmHg in the mean arterial pressure after paracentesis (Fig. 2). In addition, there was a trend with the variation in cardiac frequency (5 kHz [ $r = 0.493$ ;  $n = 13$ ;  $p = 0.087$ ] and 10 kHz [ $r = 0.490$ ;  $n = 13$ ;  $p = 0.089$ ]). There was no correlation between  $\Delta PA$  and  $\Delta TA$ , probably due to the fact that patients with pre-paracentesis PA values  $> 5$  did not show a significant drop in mean arterial pressure. Furthermore, the small number of patients included in the study meant that this correlation could not be demonstrated.

### Prognostic value of peripheral BIA

There were nine episodes of overt HE during follow-up, five events of acute kidney injury, three episodes of SBP (two also suffered a variceal bleed) and one event of variceal bleeding and hepatorenal syndrome. In addition, seven patients died within 12 months of follow-up, all due to complications derived from their liver disease.

One-year survival was influenced by BIA measurements. In particular, lower frequencies of  $\Delta PA$  impacted on the prognosis of the patients (5 kHz [ $-8.6 \pm 5$  vs  $-2.5 \pm 2.7$ ;  $p = 0.021$ ])

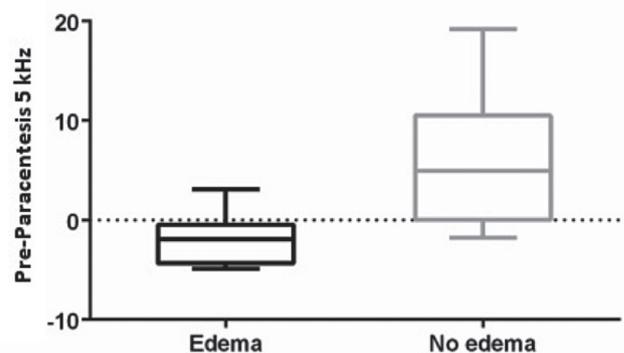


Fig. 1. Pre-paracentesis PA 5 kHz value depending on the presence of edema.

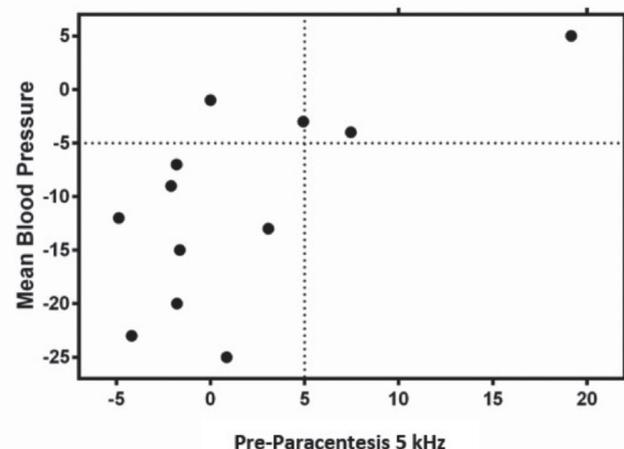


Fig. 2. Relation between PA 5 Hz value and arterial pressure after paracentesis.

Table 1. Dynamic changes of PA during the paracentesis

PA frequency	Pre-paracentesis	Post-paracentesis	Univariable analysis
5 Hz	$2.28 \pm 6.80$	$-2.16 \pm 2.34$	$p = 0.004$
10 Hz	$-1.02 \pm 2.04$	$-3.23 \pm 1.32$	$p = 0.002$
20 Hz	$-3.21 \pm 1.29$	$-4.64 \pm 1.79$	$p = 0.006$
50 Hz	$-5.80 \pm 1.59$	$-6.44 \pm 1.75$	$p = 0.254$
100 Hz	$-7.41 \pm 1.54$	$-7.32 \pm 1.50$	$p = 0.278$
200 Hz	$-9.46 \pm 1.60$	$-8.70 \pm 1.69$	$p = 0.139$

and 10 kHz [ $-3.6 \pm 2.2$  vs  $-1.4 \pm 1.3$ ;  $p = 0.052$ ]). According to ROC analysis (AUROC 0.91 [95%CI 0.74-1.00];  $p = 0.019$ ), those patients with  $\Delta PA$  5 kHz  $> -4$  had a higher mortality rate (83.3% [5/6] vs 0% [0/6]; log rank 7.306,  $p = 0.007$ ) (Fig. 3). The remaining outcomes, including all cirrhosis complications, were not influenced at 12 months by BIA measurements. However,  $\Delta R$  values were associated with overt HE at six months (10 kHz [ $4.9 \pm 2.5$  vs  $-0.4 \pm 4.7$ ;  $p = 0.046$ ]). In contrast, other complications, including survival, were not linked to BIA measurements during the short-term follow-up.

## DISCUSSION

BIA has been evaluated in the cirrhotic population in many studies, although there is a lot of heterogeneity due to several reasons: a) the frequency used (single-frequency vs multi-frequency analysis); b) the type of BIA (whole-body vs segmental analysis); and c) the aim, as most studies were performed to detect nutritional deficiencies in liver diseases (15,16), although other studies aimed to assess the potential utility for predicting prognosis and cirrhosis outcome (17). On the other hand, monitoring the hemodynamic status of decompensated cirrhotic patients is underused, due to inaccessibility and cost (i.e., echocardiography). Thus, the evaluation is based on the blood pressure (including systolic, diastolic and mean blood pressure) and heart rate, which grossly reflect the cardiovascular unbalance in these patients. However, they are not useful in situations of severe decompensation, such as refractory ascites (18). Based on the evidence compiled, we conducted a pilot study in patients with refractory ascites to assess the applicability peripheral and multi-frequency BIA measurements on paracentesis-related hemodynamic changes and prognosis.

Decompensated cirrhotic patients with refractory ascites can be exposed to paracentesis-induced circulatory dysfunction (PICD) after a large-volume paracentesis. This is definitively diagnosed via laboratory results, with increases of more than 50% of baseline plasma renin activity to  $>4$  ng/ml/h on the 5<sup>th</sup> to 6<sup>th</sup> days after paracentesis. Therefore, early detection and treatment of PICD are essential to decrease the paracentesis-related mortality and morbidity (19). The

management of PICD is standardized, including the infusion of albumin to prevent the risk of renal impairment and mortality by preventing systemic hemodynamic alterations (20). In addition, other drugs have been tested such as midodrine (21) or terlipressin (22). However, there is little information about how to anticipate PICD and its prognosis with non-invasive tests. In this study, we found a significant correlation between peripheral BIA (pre-paracentesis PA at 5 and 10 kHz) and hemodynamic changes, including mean blood pressure and cardiac frequency. However, we did not determine the values of plasma renin activity in order to reliably establish the PICD diagnosis. This was mainly due to the lack of financial support, and these hemodynamic changes occur at the beginning of the cascade of deleterious effects caused by large-volume paracentesis (LVP), which in some cases will end in PICD. In particular, most of the patients (89%) with a pre-paracentesis PA 5 kHz lower than 5 showed a consistent decrease in mean arterial pressure. Pre-paracentesis measurements are highly relevant as they could allow the prediction of the risk of PICD before starting the procedure. For instance, it could help to determine how many liters of ascitic fluid should be evacuated in order to prevent paracentesis-related complications. Further research is needed to properly establish the relationship of this measure with PICD. However, the results extracted from this study open a new door in the management of patients with refractory ascites.

Decompensated cirrhotic patients with refractory ascites in a large-volume paracentesis program have a poor prognosis (up to 50% of 1-year mortality) if they do not undergo liver transplantation (23). Therefore, clinicians need non-invasive tools that can predict short- and mid-term prognosis in this population. In this setting, we found that  $\Delta PA$  at lower frequencies (5 kHz and 10 kHz) was related to mortality within 12 months of follow-up. In particular, there were no fatal events in patients with  $\Delta PA$  5 kHz  $< -4$ . In addition,  $\Delta R$  was able to predict overt hepatic encephalopathy within six months. Therefore, the peripheral BIA measurement could help, not only to decrease the risk of paracentesis-related outcomes but also to predict some cirrhosis-related complications.

This study was designed as a prospective proof-of-concept study. Therefore, a limited sample size was included and, consequently, our conclusions must be validated in larger populations. In addition, some circumstances (peripheral edema) could result in variations in BIA values in cirrhotic patients. Therefore, a subgroup analysis will probably be needed. Furthermore, the results regarding the prognostic value of the device must be carefully considered as almost half of the population of the study (42%) had hepatocarcinoma at the time of inclusion. This condition deeply influences the survival of these patients. In contrast, this study had several strengths. First, the BIA measurement included a multi-frequency analysis that was not frequent in previous studies. Particularly, lower frequencies (5 and 10 kHz) influenced the outcome much more than higher values (data not shown, apart from table 1). This is a relevant issue as the majority of the studies of BIA in cirrhotic patients were performed with a frequency of 50 kHz (12-16,24,25). Second, the peripheral BIA measurement (based on a small and portable device) is a quick and bedside test which can be used easily and repeatedly, both in the outpatient clinic and during hospitalization.

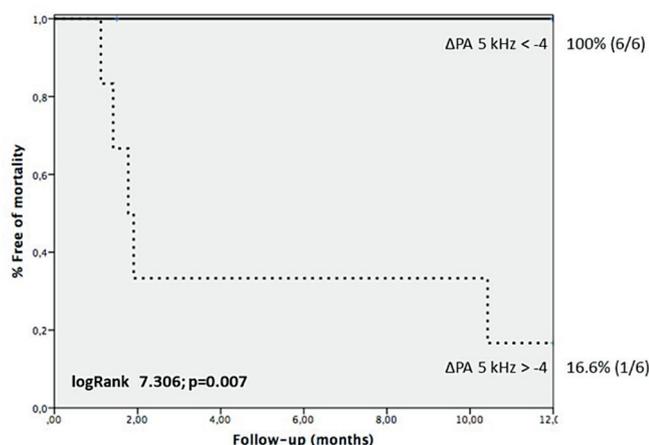


Fig. 3. Kaplan-Meier survival curve at one year according to the  $\Delta PA$  5 kHz value.

Peripheral BIA measurements, particularly PA at lower frequencies, is a simple and quick bedside test that provides useful information for the management of patients with refractory ascites. This technique could lead to a safer large-volume paracentesis and determine a subgroup of patients at risk of short-term hepatic encephalopathy and death.

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