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ORIGINAL PAPER

Bioelectrical Impedance Analysis for the Evaluation of Hepatic Fibrosis in Patients with Chronic Hepatitis C Infection

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Abstract Bioelectrical impedance analysis (BIA) is a non-invasive technique that measures electrical resistance (*R*) and reactance (*Xc*), which are then used to calculate phase angle (*PA*). The aim of this pilot study was to assess whether BIA can differentiate between minimal and advanced hepatic fibrosis in patients with chronic hepatitis C (HCV) infection. Twenty patients with HCV participated in this study, and were divided into minimal (Metavir 1) and advanced (Metavir 3 or 4) fibrosis groups. We obtained BIA measurements (*R* and *Xc*) in several axes and calculated *PA* from each pair of measurements. We found no statistically significant differences between the two groups with respect to *PA*, *R*, or *Xc* for the whole body, the trunk or the right upper quadrant measurements in any axis. Mean whole body *PA* was 7.0 and 7.1 ($P = 0.9$) in the minimal and advanced fibrosis groups, respectively. Bioelectrical impedance analysis did not demonstrate the ability to distinguish between minimal and advanced degrees of hepatic fibrosis in patients with chronic HCV infection.

Keywords Fibrosis · Liver · Bioelectrical impedance · Chronic hepatitis C

Introduction

The degree of hepatic fibrosis in patients with chronic liver disease has several prognostic and therapeutic implications [1, 2]. It can be an important factor when making treatment decisions in patients with chronic hepatitis C (HCV) infection. The evaluation of hepatic fibrosis has traditionally required the performance of a needle biopsy of the liver [3, 4]. This procedure, which can be performed by the percutaneous or transjugular routes, carries a small but definite risk of complications [5–7]. Several non-invasive methods for the determination of hepatic fibrosis, including serum panels, magnetic resonance imaging, and ultrasound scanning techniques, have recently been evaluated [8–13]. All of these methods have a limited accuracy and none has yet replaced liver biopsy as the gold standard [3, 14].

Bioelectrical impedance analysis (BIA) [15] is an easily-performed non-invasive technique that measures electrical resistance (*R*) and reactance (*Xc*) to the passage of a low-voltage, high-frequency electrical current through tissues. Phase angle (*PA*) is calculated as the arctangent of the ratio of these two variables. It can be interpreted as an indicator of water distribution between the extra-cellular and intra-cellular spaces. However, the relationship of BIA to body composition is indirect and not completely understood. BIA has been studied in several different illnesses and *PA* was found to negatively correlate with prognosis in many conditions including advanced neoplastic disease, decompensated liver cirrhosis, chronic obstructive pulmonary disease, hemodialysis, and HIV infection [16–21]. The aim of this pilot study was to assess whether BIA can be used to

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differentiate minimal from advanced hepatic fibrosis in patients with chronic HCV infection.

Methods

Subjects

Study subjects were recruited from the patients evaluated in the hepatology clinic of the Henry Ford Health System (Detroit, MI, USA). Inclusion criteria were age $\geq$ 18, chronic hepatitis C infection, and a liver biopsy performed within the last 18 months. Exclusion criteria included decompensated liver disease, peripheral edema, hepatocellular carcinoma, active alcohol abuse, co-infection with hepatitis B or human immunodeficiency virus (HIV), hemodialysis, and unwillingness to participate in the study. We also excluded patients for whom there was evidence of advanced liver disease, such as decreased albumin levels or malnutrition. As BIA measurements were obtained in a supine position, the inability to lie flat for 5 min was also an exclusion criterion. The study received approval from our Institutional Review Board (IRB) and all study subjects signed informed consent.

Liver biopsy

All patients had a liver biopsy in the preceding 18 months as part of their evaluation at the hepatology clinic. The biopsies were interpreted by multiple pathologists and described using the Metavir scoring system [22]. The degree of fibrosis was assessed by a review of the pathology reports. The patients were divided into a minimal fibrosis group (fibrosis score of 1) and an advanced fibrosis group (fibrosis score of 3 or 4). None of the patients received anti-viral therapy prior to BIA measurements.

Bioelectrical impedance analysis (BIA)

The Quantum X impedance analyzer (RJL Systems, Clinton Twp, MI, USA) was used for the BIA measurements. This device is commercially available and is approved by the US Food and Drug Administration (FDA) as an impedance plethysmograph. The BIA measurements were obtained, after 10 min of rest, with the study subjects lying supine on an examination table with their arms and legs slightly apart to avoid contact with the torso. A tetrapolar electrode configuration was used, with the signal electrodes placed on the right hand and foot in a standardized fashion, while the detection electrodes were moved to the area of interest for each pair of measurements. We measured the resistance (R) and reactance (Xc) for the whole body, the trunk, and also in the right upper quadrant of the abdomen in the horizontal, vertical, and sagittal directions. Age, gender, height, and weight were recorded for each study subject.

Statistical analysis

A sample size of 10 in each group was arbitrarily chosen for this pilot study as no previous data on the performance of BIA in this patient population were available. Results were compiled in an Excel spreadsheet (XP version, Microsoft, Richmond, WA, USA). Body mass index (BMI) was calculated using the formula BMI = body mass (kg) $\times$ body height^{-2} (m^{-2}). Phase angle was calculated for each pair of measurements using the formula $PA = \arctan(Xc/R)$ in degrees. Statistical analysis was performed using SAS software (Version 9.1, SAS Institute, Cary, NC, USA). Continuous variables are presented as mean and standard deviation, whereas categorical variables are presented as count and proportion. Two-sample t-tests and χ^2 tests were used to compare the means and proportions between the groups as appropriate. For all tests, a P-value less than 0.05 was considered significant.

Results

Twenty patients with chronic HCV infection and no evidence of decompensated liver disease participated in this prospective study. Liver biopsy was performed within 6 months of BIA testing in 17 cases (85%). The minimal fibrosis group included 10 patients with Metavir stage 1 fibrosis. The advanced fibrosis group included 10 patients with Metavir stage 3 or 4 fibrosis (six patients and four patients, respectively). Age, BMI, and gender distribution were comparable (Table 1).

We compared the BIA measurements between the two groups. There were no statistically significant differences with respect to R, Xc or PA for the whole body (Table 2) between the minimal and advanced fibrosis groups. We also found no statistically significant differences with respect to R and Xc between the two groups for measurements taken at the level of the trunk or the right upper quadrant of the abdomen in any axis (data not shown). PA was calculated for each pair of measurements. The calculated PA values for the measurements taken at all levels did not show any statistically significant differences (Table 3). We also found no correlation between BIA measurements and age or gender (data not shown).

Table 1 Patient characteristics

	Minimal fibrosis group, $N = 10$	Advanced fibrosis group, $N = 10$	P value
Age, mean (SD), (years)	45.7 (9.8)	52.2 (5.4)	0.082
Male gender, n (%)	5 (50%)	7 (70%)	0.64
BMI, mean (SD), (kg m^{-2})	30.1 (4.8)	28.0 (5.2)	0.36

Table 2 Bioelectrical impedance measurements for the whole body

	Minimal fibrosis group, $N = 10$	Advanced fibrosis group, $N = 10$	P value
Resistance, mean (SD), (Ω)	476.1 (69.5)	492.3 (105.8)	0.69
Reactance, mean (SD), (Ω)	58.5 (10.7)	60.8 (13.4)	0.67
Phase angle, mean (SD), (°)	7.0 (0.8)	7.1 (0.7)	0.90

Table 3 Phase angle for the different body segments

	Minimal fibrosis group, $N = 10$	Advanced fibrosis group, $N = 10$	P value
Whole body *PA*, mean (SD), (°)	7.0 (0.8)	7.1 (0.7)	0.90
Trunk *PA*, mean (SD), (°)	8.6 (2.0)	9.8 (3.8)	0.41
RUQ horizontal *PA*, mean (SD), (°)	13.8 (22.7)	16.4 (25.6)	0.81
RUQ vertical *PA*, mean (SD), (°)	4.1 (3.9)	1.5 (3.7)	0.32
RUQ sagittal *PA*, mean (SD), (°)	12.1 (18.1)	7.9 (21.2)	0.64

PA, phase angle; RUQ, right upper quadrant of the abdomen; *R*, resistance; *Xc*, reactance

PA was calculated from the *R* and *Xc* measurements: $PA = \arctan(Xc/R)$

Discussion

There is a potential role for a non-invasive method to determine the severity of hepatic fibrosis in patients with chronic liver disease. This pilot study suggests, however, that bioelectrical impedance analysis does not have the sensitivity required to distinguish significant differences in hepatic fibrosis in patients with chronic hepatitis C infection. In addition to the standardized "whole body" measurements, we obtained additional regional measurements in the trunk and right upper quadrant, as close as possible to the organ of interest (the liver in patients with chronic hepatitis C). None of these measurements showed differences that would encourage us to extend this pilot study further.

Our study did not include a healthy control group. However, several studies of BIA in healthy subjects have shown mean *PA* values ranging from 6.3 to 8.2 [21, 23]. Our findings for *PA* in chronic HCV patients fall in that range. A previous study of 305 patients with biopsy-proven liver cirrhosis has shown that whole-body *PA* correlated with the Child–Pugh score and also that patients with a $PA < 5.4$ had a shorter survival time than patients with a higher *PA* [21]. Our study is different in many aspects. We specifically excluded patients with decompensated cirrhosis as the presence of ascites might affect BIA measurements. In addition, we used fibrosis as an endpoint instead of survival.

It should be noted that BIA can be affected by both BMI and age. A higher BMI is known to correlate with a higher *PA* [24], possibly secondary to the effect of adipose tissues on resistance. The mean BMI in our study was 30.1 and 28.0 kg m^{-2} in the minimal and advanced fibrosis groups, respectively, which fall in the obesity and overweight ranges. It is possible that the excessive adipose tissues in our patients interfered with our ability to measure hepatic fibrosis. Other studies have suggested a gradual decrease in *PA* with age [23, 25]. Our results did not show a correlation between *PA* and gender or age, in either group, probably due to the small sample size. However, the ideal non-invasive test should be able to discriminate between extremes of fibrosis without being affected by age, weight, or BMI. Other modalities that are currently being evaluated, including serum panels of fibrous matrix markers, measures of liver elasticity by ultrasound, and other imaging techniques, might become, alone or in combination, the new gold standard [8–14].

This study has several limitations. It was designed as a pilot trial with a small group of patients, which raises the possibility of a type-2 error. However, even if a small difference in the mean values truly existed, BIA among individual patients does not appear by itself to be sensitive enough to categorize them into minimal and advanced fibrosis groups due to the large overlap between the two groups. We only recruited patients with chronic HCV infection for this pilot study, in part, because many of them undergo a liver biopsy during their evaluation. However, we have no reason to believe that testing individuals with other etiologies of liver disease will show different results. A single operator performed the BIA measurements in all cases and we did not evaluate inter-operator variability in the performance of BIA in this study. We also did not assess the concordance of the different pathologists at our center in regard to the interpretation of liver biopsies.

Our results suggest that bioelectrical impedance analysis does not have the ability to distinguish between minimal and advanced degrees of hepatic fibrosis in patients with chronic HCV infection. Investigations into other non-invasive modalities for the assessment of hepatic fibrosis should be pursued.

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