Can non-invasive measurements aid clinical assessment of volume in patients with cirrhosis?

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Abstract

AIM: To evaluate the non-invasive assessments of volume status in patients with cirrhosis.

METHODS: Echocardiography and multifrequency bioimpedance analysis measurements and short synacthen tests were made in 20 stable and 25 acutely decompensated patients with cirrhosis.

RESULTS: Both groups had similar clinical assessments, cortisol response and total body water (TBW), however the ratio of extracellular water (ECW)/TBW was significantly greater in the trunk (0.420 ± 0.004 vs 0.404 ± 0.005), and limbs (R leg 0.41 ± 0.003 vs 0.398 ± 0.003, P < 0.05, and L leg 0.412 ± 0.003 vs 0.399 ± 0.003) with decompensated cirrhosis compared to stable cirrhotics, P < 0.05). Echocardiogram derived right atrial and ventricular filling and end diastolic pressures and presence of increased left ventricular end diastolic volume and diastolic dysfunction were similar in both groups. The decompensated group had lower systemic blood pressure, mean systolic 101.8 ± 4.3 vs 122.4 ± 5.3 and diastolic 58.4 ± 4.1 mmHg vs 68.8 ± 3.1 mmHg respectively, P < 0.01, and serum albumin 30 (27-33) vs 32 (31-40.5) g/L, P < 0.01.

CONCLUSION: Decompensated cirrhotics had greater leg and truncal ECW expansion with lower serum albumin levels consistent with intravascular volume depletion and increased vascular permeability.

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Key words: Cirrhosis; Bioimpedance; Echocardiography; Extracellular water; Ascites; Cortisol

Core tip: Despite peripheral oedema and ascites patients with cirrhosis may be intravascularly volume deplete and require parenteral fluids to prevent acute kidney injury. We assessed whether non-invasive measurements with multifrequency bioimpedance and echocardiography aided clinical assessment of volume status. Multifrequency bioimpedance showed that patients with decompensated cirrhosis had similar total body water to stable cirrhotics, but with an expanded extracellular volume, suggesting increased vascular permeability. Echocardiography was not helpful in assessing volume status in the two groups, and neither echocardiography nor multifrequency bioimpedance could aid assessment of intravascular volume.

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INTRODUCTION

Cirrhotic patients with progressive liver disease typically develop a hyper-dynamic circulation characterised by increased cardiac output, with reduced systemic vascul-
lar resistance with a normal or even low systemic blood pressure[6], and may have an associated cardiomyopathy[9]. Optimizing intravascular volume is essential in man-
gaging patients with cirrhosis to avoid acute kidney injury induced by hypovolaemia, and also reduce the risk of developing hepatorenal syndrome (HRS)[10]. Intravascular volume expansion, which is often necessary to treat these patients, can potentially lead to worsening of ascites, pleural effusion or heart failure.

Clinical assessment of volume status in patients with cirrhosis and progressive liver disease may be difficult as patients with ascites and peripheral oedema may still be relatively under filled in terms of intravascular volume, as some 40%-50% of the extracellular fluid volume can be in the microcirculation.

In addition, central venous pressure and pulmonary capillary wedge pressure often provide unreliable markers of circulatory volume[6][9].

Other techniques for assessing volume status, include, inferior vena caval diameter and cardiac end diastolic volumes as measured by echocardiography[6-8], although experience with these static monitoring measurements of volume have not been generally translated into daily clin-
ical practice[9].

Recently multifrequency bioelectrical impedance analysis (MF-BIA) has become available, which measures total body water and compartmental volumes by passing a series of different electrical currents and electrical frequen-
cies through the body. We therefore compared vol-
ume assessment of patients with standard 2-dimensional trans-thoracic echocardiography with MF-BIA.

MATERIALS AND METHODS

Patients
Twenty patients with cirrhosis with chronic decen-
ompensation but stable liver function being assessed for potential liver transplant work up or transjugular intrahepatic por-
to-systemic shunting (TIPS) were evaluated along with
25 patients with acute decompensation on a background of cirrhosis, who had been admitted to hospital as acute emergencies, due to acute variceal haemorrhage, sponta-
neous bacterial peritonitis, sepsis and hypovolaemia sec-
ondary to diarrhoea. Plasma cortisol was measured prior to and at 30 min following 250 μg of synacthen.

Methods
All patients had MF-BIA, where assessments were made in the supine position, using an eight hand and feet tactile electrode system (Biospace in body 720, Seoul, South Korea)[10][11]. No patient had a peripheral amputation, or cardiac pacemaker/defibrillator, and no female patient was pregnant. Height was measured by a standard wall mounted measure (Sigmeas 1, Doherty signature range, www.mediclick.co.uk), and weight by calibrated scales (MPSS250, Marsden, Henley on Thames, United King-
dom). MF-BIA measurements were repeated three times over 30 min to determine reliability of measurements.

Standard 2-dimensional transthoracic echocardiograms (Philips IE33, Philips Medical Systems, Eindhoven, the Netherlands) with measurement of inferior vena cava width and collapsibility were recorded and analysed offline by a single experienced observer. Left ventricular volumes and ejection fraction were estimated using Simpson’s modified biplane method[52]. Ethical ap-
proval was granted by the local ethical committee as audit and clinical service development.

Statistical analysis
Statistical analysis was by student’s t test for normally dis-
distributed data and Mann Whitney U test for nonparamet-
ric data (GraphPad Prism version 6.0, San Diego, United States). In addition χ² analysis with correction for small numbers and one way ANOVA with Tukey post analysis correction were also performed using SPSS software for Windows version 15.0 (SPSS Inc., Univ Chicago, Illinois, United States), and agreement of repeated MF-BIA by Bland Altman analysis and Pearson correlation (Analyse It, Leeds, United Kingdom). Data are expressed as mean ± SE of the mean, median and inter-quartile range, or
percentages. Statistical significance was taken at or below the 5% level.

RESULTS

Twenty patients, mean age 53.4 ± 1.5 years, 60% male with compensated cirrhosis (9 hepatitis C, 6 alcohol related, 2 primary biliary cirrhosis, 1 each of hepatitis B, non-
 alcoholic steatosis and cryptogenic) of whom additionally
8 had primary hepatocellular carcinoma being assessed for liver transplant or TIPS insertion, had their volume assessed clinically and also by 2 dimensional echocardiography and MF-BIA (Table 1). We compared these volume assessments with those from 25 acutely decompensated cirrhotic patients (underlying chronic liver disease due to 13 alcohol, 6 hepatitis C, 4 non-alcoholic steatosis, and 1 each of autoimmune and primary biliary cirrhosis), mean age 53.9 ± 2.7 years, 64% male. Fourteen of these patients had decompensation precipitated by acute variceal haemorrhage, 6 spontaneous bacterial peritonitis, 3 with other sources of sepsis and 2 with acute dehydration and hypovolaemia secondary to diarrhoea. Ten/twenty five were encephalopathic at presentation. However, clin-
ical grading of encephalopathy was similar for both the decompensated and compensated groups, median 2 (1-2) vs 2 (1-2.5) respectively. Similarly clinical assessment of ascites was similar for both groups, 65% of the comp-
ensated group and 62% of the decompensated group, with both groups having a median ascites grading of 2 (1-3) vs 2 (1-3). Twenty six percent of the decompensated
of the compensated group and 84% in the decompensated group ($\chi^2 = 1.22, P = 0.269$).

In keeping with clinical assessment of the jugular venous pulse wave transthoracic echocardiographic measured right atrial filling pressures were not elevated. Whereas the right atrium was mildly dilated in the majority of the compensated group, all patients in the decompensated group had a dilated right atrium, with most having moderate to severe dilatation. 85% of the compensated group, and 64% of the decompensated group had evidence of diastolic dysfunction on echocardiography with an early to late atrial filling ratio (E/A) of less than one. Inferior vena cava width was < 1.5 cm in 70% of the compensated group, and between 1.5 and 2.5 cm in the remainder, whereas it was less than 1.5 cm in all those measured in the decompensated group, but in all cases moved normally with respiration, showing normal collapse.

MF-BIA showed that both groups of patients had excess total body water, with mean ratio of ECW/TBW in the decompensated group above the 95% confidence limit for a healthy population. However, in a segmental analysis, showed normal hydration status in the arms, but increased extracellular fluid in the trunk and legs. In addition although total body water was not different between the groups, the ratio of extracellular water (ECW) to total body water (TBW) was greater for the decompensated group, in particular for both the trunk and legs (Table 3). Repeated MF-BIA were very reproducible with minimum differences on repeated measurements (Table 4).

We then compared those patients who on clinical examination were thought to have ascites and those with moderate to severe ascites. There was no difference in patient weights, or total body water, intracellular or extracellular water measured by MF-BIA (Table 5). Similarly there was no difference in the ratio of ECW in the arms to total ECW, but patients with ascites had greater amounts of ECW in the trunk and legs (Table 5). Subdividing the decompensated group into those with moderate to severe ascites and those with no or mild ascites,
then although the ECW/TBW ratio for those with moderate to severe ascites, was greater (total 0.416 ± 0.004 vs 0.405 ± 0.005, trunk 0.425 ± 0.004 vs 0.409 ± 0.007, right leg 0.413 ± 0.003 vs 0.403 ± 0.004, and left leg 0.414 ± 0.004 vs 0.408 ± 0.005), with these smaller patient groups these values were no significant \( (P = 0.27 \text{ to } 0.063) \).

We also divided the decompensated group into those in whom decapsulation was primarily varying varicel haemorrhage or dehydration, and those in whom decapsulation was primarily due to infection (spontaneous bacterial peritonitis and pneumonia). The mean ECW/TBW on admission in the varicel haemorrhage group was 0.417 ± 0.005, which was lower but not statistically different from the sepsis group, 0.422 ± 0.006.

**DISCUSSION**

Clinical examination of the two groups was not significantly different in terms of ascites and jugular venous pulse wave, although the majority of the decompensated group were thought to be clinically hypovolemic. Although peripheral systolic and diastolic blood pressure was lower and heart rate greater in the decompensated group, both groups had similar basal cortisol levels, and also following a synchon challenge. It has been suggested that for critically ill patients that the baseline cortisol should be > 280 \( \mu \text{mol/L} \), and an appropriate response > 250 \( \mu \text{mol/L} \). In our cohort around 53% of both groups had a relatively low baseline cortisol, and an inappropriate response to synchon in 63% and 84%. Thus it would appear that the differences in blood pressure were not due to steroid deficiency. Previous reports have suggested a relationship between cardiac function and severity of liver disease[14], characterised by cardiac dilatation, with increased left atrial diameter, left ventricular end diastolic volume, and increased cardiac output and aortic flow[15]. In our study both groups had a normal mean right atrial pressure and cardic ejection fraction of > 55%, although some studies have reported reduced cardic output[16]. As with previous reports of diastolic dysfunction in patients with cirrhosis the majority of both groups had an E/A ratio of < 1.0[17], although no patient had grade 2 diastolic dysfunction. Although an E/A ratio of < 1.0 can be considered a normal finding in the older patient, both groups had a mean age of less than 55 years. Right ventricular end systolic pressure was greater than normal (> 30 mmHg) in 50% of the compensated group and 75% of those measured in the acutely decompensated cirrhotic group, with normal pulmonary valve flow velocity in all cases. Similarly left ventricular end diastolic volumes were greater than normal (> 128 mL) in 80% and 55% respectively, with normal aortic valve flow velocities. Thus the main changes in echocardiography were found estimating right sided cardiac function with the decompensated group having modestly lower right atrial pressures, but with increased atrial dilatation and mildly increased right ventricular end systolic pressures. Whereas, although left ventricular diastolic dysfunction was prominent in both groups, it was not different.

Clinical examination for ascites was similar in both groups, as was total body water, extracellular and intracellular volumes as measured by MF-BIA. Bioimpedance works by passing an electrical current through the body and measuring both the response to flow and reactivity, and has developed from current and frequency devices[13], to those using multiple currents and frequencies, and from devices which simply record total body water, to those with eight electrodes which can provide

### Table 3 Multi-frequency bioelectrical impedance analysis data in the stable cirrhotic and the acutely decompensated cirrhotic patients

| Assessment | Compensated | Decompensated |
|------------|-------------|---------------|
| %ECW/TBW   | 0.416 ± 0.004 | 0.405 ± 0.005 |
| Bias (95%CI) | 0.14 (-0.16-0.44) | 0.12 (-0.23-0.46) |
| Pearson r  | 0.81          | 0.77          |
| Pearson P  | < 0.001       | < 0.001       |

### Table 4 Reliability of multi-frequency bioelectrical impedance assessments

| Assessment | 1st | 2nd | 3rd |
|------------|-----|-----|-----|
| %ECW/TBW   | 0.407 ± 0.26 | 0.408 ± 0.21 | 0.408 ± 0.22 |
| Bias (95%CI) | 0.12 (-0.23-0.46) | -0.03 (-0.16-0.00) |
| Pearson r  | 0.81          | 0.77          |
| Pearson P  | < 0.001       | < 0.001       |

### Table 5 Multi-frequency bioelectrical impedance analysis measurements in those patients with no clinically detectable ascites those patients with moderate to severe ascites judged clinically

| Assessment | No ascites | Moderate/severe ascites |
|------------|------------|-------------------------|
| Weight (kg) | 75.1 ± 3.9 | 75.4 ± 3.0 |
| Total body water (L) | 39.4 ± 1.8 | 37.9 ± 1.9 |
| ICW (L) | 23.7 ± 0.66 | 22.8 ± 1.12 |
| ECW (L) | 15.6 ± 0.66 | 15.6 ± 0.76 |
| Total body ECW/TBW | 0.399 ± 0.004 | 0.413 ± 0.003 |
| R arm ECW/TBW | 0.384 ± 0.002 | 0.386 ± 0.002 |
| L arm ECW/TBW | 0.385 ± 0.003 | 0.410 ± 0.003 |
| L leg ECW/TBW | 0.398 ± 0.003 | 0.410 ± 0.003 |

Results expressed as mean ± SE, *P* < 0.05 vs No ascites group. ICW: Intracellular water; ECW: Extracellular water; TBW: Total body water.
compartamental assessments[20,21], as used in this study. As the resistance to the passage of electricity depends upon circuit length, the majority of resistance occurs in the arms and legs, with much less for the trunk, and earlier reports suggested that intra-abdominal fluid had little effect on bioimpedance measurements[22]. We found that MF-BIA results were highly reproducible and using MF-BIA we could detect significant segmental differences. We found that those patients with moderate to severe ascites had greater ECW volumes in both the trunk and legs. Thus compared to previous reports using single frequency bioimpedance machines, MF-BIA with segmental analysis could show increased ascitic fluid[23]. Similarly both the compensated and decompensated groups had normal hydration status of the upper limbs, however the ratio of extracellular to total body water, a marker of extracellular fluid excess was increased in the trunk and both legs compared to reported data from healthy controls, and was significantly greater for those patients with decompensated cirrhosis, more so for the trunk than the legs. Thus although total body water was similar in both groups, the decompensated group had more fluid in the trunk and legs. This redistribution of fluid is in keeping with the clinical assessments which suggested that the majority of decompensated patients were hypovolemic, whereas the compensated group were thought to be euvoolemic. The whole body ratio of ECW/TBW was lower in those patients who had decompensated due to variceal hemorrhage, in keeping with the clinical assessment of volume status, but was not statistically different from those who had decompensated secondary to sepsis. This was a small pilot study and as such the number of subjects many have been too small to show any statistical effect.

Thus patients with both compensated and decompensated cirrhosis had evidence of increased fluid retention in the trunk and legs, despite normal right atrial filling pressures and lack of clinically detectable peripheral oedema, presumably due to increased interstitial fluid formation or reduced removal. Serum albumin concentrations were lower in the decompensated cirrhotic group, and although this could be secondary to reduced synthesis, increased passage of albumin into the extracellular fluid compartment, due to increased vascular permeability could be an alternative explanation, as described in other chronic disease states, such as chronic kidney disease[24-27]. This increased leak and increased extracellular fluid was not associated with changes in cortisol. In keeping with a hyperdynamic circulation there was dilatation of the right atrium, increased end systolic right atrial pressure and increased left ventricular end diastolic volume, but derived right atrial pressure and inferior vena cava diameter were not increased. Single transthoracic echocardiography assessments could not differentiate those with stable chronic liver disease from those acutely admitted to hospital with decompensated cirrhosis, whereas MF-BIA showed that although both groups had similar overall TBW, the decompensated group had increased ECW/TBW, particularly in the legs and trunk, suggesting that plasma volume was decreased. However none of these techniques reliably predicted intravascular volume, and clinical assessment remains a crucial element in the examination of patients with chronic liver disease to determine volume assessment.

COMMENTS

Background
Cirrhotic patients with progressive liver disease typically develop a hyper-dynamic circulation characterised by increased cardiac output, with reduced systemic vascular resistance with a normal or even low systemic blood pressure, and may have an associated cardiomyopathy. Optimizing intravascular volume is essential in managing patients with cirrhosis to avoid acute kidney injury induced by hypovolaemia, and also reduce the risk of developing hepatorenal syndrome. Intravascular volume expansion, which is often necessary to treat these patients, can potentially lead to worsening of ascites, pleural effusion or heart failure.

Research frontiers
Clinical assessment of volume status in patients with cirrhosis and progressive liver disease may be difficult as patients with ascites and peripheral oedema may still be relatively under filled in terms of intravascular volume, as some 40%-50% of the extracellular fluid volume can be in the microcirculation. In addition, central venous pressure and pulmonary capillary wedge pressure often used to measuring static haemodynamics are not reliable markers of circulatory volume. Other techniques for assessing volume status, include, inferior vena cava diameter and cardiac end diastolic volumes as measured by echocardiography, although experience with these static monitoring measurements of volume have not been generally translated into daily clinical practice.

Innovations and breakthroughs
The authors assessed whether non-invasive measurements with multifrequency bioimpedance and echocardiography aided clinical assessment of volume status. Multifrequency bioimpedance showed that patients with decompensated cirrhosis had similar total body water to stable cirrhotics, but with an expanded extracellular volume, suggesting increased vascular permeability. Echocardiography was not helpful in assessing volume status in the two groups, and neither echocardiography nor multifrequency bioimpedance could aid assessment of intravascular volume.

Applications
 Decompensated cirrhotics had greater leg and truncal extracellular water expansion with lower serum albumin levels consistent with intravascular volume depletion and increased vascular permeability.

Peer review
This manuscript is very interesting. This paper describes the results of assessment of volume status in patients with cirrhosis.

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