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Functional status and heart rate variability in end-stage liver disease patients: Association with nutritional status

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ABSTRACT

Objectives: Muscle dysfunction and reduced heart rate variability (HRV) are common in patients with advanced liver disease, and both are related to poor outcomes. Malnutrition is also highly prevalent in these patients, however, the association between the malnutrition and HRV has not yet been assessed. The aim of this study was to evaluate the short-term HRV, functional and nutritional statuses in patients with advanced liver disease.
Methods: The nutritional and functional statuses were determined by subjective global assessment, handgrip strength (dynamometer, JAMAR) and gait speed during a 6-minute walk text (6MWT), respectively. The cardiac workload index (CWI) was used to evaluate the cardiac response to the 6MWT. The time domain (SD of all normal-to-normal intervals [SDNN]) and very-low, low-, and high-frequency domains of short-term HRV were evaluated with RS800 CX (Polar, Finland) and Cardioseries software (Brazil).
Results: The study evaluated 42 patients with liver disease (62% men) and malnutrition was found in 62% of this population. The malnourished participants presented with reduced functional status, 41% decreased SDNN, and 14% greater CWI compared with well-nourished individuals ($P < 0.05$). Additionally, the CWI was negatively associated to SDNN ($r = 0.414$; $P < 0.05$) and gait speed ($r = 0.598$; $P < 0.05$), especially in malnourished individuals ($r = 0.650$; $P < 0.05$). These data indicate that malnourished patients with liver disease have higher cardiovascular risk related to reduced functional status, which may be associated to poor outcomes during the course of the disease before and after transplant. Another relevant aspect is that the 6MWT associated to HRV could be a useful tool to screen liver disease patients who have a higher risk for cardiovascular complications.

Introduction

Patients with end-stage liver disease (ESLD) display a higher prevalence of malnutrition, which is associated with reduced functional status and increased morbidity and mortality before and after liver transplantation [1–3]. Clinical complications associated with decreased functional status are consequences of generalized tissue wasting, especially loss of muscle territories, which includes the heart [4,5]. This condition may be one of the causes of sudden cardiac events in malnourished individuals [5].

It has been established that patients with liver disease present with cardiac dysfunction, such as cirrhotic cardiomyopathy, portal hypertension [6,7], and cardiac failure [7], most of which are related to reduced heart rate variability (HRV) [8]. Cardiac function impairment has also been observed in patients who underwent liver transplantation due to the presence of metabolic syndrome [9], arrhythmia, acute heart failure, and

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myocardial infarction induced by post-transplant reperfusion [6]. Additionally, it is well known that cardiac comorbidities before liver transplantation are potential complications that may lead to worse outcomes in liver recipients [6]. Although the presence of cardiovascular complication supports the high cardiac risk in these patients, the involvement of nutritional status on cardiac function is not clear. Based on these data, we concur that greater cardiac dysfunction is partially mediated by lower muscle function in malnourished patients with liver disease.

Some studies have already indicated that the 6-minute walk test (6MWT) is an adequate predictor of mortality in candidates for liver transplantation candidates [10,11] and hospital readmission in patients with chronic heart failure [12]. Therefore, the possibility for using this approach to predict cardiac events in advanced liver disease should be considered because it is inexpensive and easy to perform. Additionally, the short-term HRV could be used as a predictor of poor outcome in these patients because it has been used as a tool for initial screening of post-infarction risk [8]. Based on this, our hypothesis is that gait speed during 6MWT associated to HRV could be a good approach to predict poor cardiac outcomes during the course of ESLD, especially in malnourished patients. Therefore, the present study was performed to evaluate cardiac and muscle functions in patients with ESLD and its association with the nutritional status, aiming to assess both as potential tools for screening patients with cardiac risk and other short- and long-term transplant outcomes.

Materials and method

This study was conducted with patients with ESLD who were followed up at the Transplantation Outpatient Clinic of the University Hospital, Universidade Federal de Minas Gerais. Informed consent was obtained from each patient included in the study. The study was approved by the ethics committee of the University Federal of Minas Gerais (CAAE: 24015614.8.0000.5149).

Patients' nutritional status was evaluated by the Subjective Global Assessment (SGA) [13] and functional status by handgrip strength (dynamometer, JAMAR) and gait speed during the 6MWT, respectively. The 6MWT was performed indoors, in a 30-m long, flat corridor with an adequate surface [14]. After having checked for clinical contraindications to the walk test, patients were instructed to walk the maximum distance in their usual pace for 6 min [14]. The patients' reduced muscle function was classified by gait speed <1 m.s^{-1} [15]. Patients did not undergo any kind of training to perform the walk test because the first test attempt was more reliable to measure daily functional capacity [14].

The cardiac workload index (CWI) was acquired during the 6MWT to evaluate patients' cardiac response to the walk test. The CWI was calculated using values of maximal heart rate achieved during the walk test. It predicted maximal heart rate [16] and total distance walked. The predicted heart rate equation previously proposed [16] was chosen due to the high clinical risk when submitting these patients to progressive exercise tests on a treadmill or cycle ergometer to achieve maximal heart rate. The equation of CWI is described below:

$$CWI = \left[(maximal\ heart\ rate\ on\ 6MWT \times\ predicted\ maximal\ heart\ rate)^{-1} \times walk\ distance\right]^{-1}$$

The HRV was assessed using short-term evaluation [8]. The heart rate recording was acquired by RS800 CX (Polar, Finland) and a 5-min stable cardiac recording was analyzed to assess the time domain (SD of all normal-to-normal interval [SDNN]) and frequency domain of HRV (very-low frequency [VLFα] 0.00–0.04 Hz; low frequency [LFα] 0.04–0.15 Hz; and high frequency [HFα] 0.15–0.40 Hz).

After these evaluations, all patients received a standard nutritional orientation encompassing oral nutritional strategies to promote health and to restore the nutritional status based on key aspects of their 24-h dietary recall evaluation.

All statistical analyses were tested using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA). The sample size was calculated using the Pearson correlation coefficient between CWI and HRV/gait speed with α, β, expected correlation coefficient, and design effect equal to 0.05%, 0.20%, 0.70%, and 10%, respectively. The Kolmogorov-Smirnov test was used to check normal distribution of the variables. The statistic differences were assessed by Student's *t* test and Fischer's Exact test, according to quantitative and qualitative values, respectively, and correlations were analyzed by the Pearson correlation test. The significance level was set at $P < 0.05$.

Results

The demographic and clinical characteristics of the patients with ESLD are cited in Table 1. According to the SGA, malnutrition was observed in 62% patients, and 27% were classified as severely malnourished. Patients with malnutrition presented with 34% lower muscle strength and 24% lower gait speed during 6MWT compared with well-nourished group ($P < 0.05$). Malnourished patients displayed gait speed below the normal muscle function range (<1 m.s^{-1}). Additionally, malnourished patients had 41% reduction in time domain HRV (SDNN) compared with the well-nourished patients ($P < 0.05$), without any difference in the frequency domain components of HRV (VLFα, LFα, HFα, and the ratio of LF to HF). The CWI was 14% higher in malnourished than in well-nourished patients ($P < 0.05$).

A negative correlation was observed between CWI and SDNN, as well as CWI and gait speed during the 6MWT in all patients with ESLD ($P < 0.05$; Fig. 1A and B). After the adjusted regression analysis by nutritional status, we observed that only the malnourished patients had a negative relationship between CWI and gait speed during the walk test ($P < 0.05$). The correlation between CWI and HRV was not affected by nutritional status.

Seven patients did not perform the 6MWT due to physical derangements. Five presented with malnutrition (3 severely malnourished and 2 moderately malnourished) and were too ill to carry out the exercise test. Therefore, a walking distance of 0 m, based on the assumption of zero score as the most accurately screening of their functional status, was assigned to them [10]. The remaining two patients chose not to perform the 6MWT, and they were excluded from the gait-speed analysis.

Table 1
Demographic and clinical characteristics of patients with end-stage liver disease

Variables	Well-nourished (n = 16)	Malnourished (n = 26)	*P*-value
Demographic and clinical profile			
Sex (% male)	63	65	1.000
Age (y)	52 (47–58)	52 (48–57)	0.994
MELD score	15 (12–18)	16 (14–19)	0.452
Time domain of HRV			
HRV (SDNN, ms)	45 (36–55)	25 (22–28)	<0.0001
Frequency domain of HRV			
VLF (%)	34 (26–41)	38 (32–44)	0.305
LF (%)	32 (26–39)	27 (23–31)	0.159
HF (%)	35 (25–44)	34 (26–43)	0.981
LF/HF*	2.13 (1.206–3.047)	1.93 (1.230–2.629)	0.640
Functional profile			
Handgrip strength (kg)	32 (26–39)	21 (18–25)	0.002
Did not performed the 6MWT (%)	13	19	0.687
Gait speed (m/s)	1.13 (1.032–1.237)	0.86 (0.685–1.031)	0.025
CWI during 6MWT (%max bpm/m^{-1})	0.18 (0.155–0.201)	0.21 (0.191–0.235)	0.031

CWI, cardiac workload index; HF, high frequency; HRV, heart rate variability; LF, low frequency; MELD, Model for End-Stage Liver Disease; SDNN, standard deviation of normal-to-normal interval; VLF, very low frequency; 6MWT, 6-minute walk test

Data are described as mean followed by 95% confidence interval (minimum–maximum) Legend

* LF/HF is calculated by values expressed as ms^2.

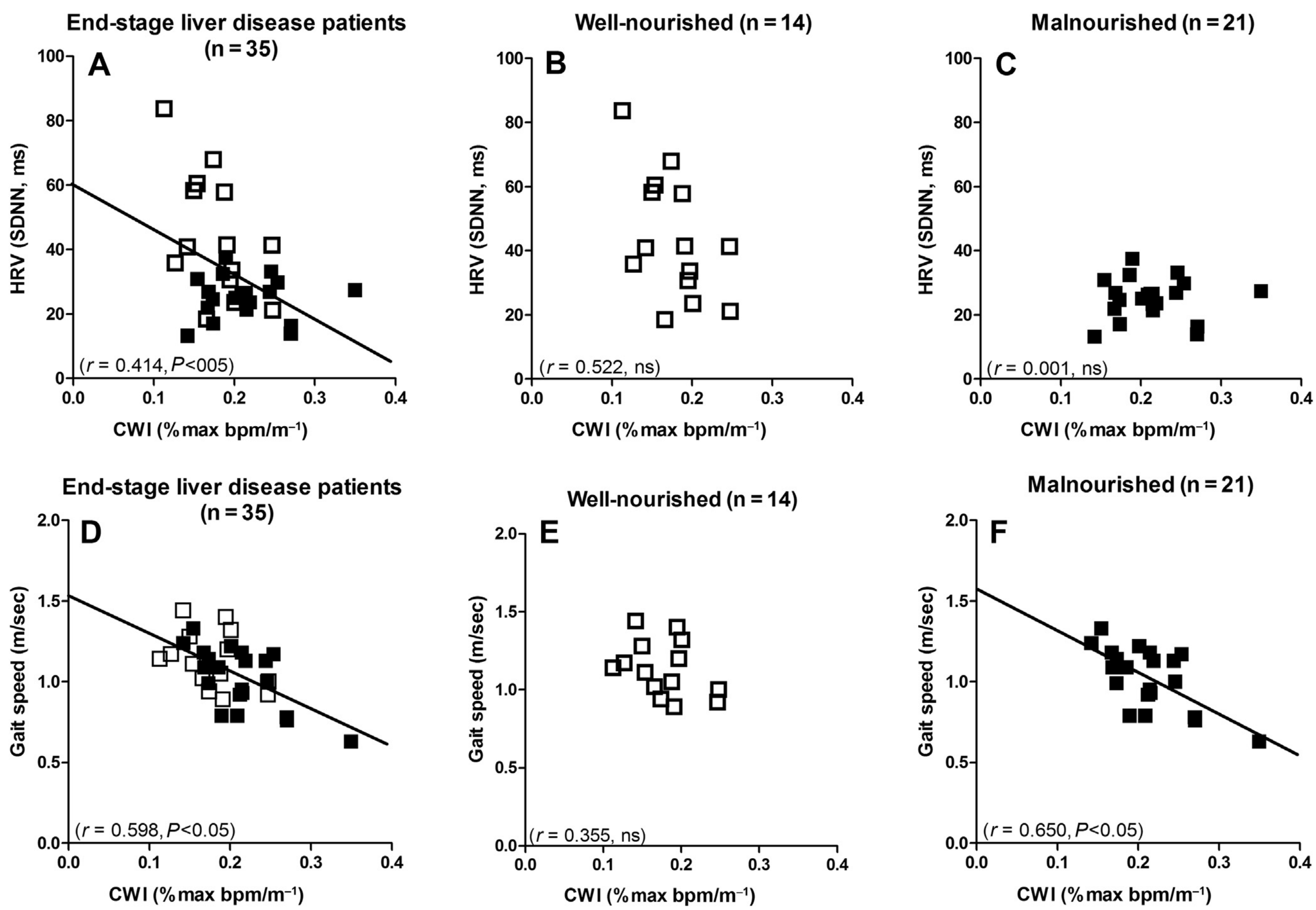

Fig. 1. The relationship between CWI and resting HRV in all well-nourished and malnourished patients and the relationship between CWI and gait speed in all well-nourished and malnourished patients. CWI, cardiac workload index; HRV, heart rate variability; SDNN, standard deviation of normal-to-normal interval.

Discussion

This study indicated that malnourished patients with liver disease present with reduced functional status that may negatively influence the cardiovascular outcome during the disease course and that places them at higher risk for complications [8]. Additionally, lower HRV and higher CWI during 6MWT were observed in malnourished compared with well-nourished patients. Interestingly, the CWI during the 6MWT was inversely related to the resting HRV and gait speed, mainly in the malnourished patients, which brings to light the importance of the 6MWT being associated to HRV as a reliable tool to assess cardiac risk in ESLD. Taking all data together, the study indicates that patients with liver disease and malnutrition are more likely to develop cardiac complications due to the reduced functional status.

Other authors also have found that cardiovascular abnormalities in patients with liver disease are associated with changes in HRV [17]. However, to our knowledge, there are no data on the nutritional status effect on cardiac function in patients with advanced liver disease, who present with a high prevalence of malnutrition of ≤81% [1]. We have addressed this question and observed reduced HRV in malnourished compared with well-nourished patients. To our knowledge, this is the first study to report that patients with liver disease and malnutrition display resting cardiac autonomic dysfunction and probably have worse cardiac clinical conditions than their well-nourished counterparts.

Cardiac dysfunction in malnourished individuals has been connected to the reduction of cardiac muscle mass [18,19]. Changes in the cardiac system in malnourished infants were related to decreased myocardial mass, as represented by shorter intraatrial and atrioventricular conduction time (PR interval), prolonged QT interval, [18] and the inability to respond to the ventricular preload stimulus [4]. However, this has not yet been reported in adults with liver disease. The greater CWI related to reduced muscle function in malnourished patients with liver disease points in this direction. However, the evaluation of cardiac mass profile should be considered in future studies.

Some authors have shown that malnutrition leads to important clinical complications that are associated with increased mortality due to cardiac failure [20], renal perfusion changes, and delayed respiratory tract infection recovery [19]. All of these complications have been seen in patients undergoing liver transplantation [2,6,21]. Our group has already observed an important mortality rate per year in severely malnourished patients on the waiting list for liver transplantation [2]. According to one study [10], 1-y survival in these patients may be predicted by the 6MWT. Thus, we speculated that malnourished patients with liver disease who presented with a gait speed of 0.86 m.s^{-1}, may be at higher risk (40%) before and after 1 y of liver transplantation, as previously observed [2]. The latter supports the

6MWT as a potential predictor of mortality in this population. Additionally, it is important to point out that 43% of the severely malnourished patients in this study were not able to perform the walking test due to poor clinical conditions and, those who underwent the 6MWT showed the lowest HRV. Once more, this indicates that reduced functional status in malnourished patients with liver disease leads to higher cardiovascular risk, increasing the possibility of poor outcomes during the course of the disease. Based on these data, the need to identify these patients early is of utmost importance so their overall clinical and nutritional conditions can be improved. Furthermore, nutritional interventions, such as enteral nutrition, in the perioperative period should be considered when requirements are not reached with individualized caloric-dense oral diets. Therefore, the association of gait speed during 6MWT and the short-term HRV, which has been used to assess post-infarction cardiac risk, could be an easy tool to help screen patients with liver disease who are at increased cardiac risk.

This study did not address the relationship between nutritional and functional status and poor outcomes in patients with ESLD due to the small number of patients enrolled. Also, we did not assess functional and nutrition interventions, such as exercise rehabilitation and nutrition therapy. These will be addressed in future studies.

Conclusion

This study revealed that malnourished patients with advanced liver disease display lower muscle function, which is related to reduced HRV and increased CWI during 6MWT, which are risk factors for poorer outcomes.

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