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# Muscle circulation contributes to hyperdynamic circulatory syndrome in advanced cirrhosis☆

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***Background/Aims*: Muscle wasting likely influences blood flow to muscle districts in advanced cirrhosis. Thus, we assessed systemic hemodynamics and femoral artery blood flow corrected by muscle mass of the lower limb in 13 patients (Child-Pugh classes B and C) and 11 healthy controls.**

***Methods*: Systemic hemodynamics were assessed by transthoracic electrical bioimpedance, femoral artery blood flow by duplex-Doppler and muscle mass by magnetic resonance imaging.**

***Results*: As expected, patients exhibited increased cardiac index and reduced peripheral vascular resistance. Femoral artery blood flow did not differ between patients and controls. However, when this parameter was indicized by the muscle mass of the lower limb, which was reduced in patients (median: 3391; range: [2546–4793] vs 5118 [3562–7077] $cm^3$, $p = 0.0006$), it proved almost doubled in patients (91.1 [59.9–119.4] vs 50.5 [38.6–69.8] µl/min $cm^3$; $p = 0.0001$). Patient femoral blood flow indicized by muscle mass correlated inversely with peripheral vascular resistance ($r = -0.65$; $p = 0.017$) and directly with cardiac index ($r = 0.57$; $p = 0.042$).**

***Conclusions*: Vasodilation of muscle districts contributes to the reduced peripheral vascular resistance in advanced cirrhosis. Our findings provide a stronger rationale for the use of non-selective vasoconstrictors to treat hemodynamic-dependent complications of cirrhosis, such as hepatorenal syndrome.**

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***Keywords*: Cirrhosis; Systemic hemodynamics; Femoral artery blood flow; Muscle mass**

## 1. Introduction

Patients with advanced cirrhosis often develop systemic hemodynamic abnormalities which clinically manifest with arterial hypotension, wide pulse pressure, tachycardia, warm extremities and palmar erythema. Such a hyperdynamic circulatory syndrome was recognized more than half a century ago [1,2] and attributed to arteriolar vasodilation leading to a drop in peripheral vascular resistance and a compensatory increase in cardiac output [3]. Several complications of cirrhosis, such as renal sodium and water retention, with consequent ascites, edema and hyponatremia, hepatorenal syndrome, paracentesis-induced circulatory dysfunction,

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*Abbreviations:* PRA, plasma renin activity; TEB, transthoracic electrical bioimpedance; SV, stroke volume; CO, cardiac output; MAP, mean arterial pressure; PVR, peripheral vascular resistance; MRI, magnetic resonance imaging.

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and hepatopulmonary syndrome can be attributed to systemic hemodynamic abnormalities, which also contribute to portal hypertension [3]. To this end, vasoconstrictor drugs have been successfully employed in the treatment of some of these complications, such as variceal bleeding [4] and hepatorenal syndrome [5].

The hemodynamic changes leading to hyperdynamic circulatory syndrome do not uniformly involve all the vascular beds. Intrarenal vasoconstriction is undisputed, and splanchnic arterial circulation is universally thought to be vasodilated [3]. The hemodynamic condition of other vascular beds is less defined. Seminal studies suggested that the blood flow to skin and muscle masses was increased [6]. This was held true for years, and substantiated by venous occlusion plethysmography studies evaluating forearm blood flow [7–10]. However, contrasting results emerged as either unaltered skeletal muscle blood flow, as measured by $^{133}$Xenon clearance technique [11], or even increased skin and muscle vascular resistance in parallel with the severity of cirrhosis [12] were reported.

Ultrasonography with duplex-Doppler technique yielded new insights on the issue, but again provided varying results. Femoral artery blood flow was found increased in cirrhotic patients with hyperdynamic circulatory syndrome and preserved glomerular filtration rate, and normal in patients with hepatorenal syndrome [13]. Accordingly, femoral artery blood flow was increased in Child-Pugh class B and normal in Child-Pugh C cirrhotic patients [14]. However, another study showed preserved femoral artery and reduced brachial artery blood flows in nonazotemic cirrhotic patients with ascites, both districts being underperfused in patients with renal failure [15].

Resting muscle blood flow depends upon metabolic rate and oxygen consumption, which is dictated almost exclusively by muscle mass [16,17]. As patients with advanced cirrhosis commonly exhibit muscle wasting [18], it is surprising that the evaluation of blood flow to their muscular districts by duplex-Doppler technique has not taken into account that muscle wasting *per se* may affect the amount of blood delivered to that district.

The present study aimed to evaluate systemic hemodynamics and muscular blood flow corrected by muscle mass in patients with advanced cirrhosis.

## 2. Patients and methods

### 2.1. Patients and controls

Thirteen Caucasian patients with cirrhosis and ascites, whose demographic, clinical and laboratory features are reported in Table 1, were consecutively enrolled. Eleven untrained healthy Caucasian subjects of comparable age and sex served as controls. Cirrhosis was diagnosed on clinical findings, oesophageal varices at endoscopy and ultrasonographic features, such as hypertrophy of left liver lobe, irregular liver margins and evidence of portal hypertension (dilated portal vein, splenomegaly, slowered portal blood flow). Hepatorenal syndrome was diagnosed according to the criteria set by the International Ascites Club [19].

**Table 1**
**Demographic and anthropometric features of patients with decompensated cirrhosis and healthy controls**

| | Patients with cirrhosis ($n = 13$) | Healthy controls ($n = 11$) |
|---|---|---|
| Age (years) | 52 (38–72) | 50 (35–70) |
| Sex (M/F) | 11/2 | 10/1 |
| Body surface area (cm$^2$) | 1.83 (1.4–2.3) | 1.94 (1.56–2.11) |
| Etiology of cirrhosis | | |
| HBV | 2 | – |
| HCV | 4 | – |
| Alcohol | 5 | – |
| Cryptogenic | 2 | – |
| Child-Pugh class (B/C) | 6/7 | – |
| Child-Pugh score | 10 (7–13) | |
| Serum creatinine(mg/dl) | 1.16 (0.79–1.53) | – |
| Serum sodium (mmol/L) | 134 (130–145) | – |
| Plasma renin activity (ng/ml/h) | 4.68 (1.60–31.11) | – |

Etiology of cirrhosis and patient laboratory and clinical features are also reported.

Patients with alcoholic cirrhosis had been abstinent for at least one year, and their resting ventricular performance, as evaluated by echocardiography, was normal. No patient had recent (at least one month) bacterial infection or gastrointestinal bleeding, organic renal failure, diabetes requiring insulin treatment, or cancer. Patients and controls received a diet providing 100 mmol of sodium/day for one week prior to the study. During that period, drugs able to influence the parameters under study, such as diuretics, β-blockers, vasoactive agents, non-steroidal anti-inflammatory drugs, were withdrawn, if given.

Informed consent was obtained from each patient and healthy control included in the study, which was performed according to the 1975 Declaration of Helsinki and approved by our Institution.

### 2.2. Protocol of the study

On the morning preceding the hemodynamic study, blood was taken from patients to determine the parameters needed to calculate the Child-Pugh score [20], serum creatinine, sodium and potassium, and plasma renin activity (PRA). Height and body weight were also determined to calculate body surface area. Patient body weight was evaluated once ascites had been removed by diuretic treatment or total paracentesis after the study.

Hemodynamic studies, i.e. evaluation of systemic hemodynamics and femoral blood flow, were performed with the patients and controls fasted overnight and maintained supine for at least 1 h in a quiet room at a constant temperature. Magnetic resonance imaging (MRI) to determine the dominant leg muscle mass was performed within seven days after the hemodynamic study.

### 2.3. Systemic hemodynamic evaluation

Systemic hemodynamics were evaluated by transthoracic electrical bioimpedance (TEB) (BioZ.com™; CardioDynamics International Corporation, San Diego, USA) as described in detail elsewhere [21].

*Heart rate* was recorded automatically by TEB.

*Stroke volume* (SV) was measured according to the formula [22]: $SV = VEPT \times LVET \times [(dZ/dt_{max})/BTI]$, where VEPT is the volume of electrically participating tissue; LVET, the left ventricular ejection time; $dZ/dt_{max}$, the rate of change in impedance during systole and BTI the basal thoracic impedance. In order to ensure accuracy and stability of parameters, the data displayed by TEB were the average of values collected over a 30-heartbeat interval. This value is automati-

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