

Summer 7-18-2015

## Assessment of cardiovascular physiology using dobutamine stress cardiovascular magnetic resonance reveals impaired contractile reserve in patients with cirrhotic cardiomyopathy.

Francisco Sampaio  
*University of Porto Medical School*


Pablo Lamata  
*Kings College, London, United Kingdom*

Nuno Bettencourt  
*University of Porto Medical School*

Sophie Charlotte Alt  
*Georg-August University, Goettingen*

Nuno Ferreira  
*Centro Hospitalar de Gaia/Espinho,*

Follow this and additional works at: [https://digitalcommons.unmc.edu/com\\_peds\\_articles](https://digitalcommons.unmc.edu/com_peds_articles)

 See next page for additional authors  
Part of the [Pediatrics Commons](#)

---

### Recommended Citation

Sampaio, Francisco; Lamata, Pablo; Bettencourt, Nuno; Alt, Sophie Charlotte; Ferreira, Nuno; Kowallick, Johannes Tammo; Pimenta, Joana; Kutty, Shelby; Fraga, José; Steinmetz, Michael; Bettencourt, Paulo; Gama, Vasco; and Schuster, Andreas, "Assessment of cardiovascular physiology using dobutamine stress cardiovascular magnetic resonance reveals impaired contractile reserve in patients with cirrhotic cardiomyopathy." (2015). *Journal Articles: Pediatrics*. 3.  
[https://digitalcommons.unmc.edu/com\\_peds\\_articles/3](https://digitalcommons.unmc.edu/com_peds_articles/3)

This Article is brought to you for free and open access by the Pediatrics at DigitalCommons@UNMC. It has been accepted for inclusion in Journal Articles: Pediatrics by an authorized administrator of DigitalCommons@UNMC. For more information, please contact [digitalcommons@unmc.edu](mailto:digitalcommons@unmc.edu).

---

**Authors**

Francisco Sampaio, Pablo Lamata, Nuno Bettencourt, Sophie Charlotte Alt, Nuno Ferreira, Johannes Tammo Kowallick, Joana Pimenta, Shelby Kutty, José Fraga, Michael Steinmetz, Paulo Bettencourt, Vasco Gama, and Andreas Schuster

RESEARCH

Open Access



# Assessment of cardiovascular physiology using dobutamine stress cardiovascular magnetic resonance reveals impaired contractile reserve in patients with cirrhotic cardiomyopathy

Francisco Sampaio<sup>1,2\*</sup>, Pablo Lamata<sup>3</sup>, Nuno Bettencourt<sup>1,2</sup>, Sophie Charlotte Alt<sup>4</sup>, Nuno Ferreira<sup>1</sup>, Johannes Tammo Kowallick<sup>5,6</sup>, Joana Pimenta<sup>2</sup>, Shelby Kutty<sup>7</sup>, José Fraga<sup>8</sup>, Michael Steinmetz<sup>4,6</sup>, Paulo Bettencourt<sup>2</sup>, Vasco Gama<sup>1</sup> and Andreas Schuster<sup>3,6,9</sup>

## Abstract

**Background:** Liver cirrhosis has been shown to affect cardiac performance. However cardiac dysfunction may only be revealed under stress conditions. The value of non-invasive stress tests in diagnosing cirrhotic cardiomyopathy is unclear. We sought to investigate the response to pharmacological stimulation with dobutamine in patients with cirrhosis using cardiovascular magnetic resonance.

**Methods:** Thirty-six patients and eight controls were scanned using a 1.5 T scanner (Siemens Symphony TIM; Siemens, Erlangen, Germany). Conventional volumetric and feature tracking analysis using dedicated software (CMR42; Circle Cardiovascular Imaging Inc, Calgary, Canada and Diogenes MRI; Tomtec; Germany, respectively) were performed at rest and during low to intermediate dose dobutamine stress.

**Results:** Whilst volumetry based parameters were similar between patients and controls at rest, patients had a smaller increase in cardiac output during stress ( $p = 0.015$ ). Ejection fraction increase was impaired in patients during 10  $\mu\text{g}/\text{kg}/\text{min}$  dobutamine as compared to controls (6.9 % vs. 16.5 %,  $p = 0.007$ ), but not with 20  $\mu\text{g}/\text{kg}/\text{min}$  (12.1 % vs. 17.6 %,  $p = 0.12$ ). This was paralleled by an impaired improvement in circumferential strain with low dose (median increase of 14.4 % vs. 30.9 %,  $p = 0.03$ ), but not with intermediate dose dobutamine (median increase of 29.4 % vs. 33.9 %,  $p = 0.54$ ). There was an impaired longitudinal strain increase in patients as compared to controls during low (median increase of 6.6 % vs 28.6 %,  $p < 0.001$ ) and intermediate dose dobutamine (median increase of 2.6%vs, 12.6 %  $p = 0.016$ ). Radial strain response to dobutamine was similar in patients and controls ( $p > 0.05$ ).

**Conclusion:** Cirrhotic cardiomyopathy is characterized by an impaired cardiac pharmacological response that can be detected with magnetic resonance myocardial stress testing. Deformation analysis parameters may be more sensitive in identifying abnormalities in inotropic response to stress than conventional methods.

**Keywords:** Liver, Cardiomyopathy, Magnetic resonance, Feature tracking, Strain, Dobutamine stress

\* Correspondence: fpasampaio@gmail.com

<sup>1</sup>Cardiology Department, Centro Hospitalar de Gaia/Espinho, Rua Conceição Fernandes, 4430-502 Vila Nova de Gaia, Espinho, Portugal

<sup>2</sup>University of Porto Medical School, Porto, Portugal

Full list of author information is available at the end of the article

## Background

Systolic and diastolic dysfunction, as well as electrophysiological abnormalities have been described in patients with cirrhosis [1–3]. Although previous studies have reported the presence of myocardial dysfunction at resting states [4–6], cirrhotic cardiomyopathy is usually clinically silent and may only be unmasked during physiological or inotropic stress [7].

Pharmacological stress tests using echocardiography or SPECT are often used in cirrhotic patients for diagnosing coronary artery disease before liver transplantation. Although blunted responses of stroke volume and ejection fraction (EF) to dobutamine have also been reported [8], other studies have questioned these findings, particularly in patients with mild disease [9]. Therefore, most authors recommend that dobutamine stress tests should be reserved for excluding ischaemic heart disease before liver transplantation [10].

The inability to increase cardiac output under stress conditions has been associated with the development of hepatorenal syndrome and mortality in cirrhosis [11, 12]; therefore, inotropic incompetence detection may be clinically relevant, identifying patients with a higher risk of complications, which should probably be managed more aggressively.

Cardiovascular magnetic resonance (CMR) has evolved into the reference standard methodology for assessment of cardiac morphology and volumes [13, 14]. Myocardial strain – which may reflect systolic function more accurately than conventional, highly load dependent, indices such as ejection fraction – can also be assessed using CMR, both at rest and during inotropic stimulation with dobutamine [15]. The response of strain to stress has not been previously studied in patients with cirrhosis.

To test the hypothesis that a pharmacological stress test could reveal systolic incompetence in patients with cirrhosis, we performed a comprehensive analysis of systolic function during pharmacological stress, using CMR.

## Methods

The study protocol was approved by the hospital's ethics committee (Comissão de ética CentroHospitalar de Gaia/espinho EPE) and complies with the declaration of Helsinki. Written informed consent was obtained from all participants.

Thirty-six patients with cirrhosis followed in a hepatology outpatient clinic, able to comply with the instructions during the exam, were recruited and referred to CMR. The diagnosis of cirrhosis was based on clinical, laboratory and ultrasonographic criteria and was also confirmed by liver biopsy in 22 % of the cases. Patients with a known history of hypertension, diabetes, cardiac disease or relevant ECG abnormalities were excluded. Patients with large volume ascites and/or unable to

tolerate breath-holding, renal insufficiency (creatinine clearance  $\leq 60$  ml/min/1.73 m<sup>2</sup>) or standard contraindications to CMR or gadolinium were also excluded.

A group of eight subjects, with similar age and sex distribution as the patient group, without known cardiovascular risk factors, referred to CMR for a different indication (mostly atypical chest pain evaluation) and with a completely normal scan, was used as control.

## CMR acquisition

### Patient preparation

Patients were instructed to refrain from smoking, coffee, tea, aminophylline, for 24 h before the scan. Beta-blockers were suspended 48 h before the study.

## CMR protocol

Images were acquired using a 1.5 T scanner (Siemens Symphony TIM; Siemens, Erlangen, Germany) with a 6-channel anterior chest coil and spinal coils within the gantry table.

## Cine imaging

After scout images, cine images using a retrospective ECG-gated balanced steady state free-precession sequence (TR 3.0 ms, TE 1.3 ms, flip angle  $< 90^\circ$ ) were acquired during brief periods of end-expiratory breath-hold. Two-, four and three-chamber orientations, as well as multiple equidistant short-axis planes (slice thickness 8 mm; gap 2 mm) allowing coverage of the entire cardiac volume were performed. Thirty phases were obtained per cardiac cycle.

For dobutamine stress imaging, three long-axis and three short-axis slices (basal, mid-ventricular and apical) were acquired, in order to cover 16 myocardial segments [16]. Dobutamine was infused intravenously at 3-min stages at doses of 10 and 20  $\mu\text{g}/\text{kg}/\text{min}$ . Repeat short-axis images as well as long-axis images were acquired at the end of each stage. During dobutamine infusion, patient symptoms, heart rate, blood pressure, and electrocardiogram were monitored.

## Aortic flow imaging

Aortic flow was measured using phase contrast gradient echo pulse sequence with one-direction “through-plane” motion-encoding (slice thickness 5 mm; FOV  $320 \times 320$  mm<sup>2</sup>, in-plane resolution  $\leq 1$  mm, TR/TE = 5.9/3.0 ms, flip angle  $22^\circ$ , bandwidth  $\sim 350$  Hz/pixel), centered in ascending aorta and aligned orthogonally to the expected main blood flow direction in two spatial directions, at the level of the pulmonary bifurcation. Velocity encoding sensitivity (Venc) was adapted to the expected velocities (typically 150 for the rest images and 300 during the dobutamine-stress acquisitions). Thirty frames were acquired per cardiac cycle using a

free-breathing technique with three excitations per k-space line.

### Perfusion imaging

Our protocol for stress perfusion imaging has been previously described [17]. Maximal hyperemia was achieved with intravenous adenosine ( $140 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) infusion for 5 min. Within the last 2 min of infusion, an intravenous bolus of  $0.07 \text{ mmol/Kg}$  of gadobutrol (Gadovist, Bayer HealthCare Pharmaceuticals, Berlin, Germany), was injected. Three short-axis slices (basal, mid-ventricular and apical) were imaged during the first pass of the bolus of gadolinium using a gradient echo pulse sequence with a single saturation pre-pulse per R–R interval shared over the three slices. Typical sequence parameters were: echo time, 1.18 ms; repetition time, 192 ms; inversion time, 110 ms; flip angle,  $12^\circ$ ; slice thickness, 10 mm; field of view, 290–460 mm; matrix,  $192 \times 128$  mm; in-plane spatial resolution, 1.5–2.4 mm [2]; bandwidth, 789 Hz per pixel. Patients were asked to hold their breath on full expiration for the duration of the first pass of the gadolinium bolus.

### Late gadolinium enhancement

Late gadolinium-enhancement (LGE) was assessed using a gradient-recalled phase-sensitive inversion-recovery (PSIR) sequence (TR 46 ms, TE 3.4 msec, flip angle  $15^\circ$ , IR time 280–360 msec)  $\geq 10$  min after the administration of  $0.2 \text{ mmol/kg}$  of gadobutrol.

### CMR analysis

Images were anonymized and analysis was performed by operators blinded to clinical data.

A commercially available software (CMR42; Circle Cardiovascular Imaging Inc., Calgary, Canada) was used to assess left and right ventricular volumes and function, from the short-axis cine images stack. Left ventricular ejection fraction (EF) during stress was derived from two long axis and one short axis; for comparison the same method was also used to calculate resting EF. Phase-contrast pulse sequences at rest and peak dobutamine dose were analyzed with the same software, to determine cardiac output.

Feature tracking (FT), a technique analogous to echocardiographic speckle tracking, which allows tracking of tissue voxel motion of CMR cine images [18–21] was used to assess left ventricular strain. Four-, two- and three-chamber views were used to calculate longitudinal strain. Radial strain and circumferential strain were derived from the three short-axis planes. For each parameter three repeated measurements were performed and subsequently averaged. Global longitudinal strain (GLS), global radial strain (GRS) and global circumferential strain (GCS) were defined as the mean strain of the

three individual planes. Measurements were performed at rest and at each stage of dobutamine infusion.

For the stress perfusion analysis, perfusion defects were defined as subendocardial or transmural visually dark myocardial areas when compared with remote healthy myocardium, persisting for at least 10 frames.

### Reproducibility

Reproducibility of FT derived strain was assessed in 10 randomly selected subjects. For intraobserver variability, the same operator repeated the measurements, more than 4 weeks after the initial analysis. For interobserver variability, a second operator re-analysed the images.

### Statistical analysis

Data were stored and analyzed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). Results are presented as median (25th–75th percentile) for quantitative variables and as n (%) for categorical variables. A significance level of 5 % was used.

The Mann–Whitney test was used to evaluate differences in continuous variables between groups. The Chi-squared test was used to compare proportions. Spearman's coefficient was used to test correlations. Bland–Altman analysis was performed for reproducibility testing.

### Results

Clinical characteristics and laboratorial characteristics of patients and controls are shown in Table 1. Most patients ( $n = 27$ , 75 %) were in Child-Pugh class A, eight patients (17.8 %) were in class B and only one patient was in class C.

CMR –derived morphological and functional parameters were similar at rest in patients and controls (Table 2). We found no differences in resting GLS, GCS or GRS between patients and controls. Child-Pugh class A patients had a trend towards lower left atrial volume compared to patients with more severe (class B and C) disease [ $43.3 \text{ ml/m}^2$  (35.4–49.5) vs  $47.6 \text{ ml/m}^2$  (44.1–56.7);  $p = 0.08$ ]. No differences in any of the other parameters were found, in resting conditions, between these two groups of patients.

### Dobutamine stress

The response of hemodynamic and strain parameters to increasing doses of dobutamine is shown in Table 3 and Figs. 1 and 2. Compared to controls, patients had a smaller increase of stroke volume and cardiac output during dobutamine perfusion. There was no difference in heart rate response to stress in the two groups. The increase in EF was lower in patients than in controls at the dose of  $10 \mu\text{g/kg/min}$  of dobutamine (median percentual increase of 6.9 % (3.5–12.1) vs 16.5 % (8.5–23.3),  $p = 0.007$ ),

**Table 1** Clinical and laboratorial characteristics of patients and controls

	Patients (n = 36)	Controls (n = 8)	p
Age	54 (48-61)	52 (45-54)	0.12
Male gender (n, %)	30 (83.3)	5 (62.5)	0.33
Cirrhosis aetiology			
Alcoholic (n, %)	21 (58.3)		
Viric (n, %)	10 (27.8)		
Other (n, %)	5 (13.9)		
Child-Pugh score	5 (5-7)		
MELD score	9 (7-11)		
Diuretic use (n, %)	7 (19.4 %)		
Heart rate	72 (58-78)	69 (51-72)	0.20
Mean blood pressure	98 (88-106)	100 (99-104)	0.64
Blood analysis			
Haemoglobin (g/dL)	13.4 (11.5-15.3)	14.4 (13.6-15.5)	0.21
Platelet count ( $\times 10^9/L$ )	101 (76-142)	225 (182-256)	<0.001
Creatinine (mg/dL)	0.63 (0.52-0.79)	0.74 (0.49-0.95)	0.66
Sodium (mEq/L)	139 (137-141)	142 (140-143)	0.035
Total bilirubin (mg/dL)	0.92 (0.61-1.30)	0.34 (0.22-0.48)	<0.001
Albumin (g/dL)	4.1 (3.6-4.5)	4.6 (4.5-4.9)	0.005
NT-ProBNP (pg/mL)	58 (30-140)	32 (22-53)	0.20
CRP (mg/dL)	0.25 (0.11-0.52)	0.16 (0.06-0.38)	0.42
INR	1.2 (1.1-1.3)	1.0 (0.9-1.1)	0.001

Results are presented as median (25th–75th percentile) for quantitative variables  
 CRP C-Reactive Protein, INR International Normalized Ratio, MELD Model for End-Stage Liver Disease, NT-proBNP N-terminal pro-B-type natriuretic peptide

**Table 2** CMR parameters at rest of patients and controls

	Patients (n = 36)	Controls (n = 8)	p
Left atrial volume (ml/m <sup>2</sup> )	44.9 (36.1-51.9)	44.2 (37.5-49.4)	0.92
Right atrial area (cm <sup>2</sup> )	21 (18-23)	22 (20-25)	0.35
Left ventricular diastolic volume (ml/m <sup>2</sup> )	75.1 (65.1-92.1)	87.7 (74.1-94.6)	0.27
Left ventricular systolic volume (ml/m <sup>2</sup> )	24.4 (19.1-28.9)	28.0 (23.2-33.3)	0.19
Left ventricular ejection fraction (%)	67 (64-72)	66.0 (64-70)	0.66
Left ventricular mass (g/m <sup>2</sup> )	54.7 (46.7-62.0)	55.7 (45.7-63.5)	0.96
Right ventricular diastolic volume (ml/m <sup>2</sup> )	84.5 (67.9-92.2)	84.1 (70.5-97.7)	0.46
Right ventricular ejection fraction (%)	57 (52-62)	58 (56-61)	0.46
Cardiac output (l/min)	6.5 (5.1-7.9)	6.1 (5.1-6.6)	0.74
GLS (%)	-18.9 (-16.0 to -20.5)	-19.0 (-16.1 to -20.6)	0.96
Time to Peak GLS (ms)	263 (206-317)	253 (225-281)	0.96
GCS (%)	-27.5 (-24.1 to -30.6)	-27.7 (-24.9 to -30.1)	0.84
Time to Peak GCS (ms)	264 (208-315)	223 (216-316)	0.71
GRS (%)	33.9 (25.4-39.1)	39.1 (34.8-41.8)	0.80
Time to Peak GRS (ms)	275 (216-308)	223 (215-303)	0.36

Results are presented as median (25th–75th percentile)  
 GCS Global Circumferential Strain, GLS Global Longitudinal Strain, GRS Global Radial Strain

but not at 20  $\mu\text{g}/\text{kg}/\text{min}$  (median percentual increase of 12.1 % (6.8-17.9) vs 17.6 % (10.4-28.0),  $p = 0.12$ ). The improvement in GLS during the infusion was significantly lower in patients compared to controls, both at 10  $\mu\text{g}/\text{kg}/\text{min}$  (median percentual increase of 28.6 % (6.6 % (-5.8-17.0) vs 18.9-54.4),  $p < 0.001$ ) and at 20  $\mu\text{g}/\text{kg}/\text{min}$  (median percentual increase of 2.6 % (-5.5-16.7) vs 12.6 % (10.4-29.2),  $p = 0.016$ ). Global circumferential strain increased less significantly in patients as compared to controls at 10  $\mu\text{g}/\text{kg}/\text{min}$  (median percentual increase of 14.4 % (0.6-22.9) vs 30.9 % (8.6-41.5),  $p = 0.03$ ); the response of GCS to 20  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine was not significantly different between the two groups (median percentual increase of 29.4 % (10.9-41.1) vs 33.9 % (16.7-48.5),  $p = 0.54$ ). The response of GRS to pharmacological stress was not different in patients versus controls (median percentual increase of 7.7 % (-2.4-15.2) vs 13.6 % (5.7-26),  $p = 0.11$  at 10  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine and 4.3 % (0.6-8.1) vs 3.1 % (-0.2-9.3),  $p = 0.82$  at 20  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine).

We found no differences in the response of hemodynamic and strain parameters to dobutamine between patients in Child-Pugh class A versus the others or between patients on diuretics versus patients without prior diuretic use.

There was a correlation between the percentual change of GLS and the percentual change in left ventricular stroke volume (Spearman's rho = 0.42,  $p = 0.007$ ). Changes in stroke volume and GCS (Spearman's rho = 0.11,  $p = 0.48$ ) or GRS (Spearman's rho = 0.07,  $p = 0.69$ ) were not correlated.

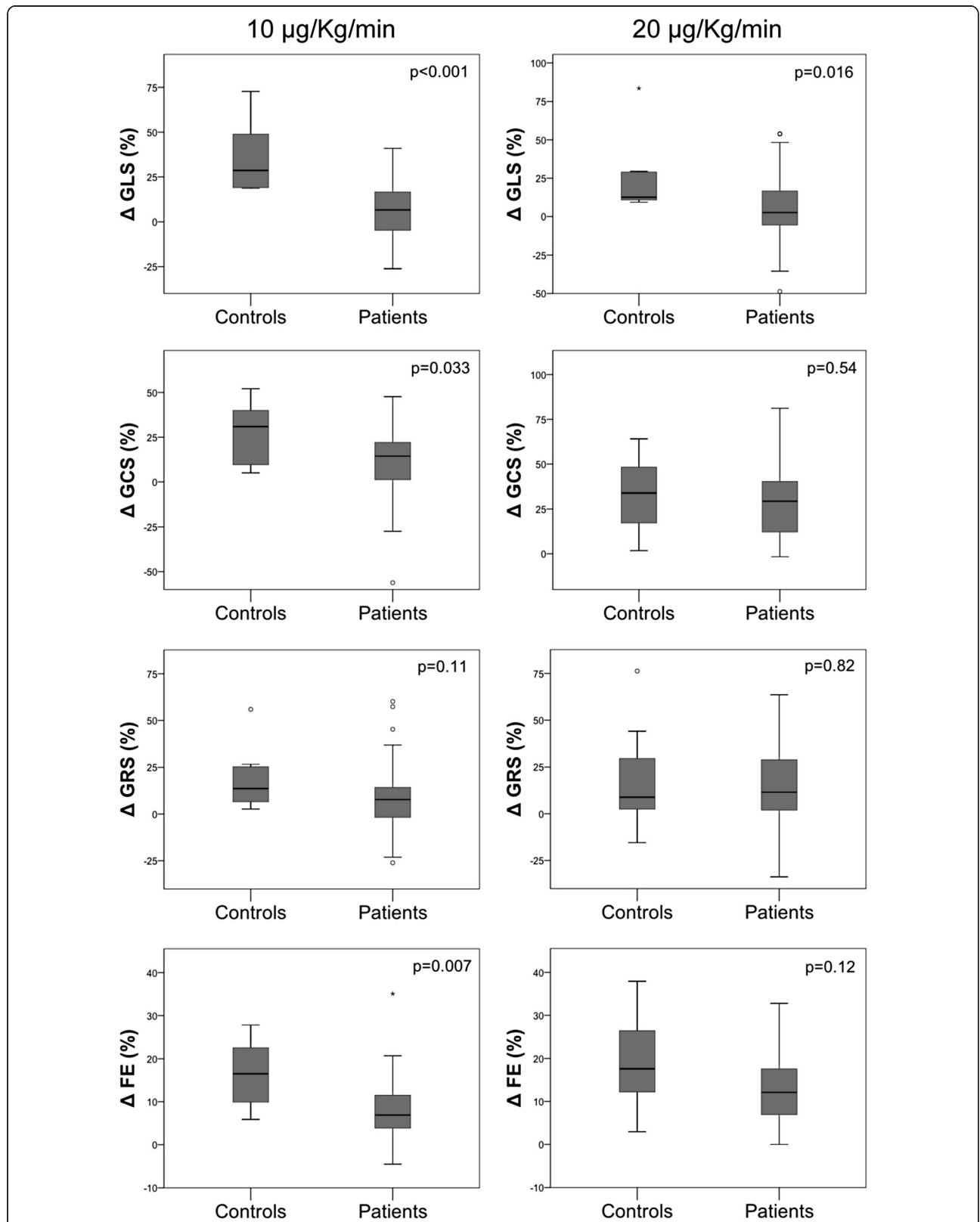
**Table 3** Hemodynamic and strain response to dobutamine

	Patients			Controls			p
	Rest	10 µg/Kg/min	20 µg/Kg/min	Rest	10 µg/Kg/min	20 µg/Kg/min	
Heart Rate (beats/min)	72 (58-78)	75 (63-84)	94 (75-111)	69 (51-72)	65 (53-91)	90 (72-118)	
Δ Heart Rate (beats/min)		3 (-2-10)			3 (-5-14)		0.94
Stroke volume (ml)	92 (80-110)		24 (5-34)			25 (18-42)	0.44
Δ Stroke volume (ml)			95 (73-113)			117 (86-144)	
Cardiac Output (l/min)	6.5 (5.1-7.9)		-1.0 (-1.5-18)			18 (4-29)	0.037
Δ Cardiac Output (l/min)			9.2 (7.0-10.4)			9.4 (8.6-11.5)	
Ejection Fraction (%) <sup>a</sup>	66 (60-69)	71 (65-74)	2.2 (1.7-3.2)	63 (61-67)	73 (72-76)	3.8 (3.4-4.9)	0.015
Δ Ejection Fraction (%)		4 (2-8)	73 (70-76)		10 (6-14)	75 (73-79)	0.006
GLS (%)	-18.9 (-16.0 to -20.5)	-19.7 (-15.9 to -22.4)	8 (5-11)	-19.0 (-16.1 to -20.6)	-23.4 (-22.1 to -26.7)	11 (7-17)	0.08
Δ GLS (%)		-1.4 (1.0 to -3.1)	-19.5 (-16.6 to -21.6)		-5.9 (-3.6 to -8.2)	-21.8 (-19.9 to -23.6)	<0.001
GCS (%)	-27.5 (-24.1 to -30.6)	-31.2 (-25.6 to -35.7)	-0.6 (1.0 to -3.0)	-27.7 (-24.9 to -30.1)	-34.7 (-32.2 to -36.3)	-2.5 (-2.3 to -5.1)	0.018
Δ GCS (%)		-4.0 (-0.1 to -5.8)	-35.7 (-30.3 to -39.3)		-8.3 (-2.6 to -10.5)	-36.1 (-34.8 to -37.3)	0.04
GRS (%)	33.9 (25.4-39.1)	35.6 (28.9-41.8)	-7.6 (-3.7 to -11.0)	31.8 (28.5-40.0)	39.1 (34.8-41.8)	-9.1 (-5.0 to -13.2)	0.48
Δ GRS (%)		1.9 (-0.9-5.3)	38.1 (29.7-43.1)		4.2 (2.2-8.2)	36.3 (33.9-41.4)	0.10
			4.2 (0.6-8.1)			3.1 (-0.2-9.3)	0.79

Results are presented as median (25th-75th percentile)

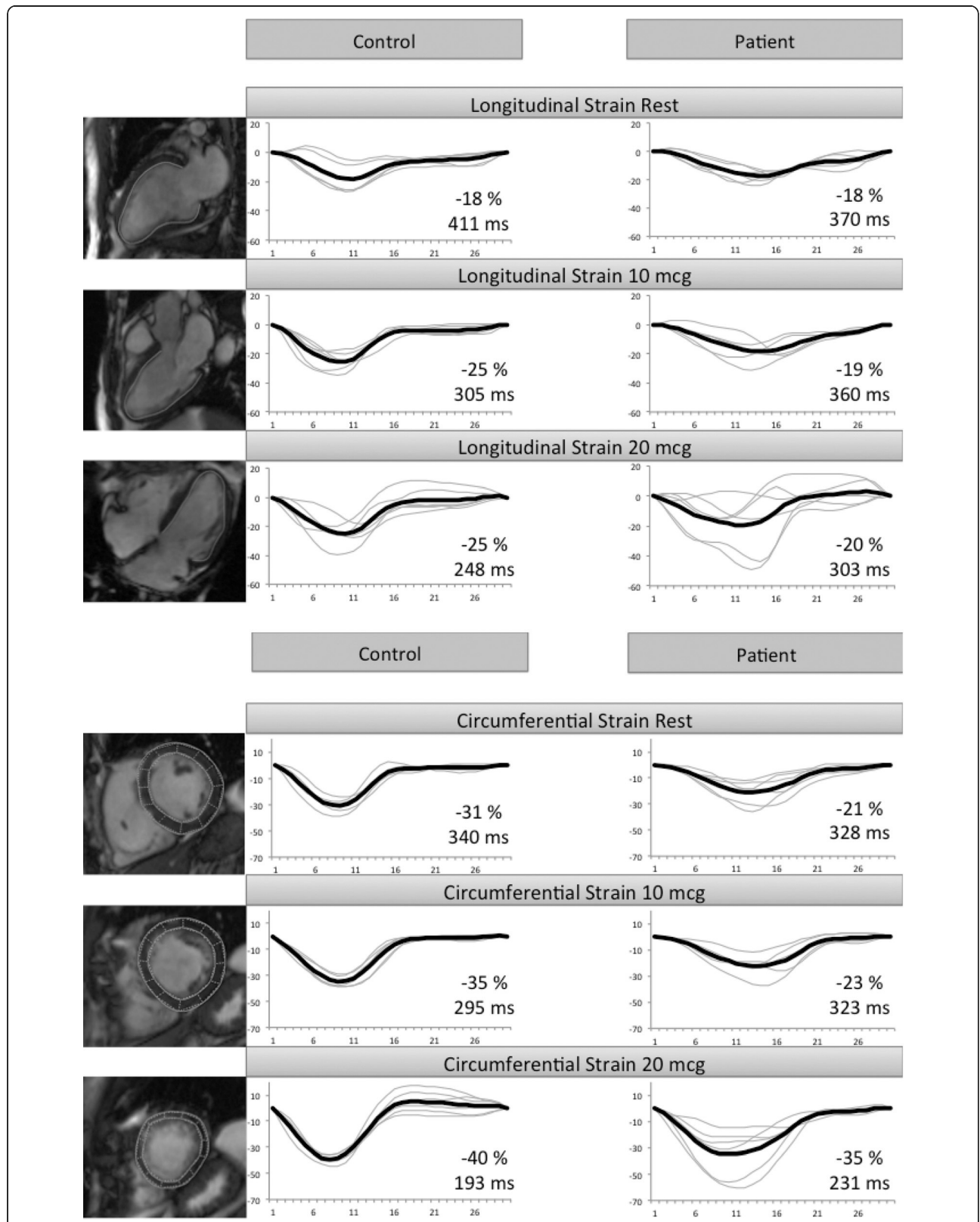
GLS global longitudinal strain, GCG global circumferential strain, GRS global radial strain, Δ absolute variation from baseline

<sup>a</sup>Derived from two long axis and one short axis



**Fig. 1** Strain and ejection fraction response to pharmacological stress. Percentual variation of strain parameters and ejection fraction with 10 µg/Kg/min and 20 µg/Kg/min of dobutamine in patients and controls. GLS – global longitudinal strain; GCS – global circumferential strain; GRS – global radial strain; EF – ejection fraction





**Fig. 2** Blunted response of strain to dobutamine. Representative example of the blunted response of longitudinal and circumferential strain to dobutamine in a patient, as compared to a control. Values written in the diagrams correspond to peak strain (%) and time to peak strain (ms), respectively

### Stress perfusion and late gadolinium enhancement

No perfusion abnormalities were detected in any subject during adenosine stress. There was no LGE in patients and controls.

### Reproducibility

The mean differences and confidence intervals between repeated strain measurements are displayed in Table 4. Reproducibility was similar at rest and with dobutamine stress. Variability was higher for GRS than for GLS and GCS.

### Discussion

Our results suggest that a dobutamine stress test can be useful in revealing systolic abnormalities in patients with mild cirrhosis. Using cardiovascular magnetic resonance derived strain, we have shown that, during low-to intermediate dose dobutamine stimulation, patients with cirrhosis had a smaller improvement in longitudinal and a delayed increase in circumferential strain compared to controls. This is, to the best of our knowledge, the first study to evaluate myocardial deformation during stress in cirrhosis.

Subendocardial fibre damage with consequent left ventricular longitudinal function impairment are usually the first manifestations of myocardial disease [22–24]. Longitudinal dysfunction was previously documented in cirrhosis, at rest [5, 6], using echocardiography. In the present study, we could not find differences in any CMR parameters at rest between patients and controls. This may be related to the early stage of disease of the majority of the patients. Patients exhibited a blunted response of GLS to dobutamine, compared to controls. The normal response of strain to dobutamine is an initial increment followed by a plateau or decrement (when

filling is reduced by increased heart-rate) [25, 26]. Our results are in line with this pattern in controls but not in the patient group. This suggests that, while in controls, the maximal inotropic effect of dobutamine is achieved with the lower dose (the higher dose having mainly a positive chronotropic effect), patients may also have a delayed response of longitudinal strain to dobutamine, with some strain still further developing at 20  $\mu\text{g}/\text{kg}/\text{min}$ . Several abnormalities in cardiomyocyte structure and function - including decreased density and down-regulation of beta-adrenergic receptors and impaired intracellular signaling pathways - have been described in animal models of cirrhosis [27, 28] and may account for our findings.

Compared to controls, patients also had a smaller increase of GCS with 10  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine; the response of GCS to 20  $\mu\text{g}/\text{kg}/\text{min}$  did not differ between the two groups. This also suggests a delayed response of circumferential strain to inotropic stimuli in cirrhosis with patients requiring higher doses of dobutamine (or more time) to equalize with the controls. Ejection fraction showed a similar behaviour: patients had a smaller improvement at the dose of 10  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine but no differences were found between the groups at 20  $\mu\text{g}/\text{kg}/\text{min}$ . The response of GRS to dobutamine was not different in patients and controls; this is in line with previous studies in ischemic heart disease patients, which have reported radial strain to be the last component of myocardial mechanics to be affected by ischemia [29].

Although previous studies have reported an abnormal cardiac response to exercise or pharmacological stress in cirrhotic patients using echocardiography and SPECT [7, 30, 31], the role of dobutamine stress testing in diagnosing cirrhotic cardiomyopathy is still a matter of debate, since its ability to detect abnormalities – mainly

**Table 4** Variability of different strain parameters at rest and during dobutamine stress

Parameter	Intraobserver variability			Interobserver variability		
	Mean difference (%)	95 % CI	p	Mean difference (%)	95 % CI	p
Rest						
GLS	0.17	−0.83-0.87	0.96	0.78	−0.57-2.13	0.23
GRS	0.92	−3.11-3.29	0.96	3.64	0.96-6.32	0.01
GCS	0.47	−0.21-1.15	0.24	0.39	−0.35-1.13	0.26
Dobutamine 10 $\mu\text{g}/\text{kg}/\text{min}$						
GLS	0.49	−1.01-2.0	0.29	1.12	0-2.24	0.05
GRS	0.64	−3.01-4.29	0.68	3.77	0.20-7.35	0.04
GCS	0.45	−0.51-1.41	0.31	0.39	−0.49-1.27	0.34
Dobutamine 20 $\mu\text{g}/\text{kg}/\text{min}$						
GLS	0.56	−0.53-1.66	0.17	0.77	−0.36-1.91	0.16
GRS	2.02	0.09-3.94	0.04	2.96	−0.70-6.63	0.10
GCS	0.39	−0.39-1.18	0.17	0.94	−0.34-2.22	0.13

GLS Global Longitudinal Strain, GRS Global Radial Strain, GCS Global Circumferential Strain

changes in volumes and EF – has been inconsistent using these imaging modalities [8, 9, 32]. The role of dobutamine stress MRI in cirrhosis has not been previously studied. Myocardial deformation analysis in this setting has also never been reported, either with CMR or echocardiography (probably because its feasibility under stress with the latter may be limited). Unlike echo, CMR does not depend on a good “acoustic window” for image acquisition, and its feasibility in quantifying strain during dobutamine stress has been demonstrated [15, 33]. Our findings may explain previous negative results [9] since preserved radial mechanics and a normal response of circumferential strain to higher doses of dobutamine, may contribute to a normal EF response during these doses, despite the smaller longitudinal strain increase.

Cardiac output increased less significantly in patients than in controls. This seems to be explained by the higher increase in stroke volume found in controls, since heart rate variation was similar in the two groups. We also found a significant correlation between the dobutamine-induced changes of GLS and stroke volume. According to these observations, inotropic incompetence, which has been reported as a feature of cirrhotic cardiomyopathy may be at least partially explained by longitudinal myocardial dysfunction. Our findings may be clinically relevant since the inability to increase cardiac output under stress conditions (such as infection or haemorrhage) may play a role in the development of hepatorenal syndrome, influencing mortality in patients with cirrhosis [11, 12]. Hence, patients exhibiting an abnormal inotropic response under pharmacological stress may need a closer follow-up and a more aggressive management of complications. However, since other studies have failed to establish a relation between cardiac dysfunction and prognosis [34–36] and we did not assess prognosis, this hypothesis remains speculative, and warrants future research.

Resting hemodynamic conditions may influence inotropic response to pharmacological stress, and our results might have been related to differences in volemia (particularly in the presence of diuretics), or neuro-humoral stimulation. However, only seven patients were on diuretics and we could not find any differences in inotropic response between them and the other patients; we also failed to find differences in cardiac chambers size, resting heart rate, blood pressure or cardiac output between patients and controls. Taken altogether, these findings argue against an effect of different basal hemodynamics on our results.

Under adenosine stress, we did not detect ischemia, which could have influenced inotropic response to dobutamine, in any subject. Although a quantitative perfusion analysis was not performed, our methodology has been shown to be highly accurate in detecting functionally significant coronary artery disease [17].

In contrast with a previous study [37], we did not find LGE in any patient. The difference in disease severity between the two studies probably accounts for these findings since myocardial fibrosis may only be detectable in more advanced disease states as a result of the chronic activation of the renin-angiotensin-aldosterone system.

### Limitations

This is a single center study performed in patients mainly with alcoholic cirrhosis and mild disease. Since we have excluded patients that would not be able to comply with the instructions or tolerate the breath holding at rest our results may not be generalized to all patients with cirrhosis. Furthermore, we cannot exclude the occurrence of type two errors, due to the small size of the control group.

We aimed to evaluate the contractile response to dobutamine stress with the maximum extent of inotropic response expected with doses of 10–20  $\mu\text{g}/\text{kg}/\text{min}$  of dobutamine [38]. However we cannot exclude that a full test (40  $\mu\text{g}/\text{kg}/\text{min}$ ) would have potentially added valuable information despite the fact that we didn't observe significant perfusion defects with adenosine stress.

Due to time constraints, no full cine short axis stacks for volumetric analysis were obtained during stress. Additionally, it would have been interesting to evaluate diastolic function, particularly under stress. Although diastolic strain rate can be computed with feature tracking, the relatively low temporal resolution of cine imaging (further reduced at faster heart rates during stress), may limit its feasibility.

There is no widely accepted gold-standard method to diagnose cirrhotic cardiomyopathy; on the other hand, there are no well-established normal values of CMR-derived strain parameters at rest and under pharmacological stress. Hence, the diagnostic accuracy of our methodology cannot be objectively determined and definitive cut-offs cannot be provided.

We could not perform a T1-mapping analysis, which might have allowed us to detect the presence of diffuse myocardial fibrosis.

### Conclusions

Patients with cirrhosis show inotropic incompetence to pharmacological stress, due to intrinsic myocardial dysfunction.

CMR with myocardial deformation analysis may be a sensitive diagnostic tool to identify abnormal inotropic responses to stress already present at early disease states, which may be difficult to detect with other non-invasive imaging modalities. The significance of this impaired response to pharmacological stress in cirrhotic cardiomyopathy and its prognostic implications should be further explored in future prospective clinical investigations.

**Abbreviations**

SPECT: Single-photon emission computed tomography; EF: Ejection fraction; CMR: Cardiovascular magnetic resonance; FT: Feature tracking; GLS: Global longitudinal strain; GRS: Global radial strain; GCS: Global circumferential strain; LGE: Late gadolinium enhancement.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

FS and NB were involved in the conception and design of the study as well as data collection, analysis, interpretation, and drafting of the manuscript. JP and PB participated in the conception and design of the study, interpretation of the data and revision of the manuscript. NF was involved in data acquisition and revision of the manuscript. JF and VG were involved in data gathering and revision of the manuscript. PL, SCA, JTK and SK were involved in data analysis and revision of the manuscript for important content. AS participated in the scientific discussion involving study design, performed data analysis, interpretation, and drafting of the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

The authors would like to thank the radiographers David Monteiro, Nuno Almeida, Júlio Antunes and Pedro Rodrigues for their hard work. PL holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant Number 099973/Z/12/Z).

**Author details**

<sup>1</sup>Cardiology Department, Centro Hospitalar de Gaia/Espinho, Rua Conceição Fernandes, 4430-502 Vila Nova de Gaia, Espinho, Portugal. <sup>2</sup>University of Porto Medical School, Porto, Portugal. <sup>3</sup>Division of Imaging Sciences and Biomedical Engineering, The Rayne Institute, Kings College London, St. Thomas' Hospital, London, UK. <sup>4</sup>Department of Pediatric Cardiology and Intensive Care Medicine, Georg-August University, Göttingen, Germany. <sup>5</sup>Institute for Diagnostic and Interventional Radiology, Georg-August University, Göttingen, Germany. <sup>6</sup>DZHK (German Centre for Cardiovascular Research), Göttingen, Germany. <sup>7</sup>University of Nebraska Medical Center/Children's Hospital and Medical Center, Omaha, NE, USA. <sup>8</sup>Gastroenterology Department, Centro Hospitalar de Gaia/Espinho, Espinho, Portugal. <sup>9</sup>Department of Cardiology and Pneumology, Georg-August University, Göttingen, Germany.

Received: 10 September 2014 Accepted: 22 June 2015

Published online: 18 July 2015

**References**

- Møller S, Hove JD, Dixen U, Bendtsen F: New insights into cirrhotic cardiomyopathy. *Int J Cardiol* 2013;167:1101-8.
- Wong F: Cirrhotic cardiomyopathy. *Hepatol Int*. 2009;3:294-304.
- Møller S, Henriksen JH: Cardiovascular complications of cirrhosis. *Gut*. 2008;57:268-78.
- Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, et al: Left atrial function is impaired in cirrhosis: a speckle tracking echocardiographic study. *Hepatol Int*. 2014;8:146-53.
- Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, et al: Systolic and diastolic dysfunction in cirrhosis: a tissue-Doppler and speckle tracking echocardiography study. *Liver Int* 2013;33:1158-65.
- Kazankov K, Holland-Fischer P, Andersen NH, Torp P, Sloth E, Aagaard NK, et al: Resting myocardial dysfunction in cirrhosis quantified by tissue Doppler imaging. *Liver Int*. 2011;31:534-40.
- Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S: Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. *Eur J Gastroenterol Hepatol*. 2010;22:1085-92.
- Kim MY, Baik SK, Won CS, Park HJ, Jeon HK, Hong HI, et al: Dobutamine stress echocardiography for evaluating cirrhotic cardiomyopathy in liver cirrhosis. *Korean J Hepatol*. 2010;16:376-82.
- Dahl EK, Møller S, Kjær A, Petersen CL, Bendtsen F, Krag A: Diastolic and autonomic dysfunction in early cirrhosis: a dobutamine stress study. *Scand J Gastroenterol*. 2014;49:362-72.
- Møller S, Henriksen JH: Cirrhotic cardiomyopathy. *J Hepatol*. 2010;53:179-90.
- Krag A, Bendtsen F, Henriksen JH, Møller S: Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut*. 2010;59:105-10.
- Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Gines P, Moreira V, et al: Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology*. 2005;42:439-47.
- Lima JAC, Desai MY: Cardiovascular magnetic resonance imaging: current and emerging applications. *J Am Coll Cardiol*. 2004;44:1164-71.
- Attali AK, Schuster A, Nagel E, Reiber JH, van der Geest RJ: Quantification in cardiac MRI: advances in image acquisition and processing. *Int J Cardiovasc Imaging*. 2010;26 Suppl 1:27-40.
- Schuster A, Kutty S, Padiyath A, Parish V, Gribben P, Danford DA, et al: Cardiovascular magnetic resonance myocardial feature tracking detects quantitative wall motion during dobutamine stress. *J Cardiovasc Magn Reson*. 2011;13:58.
- Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al: Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539-42.
- Bettencourt N, Chiribiri A, Schuster A, Ferreira N, Sampaio F, Duarte R, et al: Cardiac magnetic resonance myocardial perfusion imaging for detection of functionally significant obstructive coronary artery disease: a prospective study. *Int J Cardiol*. 2013;168:765-73.
- Hor KN, Gottliebson WM, Carson C, Wash E, Cnota J, Fleck R, et al: Comparison of magnetic resonance feature tracking for strain calculation with harmonic phase imaging analysis. *JACC Cardiovasc Imaging*. 2010;3:144-51.
- Kowallick J, Kutty S, Edelmann F, Chiribiri A, Villa A, Steinmetz M, et al: Quantification of left atrial strain and strain rate using Cardiovascular Magnetic Resonance myocardial feature tracking: a feasibility study. *J Cardiovasc Magn Reson* 2014;16:60.
- Morton G, Schuster A, Jogiya R, Kutty S, Beerbaum P, Nagel E: Inter-study reproducibility of cardiovascular magnetic resonance myocardial feature tracking. *J Cardiovasc Magn Reson*. 2012;14:43.
- Padiyath A, Gribben P, Abraham JR, Li L, Rangamani S, Schuster A, et al: Echocardiography and cardiac magnetic resonance-based feature tracking in the assessment of myocardial mechanics in tetralogy of Fallot: an intermodality comparison. *Echocardiography*. 2013;30:203-10.
- Poulsen SH, Andersen NH, Heickendorff L, Mogensen CE: Relation between plasma amino-terminal propeptide of procollagen type III and left ventricular longitudinal strain in essential hypertension. *Heart*. 2005;91:624-9.
- Cardim N, Oliveira AG, Longo S, Ferreira T, Pereira A, Reis RP, et al: Doppler tissue imaging: regional myocardial function in hypertrophic cardiomyopathy and in athlete's heart. *J Am Soc Echocardiogr*. 2003;16:223-32.
- Andersen NH, Poulsen SH, Eiskjaer H, Poulsen PL, Mogensen CE: Decreased left ventricular longitudinal contraction in normotensive and normoalbuminuric patients with Type II diabetes mellitus: a Doppler tissue tracking and strain rate echocardiography study. *Clin Sci*. 2003;105:59-66.
- Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al: Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12:167-205.
- Bijnens BH, Cikes M, Claus P, Sutherland GR: Velocity and deformation imaging for the assessment of myocardial dysfunction. *Eur J Echocardiogr*. 2009;10:216-26.
- Lee SS, Marty J, Mantz J, Samain E, Brailon A, Lebrec D: Desensitization of myocardial beta-adrenergic receptors in cirrhotic rats. *Hepatology*. 1990;12:481-5.
- Gerbes AL, Remien J, Jungst D, Sauerbruch T, Paumgartner G: Evidence for down-regulation of beta-2-adrenoceptors in cirrhotic patients with severe ascites. *Lancet*. 1986;1:1409-11.
- Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, et al: Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. *J Am Coll Cardiol*. 2008;51:149-57.
- Kelbaek H, Rabol A, Brynjolf I, Eriksen J, Bonnevie O, Godtfredsen J, et al: Haemodynamic response to exercise in patients with alcoholic liver cirrhosis. *Clin Physiol*. 1987;7:35-41.
- Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L: The cardiac response to exercise in cirrhosis. *Gut*. 2001;49:268-75.

32. Krag A, Bendtsen F, Dahl EK, Kjaer A, Petersen CL, Moller S. Cardiac function in patients with early cirrhosis during maximal beta-adrenergic drive: a dobutamine stress study. *PLoS One*. 2014;9:e109179.
33. Schuster A, Paul M, Bettencourt N, Morton G, Chiribiri A, Ishida M, et al. Cardiovascular magnetic resonance myocardial feature tracking for quantitative viability assessment in ischemic cardiomyopathy. *Int J Cardiol*. 2013;166:413–20.
34. Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva A-P, Valente J, et al. Systolic dysfunction and diastolic dysfunction do not influence medium-term prognosis in patients with cirrhosis. *Eur J Intern Med* 2014;25:241-6
35. Nazar A, Guevara M, Sitges M, Terra C, Solà E, Guigou C, et al. LEFT ventricular function assessed by echocardiography in cirrhosis: Relationship to systemic hemodynamics and renal dysfunction. *J Hepatol*. 2013;58:51–7.
36. Alexopoulou A, Papatheodoridis G, Pouriki S, Chrysohoou C, Raftopoulos L, Stefanadis C, et al. Diastolic myocardial dysfunction does not affect survival in patients with cirrhosis. *Transpl Int*. 2012;25:1174–81.
37. Lossnitzer D, Steen H, Zahn A, Lehrke S, Weiss C, Weiss KH, et al. Myocardial late gadolinium enhancement cardiovascular magnetic resonance in patients with cirrhosis. *J Cardiovasc Magn Reson*. 2010;12:47.
38. Jewitt D, Birkhead J, Mitchell A, Dollery C. Clinical cardiovascular pharmacology of dobutamine, A selective inotropic catecholamine. *Lancet*. 1974;2:363–7.

**Submit your next manuscript to BioMed Central  
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

