

Non invasive continuous hemodynamic evaluation of cirrhotic patients after postural challenge

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of higher values of cardiac index, stroke volume index and cardiac cycle efficiency.

CONCLUSION: Most Care proved to be able to detect cardiovascular abnormalities bedside in the resting state and after postural challenge in cirrhotic patients.

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Key words: Liver cirrhosis; Non-invasive hemodynamic; Pressure recording analytical method; Posture

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Abstract

AIM: To assess whether Most Care is able to detect the cardiovascular alterations in response to physiological stress (posture).

METHODS: Non invasive hemodynamic was assessed in 26 cirrhotic patients compared to healthy subjects, both in the supine and standing positions.

RESULTS: In baseline conditions, when compared to healthy subjects, cirrhotic patients showed significantly lower values of diastolic and diastolic pressures and systemic vascular resistance. While in the standing position, cirrhotic patients showed higher values of cardiac index, stroke volume index and cardiac cycle efficiency. When returning to the supine position, cirrhotic patients exhibited lower values of diastolic and diastolic pressures and systemic vascular resistance in the presence

INTRODUCTION

Historically, liver cirrhosis has not been associated with any cardiac abnormalities, despite the fact that a hyperdynamic circulation was described in patients with cirrhosis over 50 years ago^[1]. Beginning in the late 1980s, occasional reports of unexpected deaths due to heart failure following liver transplantation^[2], transjugular intrahepatic portosystemic stent shunt (TIPS) insertion^[3] and surgical portocaval shunts^[4] led to growing interest in investigating cardiac dysfunction related to cirrhosis. Over the last 2 decades, there is accumulating evidence to suggest that the presence of cirrhosis per se is associated with significant cardiovascular abnormalities, irrespective of the cause of cirrhosis^[5]. The majority of patients are diagnosed during phases of clinical decompensation of

cirrhosis in which they present with features of diastolic heart failure and/or high-output heart failure. Investigators have reported an increased risk of death due to cardiovascular complications following the insertion of a transjugular intrahepatic TIPS^[6,7] and after liver transplantation^[8]. Patients who experienced these complications had pre existing changes in cardiac performance that suggest a diagnosis of cirrhotic cardiomyopathy^[9].

The identification of cardiovascular abnormalities has been made mainly by means of echocardiography^[5,9]. Recently, non invasive technologies based on the analysis of the peripheral arterial waveform pulse contour methods are gaining popularity in various settings. Among them, Most Care [pressure recording analytical method, (PRAM)] has been recently introduced and it has been proved to be feasible and accurate in different clinical settings, both in stable and unstable patients^[10-14]. Unlike echo-cardiography, it is operator-independent and it allows a beat-by-beat hemodynamic evaluation, lasting even for hours.

The aim of the present investigation was to assess whether the PRAM methodology which allows a non invasive beat-to-beat hemodynamic evaluation, is able to detect the cardiovascular alterations in response to physiological stress (posture) in 26 cirrhotic patients compared to healthy subjects.

MATERIALS AND METHODS

Twenty-six consecutive non-smoking patients with liver cirrhosis [indicated by Child-Pugh score in 17 A, 8 B, 6 C; 11 patients with ascites (AC), 15 without (CC); 19 males; mean age 59.45 ± 13.4 years, range 32-86 years] who attended outpatients at the Department of Internal Medicine, University of Florence, Italy, from March to July 2008, were included in the study. The diagnosis of cirrhosis was based on the patients' history, physical examination, liver ultrasound and laboratory findings, and was confirmed by transjugular liver biopsy when not contraindicated. Cirrhosis was hepatitis C virus-related in 24 patients and hepatitis B virus-related in 2. All patients had portal hypertension, as indicated by measuring hepatic venous pressure gradient. No patient had infection, organic cardiovascular, renal or pulmonary diseases, hypoxemia in clino- or orthostatic position; diabetes, type 1 hepatorenal syndrome^[15], hepatocellular carcinoma or other malignancies; recent gastrointestinal bleeding or a North Italian Endoscopic Club score ≥ 35 ^[16]. No patient was taking β -blockers or nitrates in the 7 d preceding or during the study. Ten healthy subjects of comparable sex and age from the medical and laboratory staff of our unit constituted the control group healthy subjects. The investigation conforms to the principles outlined in the Declaration of Helsinki, was approved by the Local Ethical Committee and all subjects gave their informed written consent to participate in the study.

On the day of the study, after a 30 min resting period (equilibrium), data were obtained, in each subject, for a supine resting period (baseline phase) throughout the

standing period (stress phase) and after return to the supine position (recovery phase). Each step lasted 10 min. The blood pressure (BP) measurements were assessed by digital photoplethysmography (Finapres)^[11].

We performed the hemodynamic evaluation from the signal pressure obtained by Finapres from the analogical output. Analysis of the signal blood pressure was performed, in real time, beat-by-beat, by MostCare[®] monitor (Vytech, Padova, Italy). This device uses the hemodynamic estimation by the PRAM^[10-14] of the systemic BP waves from the Finapres. The computed values of stroke volume PRAM were displayed in real time and the corresponding results beat-to-beat were recorded and stored for subsequent check of the data.

The data from each subject were reviewed and edited manually to remove artefacts (which consisted of the calibration intervals, devoid of pressure signal by the Finapres). Data from pressure signals were evaluated, averaging 1 min periods at halfway of the baseline, halfway of the stress phase, and halfway of the recovery phase, by averaging 30 s before and 30 s after the selected time.

PRAM sampling BP morphology wave at 1000 Hz and data were electronically stored. PRAM needs neither calibration nor pre-estimated parameters of patients (such as gender, age, anthropometric data). The hemodynamic variables obtained beat to beat by this monitoring system were: systolic, diastolic, dicrotic and mean arterial pressures (mmHg); cardiac index (CI; L/min/m²); stroke volume index (SVI; mL/m²); dp/dt_{max} (mmHg/s)^[11,14]; cardiac cycle efficiency (CCE; units)^[10-14]; Systemic Vascular Resistance Index (SVRI; dyne*sec/cm⁵); and Pulse Pressure variation (%).

PRAM methodology

The analysis of the wave form is based on the theory that in any given vessel, volume changes occur mainly because of radial expansion in response to variations in pressure^[10]. This process involves the interplay of several physical parameters, including force of left ventricular ejection, arterial impedance counter acting the pulsatile blood inflow, arterial compliance and peripheral, small vessel resistance. These variables are tightly interdependent and simultaneously estimated by PRAM. Thus, any kind of flow that is perceived at the peripheral arterial level, whether pulsatile or continuous as in physiological conditions, can be evaluated. The PRAM technique, based on the analysis of the peripheral artery waveform morphology, has been extensively described elsewhere^[10,12], in various clinical and experimental settings^[10-14]. The PRAM analyzes and identifies the characteristic points of the pressure wave during each beat (diastolic, systolic, dicrotic and resonant points pressure during the systolic and end-diastolic phases), thus performing a beat-to-beat hemodynamic assessment^[10,12-14].

Statistical analysis

Data were entered in a dedicated data-base and processed by means of SPSS 13.0 statistical package (SPSS Inc. Chicago, IL). Data were expressed as mean \pm SD and were

Table 1 Beat-to-beat, non invasive hemodynamic evaluation in healthy subjects

	SBP	DBP	DIC	HR	SVR	CCE	SVI	CI	dP/dT
Baseline	117 ± 13	65 ± 7	82 ± 8	68 ± 10	1252 ± 144	0.111 ± 0.12	0.0412 ± 0.009	2.81 ± 0.35	0.81 ± 0.14
Standing	111 ± 11	68 ± 15	84 ± 13	78 ± 11 ^a	1504 ± 301 ^b	-0.193 ± 0.223 ^b	0.0305 ± 0.009 ^b	2.34 ± 0.46 ^a	0.72 ± 0.17
Recovery	121 ± 16	67 ± 8	86 ± 10	66 ± 10 ^a	1260 ± 139 ^b	0.040 ± 0.25	0.0424 ± 0.007 ^a	2.86 ± 0.32 ^b	0.82 ± 0.16

^a $P < 0.05$; ^b $P < 0.01$ vs baseline. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DIC: Dicrotic pressure; HR: Heart rate; SVR: Systemic vascular resistance; CCE: Cardiac cycle efficiency; SVI: Stroke volume indexed; CI: Cardiac index.

analysed by Student-*t* test for paired and unpaired measure. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Healthy subjects

As depicted in Table 1, healthy subjects showed, when assuming the standing position, a significant increase in heart rate and SVR ($P < 0.05$ and $P < 0.01$, respectively) associated with a significant reduction ($P < 0.05$) in stroke volume index, cardiac index and CCE.

The standing *vs* recovery phase was associated with a significant reduction in heart rate ($P < 0.05$) and SVR ($P < 0.05$) and increase for CI and SVI ($P < 0.05$ and $P < 0.01$ respectively).

For all variables, there were no significant changes between phases, base-returning supine.

Cirrhotic patients

Cirrhotic patients exhibited, with the assumption of the standing position, an increase heart rate and SVR ($P < 0.05$ and $P < 0.01$, respectively) associated with a significant reduction in cardiac index and stroke volume index (Table 2). From the standing to the recovery phase, heart rate and SVR decreases ($P = 0.038$ and $P = 0.043$). The CI, SVI and CCE significantly increase from the standing position to recovery phase ($P = 0.037$, $P < 0.001$ and $P = 0.002$ respectively). From the comparison between the phases base *vs* recovery, there are no significant variations in our variables.

Comparison between healthy subjects and cirrhotic patients

In baseline conditions, when compared to healthy subjects, cirrhotic patients showed significant lower values of dicrotic and diastolic pressures and SVR, no difference in heart rate and higher CI, SVI and CCE (Table 3).

In the standing position, dicrotic pressure and SVR were lower in cirrhotic patients, who showed higher values of CI, SVI and CCE in cirrhotic patients compared to healthy subjects.

When returning to the supine position, cirrhotic patients exhibited lower values of dicrotic and diastolic pressures and SVR. In cirrhotic patients, there were no significant differences for the HR and systolic pressure. CI, SVI and CCE were higher when compared to healthy subjects (Table 3).

DISCUSSION

The main finding of the present investigation is that cardiovascular abnormalities, as indicated by increased cardiac output and reduced SVR, are detectable in cirrhotic patients when compared to healthy patients, both in the supine and in the standing position, bedside, by means of PRAM methodology, a non invasive beat-to-beat hemodynamic monitoring.

While previous studies investigating hemodynamics in liver cirrhosis were mainly performed by echocardiography^[5,9], which is known to be operator-dependent, in the present study we used PRAM monitoring, which proved to be feasible since it is non invasive and does not need calibration.

Recent studies documented the clinical impact of cardiovascular abnormalities in cirrhotic patients^[17], especially when submitted to surgical procedures, such as TIPS insertion^[6,7,18] and liver transplantation^[19]. Sampathkumar and colleagues^[19] reported severe myocardial dysfunction in 1% of patients after liver transplantation, since during reperfusion, the return of a significant volume to the heart can unmask any diastolic dysfunction. When followed long-term for over 1 year, there is complete reversal of cardiac changes in post transplant patients.

Although cardiac complications are usually seen in patients with more advanced liver disease, adverse cardiac outcomes can still occur in patients who are not as ill^[20] and overt manifestations of cardiovascular dysfunction often only become evident after a cirrhotic patient is exposed to physiological, surgical or drug-induced stress. In this context, PRAM methodology appears, according to our data, able to detect cardiovascular alterations in cirrhotic patients, both at rest and during postural change, by means of a bedside non invasive evaluation.

In the present investigation, we furthermore documented that cirrhotic patients, when evaluated by means of PRAM, showed an altered cardiovascular response to physiological stress (both assuming the standing position and returning to the resting state).

This is in keeping with previous studies^[21-24] performed by means of echocardiography during active tilting. Laffi *et al*^[21] assessed the inotropic and chronotropic response in a group of non alcoholic cirrhotic patients and reported a significantly decreased stroke volume in response to active tilting, leading to a reduced cardiac index despite a significant increase in heart rate. In 1999, Gentilini *et al*^[22] observed that compensated cirrhotic

Table 2 Beat-to-beat, non invasive hemodynamic evaluation in cirrhotic patients

	SBP	DBP	DIC	HR	SVR	CCE	SVI	CI	dP/dT
Baseline	112 ± 16	53 ± 8	65 ± 11	69 ± 9	973 ± 169	0.29 ± 0.13	0.051 ± 0.008	3.57 ± 0.52	1.06 ± 0.23
Standing	117 ± 18	61 ± 9 ^b	71 ± 10	79 ± 13 ^a	1150 ± 281 ^a	0.183 ± 0.17 ^a	0.042 ± 0.009 ^b	03.31 ± 0.63	1.01 ± 0.24
Recovery	116 ± 20	56 ± 11	69 ± 16	70 ± 10 ^a	1047 ± 158	0.253 ± 0.12	0.0514 ± 0.001 ^a	3.32 ± 0.42	1.02 ± 0.21

^a*P* < 0.05; ^b*P* < 0.01 *vs* baseline. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DIC: Dicrotic pressure; HR: Heart rate; SVR: Systemic vascular resistance; CCE: Cardiac cycle efficiency; SVI: Stroke volume indexed; CI: Cardiac index.

Table 3 Comparison between healthy subjects and cirrhotic patients

	SBP	DBP	DIC	HR	SVR	CCE	SVI	CI	dP/dT
Baseline									
HS <i>vs</i> C	NS	< 0.001	< 0.001	NS	< 0.001	< 0.001	0.01	< 0.001	< 0.001
Standing									
HS <i>vs</i> C	NS	NS	0.02	NS	< 0.001	0.02	0.01	< 0.001	< 0.001
Recovery									
HS <i>vs</i> C	NS	< 0.01	< 0.001	NS	< 0.001	NS	< 0.05	< 0.01	0.02

HS: Healthy subjects; C: Cirrhotic patients; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DIC: Dicrotic pressure; HR: Heart rate; SVR: Systemic vascular resistance; CCE: Cardiac cycle efficiency; SVI: Stroke volume indexed; CI: Cardiac index.

patients, both normotensive and hypertensive, showed an altered cardiovascular response to postural challenge characterized by reduced left ventricular telediastolic volume and stroke volume and cardiac index associated with a marked activation of the renin-angiotensin system. Similarly, Bernardi *et al*^[23] observed (by means of Doppler echocardiography) that while standing, hemodynamic patterns of cirrhotic patients and controls did not differ and increased cardiac index and reduced systemic vascular resistance were detectable in cirrhotic patients in the supine position compared to controls. The authors concluded that hyperdynamic circulation appeared, or was enhanced, by the lying position. An altered cardiovascular response was also documented in cirrhotic patients by Moller *et al*^[24] after 30 degrees head-down tilting and after 60 degrees passive head-up tilting.

A possible limitation of the study is that the number of enrolled patients is small. However, the behavior of hemodynamic parameters, as assessed by PRAM methodology, was uniform in cirrhotic patients, so that differences were clearly detectable between patients and healthy subjects.

In conclusion, PRAM methodology proved to be able to detect cardiovascular abnormalities both in the resting state and after postural challenge by means of a non invasive continuous bedside hemodynamic evaluation in cirrhotic patients when compared to healthy subjects. This new methodology could therefore represent a feasible tool for a clinically more accurate non invasive continuous hemodynamic monitoring in these patients.

COMMENTS

Background

The presence of cirrhosis per se has been associated with significant cardiovascular abnormalities, irrespective of the cause of cirrhosis and an increased risk of death due to cardiovascular complications has been recently reported following surgical procedures in cirrhotic patients.

Research frontiers

So far, cardiovascular assessment in cirrhosis has been performed mainly by echocardiography, which is operator-dependent and does not allow a beat-to-beat evaluation. Recently non invasive technologies based on the analysis of the peripheral arterial waveform pulse contour methods are gaining popularity in various settings. Among them, Most Care [pressure recording analytical method (PRAM)] has been recently introduced and it has been proved to be feasible and accurate in different clinical settings, both in stable and unstable patients.

Innovations and breakthroughs

This is the first investigation assessing whether the PRAM methodology which allows a noninvasive beat-to-beat hemodynamic evaluation, is able to detect the cardiovascular alterations in response to physiologic stress (posture) in cirrhotic patients in respect to healthy subjects.

Applications

Cardiovascular abnormalities, as indicated by increased cardiac output and reduced systemic vascular resistance, are detectable in cirrhotic patients, when compared to healthy patients, both in the supine and in the standing position, bedside, by means of PRAM methodology. A continuous non invasive hemodynamic monitoring is therefore feasible by PRAM methodology in cirrhotic patients in stable conditions and during procedures.

Terminology

The terminology has been explained in the text.

Peer review

This study investigated the cardiovascular alternations in response to physiologic stress by PRAM methodology in 26 cirrhotic patients and 10 healthy subjects. The main findings of the study are that the cardiac output is higher and SVR lower in the cirrhotic patients than the healthy subjects by means of PRAM methodology both in the supine and standing position.

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