Research Article

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Non-Invasive measurement of systemic haemodynamics by finometry in patients with cirrhosis

Abstract

Background and aim: Cirrhosis and portal hypertension are characterized by a hyperdynamic circulation, which is independently associated with portal pressure and variceal size. Measurement is invasive and performed in limited centers; non-invasive techniques are available. We assessed whether non-invasive measurement of systemic haemodynamics can identify the hyperdynamic circulation and its associations with portal pressure and variceal size.

Methods: We studied 29 cirrhotic patients. Systemic haemodynamics were studied non-invasively using the Finometer® (cardiac output/index CO/CI, heart rate HR, peripheral vascular resistance PVR). Gastroscopy assessed variceal presence, size and bleeding risk. Portal pressure was assessed by hepatic venous pressure gradient (HVPG).

Results: A significant negative correlation was seen between CO and PVR (r=-0.95, p<0.001). Significant positive correlations were seen between CI, HR, HVPG and Child-Pugh score (r=0.36, r=0.37 and r=0.58 respectively). HVPG correlated positively with HR and CI (r=0.62, p<0.001 and r=0.53, p=0.05 respectively). Significant differences in haemodynamic parameters were seen according to variceal size.

Conclusion: Assessment of systemic haemodynamics by finometry can identify the hyperdynamic circulation in cirrhosis and may aid non-invasive diagnosis of portal hypertension and oesophageal varices.

Keywords: finometer, cardiac output, cirrhosis, varices, child-pugh, haemodynamics, esophageal varices

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Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; CI, cardiac index; PVR, peripheral resistance; HVPG, hepatic venous pressure gradient

Introduction

Kowalski and Abelmann originally described the hyperdynamic circulation associated with cirrhosis in 1953, which is characterized by an increased cardiac output, heart rate, and stroke volume and reduced peripheral vascular resistance.[1] The hyperdynamic circulation of cirrhosis is characterized by increased cardiac output and decreased systemic vascular resistance being independently associated with portal pressure.[2–5] In cirrhotic patients these haemodynamic parameters may be a good marker of the development of portal hypertension and its complications. Traditionally, measurement of cardiac output is by the thermodilution method, but it is invasive carrying significant complication risks. The Finometer® Finapres Medical Systems, Amsterdam, The Netherlands is a non-invasive device for measuring systemic haemodynamics, that allows continuous beat-to-beat blood pressure and haemodynamic monitoring utilizing a volume-clamp from which aortic flow waveform can be calculated. Using the Model flow method the computed output of the model gives aortic flow as a function of time from which stroke volume can be derived and subsequently Cardiac output can be calculated as the product of stroke volume and heart rate.[6] The aim of this prospective study was to assess whether non-invasive measurement of systemic haemodynamics using Finometry can identify the hyperdynamic circulation in cirrhosis and whether these haemodynamic changes correlate with portal pressure and the presence or size of oesophageal varices.

Patients and methods

Patients: 29 cirrhotic patients, irrespective of aetiology, diagnosed either on the basis of liver histology, radiological findings or other supporting evidence of clinically significant portal hypertension oesophago-gastric varices, ascites, and hepatic encephalopathy were studied. All patients were known to have oesophageal varices or to require endoscopy to survey for suspected oesophageal varices. Patients were excluded if they had a prior history of variceal bleeding, transjugular portosystemic shunt or known portal vein thrombosis. Other exclusions included a history of ischaemic heart disease, hypertension, or cardiomyopathy. Patients taking β-blockers as primary prophylaxis, and other drugs which could modify haemodynamics, had their drugs discontinued 14 days prior to any haemodynamic measurements. Each patient gave informed written consent and our local research ethics committee approved the study.

Methods: At the first visit detailed clinical assessment age, sex, body mass index, aetiology of liver disease, alcohol intake, presence of stigmata of chronic liver disease, complications of cirrhosis and calculation of Child-Pugh and MELD scores, laboratory assessment bilirubin, albumin, platelet count, Prothrombin time, AST, ALT, and sodium were undertaken. Subsequently non-invasive systemic haemodynamic studies and endoscopy were undertaken. On the second visit non-invasive measurements were repeated, portal pressure was assessed and if possible abdominal ultrasound

performed to assess bipolar spleen size. After calibration, a 20 minute continuous measurement of beat-to-beat blood pressure using the Finometer® was taken with the patient lying at 45° and under steady state conditions. The same arm and middle finger were used for both finometer readings taken on different days and at different times. For the first recordings patients were fasted whereas for the second reading patients were allowed to eat and drink freely. Set up of the equipment was by a single operator trained in the technique. The results of the recordings were blinded to the endoscopist and the measurement of portal pressure From the Finometry the following haemodynamic variables were calculated: systolic and diastolic blood pressure SBP, DBP, mean arterial pressure MAP, heart rate HR, stroke volume SV, cardiac output CO, cardiac index CI, and peripheral resistance PVR.

One experienced endoscopist performed endoscopy, and the findings were agreed between the endoscopist and a second clinician observing the procedure. Oesophageal varices were classified according to the Japanese Research Society for Portal Hypertension and the Japanese score, NIEC index, and 1-year probability of bleeding calculated.[7–9] Patients were separated into two groups, Group 1-absent or small varices; Group 2-medium or large varices, or gastric varices. Portal pressure was assessed by measurement of the hepatic venous pressure gradient HVPG as described by Groszmann and Wongcharatrawee.[10] A 7F venous introducer Avanti sheath, Cordis, USA was inserted in the right internal jugular vein under ultrasound guidance. A 6F balloon catheter Berenstein occlusion catheter, Boston Scientific, Natick, MA, USA was positioned into a hepatic vein under fluoroscopic guidance. HVPG was obtained by means of a pressure recorder MP50, Philips Healthcare, Surrey, UK in the occluded position and then after deflation of the balloon and a permanent tracing of the readings obtained. HVPG was calculated as the difference between the occluded and the free hepatic venous pressure mmHg. Three consecutive measurements were taken and the results averaged.

Statistical analysis: Results are expressed as median interquartile range, IQR. Differences between groups were compared using the Mann-Whitney test and the association between two variables was assessed by the Spearman correlation co-efficient. Analyse-It for Microsoft Excel Version 2.20 was used for statistical analysis. P values <0.05 were considered statistically significant.

Results

Clinical characteristics of the patients: The characteristics of the 29 patients are shown in Table 1. There were 20 men and 9 women with a median age of 47 years 42-55 years. The aetiology of cirrhosis was alcohol abuse for 18 patients 62%, alcohol abuse and hepatitis C for 5 patients 17%, alcohol abuse and autoimmune hepatitis for 3 patients 10%, autoimmune hepatitis for 2 patients 7% and hepatitis C for 1 patient 4%. 19 patients 66% were abstinent from alcohol. 18 patients were Child-Pugh class A 62%, 10 were Class B 34% and 1 Class C 4%. Oesophageal varices were present in 23 patients 79%, being small in 12 patients, medium in 8 patients and large in 3 patients. As a whole, 18 patients belonged to Group 1 absent/small varices and 11 patients to Group 2 medium/large varices. 5 patients had ascites 17%.

Comparison of haemodynamics and laboratory values according to liver disease severity Table 1: Significant positive correlations were seen between CI, HR and HVPG and disease severity as assessed by Child-Pugh score r=0.36, r=0.37 and r=0.58 respectively. As there was only a single Child-Pugh class C patient recruited this was not

felt to be representative of the group and was therefore excluded from this part of the analysis. Significant differences in cardiac index and HVPG were seen between Child-Pugh class A and B cirrhotics, together with a significantly prolonged prothrombin time, higher bilirubin and lower albumin with worsening liver disease severity.

The hyperdynamic circulation: A strong negative correlation was seen to exist between PVR and both CO and CI, demonstrating the hyperdynamic circulation that occurs in liver disease r=-0.95, p<0.0001 and r=-0.81, p<0.0001 respectively. This relationship is demonstrated in Figures 1 and 2. An increase in stroke volume as opposed to an increase in heart rate was responsible for this as evidenced by a strong positive correlation between CO, CI and SV r=0.83, p<0.0001 and r=0.59, p=0.0008 respectively and a strong negative correlation between PVR and SV r= -0.84, p<0.0001 but no correlation of these parameters with heart rate Figures 3 & 4..
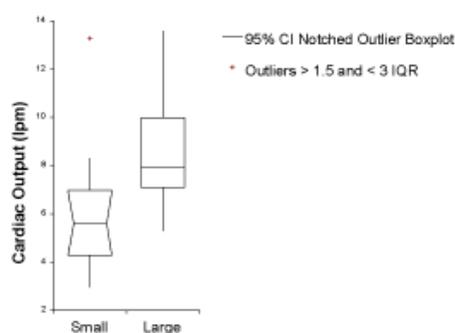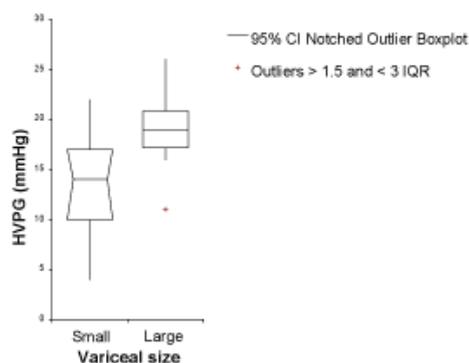

Figure 1 Cardiac output stratified according to variceal size (Small=absent/small varices, Large=medium/large varices).
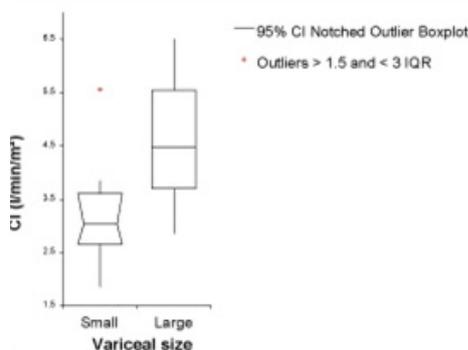
Figure 2 Cardiac index stratified according to variceal size (Small=absent/small varices, Large=medium/large varices).
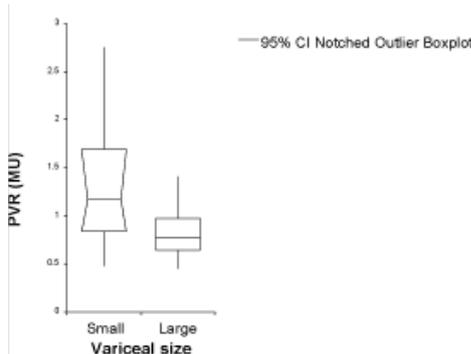
Figure 3 Peripheral vascular resistance stratified according to variceal size (Small=absent/small varices, Large=medium/large varices).

Figure 4 HVPG stratified according to variceal size (Small=absent/small varices, Large=medium/large varices).

Factors associated with size of oesophageal varices, and hepatic venous pressure gradient Table 2–3, Figures 1–4: Significant differences in systemic haemodynamics were seen according to size of varices but no significant differences in laboratory parameters were detected. The haemodynamic variables HR and CI showed significant positive correlation with HVPG r=0.62, p<0.001, r=0.53, p=0.05 respectively. Statistically significant differences in HR and CI were seen when the cohort of cirrhotic patients were split according to whether they had clinically significant portal hypertension HVPG ≥12mmHg.

Discussion

This is the first study of non-invasive haemodynamic assessment of the hyperdynamic circulation characteristic of cirrhosis, and correlates these haemodynamic changes with portal pressure, and variceal size. Non-invasive diagnosis of portal hypertension and its complications is likely to be increasingly important with the growing number of patients with chronic liver disease requiring endoscopic screening, as outlined by the Baveno Consensus.[11] Oesophageal varices form as a consequence of portal hypertension requiring a critical pressure of 10mmHg for the formation of varices and 12mmHg for bleeding to occur.[12–14] Varices bleed at a rate of 5-15% per year and the risk of bleeding relates to variceal size, Child-Pugh score, and the presence of red wale markings at endoscopy. Despite improvements in treatment mortality remains high 20-30% for a first variceal bleed. Primary prophylaxis is known to be vital in reducing mortality[15] in large or high-risk oesophageal varices but not all patients respond to treatment. The pathophysiology of portal hypertension is complex but is initiated by increased intra-hepatic resistance and perpetuated by splanchnic vasodilatation, angiogenesis and remodelling.[16-19] The hyperdynamic circulatory syndrome occurs as a result of these changes, correlates with liver disease severity, portal pressure and oesophageal varices[2–5] but traditionally requires invasive measurement.

Table 1 Baseline characteristics of the cirrhotic population and relationship of systemic haemodynamics and laboratory parameters to liver disease severity

	Total n=29	CPA n=18	CP B n=10	p value
Age (years)	47 (42-55)	48 (37-55)	44 (30-54)	p=0.35
Gender (M/F)	20/9 (69%)	12/6 (67%)	7/3 (70%)	
CP score	6 (5-7)	5 (5-6)	8 (7-8)	p<0.001
CP class	18-10-01			
MELD	10 (8-13)	9 (7-10)	13 (12-17)	p<0.001
Abstinent (%)	19/29 (66%)	12/18 (67%)	6/10 (60%)	
Height (cm)	171 (161-177)	171 (161-177)	170 (154-175)	p=0.52
Weight (kg)	72.0 (60.7-89.8)	73.1 (61.0-91.7)	65.8 (60.0-81.6)	p=0.39
BMI (kg/m²)	25.4 (22.5-29.0)	25.3 (22.6- 30.0)	25.6 (20.4-27.7)	p=0.67
SBP (mmHg)	147 (131-163)	141 (129-161)	154 (137-163)	p=0.31
DBP (mmHg)	83 (75-91)	78 (74-91)	85 (82-92)	p=0.25
MAP (mmHg)	108 (96-115)	103 (95-114)	111 (89-121)	p=0.34
HR (bpm)	80 (71-91)	74 (67-87)	85 (81-99)	p=0.08
SV (ml)	89 (58-104)	88 (58-103)	90 (55-122)	p=0.74
CO (lpm)	6.9 (4.8-8.3)	6.6 (4.7-7.7)	8.2 (5.2-10.2)	p=0.18
CI (l/min/m²)	3.5 (2.9-4.2)	3.3 (2.8-3.8)	4.7 (3.2-5.6)	p=0.03
PVR (MU)	0.96 (0.72-1.34)	0.93 (0.77-1.61)	0.96 (0.63-1.27)	p=0.40
HVPG (mmHg)	17 (11-19)	14.5 (10.0-17.6)	18.5 (16.8-22.3)	p=0.02
ALT (U/L)	33 (21-49)	37 (24-49)	26 (18-42)	p=0.157

Table Continued

	Total n=29	CPA n=18	CP B n=10	p value
AST (U/L)	53 (36-74)	52 (35-80)	52 (37-65)	p=0.943
Platelets x109/L	115 (75-158)	115 (77-175)	113 (62-157)	p=0.774
PT (s)	13 (12-13)	12 (12-13)	13 (13-14)	p=0.007
Albumin (g/L)	35 (32-40)	38 (33-44)	32 (29-34)	p=0.005
Bilirubin (μmol/L)				
	25 (18-41)	20 (14-26)	42 (28-64)	p=0.001
Sodium(mmol/L)	139 (136-141)	139 (132-141)	137 (135-140)	p=0.23

Table 2 Haemodynamic and clinical parameters according to variceal size

	Small varices n=18	Large varices n=11	p value
CO (lpm)	5.59 (4.29-6.98)	7.95 (7.12-10.0)	0.003
CI (l/min/m²)	3.0 (2.6-3.6)	4.5 (3.7-5.5)	0.001
PVR (MU)	1.2 (0.8-1.7)	0.8 (0.6-1.0)	0.018
HVPG (mmHg)	14 (10-17)	19 (17-21)	0.008
CPS	5 (5-6)	7 (5-9)	0.023
MELD	10 (7-12)	11 (8-14)	0.17

Table 3 Haemodynamic and laboratory parameters according to portal pressure

	Correlation	p value	HVPG <12mmHg n=7	HVPG ≥12mmHg n=20	p value
HR	r=0.62	p<0.001	65 (57-69)	85 (78-94)	p<0.001
CI	r=0.53	p=0.05	2.9 (2.5-3.5)	3.8 (3.1-5.4)	p=0.033
CPS	r=0.58	p=0.001	5 (5)	7 (5-8)	p=0.020
MELD	r=0.48	p=0.071	7 (7-8)	11 (9-13)	p=0.008
PT	r=0.55	p=0.003	12 (11-12)	13 (12-14)	p=0.021
Albumin	r= -0.68	p<0.001	40 (38-45)	33 (31-37)	p=0.010
Bilirubin	r=0.41	p=0.034	15 (12-22)	30 (21-44)	p=0.035
Sodium	r= -0.36	p=0.063	140 (139-141)	137 (134-141)	p=0.037

Numerous studies have tried to identify factors to allow accurate non-invasive diagnosis of oesophageal varices. These include tests assessing the degree of liver fibrosis such as Fibroscan[20–24] or fibrotest,[25] or identifying consequences of portal hypertension such as with platelet count or platelet count to spleen diameter ratio.[26–31] To date, none of these tests have proved accurate enough to replace endoscopic screening. The results of this present prospective study show that non-invasive assessment of systemic haemodynamics using finometry can identify the classical haemodynamic changes associated with the hyperdynamic circulation and confirms the association of these changes with worsening liver disease severity as assessed by Child-Pugh class, and with portal pressure as assessed by measurement of portal pressure.

We found significant differences in systemic haemodynamics, HVPG and Child-Pugh score according to variceal size, but no difference in laboratory parameters was seen. The same haemodynamic parameters, HVPG, MELD and in addition serum sodium were found to correlate with the 1 year probability of bleeding. This suggests that non-invasive haemodynamics may be able to predict which patients are at highest risk and most likely to benefit from endoscopy and primary prophylaxis, thus reducing the numbers requiring endoscopic surveillance. Non-invasive assessment of systemic haemodynamics was also seen to correlate with the hepatic venous pressure gradient with significant differences seen in patients with a HVPG greater than or less than 12mmHg in whom the development of other complications such as ascites or hepatocellular carcinoma are known to occur. Therefore non-invasive assessment may be able to predict this at risk group allowing closer surveillance for complications.

There are limitations to this study. Firstly, there is population bias in that the study cohort was selected on the basis of absence of factors that would affect systemic haemodynamics, such as the existence of hypertension or prescription of medications that are known to affect systemic haemodynamics, both of which occur frequently in the general population and have the potential to limit the applicability of the test to a wider audience. Secondly, there are issues regarding the validity of measurements of absolute arterial blood pressure using the finometer, which have been raised in a number of studies. Studies comparing non-invasive measurements by finometry and indicator

dilution technique have found that finometry overestimated CO when compared to the gold standard technique.[32,33] We feel we were justified in using finometry in our study, as we were not concerned with the absolute values of CO, but more in assessing the relationship of the haemodynamic values to the other parameters such as variceal size or HVPG, relationships that have been demonstrated in other studies using invasive techniques for CO measurement. Modelflow is known to be reliable and precise in tracking changes in CO over time in many different patient populations including a small cohort of cirrhotic patients in the above study.[32,34] As such this technique has future potential to assess responses to drug therapy, which may aid non-invasive identification of non-responders to primary prophylaxis. The advantages of this technique are that it is non-invasive, easily tolerated by patients, reproducible, operator independent and readily performed at the bedside or in the outpatient department. It provides a wealth of information that can be readily downloaded and analyzed within a matter of minutes.

In conclusion, the results of this prospective study suggest that in cirrhotic patient's non-invasive assessment of systemic haemodynamics using Finometry may aid identification of patients at high risk for varices formation and may ensure that endoscopic surveillance is provided to those who are most likely to benefit. Another potential role for finometry is the assessment of the use of beta-blockers as primary prophylaxis as it may distinguish between responders and non-responders. Due to the population bias in our study further large studies are required in order to validate the above findings in all cirrhotics requiring endoscopic surveillance independent of co-morbid disease or prior medication.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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