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Utilization of impedance cardiography in noninvasive assessment of hemodynamic status in cirrhotic patients

Siroz hastalarında hemodinamik durumun noninvasiv değerlendirmesinde impedans kardiyografinin kullanımı

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Background/aims: *This study aimed to assess hemodynamic alterations noninvasively using a dedicated device Task Force® Monitor providing various hemodynamic data utilizing impedance cardiography and beat-to-beat blood pressure analysis via a vascular unloading unit.* ***Methods:*** *Forty-seven patients with cirrhosis awaiting hepatic transplantation and 26 healthy volunteers matched for age and gender were enrolled. Basic hemodynamic status of these patients (following temporary interruption of any drugs affecting the cardiovascular system) was evaluated noninvasively by Task Farce® Monitor with patients in the supine position.* ***Results:*** *Mean age of the patients was 46 years and 74.5% were male. The etiology of cirrhosis was viral hepatitis in 59.5% and alcoholic cirrhosis in 19.1% of cases, whereas 17% had cryptogenic cirrhosis. 38.3%, 25.5%, and 36.1% of the patients were stratified into groups A, B and C according to the Child-Pugh classification, respectively. Heart rate, cardiac output and cardiac index were significantly higher in patients with cirrhosis compared to the control group. However, diastolic blood pressure, total peripheral resistance and total peripheral resistance index were significantly lower in the cirrhosis group. This situation representing a hyperdynamic circulatory state became more prominent in conjunction with advanced disease severity.* ***Conclusions:*** *The present study demonstrates that the Task Farce® Monitor device is capable of delineating the hyperdynamic circulatory state in cirrhotic patients and satisfactorily indicates differences between controls and patients at diverse levels of severity. Regarding potential applications in clinical practice and research, noninvasive hemodynamic monitoring by Task Force® Monitor may be a reliable and reasonable alternative tool to invasive procedures.*

Key words: Cirrhosis, impedance cardiography, noninvasive, hemodynamic assessment, hyperdynamic circulatory state

Amaç: *Bu çalışmada sirotik hastalardaki hemodinamik değişikliklerin impedans kardiyografi ve atım temelli kan basıncı analizleri yapan özgün bir Task Force® Monitor cihazla değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *Çalışma karaciğer nakli bekleyen 47 sirotik hasta ile yaş ve cins uyumlu 26 sağlıklı birey üzerinde yapılmıştır. Hastalarda ve sağlıklı bireylerde temel hemodinamik (kalp hızı, kan basıncı, total periferik direnç ve kalp debisi) değerlendirmeler supin pozisyonda (kardiyovasküler sistemi etkileyen ilaçlar geçici olarak kesilerek) Task Farce® Monitor ile ölçülmüştür.* ***Bulgular:*** *Hastaların yaş ortalaması 46, erkek cinsiyet oranı %74.5 idi. Sirozun etyolojisi hastaların %59,5'inde viral hepatit, %19.1'inde alkol, %17'sinde kriptojenikti. Child-Pugh sınıflandırmasına göre hastaların %38.3'ü A sınıfı, %25,5'i B sınıfı, %36.1'i ise C sınıfında idi. Kalp hızı, kalp debisi ve kalp indeksi sirotik hastalarda kontrol grubuna göre anlamlı şekilde yüksekti. Bununla beraber, diastolik kan basıncı, total periferik direnç ve total periferik direnç indeksi siroz grubunda belirgin şekilde düşüktü. Hiperdinamik dolaşım örneği oluşturan bu durum, hastalığın şiddetinin ilerlemesi ile daha da belirginleşmiştir.* ***Sonuç:*** *Bulgularımız, Task Force® Monitor cihazının sirotik hastalardaki yüksek debi ve düşük periferik dirençle karakterize hiperdinamik dolaşım durumunu ve kontrollerle değişen şiddetteki hastalar arasındaki farkları tatmin edici bir şekilde ortaya koyabildiğini göstermiştir. Sirotik hastalardaki rutin ve araştırma amaçlı uygulamalarda Task Force® Monitor cihazı ile yapılan non-invazif hemodinamik izlem, invazif yöntemlere karşı güvenilir ve uygun bir alternatif yöntem olabilir.*

Anahtar kelimeler: Siroz, impedans kardiyografi, noninvazif, hemodinamik değerlendirme, hiperdinamik dolaşım

INTRODUCTION

Cirrhosis represents the final common histologic pathway for a wide variety of chronic liver diseases and is associated with increased morbidity and mortality in these patients. Cirrhotic patients (especially with advanced portal hypertension) may display signs and symptoms of cardiovascular

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dysfunction during the course. These cardiovascular manifestations are mainly related to a well-known pathophysiological state - "the hyperdynamic circulation" - which simply involves increased cardiac output (CO) and heart rate in addition to decreased systemic vascular resistance with low arterial blood pressure (1). Moreover, it is postulated that autonomic dysfunction and cirrhotic cardiomyopathy contribute and augment these abnormal hemodynamic alterations (2). Cardiovascular involvement is particularly important for the patients awaiting liver transplantation (3), and the hemodynamic state of these patients has to be evaluated properly.

Traditionally, cardiac catheterization allowing angiographic evaluation and dye- or thermodilution have been the most reliable methods of assessing systemic hemodynamic status in patients with cirrhosis (4). However, performing these invasive procedures in a patient population with hemorrhagic diathesis is a concern, impelling researchers to employ noninvasive methods to evaluate hemodynamics. Doppler echocardiography is one of these measures but has some important limitations related to methodological issues involving the availability of a good acoustic window and inter- and intraobserver variability influencing the reproducibility (4). On the other hand, impedance cardiography (ICG) is an emerging noninvasive tool to assess cardiac hemodynamics, and unlike echocardiography, it is operator-independent.

Thoracic ICG is a method that calculates the CO from the measurement of changes in impedance across the chest over the cardiac cycle. Lower impedance indicates greater intrathoracic fluid volume, and as the only fluid volume that changes beat-to-beat within the thorax is the blood, the change in impedance can be used to calculate the stroke volume (SV) and, combined with the heart rate, the CO. Although preliminary results were conflicting (5), recent studies utilizing second-generation ICG systems with improved processing have revealed promising results in terms of replacing invasive methods (6, 7). While evidence is gathering related to use of ICG in a wide spectrum of different medical conditions, data about its utility in cirrhosis patients are limited (4, 8). Therefore, we designed this study to document the role of ICG as an alternative noninvasive method of hemodynamic assessment in patients with cirrhosis utilizing a novel equipment: the Task Force® Monitor (TFM, CNSystems, Medizintechnik, Graz, Austria).

MATERIALS AND METHODS

Study Population

We enrolled 47 patients with cirrhosis awaiting liver transplantation and 26 age- and sex- matched healthy controls. The diagnosis was based on liver biopsy and accepted clinical, biochemical and ultrasonographic criteria of cirrhosis. Beta-blocker and diuretic treatments were discontinued temporarily prior to the investigative studies. Patients with hepatocellular carcinoma, anemia, diabetes mellitus, renal failure, ischemic heart disease, dysrhythmia, and neurologic disorders, and those who experienced variceal bleeding, peritonitis or hepatic encephalopathy in the preceding two months were excluded. All patients included in the study provided a written informed consent, and the research was approved by the local ethics board of our institution.

Hemodynamic Assessment

Hemodynamic evaluation of the subjects at rest was performed and acquired in the morning for a minimum of 15 minutes in the supine position followed by a 10-minute equilibrium phase of recording. The TFM, which we used to assess the hemodynamic status of subjects, is a dedicated device intended to noninvasively measure and display a patient's hemodynamic parameters by integrated modules using electrocardiography (ECG), continuous blood pressure, oscillometric blood pressure, and ICG. Brief explanations of these modules and measured and calculated parameters are as follows: i) Electrocardiography: a 6-channel ECG recording with the electrodes placed on the thorax is provided with high sampling rate to provide exact R-R detection; ii) Finger plethysmography allows continuous (beat-to-beat) monitoring of blood pressure by vascular unloading technique; iii) Oscillometric blood pressure measurement from the contralateral arm is automated for preset intervals and the obtained data are used to calibrate concurrent beat-to-beat blood pressure values; iv) Impedance electrocardiogram is recorded by means of three surface electrodes, each consisting of two electrode bands set at a defined distance. One electrode is placed on the nape of the neck while the other set of electrodes is placed on the lower thorax, with the superior electrode at the xiphoid level. Furthermore, a neutral electrode (grounding pad) is placed on the right lower leg of the patient. Figure 1 shows the TFM modules and a patient model demonstrating correct placement of

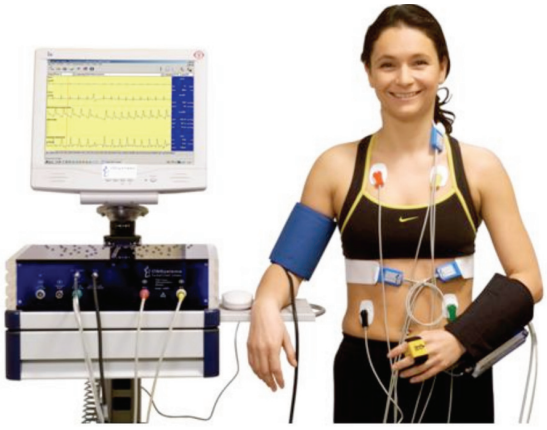

Figure 1. Overview of the Task Force Monitor modules and an equipped patient: the integrated TFM modules (left panel) and a patient model demonstrating correct placement of ECG and ICG electrodes (right panel) are shown.

the ECG and ICG electrodes. Through the outer electrodes, a constant low amplitude current (<400 μA) with high frequency (40 kHz) is applied to the body. The voltage between the inner electrodes reflects the impedance in the thorax (Ohm's law). The impedance is mainly modulated by the SV (fluid changes from one beat to the next). Mathematical models allow calculation of the SV and other mechanical parameters of the heart from this impedance signal. Eventually, besides the heart rate and blood pressure measurements, SV, stroke index (SI), cardiac output (CO), cardiac index (CI), total peripheral resistance (TPR) and total peripheral resistance index (TPRI) are obtained with the hemodynamic study.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation whereas categorical variables were expressed as number and percent (%) values. The variable distribution pattern was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov normality tests. Student t test and Mann-Whitney U test were performed appropriately to compare continuous variables. For comparison of multiple groups, ANOVA was used. All statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) package software.

RESULTS

Demographic and Basic Clinical Data

Forty-seven patients with cirrhosis (mean age: 46.7±13 years; 74.5% male) and 26 age- and sex-matched healthy controls (mean age: 44.3±12.8 years; 69.2% male) were included in the study. Body mass index of each group was similar (p: NS). Basic clinical variables of the subjects are depicted in Table 1. The pathological diagnosis had been established in most of the cases (liver biopsy was available in 37/47 patients, 78.7%). Mean duration of cirrhosis since the initial diagnosis was 3.3 years (median: 2.5 years; interquintile range: 4.2 years). In approximately 60% of the patients, the etiological factor was viral hepatitis, and 40% of the patients were receiving antiviral treatment. Patients were also stratified according to their Child-Pugh Scores (CPS) as follows: 18 patients, Child class A (CPS-A), 12 patients, Child class B (CPS-B) and 17 patients Child class C (CPS-C).

Hemodynamic Differences Between Patients and Controls

Comparison of the overall hepatic cirrhosis patient group (HCG) with controls (CG) revealed that all hemodynamic parameters were significantly different (Table 2). The heart rate, SV, SI, CO and CI were higher in the HCG group, whereas systolic, diastolic and mean blood pressures, TPR and TPRI were lower in the HCG group.

Hemodynamic Profiles Within Patient Groups

Hemodynamic parameters within the HCG were also analyzed according to Child-Pugh classifications. As realized from Table 2, there was an increasing linear trend for SV and SI through CPS-A to CPS-C subgroups and a decreasing linear trend for TPR and TPRI. On the other hand, heart rate, CO and CI showed a slight dichotomic trend through CPS subgroups. However, none of these differences reached statistical significance when the three patient subgroups were compared.

Hemodynamic Differences Regarding the Severity of Cirrhosis

Hemodynamic data of each CPS subgroup were compared with controls (Table 2). It was determined that blood pressures, TPR and TPRI values were significantly lower in the CPS-A subgroup than the CG. This was also valid for the CPS-B group with the exception of systolic blood pressure (which was similar in both groups). A significant increase in heart rate, CO and CI were noted in the CPS-B group. On the other hand, diastolic and mean blood pressures along with TPR and TPRI were significantly lower in the CPS-C group compared to CG, while SV, SI, CO and CI were significantly higher.

Table 1. Basic demographic and clinical data of the patients

	Cirrhosis (n: 47) (mean ± SD) or (n/%)	Controls (n: 26) (mean ± SD) or (n/%)	P value
Age	46.78 ± 13.4	44.34 ± 12.8	NS
Gender (males)	35 (74.5)	18 (69.2)	NS
Height (cm)	168.60 ± 10.0	166.46 ± 6.7	NS
Weight (kg)	72.06 ± 13.2	72.80 ± 14.5	NS
Body mass index (kg/m^2)	25.14 ± 3.6	26.24 ± 5.0	NS
Active smoking	10 (21.3)	-	
Hx. of alcohol use	9 (19.1)	-	
Ascites	18 (39.1)	-	
Cholelithiasis	7 (15.2)	-	
Hx. of bleeding varices	10 (21.3)	-	
Hx. of encephalopathy	11 (23.4)	-	
Hx. of peritonitis	7 (14.9)	-	
Bx. diagnosis	37 (78.7)		
Etiology of cirrhosis:			
Viral hepatitis B	22 (46.8)	-	
Viral hepatitis C	5 (10.6)	-	
Viral hepatitis D+B	1 (2.1)	-	
Alcoholic	9 (19.1)	-	
Cryptogenic	8 (17.0)	-	
Others	2 (4.3)		
Severity of cirrhosis:			
Child-Pugh Class A	18 (24.7)	-	
Child-Pugh Class B	12 (16.4)	-	
Child-Pugh Class C	17 (23.3)	-	
Treatment:			
Beta-blocker	28 (59.6)	-	
Furosemide	14 (29.8)	-	
Spironolactone	26 (35.6)	-	
Antiviral	19 (40.4)	-	

Hx: History. Bx: Biopsy.

DISCUSSION

The present study demonstrates that the TFM device is capable of delineating the "hyperdynamic circulatory state" in cirrhotic patients and satisfactorily indicates differences between controls and patients at diverse levels of severity. These hemodynamic alterations are a long-standing fact and have been better understood after Schrier's peripheral arterial vasodilatation hypothesis (9). These hemodynamic alterations mainly arise from portal hypertension, which is associated with changes in the intrahepatic, systemic and portosystemic collateral circulation. Alteration in vasoreactivity is a key element in the progression of this pathophysiological course. Increased shear stress due to high blood flow by portosystemic shunting provokes upregulation of endothelial nitric oxide synthases, resulting in nitric oxide overproduction (10). Additionally, decreased degradation related to bypassing through portosystemic collaterals and hepatic dysfunction, results in increased the bioavailability of these vasodilatory compounds, augmenting peripheral vasodilatation. This triggers the baroreceptor-mediated activation of the renin-angiotensin-aldosterone system and sympathic nervous system and non-osmotic release of vasopressin to restore circulatory integrity (2, 11). Eventually, salt and water retention occurs. As the cirrhotic process advances, these hemodynamic alterations become more profound due to hyporesponsiveness to vasoconstrictors and increased shunt formation in conjunction with autonomic neuropathy (1, 2, 10). The result is maintenance of splanchnic arterial vasodilatation and portal hypertension, which perpetuates the vicious cycle. Interpretation of the hemodynamic data of our patient subgroups somewhat reflects this pathophysiological information. In the CPS-A group, significantly decreased blood pressure and peripheral resistance values indicate the initial vasodilatory state. Most of these differences are preserved in patients in the CPS-B group. Additional increase in heart rate and accompanying increment in CO in the CPS-B group may be associated with activation of the sympathic nervous system and vasoconstrictive mediators trying to counterbalance vasodilatation. However, the hemodynamic profile of patients in the CPS-C group is consistent with an established "hyperd-

Table 2. Comparison of hemodynamic parameters within patient subgroups and between the patients and controls

	Control group	Hepatic cirrhosis group				Hepatic cirrhosis patient subgroups				
	CG (n=26)	Overall HCG (n=47)	p value (HCG vs. CG)	CPS-A (n=18)	p value (CPS-A vs. CG)	CPS-B (n=12)	p value (CPS-B vs. CG)	CPS-C (n=17)	p value (CPS-C vs. CG)	P value (between CPS groups)
Heart rate (bpm)	71.65±7.3	77.13±11.4	0.031	76.17±13.0	NS	81.75±9.9	0.001	74.74±9.8	NS	NS
SBP (mmHg)	109.68±10.5	103.92±10.6	0.031	102.69±8.6	0.028	104.60±9.9	NS	104.68±13.2	NS	NS
DBP (mmHg)	75.05±8.6	66.83±10.4	0.001	67.41±8.6	0.007	67.31±10.2	0.020	65.91±12.5	0.007	NS
MBP (mmHg)	85.77±9.2	77.38±10.4	0.001	77.58±8.5	0.006	78.36±11.1	0.038	76.49±12.1	0.007	NS
SV	68.71±15.6	81.53±21.6	0.018	73.66±20.8	NS	83.30±25.8	NS	88.82±18.0	0.001	NS
SI	38.56±10.2	44.70±9.7	0.023	42.50±9.6	NS	45.05±12.4	NS	46.82±8.1	0.011	NS
CO	4.91± 1.2	6.04±1.3	0.002	5.51±1.4	NS	6.58±1.4	0.003	6.31±0.8	0.001	NS
CI	2.77± 0.8	3.34±0.6	0.005	3.17±0.6	NS	3.57±0.7	0.018	3.38±0.5	0.021	NS
TPR	1430.19±447.2	1025.76±287.3	<0.001	1139.35±261.2	0.023	1009.90±378.1	0.016	915.00±219 .0	<0.001	NS
TPRI	2631.33±920.9	1841.65±472.9	<0.001	1980.11±452.8	0.014	1872.00±612.7	0.021	1703.56±374.3	0.001	NS

CG: Control group. CPS: Child-Pugh Score. HCG: Hepatic cirrhosis group. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MBP: Mean blood pressure. SV: Stroke volume (ml/beat). SI: Stroke index (ml/m^2/beat). CO: Cardiac output (L/min). CI: Cardiac index (L/min/m^2). TPR: Total peripheral resistance (dyn*sec/cm^5). TPRI: Total peripheral resistance index (dyn*sec*m^2/cm^5).

ynamic circulatory state" evident with lower peripheral resistance and increased SV and CO values. Nevertheless, as our study did not involve a mechanistic approach in this issue (neurohumoral markers were not assessed), these inferences remain only as assumptions based on our knowledge.

Impedance cardiography has been widely used in diverse clinical settings, and its applicability has been validated with confirmatory results in comparison to both invasive methods (pulmonary artery catheterization, Fick and thermodilution) (6, 7, 12, 13) and noninvasive (echocardiography) measures (4, 14, 15). ICG is based on the application of a high-frequency, low-alternating electrical current to the thorax to define changes in the current, which are associated with the cardiac events and blood flow in the thorax (16). Depending on different mathematical models and formulas, the change in impedance is used to calculate SV and other derived hemodynamic parameters. Thus, the method of calculations and electrode sensitivity to detect the voltage are important in this technique. From this point of view, TFM, which has already obtained FDA 510(k) (K014063) clearance, is a novel noninvasive hemodynamic monitoring tool utilizing an improved estimate of thoracic volume (considering the influence of the patient's body weight on the thorax shape, a mathematical model based on a "modified" Kubicek and Sramek designs is applied) and new shortband electrodes to generate a good homogeneous thoracic field (6). Previous reports have proven the applicability of TFM in various clinical conditions, including hemodynamic monitoring in heart transplant candidates in comparison with both thermodilution and another commercially available ICG device (6) and in hemodialysis patients (17), and its utility for optimization of cardiac resynchronization therapy (18) and for evaluation of exercise physiology (19, 20) and vasovagal syncope (21). However, there are only a few reports (with very small sample sizes) involving ICG as a noninvasive measure of hemodynamics in cirrhosis patients (4, 8). Therefore, the present study utilizing TFM extended our knowledge on this issue, being particularly confirmatory compared with literature data. First, the hemodynamic data of the control group was compatible (for the appropriate age group) with the hemodynamic parameters (obtained by ICG method) reported in a recent paper providing reference values according to age and gender (22). The hemodynamic parameters of the overall HCG group

were also extremely close to the values of cirrhotic patients reported in a recent publication (8). Furthermore, the decremental, incremental or dichotomic trends between the different CPS groups as mentioned above were consistent with the results of a previous report presenting similar trends for TPR, CI, CO, and SV values (provided by cardiac catheterization) (23). On the other hand, some of the hemodynamic parameters were individually more pronounced in some investigations (4,24) compared to our report, despite compatibility of the global hemodynamic profile of patients with cirrhosis indicating a hyperdynamic circulatory state. We considered that this nuance may be a result of the exclusion of anemic patients in our study since it is known that anemia can exaggerate hemodynamic alterations in cirrhosis (25). We believe the present study confirms the applicability of noninvasive hemodynamic evaluation of patients with cirrhosis by ICG.

Lack of an invasive hemodynamic assessment for comparison to confirm the noninvasive measurements can be questioned and regarded as a limitation. However, our study was not planned as a validation study; rather, we aimed to demonstrate the applicability of ICG-derived hemodynamic measurements in cirrhotic patients. The TFM and other commercially available devices equipped with ICG to define hemodynamic status were already utilized in previous researches where ICG results were confirmed and validated in comparison with invasive and noninvasive methods (4, 6, 7, 12-15, 17). Therefore, we did not need to involve any invasive or noninvasive comparative hemodynamic assessment tool. We also considered that such a comparative invasive method would be unjustifiable and harmful in a specific patient group who are prone to bleeding complications due to hemorrhagic diathesis and whose expected hemodynamic profile is established textbook information. We thus only included a control group to compare patients' results, instead of utilizing an invasive hemodynamic assessment tool.

Our study showed that TFM is a reliable device to assess hemodynamic parameters noninvasively in cirrhotic patients, and it can discriminate the degree of hemodynamic alterations during different severity stages of the clinical course. Therefore, as a user-friendly and noninvasive tool that may avoid invasive procedures (potentially exposing cirrhotic patients -who are prone to bleeding- to increased risk of complications), it can be a viable option in evaluation of the hemodynamic state of patients with cirrhosis both in clinical practice and for research purposes (such as documenting hemodynamic effects of investigative drugs in cirrhosis patients). It is postulated that abnormal baroreceptor function and autonomic dysfunction contribute in the progression of abnormal hemodynamic status (1, 2). The device utilized in our study (TFM) also has a built-in software that allows beat-to-beat analysis of variations in blood pressure and heart rate, and provides the opportunity to evaluate baroreceptor and autonomic functions. Thus, besides evaluation of the hemodynamic state, TFM can help in delineating the autonomic functions in these patients and thus offers a comprehensive evaluation of cirrhosis patients.

In conclusion, the present study revealed that noninvasive hemodynamic profiling of cirrhotic patients is concordant with the expected hyperdynamic circulatory state, being more profound in parallel to the advanced stages of cirrhosis, and the obtained hemodynamic parameters are consistent with literature data derived using both invasive and noninvasive measures. Regarding potential applications, such as clinical evaluation of patients and clinical research involving hemodynamic alterations in cirrhosis, noninvasive hemodynamic monitoring with the Task Force® Monitor may be a reliable and reasonable alternative tool to invasive procedures.

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