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ORIGINAL RESEARCH

Validation of electrical velocimetry in resuscitation of patients undergoing liver transplantation. Observational study

Ahmed M. Mukhtar[1] · Mohamed Elayashy[1] · Amr H. Sayed[1] · Gihan M. Obaya[1] · Akram A. Eladawy[1] · Mai A. Ali[1] · Hisham M. Dahab[1] · Dina Z. Khalaf[1] · Mostafa A. Mohamed[2] · Amr H. Elfouly[3] · Gad M. Behairy[2] · Amr A. Abdelaal[2]

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Abstract

Major hemodynamic changes are frequently noted during liver transplantation (LT). We evaluated the performance of electrical velocimetry (EV) as compared to that of TEE in SV optimization during liver transplantation. This was an observational study in 32 patients undergoing LT. We compared SV values measured simultaneously by EV (SV_{EV}) and TEE (SV_{TEE}) at baseline 30 min after induction, at the end of dissection phase, 30 min after anhepatic phase, 30 min after reperfusion. We also evaluated the reliability of EV to track changes In SV before and after 49 fluid challenges. Finally, the SV variation (SVV) and pulse pressure variation (PPV) were tested as predictors for volume responsiveness, defined as an increase in SV ≥ 10% after 250 ml of colloid. For 112 paired SV data, the overall correlation was 0.76 and bias (limits of agreement) 0.3 (− 29 to 29) ml percentage error 62%. The EV was able to track changes in SV with a concordance rate of 97%, and a sensitivity and specificity of 93% to detect a positive fluid challenge. The AUC values (with 95% confidence intervals) for SVV and PPV were 0.68 (0.52–0.83) and 0.72 (0.57–0.86), respectively, indicating low predictive capacity in these setting. The absolute values of SV derived from EV did not agree with SV derived from TEE. However, EV was able to track the direction of changes in SV during hemodynamic management of patients undergoing liver transplantation.

Clinical trial registration: Clinicaltrials.gov Identifier: NCT03228329 prospectively Registered on 13-July-2017.

Keywords Electrical velocimetry · Transesophageal Echo · Stroke volume · Liver transplantation

1 Introduction

Major hemodynamic changes are frequently noted during liver transplantation (LT) [1]. Major blood loss, decrease venous return, and reperfusion injury-induced vasodilatation are the main causes of these hemodynamic derangements.

Fluid therapy is the cornerstone of hemodynamic management in unstable patients. The sole goal of fluid challenge is to increase CO and improve tissue perfusion (fluid responsiveness) [2]. Therefore, accurate measurement of CO is essential for safe management of hemodynamic instability during liver transplantation.

Several studies have attempted to validate minimally invasive and noninvasive CO monitors against reference standards which traditionally have been either pulmonary artery catheters or TEE [3–6]. Most of these studies found a large bias between the new approaches and standard methods in analysis of single data points. However, in a real-life setting, tracking changes in CO in response to therapy is more relevant than absolute measurements.

Electric velocimetry (EV) is a new version of impedance cardiography, and uses changes in orientation of red blood cells in the aorta to measure CO [7]. The accuracy of EV in published studies has been inconsistent [8, 9]. One animal study suggested that EV provided an accurate measurement of CO but that its trending ability was poor [10].

No previous studies have investigated the validity of EV in tracking dynamic preload indicator in patients undergoing liver transplantation. Therefore, we sought to investigate

✉ Ahmed M. Mukhtar
ahmed.mukhtar@kasralainy.edu.eg

[1] Department of Anesthesia, Faculty of Medicine, Cairo University, Al Saraya Street, Almanial, Cairo, Egypt

[2] Department of Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[3] Department of Tropical Medicine, Faculty of Medicine, Helwan University, Cairo, Egypt

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the validity of EV in patients undergoing living donor liver transplantation (LDLT) using TEE as the reference standard. The key hemodynamic variable of interest in the present validation study was SV, measured at predetermined intervals including before and after fluid challenges.

2 Materials and methods

2.1 Study population

The study followed a prospective observational design and was approved by the Ethics Committee of Kasralainy faculty of medicine, Cairo University (N-43-2017) on 27 may 2017 and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03228329), Date of registration: 13-July-2017).

The study was designed to recruit 32 patients with end stage liver disease, scheduled for LDLT. Exclusion criteria were age < 18 years, arrhythmia, and failure to obtain a good quality signal index defined as index > 50%.

2.2 Study protocol

Liver transplantation was performed with preservation of the retrohepatic caval vein (the piggyback technique). A standardized anesthesia protocol was used [11]. After induction of anesthesia, all patients were monitored to obtain 5-lead electrocardiograms and measurements of temperature, arterial blood pressure (noninvasive and invasive methods), peripheral oxygen saturation, end-tidal carbon dioxide tension, hourly urinary output, central venous pressure, and SV). SV was measured using EV and TEE.

2.2.1 Fluid therapy and hemodynamic management

Ringer's acetate was administered at 3 ml/kg/h. If pulse pressure variation (PPV) was more than 10%, the patient was considered as a fluid responder and received a 250-ml bolus of 5% albumin to maintain ≤ 10% PPV. PPV was measured continuously using a Philips Intellivue MP 70 monitor (Philips, Suresnes, France). Fluid responsiveness was confirmed by measuring changes in SV before and after fluid bolus. Patients in whom volume expansion increased SV by more than 10% were defined as fluid responders and the remaining ones as fluid non-responders. If MAP remained at < 65 mm Hg after administration of the fluid bolus, norepinephrine infusion was titrated to maintain MAP at ≥ 65 mm Hg. Blood transfusion was given based on a low hemoglobin level (< 7 g/dl).

2.2.2 Stroke volume measurement

EV measurements were obtained with the ICON® monitor (Osypka Medical, Inc., La Jolla, California and Berlin Germany). ECG electrodes was placed on the bare skin of patients in the following positions. (1) On the left neck below the ear; (2) directly above the midpoint of the left clavicle; (3) along the left mid-axillary line at the level of the xiphoid process; and (4) two inches caudal from the third electrode. Only EV data with a signal quality index of ≥ 70 were included in the analysis as the signal quality is interrupted by electrical interference (e.g. from electrocautery). TEE examinations were performed using a Siemens ultrasound machine (Siemens Medical Systems Mountain view CA) equipped with a multiplane TEE probe (multifrequency phased-array transducer). SV of the reference method (SV_{TEE}) was calculated using the formula SV = LVOT CSA × LVOT VTI, where CSA is the cross-sectional area of the left ventricular outflow tract (LVOT) and VTI is the velocity–time integral across the LVOT. LVOT VTI was measured by tracing the pulsed Doppler waveform across the aortic valve. Calculation of the LVOT CSA was performed by measuring the LVOT diameter from the mid-esophageal long-axis view, assuming a circular LVOT. For measurements of the VTI, the Doppler signal was obtained from the deep transgastric long-axis view of the left ventricle. Stroke volume variation in transesophageal echo (SVV_{TEE}) was calculated as (SV_{TEE} max − SV_{TEE} min)/SV_{TEE} mean. SV_{TEE} was paired with a corresponding stroke volume in EV (SV_{EV}) that was closest in terms of occurrence, and only TEE and EV data pairs measured within 20 s of each other were included in the analysis. Typically, EV data is obtained by averaging data of the previous 10 heart beats whereas TEE data reflect one VTI image captured at a single instant.

2.2.2.1 Hemodynamic data Heart rate, systolic blood pressure, CVP, PPV, SV_{EV}, SV_{TEE}, SVV_{EV}, and SVV_{TEE} were recorded at baseline 30 min after induction, at the end of the dissection phase, 30 min after the anhepatic phase, and 30 min after reperfusion. SV_{EV} and SV_{TEE} were also measured before and after each fluid bolus.

2.2.2.2 Other data collection Patient characteristics documented included age, weight, model of end stage liver disease (MELD) score, Child-Pough score, and cause of transplantation.

2.3 Statistical analysis

The sample size (at least 106 measurements) was calculated for an equivalence trial with a range of equivalence of ± 5 ml (5% of a mean SV equal to 100 ml) and acceptable limits of agreement of ± 30 ml (i.e. 30% of a mean SV equal to

100 ml), with a two-sided significance of 0.05 and a power of 0.80. [12].

Data were represented as means with standard deviations. Correlations between various variables were analyzed using Pearson correlation. Bland–Altman analyses were used to quantify degrees of agreement between the two methods of SV measurements. The results of the analysis were represented as mean bias, percentage error, and 95% limits of agreement. The SV_{TEE} value was used as reference. To assess the trending abilities of the continuous measurement techniques, concordance, and polar plot analyses were performed as recently suggested [13]. Central data points correspond to small changes in SV and reflect random measurement errors rather than trending ability. Therefore, an exclusion zone of 10% was used. Trending ability was considered sufficient for clinical practice if polar plot analysis showed an angular bias within ±5°, radial limits of agreement within ±30°, and a polar concordance rate of over 95% at 30°. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of preload indices of fluid responsiveness. MedCalc version 18.0 (MedCalc Software bvba, Mariakerke, Belgium) was used to generate values with the highest sensitivity and specificity (Youden index). The level of significance was set at $p < 0.05$ in two-tailed tests.

3 Results

Forty patients were included in the study. Eight patients were excluded either because of inability to obtain adequate transgastric TEE views or because of inadequate signals from the EV device. Data of a total of 32 patients were available for final analysis. The underlying diseases necessitating liver transplantation were postviral liver cirrhosis in 25 cases, cryptogenic cirrhosis in five cases, and primary biliary cirrhosis in two cases. The mean MELD score of the study population was 16 ± 6. Thirteen (40%) patients received vasopressors during surgery. Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Variable	
Age (years)	53 ± 10
Gender [male, n (%)]	27 (84.4%)
BMI	27 ± 4
CHILD (A/B/C)	3/12/17
MELD	16 ± 6
Causes of liver disease	
Post viral liver cirrhosis	25
Cryptogenic cirrhosis	5
Primary biliary cirrhosis	2
Duration of surgery	10 ± 2
Intraoperative use of vasopressors (%)	13 (40%)
Use of PRBCs (units)	2 (0–5)
Use of FFPs (units)	4 (0–8)

Data are presented as mean ± SD, median (range), number (%), or ratio

BMI body mass index, *MELD* Model for end stage liver disease, *PRBCs* packed red blood cells, *FFPs* fresh frozen plasma

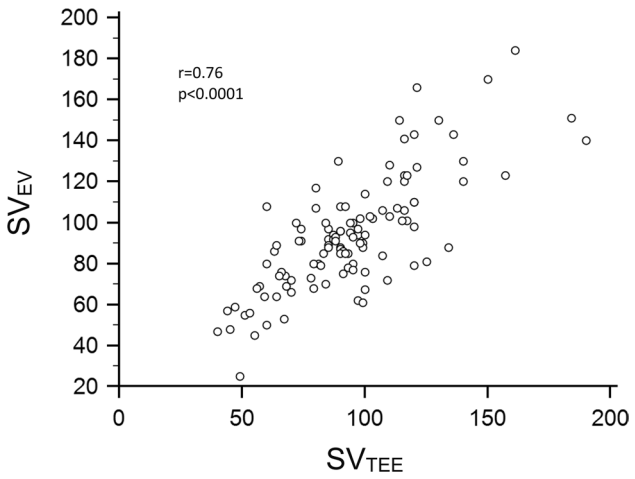

Fig. 1 Correlation between SV_{TEE} and SV_{EV} in terms of all 112 data points from 32 patients. SV_{TEE} stroke volume calculated using TEE, SV_{EV} stroke volume calculated using EV

3.1 Validation of EV at predefined measurement time points

One hundred twelve paired readings were collected. The overall mean SV_{TEE} was 94 ± 27 ml, which was similar to the overall mean SV_{EV} which was 94.3 ± 27 ml. Paired SV measurements showed a good correlation at $r = 0.76$, with $p < 0.0001$ (Fig. 1). The bias was 0.3 ml with 95% limits of agreement at −29 to 29 ml. The percentage error was 62%. Bland–Altman statistical analysis was performed separately at each of the four predefined measurement time points and showed a wide limit of agreement between SV_{TEE} and SV_{EV} (Table 2).

3.2 Validation of EV during fluid responsiveness

Forty-nine fluid challenges were given during surgery; 35 during the dissection phase, six during the anhepatic phase, and eight during the reperfusion phase. The total volume of infused colloid was 2400 ± 1100 ml. Thirty-three out of the 49 fluid challenges were positive. Hemodynamics before and after fluid challenges in responders and non-responders are shown in Table 3. The relationship between TEE and EV in

Table 2 Perioperative correlations, results of Bland–Altman analysis, and percentage of error of the methods studied

Variable	After induction	End of the dissection phase	End of the anhepatic phase	30 min after reperfusion
Pearson's r	0.7	0.9	0.8	0.7
p value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Bias	− 2.3	− 4.2	5.8	1.7
± 1.96 SD	31	23.5	28.6	30.7
Percentage error	64%	50%	61	63

SD standard deviation

Table 3 Hemodynamic parameters before and after fluid challenge

	Responder (n = 33)		Non-responder (n = 16)	
	Before	After	Before	After
SV_{TEE} (ml)	74 (56–85)	87 (70–107)†	87 (67–98)	93 (70–97)
SV_{EV} (ml)	86 (70–105)	99 (83–119)†	94 (84–109)	94 (81–109)
SVV_{TEE} (%)	13 (7)*		8 (4)	
SVV_{EV} (%)	12 (3)*		10 (6)	
PPV (%)	16 (5)*		12 (4)	
ΔSV_{TEE} (ml)	15 (10–23)*		1.9 (− 1.5 to 4.7)	
ΔSV_{TEE} (%)	23 (11–38)*		2 (− 1 to 7)	
ΔSV_{EV} (ml)	15 (10–17.5)*		0 (− 2 to 5.7)	
ΔSV_{EV} (%)	15 (12–21)*		0 (− 2 to 7)	

SV_{TEE} stroke volume calculated using transesophageal echo, SV_{EV} stroke volume calculated using EV, *SVV* stroke volume variation, *PPV* pulse pressure variation, ΔSV_{TEE} stroke volume change before and after fluid loading calculated using TEE, ΔSV_{EV} stroke volume change before and after fluid loading calculated using EV

*Denotes significance between both groups $p < 0.05$

†Denotes significance relative to baseline $p < 0.05$

terms of SV percentage changes was assessed using Spearman correlation, Bland–Altman analysis, and polar plots. There was a good correlation between changes in SV_{TEE} and SV_{EV} before and after fluid loading ($r = 0.8$; $p < 0.001$). The bias (limit of agreement) was 1.7 ml (−14 to +18). Using polar plot analysis, an angular bias of −3.9 was calculated with a radial limit of agreement at 95% CI (− 30.1 to + 22.3). Based on the 30° radial limits, the polar concordance rate was 97% (Fig. 2).

3.3 Accuracy of EV in detecting fluid responsiveness

The sensitivity of the EV device in accurately detecting a positive volume response ($\Delta SV_{TEE} \geq 10\%$) was 93% with a specificity of 93%.

3.4 Prediction of volume responsiveness

Both PPV and SVV were significantly higher in responders than in non-responders (Table 3). The AUC values (with 95% confidence intervals) for SVV and PPV were 0.68 (0.52–0.83) and 0.72 (0.57–0.86), respectively. The optimal cut-off value was 7% for both SVV (sensitivity 0.96; specificity 0.25) and PPV (sensitivity 0.96; specificity 0.15).

4 Discussion

To our knowledge, the present study is the first to evaluate the performance of EV against TEE in cirrhotic patients undergoing liver transplantation. The overall agreement between them in terms of absolute SV values was low, with a high percentage of error of 62%, however, EV was able to track the direction of changes in SV during fluid loading with a concordance rate 97%.

In the present study, the absolute values of SV_{EV} and SV_{TEE} had an unacceptably large percentage difference (error). Consistent with our findings, several studies have found that the agreement between SV_{EV} and SV values derived using other devices was also poor [9, 14]. Martin et al. found a large percentage of error of 42% between SV values derived using EV and those derived using TEE in

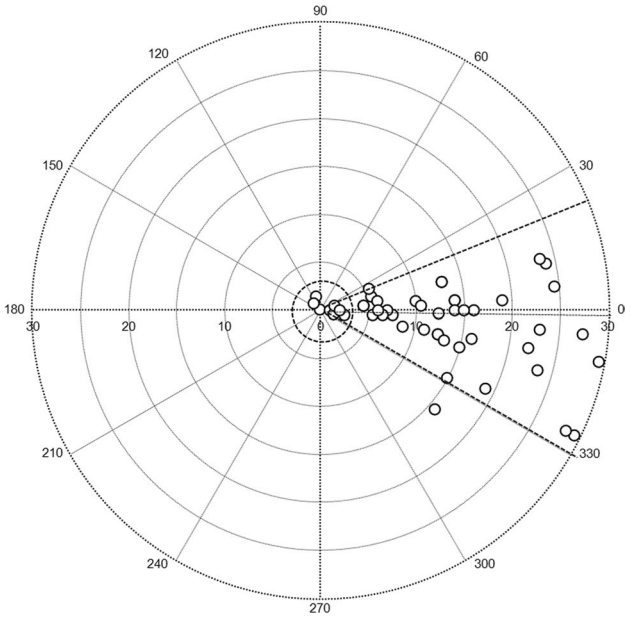

Fig. 2 Trend analysis using a polar plot for changes (Δ) in SV assessed using EV or TEE. The distance from the center represents the mean (%) ΔSV of both methods and the angle with the horizontal axis depicts the concordance of the methods. The dashed thin line indicates angular bias of −3.9° and thick line indicates radial limits (95% confidence interval) of −30% to +22%; concordance rate at <30° was 97%. Data points with changes of ≤10% were excluded

pregnant patients [9]. Electric velocimetry derives the SV by integrating the three parameters index of mean velocity, corrected flow time, and the patient constant volume of electrically participating tissue (V_{EPT}). The first two parameters are directly measured by the device while the V_{EPT} is derived from patient weight. A plausible mechanism of disagreement between the SV_{EV} and SV derived via echocardiography may be the failure of the patient constant V_{EPT} to accurately predict LVOT diameter which is used to derive SV in echocardiography. Martin et al. were able to provide a corrected model for SV measurement via EV by incorporating LVOT measurement.

Hemodynamic management during liver transplantation is challenging because of distinct hemodynamic changes in patients with liver cirrhosis. Patients with end stage liver disease have high CO and decreased peripheral vascular resistance. Moreover, cirrhotic patients have not only increased but also abnormally distributed blood volume. Such patients typically have >37% of their total blood volume located in the abdomen, which is significantly higher when compared to healthy subjects, in whom abdominal organs contain <30% the total blood volume [15]. Rapid volume loading in these patients has little impact on CO because a significant proportion of infused fluid is shifted to the splanchnic system. Because of all these hemodynamic derangements, a reliable hemodynamic monitoring system is of great importance and needs to be properly tested. EV appears to be sufficiently reliable in tracking changes in SV during a fluid challenge, and suitable to be used in liver transplantation. The reliability of EV in tracking the CO during hemodynamic changes has not been consistent in published studies. Liu et al. found that EV is reliable in tracking the direction of changes in CO during cardiopulmonary exercise testing when compared to thermodilution. However, a recent animal study described the reliability of EV in CI monitoring in dogs undergoing experimental isolated right ventricular failure [16]. They found that EV showed low reliability in tracking cardiac index (CI) changes with an angular bias slightly exceeding ±5° and a radial limit of agreement over the reference method at ±30° [16]. The difference between humans and dogs in terms of skin resistance, location of the aortic arch, and width of the thoracic cavity might explain the difference between our findings and those of the above study.

In our study, the dynamic indices PPV and SVV failed to predict fluid responsiveness in cirrhotic patients during liver transplantation. Although dynamic indices have been shown to reliably predict fluid responsiveness in mechanically ventilated patients, Gouvea et al. found that PPV was a poor predictor of fluid responsiveness during liver transplantation [17]. PPV depends not only on stroke volume but also on vascular compliance. Total vascular compliance is estimated to be 1.5–2.5 mL/mmHg/kg body weight in patients with liver cirrhosis, which is higher than that in healthy individuals at 0.5–1 mL/mmHg/kg body weight. Thus, in healthy individuals each 500 ml of fluid loading produces a 5 mmHg increase in blood pressure, however, this is not the case in cirrhotic patients. This may explain the poor predictive ability of PPV in patients with liver cirrhosis. [15].

Several limitations in the present study need to be addressed. First, all our patients had excellent cardiac function, and we cannot extrapolate our findings to patients with poor cardiac function. Second, we did not assess the reliability of EV in tracking SV changes during mini-fluid challenges. EV may be efficient in tracking SV changes when large volumes are infused but not when small volumes are given to predict volume responsiveness.

Our data showed that the absolute values of SV derived using EV did not agree with those derived using TEE. However, EV was able to track the direction of changes in SV during hemodynamic management of patients undergoing liver transplantation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Study has been approved by Kasralainy faculty of medicine ethics committee, Cairo University. (N-43-2017).

Informed consent Informed consent taken from all participants.

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