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Assessment of the carotid artery Doppler flow time in patients with acute upper gastrointestinal bleeding

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Abstract:

INTRODUCTION: Because of the subjectivity and ambiguity of the noninvasive measurements and limited use of invasive ones, there is an impending need for a real-time, fast, inexpensive, and reproducible noninvasive measurement method in acute upper gastrointestinal (GI) bleeding with active bleeding in emergency services.

AIMS: In this study, we aimed to evaluate the effect of bedside carotid artery flow time (CFT) measurement before and after the passive leg raising (PLR) maneuver on the determination of active bleeding in patients admitted to the emergency department (ED) with upper GI bleeding.

MATERIALS AND METHODS: This prospective case–control study was conducted in the ED of a training and research hospital with upper GI bleeding. Patients were placed in the supine position to perform bedside carotid Doppler ultrasonography before starting treatment. CFT, corrected CFT (CFTc), and carotid artery Doppler flow velocity were measured. After then performed PLR, the same parameters were measured again.

RESULTS: A total of 94 patients, including 50 patients with GI bleeding and 44 healthy volunteers as control group were included in the study. CFT and CFTc were shorter in the patient group than the control group ($P < 0.001$, $P = 0.004$, respectively). After PLR, there were statistically significant differences in change in the CFT (ΔCFT) and change in the corrected CFT (ΔCFTc) between the groups ($P = 0.001$, $P < 0.001$). There were also statistically significant differences in ΔCFT and ΔCFT between the patients with active bleeding and the nonbleeding ones ($P = 0.01$, $P = 0.005$, respectively). Area under curve to detect active bleeding for ΔCFT and ΔCFTc were calculated as 0.801 (95% confidence interval [CI]: 0.65–0.95) and 0.778 (95% CI: 0.63–0.91), respectively.

CONCLUSION: The corrected carotid Doppler flow time measurements in patients with GI bleeding at the time of presenting to the emergency department can be helpful to interpret the active bleeding.

Keywords:

Carotid Doppler flow time, emergency department, gastrointestinal bleeding, shock

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Introduction

It is known that excessive fluid resuscitation in critically ill patients is associated with increased complications and poor prognosis.[1-4] Therefore, an accurate assessment of volume status and predictive response to fluid replacement are very important for guiding the treatment process in these patients. Despite the possibilities of endoscopic intervention, gastrointestinal (GI) hemorrhage, with high mortality and morbidity rates, is one of the critical emergencies that require effective volume replacement in the emergency

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department (ED).[5] Early recognition of patients with active bleeding, especially hemorrhagic shock candidates with high risk of GI bleeding, by the emergency physician and the application of appropriate treatment protocols, can only be achieved with the determination of the volume status.

Numerous parameters for the assessment of volume status have been reported in the literature. However, because of the subjectivity and ambiguity of the noninvasive measurements and limited use of invasive ones, there is an impending need for a real-time, fast, inexpensive, and reproducible noninvasive measurement method in critically ill patients with volume loss in emergency services.[6-8] In recent studies, it has been suggested that carotid artery flow time (CFT) measurements give information about the volume status, and the change in CFT measurements after passive leg raising (PLR) maneuver can be used to evaluate the volume response.[9-12]

In this study, we aimed to evaluate the effect of bedside CFT measurement before and after the PLR maneuver on the determination of active bleeding in patients admitted to the ED with upper GI bleeding.

Materials and Methods

Study design and subjects

Our prospective case–control study was conducted between May 2016 and January 2017 in the ED of a training and research hospital. The protocol was approved by the Local Ethics Committee. In addition, informed consent was obtained from both patients and healthy volunteers. All patients aged ≥18 years admitted to the ED with suggestive symptoms and objective signs of upper GI bleeding such as melena, hematochezia, hematemesis, or vomiting bright red bloody content were included in the study. Patients with atrial fibrillation and history of stenosis in the carotid artery (due to inability to measure CFT), known liver cirrhosis (due to variceal abundant bleedings which the proper position for Doppler measurements may not be suitable and the possible effects of increased intra-abdominal pressure on measurements with PLR), deep-vein thrombosis (due to possible insufficient venous return for PLR maneuver), and lower-extremity amputation (due to inability to perform PLR maneuver) were excluded from the study. In addition, patients with GI bleeding, who were in hemorrhagic shock requiring vasopressor support (due to the possible effects of vasopressors on the measurements), were excluded from the study. The control group consisted of healthy controls who admitted to the ED with soft-tissue injury, had no known vascular abnormality or previous surgery on the neck or heart, and matched in terms of age and sex with the patient group in the study.

Study protocol

All patients diagnosed with GI bleeding in the study were evaluated in the critical care room after the vital signs were obtained. The necessary anamnesis receiving and monitoring procedures in the critical care room were performed by the primary physician responsible for the patient; the first sonographic measurements were simultaneously obtained by the investigator responsible for the study, and the second measurements were obtained immediately following the PLR maneuver. There was no intervention in the routine processes of the diagnosis and treatment of the patients with GI bleeding, and hence, there was no delay for patients' treatment. Upper GI system endoscopy was performed for all patients within the first 24 h following initial fluid resuscitation and medical treatment. According to the results of endoscopy, patients with ulcer bleeding were evaluated based on the Forrest classification. Patients with Forrest 1a and 1b and those without ulcer bleeding but with visible bleeding in endoscopy were defined as "active bleeding" patient group. Other patients were defined as "non-active bleeding" patient group. The vital signs at arrival, medical history, laboratory information, endoscopy results, and sonographic measurements of all patients were recorded in the study form.

Doppler sonographic assessment of carotid artery

Ultrasonographic measurements were performed by an emergency specialist with prior training. After educational sessions held for 2 days, the investigator responsible for the Doppler measurements completed the scan protocol on 15 practice patients under the supervision of radiology department director. After the patients were placed in the supine position, using Mindray DC-3 Ultrasound System device, the carotid artery was visualized on the short axis with a 5–10 MHz linear probe in B-mode by the practitioner. Then, the probe notch was rotated 90° to the head of the patient, and the carotid artery image was obtained on the long axis. The diameter of the carotid artery was found by measuring between the intima layers of both vessel walls approximately 1–2 cm proximal to the carotid bulb. Then, pulse-wave Doppler imaging was performed again on the same image, the Doppler angle was adjusted to 30°–60°, and the flow through the carotid artery of the patient was displayed as a Doppler spectrum. CFT was found by measuring between the flow start, where the graph starts to rise on the x-axis, and the dichroic notch on this spectrum in terms of milliseconds (msn) [Figure 1]. Then, the cardiac cycle time was determined by measuring the interval between the two beats in terms of msn. Corrected CFT (CFTc) using Doppler was calculated by dividing the CFT by the square root of the cardiac cycle time. Carotid artery flow velocity was determined by measuring the graph height in terms of cm/s on the y-axis. These measurements were

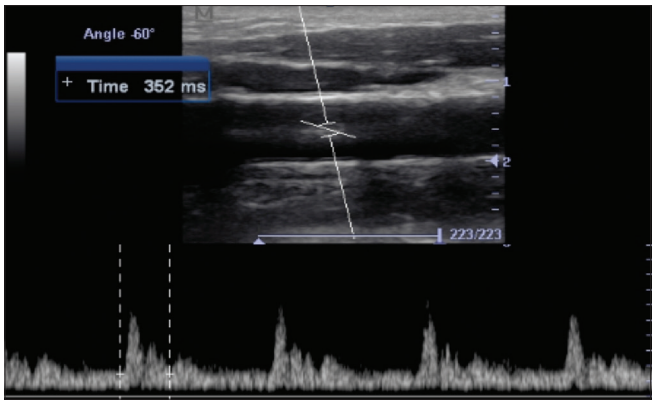

Figure 1: Measurements of time carotid artery flow

repeated after the PLR maneuver was applied by passive raising of the patient's legs at 45° and waiting for 30–60 s. All measurements were recorded.

Statistical analyses

Statistical analyses were performed using SPSS 16.0 (Chicago, IL, USA) statistical program. The Shapiro–Wilk test was used to analyze whether patients' continuous data comply with the normal distribution. The data conforming to normal distribution were expressed as mean ± standard deviation, whereas data not conforming to normal distribution were expressed as median and 25% and 75% quartiles (interquartile ranges). Pearson's Chi-square test was used to compare the categorical data of the patients among the groups. Student's *t*-test was used to compare the parametric continuous data, and Mann–Whitney U-test was used to compare the nonparametric data. In order to determine the presence of active bleeding in patients with GI bleeding, the amount of change in the CFT (ΔCFT) and the amount of change in the corrected CFT (ΔCFTc) were analyzed by receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated. Statistical significance level was accepted as $P < 0.05$ for all analyses. The sample size was not calculated because there were no clear data regarding the researched subject and the sonographic measurements to be made before the study.

Results

A total of 50 patients and 44 healthy volunteers were included in the study. The mean age of the patient group was 58 ± 18 years, and the control group was 57 ± 18 years. Demographic data, vital signs, and laboratory parameters of both groups are given in Table 1. In the comparison of the carotid Doppler measurements at the time of admission and the changes after the PLR maneuver, a statistically significant difference was found between the patient and control groups in the values of ΔCFT, ΔCFTc, and Δ carotid artery diameter ($P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively). The first and post-PLR measurement values of the patient and control groups and the changes based on the control measurements after PLR are given in Table 2.

Table 1: Demographical and clinical characteristics of patient and control groups

	Patient group (*n*=50)	Control group (*n*=44)	*P*
Age, mean±SD	58±18	57±18	0.6
Sex, *n* (%)			
Male	26 (52)	26 (59)	0.4
Female	25 (48)	18 (41)	
Comorbidities, *n* (%)			
HT	19 (38)	25 (56)	0.06
DM	9 (18)	14 (31)	0.1
CAD	15 (30)	12 (27)	0.7
Peptic ulcus	23 (46)	11 (25)	0.03
Vital signs, median (IQR 25%–75%)			
SBP, mm/Hg	120 (103-130)	135 (120-140)	<0.001
DBP, mm/Hg	66 (55-70)	70 (70-80)	0.002
Hearth rate, beat/min	97 (85-105)	80 (72-90)	<0.001
Laboratory parameters			
Hgb (g/dl)	10±3	13±1.7	<0.001
Hct (%)	30 (23-36)	40 (37-44)	<0.001
WBC (x10^3/μL)	9.4 (7-12.6)	9 (6.9-11.6)	0.3
Lactate (mmol/L)	2 (1.4-3.8)	1.4 (1-1.8)	0.001
Urea (mg/dl)	64 (34-107)	32 (23-37)	<0.001

Pearson's Chi-square test was used for the categorical data of the groups. Student's *t*-test was used for the parametric continuous data. Mann-Whitney U-test was used for the nonparametric data. HT=Hypertension, DM=Diabetes mellitus, CAD=Coronary artery disease, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, Hgb=Hemoglobin, Htc=Hematocrit, WBC=White blood count, SD=Standard deviation

According to the endoscopy result, patients with GI bleeding were divided into two groups: patients with active bleeding ($n = 9$ [18%]; of these, five patients had Forrest 1b, one patient had active bleeding on ulcerovegetant mass, one patient had active bleeding on surgical anastomosis line, and two patients had active esophageal variceal bleeding due to idiopathic portal vein thrombosis) and patients without active bleeding ($n = 41$ [82%]). Statistically significant difference was found in the ΔCFT and ΔCFTc measurements between the groups ($P = 0.005$ and $P = 0.01$, respectively). Table 3 shows the comparison of Doppler measurements in patients with and without active bleeding.

The ROC curves for ΔCFT and ΔCFTc were obtained to evaluate the ability to determine the presence of active bleeding in patients with GI bleeding [Figure 2]. AUCs for ΔCFT and ΔCFTc were determined as 0.801 (95% confidence interval [CI]: 0.65–0.95) and 0.778 (95% CI: 0.63–0.91), respectively. Considering the best cutoff values that can determine the presence of active bleeding, for ΔCFT, 12 ms was the best cutoff value with a sensitivity of 88% and a specificity of 54%

Table 2: Comparison of the amount of change between two measurements and the ultrasonography measurements of the patient and control groups at the time of admission and after passive leg raising maneuver

	Patient group	Control group	*P*
On admission			
CFT, msn	280 (262-304)	312 (290-336)	<0.001
CTC_c, msn	335 (321-352)	350 (337-367)	0.004
Carotid artery diameter, cm	0.65 (0.61-0.74)	0.68 (0.64-0.72)	0.3
Carotid artery flow velocity, cm/msn	61 (50-75)	62 (49-71)	0.6
After PLR			
CFT, msn	296 (272-322)	312 (296-342)	0.015
CTC_c, msn	360 (346-380)	358 (348-373)	0.7
Carotid artery diameter, cm	0.66 (0.61-0.74)	0.68 (0.64-0.72)	0.5
Carotid artery flow velocity, cm/msn	70 (50-80)	68 (55-76)	0.5
Amount of change			
ΔCFT, msn	16 (8-24)	8 (–8-16)	0.001
ΔCTC_c, msn	22 (10-39)	8 (–1-16)	<0.001
ΔCarotid artery diameter, cm	0 (0-0.01)	0 (0-0)	<0.001
ΔCarotid artery flow velocity, cm/msn	5 (0-10)	4 (–2-8)	0.4

Mann-Whitney U-test was used. PLR=Passive leg raising, CFT=Carotid artery flow time, CFT_c=Corrected carotid artery flow time, ΔCFT=Change in the CFT

Table 3: Comparison of carotid artery Doppler measurements with and without active bleeding in patients with gastrointestinal bleeding

	Active bleeding (+) (*n*=9)	Active bleeding (–) (*n*=41)	*P*
On admission			
CFT, msn	280 (264-307)	280 (256-304)	0.7
CTC_c, msn	330 (317-343)	339 (322-355)	0.2
Carotid artery diameter, cm	0.70 (0.61-0.79)	0.65 (0.61-0.72)	0.2
Carotid artery flow velocity, cm/msn	65 (49-77)	60 (50-74)	0.9
After PLR			
CFT, msn	296 (272-322)	312 (296-342)	0.1
CTC_c, msn	360 (346-380)	358 (348-373)	0.2
Carotid artery diameter, cm	0.66 (0.61-0.74)	0.68 (0.64-0.72)	0.3
Carotid artery flow velocity, cm/msn	70 (50-80)	68 (55-76)	0.4
Amount of change			
ΔCFT, msn	16 (8-24)	8 (–8-16)	0.005
ΔCTC_c, msn	22 (10-39)	8 (–1-16)	0.01
ΔCarotid artery diameter, cm	0 (0-0.01)	0 (0-0)	0.4
ΔCarotid artery flow velocity, cm/msn	5 (0-10)	4 (–2-8)	0.2

Mann-Whitney U-test was used. PLR=Passive leg raising, CFT=Carotid artery flow time, CFT_c=Corrected carotid artery flow time, ΔCFT=Change in the CFT

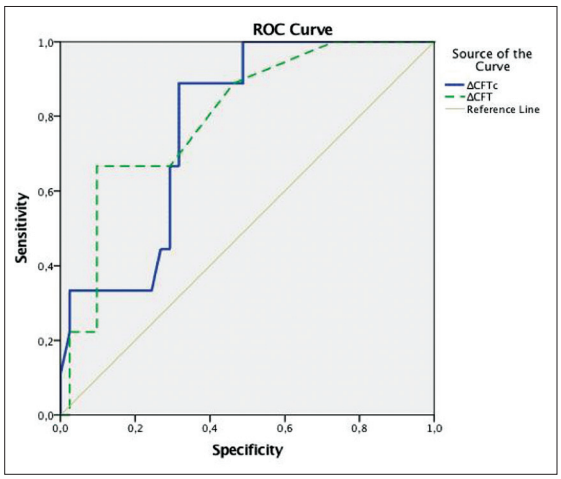

Figure 2: Receiver operating characteristic curves for change in the carotid artery flow time and change in the corrected carotid artery flow time for determining the presence of active bleeding

and for ΔCFTc, 28 ms was the best cutoff value with a sensitivity of 88% and a specificity of 69%.

Although the ΔCTFc threshold value was 28 ms, it was determined that it could predict active bleeding with sensitivity of 88% (95% CI: 51%–99%), specificity of 69% (95% CI: 51%–81%), positive likelihood ratio of 2.8 (95% CI: 1.6–4.6), negative likelihood ratio of 0.16 (95% CI: 0.03–1.04), positive predictive value of 38% (95% CI: 27%–50%), and negative predictive value of 96% (95% CI: 81%–99%).

Discussion

In our study, three significant results were obtained. First, ΔCFT and ΔCFTc values were found to be higher in patients with GI bleeding than in healthy volunteers.

We believe that the expected volume loss in patients with GI bleeding is the most likely cause of this outcome. However, our second and most important finding was that, according to endoscopy results, ΔCFT and ΔCFTc values were higher in patients with active bleeding than in those with arrested bleeding. Based on this result, we believe that the change in CFT and CFTc values, especially after the PLR maneuver provides the clinician an idea for finding patients with active GI bleeding. In the ROC analysis to determine the threshold value of ΔCFTc for finding patients with active bleeding, the most optimal ΔCFTc value was found to be 28 ms. The sensitivity, specificity, and negative predictive values calculated for this ΔCFTc value were 88%, 69%, and 96%, respectively. In other words, the lack of an increase in CFTc value after the PLR maneuver in patients admitted with symptoms and signs of GI bleeding or an increase <28 ms indicates that there is no serious bleeding in these patients. Considering these results, since the relevant sonographic measurements are considered as bedside, repeatable, and inexpensive, we believe that they can be used in clinical practice in to find patients with active bleeding.

Although it is generally accepted that invasive intervention or dynamic measurement methods that require mechanical ventilation, such as stroke volume variation and aortic blood flow measurement, provide the most accurate information about the volume status, there is a tendency for the correct use of resources by clinicians and the use of noninvasive methods for patient safety.[7] The most frequently studied noninvasive measurement method is ultrasonographic examination of the inferior vena cava; however, the technical difficulty in obese patients and those with intra-abdominal bowel gas, variability in the application methods, inconsistency in the results of different study groups, and inadequacy in the detection of volume loss at early stage create questions regarding the effectiveness and reliability of this measurement method.[13,14] However, by using carotid artery Doppler ultrasonography and by performing simultaneously a vessel examination that correlates with the aortic flow, it is possible to obtain real-time and more reliable information about the volume status, which is relatively more superficial, without any technical difficulties. Shokoohi *et al*. and Blehar *et al*. found that CFTc was low in dehydrated patients, whereas Hossesin-Nejad *et al*. detected a high CFTc in hemodialysis patients with volume load in the predialysis period, and Mackenzie *et al*. found a high CFTc in blood donors before phlebotomy.[8,10-12] In our study, we also found a statistically significant difference in CFT, CFTc, ΔCFT, and ΔCFTc measurements between patients with GI bleeding and healthy volunteers. Our study did not focus on the determination of volume status or objective blood loss, the aim of the present study was to predict active bleeding in patients with GI hemorrhage. To the best of our knowledge, it is the first study, wherein carotid artery Doppler measurement was performed in GI bleeding in clinical practice.

Prediction of the volume response of patients has gained importance recently due to the fact that approximately half of the fluid boluses in critically ill patients fail to increase cardiac output and unnecessary excess fluid supply has been shown to increase mortality.[15-17] The PLR maneuver exhibits an effect equivalent to the fluid bolus of 250–350 cc in a completely reversible manner without putting the patient at risk of overloading the volume, and it is suggested that it can be used to evaluate the volume response.[18] In the study by Mackenzie *et al*., it was reported that CFTc after the PLR maneuver before blood donation showed only an average change of 1.2%, whereas CFTc after the PLR maneuver after blood donation increased by an average of 8.3%. Based on this result, it was suggested that the CFTc measurement accompanied by the PLR maneuver may be an effective tool in detecting hypovolemia in acute blood loss.[8] In the study by Antiperovitch *et al*. on hemodialysis patients, when evaluating the power of CFTc in pre- and post-dialysis measurements and the change in CFTc after the PLR maneuver to distinguish the volume status, AUC values were found to be 0.64 and 0.91, respectively, and it was emphasized by the authors that the PLR maneuver significantly increased the CFTc's volume evaluation power.[9] In our study, we found that ΔCFT and ΔCFTc values of carotid artery Doppler measurements calculated after the PLR maneuver were significantly higher in patients with active bleeding compared to those without active bleeding. Therefore, in accordance with the literature, we believe that the PLR maneuver can increase the power of carotid artery Doppler measurements in order to distinguish the patients who may be more hypovolemic due to active bleeding than others.

In literature, an increase of 30 ms in CFTc with the PLR maneuver has been reported to determine postultrafiltration volume status with a sensitivity of 71% and specificity of 94%.[9] In another study wherein patients with fasting and nonfasting status were examined, it was suggested that a change of 5% in ΔCFTc can be used in volume status determination with a sensitivity of 73% and a specificity of 82%.[10] Similarly, a cutoff value of 5% was calculated with 66% sensitivity and 77% specificity for percentage CFTc in the hypovolemia prediction of blood donors.[8] In our study, we determined that the presence of active bleeding can be determined with sensitivity of 88%, specificity of 69%, and negative predictive value of 96% when ΔCFTc value is 28 ms in patients with GI bleeding. The difference in the threshold value and the reliability

criteria of the studies can be explained by the differences in the characteristics of the study populations and the volume changes.

Heart rate and blood pressure are traditional noninvasive parameters commonly used in daily practice in the evaluation of volume status in critically ill patients. In literature, it has been suggested that carotid artery Doppler measurements may stimulate the clinician in terms of volume deficit in the early period before the heart rate and blood pressure get affected. In a study conducted by Blehar *et al*. on dehydrated patients receiving an average of 1110 ml of the intravenous fluid bolus, a significant increase of 14.9% in CFTc measurements was observed after the fluid intake, but no significant changes in blood pressure and heart rate were reported.[11] Hossein-Nejad *et al*. found an 11.5% reduction in CFTc after 2400 ml of fluid removal in end-stage renal disease patients on hemodialysis; although this change was statistically significant, it was found that this change was accompanied only by a small mean arterial pressure reduction of 4 mmHg, and there was no significant change in heart rate during the pre- and post-dialysis periods.[12] However, since there was a difference in terms of vital signs between the patient and control groups at the beginning, we could not make this interpretation in our study.

Limitations

There are some limitations to our study. First, our study is a single-center study with limited sample size. Therefore, it is difficult to make a general inference for all centers based on our results. Studies with larger sample sizes are needed. Second, carotid artery Doppler measurements were performed by a single practitioner (emergency specialist) after educational and training sessions, and no compliance assessment was performed by another practitioner or radiologist. However, the reason why we did not include a radiologist for the second measurement was the concern that the second measurement would cause a loss of time, which would disrupt patient treatment. In addition, we believe that the application performed by the current clinician at bedside is more suitable for the actual daily practice. Furthermore, the time period between the beginning of the symptoms and CFT measurement was not considered in the present study, we only performed a cross-sectional evaluation starting from the ED admission. We performed a cross-sectional evaluation starting from the ED admission.

Conclusion

Based on the results of our study, bedside ultrasonographic carotid artery Doppler measurement at the time of admission may be one of the effective noninvasive methods that can be used to determine active bleeding in patients with GI hemorrhage. In this patient group, CFT measurements before and after PLR maneuvers may be considered in the determination of replacement protocols.

Author contribution statement

Conceived and designed the experiments; ŞKÇ and SK. Performed the experiments; SK, EE, SD. Analyzed and interpreted the data; ŞKÇ, YÇ, EE. Contributed reagents, materials, analysis tools or data; ŞKÇ, SD, EE, SK, YÇ. Wrote the paper; ŞKÇ, SK, SD.

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Conflicts of interest

The authors declared that there is no conflict of interest.

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