Ultrasound Assessment of the Change in Carotid Corrected Flow Time in Fluid Responsiveness in Undifferentiated Shock

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Objectives: Adequate assessment of fluid responsiveness in shock necessitates correct interpretation of hemodynamic changes induced by preload challenge. This study evaluates the accuracy of point-of-care Doppler ultrasound assessment of the change in carotid corrected flow time induced by a passive leg raise maneuver as a predictor of fluid responsiveness. Noninvasive cardiac output monitoring (NICOM, Cheetah Medical, Newton Center, MA) system based on a bioreactance method was used.

Design: Prospective, noninterventional study.

Setting: ICU at a large academic center.

Patients: Patients with new, undifferentiated shock, and vasopressor requirements despite fluid resuscitation were included. Patients with significant cardiac disease and conditions that precluded adequate passive leg raising were excluded.

Interventions: Carotid corrected flow time was measured via ultrasound before and after a passive leg raise maneuver. Predicted fluid responsiveness was defined as greater than 10% increase in stroke volume on noninvasive cardiac output monitoring following passive leg raise. Images and measurements were reanalyzed by a second, blinded physician. The accuracy of change in carotid corrected flow time to predict fluid responsiveness was evaluated using receiver operating characteristic analysis.

Measurements and Main Results: Seventy-seven subjects were enrolled with 54 (70.1%) classified as fluid responders by noninvasive cardiac output monitoring. The average change in carotid corrected flow time after passive leg raise for fluid responders was 14.1 ± 18.7 ms versus −4.0 ± 8 ms for nonresponders ($p < 0.001$). Receiver operating characteristic analysis demonstrated that change in carotid corrected flow time is an accurate predictor of fluid responsiveness status (area under the curve, 0.88; 95% CI, 0.80–0.96) and a 7 ms increase in carotid corrected flow time post passive leg raise was shown to have a 97% positive predictive value and 82% accuracy in detecting fluid responsiveness using noninvasive cardiac output monitoring as a reference standard. Mechanical ventilation, respiratory rate, and high positive end-

expiratory pressure had no significant impact on test performance. Post hoc blinded evaluation of bedside acquired measurements demonstrated agreement between evaluators.

Conclusions: Change in carotid corrected flow time can predict fluid responsiveness status after a passive leg raise maneuver. Using point-of-care ultrasound to assess change in carotid corrected flow time is an acceptable and reproducible method for noninvasive identification of fluid responsiveness in critically ill patients with undifferentiated shock. (*Crit Care Med* 2018; XX:00–00)

Key Words: corrected flow time; fluid responsiveness; shock; ultrasound

Fluid responsiveness assessment is defined as an increase in cardiac output (CO) in response to preload augmentation and is used in resuscitation from shock (1, 2). Temporary intravascular fluid shift maneuvers such as the passive leg raise (PLR) test (3) transiently increase venous return, thus enabling the assessment of CO change with an intervention that mimics fluid administration. Unfortunately, CO monitoring technology is expensive, not widely available, and imprecise. New technologies to assess the hemodynamic response to PLR are needed.

Flow time (FT), or left ventricular ejection time, reflects the duration of systole and is measured from the beginning of the upstroke to the trough of the incisural notch on a pulse waveform analysis (4). Corrected for the heart rate variability, it is called "corrected FT," and the change in its duration may reflect changes in stroke volume (SV). Point-of-care ultrasound is noninvasive and increasingly available in critical care settings (5, 6), and the assessment of corrected FT via Doppler ultrasound (7–9) is a safe and simple method which does not require extensive ultrasonographic expertise by the operator.

In this study, we hypothesize that the change in carotid corrected FT (ΔccFT) induced by a PLR maneuver may predict fluid responsive status in early, undifferentiated shock. The noninvasive bioreactance CO monitoring (NICOM; Cheetah Medical, Newton Center, MA) system was used as the reference standard as it has been validated in the assessment of fluid responsiveness in combination with PLR (10–14).

MATERIALS AND METHODS

This prospective, noninterventional study was conducted in a single academic quaternary care center. Adult patients with early (< 24 hr duration), undifferentiated shock, who were admitted to a medical or surgical ICU with persistent vasopressor requirements despite preenrollment fluid resuscitation of greater than 1 L of IV fluids, were enrolled after informed consent. Patients were excluded if they presented with a history of left or right heart failure, pulmonary hypertension, cardiac rhythm other than sinus, significant peripheral vascular disease, suspected or known increased intracranial pressure, recent abdominal surgery, recent history of venous thromboembolism, and body mass index less than 15 or greater than 40 kg/m^2. Enrollment period was from May 2016 to April 2017. Approval for this study was granted by the UCLA Institutional Review Board (number 15-001768).

Fluid Responsiveness Assessment

Measurements of carotid corrected FT (ccFT) were made at an increment of a 10th of a milliseconds and were obtained analyzing Doppler images of common carotid artery pulse waveforms (LOGIQ e; GE Healthcare, Wauwatosa, WI) by a trained physician sonographer (**Fig. 1**). A linear array probe was used to obtain and record Doppler images of the vessel in long-axis view. Patients were evaluated using Ultrasound and NICOM simultaneously. Measures were obtained at baseline (prior to PLR, with the patient in a semirecumbent position with 45° head of bed elevation for at least 10 min) and

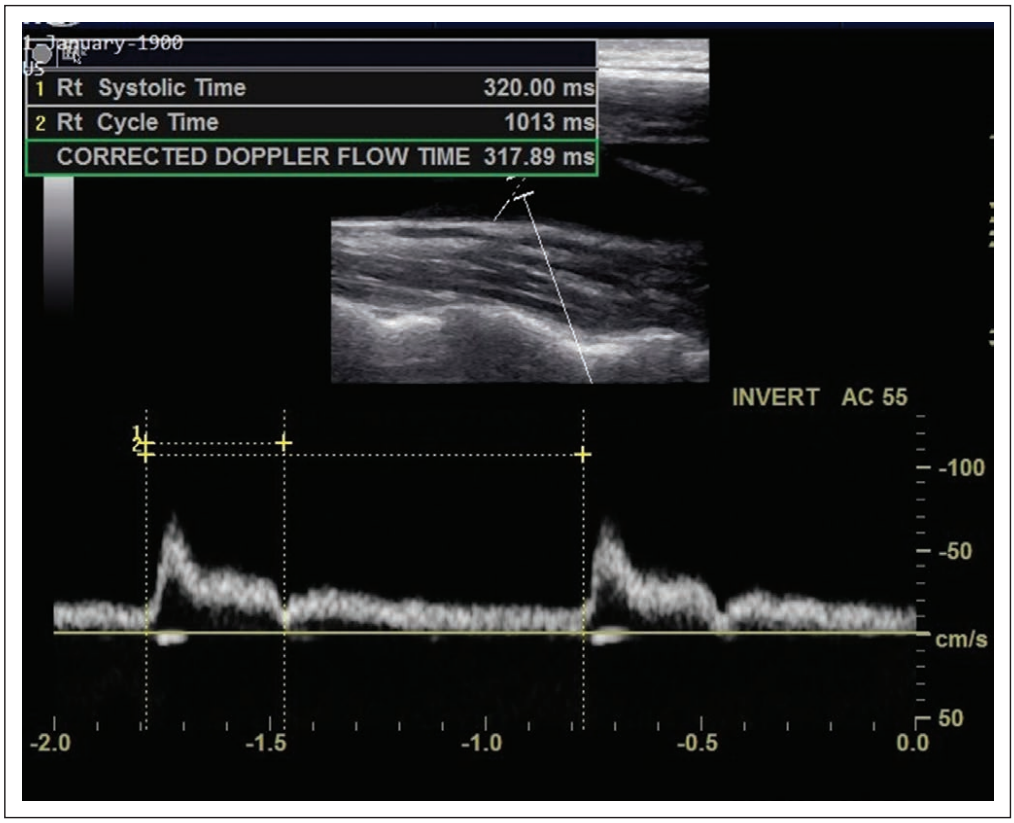


Figure 1. Carotid Doppler waveform with markings: 1) flow time (FT) and 2) cycle time. Carotid corrected FT is calculated as FT + 1.29 × (heart rate−60). AC = angle correction, Rt = right side.

during the PLR maneuver performed using NICOM manufacturer's protocol (patient in supine position for 3 min with legs passively supported by an inflated wedge at 45° elevation; **Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D912 and **legend**, Supplemental Digital Content 5, http://links.lww.com/CCM/D916). ccFT measurements were captured after 120 seconds of the PLR maneuver. Fluid responsive status was defined as greater than or equal to 10% increase in SV via NICOM (15). Systolic and cycle times were analyzed by the bedside operator's interpretation of ultrasound-captured images, and ccFT values were calculated using Wodey's formula, $FT_{corrected} = FT_{measured} + 1.29(HR\text{-}60)$, which has been shown to better correct for fast heart rates in comparison to widely used Bazett's formula ($FT_{corrected} = \frac{FT_{measrured}}{\sqrt{RR\ interval}}$) (16, 17). A second, blinded investigator reevaluated unprocessed bedside images to avoid treatment bias and assessinter-user variability.

Statistical Methods

The NICOM and carotid Doppler measures were compared by response status using the two-sample *t* test. The accuracy of ΔccFT as a predictor of fluid responsive status was assessed using receiver operating characteristic (ROC) analysis. The best threshold of ΔccFT to detect fluid responsiveness was chosen to maximize the sensitivity for a target specificity of at least 96%. The accuracy of ΔccFT as a predictor of fluid response status was evaluated by the following potential covariates: mechanical ventilation, passive breathing on mechanical ventilation, and positive end-expiratory pressure (PEEP) greater than 5 among the mechanically ventilated subset of subjects. The area under the curves (AUCs) were compared by level of each specified covariate (18). The agreement between the bedside and blinded ccFT measures was evaluated using the Bland-Altman plot, a plot of the differences versus the means. Accuracy was calculated as an average value of specificity and sensitivity of the test. *p* values of less than 0.05 were considered statistically significant. Data are presented as mean ± SD or median (interquartile range).

RESULTS

Seventy-nine patients were enrolled in the study. Two of the enrolled patients (2.5%) developed complications during PLR and did not complete the protocol. One of this pair developed atrial fibrillation, and the other had a significant decrease in the oxygen saturation of hemoglobin as measured by pulse oximetry (**Supplemental Fig. 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D913 and legend, Supplemental Digital Content 5, http://links.lww.com/CCM/D916). Baseline characteristics of the 77 patients who completed the full PLR protocol are displayed in **Table 1**. These patients were grouped according to their SV response to a PLR as measured by NICOM. "Fluid responders" included patients that had a SV increase greater than or equal to 10% by NICOM after a PLR. "Nonresponders" included patients demonstrating a SV increase less than 10% by NICOM after a PLR. The majority of the patients (70.1%) were designated as fluid responsive based on these criteria.

Fluid responsive patients had a greater increase in ccFT after PLR than nonresponsive patients (14.1 ± 19 [SD] vs –4.0 ± 8 ms; $p < 0.001$) (**Table 2**). The percentage increase from baseline in ccFT was also higher among responders than nonresponders (+4.8 ± [SD] 6.4 vs –1.4% ± 2.9%; $p < 0.001$). Dot plot analysis presented in **Figure 2** demonstrates the differences in ΔccFT between NICOM-defined fluid responders and nonresponders. ROC curve analysis for ΔccFT ability to predict fluid responsiveness is presented in **Figure 3**, and we show that using a cutoff value of 7 ms as a ΔccFT to define fluid responsiveness had a specificity of 96%, sensitivity of 68%, positive predictive value of 97%, and accuracy of 82%. Additional subgroup analyses found that mechanical ventilation, respiratory rate, and PEEP greater than 5 cmH_2O had no significant impact on the test performance (**Supplemental Table 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/D914). Blinded versus bedside-obtained results were compared via Bland-Altman plot showing a mean difference score of 0 at baseline (nonsignificant, 95% limits of agreement were –6.7 and +6.6) and a mean difference score of –0.2 (nonsignificant, 95% limits of agreement were –6.6 and +6.4) after PLR, showing good agreement between investigators (**Supplemental Fig. 3**, Supplemental Digital Content 4, http://links.lww.com/CCM/D915 and legend, Supplemental Digital Content 5, http://links.lww.com/CCM/D916).

TABLE 1. Baseline Clinical Characteristics of Study Participants

Patient Characteristics	Total, *n* = 77
Age, mean ± SD, yr	60.6 ± 17
Female, %	51
Body mass index, mean ± SD, kg/m^2	24 ± 8
Hematocrit, mean ± SD, %	29.4 ± 7
End-stage renal disease or dialysis, %	42
Total fluids received, mean ± SD, L	8 ± 5
Mechanical ventilation, %	59
Passive ventilation, perecent of ventilated patients	47
Positive end-expiratory pressure > 5 mm Hg, %	25
Pressor used, %	
Norepinephrine	71
Dopamine	5
Vasopressin	3
Phenylephrine	6
Combination	14
Acute Physiology and Chronic Health Evaluation II, mean ± SD	24.5 ± 10

TABLE 2. Corrected Carotid Flow Time and Noninvasive Cardiac Output Monitoring (Cheetah Medical, Newton Center, MA) Results Pre and Post Passive Leg Raise

Variables	Total, *n* = 77	Responders, *n* = 54 (70.1%)	Nonresponders, *n* = 23 (29.9%)	*p*
Mean arterial pressure, mean ± SD, mm Hg	60 ± 8	61 ± 8	68 ± 7	0.15
Heart rate, mean ± SD, beats/min	103 ± 24	101 ± 25	108 ± 21	0.28
Noninvasive cardiac output monitoring, mean ± SD				
Baseline cardiac index, L/min/m^2	3.7 ± 5.1	4.0 ± 6.1	3.1 ± 0.9	0.51
Post PLR cardiac index, L/min/m^2	4.3 ± 3.7	4.8 ± 4.3	3.0 ± 0.8	0.06
Baseline SV, mL	64.1 ± 24.7	65.0 ± 24.5	62.0 ± 25.6	0.63
Post PLR SV, mL	77.7 ± 32.2	85.9 ± 31.7	59.1 ± 25	0.01
Change in SV, mean ± SD, %	24.7 ± 23.6	33.9 ± 22.1	3.1 ± 6.9	
Carotid Doppler				
Baseline ccFT, mean ± SD, ms	301 ± 33	300 ± 32	302 ± 35	0.86
Post PLR ccFT, mean ± SD, ms	310 ± 37	315 ± 36	298 ± 37	0.067
ΔccFT, mean ± SD, %, ms	8.7 ± 18	14.1 ± 19	−4.0 ± 8	< 0.001
ΔccFT, mean ± SD, %	3.0 ± 6.3	4.8 ± 6.4	−1.4 ± 2.9	< 0.001

ΔccFT = change in carotid corrected flow time, ccFT = carotid corrected flow time, PLR = passive leg raise, SV = stroke volume.

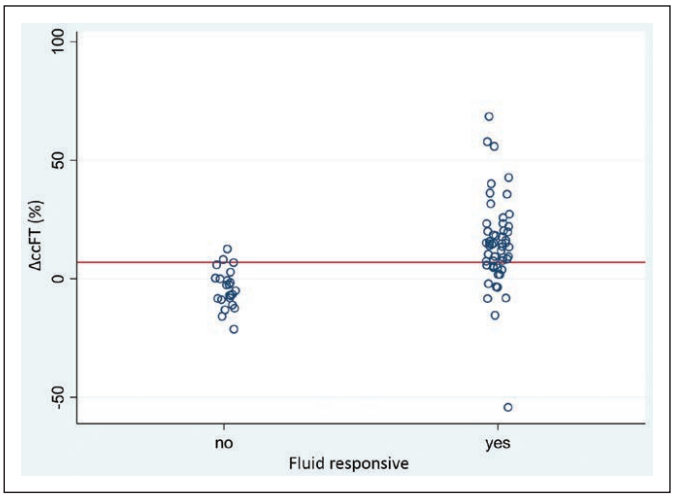


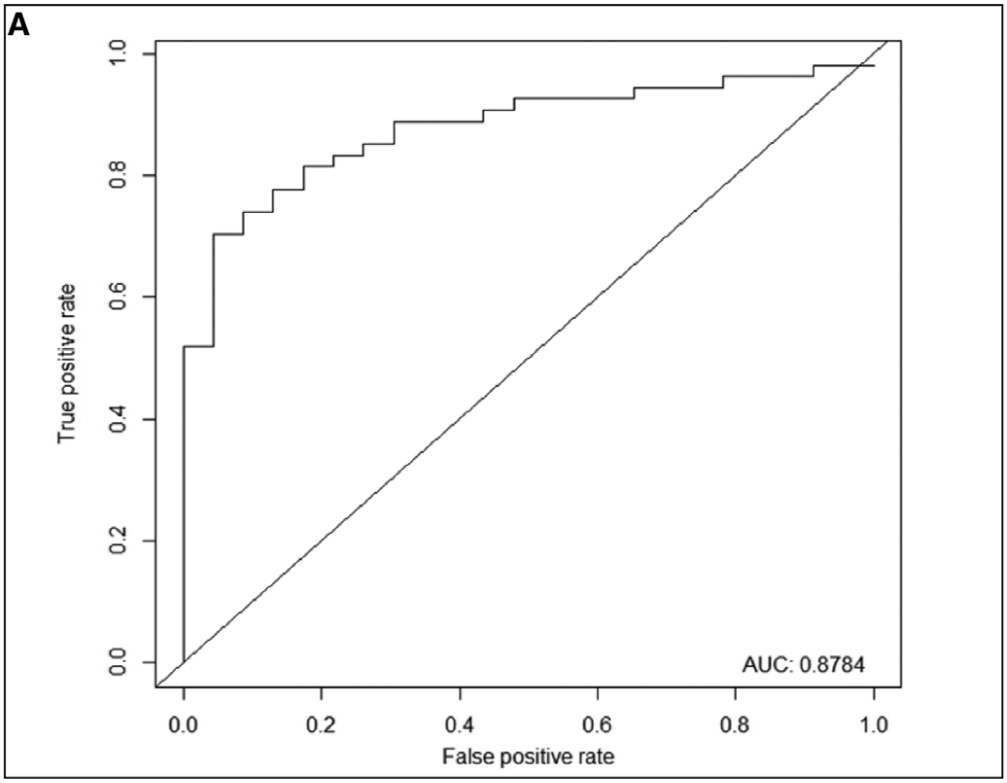
Figure 2. Dot plot analysis of change in carotid corrected flow time (ccFT) by fluid responder status.

DISCUSSION

The results suggest that ΔccFT induced by a PLR maneuver can determine fluid responsiveness in a selected population of patients with early undifferentiated shock. The area under the receiver operator curve suggests that ΔccFT can be used in place of the reference method, which was a 10% increase in SV measured by NICOM. A cutoff of a 7 ms increase in ΔccFT gave excellent positive predictive value and accuracy. Furthermore, the PLR protocol was well tolerated and able to be completed in 97.5% of patients.

There is no consensus about the best way to predict fluid responsiveness (19). In contrast to other novel hemodynamic monitoring systems, point-of-care ultrasound is widely present in ICU settings (20), and the number of indications for its use continues to grow (21). Ultrasonographic measures such as respiratory change in inferior vena cava diameter (22), respiratory change in peak aortic velocity (23), or change in echocardiography-measured end-diastolic area of left ventricle (24) have been used for hemodynamic evaluation of a patient in shock (25). The use of ultrasound to measure Doppler velocity time integral (VTI) of large arteries following PLR maneuver can predict fluid responsiveness assessment (26–28), although variability in the angle of insonation between measurements limits its precision (29).

Despite conflicting data from earlier studies (15, 30, 31), there is an increasing body of published evidence showing the usefulness of corrected FT evaluation in fluid management (32–38). However, there are a number of limitations of using the absolute value of corrected FT. First, it is not only a simple metric of preload but also depends on heart rate, inotropy, and afterload conditions (4, 39, 40). Second, its absolute duration does not correlate with the SV (41). Instead, the change in duration of ccFT can identify changes in left ventricular SV due to altered loading conditions. In order to determine if a change in preload leads to a change in the duration of FT, the heart's afterload and contractility must be constant and the FT must be corrected for a heart rate (17). Accordingly, ΔccFT decreases with fluid or blood removal (36, 42, 43), and increases with fluid administration in volume-depleted patients (38, 43, 44). A number of pilot studies show that ΔccFT also increases after IV fluid bolus challenge (33, 35) or PLR (36, 38) in fluid responsive patients. Using ultrasonographic CO monitoring (35), pulse contour based analysis (37), or the more widely used, esophageal Doppler-based assessment of SV index to define preload



B

Absolute ΔccFT (msec)	Sensitivity	Specificity	Accuracy	PPV	NPV
-3.1	88.9%	69.6%	79.2%	87.3%	72.7%
4.1	81.5%	82.6%	82.0%	91.7%	65.5%
5.5	75.9%	87.0%	81.4%	93.2%	60.6%
6.7	68.5%	95.7%	82.1%	97.4%	56.4%
9.1	59.3%	95.7%	77.5%	97.0%	50.0%
10.6	53.7%	95.7%	74.7%	96.7%	46.8%
12.1	51.9%	95.7%	73.8%	96.6%	45.8%
15.4	40.7%	100.0%	70.4%	100.0%	41.8%

Figure 3. A, Receiver operating characteristic curve analysis for change in carotid corrected flow time (ΔccFT) ability to predict fluid responsiveness. **B**, ΔccFT test characteristics when cutoff values are used to predict fluid responsiveness. ccFT = carotid corrected flow time, AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value.

responsiveness (33, 34), fluid responders show significantly higher ΔccFT in comparison to nonresponders. Combining Doppler evaluation of ΔccFT with a well-validated PLR maneuver (10–14) offers several advantages in comparison to other methods of fluid responsiveness assessment. Measuring ΔccFT is less subject to artifact that many other measures of SV, it is almost universally applicable and, based on results presented here, there is an excellent agreement between bedside and blinded investigator measurements.

There are several strengths of this study. This is the largest study to our knowledge evaluating ΔccFT after PLR as a predictor of fluid responsiveness in shock. All patients were on fixed vasopressor support during the test, thus minimizing the alteration of systemic vascular resistance during the evaluation. The study included patients spontaneously breathing and on passive mechanical ventilation. Positive pressure ventilation had no significant impact on the ability of ΔccFT to predict fluid responsiveness.

Our study has several limitations. We did not assess fluid responsiveness directly. Instead, we compared ΔccFT to a reference method. NICOM was used as a reference standard for fluid responsiveness because it has acceptable agreement with other CO monitoring systems (11, 13, 19, 45, 46), is easy to apply, and has been studied in both spontaneously breathing and mechanically ventilated patients with shock in combination with PLR (13, 47, 48).

The exclusion of patients with congestive heart failure reduces the generalizability of conclusions, although post hoc analysis of echocardiographic results obtained within the same hospital stay indicated that left ventricular ejection fraction was reduced in at least 13.7% of cases (10/73). The same applies for excluding conditions which can potentially lead to a suboptimal or potentially harmful PLR—lower extremity thromboembolism, recent abdominal surgery or hip fractures, suspected elevated intracranial pressure, or significant peripheral vascular disease. Broadening the inclusion criteria in the future should help understand better the general applicability of this method. Despite good interrater agreement, manual measurement can lead to misinterpretation of results, both due to measurement bias, or skill of the operator. Additionally, ccFT slightly varies throughout the respiratory cycle, and random averaging of the ccFT between the three beats (41) may not be able to sufficiently correct potential inaccuracy in interpretation of ccFT measurements. Automated identification of pulse waveform components combined with respiratory tracing may improve accuracy of ΔccFT interpretation in the future.

More importantly, appreciating complex relationship between hemodynamic determinants and understanding the limits of currently used dynamic variables which act as surrogates for SV change, future critical care research may lean toward utilization of composite measures of fluid responsiveness capable of predicting

fluid responsiveness with better accuracy (49). We can speculate that one such example could be combining the two carotid Doppler-derived variables—change in VTI and ΔccFT.

CONCLUSIONS

In patients with early, undifferentiated shock, ΔccFT induced by a PLR maneuver was able to predict fluid responsiveness. It compares favorably with NICOM, with an AUC of 0.88 suggesting it can be used as an alternative to other methods. Its effectiveness is not affected by mechanical ventilation, respiratory rate, or PEEP greater than 5 mmH_2O. Further studies focused on clarification of the role of ΔccFT in the assessment of fluid responsiveness are warranted.

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