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COMPENSATORY RESERVE INDEX: PERFORMANCE OF A NOVEL MONITORING TECHNOLOGY TO IDENTIFY THE BLEEDING TRAUMA PATIENT

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ABSTRACT—**Introduction:** Hemorrhage is one of the most substantial causes of death after traumatic injury. Standard measures, including systolic blood pressure (SBP), are poor surrogate indicators of physiologic compromise until compensatory mechanisms have been overwhelmed. Compensatory Reserve Index (CRI) is a novel monitoring technology with the ability to assess physiologic reserve. We hypothesized CRI would be a better predictor of physiologic compromise secondary to hemorrhage than traditional vital signs. **Methods:** A prospective observational study of 89 subjects meeting trauma center activation criteria at a single level I trauma center was conducted from October 2015 to February 2016. Data collected included demographics, SBP, heart rate, and requirement for hemorrhage-associated, life-saving intervention (LSI) (i.e., operation or angiography for hemorrhage, local or tourniquet control of external bleeding, and transfusion >2 units PRBC). Receiver-operator characteristic (ROC) curves were formulated and appropriate thresholds were calculated to compare relative value of the metrics for predictive modeling. **Results:** For predicting hemorrhage-related LSI, CRI demonstrated a sensitivity of 83% and a negative predictive value (NPV) of 91% as compared with SBP with a sensitivity to detect hemorrhage of 26% ($P < 0.05$) and an NPV of 78%. ROC curves generated from admission CRI and SBP measures demonstrated values of 0.83 and 0.62, respectively. CRI identified significant hemorrhage requiring potentially life-saving therapy more reliably than SBP ($P < 0.05$). **Conclusion:** The CRI device demonstrated superior capacity over systolic blood pressure in predicting the need for posttraumatic hemorrhage intervention in the acute resuscitation phase after injury.

KEYWORDS—Blood pressure, hemorrhage, hypotension, reserve, shock

INTRODUCTION

Hemorrhage is one of the most substantial causes of death after traumatic injury (1–4). Hemorrhage, unlike central nervous system injury, is considered most amenable to life saving intervention. After hemorrhage-associated injury, the most important objective is bleeding control. The challenge is that not all bleeding is clinically evident, particularly when the bleeding is occult. The recognition of physiological status in the field relies heavily on standard vital signs (blood pressure, heart rate (HR), oxygen saturation, and respiratory rate), and the experience of the first responder (5). Assessing a patient with occult hemorrhage becomes increasingly more difficult given the human body's extensive ability to compensate for volume loss often ''normalizing'' these physiologic parameters (1, 2, 4–6). Multiple studies have demonstrated that vital signs may fail to identify the bleeding patient, particularly in the early phases of hemorrhage (3–11). Despite such evidence, prehospital providers continue to be reliant on these suboptimal measures potentially delaying appropriate life-saving intervention only until overt signs of shock are present. In the context of standard measures of physiology, the overt manifestations of clinical shock only become apparent once normal compensatory measures begin to fail. However, once this level of decompensation has developed, the prehospital provider is already behind the critical window to initiate effective resuscitation for shock (3, 8, 9).

The critical time that needs to be recognized begins upon insult to circulating volume when mechanisms are used to maintain intravascular volume and cardiac output. These compensatory mechanisms include tachycardia, vasoconstriction, tachypnea, and various neurohormonal alterations to combat decreased perfusion (1, 2). Given the body's ability to maintain homeostasis through this complex network of compensatory mechanisms, vital signs may remain grossly unchanged reflecting the need for an accurate and sensitive physiological monitor capable of assessing the degree of physiologic compensation.

The Compensatory Reserve Index (CRI) is a novel, continuous, and noninvasive monitoring technology with the ability to assess compensatory reserve via feature extraction of real-time continuous arterial pulse waveforms. The CRI algorithm was designed using the CipherSensor platform (Flashback Technologies). This platform uses machine-learning technology to accurately assess changes in features of arterial waveforms

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secondary to alterations in volume homeostasis (9, 11). Analyzing an individual's waveform and comparing against an archived record of thousands of waveforms, CRI is able to dynamically ''learn'' the individual patient's clinical condition and accurately reflect their current status within the compensatory cascade. The device requires an initial calibration of 30 heart beats with subsequent variable output every 5 s. This dynamic analysis provides an output reading from 0 to 1 where 1 represents ''full'' tank and 0 represents the point where decompensation occurs. Output values correspond to empirically derived color schemes on the device where green (1.0–0.6) to yellow (0.6–0.3) to red (0.3–0.0) represent the continuum toward decompensation. These parameters provide a visual indicator to simplify the interpretation of device output. Several experimental studies using the lower body negative pressure model and likewise controlled hemorrhage studies have validated the ability of CRI to more accurately predict bleeding and monitor compensatory status than traditional vital sign parameters in individuals (1, 3, 7, 10–12).

Although, CRI has been extensively studied in multiple controlled experiments, there is a paucity of data to evaluate the device in a clinical trauma environment. A recent study using a similar device assessed the ability of CRI to discern those who are actively bleeding from those not bleeding. Patients were selectively chosen from a high-risk population after determining the need for intervention, either operative or admission to intensive care unit (13).

Utilizing the capabilities of CRI, the purpose of this study was to assess the ability of CRI to assess and monitor trauma patients and predict those injured patients at risk for significant hemorrhage requiring therapy or hemorrhage control intervention. We hypothesized that CRI would be a better earlier indicator of physiologic compromise secondary to hemorrhage than traditional vital signs, specifically systolic blood pressure (SBP).

MATERIALS AND METHODS

This was a prospective observational study of subjects meeting trauma center activation criteria at a single level I trauma center from October 2015 to February 2016. Subjects were obtained via convenience sampling that included trauma activations throughout the 24-h time period. Inclusion criteria included all injured patients in whom the trauma team was activated. Exclusion criteria included subjects less than 18 years of age, prisoners, pregnant females, and transfers.

Consent was obtained after initial triage resuscitation from either patient or legal-authorized representative. If subject or legal-authorized representative subsequently wished to withdrawal from the study, the device was removed and data destroyed. Patients without the capacity to consent were not enrolled in the study. Given the nature of the population studied, all potential subjects were enrolled in the study as approved by the institutional review board.

The CRI device is a small (2'' × 2'' × 1'') battery-powered unit that uses a machine-learning algorithm to evaluate a subject's arterial waveform features. Utilizing a noninvasive finger probe, the device was placed on qualifying subjects upon arrival to the trauma resuscitation unit and remained in place until hospital admission, transport to operating suite, or discharge. This resulted in a wide time range of individual patient analysis dependent on multiple factors affecting length of stay in the trauma resuscitation unit. Upon placement, CRI device was initially assessed to determine appropriate waveform reading by the research team. The device was then sealed in a closed container blinding the trauma team and patient from device analysis to ensure no intervention was performed based on readings. The device was reassessed at intermittent time intervals to ensure proper placement and continued waveform capture. All malfunctions and/or device misplacement were time recorded to ensure appropriate *post hoc* analysis of the data. No therapeutic decisions were made as a result of the CRI data and standard of care was provided to all subjects enrolled. Of the 101 subjects considered for study enrollment, 12 subjects were removed. Of these 12 potential subjects, 7 subjects were not enrolled in the study given the inability to obtain consent secondary to subject clinical status or lack of legal authorized representative, and 5 subjects were removed secondary to device malfunction corrupting CRI data. This resulted in 89 subjects for data analysis.

Additional data collected included patient demographics, vital sign parameters, laboratory values, resuscitative measures, requirement for hemorrhage-associated life-saving intervention (operation or angiography for hemorrhage, local or tourniquet control of external bleeding, transfusion >2 units PRBC), and evidence of bleeding more than 250 mL on initial clinical evaluation, upon imaging interpretation or from operative blood loss calculation. Resuscitative measures included fluid and blood product transfusion before arrival and during acute resuscitation. All interventions were time stamped to allow retrospective correlation with CRI analysis.

For data analysis, initial arrival values of CRI after calibration time were used for further analysis. These initial values were compared with the initial SBP upon arrival to the trauma resuscitation unit. All statistical analysis was performed using STATA 13 (Stata Corp). Using these values, receiver-operator characteristic (ROC) curves were formulated and statistical analysis was performed to determine each parameters capability to predict hemorrhage. Additional tests were done to determine statistical differences in each prediction curve. Thresholds for each parameter were determined based upon an extensive review of literature and previous experimental thresholds. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value were calculated using aforementioned thresholds for both CRI and SBP. The study protocol was reviewed and approved by the University of Texas Health Science Center at San Antonio Institutional Review Board.

RESULTS

The subject population exhibited an average age of 43 years with a majority being Hispanic (52%). In addition, there was a slight predisposition toward the male sex (54%). A significant majority of injuries were secondary to blunt mechanisms (87%; $P < 0.001$) with an overall mortality of 2%. Average injury severity score for enrolled subjects was 7 (range: 1–48). A summary of the demographic data is shown in Table 1.

Comparisons between the two subgroups revealed those experiencing hemorrhage had significantly higher hospital length of stay, intensive care length of stay, and injury severity scores (ISS). In addition, injured patients with hemorrhage were more likely to receive crystalloids prehospital and in the trauma resuscitation unit. There was a significantly increased rate of blood product transfusion in patients with hemorrhage. Comparisons of age, sex, race, and mechanism were statistically similar between the two groups.

Subject vital signs, shock index, CRI, and lactate are shown in Table 2. CRI, HR, and lactate were significantly different between the two groups, whereas SBP, mean arterial pressure (MAP), and shock index (SI) were not different between those experiencing hemorrhage versus those who were not.

Logistic regression analyses were used to construct predictive models for predicting hemorrhage between CRI and SBP (Table 3). When controlled for age and sex, the results show CRI ($P < 0.01$) was significantly better at predicting hemorrhage in comparison to SBP ($P = 0.25$). ROC curves calculated from the aforementioned logistic models are represented in Figure 1. Calculated area under the curves for both CRI and SBP were 0.83 and 0.62, respectively. ROC curve comparative analysis revealed CRI identified significantly more hemorrhage requiring therapy than SBP ($P = 0.02$). Using threshold values of less than110 mmHg for SBP and less than 0.70 for CRI,

TABLE 1. **Demographic, mechanism, and outcomes comparison of overall cohort and between subgroup populations of those experiencing hemorrhage and those who are not**

	All subjects	Hemorrhaging	Not hemorrhaging	*P*
Age	43.2	44.6	42.8	0.69
Sex (% male)	54%	62%	51%	0.41
Race				
Caucasian	40 (45%)	11 (52%)	29 (43%)	0.43
Hispanic	46 (52%)	10 (48%)	36 (53%)	0.67
African-American	3 (3%)	0 (0%)	3 (4%)	0.33
Mechanism				
Blunt	77 (87%)	16 (76%)	61 (90%)	0.11
Penetrating	12 (13%)	5 (24%)	7 (10%)	0.11
MVC	42	11	31	
MCC	5	0	5	
MVP	13	3	10	
Fall	13	2	11	
Assault	6	1	5	
GSW	2	2	0	
Stab wound	3	1	2	
Other	5	1	4	
Hospital length of stay	4.7	10.8	2.8	<0.001
ICU length of stay	1.5	4.7	0.5	<0.001
Mortality	2.2%	4.8%	1.5%	0.38
ISS	7	14	5	<0.001
Crystalloid				
Prehospital (mL)	451	793	328	0.01
Trauma Bay (mL)	910	1518	720	<0.001
Blood transfusion				
Trauma Bay (% receiving)	12%	43%	3%	<0.001
Total	89	21	68	

GSW, gunshot wound; ICU, intensive care unit; ISS, injury severity score; MCC, motorcycle collision; MVC, motor vehicle collision; MVP, motor vehicle versus pedestrian.

prediction analyses were developed (Table 4). For predicting hemorrhage, CRI demonstrated a sensitivity of 83% and a NPV of 91%. This is compared with SBP where the sensitivity to detect hemorrhage was 26% with an NPV of 78%. Comparisons of these proportions revealed a significant difference in CRI's sensitivity (<0.05) and clinically improved NPV.

DISCUSSION

Our results show CRI has statistically improved predictive capacity compared to vital signs, specifically systolic pressure, in identifying significant hemorrhage. This is demonstrated in the statistically higher receiver operator characteristic curve and sensitivity and improved NPV. A CRI threshold of 0.70 was chosen for reference based upon previous studies that determined an average starting value of subjects before intervention to range from 0.75 to 0.98 (1, 10, 12). Using this CRI threshold relative to a well-established threshold of hypotension (SBP 110 mmHg), we have established that CRI is more capable of assessing patient physiology upon initial presentation. These data validate previous controlled experimental studies with respect to CRI's ability to detect central circulating volume loss consistent with bleeding.

Treatment of the bleeding patient has advanced significantly over the past few decades in both combat and civilian casualty care. With improved acute management upon reaching a definitive care facility, there is a shifting emphasis to improve the prehospital phase of care. This is best demonstrated by the increased interest in evaluating the efficacy of prehospital drug administration and improved prehospital hemorrhage-control techniques (14–17). Liabilities still remain in the field, specifically surrounding decision support systems to identify blood loss to promptly triage and guide patient care in the prehospital setting (4). The tools currently available are limited to physical assessment and vital sign measurements that have been shown to have inherent liability.

Several new tools have been proposed to help facilitate field triage of trauma patients. One promising tool suggested is field

TABLE 2. **Vital sign, Compensatory Reserve Index (CRI), and lactate comparisons upon initial arrival**

	All subjects	Hemorrhaging	No hemorrhaging	*P*
Initial HR	96 (20)	112 (18)	91 (18)	<0.001
Initial SBP	140 (27)	133 (34)	142 (24)	0.18
Initial MAP	102 (18)	101 (21)	103 (18)	0.83
Initial SI	0.71 (0.21)	0.89 (0.24)	0.66 (0.16)	0.23
Initial CRI	0.63 (0.22)	0.44 (0.18)	0.68 (0.19)	<0.001
Initial lactate	2.4 (2.04)	4.57 (3.20)	1.77 (0.85)	<0.001

HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; SI, shock index.

Table 3. **Logistic regression models for Compensatory Reserve Index (CRI) and systolic blood pressure (SBP)**

	Odds ratio	CI	*P*
CRI	0.94	(0.91-0.97)	<0.01
SBP	0.99	0.97–1.01	0.25

CI, confidence interval.

Table 4. **Predictive parameters using cut-off values for Compensatory Reserve Index (CRI) of 0.70 and systolic blood pressure (SBP) of 110**

	CRI <0.70 (%)	SBP <110 (%)	*P*
Sensitivity	83	25	<0.01
Specificity	60	94	<0.01
PPV	43	60	0.33
NPV	91	77	0.06

NPV, negative predictive value; PPV, positive predictive value.

lactate measurements (18–22). Lactate is a well-studied parameter of hemorrhagic shock with a plethora of evidence validating its use as a predictor of morbidity/mortality (23–27). Although showing potential use as a field triage tool, there are a several inherent limitations. Point of care lactate is a relatively new technology with limited availability in austere or battlefield environments and derangements are appreciated only after a significant volume of blood loss has occurred (9, 11, 28, 29). In addition, elevated levels are not limited to only the hypoxic effects of hemorrhage (27, 29–33). Lastly, point of care lactate is a snapshot of the dynamic process occurring during hemorrhage with limited value in the ongoing process of hemorrhage and initial resuscitation.

This further exemplifies the need for a physiological monitor capable of rapid, sequential, and dynamic assessment of the sum total of all compensatory mechanisms, especially during the compensatory phase before vital sign and laboratory derangement (7). The ability to detect and monitor perfusion changes during the compensatory period will further enhance the early detection of hemorrhage shortly after injury. This will allow the physician and/or first responder to provide life-saving intervention earlier and with a higher probability of success (4, 9, 10). In addition, this monitor must be portable, easily interpretable, and available immediately and continuously to provide accurate triage of patients and continuous monitoring during transport.

This clinical study along with several experimental studies continues to demonstrate that measurement of compensatory reserve based on assessing changes in arterial waveform features is capable of fulfilling these basic requirements and accurately monitoring the bleeding patient (1, 3, 7, 10, 12). A recent study by Convertino et al. assessed the predictive capabilities of CRI versus traditional vital signs in a large hemorrhage experiment. They concluded arterial blood pressure remained essentially unaltered while CRI significantly correlated with blood loss (7). Similar studies by Nadler et al. and Stewart et al. assessed similar parameters on a smaller blood loss scale. Both experiments concluded that CRI was better than standard indices in detecting mild blood loss allowing for early detection of injury (10, 12). CRI is able to monitor physiological changes from the onset of compensation potentially providing the earliest evaluation of the bleeding patient well in advance of vital sign assessment. As previously mentioned, a similar study was recently performed using the CRI device on a trauma population. The results clearly show the capabilities of the CRI algorithm in accurately discerning those who are bleeding from those who are not. The critical difference in these two studies is the population evaluated. In the previous study, the population studied seemed to be significantly sicker at baseline with the ‘‘not actively bleeding’’ patients having multiple abnormalities. These patients were tachycardic (>100), and had abnormal shock indexes (>0.70), high base deficit, and elevated lactate levels. This is best appreciated in the various ROC curve thresholds that were significantly different from typically seen in literature. Even the CRI threshold of 0.21 is significantly smaller than any previous studies. One could argue the possibility that many of the patients had overt signs of hemorrhage negating the need for additional assessments. Furthermore, those in the potential ‘‘gray’’ zone (indeterminate bleeding) were not included for simplicity of comparison (13). We believe the major benefit of the CRI device is the ability to assess a patient’s status in clinical scenarios where the ability of the device to detect subtle physiologic abnormalities may have significant implications to triage and treatment before overt signs of decompensation are manifest. Unlike the previous study, this analysis sought to evaluate the composite injured population, specifically including those patients without obvious signs of clinical shock. By doing so, we have presented data on the capabilities of the CRI device in a broad range of injury situations. This is in conjunction with the numerous inherent advantages to CRI. The device is non-operator dependent, and interpretation of output is simplified to a scale from 0 to 1 with color coded representation of current compensatory status. These attributes contribute to its potential use in a wide array of patient populations, clinical scenarios, and environments.

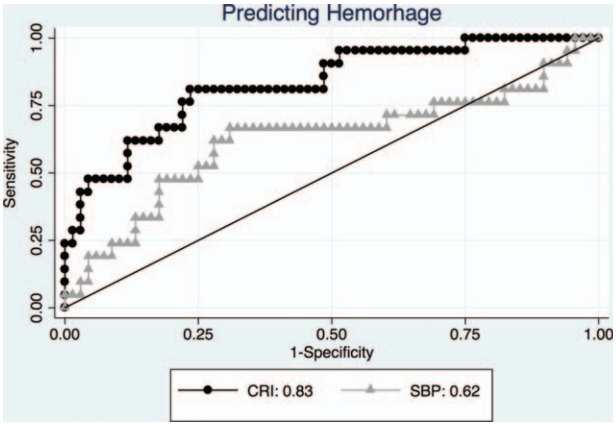

Fig. 1. **Receiver operator characteristic curves generated for both Compensatory Reserve Index (CRI) and systolic blood pressure (SBP) in relation to their ability to predict hemorrhage.** Both curves have been adjusted to compensate for age and gender. Comparison of curves shows statistical difference (*P* = 0.02).

Our study has notable limitations. Most studies with CRI involved experimental intervention with before and after analysis. This change in CRI was the focus of the comparative analysis to determine predictive value of CRI. This study did not have the opportunity of obtaining baseline CRI before ‘‘intervention’’ as injury occurred before presentation. Thus, we only had their subsequent value shortly after the incident making interpretation difficult especially given not all patients have baseline CRI value of 1 and a validated ‘‘normal’’ cutoff value has yet to be established. This variation in ‘‘starting’’ CRI value may represent the vast array of factors affecting compensation and the ever changing and complex interactions occurring to maintain homeostasis.

Additional limitations were the several confounders potentially affecting the CRI device. CRI by definition represents the body’s ability to compensate for alterations in volume status. Therefore, changes to CRI may be induced by a wide array of insults not secondary to actual hemorrhage. Individual analysis of subjects having poor CRI values and no evidence of bleeding demonstrated medication administration, intoxication, dehydration, and pain may affect CRI readings. This was reflected in the low positive predictive value of the device while maintaining a high NPV. Although this raises further questions and the need for further research in the understanding of CRI dynamics, the emphasis on other predictive values are important. Sensitivity and NPV are key components of a tool used in the triage setting and provide critical information in determining presence of injury. The higher sensitivity and NPV enable those responsible for triage and/or initial care to safely and confidently differentiate victims who are injured from those who are not.

Although our study provides evidence in CRI’s ability to act as an initial triage tool in predicting bleeding, further studies are necessary. There is a need to better understand the several factors affecting compensation especially in the acutely injured patient. These findings also suggest a prospective evaluation of the device in a prehospital setting is warranted.

CONCLUSION

The CRI device outperformed SBP in predicting hemorrhage in the acutely injured patient. This novel monitoring technology offers promise for potential applications to the triage and acute resuscitation of trauma patients.

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