Tachycardic and non-tachycardic responses in trauma patients with haemorrhagic injuries

Andrew T. Reisner[a], Shwetha Edla[b], Jianbo Liu[b], Jiankun Liu[b], Maxim Y. Khitrov[b], Jaques Reifman[b,*]

[a] Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA
[b] Department of Defense Biotechnology High Performance Computing Software Applications Institute, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, USA

A B S T R A C T

Background: Analyses of large databases have demonstrated that the association between heart rate (HR) and blood loss is weaker than what is taught by Advanced Trauma Life Support training. However, those studies had limited ability to generate a more descriptive paradigm, because they only examined a single HR value per patient.
Methods: In a comparative, retrospective analysis, we studied the temporal characteristics of HR through time in adult trauma patients with haemorrhage, based on documented injuries and transfusion of ≥ 3 units of red blood cells (RBCs). We analysed archived vital-sign data of up to 60 min during either pre-hospital or emergency department care.
Results: We identified 133 trauma patients who met the inclusion criteria for major haemorrhage and 1640 control patients without haemorrhage. There were 55 haemorrhage patients with a normal median HR and 78 with tachycardia. Median ΔHR was -0.8 and $+0.7$ bpm per 10 min, respectively. Median time to documented hypotension was 8 and 5 min, respectively. RBCs were not significantly different; median volumes were 6 (IQR: 4–13) and 10 units (IQR: 5–16), respectively. Time-to-hypotension and mortality were not significantly different. Tachycardic patients were significantly younger ($P < 0.05$). Only 10 patients with normal HR developed transient/temporary tachycardia, and only 11 tachycardic patients developed a transient/temporary normal HR.
Conclusions: The current analysis suggests that some trauma patients with haemorrhage are continuously tachycardic while others have a normal HR. For both cohorts, hypotension typically develops within 30 min, without any consistent temporal increases or trends in HR.

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Introduction

Multiple reports have demonstrated that the current Advanced Trauma Life Support (ATLS) training course is inaccurate regarding vital-sign changes in trauma patients with haemorrhage [1–4]. Analyses of large datasets have demonstrated that the association between heart rate (HR) and blood loss is weaker than what is taught by ATLS [2,3]. Studying nearly 200,000 trauma patients in a trauma registry, Guly et al. [2] reported that "[w]ith increasing estimated blood loss there is a trend to increasing HR and a reduction in systolic blood pressure (SBP), but not to the degree suggested by the ATLS classification of shock." Studying over 35,000 trauma patients, Mutschler et al. [3] concluded that "[t]his study indicates that the ATLS classification of hypovolaemic shock does not seem to reflect clinical reality accurately."

If it has been established that ATLS is not accurate in describing HR changes during haemorrhage, an alternative paradigm describing HR patterns in trauma patients has not emerged. In part, this is because the aforementioned large registry studies only examined a single HR value per patient, whereas in reality, HR is continuously monitored during trauma patient management. By studying only single HR values per patient, it cannot be determined how often tachycardia develops as haemorrhage progresses. As well, it cannot be determined whether the weak association between HR and haemorrhage was *i*) because HR varied substantially in individual trauma patients (i.e. large intra-subject variability), and/or *ii*) because HR

responses varied substantially between patients (i.e. large inter-subject variability).

Having a better understanding of the temporal characteristics of HR through time in trauma patients with haemorrhage could contribute to a more accurate and useful alternative to ATLS. Accordingly, we analysed an archived dataset of continual vital signs in trauma patients, seeking to characterise the HR patterns recorded through time. We evaluated the extent to which trauma patients demonstrated tachycardia over time, and whether there were salient clinical differences between patients who demonstrated different types of HR responses.

Materials and methods

Study design, setting, population, and outcome

This was a comparative study carried out by a secondary analysis of three pooled datasets. We studied adult trauma patients with haemorrhagic injuries during initial care (either during pre-hospital transport or upon arrival in the emergency department). Dataset 1 was originally collected aboard air ambulances between February 2010 and December 2012 [5], Dataset 2 from an emergency department between June 2012 and December 2014 [6], and Dataset 3 during air transport between August 2001 and April 2004 [7,8]. All datasets were collected with the approval of local institutional review boards.

For our outcome, haemorrhagic injury, we used the following criteria: documented haemorrhagic injuries, and transfusion of three or more units of red blood cells within 24 h (24-h RBCs). Explicitly documented haemorrhagic injuries were identified by chart review, and defined as solid organ injuries, thoracic or abdominal haematomas noted in imaging or operative reports, vascular injuries that required a procedure for haemostasis, or limb amputations.

For Dataset 1, eligible patients were identified by querying the air ambulance administrative database for adult trauma transports. Next, we queried the receiving hospital's electronic medical records to identify the subset who received at least three units of 24-h RBCs. This review was conducted by either a physician or nurse practitioner with clinical experience in trauma care, and who was blinded to subjects' physiological data. These data were collected and managed using REDCap electronic data capture tools [9]. Abstractors were first trained using training cases from Dataset 3. Next, the abstractors' adjudications about whether or not the subject had a haemorrhagic injury were confirmed by running an automated text-search through the trauma registry database, to independently corroborate that the subject had at least one of a list of haemorrhagic injuries. Cohen's K between the data abstractor adjudication and automated text search results was 0.67. All discrepancies were subsequently resolved by two-investigator adjudication.

For Dataset 2, eligible patients were first identified by electronically querying the source hospital's trauma registry for adult trauma patients. The remainder of the subject selection methodology, in terms of 24-h RBC volume and presence of haemorrhagic injury, was the same as that used for Dataset 1.

Data collection for Dataset 3 was conducted under a protocol that yielded an inventory of injuries and 24-h RBCs in a convenience sample of high-acuity trauma patients [7]. The methodology for determining presence of haemorrhagic injury was the same as that used for Dataset 1.

Study measurements

To collect HR and blood pressure (BP) data during real-time care, data streaming from patients' vital-sign monitors were electronically recorded via software solutions [8,10,11]. The electronic recording system used for Dataset 1 was an *ad hoc* software system described by Reisner et al. [10]. The recording system used for Dataset 2 was the BedMasterEx system (Excel Medical, Jupiter FL). The recording system used for Dataset 3 was another *ad hoc* system described by Cooke et al. [7].

From these recordings, we analysed vital-sign data of up to 60 min in duration, beginning with the first recorded non-zero vital sign. We studied HR from intervals with high-quality electrocardiograms (ECGs), as determined by the consensus of an automated algorithm (which has been shown to be more conservative than human expert evaluation [12]) and a human adjudicator. When there was disagreement, a second human adjudicator evaluated the reliability of the data segment.

For Datasets 1 and 2, study staff performed retrospective chart review to extract additional clinical data, including demographics, injury descriptions, clinical interventions, and mortality, using the methodology detailed above. All of these data were compared with an electronic report from the hospital's independent trauma registry, and discrepancies were resolved by two-investigator adjudication. Clinical data abstraction for Dataset 3 was conducted in accord with a previous study [7].

Data analysis

By convention, tachycardia is defined as a HR of 100 bpm or greater. We examined whether 100 bpm was a clinically valid cut-off to discriminate between patients with and without haemorrhage, and calculated the diagnostic testing characteristics of tachycardia and the associated receiver operating characteristic (ROC) curve [13]. To investigate whether patients with haemorrhage demonstrated tachycardia at variable time intervals, we calculated how often those with a normal HR developed transient/temporary tachycardia (at least 5 min of tachycardia within any 10-min time window), and how often those with tachycardia developed a transient/temporary normal HR (at least 5 min of normal HR within any 10-min time window). We also performed a sensitivity analysis to investigate whether our findings were sensitive to the definition of clinical haemorrhage, by computing ROC curves for predicting a set of secondary outcomes: 24-h RBCs ≥ 1, ≥ 3, ≥ 5, ≥ 7, and ≥ 10 units, regardless of documented injuries. In addition to the aforementioned analyses using median HR, we developed a logistic regression model using median HR for estimating the probability of haemorrhage, and tested its goodness-of-fit using the Hosmer-Lemeshow test.

We compared the haemodynamic and clinical characteristics of haemorrhage patients with a normal HR to those of haemorrhage patients with tachycardia. Variability in HR was quantified by the root mean square (RMS) around the mean of each patient's HR time series, while slope of HR as a function of time was computed using linear regression. We computed the BP characteristics of both cohorts, including the incidence of measured hypotension and the time elapsed until hypotension was first measured. Hypotension was defined as an SBP of less than 90 mmHg or a mean arterial pressure (MAP) of less than 70 mmHg. We also computed the pulse pressure (SBP – diastolic BP) and the Shock Index (SI = HR/SBP) for both cohorts. We compared clinical characteristics, including demographics, injury descriptions, clinical interventions, and mortality. We performed analyses in MATLAB version 9.0 (The MathWorks, Inc., Natick, MA). Data distributions were compared using the Wilcoxon rank-sum test for continuous variables and categorical variables using Fisher's exact test. We used a threshold for statistical significance of $P < 0.05$.

Finally, we studied the change in HR in the subset of haemorrhage patients who developed new onset hypotension. New onset hypotension was defined as follows: *i*) at least one non-hypotensive

BP measured within the 10 min *prior to* the first recording of hypotension; and *ii*) at least one subsequent hypotensive BP. We compared the HR and BP characteristics of tachycardic and non-tachycardic haemorrhage patients before and upon the onset of hypotension, and we also compared clinical characteristics. For this subgroup analysis, we only included HR data measured contemporaneously with each BP measurement, i.e. within a 2-min window, to preserve the relationship between HR and BP.

Results

The overall characteristics of the study population are shown in Table 1. From the three combined datasets we identified 142 patients who met our criteria for haemorrhagic injury (6.5%), nine of which were subsequently excluded for insufficient ECG reliability (high acuity patients with very short ECG recordings). There were 1640 control patients who survived and received no RBC transfusions, 53 of which were excluded for insufficient ECG reliability.

We computed each patient's median ("patient-median") HR. For patients with haemorrhagic injury, the population median of patient-median HR (and interquartile range [IQR]) was 102 (87–126) bpm. For the control patients, the population median of patient-median HR was 87 (74–99) bpm. The area under the receiver operating characteristic curve (ROC AUC) of HR for distinguishing between patients with haemorrhagic injury and control patients was 0.71 (95% CI: 0.65–0.76), which is consistent with a diagnostic test of low-to-moderate accuracy [13]. In our sensitivity analysis, which investigated whether the diagnostic performance of HR varied depending on alternative definitions of haemorrhage, we found similar ROC AUCs for predicting alternative haemorrhage-related outcomes, i.e. 24-h RBCs of ≥ 1, ≥ 3, ≥ 5, ≥ 7, and ≥ 10 units (see Fig. 1). Regarding the suitability of a logistic regression model for estimating the probability of haemorrhage based on median HR, we found no evidence of poor calibration ($p > 0.05$, Hosmer-Lemeshow test). Using the conventional cut-off for tachycardia (HR ≥ 100 bpm), HR was 59% sensitive for haemorrhagic injury and 75% specific for the control patients.

Of the patients with haemorrhagic injury, 78 had tachycardia (59% of all trauma patients with haemorrhage) based on median HR. Overall, this cohort had a median vital-sign recording duration of 22 min (IQR: 12–31). Most subjects in this cohort were tachycardic throughout their recording: only eleven transiently/temporarily developed a normal HR (normal HR for at least 5 min within any 10-min interval). Ten who transiently/temporarily
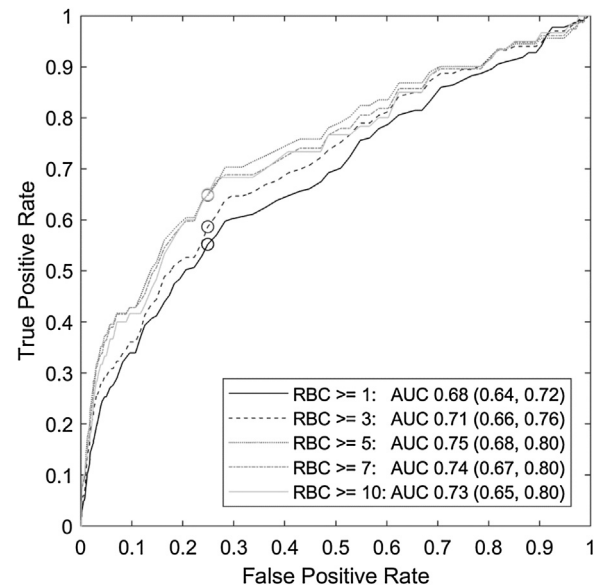

Fig. 1. Receiver operating characteristic (ROC) curves of the median heart rate (HR) for discriminating between different 24-h red blood cell (RBC) transfusion volumes (regardless of the patients' documented injuries), i.e. 24-h RBCs ≥ 1, ≥ 3, ≥ 5, ≥ 7, and ≥ 10 units. *Legend*: area under the ROC curve (AUC) with the 95% confidence interval in parentheses. *Circles* indicate a HR of 100 bpm, which is the conventional cut-off for tachycardia.

developed a normal HR had a median HR between 100 and 110 bpm, i.e. minimal degree of tachycardia.

Based on median HR, 55 had a normal HR (41% of all trauma patients with haemorrhage). Overall, this cohort had a median vital-sign recording duration of 25 min (IQR: 15–36). Most subjects in this cohort had a normal HR throughout their recording: only ten subjects transiently/temporarily developed tachycardia (tachycardia for at least 5 min within any 10-min interval). Eight who transiently/temporarily developed tachycardia had a median HR between 90 and 100 bpm, i.e. at the upper extent of normal HR.

Overall, 25% of the patients *without* haemorrhage were tachycardic, based on their median HR. Patients without haemorrhage tended to be either persistently tachycardic or persistently non-tachycardic—only 17% ever changed from one state to the other even transiently/temporarily (i.e. for at least 5 cumulative minutes within any 10-min interval).

Table 1
Characteristics of trauma population datasets.

Clinical characteristics	Dataset 1 (n = 209)	Dataset 2 (n = 1161)	Dataset 3 (n = 646)	Pooled dataset (n = 2016)
Setting	Pre-hospital	Emergency Dept	Pre-hospital	
Sex, male, n (%)	155 (74)	813 (70)	479 (74)	1447 (72)
Age, mean (SD), years	45 (20)	50 (21)	38 (15)	46 (19)
Blunt, n (%)	188 (90)	1008 (87)	577 (89)	1773 (88)
Penetrating, n (%)	21 (10)	144 (12)	61 (9)	226 (11)
ISS, median (IQR)	16 (9–26)	18 (10–26)	16 (9–34)	17 (9–29)
Inter-hospital transfer, n (%)	103 (49)	392 (34)	0 (0)	495 (25)
Glasgow Coma Scale Score (IQR)	15 (8–15)	15 (14–15)	15 (13–15)	15 (13–15)
24-h RBC volume ≥ 1 unit, n (%)	31 (15)	153 (13)	75 (12)	259 (13)
24-h RBC volume ≥ 3 unit, n (%)	18 (9)	75 (6)	57 (9)	150 (7)
24-h RBC volume ≥ 10 unit, n (%)	8 (4)	24 (2)	22 (3)	54 (3)
Haemorrhage patient[*]	18 (9)	60 (15)	55 (9)	133 (7)
Survival to discharge, n (%)	191 (91)	1103 (95)	608 (94)	1902 (94)

Abbreviations: IQR, interquartile range; ISS, Injury Severity Score; SD, standard deviation.
[*] Haemorrhage patient: Primary outcome was patients with at least one documented explicitly haemorrhagic injury (solid organ injuries, thoracic or abdominal haematomas, and/or vascular injuries requiring operative repair) and 24-h RBC volume ≥ 3 unit. Alternative definitions of haemorrhage were investigated in ancillary sensitivity analysis; see text for details.

Table 2
Comparison of clinical characteristics of tachycardic and non-tachycardic haemorrhage patients.

	Tachycardic haemorrhage patients		Non-tachycardic haemorrhage patients	
	All patients (n = 78)	Subset with hypotension onset (n = 12)	All patients (n = 55)	Subset with hypotension onset (n = 14)
Clinical characteristics				
24-h RBCs, median (IQR)	10 (5–16)	15 (7–30)*	6 (4–13)	7 (4–11)*
Age in years, median (IQR)	32 (27–49)*	34 (31–49)	50 (36–62)*	53 (36–71)
Intubation, n (%)	42 (54%)	8 (67%)	22 (40%)	8 (57%)
Pre-hospital patients, n (%)	40 (51%)	7 (58%)	33 (60%)	8 (57%)
Mortality, n (%)	25 (32%)	6 (50%)	15 (27%)	2 (14%)
Head AIS, median (IQR)	0 (0–2)	0 (0–4)	0 (0–0)	0 (0–0)
Abdomen AIS, median (IQR)	3 (1–4)	0 (0–4)	2 (0–3)	2 (0–3)
Extremity AIS, median (IQR)	1 (0–3)	3 (0–3)	0 (0–3)	0 (0–2)
Thorax AIS, median (IQR)	3 (0–4)	4 (2–4)	3 (0–4)	3 (0–4)
ISS, median (IQR)	27 (18–43)	26 (17–45)	27 (18–41)	22 (16–45)
Vital-sign characteristics				
Duration of recording in min, median (IQR)	22 (12–31)	28 (22–42)	25 (15–36)	30 (26–38)
HR[a] in bpm, median (IQR)	121 (109–136)[b]	127 (115–137)[b]	83 (73–91)[b]	86 (79–89)[b]
Slope of HR in bpm/10 min, median (IQR)	+0.7 [(−2.9)–(+3.9)]*	+3.6 [(+0.7)–(+7.1)]*	−0.8 [(−4.4)–(+0.5)]*	−2.4 [(−3.7)–(−0.5)]*
RMS about mean HR in bpm, median (IQR)	6 (3–9)	8 (3–13)	7 (5–11)	6 (5–7)
SBP[a] in mmHg, median (IQR)	110 (89–135)	95 (82–108)	104 (85–123)	98 (93–115)
PP[a] in mmHg, median (IQR)	44 (34–51)	36 (31–44)	44 (32–55)	45 (34–57)
Time to hypotension in min, median (IQR)	5 (1–16)	13 (7–18)	8 (2–14)	11 (8–14)
Shock index in bpm/mmHg, median (IQR)	1.08 (0.90–1.36)*	1.34 (1.22–1.57)*	0.83 (0.66–1.06)*	0.88 (0.70–0.96)*
Incidence of hypotension, n (%)	52 (67%)	12 (100%)	39 (71%)	14 (100%)

Tachycardic group: median HR ≥ 100 bpm; non-tachycardic group: median HR < 100 bpm.
Subset with hypotension onset: subjects with a systolic blood pressure of less than 90 mmHg or a mean arterial pressure of less than 70 mmHg.
Abbreviations: 24-h RBCs, red blood cell units transfused in 24 h; AIS, abbreviated injury scale; IQR, interquartile range; ISS, injury severity score; bpm, beats per minute; HR, heart rate; RMS, root mean square; MAP, mean arterial pressure; PP, pulse pressure = systolic blood pressure (SBP) − diastolic blood pressure.

[a] For vital signs HR, SBP, and PP, we computed the median value from each patient's record ("patient-median"); above, we report the population median of the patient-median values.

[b] Not tested for significant differences (because cohorts were defined by median HR).

* P < 0.05 via Wilcoxon rank-sum test comparing tachycardic group and non-tachycardic group.

Comparing the vital signs of the two haemorrhage cohorts (tachycardic and non-tachycardic patients with haemorrhage), both had similar BP characteristics (see Table 2) without significant differences in their average SBP, average PP, time of first recorded hypotension, and incidence of hypotension. The overall variability in the recorded HR (i.e. RMS around the mean) was not significantly different between the two cohorts. The differences in HR slope achieved statistical, but not clinical, significance; the median changes over 10 min were +0.7 and −0.8 bpm for the tachycardic and non-tachycardic cohorts, respectively. The SI was significantly higher in the tachycardic cohort. Fig. 2 illustrates the vital-sign patterns of several tachycardic and non-tachycardic patients who developed hypotension.

Fig. 3 shows the fraction of patients with haemorrhage who developed hypotension as a function of time. In both groups, after 30 min, the majority of patients had developed hypotension.

The clinical characteristics of the tachycardic and non-tachycardic cohorts were similar (Table 2). In terms of resuscitation, the volumes of 24-h RBCs for both cohorts were substantial but not significantly different; the corresponding median volumes were 10 units (IQR: 5–16) and 6 units (IQR: 4–13), respectively. Rates of mortality, endotracheal intubation, and injury severity coded by the abbreviated injury scale (AIS) were not significantly different. Only age was significantly different, although there was substantial overlap; the median ages were 32 (IQR: 27–49) and 50 (IQR: 36–62) years for the tachycardic and non-tachycardic cohorts, respectively.

We also studied the subset of patients who had documented onset of hypotension (i.e. hypotension but only after a non-hypotensive BP). We identified 26 subjects who met the inclusion criteria, 12 in the tachycardia cohort and 14 in the non-tachycardia cohort. HR did not change substantially upon the onset of hypotension (Table 3). Subjects in the tachycardic cohort had a median HR of 123 bpm (IQR: 107–132) in the 10 min prior to hypotension and a median HR of 127 bpm (IQR: 116–141) in the 10 min following the onset of hypotension. Subjects in the non-tachycardic cohort had a median HR of 87 bpm (IQR: 75–103) prior to hypotension and a median HR of 86 bpm (IQR: 78–89) in the 10 min upon the onset of hypotension. There was a statistically significant difference in the 24-h RBCs; tachycardic patients who developed hypotension received significantly more blood than did non-tachycardic patients who developed hypotension (Table 2).

Discussion

Similar to prior analyses of large databases, we found that tachycardia was neither sensitive nor specific to haemorrhagic injury. The current analysis is novel in that we analysed HR measured continuously in the early evaluation of trauma patients (median durations of vital-sign recordings were 22 min and 25 min for tachycardic and non-tachycardic haemorrhage patients, respectively). We found that approximately half of trauma patients with haemorrhagic injury evidenced tachycardia and half did not. The former cohort demonstrated consistent tachycardia throughout their recording, with some fluctuation, but the tachycardia did not consistently increase over time, and there was no consistent change in HR upon the onset of hypotension. The latter cohort demonstrated normal HR throughout their recording, with some fluctuation, but the HR neither consistently increased over time nor showed any consistent change upon the onset of hypotension.

These findings add to our understanding about why prior analyses have found that the association between tachycardia and blood loss is "not to the degree suggested by the ATLS classification of shock" [1]. In general terms, there is a cohort of patients with haemorrhage who demonstrate tachycardia, but do not show any additional increase in HR, even through time, and even upon the
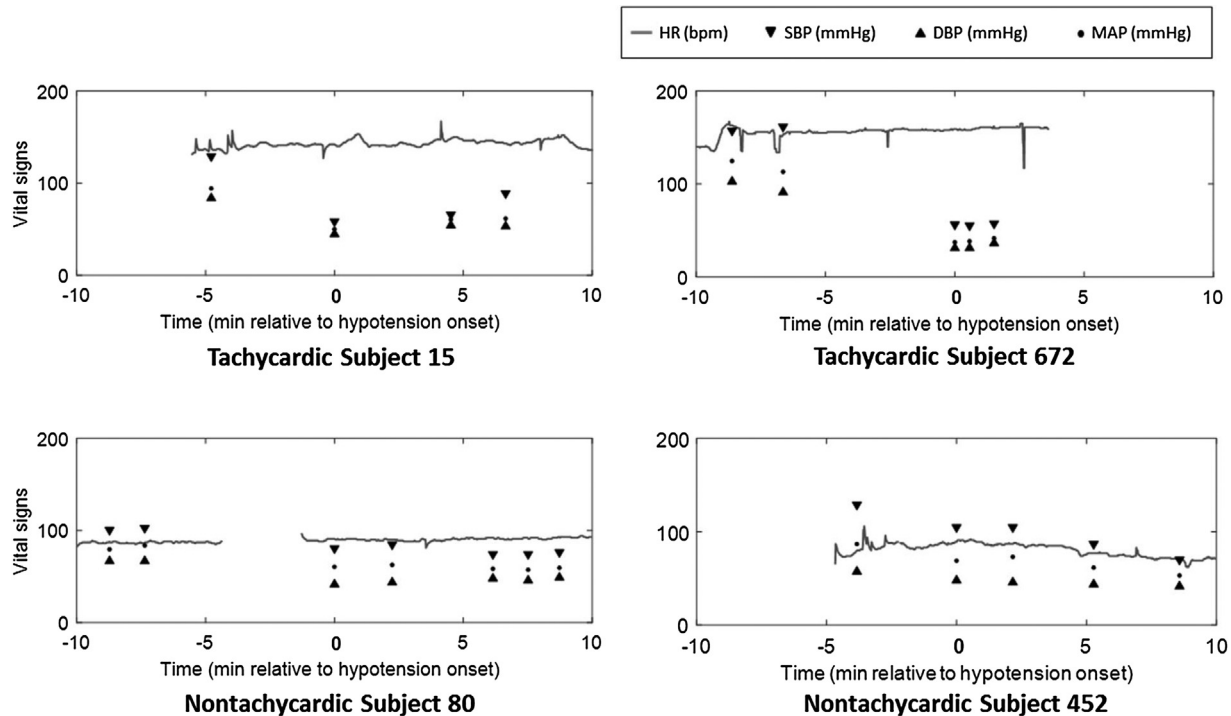
Fig. 2. Case examples of tachycardic and non-tachycardic subjects who developed hypotension. The panels above show vital signs of subjects in an analysis window that ranges from 10 min prior to 10 min after the onset of hypotension. Time *t* = 0 indicates the time of hypotension onset. Subjects in the tachycardic group had a pre-hypotension HR of at least 100 bpm, whereas those in the non-tachycardic group had a pre-hypotension HR of less than 100 bpm. *Top left:* 36-y old female, injuries included femoral fracture and arterial injury requiring angio-embolization, 24-h RBC volume = 6 units (hypotension onset after 6 min of vital-sign monitoring). *Top right:* 31-y old male, injuries included splenic laceration, 24-h RBC volume = 38 units (hypotension onset after 18 min of vital-sign monitoring). *Bottom left:* 42-y old male, injuries included liver laceration, 24-h RBC volume = 9 units (hypotension onset after 10 min of vital-sign monitoring). *Bottom right:* 76-y old female, injuries included splenic laceration, 24-h RBC volume = 13 units (hypotension onset after 5 min of vital-sign monitoring). Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; RBC, red blood cell; SBP, systolic blood pressure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
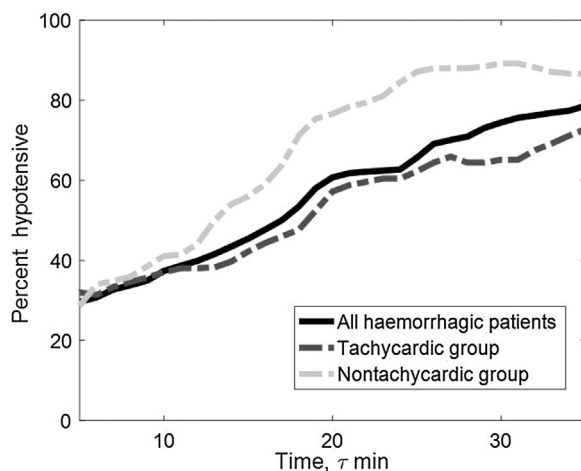

Fig. 3. Percentage of haemorrhage subjects (24-h red blood cell transfusion volume ≥ 3 units with documented haemorrhagic injury) with hypotension. The solid black line represents the percentage of haemorrhage subjects with at least τ min of recorded data and who developed hypotension in the first τ min. The total number of patients decreased as a function of time, because the durations of pre-hospital and emergency department care were heterogeneous (of the 133 total haemorrhage subjects, 45 had at least 30 min of recorded data). For comparison, subjects were split into two groups: *i*) the tachycardic group, indicated by the dark gray dashed line, and *ii*) the non-tachycardic group, indicated by the light gray dashed line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

onset of hypotension. Moreover, there is a separate cohort altogether that does not manifest tachycardia at all, even after the onset of hypotension. When we examined whether there were salient differences between these cohorts, we found few aside from age

(tachycardic patients were significantly younger). Tachycardic or not, both generally developed hypotension within 30 min of vital-sign monitoring (Fig. 3). The two cohorts were similar in terms of other metrics of haemorrhage severity. There were no differences in the median time of the first recorded hypotension, overall rate of hypotension, 24-h RBCs, or mortality. AIS scores across all anatomic regions were also similar between the cohorts.

Regarding why non-tachycardic patients were significantly older, it is possible that this subpopulation has an attenuated cardiovascular control system that is less likely to mount a tachycardic response, because of either aging or medication, e.g. beta blockers. Yet, the age ranges for patients with and without tachycardia showed substantial overlap (IQRs of 27–49 years and 36–62 years, respectively; see Table 2). This indicates that age alone is not the sole determinant of a patient's haemorrhage response.

The determinants of HR during progressive haemorrhage have been investigated over decades of *in vivo* laboratory experimentation. Animal models demonstrate a basic paradigm in which progressive blood loss triggers tachycardia and vasoconstriction via activation of carotid and aortic baroreceptors [14] and also arterial chemoreceptors that are sensitive to local metabolic changes associated with hypovolaemia [15]. Afferent signals from these peripheral receptors are received by the cardiovascular center within the medulla oblongata, resulting in both sympathetic nervous signal activation and parasympathetic system inhibition, and, ultimately, increased pace of the heart's native pacemaker, the sino-atrial node. Moreover, a wide range of investigations has further demonstrated how these basic haemodynamic responses can be modified by a multitude of factors, including nociception [16], anaesthetics and analgesics [17,18], anxiety [19], gender [20], brain injury [21], cardiopulmonary baroreceptors [22], athletic

Table 3
Vital signs before and after the onset of hypotension (subset with hypotension onset).

Vital sign	Median (IQR) of subjects	
	Tachycardic group (n = 12)	Non-tachycardic group (n = 14)
Pre-hypotension		
HR (bpm)	123 (107–132)[a]	87 (75–103)[a]
SBP (mmHg)	115 (101–148)	126 (106–132)
PP (mmHg)	46 (41–58)	44 (35–72)
MAP (mmHg)	88 (79–110)	88 (78–102)
Onset of hypotension		
HR (bpm)	127 (116–141)[a]	86 (78–89)[a]
SBP (mmHg)	73 (67–81)	86 (78–102)
PP (mmHg)	23 (20–34)[*]	41 (32–47)[*]
MAP (mmHg)	57 (52–65)	64 (56–68)

Each patient's median HR, SBP, PP and MAP (patient-median) were computed for the 10-min interval before the onset of hypotension ("pre-hypotension") and the 10-min interval starting upon the onset of hypotension ("onset of hypotension"); above, we report the population median of the patient-median values. See text for additional details.
Abbreviations: bpm, beats per minute; HR, heart rate; IQR, interquartile range; MAP, mean arterial pressure; PP, pulse pressure = systolic blood pressure (SBP) – diastolic blood pressure.
  [a] Not tested for significant differences (because cohorts were defined by median HR).
  [*] $P < 0.05$ via Wilcoxon rank-sum test comparing tachycardic group and non-tachycardic group.

pre-conditioning [23], as well as chronic diabetes mellitus [24]. In many cases, there can be excitatory and inhibitory pathways activated at the same time, and the central nervous system integrates concordant and discordant afferent signals and generates the ultimate efferent output that drives HR [25]. We speculate that, during typical trauma patient management, there is heterogeneity in the determinants of HR, e.g. differing levels of pain, analgesia, haemorrhage, etc. This could explain why we observed heterogeneous HR responses in trauma patients.

The concept of categorizing patients based on above-average versus below-average sympathetic responses is consistent with a series of physiology reports conducted in a laboratory with healthy subjects, using lower body negative pressure (LBNP) to simulate progressive blood loss. These studies determined that the group of subjects with delayed onset of hypotension had relatively elevated HR and vasoconstriction, and denoted that cohort as "high tolerant" [26–29]. Our dataset corroborates the notion that both tachycardic and normal HR responses are common with progressive blood loss. Are patients with above-average sympathetic responses more tolerant of blood loss? Overall, there were no significant differences between tachycardic and non-tachycardic patients in terms of incidence of hypotension, 24-h RBCs, or mortality (Table 2)]. In contrast, in the smaller subset of haemorrhage patients whose onset of hypotension was recorded, tachycardic patients ended up with significantly larger volumes of 24-h RBCs (median, 15 units), suggesting that this subset may have been compensating for large blood volume losses prior to hypotension onset. Tachycardic or not, most patients with haemorrhage developed hypotension within 30 min of vital-sign monitoring (Fig. 3), with no statistically significant differences between the cohorts in terms of time of first recorded hypotension.

In terms of limitations of the current report, the vital-sign data used in this analysis were obtained during routine clinical care, and not during a carefully controlled laboratory investigation. Consequently, the measurement intervals were heterogeneous and recording durations were uneven, and the reliability of measurements may have been suboptimal. For HR, we were able to rely on ECGs to retrospectively identify unreliable measurements. For BP, we had no practical method of identifying unreliable non-invasive measurements. Excessive variability due to measurement errors, and

the confounding effect of therapeutic interventions, such as volume administration or pain medication, might have masked differences between the cohorts (i.e. Type II statistical errors). Therefore, based on the current analysis, we cannot rule out subtle differences between tachycardic and non-tachycardic patients with haemorrhage. However, we note that the vital-sign data we analysed here are precisely those that a clinician must evaluate in providing treatment. Therefore, our comparative analysis would appear to be valid in terms of ruling in and ruling out significant cohort differences based on the actual vital-sign measurements that are evaluated by and acted upon by bedside clinicians.

As a second limitation, we did not have a feasible gold standard measurement of blood loss as a function of time. Therefore, the onset of hypotension may not always have indicated the progression of blood loss in some patients. However, we consider it likely that the development of frank hypotension was usually due to true hypovolaemia in this subject population with documented major haemorrhagic injuries, and who subsequently received three or more units of RBCs.

Conclusions

In conclusion, trauma patients—both haemorrhagic and non-haemorrhagic—tend to fall into persistently tachycardic or persistently non-tachycardic groups during the first 30 min of monitoring. During initial assessment, it is reasonable to have an elevated concern for haemorrhage when tachycardia is present, keeping in mind the substantial limitation that tachycardia was only modestly specific (75%) and poorly sensitive (59%) for haemorrhage. Through time, there will be HR fluctuations, but diagnostically meaningful trends were not evident in the typical haemorrhage patient. Blood pressure should be carefully monitored, since hypotension was likely to manifest within 30 min in haemorrhage patients, and without any associated change in HR.

Conflicts of interest

Andrew T. Reisner has received research funding from the Nihon-Kohden Corporation, Irvine, CA, to develop decision-support technology for sepsis patient management. Shwetha Edla, Jianbo Liu, Jiankun Liu, Maxim Khitrov, and Jaques Reifman report no conflict of interest.

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Disclaimer

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or of the U.S. Department of Defense. This paper has been approved for public release with unlimited distribution.

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