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Sepsis is frequent in initially non-critical hypotensive emergency department patients and is associated with increased mortality

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ABSTRACT

Objective: Hypotension, defined as a mean arterial pressure of maximum 70 mmHg, is associated with significant morbidity and mortality. The objective of this study was to determine in initially non-critical hypotensive adult patients the proportion of sepsis and if septic patients had different outcome and clinical factors than non-septic patients.

Methods: This retrospective observational study was conducted over a year on adult hypotensive emergency department patients initially considered by triage as non-critical. Patients were separated into three groups: hypotensive septic patients (HSP), hypotensive non-septic infected patients (HNSIP), and other hypotensive patients (OHP). Clinical scores, signs, length of stay (LOS), and mortality were compared using analysis of variance for continuous variables and chi-square analysis for categorical variables.

Results: There were 136 (35.5%) septic patients, 37 (9.7%) with non-septic infection, and 210 (54.8%) with another cause of hypotension. Overall in-hospital mortality was 12.0% and total mortality was greater in HSP than in HNSIP (20.6% vs. 5.4%, $p = 0.031$) or OHP (20.6 vs. 7.6%, $p < 0.001$). LOS was greater for HSP when compared to HNSIP (median(IQR): 9(6–17) vs. 6(1–13), $p = 0.004$) and OHP (median(IQR): 9(6–17) vs. 3(1–8) days, $p < 0.0001$).

Conclusion: Sepsis in a *priori* non-critical hypotensive adult patients, when compared with other causes of hypotension, is associated with significantly higher mortality and increased LOS. Patients that present to the emergency department and have a MAP of 70mmHg or less must be rigorously evaluated and have consistent follow-up.

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1. Introduction

Sepsis is a potentially lethal syndrome that appears following an infection and is the consequence of the host's altered physiological and chemical responses [1]. Although it is a leading cause of mortality and morbidity worldwide, its incidence remains elusive and early treatment remains a challenge [2–5]. In addition, rapid diagnosis is often difficult and non-documented sepsis in

emergency patients has been associated with increased mortality [6]. Consequently, identifying septic patients and those who are at increased risk of death remain important challenges in emergency medicine [7–9].

Hypotension, which can be defined as a mean arterial pressure (MAP) of 70 mmHg or less, is a warning sign of cardiovascular collapse and can occur during sepsis [10]. Hypotensive patients and septic patients with non-sustained hypotension have been shown to have increased mortality in the emergency department (ED) [11,12]. In a review of six observational studies Holler et al. reported that nontraumatic ED hypotension was found between 0.4 and 1.3% of the ED admissions and was associated with a mortality of 12% [13]. The proportion of sepsis in hypotensive patients at the ED, however, is not clear.

The objective of this study was to determine in initially non-critical hypotensive adult patients the proportion of sepsis and if hypotensive septic patients had different outcome and clinical factors than non-septic hypotensive patients.

Abbreviations: A2RA, aldosterone II receptor antagonist; ACEI, angiotensin converting enzyme inhibitor; ED, emergency department; HNSIP, hypotensive non-septic infected patients; HSP, hypotensive septic patients; IHP, included hypotensive patients; IQR, interquartile range; LOS, length of stay; MAP, mean arterial pressure; OHP, other hypotensive patients; SOFA, sequential organ failure assessment score.

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2. Methods

2.1. Design and setting

The Erasme University Hospital is a tertiary hospital located in Brussels, Belgium. The local institutional ethical committee approved this retrospective study and waived the need for informed consent. Critically ill patients at Erasme University Hospital are immediately treated in collaboration with the intensive care unit (ICU) in a shared ED/ICU care unit (i.e. the shock room) [14]. These include hemodynamically unstable patients (e.g., septic shock or severe trauma). Physicians base their decision to immediately transfer patients to the shock room on criteria such as blood pressure, heart rate, consciousness, diuresis, tissue perfusion, and apparent treatable cause of critical illness (e.g. pneumothorax, tamponade, myocardial infarction, or hemorrhage). Patients that were immediately transferred to the shock room upon admission were not included in this study.

2.2. Data collection

We identified all adult patients who had at least one episode of hypotension (i.e., one measurement of systolic and diastolic non-invasive blood pressure of maximum 90 mmHg and 60 mmHg, respectively) at the ED from July 1st, 2013 to June 30th, 2014, with ED dedicated software (E-Care, Turnhout, Belgium). Patients who only had hypotension while asleep or who had a falsely hypotensive value due to equipment malfunction were not considered in this study. Patients who were immediately transferred to the shock room [14] without passing by the ED were considered as critically ill and were not studied. These patients needed immediate stabilization of an acute condition. Patients were excluded if they were readmitted during the study period, transferred to or from another hospital, or refused admission.

Included hypotensive patients (IHP) were split into three groups based on their initial evaluation and management: hypotensive non-septic infected patients (HNSIP), hypotensive septic patients (HSP), and other hypotensive patients (OHP). Patients were considered infected if the physician clinically suspected or confirmed infection (i.e., sampling of body fluids for microbial analysis and antibiotic therapy at the ED or written suspicion in the ED record). Sepsis was defined as confirmed or sus-

pected infection with a SOFA score change (Δ SOFA) of at least 2 points as defined by the Sepsis-3 consensus [1]. The remaining patients made up the OHP group. Δ SOFA was calculated assuming patients had normal organ function before disease onset unless previous hospital records could attest to organ dysfunction (e.g. patients suffering from cirrhosis or chronic renal failure). Glasgow score was not always noted. The following estimates were established: confusion as 14/15, somnolence with confusion as 12/15, and coma as <6/15. Study outcomes consisted of ED mortality, ICU mortality, ward mortality, total in-hospital mortality, ICU length of stay (LOS), and hospital LOS. Clinical scores as well as anthropometric and clinical data were also investigated.

2.3. Analysis

Data analysis was carried out with Statistix 9.0 (Analytical Software, Tallahassee, FL, USA). The Shapiro-Wilk test was used to determine continuous variable normality. No continuous variable was normal and data were represented as medians with interquartile range (IQR: from percentiles 25 to 75) for continuous variables and counts with percentages for categorical variables. Group comparisons were done with non-parametric analysis of variance for continuous variables (Kruskal-Wallis test) and chi-square analysis for categorical variables. There was no missing data.

3. Results

From July 1st, 2013 to June 30th, 2014, the Erasme ED admitted 45,329 patients, 423 of which were initially non-critical adult hypotensive patients (i.e., 0.93% of all patients). 40 patients were excluded because of readmission, transfer, or admission refusal. There were 136 (35.5%) septic patients, 37 (9.7%) with non-septic infection, and 210 (54.8%) with another cause of hypotension (Appendix A Fig. A.1).

HSP were more often male than HNSIP or OHP and were older than HNSIP or OHP. HSP more frequently had a history of hypertension and heart disease as well as diuretic and beta-blocker treatment than HNSIP and OHP. Angiotensin converting enzymes inhibitors (ACEI) and angiotensin II receptor antagonist (A2RA), however, were more frequently prescribed to HSP and OHP than to HNSIP. OHP had less history of chemotherapy, immunosuppressive treatment,

Table 1
Anthropometric data.

Variables	Group 1 HSP	Group2 HNSIP	Group3 OHP	p-Value 1 vs.2	1 vs.3	2 vs. 3	Overall F
Gender (male), n (%)	82 (60.3)	16 (43.3)	100 (47.6)	0.064	0.021	0.623	0.039
Age (yr), median (IQR)	68 (55–78)	52 (34–69)	59 (42–72)	0.003	0.001	0.173	<0.001
History n (%)							
Implanted device	38 (28.1)	12(32.4)	34 (16.3)	0.611	0.008	0.020	0.010
Respiratory disease	50 (36.8)	8 (21.6)	34 (16.3)	0.087	<0.001	0.425	<0.001
Neurological disease	37 (28.0)	6 (16.2)	41 (19.6)				0.124
Heart disease	65 (47.8)	10 (27)	72(34.4)	0.024	0.013	0.377	0.015
Hypertension	67 (50.8)	9 (24.3)	76(36.5)	0.004	0.010	0.150	0.004
Diabetes	31 (23.0)	9 (24.3)	30 (14.4)				0.081
Renal disease	34 (25)	6 (16.2)	40 (19.1)				0.323
Cirrhosis	14 (10.3)	1 (2.7)	14(6.7)				0.233
Solid tumor	28 (20.6)	6 (16.2)	31 (14.8)				0.377
Hematological disease	25 (18.4)	5 (13.5)	24 (11.5)				0.198
Organ transplant	15 (11.0)	1 (2.7)	7(3.4)	0.121	0.005	0.835	0.010
Medication, n (%)							
Chemotherapy	15 (11.1)	5 (13.9)	8 (3.8)	0.645	0.008	0.013	0.012
Diuretics	50 (36.8)	3 (8.3)	53 (25.6)	0.001	0.027	0.023	0.002
ACEI orA2RA	39 (28.7)	1 (2.8)	63 (30.3)	0.001	0.749	<0.001	0.003
Immunosuppression	34 (25)	7 (19.4)	16(7.7)	0.359	<0.001	0.037	<0.001
Benzodiazepines	36 (26.5)	4 (11.1)	59 (28.2)				0.095
Beta-blocker	58 (42.6)	5 (13.5)	50 (23.8)	0.001	<0.001	0.165	<0.001

A2RA: angiotensin II receptor antagonist, ACE: angiotensin converting enzyme inhibitor, IQR: interquartile range.

Table 2
Comparison of mortality and length of stay between the 3 groups.

Variables	Group 1 HSP	Group 2 HNSIP	Group 3 OHP	All groups IHP	p-Value 1 vs. 2	1 vs. 3	2 vs. 3	Overall F
Mortality, n (%)								
In-hospital	28 (20.6)	2(5.4)	16(7.6)	46 (12.0)	0.031	<0.001	0.633	<0.001
ED	2 (1.5)	0 (0)	8 (3.8)	10 (2.6)				0.238
Ward	17 (12.5)	0 (0)	4(1.9)	21 (5.5)	0.024	<0.001	0.397	<0.001
ICU	9 (6.6)	2 (5.4)	4(1.9)	15 (3.9)				0.078
Length of stay (LOS), days [median (IQR)]								
In-hospital	9 (6–17)	6 (1–13)	3 (1–8)	6 (1–12)	0.004	<0.001	0.098	<0.001
ICU	0 (0–1)	0(0–0)	0(0–0)	0 (0–0)	0.227	<0.001	0.288	0.001

ED: emergency department, ICU: intensive care unit, IQR interquartile range, LOS: length of stay.

and medically implanted devices (e.g., Portacath® or prosthesis) than HSP and HNSIP (Table 1).

Overall in-hospital mortality was 12.0%. Total and ward mortalities were greater in HSP than in HNSIP (20.6% vs. 5.4%, $p = 0.031$; 12.5% vs. 0.0%, $p = 0.024$, respectively) or in OHP (20.6% vs. 7.6%, $p < 0.001$; 12.5% vs. 1.9%, $p < 0.001$, respectively). Although ICU mortality did not reach statistical significance between groups, ICU LOS was longer in HSP than OHP (median(IQR): 0(0–1) mean = 2.0 days vs. 0(0–0) mean = 0.7 days, $p < 0.001$). Hospital LOS was greater in HSP when compared to HNSIP (median(IQR): 9(6–17) days vs. 6(1–13) days, $p = 0.004$) and OHP (median(IQR): 9(6–17) vs. 3(1–8) days, $p < 0.001$, respectively) (Table 2). Supplementary results can be found in appendix A digital content.

4. Discussion

Initially non-critical hypotensive adult ED patients had a mortality rate of 12.0%. Sepsis occurred in 35.5% of cases. These patients had the highest mortality (20.6%) and prolonged LOS. No patient that arrived at the ED in shock, who needed immediate intensive therapy, or who suffered major trauma was included because clinicians immediately transferred these patients to the ICU via the shock room [14]. Mortality and prevalence of hypotension may consequently be even greater than reported. Clinicians must be aware of the potential danger that *a priori* non-critical hypotensive patients face.

Overall, 0.93% of non-critical adult ED patients had at least one episode of hypotension (i.e., one measurement of systolic and diastolic non-invasive blood pressure of maximum 90 mmHg and 60 mmHg, respectively). This prevalence and the overall mortality of 12.0% of hypotensive patients are comparable to other studies reviewed by Holler et al. [13]. However, an epidemiological study by the same team reported higher overall 7-day and 30-day mortality rates at 15% and 22%, respectively [15]. Mortality was very high in hypotensive septic patients and similar to William's et al.'s study on patients fulfilling the 2001 criteria for septic shock. In their study, 30 day mortality was 19.5% [16]. These preoccupying results indicate that hypotension in suspected sepsis is dangerous and must be rapidly identified and treated.

Few papers have studied the proportion of infection in hypotensive ED patients. Holler et al. classified etiologies of hypotension into the major groups that make up the International Classification of Diseases, 10th Revision. This classification, however, groups certain infectious diseases within an affected organ system (e.g., pneumonia, unspecified, is placed under respiratory diseases). Although they applied an algorithm that may have corrected for this imprecision and that calculated a proportion of 13% of hypotensive patients with discharge diagnoses of infection, their algorithm has not been validated [15]. The incongruence between our results and those of Holler et al. may be due to differences in studied populations, inclusion criteria, and definitions.

Several factors distinguished septic patients from non-septic infected patients and may have a role in organ dysfunction,

increased LOS, and mortality. When compared to non-septic infected patients, septic patients were older, suffered from chronic hypertension and cardiac disease, and received antihypertensive medication (i.e., diuretics, beta-blockers, ACEI, and A2RA) (Table 1). This may be due to their association with age, a known risk factor for sepsis severity and cardiovascular disease [9]. It may, however, also be due to either the chronic modification of tissue perfusion autoregulation thresholds due to hypertension or to the accentuation of organ injury in acutely hypotensive patients taking medication that can potentiate volume depletion and decrease systemic vascular resistance. Chronically hypertensive patients are known for having moderate hypotension when developing shock [10]. A review by Leone et al. indicated that maintaining a MAP of 75 to 85 mmHg in chronically hypertensive patients with septic shock may reduce the risk of developing acute kidney injury [17]. An inadequate driving pressure in chronically hypertensive septic patients may have been one of the factors responsible for organ failure. A history of hypertension or cardiac disease in an elderly hypotensive patient should prompt a rapid evaluation of the patient's acute hemodynamic instability since these factors are associated with organ failure and death.

This retrospective, observational, monocentric study had several limitations. Clinicians did not always use the Glasgow score and the SOFA score was consequently modified. This type of limitation contributes to information bias, which is inherent to the retrospective nature of our study, and underlines the need for further prospective cohort studies. The use of a fixed threshold value for hypotension at 90/60 mmHg (i.e., a mean blood pressure of 70 mmHg) is also a potential limitation. A more personalized definition of blood pressure may be better, especially in chronically hypertensive patients, but determining a baseline value for blood pressure is difficult in the ED. Furthermore, this value is consistent with the SOFA score, which was used to define sepsis [1,18]. Additionally, by defining the HSP as suspected or confirmed infection, we may have included patients in the HSP who had another cause of organ dysfunction than sepsis. This study nevertheless reflects clinical practice and shows the importance of quickly identifying sepsis in hypotensive patients initially considered non-critical.

5. Conclusion

Sepsis in *a priori* non-critical hypotensive adult patients, when compared with other causes of hypotension, is associated with significantly higher mortality and increased LOS. Patients that present to the ED and have a MAP of 70 mmHg or less must be rigorously evaluated and have consistent follow-up.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2019.158360>.

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