Risk stratification in emergency medicine: towards improved age and sex adjusted risk assessment

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EMERGENCY

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THE ASSOCIATION BETWEEN SYSTOLIC BLOOD PRESSURE AND HEART RATE IN EMERGENCY DEPARTMENT PATIENTS: A MULTICENTRE COHORT STUDY

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ABSTRACT

Background Guidelines and textbooks assert that tachycardia is an early and reliable sign of hypotension and an increased heart rate (HR) is believed to be an early warning sign for the development of shock, although this response may change by ageing, pain, and stress.

Objective To assess the unadjusted and adjusted associations between systolic blood pressure (SBP) and HR in Emergency Department (ED) patients of different age categories (18-50;50-80;>80 years).

Methods A multicentre cohort study using the Netherlands Emergency Department Evaluation Database (NEED) including all ED patients ≥18years from three hospitals in whom HR and SBP were registered at arrival to the ED. Findings were validated in a Danish cohort including ED patients. In addition, a separate cohort was used including ED patients with a suspected infection who were hospitalized from whom an SBP and HR were available before, during and after ED treatment. Associations between SBP and HR were visualized and quantified with scatterplots and regression coefficients (95%-CI).

Results A total of 81,750 ED patients were included from the NEED and a total of 2358 patients with a suspected infection. No associations were found between SBP and HR in any age category (18-50years: -0.03bpm/10mmHg, 95%CI -0.13-0.07, 51-80years: -0.43bpm/10mmHg, 95%CI -0.38- -0.50, >80years: -0.61bpm/10mmHg, 95%CI -0.53- -0.71)), nor in different subgroups of ED patient. No increase in HR existed with a decreasing SBP during ED treatment in ED patients with a suspected infection.

Conclusion No association between SBP and HR existed in ED patients of any age category, nor in ED patients who were hospitalized with a suspected infection, even during and after ED treatment. ED physicians may be misled by traditional concepts about HR disturbances because tachycardia may be absent in hypotension.

INTRODUCTION

Several textbooks and guidelines, such as the Advanced Trauma Life Support (ATLS) and Surviving Sepsis Campaign (SSC), assert that tachycardia is an essential part of the physiological response to hypotension.[39, 108-110] Consequently, tachycardia is often used as an early marker of hemodynamic instability.[39, 110] Nonetheless, in trauma and sepsis patients, hypotension is often not accompanied by tachycardia, and previous studies suggest not relying solely on heart rate (HR) disturbances to recognize a progressive fall in blood pressure.[111-116]

Even if heart rate increases with decreasing blood pressure, many factors, such as pain or anxiety, may cause a tachycardic response and thus heart rate may not be a reliable vital sign in an undifferentiated patient population such as in the Emergency Department (ED). More importantly, the heart rate response in situations with lowering blood pressure may be blunted with higher age, possibly by a decreased chronotropic beta-adrenergic responsiveness.[12, 117] For this reason, we hypothesized that an association between systolic blood pressure (SBP) and HR may exist in younger but is less clear or absent in older ED patients. A better understanding of the association between SBP and HR helps to assess the usefulness of HR as a vital sign to detect hypotension in acutely ill patients.

This study aims to assess the association between SBP and HR in the ED setting in different age categories.

METHODS

Study design and setting

This multicentre cohort study used three separate cohorts: the Netherlands Emergency department Evaluation Database (NEED), a quality registry for Dutch Emergency Departments (www.stichting-NEED.nl), the Danish Multicenter Cohort (DMC) to externally validate our findings, and a cohort including patients with a suspected infection (Sepsis op Spoedeisende Hulp; (SOS) cohort). The NEED contained data from three EDs, a tertiary care centre and two urban teaching hospitals (January 2017-September 2020). The DMC included all ED patients aged ≥18 years from two level II emergency departments with data between 2008 and 2013. Patients were consecutively sampled in relation to previous prospective studies at two level II emergency centers. This cohort was chosen for external validation to include a similar ED population as in the NEED, but in a different country and period. The cohort has been described in detail previously.[118, 119] The

SOS cohort included patients who were hospitalized from the ED with a suspected infection from two tertiary care centers and one urban teaching hospital in the Netherlands with data between 2011 and 2013. This was a retrospective analysis of prospectively collected data. The cohort has been described in detail previously.[120] This cohort enabled the exploration of vital signs within one patient during resuscitation, as it contained vital sign registrations at three different time points in the ED.

Patients were stratified by age categories (18-50, 51-80, >80 years). These age categories were chosen because the incidence of hypertension is low till the age of 50 years in the Netherlands after which it gradually increases (www.cbs.nl). The cut-off at 80 years has been used in previous studies.[82, 119]

Participants
In the NEED and DMC, all consecutive patients ≥18 years presenting to the ED were included if both SBP and HR were registered.

The SOS cohort included consecutive ED patients aged 17 years and older, with suspected infection and an urgent to very urgent triage category according to the Manchester triage system, who were admitted to the hospital and treated with intravenous antibiotics. For the current study, patients of 17years old were excluded from the database.

Data collection
Previously, we described in detail how vital signs were measured and which data were collected in the NEED.[82] In summary, we collected demographic variables, disease severity, proxies for comorbidity and complexity, vital signs, laboratory results and outcomes. One set of vital signs (HR, SBP, peripheral oxygen saturation, respiratory rate, temperature, diastolic blood pressure) was recorded per patient measured at the beginning of ED presentation before ED treatment. Vital signs were not recorded if this was not necessary for the ED presentation. This was similar for the DMC. In the SOS, vital signs were registered before ED treatment (Time 0h at arrival identical to the NEED cohort), during ED treatment (approximately around time 30 minutes) and after ED treatment (before admission to the ward). During ED stay, the lowest SBP and the highest HR value were registered. Also, the use of beta-blocking agents and calcium antagonists was registered only in this cohort.

Data analyses

Descriptive analyses

Data were presented as mean (standard deviation (SD)) if normally distributed and median (interquartile range (IQR)) if skewed.

Main statistical analyses

Univariable associations between SBP and HR were investigated and visualized using scatterplots for three age categories. Both a linear and locally estimated scatterplot smoothing (LOESS) fit with 95% confidence intervals (95%CI) were fitted to the data. In the figures, the size of the dots indicates the precision of the estimate for observed heart rate and is based on the inverse of the standard deviation. The larger, the higher the precision. A linear regression coefficient with 95%CI and a R squared were also presented.

To correct the association between SBP and HR for other vital sign values and pain scores, an additional analysis was performed. We investigated the association between SBP and HR using the R package mgcv, to fit a generalized additive regression model (GAM) adjusted for other vital signs and pain scores which were left constant at 'normal' values (respiratory rate (18/min.), peripheral oxygen saturation (97%), temperature (36 degrees Celsius), numeric rating scale for pain (NRS) (0)), on the NEED data. Missing NRS was considered as a score of 0. If other vital signs were missing the patient was excluded. This analysis was intended to be descriptive, and therefore we did not attempt formal statistical inference in terms of p-values and confidence intervals.

In the SOS we assessed whether the use of beta-blocking agents or calcium antagonists affected our results by linear fits for patients with beta-blocking agents and patients without beta-blocking agents. A linear regression coefficient with a p-value and an R squared was presented. In addition, we assessed whether deterioration of blood pressure was accompanied by an increasing HR. We therefore calculated the deltaSBP = SBP after ED treatment – SBP before ED treatment, and similarly a deltaHR. We assessed the relationships between those two variables using a scatterplot with linear fit.

Subgroup analyses

We performed four subgroup analyses in the NEED. The first subgroup analysis included all patients with an SBP<120mmHg, to put more focus on the hypotensive patients in this study. In this subgroup, we compared the

in-hospital mortality rates in patients with a low HR response (below the median) to hypotension and with a high HR response (above the median). In this way we could study whether the absence of a tachycardic response had a poor outcome compared to patients with a tachycardic response.

To assess whether the aetiology of a low SBP and severity of illness affected the univariable association with HR, the relationship between SBP and HR were also investigated for the subgroups suspected infection and trauma patients (potentially having haemorrhage) in the NEED, and for patients admitted to the Intensive Care Unit (ICU). In the subgroups suspected infection and trauma, the most likely cause for hypotension is septic shock and hemorrhagic shock, respectively, while other reasons are less likely. In this way, we could assess the association between SBP and HR in two types of shock patients. Patients with a suspected infection were selected in the NEED if blood cultures were obtained and if they were hospitalized. Trauma patients were selected if they were triaged as very urgent or immediate (according to the Manchester Triage System or Dutch Triage Standard) and by the following triage presenting complaints: Severe trauma; facial complaints; fall; extremity complaints; large scale incidents; neck pain; thorax injury; head injury; wounds. Additionally, a radiological test had to be performed. Patients admitted to the ICU were registered in the NEED and were studied as last subgroup.

All statistical analyses were performed in Rstudio (packages rms, dplyr, and mgcv).

RESULTS

Patient characteristics

The NEED contained 148,828 patients ≥18 years. In total, 81,750 (54.9%) patients could be included in whom both SBP and HR were registered. See a flow diagram in figure 1. The mean age of patients in the NEED was 61 years (SD 19). Mean SBP was higher in older patients >80 years with 141mmHg (SD 34) compared to the youngest age category with mean SBP of 124mmHg (SD 26). Patient characteristics are described in table 1.

Table 1: Patient characteristics from the NEED

NEED cohort	18-50years (N=22617)	51-80years (N=46350)	>80years (N=12783)	All (N=81750)
Age, years				
Mean (SD)	35 (9.8)	6 (8.4)	86 (3.9)	61 (19)
Sex				
female	12170 (53.8%)	21054 (45.4%)	7144 (55.9%)	40368 (49.4%)
Triage category, N (%)				
immediate	1044 (4.6%)	3050 (6.6%)	788 (6.2%)	4882 (6.0%)
very urgent	6534 (28.9%)	15037 (32.4%)	3891 (30.4%)	25462 (31.1%)
urgent	9771 (43.2%)	19349 (41.7%)	5362 (41.9%)	34482 (42.2%)
non-urgent	4885 (21.6%)	8181 (17.7%)	2516 (19.7%)	15582 (19.1%)
Missing	383 (1.7%)	733 (1.6%)	226 (1.8%)	1342 (1.6%)
Systolic Blood Pressure (mmHg)				
Mean (SD)	124 (26)	135 (32)	141 (34)	133 (31)
Heart rate (bpm)				
Mean (SD)	87 (20)	86 (22)	83 (21)	86 (21)
Respiratory Rate (/min.)				
Mean (SD)	17 (5)	18 (5)	19 (6)	18 (5)
Missing	6865 (30.4%)	9729 (21.0%)	2385 (18.7%)	18979 (23.2%)
Peripheral oxygen saturation (%)				
Mean (SD)	98.4 (2.5)	96.7 (3.6)	96.0 (3.8)	97.1 (3.5)
Missing	823 (3.6%)	1819 (3.9%)	509 (4.0%)	3151 (3.9%)
Temperature (degrees Celcius)				

Table 1: Patient characteristics from the NEED (continued)

NEED cohort	18-50years (N=22617)	51-80years (N=46350)	>80years (N=12783)	All (N=81750)
Mean (SD)	37.1 (0.8)	37.0 (0.9)	36.9 (0.9)	37.0 (0.9)
Missing	4573 (20.2%)	7944 (17.1%)	2312 (18.1%)	14829 (18.1%)
Numeric Rating scale for pain (1 to 10)				
Median (IQR)	4 (1-6)	2 (0-5)	2 (0-4)	3 (0-5)
Missing	13088 (57.9%)	30002 (64.7%)	8698 (68.0%)	51788 (63.3%)
Supplemental Oxygen				
yes	429 (1.9%)	2879 (6.2%)	1353 (10.6%)	4661 (5.7%)
Missing	6086 (26.9%)	10745 (23.2%)	2237 (17.5%)	19068 (23.3%)
Fluid administration (ml)				
0cc	11407 (50.4%)	26027 (56.2%)	7289 (57.0%)	44723 (54.7%)
0-500cc	2031 (9.0%)	4314 (9.3%)	1322 (10.3%)	7667 (9.4%)
>500cc	2320 (10.3%)	5159 (11.1%)	1239 (9.7%)	8718 (10.7%)
Missing	6859 (30.3%)	10850 (23.4%)	2933 (22.9%)	20642 (25.3%)
In-hospital mortality, N(%)				
died	90 (0.4%)	1197 (2.6%)	770 (6.0%)	2057 (2.5%)
Missing	188 (0.8%)	688 (1.5%)	264 (2.1%)	1140 (1.4%)
ICU admission, N (%)				
ICU admission	350 (1.5%)	924 (2.0%)	140 (1.1%)	1414 (1.7%)
Missing	318 (1.4%)	397 (0.9%)	66 (0.5%)	781 (1.0%)

Abbreviations= N: number, SD: standard deviation, IQR: interquartile range, GCS: Glasgow Coma Scale, ICU: Intensive Care Unit

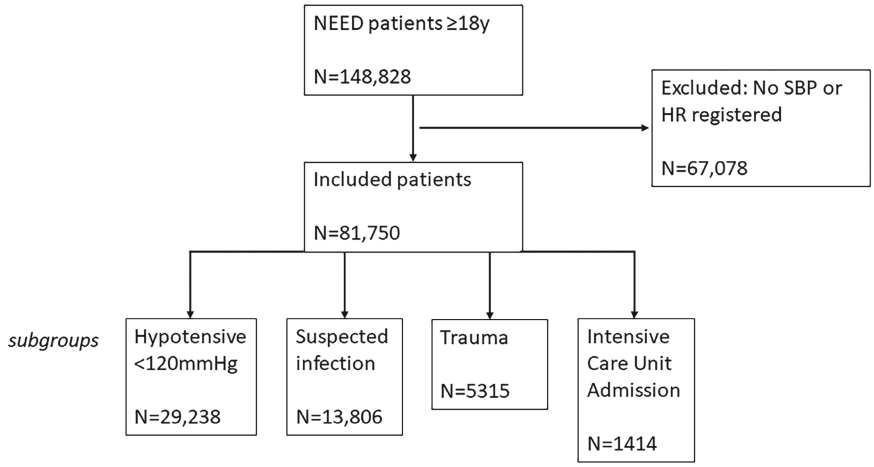


Figure 1 Flow diagram throughout the NEED cohort.

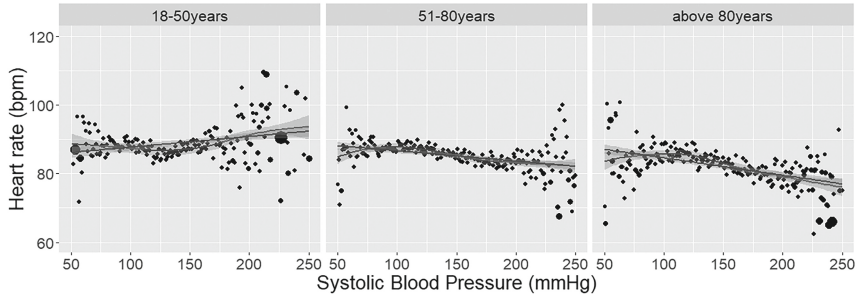


Figure 2 The univariable relationship between systolic blood pressure (SBP) and heart rate (HR) stratified by age categories in the NEED cohort (N=81,750). The size of the dots indicates the precision of the estimate for observed heart rate and is based on the inverse of the standard deviation. The larger, the higher the precision. Both a linear and locally estimated scatterplot smoothing (LOESS) fit with 95% confidence intervals were fitted to the data. No association was found in any age category between SBP and HR.

Main results

Figure 2 demonstrates the association between SBP and HR in three age categories at arrival in the ED. No association between HR and SBP was found in any age group. No association between SBP and HR was found in any subgroup of hypotensive patients, trauma patients, patients with a suspected infection, and ED patients admitted to the ICU (see figure 3). Adjustment for other vital signs and pain scores did not affect the association between SBP and HR (Figure 4).

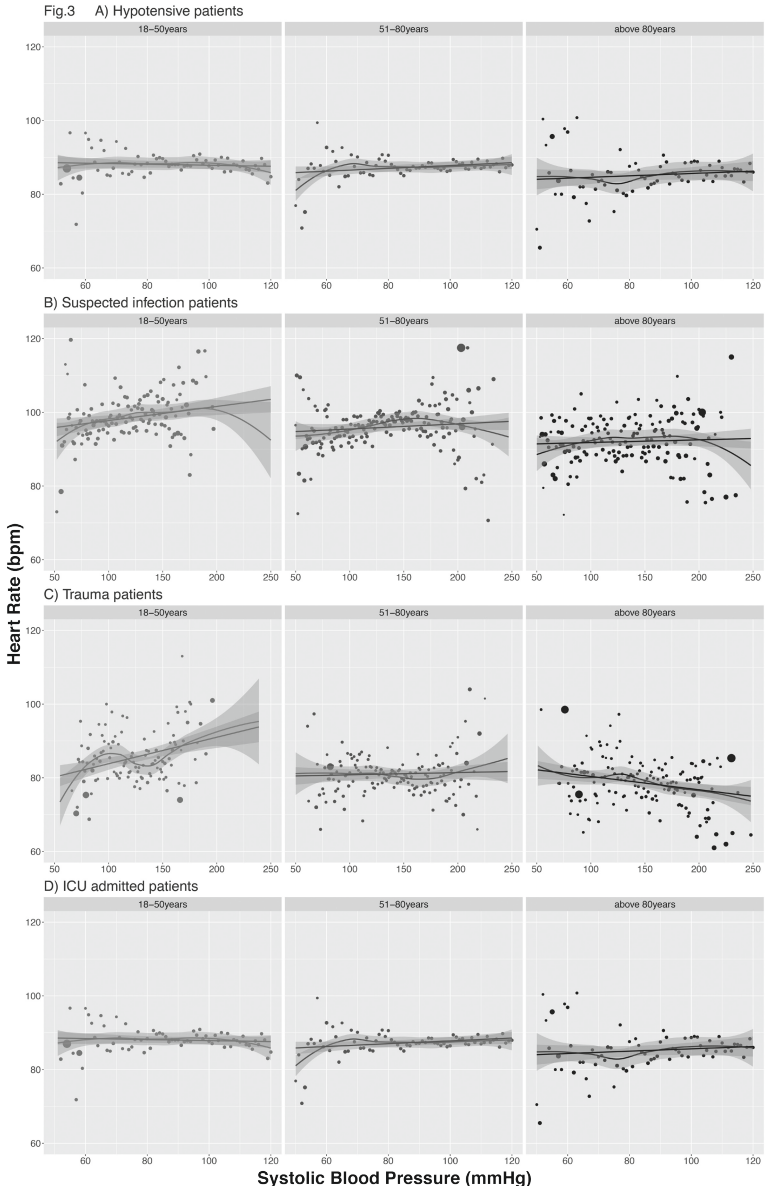


Figure 3. Subgroup analyses in the NEED registry. Scatterplots are presented for the association between systolic blood pressure and heart rate in different age categories. Panel A shows the association between systolic blood pressure (SBP) and heart rate in a subgroup of patients with an SBP <120mmHg (N=29,238). Panel B shows a subgroup of patients with a suspected infection (N=13,806). Panel C shows a subgroup of trauma patients (N=5315). Panel D shows a subgroup of ED patients who were admitted to the Intensive Care Unit (N=1414). No association was found in any age category between SBP and HR.

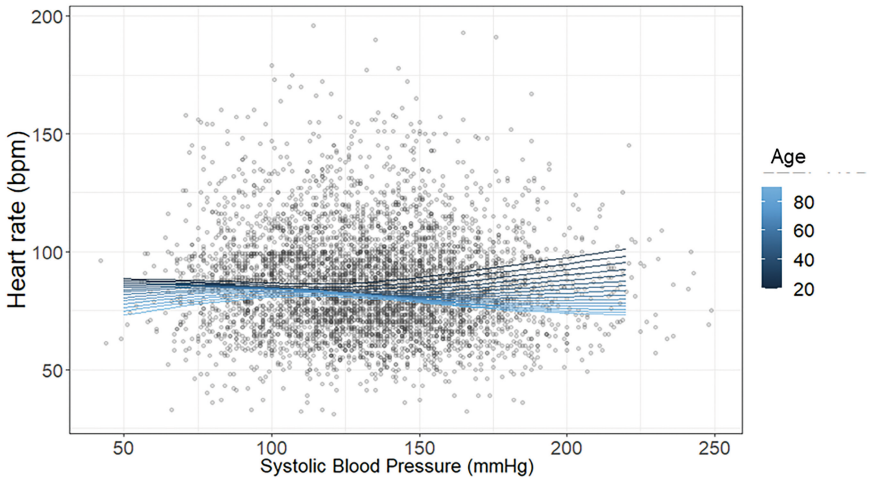


Figure 4 The associations between systolic blood pressure, heart rate, and age are shown using a generalized additive logistic regression model, adjusted for temperature, peripheral oxygen saturation, pain score and respiratory rate.

The SOS cohort included 2358 patients with a suspected infection. Patient characteristics are described in supplementary file 1. No clear increase in HR could be found with decreasing SBP for any age category neither before, during or after ED treatment (Figure 5). The use of beta-blocking agents or calcium antagonists did not affect the relationship. If the vital signs after ED treatment of an individual patient were compared with the vital signs before ED treatment, no increase in deltaHR existed with a decreasing SBP during resuscitation in the ED (e.g., a negative deltaSBP; see supplementary file 2).

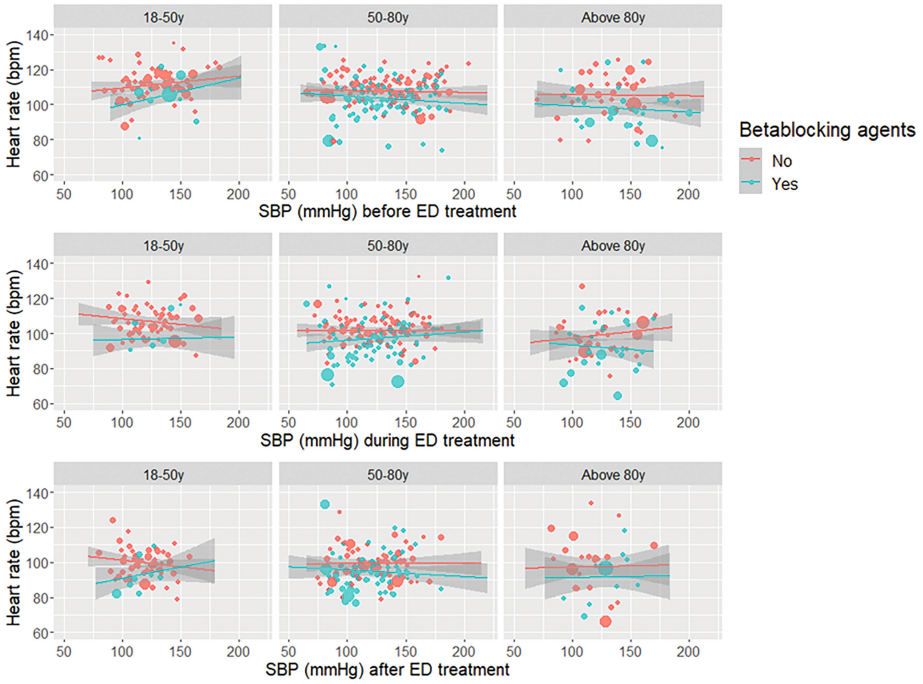


Figure 5 The univariable relationship between SBP and HR stratified by age categories and time of registration in a cohort of patients with a suspected infection (N=2358). A linear line was fitted to the data. The relationship was assessed before ED treatment (T0), during ED treatment (T30min.) and after ED treatment just before ward admission. Patients with beta-blocking agents or calcium antagonists were marked. No association was found in any age category between SBP and HR.

External validation in a Danish cohort of ED patients showed similar results (supplementary file 3). No clear increase in HR could be found with decreasing SBP for any age category.

Regression coefficients and R squared for the different cohorts and subgroups are presented in supplementary file 4. Although some regression coefficients were statistically significant, they were close to zero and therefore not clinically relevant.

In the subgroup with hypotensive patients (SBP <120mmHg) we compared mortality rates of patients with a low HR and patients with a high HR response. Mortality was higher in the patients with a high HR (see

supplementary file 5). However, the hypotensive patients >80years still had a 7.3% mortality risk in the absence of a tachycardic response.

DISCUSSION

In this multicentre cohort study, no association between SBP and HR was found in ED patients of any age category or subgroup including suspected infection, trauma and ICU admitted patients. In the ED, tachycardia alone may therefore not be helpful in detecting hypotension.

Although several textbooks and guidelines assert that tachycardia is an early and reliable sign of hypotension to maintain sufficient cardiac output and circulating volume,[39, 108-110, 121] low blood pressure was not accompanied by an increase in HR in the present study. Textbooks are based on theoretic physiological principles explaining that compensated hypotension is characterized by intense sympathetic stimulation of the circulation elicited by baroreceptor reflexes.[108, 109, 121, 122] However, several animal studies have shown an absence of tachycardia in haemorrhage, which is in line with the findings of the present study.[122-125] The absence of tachycardia as a response to hypotension during haemorrhage has been explained to be a vagal reflex.[114, 125-127]

In sepsis it is currently believed that inflammation leads to vasodilation which alters cardiac output due to preload reduction.[39, 128, 129] As a result, sympathetic activation is triggered and should lead to a compensated tachycardia and vasoconstriction. Nevertheless, decreasing blood pressure was not accompanied by an increased HR in younger and older patients on average cohort level. This finding follows several studies which have demonstrated that an altered heart rate variability in sepsis is common and correlates with the severity of the systemic infection with a higher mortality rate.[115, 116]

At the start of this study we hypothesized that an association between SBP and HR could be absent in older patients due to the decreasing chronotropic response with increasing age.[12, 117] However, the association was also lacking in younger patients. Our results were confirmed in a Danish multicentre cohort, implying that they can be generalized to other ED settings and times. Also, we have shown that adjusting for other vital signs and pain did not affect the association between SBP and HR in ED patients. We can only speculate why an increased HR did not accompany hypotension in the ED. A potential explanation is the large variety in ED presentations. While patients with deranged hemodynamics, such as septic patients, would be

expected to have a combination of tachycardia and low blood pressure, other ED patients presenting with pain or anxiety disorders could have tachycardia with high blood pressure. Other factors such as changes in blood volume, pain, anxiety, parasympathetic and sympathetic stimuli and circulating hormones are likely explanations that may play an essential role in ED patients. Because of this heterogeneity, no association between SBP and HR may have been found.

The NEED only contained vital sign registrations at arrival to the ED, but repeated analyses in a cohort with multiple registrations during and after ED treatment showed similar results. Remarkably, a decrease in SBP during and after resuscitation was not accompanied by an increase in HR in individual patients with a suspected infection.

The importance of our observations lies in the fact that hypotension cannot be recognized solely by the presence of tachycardia, and so HR may be an unreliable vital sign to screen for physiological derangement and hypotension in ED patients of all age categories, while guidelines such as the ATLS continue to use HR as one of the vitals to classify the degree of haemorrhagic shock.[39, 108-110] In this study we demonstrated that mortality rates are lower in hypotensive patients without a tachycardic response than in patients with a tachycardia. Hypothetically, the patients with an SBP below 120mmhg and absent tachycardic response might not have essential hypotension, e.g., a perfusion problem. Nonetheless, the in-hospital mortality rate was still substantially high in older patients, possibly caused by a decreased chronotropic beta-adrenergic responsiveness or by beta-blocking medication. Therefore ED physicians should not be misled by traditional concepts about HR disturbances.[39, 108-110]

Despite several strengths like the large sample size and the fact that we performed analyses in multiple independent cohorts, several limitations merit emphasis. First, only one set of vital signs at ED arrival was available in the NEED database, which may have affected our results. Possibly the first set of vital signs is affected by measurement artifacts, or many more confounders, such as mental stress and pain affecting HR, which could blur the association with SBP. However, we assessed the relationship between SBP and HR in a cohort including patients with a suspected infection at three different times during ED stay (supplementary file 2), which showed similar results. Secondly, we could not adjust the analyses for potential confounders such as anxiety or vasopressor/inotropic agents. Nonetheless, we have shown no clear relationship between SBP and HR even after adjusting for vital signs and pain. Finally, we assessed the relationship between SBP

and HR at cohort level. A decreasing SBP may still be accompanied by an increasing HR in individual patients, even though no increased HR was found with a decreasing SBP in patients with suspected infection in the SOS cohort.

In summary, the present study indicates that an association between SBP and HR cannot be detected in ED patients of any age category or subgroup. Acute care guidelines should acknowledge that HR may not be a reliable vital sign to detect physiological derangement in the ED.

SUPPLEMENTARY FILE 1

Patient characteristics from the SOS multicenter cohort including patients with suspected infection

Patients with suspected infection	18-50y (N=573)	50-80y (N=1497)	Above 80y (N=288)	All (N=2358)
Age, years, median (IQR)	40 (31-46)	66 (60-72)	85 (82-88)	64 (51-74)
Sex, female	503 (49.4%)	593 (39.4%)	120 (41.2%)	1001 (42.5%)
Systolic Blood Pressure (mmHg) before ED treatment				
Median [IQR]	125[113-145]	132 [115-151]	135 [110-155]	130 [114-149]
Missing	94 (9.2%)	140 (9.3%)	10 (3.4%)	244 (8.7%)
Systolic Blood Pressure (mmHg) during ED treatment				
Median [IQR]	114 [72.5-130]	123 [106-140]	122 [103-142]	121 [102-137]
Missing	511 (50.2%)	418 (27.8%)	87 (29.9%)	1016 (36.1%)
Systolic Blood Pressure (mmHg) after ED treatment				
Median [IQR]	118 [107-130]	120 [106-135]	120 [107-138]	120 [106-134]
Missing	723 (71.0%)	701 (46.5%)	136 (46.7%)	1560 (55.4%)
Heart rate (bpm) before ED treatment				
Median [IQR]	93.0 [3.00-115]	107 [94.0-120]	102 [90.0-115]	104 [84.0-117]
Missing	15 (1.5%)	29 (1.9%)	2 (0.7%)	46 (1.6%)
Heart rate (bpm) during ED treatment				
Median [IQR]	98.0 [70.0-111]	100 [87.0-112]	96.0 [82.0-110]	99.0 [85.0-111]
Missing	495 (48.6%)	389 (25.8%)	79 (27.1%)	963 (34.2%)

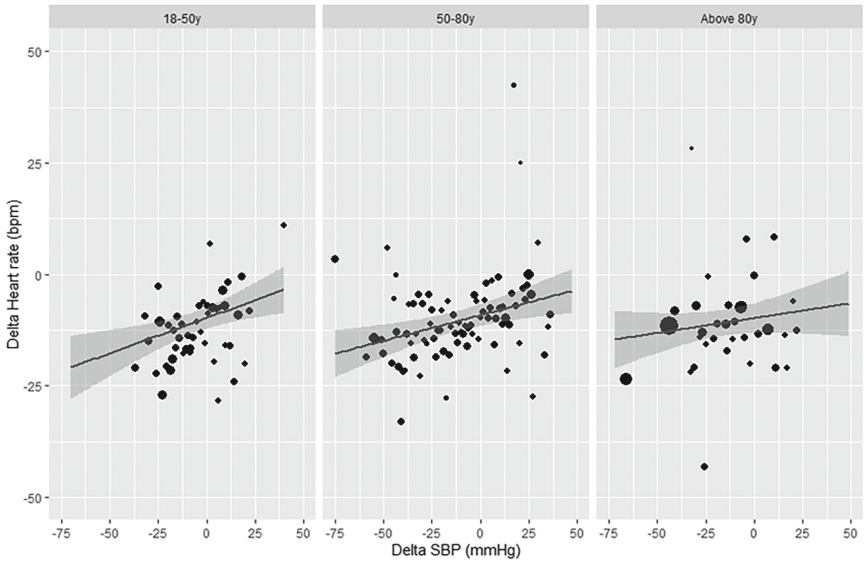
Patient characteristics from the SOS multicenter cohort including patients with suspected infection (continued)

Patients with suspected infection	18-50y (N=573)	50-80y (N=1497)	Above 80y (N=288)	All (N=2358)
Heart rate (bpm) after ED treatment				
Median [IQR]	99.0 [90.0-108]	96.0 [85.0-109]	96.0 [80.0-108]	97.0 [85.0-108]
Missing	701 (68.9%)	627 (41.6%)	130 (44.7%)	1458 (51.8%)
Use of betablocking agents or calcium antagonists				
Yes	69 (12.0%)	540 (36.1%)	125 (43.0%)	731 (31%)
Missing	2 (0.3%)	11 (0.7%)	3 (1.0%)	16 (0.7%)
Use of other Antihypertensiva				
Yes	73 (12.7%)	568 (37.9%)	150 (52.1%)	791 (30.0%)
Missing	1 (0.2%)	11 (0.7%)	3 (1.0%)	15 (0.6%)
Fluid administration in the ED				
0ml	60 (10.5%)	166 (11.1%)	32 (11.1%)	258 (10.9%)
0-1000ml	159 (27.7%)	410 (27.4%)	100 (34.7%)	669 (28.4%)
1000-2000ml	282 (49.2%)	682 (45.6%)	115 (39.9%)	1079 (45.8%)
>2000ml	72 (12.6%)	239 (16.0%)	41 (14.2%)	352 (14.9%)
In-hospital mortality				
Yes	13 (2.3%)	96 (6.4%)	39 (13.5%)	148 (6.3%)
Missing	4 (0.7%)	11 (0.7%)	6 (2.1%)	21 (0.9%)

Abbreviations= N: number, SD: standard deviation, IQR: interquartile range, GCS: Glasgow Coma Scale, ICU: Intensive Care Unit, mmHg: Millimeter Mercury.

SUPPLEMENTARY FILE 2

The association between delta SBP and delta HR



The association between delta systolic blood pressure and delta heart rate in patients with suspected infection. Delta SBP was calculated as the SBP after ED treatment – SBP before ED treatment. Delta heart rate was calculated as the HR after ED treatment – HR before ED treatment.
If the SBP is lower after ED treatment (a negative delta SBP), the heart rate does not respond with a positive delta HR in individual patients as can be seen in the figure.

SUPPLEMENTARY FILE 3

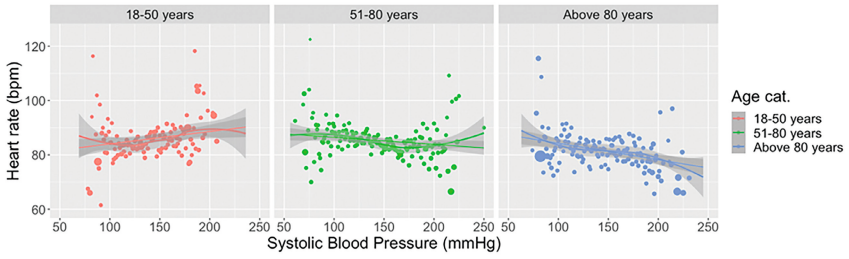
External validation in Denmark: To validate our findings in a different country and period, a Danish multicentre Cohort (DMC) was used, including patients from two level II emergency departments with data between 2008 and 2013.

Patient characteristics

DMC	18-50 (N=4724)	51-80 (N=7456)	>80 (N=2462)	All (N=14642)
Age				
Mean (SD)	35.5 (9.78)	66.8 (8.32)	86.1 (4.09)	60.0 (20.0)
Gender				
female	2096 (44.4%)	3820 (51.2%)	1131 (45.9%)	7047 (48.1%)
Systolic blood pressure (mmHg)				
Mean (SD)	132 (18.9)	140 (25.4)	140 (27.3)	137 (24.1)
Pulse (/min)				
Mean (SD)	84.4 (19.1)	84.9 (20.3)	81.6 (19.6)	84.2 (19.8)
inhospital mortality				
Yes	11 (0.2%)	185 (2.5%)	159 (6.5%)	355 (2.4%)
Admission to Intensive Care Unit				
Yes	100 (2.1%)	233 (3.1%)	72 (2.9%)	405 (2.8%)

Abbreviations= N: number, SD: standard deviation, DMC: Danish Multicenter Cohort, mmHg: Millimeter Mercury.

The figure below shows the association between SBP and HR for the external validation cohort.



SUPPLEMENTARY FILE 4

Correlation coefficients: For each cohort or subgroup, the correlation coefficient is presented as a change in heart rate (bpm) per 10mmHg increase in Systolic blood pressure is presented for the linear fit on the data for all patients with an SBP between 50 and 250mmHg. Also, the R squared is presented for the linear fit.

	Change in HR (bpm) per 10mmHg increase in SBP (95%-CI)	R squared
NEED cohort (all patients, N=81,750)		
18-50y	-0.031 (-0.13- 0.07)	0,000
51-80y	-0.43 (-0.38- -0.50)	0.004
>80y	-0.61 (-0.53- -0.71)*	0.010
NEED cohort (subgroup trauma patients, N=5315)		
18-50y	0.34 (-0.05- 0.72)	0.003
51-80y	-0.10 (-0.31- 0.10)	0.000
>80y	-0.38 (-0.65- -0.12)*	0.007
NEED cohort (subgroup suspected infection, N= 13806)		
18-50y	0.54 (0.26-0.82)*	0.005
51-80y	0.43 (0.29-0.58)*	0.004
>80y	0.15 (-0.11-0.40)	0.001
NEED cohort (ICU admitted patients, N= 1414)		
18-50y	-0.59 (-1.4-0.23)	0.007
51-80y	0.30 (-0.13-0.74)	0.001
>80y	-0.73 (-1.7-0.28)	0.015
DMC cohort (All patients, N=14642)		
18-50y	0.64 (0.35-0.92)*	0.004
51-80y	-0.55 (-0.73- -0.37)*	0.005
>80y	-0.53 (-0.80- -0.26)*	0.005

Abbreviations= N: number, 95%-CI: 95% Confidence Intervals, ICU: Intensive Care Unit, NEED: Netherlands Emergency department Evaluation Database, DMC: Danish Multicenter Cohort, bpm: beats per minute, SBP: systolic blood pressure, HR: heart rate.
*Statistically significant correlation coefficient ($p<0.05$)

SUPPLEMENTAL FILE 5.

Patients with systolic blood pressure below 120 mmHg stratified by heart rate below or above median.

	18-50y		51-80y		>80y		Total	
Number	**LOW HR (N=5056)**	**HIGH HR (N=4787)**	**LOW HR (N=8164)**	**HIGH HR (N=7614)**	**LOW HR (N=1879)**	**HIGH HR (N=1738)**	**LOW HR (N=15099)**	**HIGH HR (N=14139)**
Age								
Median [IQR]	35 [27-44]	33 [25-43]	67 [59-73]	66 [59-73]	85 [83-88]	85 [83-88]	61 [44-74]	61 [43-73]
Sex								
male	2088 (41.3%)	2004 (41.9%)	4754 (58.2%)	4195 (55.1%)	986 (52.5%)	875 (50.3%)	7828 (51.8%)	7074 (50.0%)
Heart rate (bpm)								
Median [IQR]	74 [66-80]	98 [92-110]	73 [65-80]	99 [93-110]	72 [64-78]	97 [91-110]	73 [65-80]	98 [92-110]
Systolic blood pressure (mmHg)								
Median [IQR]	105 [92-114]	102 [91-112]	103 [90-112]	102 [90-112]	103 [90-113]	104 [91-113]	103 [91-113]	103 [91-112]

Supplemental file 5. Patients with systolic blood pressure below 120 mmHg stratified by heart rate below or above median. (continued)

	18-50y		51-80y		>80y		Total	
Number	**LOW HR (N=5056)**	**HIGH HR (N=4787)**	**LOW HR (N=8164)**	**HIGH HR (N=7614)**	**LOW HR (N=1879)**	**HIGH HR (N=1738)**	**LOW HR (N=15099)**	**HIGH HR (N=14139)**
In-hospital mortality								
died	19 (0.4%)	38 (0.8%)	207 (2.5%)	394 (5.2%)	138 (7.3%)	184 (10.6%)	364 (2.4%)	616 (4.4%)
Missing	34 (0.7%)	68 (1.4%)	233 (2.9%)	242 (3.2%)	98 (5.2%)	76 (4.4%)	365 (2.4%)	386 (2.7%)
Intensive Care Unit Admission								
ICU admission	49 (1.0%)	145 (3.0%)	192 (2.4%)	295 (3.9%)	29 (1.5%)	44 (2.5%)	270 (1.8%)	484 (3.4%)
Missing	76 (1.5%)	65 (1.4%)	82 (1.0%)	57 (0.7%)	13 (0.7%)	7 (0.4%)	171 (1.1%)	129 (0.9%)

NEED: Netherlands Emergency department Evaluation Database, HR: Heart rate, bpm: beats per minute, mmHg: millimeter Mercury, ICU: Intensive Care Unit, IQR: Interquartile Range.
The table includes patients with a Systolic Blood Pressure <120mmHg (N=29,238). Patients were divided in a low heart rate response below the median heart rate and a high heart rate response above the median heart rate. Median heart rate was 86bpm for both the age-group 18-50years and 51-80years, and 84bpm for the >80years.