

Vasopressors and Mean Arterial Pressure in Septic Shock: Do We Bend the Rules for Young Adults?

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ABSTRACT **Background:** Younger patient age and relatively good prognosis have been described as factors that may increase caregiver motivation in treating patients with septic shock in the intensive care unit (ICU).

Objectives: To examine whether clinical teams tended to achieve unnecessarily higher mean arterial pressure (MAP) values in younger patients.

Methods: We conducted a population-based retrospective cohort study of patients presenting with septic shock who were treated with noradrenaline and hospitalized in a general ICU between 2006 and 2018. The patients were classified into four age groups: 18-45 (n=129), 46-60 (n=96), 61-75 (n=157), and older than 75 years (n=173). Adjusted linear mixed models and locally weighted scatterplot smoothing (LOWESS) curves were used to assess associations and potential non-linear relationships, respectively, of age group with MAP and noradrenaline dosage.

Results: The cohort included 555 patients. An inverse relation was observed between average MAP value and age. Among patients aged 18-45 years, the average MAP was 4.7 mmHg higher (95% confidence interval 3.4-5.9) than among patients aged > 75 years (*P*-value <0.001) after adjustment for sex, death in the intensive care unit, and Sequential Organ Failure Assessment scores.

Conclusions: Among patients with septic shock, the titration of noradrenaline by staff led to a higher average MAP for younger patients. Although the MAP target is equal for all age groups, staff may administer noradrenaline treatment according to a higher target of MAP due to attitudes toward patients of different ages, despite any evidence that such practice is beneficial.

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KEY WORDS: elderly, intensive care unit, mean arterial pressure, noradrenaline, septic shock

Sepsis, and septic shock in particular, is characterized by altered tissue perfusion due to sustained atrial hypotension, commonly defined as systolic arterial blood pressure of less than 90 mmHg [1,2]. The main organs can be protected from systemic hypotension by autoregulation of regional perfusion; however, below a certain threshold, tissue perfusion becomes linearly dependent on mean arterial pressure (MAP) [3].

According to the 2021 Guidelines for Management of Severe Sepsis and Septic Shock, MAP should be maintained ≥ 65 mmHg, using vasoactive agents if necessary [2]. In the intensive care unit (ICU), MAP is monitored invasively and continuously using an arterial line, and vasopressor dose is titrated by the nursing staff to achieve MAP ≥ 65 mmHg. Previous studies in patients with septic shock treated with noradrenaline found that the actual MAP frequently varies during treatment and may be associated with the severity of illness [4], sex, and volemic status [5].

Among factors that have been described to increase the motivation of caregivers in the treatment of patients in the ICU are younger patient age and relatively good prognosis [6,7]. Older patients have been documented as receiving suboptimal care, regardless of their illness [7-9]. The differential treatment of hypotensive patients based on age is yet to be described.

We hypothesized that clinical teams would be prone to achieve higher MAP values in younger patients. Thus, the primary aim of the current study was to assess the average MAP in patients with septic shock, based on age, who were treated with noradrenaline according to an identical protocol in a single tertiary care medical center.

PATIENTS AND METHODS

STUDY DESIGN AND STUDY POPULATION

We conducted a population-based retrospective cohort study at Soroka University Medical Center, a tertiary care medical center that serves as the only regional hospital in southern Israel, with an estimated population of 1,000,000. We included all the patients aged 18 years or older who were hospitalized in the general ICU for 24 hours or more with a diagnosis of septic shock and treated with noradrenaline between December 2006 and January 2018. We identified patients with septic shock either according to the International Classification of Diseases, 9th revision (ICD-9) codes or by diagnoses in the internal ICU medical record. Co-morbidities were also defined by ICD-9 codes. We used the Sequential Organ Failure Assessment (SOFA) score to evaluate organ dysfunction at ICU admission. Exclusion criteria were the use of any vasoactive agent other than noradrenaline, such as adrenaline, dobutamine, dopamine, phenylephrine, vasopres-

sin, or isoproterenol. For patients who had more than one admission in the ICU during the study period, we considered only the first admission.

All the patients admitted to the ICU requiring vasoactive treatments receive arterial lines that measure their blood pressure invasively and continuously. The data for mean arterial pressure (MAP) were automatically recorded at 1-minute intervals from the blood pressure monitors and transferred to the MetaVision system, where it was managed and stored. Nurses administered noradrenaline to patients with septic shock following a specific protocol designed to achieve a target MAP of ≥ 65 mmHg. Consequently, each time the nursing staff adjusted the noradrenaline dose to reach the target MAP, they manually entered the dosage into the MetaVision system, thereby creating a comprehensive sequence of the administered doses. The primary outcome was the mean MAP per shift. We divided every admission day according to the 8-hour shifts of the nurses: night, morning, and evening. We included only the time intervals during which the patients were receiving noradrenaline. We calculated the mean MAP

Table 1. Characteristics of the study population according to age groups

Variable	Age groups (years)				P-value
	18-45 (n=129)	46-60 (n=96)	61-75 (n=157)	> 75 (n=173)	
Male, n (%)	80 (62.0%)	64 (66.7%)	97 (61.8%)	87 (50.3%)	0.03
Co-morbidities, n (%)					
Coronary artery disease	5 (3.9%)	17 (17.7%)	45 (28.7%)	60 (34.7%)	< 0.001
COPD	2 (1.6%)	6 (6.3%)	5 (3.2%)	9 (5.2%)	0.24
Heart failure	2 (1.6%)	7 (7.3%)	13 (8.3%)	27 (15.6%)	< 0.001
Hypertension	5 (3.9%)	29 (30.2%)	103 (65.6%)	143 (82.7%)	< 0.001
Cancer	6 (4.7%)	22 (22.9%)	51 (32.5%)	55 (31.8%)	< 0.001
Diabetes mellitus	12 (9.3%)	36 (37.5%)	82 (52.2%)	76 (43.9%)	< 0.001
PVD	2 (1.6%)	6 (6.3%)	11 (7%)	13 (7.5%)	0.13
Stroke/TIA	3 (2.3%)	8 (8.3%)	18 (11.5%)	24 (13.9%)	0.006
Myocardial infarction	2 (1.6%)	6 (6.3%)	14 (8.9%)	15 (8.7%)	0.049
In-ICU death, n (%)	19 (14.7%)	24 (25%)	50 (31.8%)	87 (50.3%)	< 0.001
SOFA score, median (IQR)	11 (10-13)	12 (10-13)	12 (11-14)	12 (11-14)	0.001
Days of admission among survivors, median (IQR)	24 (8.8-37.3)	12 (8-27)	10 (5-21)	11 (4-26.3)	< 0.001

CNS = central nervous system, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, PVD = peripheral vascular disease, SOFA = Sequential Organ Failure Assessment, TIA = attack

Table 2. Coefficient estimates of age with average mean arterial pressure (MAP) in patients with sepsis treated with noradrenaline in the intensive care unit

Variable	Coefficient estimate (95%CI)	Estimated marginal means (95%CI)	P-value
Age in years			
18–45	4.7 (3.4–5.9) mmHg	75.8 (74.9–76.8) mmHg	< 0.001
46–60	4.1 (2.8–5.4) mmHg	75.2 (74.2–76.3) mmHg	< 0.001
61–75	2.4 (1.2–3.7) mmHg	73.6 (72.7–74.5) mmHg	< 0.001
> 75	Reference	71.2 (70.3–72) mmHg	N/A
Male	-0.7 (-1.6–0.2) mmHg	73.6 (73–74.2) mmHg	0.15
Died during ICU admission	-4.4 (-5.4–3.5) mmHg	71.8 (71–72.5) mmHg	< 0.001
SOFA score at admission	-0.2 (-0.4–0) mmHg		0.049

95%CI = 95% confidence interval, ICU = intensive care unit, SOFA = Sequential Organ Failure Assessment

for every shift on every admission day. MAP values in the range of 30–120 mmHg were included in the analysis. These values represented over 99% of the measurements. Outlying values were assumed to be erroneous.

Mean noradrenaline dosage per shift was calculated similarly to the MAP values. To avoid the consideration of bolus doses as the mean value of an entire shift, only dosages that were given for more than one continuous hour during every shift were included in the analysis.

STATISTICAL ANALYSIS

Results are presented as medians and interquartile ranges for ordinal variables and as percentages for categorical data. The chi-square test was used for categorical variables and the Kruskal-Wallis test for ordinal variables.

The patients were classified into four age groups: 18–45, 46–60, 61–75, and > 75 years. Linear mixed models were used to estimate associations of age groups with mean MAP values and with mean noradrenaline dosages. Mixed models were used to account for the repeated measurements of blood pressure in every patient using autoregressive moving average (ARMA) repeated covariance type. The mean MAP or mean noradrenaline dosage for every shift was the dependent variable. The independent variables were the age groups, patient sex,

death during ICU admission, SOFA score at admission, and total admission days in the ICU. These values were predefined. We used locally weighted scatterplot smoothing (LOWESS) curves to assess potential non-linear relationships of age groups with MAP and noradrenaline dosage. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

The study was approved by the Soroka University Medical Center institutional review board (confirmation number 0305-17).

RESULTS

STUDY POPULATION

The study included 555 patients, stratified by four age groups: 18–45 years (n=129), 46–60 years (n=96), 61–75 years (n=157), and older than 75 years (n=173). Table 1 summarizes characteristics of the study population. Most patients in all the age groups were males (*P*-value < 0.03 for comparison between age groups). Prevalence of all the co-morbidities were higher in the oldest age group, and hypertension was the most common co-morbidity among patients aged 61 years and older (74.6%). ICU mortality was the highest in the oldest group (n=87, 50.3%) and lowest in the youngest group (n=19, 14.7%), *P*-value < 0.001. The median admission SOFA Score was 11 (interquartile range [IQR] 10–13) in the youngest age group and 12 (IQR 11–14) in all the other age groups, *P*-value < 0.001. The longest length of stay in the ICU among survivors was in the youngest group (24 days, IQR 8.8–37.3), and the shortest in the oldest group (11 days, IQR 4–26.3), *P*-value < 0.001.

MEAN ARTERIAL PRESSURE AND NORADRENALINE

An inverse relationship was observed between average MAP value and age [Table 2]. Among patients aged 18–45 years, the average MAP was 4.7 mmHg (95% confidence interval 3.4–5.9) higher than among patients aged 75 years or more (*P*-value < 0.001) after adjustment for sex, in-ICU death, and SOFA score. Sex was not found to be associated with MAP. The average MAP of patients who died during their ICU stay was 4.4 mmHg lower than that of those who survived (*P*-value < 0.001).

Table 3 shows the association between age, sex, ICU death, SOFA score, and average noradrenaline dose. The average noradrenaline dosage (mcg/kg/min) in ICU

patients with septic shock was similar between the age groups and the sexes [Table 3].

Figure 1 presents the average MAP per shift by treatment. For a given noradrenaline dose, MAP was lower

in the two oldest groups (ages 61–75, and older than 75 years).

DISCUSSION

In our cohort of patients with septic shock treated with noradrenaline, the main finding was that the titration of noradrenaline by the staff led to a higher average MAP for younger patients.

The similarity of the noradrenaline doses and the MAP values (≥ 65 mmHg for all age groups) demonstrated that all the patients received acceptable treatment, without discriminating against the elderly, and according to the International Guidelines for Management of Severe Sepsis and Septic Shock [2]. Lower MAP values in the older population treated with similar noradrenaline dosages as the young population could suggest a diminished physiological response to vasopressors, as explained by the decreased responsiveness to alpha- and beta-adrenergic receptor stimulation [10,11]. Furthermore, a significant proportion of older patients in our study (65–83%) presented with a history of chronic hypertension, whereas

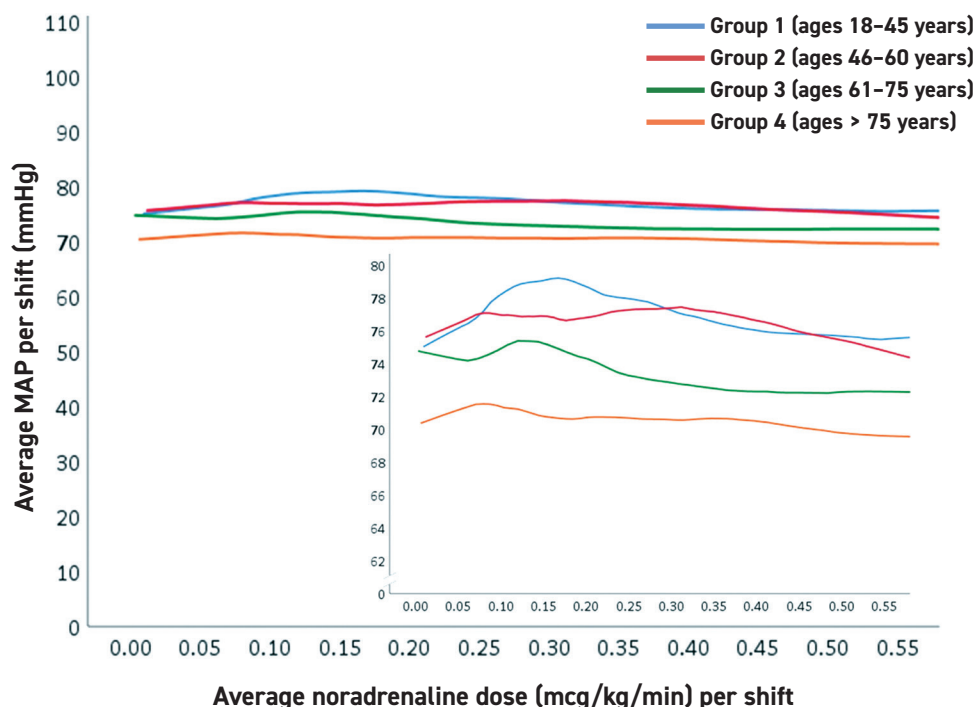
Table 3. Coefficient estimates of age with average noradrenaline dosage (mcg/kg/min) in patients with sepsis treated with noradrenaline in the intensive care unit

Variable	Coefficient estimate (95%CI)	P-value
Age in years		
18–45	-0.01 (-0.05–0.02)	0.41
46–60	0 (-0.04–0.04)	0.96
61–75	0 (-0.03–0.03)	0.99
> 75	Reference	N/A
Male	-0.02 (-0.05–0)	0.10
Died during ICU admission	0.01 (0.004–0.015)	< 0.001
SOFA score at admission	0.14 (0.11–0.16)	< 0.001

95%CI = 95% confidence interval, ICU = intensive care unit, SOFA = Sequential Organ Failure Assessment

Figure 1. Average MAP per shift by age presented by locally weighted scatterplot smoothing (LOWESS) curves

MAP = map arterial pressure



this was observed in only 4–30% of the younger age groups. This discrepancy raises the plausible hypothesis that chronic hypertension may elicit distinct responses to vasopressors. In addition, it is reasonable to assume that patients with a history of hypertension received chronic antihypertensive medications to control their blood pressure. Consequently, this treatment might have influenced the response to vasopressors, particularly during the early stages of hospitalization, potentially leading to a lower mean arterial pressure (MAP) despite receiving similar noradrenaline dosages. However, since noradrenaline doses were titrated according to the same protocol for all age groups, and MAP was the main target, similar MAP values would be expected in all the age groups, even if this would require higher doses of noradrenaline for the older patients. Thus, the difference between the age groups in average MAP values suggests the involvement of an extrinsic factor related to staff behavior, such as a tendency to achieve higher MAP values in younger patients. However, it is also possible that the staff was reluctant to increase the noradrenaline dose to elderly patients with a more limited response to reduce side effects and complications of the treatment.

The impact and prevalence of age-based alterations in the care provided by medical staff has been controversial. Published research results showed that attitudes of medical staff regarding the care of older patients are complex and ambivalent [4–6,12]. However, many studies failed to provide substantial evidence of measurable and objective data [7]. Likewise, position papers have been published regarding specific caring standards for elderly critically ill patients [13]. Although in our ICU identical protocols are used for all age groups, published position papers might reflect an attitude among caregivers that leads them to target lower MAP values in older patients. This treatment is given despite evidence that different targets of MAP may be appropriate for different ages. Thus the behavior of the staff is potentially harmful.

In our analysis, higher SOFA scores and higher mortality rates during ICU stay were found to be associated with lower MAP values. These results are consistent with previous studies that established an association between low MAP values and higher rates of mortality [14,15].

Strengths of our study include a lengthened period of data collection and a relatively large cohort. In addition, we were able to achieve good temporal resolution in the analysis of the association between MAP and noradrenaline. Yet, our study has limitations. First, it is a retro-

spective study that included patients with sepsis from a single center. Second, patients who were treated with any vasoactive drug other than noradrenaline were excluded. Furthermore, we did not assess the concomitant use of other medications that could have secondary effects on blood pressure (e.g., sedatives, beta blockers, corticosteroids, thyroid hormone replacement) and that could have affected the observed results of some of the patients.

CONCLUSIONS

For younger patients with septic shock, staff may administer noradrenaline treatment according to a higher target of MAP, despite any evidence that such practice is beneficial. Thus, although the MAP target is equal for all age groups, elderly patients may have lower MAP values during their ICU stay due to attitudes of caregivers to patients of different ages.

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**Life is just a short walk from the cradle to the grave
and it sure behooves us to be kind to one another along the way.**

Alice Childress (1916–1994), American novelist, playwright, and actress

Capsule

mRNA vaccine against malaria tailored for liver-resident memory T cells

Malaria is caused by *Plasmodium* species transmitted by *Anopheles* mosquitoes. Following a mosquito bite, *Plasmodium* sporozoites migrate from skin to liver, where extensive replication occurs, emerging later as merozoites that can infect red blood cells and cause symptoms of disease. As liver tissue-resident memory T cells (Trm cells) have recently been shown to control liver-stage infections, **Ganley et al.** embarked on a messenger RNA (mRNA)-based vaccine strategy to induce liver Trm cells to prevent malaria. Although a standard mRNA vaccine was unable to generate liver Trm or protect against challenge

with *Plasmodium berghei* sporozoites in mice, addition of an agonist that recruits T cell help from type I natural killer T cells under mRNA-vaccination conditions resulted in significant generation of liver Trm cells and effective protection. Moreover, whereas previous exposure of mice to blood-stage infection impaired traditional vaccines based on attenuated sporozoites, mRNA vaccination was unaffected, underlining the potential for such a rational mRNA-based strategy in malaria-endemic regions.

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Capsule

The burden and dynamics of hospital-acquired SARS-CoV-2 in England

Using data from acute hospitals in England, **Cooper** and colleagues quantified within-hospital SARS-CoV-2 transmission, evaluated likely pathways of spread and factors associated with heightened transmission risk, and explored the wider dynamical consequences. The authors estimated that from June 2020 until March 2021 between 95,000 and 167,000 inpatients acquired SARS-CoV-2 in hospitals (1% to 2% of all hospital admissions in this period). Analysis of time series data provided evidence that patients who themselves acquired SARS-CoV-2 infection in hospital were the main sources of transmission to other patients. Increased transmission to inpatients was

associated with hospitals having fewer single rooms and lower heated volume per bed. Moreover, they showed that reducing hospital transmission could have substantially enhanced the efficiency of punctuated lockdown measures in suppressing community transmission. These findings revealed the previously unrecognized scale of hospital transmission, had direct implications for targeting of hospital control measures, and highlighted the need to design hospitals better equipped to limit the transmission of future high-consequence pathogens.

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