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## Personalized Blood Pressure Targets in Shock: What If Your Normal Blood Pressure Is “Low”?

The cornerstone of resuscitation of septic shock is volume infusion followed by vasopressors if fluid volume does not restore adequate perfusion (1). Surviving Sepsis Campaign guidelines recommend an initial target mean arterial pressure (MAP) of 65 mm Hg (1), subsequently adjusted. The target MAP and the relative proportions of use of volume versus vasopressors varies widely (2, 3). But there remains the overarching large question of how to *personalize* a MAP target in shock (Figure 1).

In patients with hypertension, targeting a higher MAP (80–85 mm Hg) was associated with enhanced renal function but not with lower mortality (4). There are no large studies regarding resuscitation of patients with naturally low blood pressure. Do we resuscitate to 65 mm Hg? Would we use excessive vasopressors and increase organ dysfunction and mortality?

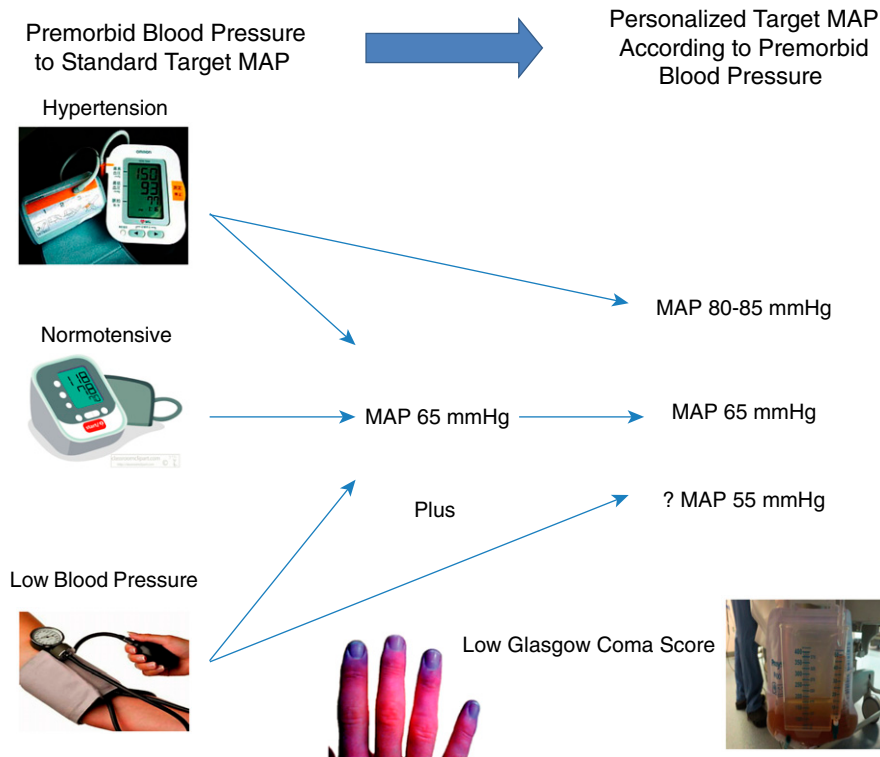
In this issue of the *Journal*, Gershengorn and colleagues (pp. 91–99) determined an inverse relationship between premorbid systolic arterial pressure (SAP) with dose and duration of vasopressors in shock in a single healthcare system cohort

( $n = 4,689$ , from 2012 to 2018) (5). Patients were classified as having low blood pressure (SAP < 100 mm Hg), normal blood pressure (SAP 100–139 mm Hg), or high blood pressure (SAP > 140 mm Hg) before shock. The actual MAP during vasopressor infusion was lower in the group with low SAP than in the groups with normal and high SAP (Table 1). We do not know the MAP targets of these groups. Patients with low SAP were treated for longer with higher doses of norepinephrine and had greater ICU length of stay (LOS) and higher mortality. There was no association of premorbid blood pressure and duration of vasopressors with renal replacement therapy (RRT); one might have expected greater duration of RRT if renal function had worsened because of overuse of vasopressors.

The results were robust and consistent across subgroups. These authors tested a very relevant clinical question and used strong analytic methods, and the study’s implications are important. The study was of a large, single healthcare system cohort, limiting the interpretation of generalizability and causality. It would have been insightful to examine cardiovascular outcomes such as arrhythmias (especially atrial fibrillation), stroke (new-onset atrial fibrillation was associated with the higher MAP target group in Asfar and colleagues [6], and new-onset atrial fibrillation is associated with stroke in septic shock [7]), and acute myocardial infarction. These data would further strengthen the argument that the higher dose and

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**Figure 1.** At present, the target resuscitation mean arterial pressure (MAP) is 65 mm Hg, despite patients having premorbid blood pressures ranging from hypertension to normal-to-low blood pressure. The goal now is to *personalize* the initial MAP target according to premorbid blood pressure, aiming for 80–85 mm Hg in patients with previous hypertension; 65 mm Hg in patients with previous normotension; and a lower target, perhaps 55 mm Hg, in patients having a low premorbid blood pressure. In all patients, resuscitation should also aim to achieve normal peripheral perfusion (normal capillary refill time < 2 s, absence of cyanosis), improved mentation (Glasgow Coma Score > 12 mm Hg without sedation), and adequate urine output > 0.5 ml/kg/h.

greater duration of vasopressors are harmful and would suggest additional mechanisms for the association between increased vasopressor duration and increased mortality.

Gershengorn and colleagues (5) found that the maximal dose of norepinephrine varied inversely by SAP group, the low-SAP group having a higher median norepinephrine dose. Thus, patients with low premorbid blood pressure had a higher median norepinephrine dose for longer, presumably yielding a greater area under the curve (my assumption) that would increase the risks of norepinephrine-associated serious adverse events.

The duration of vasopressors is not only determined by the target MAP but is also guided by peripheral perfusion, mentation, urine output, and lactate. This study did not have such data. What is the relationship between the duration of vasopressor support and mentation (e.g., Glasgow Coma Score), normalization of urine output, and lactate? Is there still a relationship of premorbid blood pressure and duration of vasopressor use if one controls for effects of vasopressors on these measures of perfusion?

Why would a premorbid blood pressure be associated with increased ICU LOS and higher mortality? Perhaps the higher dose and duration of vasopressors caused serious adverse effects that increased ICU LOS and mortality. Another explanation is that low premorbid blood pressure itself somehow increased ICU LOS and mortality.

Having a low blood pressure is surprisingly common, occurring in nearly half of a cohort having 24-hour blood pressure monitoring (8); only 5% of Gershengorn's patients had low premorbid SAP, and they were younger and had more heart failure, liver disease, and renal failure. Having a low nonshock blood pressure is also associated with increased risks of depression (9, 10), cognitive dysfunction (11), Alzheimer's disease (12), cardiovascular events (13), and increased mortality in chronic kidney disease (14). Although adverse effects of excessive vasopressors are the more likely the potential cause of the association of low premorbid blood pressure with shock mortality, the above studies suggest low premorbid blood pressure as a causal contribution, a tenable and testable hypothesis.

There was no association of premorbid blood pressure and higher doses and/or greater duration of norepinephrine with organ dysfunction (sepsis organ failure score), an important negative result. However, there are statistical concerns with how to evaluate continuous data (e.g., sepsis organ failure) in the critically ill because of informative censoring due to early deaths. Harhay and colleagues (15) used joint longitudinal modeling in the VASST (Vasopressin and Septic Shock Trial) cohort to illustrate an improved analytic technique for adjusting informative censoring by deaths in critical-care studies (5).

Low premorbid SAP was associated with more use of vasopressors and greater ICU LOS. ICU duration is composed of the

**Table 1.** Median MAPs during Vasopressor Infusion and Literature Target MAPs in the Low-, Normal- and High-SAP Groups

Blood Pressure Group	Median MAPs during Vasopressor Infusion (mm Hg) ( $P < 0.001$ )	Literature-recommended Target MAP (mm Hg)
Low SAP (<100 mm Hg)	63–71	NA
Normal SAP (110–139 mm Hg)	68–72	65 (1)
High SAP ( $\geq 140$ mm Hg)	64–74	80–85 (4)

Definition of abbreviations: MAP = mean arterial pressure; NA = not applicable; SAP = systolic arterial pressure.

duration of vasopressor use plus the remaining duration (for ventilator and/or RRT use and weaning). The medians of vasopressor duration and ICU LOS of the three SAP groups differed directly; ICU LOS minus vasopressor duration was 3.7 days for low SAP, 4.2 days for normal SAP, and 4.8 days for high SAP. Other non-vasopressor-related reasons contributed about 1 day more in the high-SAP group than in low-SAP group.

This study of low pre-morbid blood pressure complements Asfar and colleagues' (4) evaluation of prior hypertension. Asfar and colleagues (4) found that targeting a higher blood pressure in patients with hypertension decreased need for RRT; Gershengorn and colleagues (5) did not find that greater vasopressor duration was associated with more RRT.

In conclusion, patients with low pre-morbid blood pressure receive higher doses of norepinephrine for longer and have longer ICU stays and higher mortality but have neither a greater need for RRT nor more organ dysfunction. A randomized trial is needed to define the optimal target MAP in individuals with low blood pressure. For now, I recommend that clinicians personalize their blood pressure target on the basis of pre-morbid blood pressure (16); if low, consider a lower target MAP than the commonly recommended 65 mm Hg. Conversely, if there is pre-morbid hypertension, then use a higher MAP target (80–85 mm Hg). ■

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