Impact of individualized target mean arterial pressure for septic shock resuscitation on the incidence of acute kidney injury: a retrospective cohort study

Rajat N. Moman1,2, Stuart A. Ostby1,3, Abbasali Akhoundi1,4, Rahul Kashyap1,5 and Kianoush Kashani1,4,6*

Abstract
Background: To examine the relationship between delta mean arterial pressure (ΔMAP; MAP change between pre-admission minus post-resuscitation) and acute kidney injury (AKI) among patients with septic shock. In this retrospective, single-center cohort study of adult patients pre-admission MAP is defined as the median MAP recorded from 365 to 7 days before admission. Post-resuscitation MAP was median MAP during the 7th hour after initiating resuscitation.

Results: In our cohort (N=233; 55% male), the median (interquartile range [IQR]) age was 71 (58–81) years and the median (IQR) acute physiology, age, chronic health evaluation (APACHE) III score was 81 (66–97). Although those in the lowest ΔMAP quartile (−24.5 to 3.9 mmHg) had no demographic differences compared with the rest of the cohort, the odds ratio for AKI was 0.26 (95% CI 0.11–0.57) after adjustment for other known AKI risk factors. Among patients with a history of hypertension, the lowest quartile had an odds ratio for AKI of 0.12 (95% CI 0.04–0.37) after adjusting for risk factors for AKI in this cohort.

Conclusions: The incidence of AKI was lowest among those whose post-resuscitation MAP was closest to or higher than their pre-admission MAP. Further study regarding the effect of targeting the pre-admission MAP for post-resuscitation on the incidence of AKI is warranted.

Keywords: Blood pressure target, Early goal-directed therapy, Fluid resuscitation, Hypertension, Severe sepsis

Background
Acute kidney injury (AKI) is a devastating sequela of critical illnesses [1]. Sepsis is a common pathway to AKI. The Surviving Sepsis Campaign Guidelines [2] recommend a mean arterial pressure (MAP) of 65 mmHg or higher as the goal of resuscitation (Grade 1C recommendation) to minimize the risk of death and end-organ failure. However, this recommendation is not supported by substantial evidence, and whether a goal MAP of 65 mmHg is adequate for all patients remains controversial [3, 4].

Sepsis-associated AKI (SA-AKI) is a common and clinically significant condition. Sepsis is associated with AKI in 42–48% of cases in the intensive care unit (ICU) [1, 5, 6]. Compared with other non-sepsis causes of AKI, SA-AKI is associated with higher ICU and in-hospital mortality rates [5]. Patients with severe sepsis and AKI had higher 90-day mortality rates than those with severe sepsis alone [7]. Patients with even a modest increase in serum creatinine (sCR) have markedly higher health care costs, hospital length of stay, and risk of death [8]. A critical need exists to determine optimal resuscitation strategies that prevent SA-AKI or its progression in patients with septic shock.

In a recent investigation, Asfar et al. [4] randomized patients with septic shock to high (80–85 mmHg) or low (65–70 mmHg) MAP targets and observed no difference...
in 28-day mortality rates between groups. A subset of 167 patients with chronic arterial hypertension had a lower incidence of sCR doubling and required less renal replacement therapy when randomized to the high MAP target group. However, the higher MAP target group also had a higher incidence of atrial fibrillation. Chronic arterial hypertension results in a rightward shift of the autoregulatory pressure-organ perfusion curve [9, 10]. Therefore, an increased MAP target may improve organ perfusion for patients with higher pre-admission MAP [3, 4, 11]. Given the results of previous studies, the pre-admission blood pressure of patients in septic shock may need to be considered when defining an appropriate MAP goal for optimal resuscitation [3, 4, 11–13].

Appropriate MAP targets for resuscitation are controversial, and previous studies suggest that the pre-admission blood pressure may help determine the optimal resuscitation MAP target. To date, no published studies have assessed whether patients would benefit from a specific post-resuscitation MAP target that is similar to or higher than the pre-admission MAP. We conducted a retrospective cohort study of patients who were treated for severe sepsis and septic shock. We examined the association between the achieved MAP target and the pre-admission MAP, and AKI incidence was the primary outcome.

Methods
Approval of study design
This retrospective cohort study was reviewed and approved by the Mayo Clinic Institutional Review Board (protocol number 14-002109). Informed consent was waived for patients who provided research authorization.

Participants
We conducted a study of adult patients (≥ 18 years old) who received care at a tertiary care academic hospital for severe sepsis or septic shock. Consecutive adult patients admitted to the Medical ICU from January 2007 through January 2009 were included in the study if their records included a history of noninvasive blood pressure monitoring. We excluded patients who developed AKI before sepsis and those with end-stage renal disease or receiving hemodialysis before sepsis. We also excluded patients who never had urine output measured with a Foley catheter, had a ureteral stent, were in the ICU for fewer than 6 h, or did not have sufficient clinical information available. In order to evaluate the impact ΔMAP on the AKI incidence, we excluded patients who met AKI criteria by oliguria during first 6 h of resuscitation.

Data collection
Patient demographics, pre-admission and post-resuscitation MAP, body mass index (BMI), baseline sCR from 6 months to 7 days prior to hospitalization, sCR during hospitalization, use of inotropic and vasoactive agents, fluid balance, preexisting conditions, and urine output were abstracted from the electronic health record. Charlson comorbidity index (CCI) [14], sequential organ failure assessment (SOFA) score [15], and acute physiology, age, chronic health evaluation (APACHE) III [16] scores at 24 h were calculated.

Study definitions
The pre-admission MAP was defined as the median of all MAPs recorded from 365 to 7 days before ICU admission. We chose the median because it was less likely to be skewed by an outlier MAP measurement compared to a mean value. By comparing the median and mean pre-admission MAPs of the cohort, we found the mean pre-admission MAP had a mean of 82.2 mmHg and standard deviation of 10.5 mmHg; the median pre-admission MAP had a mean of 81.5 mmHg and standard deviation of 10.8 mmHg ($R^2$ 0.97, $p < .0001$). Post-resuscitation MAP was defined as the median of all MAPs during the 7th hour after initiation of sepsis resuscitation. This definition of post-resuscitation MAP was chosen because the goal of resuscitation is to have a stable blood pressure at the end of 6 h of treatment. The ΔMAP, as an independent variable, was defined as the pre-admission MAP minus the post-resuscitation MAP. Therefore, if the value of a patient’s post-resuscitation MAP is higher than their pre-admission MAP, the ΔMAP would be negative. Conversely, if the value of their post-resuscitation MAP is lower than their pre-admission MAP, the ΔMAP would be positive. All MAPs before admission were determined from noninvasive blood pressure measures. The primary outcome, AKI, was defined by Kidney Disease Improving Global Outcomes criteria [17]. sCR and urine output (UOP) were used where: stage 1 was defined as sCR 1.5–1.9 times baseline or greater than or equal to 0.3 mg/dl increase, UOP < 0.5 cc/kg/h for 6–12 h; stage 2 defined as sCR 2.0–2.9 times baseline, UOP < 0.5 cc/kg/h for greater than or equal to 12 h; and stage 3 defined as sCR 3.0 times baseline or increase to greater than or equal to 4.0 or initiation of renal replacement therapy, UOP < 0.3 cc/kg/h for greater than or equal to 24 h or anuria for greater than or equal to 12 h.

Statistical analysis
Demographic data are shown as frequency count and percentage for categorical variables and median and interquartile range (IQR) for continuous variables.
Categorical variables were analyzed with the $\chi^2$ test. ΔMAP was examined as a continuous variable and also by quartiles as a categorical variable, with comparisons made between the ΔMAP quartiles. Backward stepwise logistic regression analyses were performed. Odds ratios (ORs) and c-statistics were calculated. All $p$ values < .05 in a 2-sided hypothesis were considered statistically significant. Statistical analyses were conducted with JMP software (version 10.0.0; SAS Institute Inc).

Results
We identified 651 patients with severe sepsis or septic shock during the study period. After exclusions, 233 patients were included in the final analysis (Fig. 1); the median (IQR) age was 71 (58–81) years, 55% of patients were male, and the median (IQR) APACHE III score was 81 (66–97). One hundred sixty patients (69%) had AKI developed during treatment for severe sepsis or septic shock. Table 1 shows patient characteristics, stratified by presence or absence of AKI.

Regression analysis of ΔMAP as a continuous variable was not significantly associated with the rate of AKI (OR 0.99 [95% CI 0.97–1.01]; $p = .31$). The relationship of ΔMAP and AKI did not become significant with the addition of fluid balance to the model. Regression analysis of post-resuscitation MAP ≥ 65 mmHg was not significantly associated with AKI (OR 0.9 [95% CI 0.27–3.74]). When patients were categorized into quartiles on the basis of ΔMAP values (first quartile, −24.5 to 3.9 mmHg; second quartile, 4.0–12.4 mmHg; third quartile, 12.5–19.9 mmHg; fourth quartile, 20.0–43.8 mmHg), in terms of age, sex, BMI, history of hypertension, CCI, APACHE III score, SOFA score, and fluid balance, patients in quartile 1 were similar to patients in quartiles 2 through 4. Patients in the first quarter had a lower percentage and odds of AKI compared with the other three quartiles ([56.9% vs. 72.6%, respectively; $p = .03$] and [OR 0.50, 95% CI 0.27–0.93], respectively) (Additional file 1: Fig. S1 and Additional file 2: Fig. S2). Patients in the first quartile had a lower pre- ($p < .01$) and higher post-resuscitation MAP ($p < .01$) (Table 2). Rates of AKI for patients in second, third and fourth quartiles ($p = .11$, $p = .51$, $p = .87$, respectively) were not significantly different when compared with the rest of the cohort. In addition, following adjusting for history of hypertension, being within the

Fig. 1 Flow diagram. The chart shows patient inclusion and exclusion in the study. AKI indicates acute kidney injury; EGDT, early goal-directed therapy; ESRD, end-stage renal disease; MAP, mean arterial pressure; ΔMAP, pre-admission MAP minus the post-resuscitation
Table 1  Patient characteristics, stratified by acute kidney injury status (N = 233)

| Patient characteristics | No AKI (n = 73) | AKI (n = 160) | p value |
|-------------------------|----------------|--------------|---------|
| Age, median (IQR), year | 66.8 (56.0–80.8) | 72.8 (59.7–81.6) | .21     |
| Body mass index, median (IQR), kg/m² | 25.2 (21.8–28.6) | 27.9 (23.2–33.1) | .01     |
| Male sex, No. (%) | 45 (61.6) | 83 (51.9) | .20     |
| Pre-admission MAP, median (IQR), mmHg<sup>a</sup> | 83.8 (76.0–91.5) | 78.5 (73.4–87.6) | .05     |
| MAP at first hour of admission, median (IQR), mmHg | 67.5 (59.0–78.0) | 65.0 (57.0–73.3) | .1      |
| MAP at first hour of resuscitation, median (IQR), mmHg | 62.3 (57.0–73.3) | 63.0 (55.8–70.9) | .2      |
| Post-resuscitation MAP, median (IQR), mmHg<sup>b</sup> | 71.0 (66.0–79.0) | 66.0 (61.0–73.0) | .01     |
| ΔMAP from Baseline to 7th hour of resuscitation, median (IQR), mmHg<sup>c</sup> | 11.0 (0.5–20.3) | 12.4 (5.7–19.8) | .31     |
| Charlson comorbidity index, median (IQR) | 6 (4–8.5) | 7 (5–11) | .02     |
| APACHE III score, 24 h, median (IQR) | 67 (55.5–79) | 88 (72–103) | .01     |
| SOFA score, day 1, median (IQR) | 5 (3–7) | 7 (5–10.8) | .01     |
| Culture positive septic shock (%) | 31 (42) | 85 (53) | .2      |
| Positive culture source | .7 | | |
| Blood (%) | 7 (10) | 20 (13) | | |
| Urine (%) | 5 (7) | 19 (12) | | |
| Respiratory (%) | 16 (22) | 33 (20) | | |
| Wound (%) | 1 (1) | 6 (4) | | |
| Other (%) | 2 (2) | 7 (4) | | |
| Culture negative septic shock (%) | 42 (58) | 75 (47) | .2      |
| Preexisting condition, No. (%) | | | |
| Hypertension | 38 (52.1) | 115 (71.9) | .01     |
| Myocardial infarction | 10 (13.7) | 39 (24.4) | .08     |
| Congestive heart failure | 8 (11.0) | 37 (23.1) | .03     |
| Peripheral vascular disease | 3 (4.1) | 25 (15.6) | .02     |
| Dementia | 5 (6.8) | 7 (4.4) | .52     |
| Cerebrovascular accident | 6 (8.2) | 34 (21.3) | .01     |
| Chronic pulmonary disease | 16 (21.9) | 54 (33.3) | .09     |
| Rheumatic heart disease | 8 (11.0) | 15 (9.4) | .81     |
| Diabetes mellitus | 15 (20.5) | 61 (38.1) | .01     |
| Peptic ulcer disease | 6 (8.2) | 20 (12.5) | .38     |
| Cirrhosis | 4 (5.5) | 10 (6.3) | > .99   |
| Hemiplegia | 4 (5.5) | 3 (1.9) | .21     |
| Kidney disease | 10 (13.7) | 45 (28.1) | .02     |
| Brittle diabetes mellitus | 4 (5.5) | 26 (16.3) | .02     |
| Cancer | 28 (38.4) | 49 (30.6) | .29     |
| Leukemia | 1 (1.4) | 9 (5.6) | .18     |
| Lymphoma | 2 (2.7) | 8 (5.0) | .73     |
| Moderate or severe liver disease | 3 (4.1) | 5 (3.1) | .71     |
| Metastatic cancer | 7 (9.6) | 14 (8.8) | .81     |
| Any inotropic agent, No. (%) | 4 (5.5) | 28 (17.5) | .01     |
| Any vasoactive agent, No. (%) | 32 (43.8) | 108 (67.5) | .01     |
| Fluid balance, median (IQR), mL | 4945 (2019–8282) | 6948 (3658–10,810) | .01     |

**APACHE** acute physiology, age, chronic health evaluation, **MAP** mean arterial pressure, **SOFA** sequential organ failure assessment

<sup>a</sup> From noninvasive blood pressure monitoring

<sup>b</sup> Seventh hour of early goal-directed therapy

<sup>c</sup> Defined as pre-admission minus post-resuscitation MAP
Table 2: Comparison of patients in quartile 1 versus quartiles 2–4 of delta mean arterial pressure (N = 233)

| Characteristic                              | Quartile 1 (n = 58)     | Quartiles 2–4 (n = 175) | p value |
|---------------------------------------------|-------------------------|-------------------------|---------|
| Age, median (IQR), year                     | 66.3 (55.7–79.9)        | 72.1 (59.4–81.7)        | .60     |
| Body mass index, median (IQR), kg/m²        | 27.8 (23.7–32.8)        | 26.8 (22.2–31.6)        | .23     |
| Male sex, No. (%)                           | 32 (55.2)               | 96 (54.9)               | > .99   |
| Pre-admission MAP, median (IQR), mmHg⁺       | 73.9 (67.8–81.9)        | 82.0 (76.3–91.0)        | .01     |
| Post-resuscitation MAP, median (IQR), mmHgᵇ  | 79.0 (70.5–87.1)        | 66.0 (61.0–71.0)        | .01     |
| Acute kidney injury, No. (%)                | 33 (56.9)               | 127 (72.6)              | .03     |
| Stage 1                                     | 13 (17.8)               | 60 (82.2)               |         |
| Stage 2                                     | 14 (26.0)               | 40 (74.1)               |         |
| Stage 3                                     | 6 (18.2)                | 27 (81.8)               |         |
| Charlson comorbidity index, median (IQR)    | 7 (4.8–10.3)            | 7 (5.0–10.0)            | .55     |
| APACHE III score, 24 h, median (IQR)        | 78 (64.8–97.3)          | 82 (66–97)              | .66     |
| SOFA score, day 1, median (IQR)             | 6 (4–9)                 | 7 (4–10)                | .76     |
| Culture positive septic shock (%)           | 29 (50)                 | 87 (50)                 | .96     |
| Positive culture source                     |                         |                         | .5      |
| Blood (%)                                   | 5 (9)                   | 22 (13)                 |         |
| Urine (%)                                   | 5 (9)                   | 19 (11)                 |         |
| Respiratory (%)                             | 16 (28)                 | 33 (19)                 |         |
| Wound (%)                                   | 2 (3)                   | 5 (3)                   |         |
| Other (%)                                   | 1 (1)                   | 8 (4)                   |         |
| Culture negative septic shock (%)           | 29 (50)                 | 88 (50)                 | .96     |
| Preexisting condition, No. (%)              |                         |                         |         |
| Hypertension                                | 36 (62.1)               | 117 (66.9)              | .53     |
| Myocardial infarction                       | 11 (19.0)               | 38 (21.7)               | .71     |
| Congestive heart failure                    | 16 (27.6)               | 29 (16.6)               | .08     |
| Peripheral vascular disease                 | 5 (8.6)                 | 23 (13.1)               | .49     |
| Dementia                                    | 0 (0)                   | 12 (6.9)                | .04     |
| Cerebrovascular accident                    | 9 (15.5)                | 31 (17.7)               | .84     |
| Chronic pulmonary disease                   | 16 (27.6)               | 54 (30.9)               | .74     |
| Rheumatic heart disease                     | 7 (12.1)                | 16 (9.1)                | .61     |
| Diabetes mellitus                           | 22 (37.9)               | 54 (30.9)               | .34     |
| Peptic ulcer disease                        | 7 (12.1)                | 19 (10.9)               | .81     |
| Cirrhosis                                   | 2 (3.4)                 | 12 (6.9)                | .53     |
| Hemiplegia                                  | 5 (8.6)                 | 2 (1.1)                 | .01     |
| Kidney disease                              | 14 (24.1)               | 41 (23.4)               | > .99   |
| Brittle diabetes mellitus                   | 7 (12.1)                | 23 (13.1)               | > .99   |
| Cancer                                      | 19 (32.8)               | 58 (33.1)               | > .99   |
| Leukemia                                    | 3 (5.2)                 | 7 (4.0)                 | .71     |
| Lymphoma                                    | 7 (12.1)                | 3 (1.7)                 | .01     |
| Moderate or severe liver disease            | 2 (3.4)                 | 6 (3.4)                 | > .99   |
| Metastatic cancer                           | 6 (10.3)                | 15 (8.6)                | .79     |
| Any inotropic agent, No. (%)                | 5 (8.6)                 | 27 (15.4)               | .27     |
| Any vasoactive agent, No. (%)               | 35 (60.3)               | 105 (60.0)              | > .99   |
| Fluid balance, median (IQR), mL             | 6405 (2141–9723)        | 6102 (3210–9742)        | .31     |

APACHE acute physiology, age, chronic health evaluation, MAP mean arterial pressure, SOFA Sequential organ failure assessment

⁺ From noninvasive blood pressure monitoring

ᵇ Seventh hour of early goal-directed therapy
first quartile was significantly associated with a lower rate of AKI \(^{(p = 0.04)}\).

We used backward stepwise regression analysis of all relevant variables with 25\% probability to enter and 10\% probability to leave the model. The final model included being in the first quartile, CCI, APACHE III score, SOFA score, comorbidities, vasoactive agents, inotropic agents, pre-admission MAP, and post-resuscitation MAP. BMI, pre-admission MAP, inclusion in quartiles 2 through 4, and APACHE III scores were significant predictors of AKI, and these were entered into a nominal logistic regression analysis (Table 3). Compared with patients in quartiles 2 through 4 combined, those in quartile 1 had decreased odds of AKI (OR 0.26 [95\% CI 0.11–0.57]) in a multivariate analysis controlling for all significant predictors. The c-statistic of this model was 0.80 for AKI, and Hosmer–Lemeshow test for goodness of fit showed excellent calibration (Chi-squared 3.6 and \(p\) value 0.9). When this same nominal logistic regression analysis was run with the addition of the history of hypertension variable, all four variables listed in Table 3 remained significant, and history of hypertension was not a significant predictor of AKI \((p = 0.28)\).

**Hypertension subgroup analysis**

One hundred fifty-three patients (66.0\%) had a history of high blood pressure. When comparing those who did and did not have a history of hypertension, age \((p = 0.01)\), BMI \((p = 0.01)\), incidence of AKI (75.2\% and 56.3\%, respectively; \(p = 0.01\)), CCI \((p = 0.01)\), and APACHE III score \((p = 0.01)\) were significantly different (Table 4).

In the subgroup analysis of patients with a history of hypertension, the \(\Delta MAP\) values that fell into each quartile did not change significantly from the entire cohort (as described above). The \(\Delta MAP\) in the first quartile ranged from −24.5 to 4 mmHg; quartile 2, from 4.1 to 12.7 mmHg; quartile 3, from 13 to 21 mmHg; and quartile 4, from 21.1 to 43.8 mmHg. Patients in the first quartile had similar risk factors for AKI as those in quartiles 2 through 4. AKI was less common for patients in the first quartile than the other 3 quartiles combined (62\% vs. 80\%, respectively; \(p = 0.03\)) (Table 5). Similarly, the odds of AKI was lowest for those in quartile 1 vs. quartiles 2 through 4 (OR 0.40 [95\% CI 0.18–0.90]).

In the subgroup analysis of patients with a history of hypertension, backward stepwise regression analysis with all variables entered, as described above, showed that BMI, pre-admission MAP, APACHE III score, the presence of brittle diabetes mellitus, inclusion in quartiles 2 through 4, and norepinephrine use were statistically significant predictors of AKI (Table 6). Compared with the patients in quartiles 2 through 4 combined, patients in quartile 1 had lower odds of AKI (OR 0.12 [95\% CI 0.04–0.37]) in multivariate analysis after controlling for significant predictors (Table 6). The c-statistic for this model of AKI was 0.87.

---

**Table 3 Regression model for prediction of acute kidney injury for all patients**

| Characteristic                      | Odds ratio | 95\% confidence interval | \(p\) value |
|-------------------------------------|------------|--------------------------|-------------|
| Being in the first quartile\(^a\)   | 0.26       | 0.11–0.57                | 0.01        |
| Body mass index                     | 0.92       | 0.87–0.96                | 0.01        |
| APACHE III score, 24 h              | 0.96       | 0.94–0.97                | 0.01        |
| Pre-admission MAP                   | 1.04       | 1.01–1.08                | 0.01        |

\(^a\) Patients had \(\Delta MAP\) values in the lowest quartile

**Table 4 Patient characteristics, stratified by history of hypertension \((N = 233)\)**

| Characteristic                      | No hypertension \((n = 80)\) | History of hypertension \((n = 153)\) | \(p\) value |
|-------------------------------------|-----------------------------|---------------------------------|-------------|
| Age, median (IQR), year             | 62.5 (50.6–78.0)            | 74.5 (63.4–82.6)                | 0.01        |
| Body mass index, median (IQR), kg/m\(^2\) | 25.0 (21.2–28.7)          | 28.0 (23.3–33.6)                | 0.01        |
| Male sex, No. (%)                   | 45 (56.3)                   | 83 (54.2)                       | 0.78        |
| Pre-admission MAP, median (IQR), mmHg\(^a\) | 77.3 (72.1–87.3)           | 81.3 (75.0–90.5)                | 0.13        |
| Post-resuscitation MAP, median (IQR), mmHg\(^b\) | 68.0 (62.2–76.5)           | 68.0 (62.0–74.4)                | 0.98        |
| \(\Delta MAP\), median (IQR), mmHg\(^c\) | 11.3 (3.0–17.9)            | 12.7 (4.0–21.0)                 | 0.18        |
| Acute kidney injury, No. (%)        | 45 (56.3)                   | 115 (75.2)                      | 0.01        |
| Stage 1                             | 25 (34.3)                   | 48 (65.8)                       |             |
| Stage 2                             | 12 (22.2)                   | 42 (77.8)                       |             |
| Stage 3                             | 8 (24.2)                    | 25 (75.8)                       |             |
| Charlson comorbidity index, median (IQR) | 5 (3–7)                   | 8 (6–11)                        | 0.01        |
| APACHE III score, 24 h, median (IQR) | 71 (61.3–88.8)             | 86 (69.5–103)                   | 0.01        |
| SOFA score, day 1, median (IQR)     | 6 (4–9)                     | 7 (4–10)                        | 0.40        |
| Any inotropic agent, No. (%)        | 8 (10.0)                    | 24 (15.7)                       | 0.32        |
| Any vasoactive agent, No. (%)       | 46 (57.5)                   | 94 (61.4)                       | 0.58        |
| Fluid balance, median (IQR), mL     | 6419 (3334–8953)            | 6073 (2398–10,225)              | 0.43        |

\(^a\) From noninvasive blood pressure monitoring

\(^b\) Seventh hour of early goal-directed therapy

\(^c\) Defined as pre-admission minus post-resuscitation MAP

**APACHE** acute physiology, age, chronic health evaluation, MAP mean arterial pressure, SOFA Sequential organ failure assessment

---
In this report, we identified a hemodynamic variable that was associated with AKI among patients with septic shock. When stratifying patients by $\Delta$MAP, those in the first quartile of MAP change ($-24.5$ to $3.9$ mmHg, i.e., patients with post-resuscitation MAP higher than or equal to their pre-admission MAP) had a significantly lower incidence of AKI. Being in the second to fourth delta-MAP quartiles, body mass index, APACHE III score, and pre-admission MAP were independently associated with risk of AKI.

These results suggest that having a $\Delta$MAP value within the first quartile could be a modifiable risk factor that is associated with a lower risk of AKI in patients with severe sepsis and septic shock. Thus, pre-admission MAP values could be used to guide post-resuscitation MAP...
being in the first quartile, 0.12
Body mass index, 0.90
APACHE III score, 24 h, 0.97
Pre-admission MAP, 1.07
Brittle diabetes mellitus, 6.03
Norepinephrine use, 3.72

| Characteristic | Odds ratio | 95% confidence interval | p value |
|---------------|------------|------------------------|---------|
| Being in the first quartile | 0.12 | 0.04–0.37 | .01 |
| Body mass index | 0.90 | 0.84–0.96 | .01 |
| APACHE III score, 24 h | 0.97 | 0.95–0.99 | .01 |
| Pre-admission MAP | 1.07 | 1.01–1.12 | .01 |
| Brittle diabetes mellitus | 6.03 | 1.36–44.19 | .04 |
| Norepinephrine use | 3.72 | 1.42–10.54 | .01 |

APACHE: acute physiology, age, chronic health evaluation, MAP: mean arterial pressure

* Patients had ΔMAP values in the lowest quartile

Table 6: Regression model for prediction of acute kidney injury for all patients with hypertension history

In other words, our report suggests that a post-resuscitation MAP that is no more than 4 mmHg lower than pre-admission MAP may be protective against the development of AKI in this cohort. This guideline could potentially provide a specific, individualized MAP target for each patient with severe sepsis or septic shock. While our results provide a new hypothesis, the lack of a clear dose-response relationship between ΔMAP quartiles 2–4 and AKI could mean another variable plays a role in the development of SA-AKI. In either case, this deserves further attention in terms of prospective study.

The concept of ΔMAP itself is not quite novel. ΔMAP previously was investigated in high-risk patients undergoing cardiopulmonary bypass [18]. The authors reported a higher rate of AKI when MAP was at least 26 mmHg lower than baseline during cardiopulmonary bypass. We note that the ΔMAP targets described in that study specifically pertained to patients undergoing cardiac surgery and is not applicable to SA-AKI.

In a previous study of SA-AKI, Badin et al. [11] found that the time-averaged MAP in the early phase of acute circulatory failure was lower in patients who had septic shock, prior renal function impairment, and AKI. Our results confirm those of Badin et al. and go a step further; the decrement of post-resuscitation MAP relative to pre-admission MAP seems to be associated with the incidence of AKI. Having ΔMAP values in quartile 1 (i.e., patients with post-resuscitation MAP mostly higher than their pre-admission MAP) was significantly associated with a lower incidence of AKI for the total cohort. Additionally, the association of ΔMAP values in quartile 1 was independent of a history of hypertension. Our results further suggest that ΔMAP values may help better define an individualized goal MAP for each patient by taking into consideration pre-admission blood pressures and preexisting conditions such as chronic hypertension. Our results are similar to those of the SEPSISPAM (Sepsis and Mean Arterial Pressure) investigators’ trial [4], which reported an association between patients with a history of hypertension and a need for a higher goal MAP.

In our study, the non-AKI group had a median (IQR) post-resuscitation MAP of 71 (66–79) mmHg, whereas, among the AKI group, it was 66 (61–73) mmHg. These values were consistent with the findings of other reports [11, 12]. The mean post-resuscitation MAP of the group without AKI was lower than that suggested by the FINNAKI (Finnish Acute Kidney Injury) study [13]. Although Asfar et al. [4] proposed a lower MAP to avoid adverse effects of resuscitation, their low-target MAP group had an actual MAP of 75 mmHg, which is similar to our non-AKI group’s post-resuscitation MAP and the findings of other studies [4, 11, 13].

Our study has some limitations, including its retrospective and observational nature and that it was restricted to a single center. We could not control for interventions, including patients’ resuscitation MAP goals. While our investigation focused on the association of ΔMAP with an important renal outcome, effects on other organ systems were not included in this investigation and are unknown. The retrospective collection of noninvasive blood pressure readings from the electronic health record was not ideal since these blood pressures are collected in the hospital setting and may not reflect patients “healthy” blood pressure; we attempted to mitigate this problem by using the median of MAPs to prevent an outlier from skewing the patients’ pre-admission MAP values. As the main focus of this retrospective analysis was generating hypothesis for targeted AKI preventive interventions for future prospective study, we did not report the impact of delta-MAP on other organs including the cardiovascular system. Further, a retrospective collection of noninvasive blood pressure readings may have limited the number of patients in our analysis and may have inadvertently included more patients with preexisting hypertension or other comorbidities associated with regular blood pressure monitoring. We corrected for the higher prevalence of hypertension by including it in our multivariate model and confirming that it does not account for our findings. Indeed, our results were independent of a history of hypertension. Due to these limitations, this study may have limited generalizability. The strengths of this study include the detailed characterization of enrolled patients.

Conclusions

Our study is the first to analyze ΔMAP, defined as pre-admission MAP minus post-resuscitation MAP, as a risk factor for SA-AKI. Patients with ΔMAP values in the lowest quartile (i.e., patients with post-resuscitation MAP mostly higher than their pre-admission MAP) had a significantly lower incidence of AKI independent of
a history of hypertension. Analysis of the subgroup of patients with hypertension showed the same relationship. Our results are hypothesis generating and suggest that, for patients with severe sepsis or septic shock, clinicians may better define an individualized target MAP for the resuscitation phase goals by considering the patient’s pre-admission MAP. We recommend future studies to further explore the usefulness of this hemodynamic target for sepsis resuscitation.

Additional files

Additional file 1: Fig. S1. Quartile of δMAP and Incidence of AKI (p-value = 0.3). Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury.

Additional file 2: Fig. S2. Quartile of δMAP and highest stage of severity of AKI during hospitalization (p-value = 0.3). Abbreviations: MAP, mean arterial pressure; AKI, acute kidney injury.

Abbreviations
AKI: acute kidney injury; APACHE: acute physiology, age, chronic health evaluation; BMI: body mass index; CCI: Charlson comorbidity index; EGDT: early goal-directed therapy; ICU: intensive care unit; IQR: interquartile range; MAP: mean arterial pressure; OR: odds ratio; SA-AKI: sepsis-associated acute kidney injury; SCR: serum creatinine; SOFA: sequential organ failure assessment; UOP: urine output.

Authors’ contributions
RNM helped in study design, data collection, data interpretation, and preparation of the manuscript; SAO and AA contributed to data collection; RK helped in study design, data collection, data interpretation, and preparation of the paper. Dr. Kianoush Kashani had full responsibility of the authors and do not necessarily represent the official views of the NIH.

Author details
1 Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC), Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. 2 Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA. 3 Department of Obstetrics and Gynecology, University of Alabama Birmingham, Birmingham, AL, USA. 4 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA. 5 Anesthesia Clinical Research Unit, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA. 6 Department of Obstetrics and Gynecology, University of Alabama Birmingham, Birmingham, AL, USA. 7 Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA.

Acknowledgements
This work was supported by the National Center for Advancing Translational Sciences (NCATS) [Grant Number UL1 TR000135]. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The sponsor had no role in the development of the research and manuscript.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Limited de-identified dataset is available per request. Please contact the corresponding author for data.

Consent for publication
Authors provide consent for publication of this paper in the Annals of Intensive Care.

Ethics approval and consent to participate
This study was reviewed and approved by Mayo Clinic IRB and informed consent for patients who provided Minnesota Research Authorization was waived due to its minimal risk nature.

Funding
This publication was supported by Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 15 December 2017 Accepted: 3 December 2018
Published online: 10 December 2018

References

1. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Maceo E, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sessler DJ, Sprung CL, Nunnally ME, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. Intensive Care Med. 2016;2017:1–74.
3. Russell JA. Is there a good map for septic shock? N Engl J Med. 2014;370(17):1649–51.
4. Asfar P, Meziani F, Hamel J-F, Grelon F, Megarbane B, Anguel N, Mira J-P, Dequin P-F, Gergaud S, Weiss N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583–93.
5. Bagshaw SM, George C, Bellomo R, Committee ADM. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care (London, England). 2008;12(2):R47.
6. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Maceo E, Glibney N, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol CJASN. 2007;2(3):431–9.
7. Poukkanen M, Vaara ST, Pettila V, Kaukonen KM, Korhonen AM, Hovilehto S, Inkinen O, Laru-Sompa R, et al. Hemodynamic variations in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed by Doppler ultrasonography. Crit Care. 2011;15(3):R135.
8. Lefevre D, Mercier E, Runge I, Garot D, et al. Relation between mean arterial pressure and renal function in the early phase of shock: a prospective, explorative cohort study. Crit Care. 2011;15(3):R135.
9. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365–70.
10. Hill JV, Findon G, Appenhoff R, Endre ZH. Renal autoregulation and passive pressure-flow relationships in diabetes and hypertension. Am J Physiol Renal Physiol. 2010;299(4):F837–44.
11. Iversen BM, Sekse I, Oftedal J. Resetting of renal blood flow autoregulation in spontaneously hypertensive rats. Am J Physiol. 1987;252(3 Pt 2):F480–6.
12. Badin J, Boulian T, Ehrmann S, Skarzynski M, Bretagnol A, Benzekri-Lefevre D, Mercier E, Runge I, Garot D, et al. Relation between mean arterial pressure and renal function in the early phase of shock: a prospective, explorative cohort study. Crit Care. 2011;15(3):R135.
13. Poukkanen M, Wilkman E, Vaara ST, Pettila V, Kaukonen KM, Korhonen AM, Luusaro A, Hovilehto S, Inkinen O, Laru-Sompa R, et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care. 2013;17(6):R295.
14. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–51.

15. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–10.

16. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619–36.

17. Section 2: AKI Definition. Kidney inter, Suppl 2012;2(1):19–36

18. Kanji HD, Schulze CJ, Hervas-Malo M, Wang P, Ross DB, Zibdawi M, Bagshaw SM. Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg. 2010;5:71.