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Standard care *versus* individualized blood pressure targets among critically ill patients with shock: A multicenter feasibility and preliminary efficacy study

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ABSTRACT

Purpose: Emerging evidence suggests that minimizing mean perfusion pressure (MPP) deficit during vasopressor therapy for shock can potentially reduce adverse kidney-related outcomes in ICU. We assessed feasibility and preliminary efficacy of individualizing MPP targets based on patients' own pre-illness basal-MPP among vasopressor-treated patients with shock.
Material and methods: In this prospective before-and-after trial, 31 patients during the 'before'/observational phase and 31 patients during the 'after'/intervention phase were enrolled at two tertiary-level Australian ICUs. Feasibility endpoint was time-weighted average MPP-deficit during vasopressor therapy. Preliminary efficacy outcomes were new significant AKI, major adverse kidney events within 14 days (MAKE-14), and 90-day mortality.
Results: Patients in the after group had lower MPP-deficit (median 18%, [interquartile range [IQR]: 11–23] *vs.* 4%, [IQR: 2–9], $p < 0.001$) and lower incidence of new significant AKI (8/31 [26%] *vs.* 1/31 [3%], $p = 0.01$) than the before group. The between-group differences in MAKE-14 (9/31 [29%] *vs.* 4/31 [13%], $p = 0.12$) and 90-day mortality (6/31 [19%] *vs.* 2/31 [6%], $p = 0.13$) were not statistically significant.
Conclusions: An individualized blood pressure target strategy during vasopressor therapy in ICU was feasible and appeared to be efficacious in this preliminary study. Testing this strategy in a larger randomized controlled trial is warranted.
Study registration: ACTRN12617001459314.

1. Introduction

Shock is a common cause of mortality and morbidity in an intensive care unit (ICU) [1,2]. A majority of patients with shock develop acute kidney injury (AKI) [3-6], which often results in prolonged ICU stay and is associated with worse outcomes [7]. There is a heightened interest in evaluating strategies that can potentially reduce the risk of new AKI or AKI progression among ICU patients with shock.

Current guidelines strongly recommend an initial target mean arterial pressure (MAP) of 65 mmHg over higher MAP targets for critically ill patients with shock [8-11]. However, underlying evidence for these recommendations is mainly based on RCTs [12,13] that did not take patients' pre-illness blood pressure into account while evaluating different MAP targets. This practice, although standard, may lead to some patients having a degree of blood pressure deficit relative to their pre-illness blood pressure (or relative hypotension) and some patients having a degree of blood pressure surplus (or relative hypertension) [14]. Whether avoiding such relative hypotension or hypertension during vasopressor support in ICU can improve clinical outcomes is unknown and has not been investigated in an interventional trial [15].

Recent evidence from a pivotal multicenter prospective study among critically ill patients with shock highlighted an association between new-onset adverse kidney-related outcomes and relative

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hypotension, which was assessed as time-weighted average mean perfusion pressure (MPP) deficit during vasopressor therapy [14]. In this study, ICU patients experienced near-universal relative hypotension, although to a variable degree, despite near-perfect maintenance of target MAP of at least 65 mmHg [16]. This leads to a hypothesis whether an intervention that adjusts MPP targets according to patients' own pre-illness basal MPP may have a potential to improve kidney-related outcomes among ICU patients with shock. An RCT to investigate the value of such individualized blood pressure targets is warranted [14-16]. Before testing this intervention in a large clinical trial setting, it is essential to first demonstrate its feasibility and preliminary efficacy.

2. Materials and methods

2.1. Study design

We conducted a prospective, open label, before-and-after feasibility and preliminary efficacy study at two multidisciplinary tertiary-level Australian ICUs. The 'before' or the observation phase was conducted from August 2017 to December 2017, followed by a phase out period of six weeks, and an 'after' or the intervention phase from January 2018 to January 2020. The main reason for choosing a before-and-after design over a parallel-arm design was to avoid the carry-over effect from the intervention arm to the standard care arm. The study was prospectively registered at the Australian New Zealand clinical trial registry (ACTRN12617001459314). Approval from relevant ethics committees was obtained at each participating site (HNEHREC 17/08/16/4.01 and ETH.1.18.004E). The need for informed consent was waived for patients enrolled during the observation phase, and written informed consent was obtained from patients or their legal surrogates during the intervention phase.

2.2. Patient recruitment

During each study phase, trained research coordinators manually screened adult ICU patients, who were receiving vasopressor or inotrope agent and were within 48 h of ICU admission, to identify potentially eligible patients. The screening process was on convenience basis. Study eligibility criteria (Table E1) were identical to that of our previous prospective observational study [14]. Patients were considered eligible if they were aged 40 years or more, were receiving a vasopressor or an inotrope agent for at least 4 h for a suspected shock state and were receiving respiratory support with either high flow nasal oxygen therapy or positive pressure ventilation. Exclusion criteria were either life expectancy of less than six months or a moribund state, end stage renal disease or renal failure in imminent need of renal replacement therapy, lack of a central venous line, trauma as a primary reason for the current ICU admission, already enrolled in the study, known pregnancy, need for extracorporeal support, active bleeding, unavailability of at least two pre-illness blood pressure readings, or any condition specifically requiring a higher or a lower blood pressure target in the view of a treating clinician [14].

2.3. Data collection

We collected baseline demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) III risk score [17], comorbidities, pre-illness blood pressure readings, pre-illness echocardiography reports based on which central venous pressure (CVP) was estimated, diagnosis at ICU admission, time of enrolment, type of shock, requirement for mechanical ventilation, time when a vasopressor or an inotrope agent was initiated (T0), volume of intravenous fluid administered within the prior 24 h, exposure to nephrotoxic agents within 72 h prior to T0, pre-morbid creatinine level, and the most recent serum lactate and serum creatinine levels obtained at or just prior to T0. Exposure to nephrotoxic agents and packed red blood cell transfusions after T0 were also recorded. CVP measurements were performed during vasopressor therapy (hereto referred as achieved-CVP) for all enrolled patients at regular 4 hourly intervals to derive achieved-MPP [14]. Four-hourly interval data on achieved-MPP, achieved-MAP and norepinephrine-equivalent vasopressor dose [18] were collected for up to five days of vasopressor therapy. Achieved-CVP was measured in reference to the phlebostatic axis according to standard ICU guidelines at each participating site. For all enrolled patients, the pre-illness basal MPP was determined using a preset protocol, as described previously [14,19], and detailed in Table E2.

2.4. Study periods and procedures

During the before period, standard care or the conventional practice related to blood pressure management among enrolled patients was observed. Following the phase-out period to account for educating and preparing the ICU staff, the after or the intervention period began, during which patients' own pre-illness basal MPP was targeted during vasopressor therapy. To achieve the set MPP targets (intervention), MAP targets for patients were derived as the sum of achieved-CVP and basal-MPP. The ceiling for MAP target was 95 mmHg and a range of ± 2 mmHg around the set target was permitted. The ceiling for norepinephrine-equivalent dose to achieve the set MPP targets was 0.75 microgram/kg/min. Study protocol allowed initial MPP targets to be adjusted as deemed fit by the treating clinician according to patients' current clinical state. The dose and choice of vasopressor agents or intravenous fluid administration during the entire study period was at the discretion of the treating clinician. Study intervention was ceased when a patient either stopped receiving respiratory support in ICU or was considered well enough by the treating clinician for invasive hemodynamic monitoring to cease. If a patient was transported out of ICU for procedural intervention, then standard treatment was provided.

2.5. Outcome measures

The key feasibility outcomes were time-weighted average MPP-deficit and percentage time spent with MPP-deficit >20%, both measures of quantifying the degree and duration of relative hypotension, as described previously [14]. The MPP-deficit was defined as the percentage difference between a patient's pre-illness basal-MPP and achieved-MPP whilst on vasopressor support [14,19]. The time-weighted average value was derived as an aggregate area-under-the-curve divided by the cumulative time exposure for each individual patient, where area-under-the-curve was measured as an integrated expression over time using a positive incremental method, without imputation for missing timepoints [14]. Other exposure variables were time-weighted average MAP-deficit and percentage time spent with MAP <65 mmHg.

The primary clinical efficacy outcomes were new significant AKI and major adverse kidney events within 14 days (MAKE-14). New significant AKI was defined as an increase of at least two AKI stages (*i.e.*, peak serum creatinine level ≥ 2 times the baseline creatinine level at T0), as per the Kidney Disease: Improving Global Outcome (KDIGO) criteria for AKI [20], based on the peak incremental change in serum creatinine within 14 days after T0. MAKE-14 was defined as a composite measure of death, new initiation of renal replacement therapy (RRT), or doubling of serum creatinine from the pre-morbid level at day 14 [21,22]. The pre-morbid serum creatinine level was sourced as the last available value from medical records within the one year prior to hospital admission, or if unavailable, then during the hospital stay at least 7 days prior to ICU admission [14]. Where neither of these were available, the pre-morbid serum creatinine was estimated as per the KDIGO guidelines using the Modification of Diet in Renal Disease equation as described previously [20]. Secondary clinical efficacy outcomes were day-14 all-cause mortality, peak percentage increase in serum creatinine, receipt of RRT within 14 days, RRT-free days within 28 days, and day-90 all-cause mortality.

2.6. Statistical analyses

Analyses were performed using a standard statistical software (Stata 14.2, StataCorp). Based on our pilot study [19], a sample size of 60 patients was deemed enough to demonstrate an absolute reduction of at least 50% in the MPP-deficit during the intervention period, compared to the observation period assuming a mean MPP-deficit of 18%, at an alpha level of 0.05 and power of 80%. Continuous normally distributed variables were compared using student *t*-tests and reported as mean (± standard deviation or 95% confidence interval (CI)), whilst non-normally distributed data were compared using Wilcoxon Rank Sum tests and reported as median (interquartile range [IQR]). Between-group comparison of categorical variables was made using Chi-square tests and were reported as numbers (%). As a supplementary analysis, relationships between the MPP-deficit and the key clinical efficacy outcomes were assessed using multivariable logistic regression models adjusted for study site, APACHE III score and the need for mechanical ventilation. Time-to-event data for MAKE-14 and day-90 mortality were displayed as Kaplan-Meier curves and analysed using a log-rank test. A two-sided *p*-value of 0.05 was considered statistically significant. All analyses followed the intention-to-treat principle.

3. Results

During the study period, 410 patients were screened and 62 patients (31 during the before or observation period *vs.* 31 during the after or intervention period) were enrolled (Fig. 1), with a mean study duration of 56 ± 40 h *vs.* 57 ± 33 h respectively. The study achieved its pre-planned sample size with an overall enrolment rate of one patient per site per month. All enrolled patients were followed up until day 90 and data on clinical outcomes were available for all participants.

3.1. Patient characteristics at baseline

Demographic and clinical characteristics at baseline for the two groups are presented in Table 1. There were no significant between-group differences regarding age, gender, APACHE III score, comorbidities, diagnosis organ system, type of shock, serum lactate, serum creatinine, MAP or MPP at T0, norepinephrine-equivalent dose at T0, the time from ICU admission to enrolment, or the time from T0 to enrolment. The amount of intravenous fluid administration and exposure to nephrotoxic agents prior to T0 was similar in-between the two groups. Incidence of mechanical ventilation at T0 was lower among enrolled patients during the after period.

3.2. Process of care

A median of 5 [IQR 4–5] pre-illness blood pressure readings were traced for each enrolled patient during both study periods. The pre-illness basal MAP and the MAP at T0 were similar in between the two groups. Exposure to nephrotoxic agents and blood transfusion after T0 during study period, were also similar across both groups. Achieved-MPP (65 ± 7 *vs.* 73 ± 7, mmHg; $p = 0.0001$) was significantly higher during the intervention period (Table 1). The intervention period had significantly higher norepinephrine-equivalent dose on the first day after enrolment but not on the subsequent days (Fig. E1).

3.3. Feasibility outcomes

As shown in Table 2, compared to the before phase, patients enrolled during the after phase had a significantly lower time-weight average MPP-deficit (18% [11−23] *vs.* 4% [2–9], $p = 0.0001$) and spent less time with >20% MPP-deficit (45% [IQR: 20–69] *vs.* 5% [IQR: 0–15], p = 0.0001). A wide separation was achieved between the two groups in relation to the daily MPP-deficit (Fig. 2A) and the achieved-MAP (Fig. 2B) over the first five days of vasopressor therapy. The Fig. 2B also shows that once the desired MAP was achieved it remained stable over the duration of vasopressor therapy. However, there was no difference in the time spent with <65 mmHg between the two groups (Table 2). Achieved CVP was also similar for both the groups (Fig. E2). Fig. 3 demonstrates the randomness in the relationship between the time-weighted average norepinephrine-equivalent dose and MPP-deficit for both study groups.

3.4. Clinical efficacy outcomes

The primary efficacy outcome of development of new significant AKI within 14 days occurred in 8 of 31 (26%) patients in the before group and 1 or 31 (3%) patients in the after group (Table 2). The peak incremental change in serum creatinine from T0 was significantly lower in

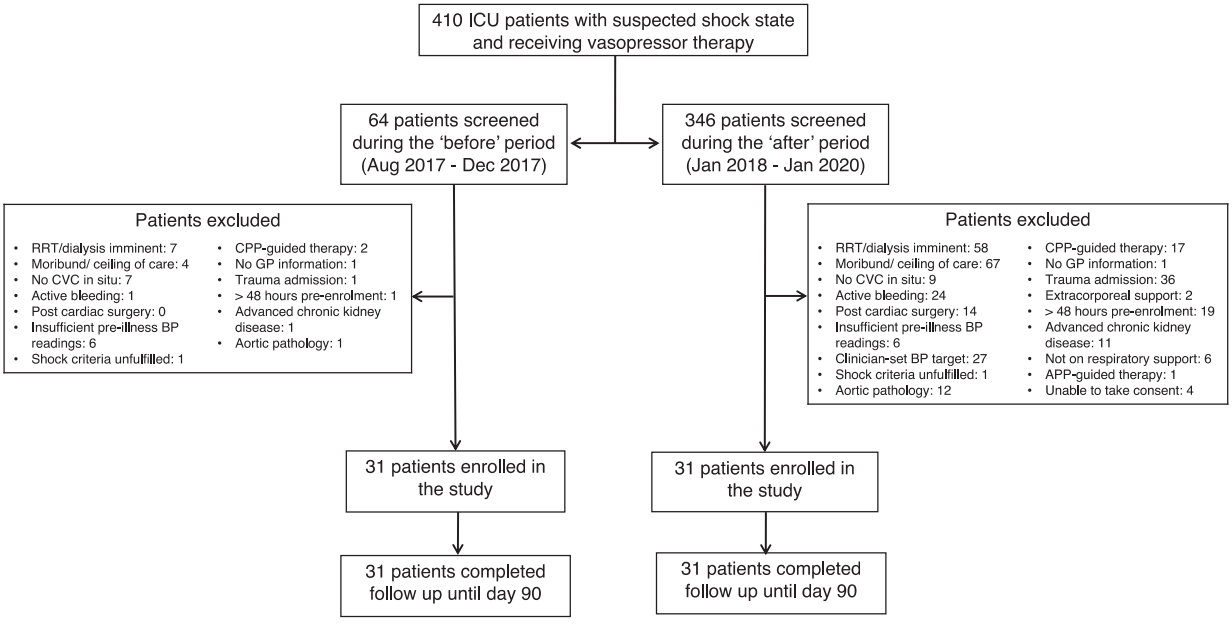

Fig. 1. Patient flow diagram.

Table 1
Baseline characteristics and key process of care variables.

Characteristics	Before phase ($n = 31$)	After phase (n = 31)	*P* value
Age, mean (SD), years	67 (12)	69 (11)	0.51
Males, n (%)	22 (71%)	22 (71%)	1.00
APACHE III score, mean (SD)	80 (22)	72 (23)	0.16
Co-morbidities, n (%)			
Chronic hypertension	17 (55%)	21 (68%)	0.30
Diabetes mellitus	13 (42%)	10 (32%)	0.43
Chronic obstructive pulmonary disease	8 (26%)	7 (23%)	0.77
Ischemic heart disease	8 (26%)	7 (23%)	0.77
Congestive heart failure	3 (10%)	5 (16%)	0.45
Chronic kidney disease	4 (13%)	1 (3%)	0.16
Valvular heart disease	1 (3%)	2 (6%)	0.55
Peripheral vascular disease	1 (3%)	3 (10%)	0.30
History of atrial arrhythmia, n (%)	5 (16%)	9 (29%)	0.22
Diagnosis organ system, n (%)			0.19
Gastrointestinal	8 (26%)	7 (23%)	
Respiratory	7 (23%)	5 (16%)	
Cardiovascular	4 (13%)	6 (19%)	
Sepsis	5 (16%)	12 (39%)	
Neurological	3 (10%)	1 (3%)	
Metabolic	3 (10%)	0 (0%)	
Musculoskeletal/ soft tissue	1 (3%)	0 (0%)	
Type of Shock, n (%)			0.44
Septic	23 (74%)	21 (68%)	
Cardiogenic	3 (10%)	7 (23%)	
Mixed	2 (7%)	2 (7%)	
Other	3 (10%)	1 (3%)	
Period between pre-illness blood pressure (BP) measurements and enrolment, mean (SD), weeks	46 (33)	46 (26)	0.99
Number of pre-illness BP readings[*] per patient, median [IQR]	5 [4–5]	5 [4–5]	0.62
Pre-illness basal Mean Arterial Pressure[*], mean (SD), mmHg	83 (8)	80 (6)	0.07
MAP at T0[§], mean (SD), mmHg	73 (10)	73 (9)	0.86
Serum lactate at or just prior to T0[§], mean (SD), mmol/l	2.6 (2.3)	3.5 (2.4)	0.13
Norepinephrine-equivalent dose at T0[§], mean (SD), microgram/ kg/min	0.15 (0.25)	0.11 (0.12)	0.38
Pre-morbid[χ] serum creatinine, mean (SD), micromole/l	76 (13)	82 (33)	0.39
Serum creatinine at or just prior to T0[§], mean (SD), micromole/l	122 (69)	128 (67)	0.71
Mechanical ventilation at T0[§], n (%)	25 (81%)	15 (48%)	0.01
Intravenous fluid given within 24 h prior to T0, mean (SD), ml	2013 (1708)	2289 (1829)	0.55
Exposure to nephrotoxic agents within 72 h prior to T0[§], n (%)			
ACE inhibitor or Angiotensin receptor blocker	11 (36%)	18 (58%)	0.08
Intravenous contrast	10 (32%)	6 (19%)	0.25
Non-steroidal anti-inflammatory drug	7 (23%)	9 (29%)	0.56
Aminoglycoside	4 (13%)	4 (13%)	1
Vancomycin	2 (6%)	1 (3%)	0.55
Gancyclovir	0 (0%)	1 (3%)	0.31
Number of nephrotoxic agents within 72 h prior to T0[§], median per patient [IQR]	1 [0–2]	1 [0–2]	0.39
Exposure to nephrotoxic agents within 14 days after T0[§], n (%)			
Intravenous contrast	8 (26%)	6 (19%)	0.41
Vancomycin	6 (19%)	4 (13%)	0.66
ACE inhibitor or Angiotensin receptor blocker	8 (26%)	7 (24%)	0.53
Non-steroidal anti-inflammatory drug	6 (19%)	6 (19%)	0.33
Aminoglycoside	3 (10%)	4 (13%)	0.69
Gancyclovir	0 (0%)	1 (3%)	0.31
Calcineurin inhibitor	0 (0%)	2 (6%)	0.15
Number of nephrotoxic agents within 14 days after T0[§], median per patient [IQR]	1 [0–2]	2 [0–4]	0.71
Exposure to blood transfusion within 5 days after T0[§], n (%)	9 (29%)	6 (19%)	0.37
Achieved-MAP[#] during the study period, mean (SD), mmHg	75 (5)	83 (5)	0.0001
Achieved-MPP[#] during the study period, mean (SD), mmHg	65 (7)	73 (7)	0.0001
Time from ICU admission to enrolment, mean (SD), hrs	21 (19)	18 (11)	0.45
Time from T0[§] to enrolment, mean (SD), hrs	16 (13)	18 (10)	0.60
Study duration, mean (SD), hours	56 (40)	57 (33)	0.89

SD: Standard deviation; IQR: Interquartile range; APACHE: Acute Physiology and Chronic Health Evaluation; BP: Blood pressure.

** Basal MAP was estimated following a validated preset protocol as described previously [24].

§ T0- Time-point, when vasopressor or inotrope support was initiated; MAP- Mean Arterial Pressure; MPP- Mean Perfusion Pressure (=MAP−CVP); AKI: Acute Kidney Injury; ACE: Angiotensin converting enzyme.

χ The pre-morbid serum creatinine level was sourced (latest available) from medical records within the last one year prior to hospital admission, or if unavailable, then during the hospital stay but at least one week prior to ICU admission. The pre-morbid serum creatinine was estimated using the Modification of Diet in Renal Disease equation for 14 patients (6 during the before phase *versus* 8 during the after phase), as described previously.

* Data on pre-illness BP were sourced from outpatient letters, correspondence or telephone conversation with general practitioners, or nursing observations recorded on the day of a recent previous hospital discharge,

Achieved-MAP and Achieved-MPP were derived as the time-weighted average of 4-hourly values over the study period.

Table 2
Pre-specified study outcomes.

	Before phase ($n = 31$)	After phase (n = 31)	*P* value
MPP-deficit* (time-weighted average), median [IQR], %	18 [11–23]	4 [2–9]	0.0001
Time spent with >20% MPP-deficit$^{\chi}$, median [IQR], %	45 [20–69]	5 [0–15]	0.0001
MAP-deficit** (time-weighted average), median [IQR], %	10 [7–14]	2 [0–5]	0.0001
Time spent with MAP <65 mmHg$^{\Omega}$, median [IQR], %	3 [0–6]	3 [0–8]	0.95
New significant AKI$^{\Phi}$ within 14 days after T0§, n (%)	8 (26)	1 (3)	0.01
Number of AKI stage*** increase, median [IQR]	0 [0–2]	0 [0–0]	0.03
Major Adverse Kidney Event$^{\delta}$ within 14 days of T0§, n (%)	9 (29)	4 (13)	0.12
Day 14 all-cause mortality, n (%)	4 (13)	2 (6)	0.39
Need for renal replacement therapy within 14 days of T0§, n (%)	5 (16)	1 (3)	0.09
Renal replacement therapy free days at day 28, median [IQR]	28 [20–28]	28 [28–28]	0.03
Peak change in serum creatinine$^{\gamma}$ within 14 days, median [IQR], %	125 [100–174]	96 [73–120]	0.001
New-onset atrial arrhythmia, n (%)	4 (13)	4 (13)	1.00
Day 90 all-cause mortality, n (%)	6 (19)	2 (6)	0.13

IQR: Interquartile range; MAP: Mean Arterial Pressure, mmHg; MPP- Mean Perfusion Pressure, mmHg; AKI: Acute Kidney Injury;
* MPP-deficit = [(basal MPP − achieved MPP)/ basal MPP]*100, using positive incremental area-under-the-curve method.
$^{\chi}$ % Time spent with >20% MPP-deficit = [Σ(time-periods with >20% MPP-deficit) /total time with available MPP data]*100.
** MAP-deficit = [(basal MAP−achieved MAP) /basal MAP]*100, using positive incremental area-under-the-curve.
$^{\Omega}$ % Time spent with MAP <65 mmHg = [Σ(time-periods with MAP <65 mmHg) /total time with available MAP data]*100.
*** The AKI was defined and staged for severity according to the KDIGO criteria, based on peak change in serum creatinine during the first 14 days after T0. Any positive shift or increase of AKI stage within 14 days after T0 was considered as 'new AKI'.
§ T0 was the time-point, when vasopressor support was initiated.
$^{\Phi}$ New significant AKI was defined as a peak shift of at least two AKI stage within 14 days after T0.
$^{\delta}$ Major adverse kidney event (MAKE)-14 was a composite outcome of death, or new renal replacement therapy during the first 14 days after T0, or doubling of serum creatinine from pre-morbid level on day 14 or on day of discharge from ICU, whichever was earlier.
$^{\gamma}$ % Peak change in serum creatinine = [(Peak creatinine value during 14 days after T0 – creatinine level at T0) /creatinine level at T0]*100, among patients who did not receive renal replacement therapy within the first 14 days after T0.

the after group. There were no significant between-group differences in the incidence of MAKE-14, new-onset atrial arrhythmia, and day-14 or day-90 mortality (Table 2).

3.5. Additional analyses

Kaplan-Meier curves for MAKE-14 and day-90 mortality, displayed in Fig. 4, did not show a statistically significant association. Multivariable regression models, adjusted for study site, APACHE III score and the need for mechanical ventilation, demonstrated significant association between the MPP-deficit and the clinical efficacy outcomes of new significant AKI and MAKE-14 (Table E3).

4. Discussion

In this multicenter, prospective, before-and-after study that compared current standard care to an individualized blood pressure target strategy, among vasopressor-treated ICU patients with shock, the intervention was demonstrated to be feasible. This study achieved its pre-planned sample size. Complete follow up data on clinical outcomes up until day 90 were available for all enrolled patients. The intervention

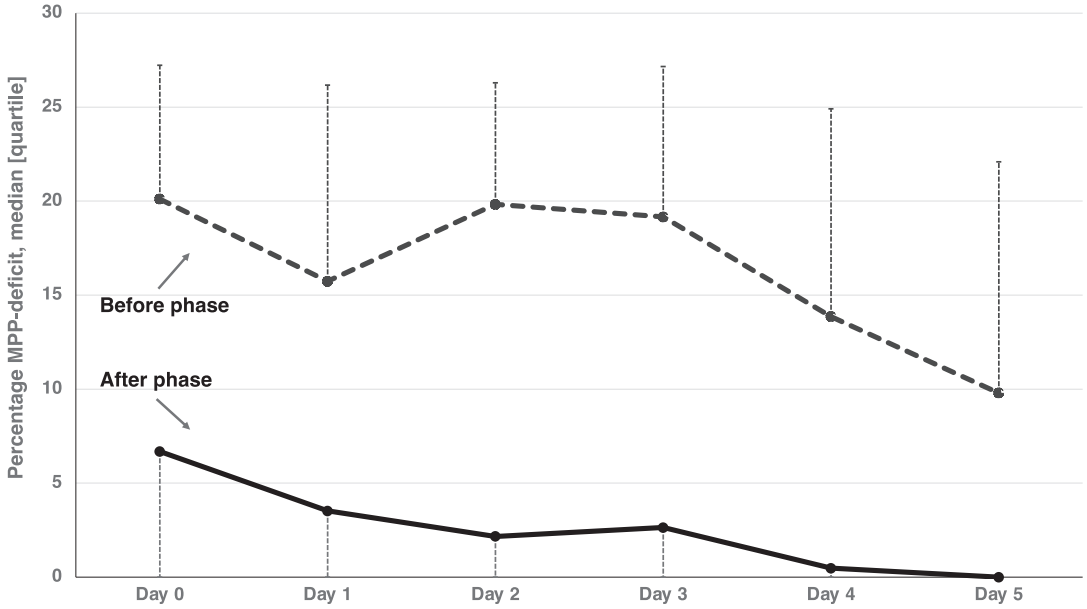

Fig. 2. A: MPP-deficit over time in the two groups. B MAP over time in the two groups.

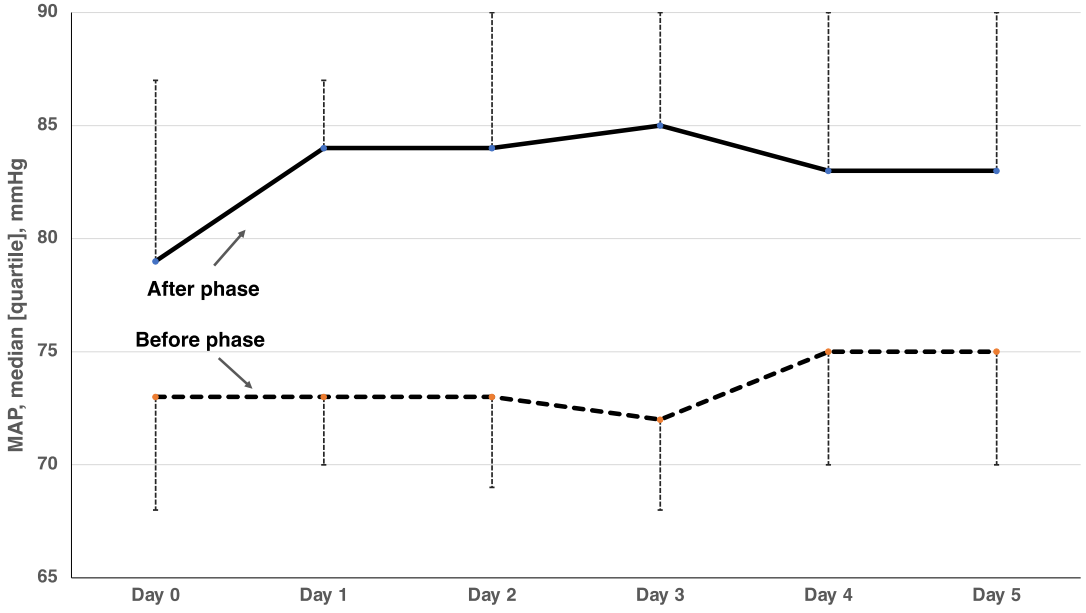

Fig. 2 (*continued*).

was effective in significantly reducing the degree and duration of relative hypotension, with a clear and wide separation in time-weighted average MPP-deficit and percentage time with >20% MPP-deficit during the after phase compared to the before phase. In terms of preliminary clinical efficacy, patients in the intervention group were less likely to develop new significant AKI, although there were no significant between-group differences in MAKE-14 and other secondary endpoints including new atrial arrhythmia and 90-day mortality.

To our knowledge, no prior study has evaluated either feasibility or efficacy of this intervention where blood pressure targets during vasopressor therapy in ICU are based on patients' own pre-illness basal blood pressure. The quantitative measures of relative hypotension and the incidence of new adverse kidney-related outcomes in this study during the before or observation phase were nearly identical to previous observational studies [14,19], indicating a real-world setting. An observation of significantly reduced degree of relative hypotension and numerically lower incidence of adverse kidney-related outcomes during the after or intervention phase is hypothesis-generating. These findings are consistent with a recent RCT, among patients undergoing abdominal surgery, that showed a reduction in the risk of postoperative organ dysfunction with an individualized systolic BP strategy based on preoperative resting BP level, when compared to standard management [23].

We acknowledge several limitations of this study. As a non-randomized, open-label study, there is an inherent potential of

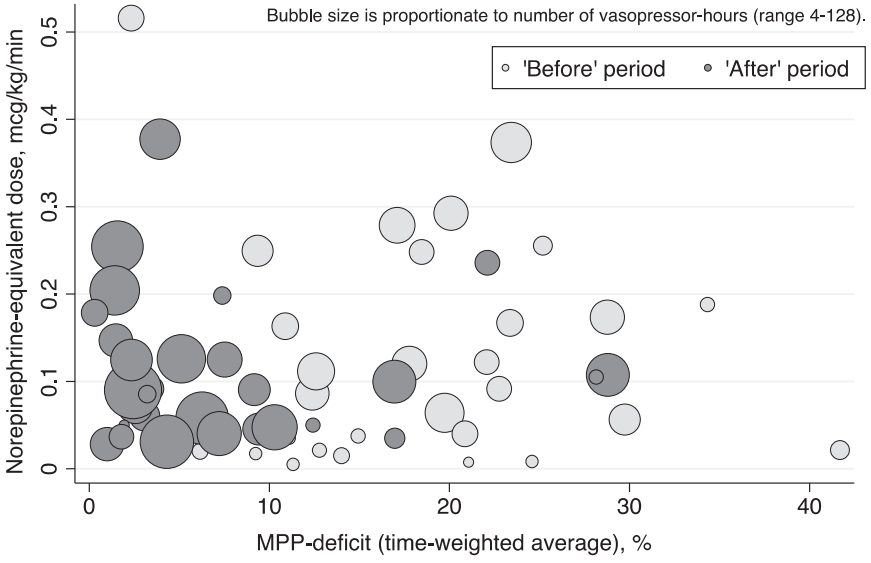

Fig. 3. MPP-deficit and vasopressor dose.

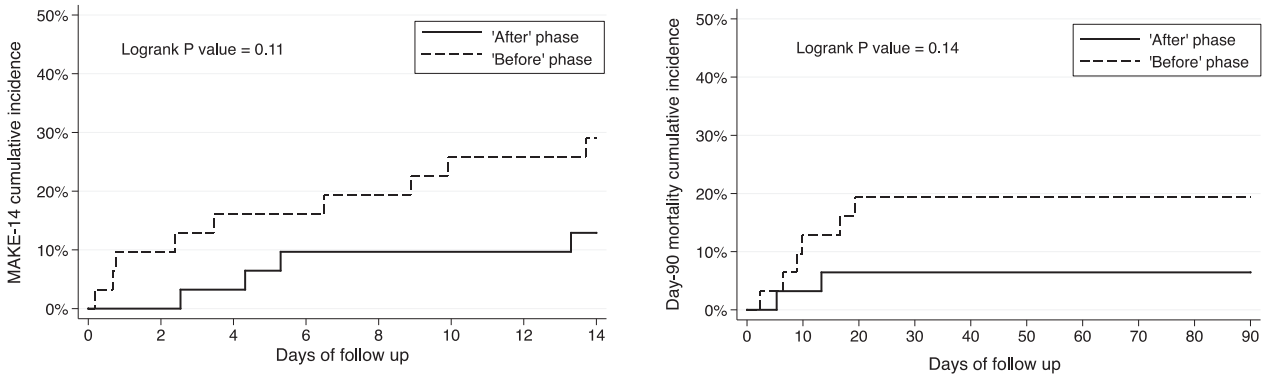

Fig. 4. Kaplan-Meier plots.

unknown or unmeasured confounding factors including investigator bias. Causal relationships cannot be ascertained. The comparatively long duration for recruitment in the intervention phase was more than what we anticipated and although it might be due to the usual ebb and flow in recruitment or changes in local research workforce in participating sites, but it could also reflect the rigor involved in an interventional trial where patients could only be enrolled after obtaining informed consent, possibly resulting in minimal recruitment during afterhours. Limitations related to methodology and choice of clinical and feasibility endpoints are similar to those acknowledged in our previous study [14,24]. Since urine output could be easily influenced by several confounders, we assessed kidney-related adverse outcomes based on the incremental change in serum creatinine. This was done to enhance objectivity in diagnosing new AKI. Clinicians' decisions regarding RRT initiation could also have been subject to individual biases. However, the multicenter design imparts a sense of external validity. Study endpoints and outcomes were objective and prespecified. Protocol adherence was overall quite good, achieving a clear wide separation in relation to the key exposure variable of MPP-deficit in-between groups. All enrolled patients were retained in the study, with a follow up rate of 100% and recording of detailed longitudinal data. The study design was pragmatic and allowed for clinicians' discretion to adjust blood pressure target if required clinically.

The main strength of this study is that it provides preliminary data on feasibility and clinical efficacy for this intervention for the first time. Although this study was by design underpowered to assess clinical efficacy outcomes, but data from this study and the methodology used would be helpful for future RCTs aimed at testing this intervention in a larger setting. Based on the data on MAKE-14 from this study, for a future definitive RCT, a sample size of 400 will be required to demonstrate a relative risk reduction of 40% in the primary endpoint of MAKE-14 between the two parallel arms, assuming a 30% incidence of MAKE-14 in the control arm, at an alpha level of 0.05 and power of 80%.

5. Conclusions

In conclusion, this preliminary study demonstrates that an individualized blood pressure target strategy is feasible and effective in reducing the exposure to relative hypotension during vasopressor support in ICU, when compared to the usual standard care therapy. These data seem compelling enough to justify a large RCT on individualizing blood pressure targets among critically ill patients with shock.

Ethics approval and consent to participate

Approval from relevant ethics committees was obtained at each participating site (HNEHREC 17/08/16/4.01 and ETH.1.18.004E). The need for informed consent was waived for patients enrolled during the observation phase, and written informed consent was obtained from patients or their legal surrogates during the intervention phase.

Consent for publication

All authors consent for the publication of this study report.

Data access and availability of supporting data

Data can be made available to prospective researchers on a reasonable request to the corresponding author after an interval of two years. Supporting data is available on request.

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Authors contribution

RP: Study concept; RP, FC, MN, GB,: Data acquisition; RP, FC, GB: Full access to study data and take responsibility for the integrity of the data; RP, FvH, AQ: Study design; RP, FvH, AQ: obtained funding, and contributed to analysis and interpretation of data; RP: Drafting of the manuscript; RP, FvH, AQ: Critical revision of the manuscript for important intellectual content; All authors: Administrative, technical, or material support.

Declaration of Competing Interest

Authors have no competing interests to declare.

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Appendix A. Appendix

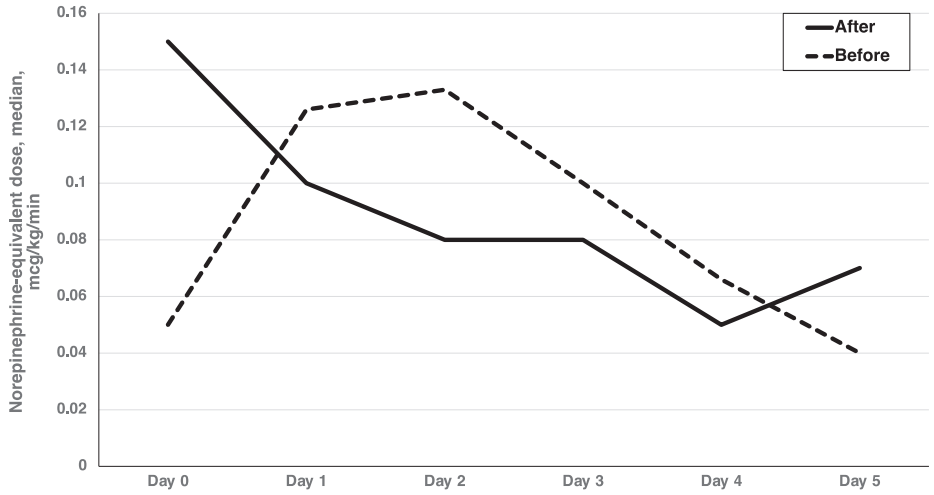

Fig. E1. Vasopressor dose over study period in the two groups.

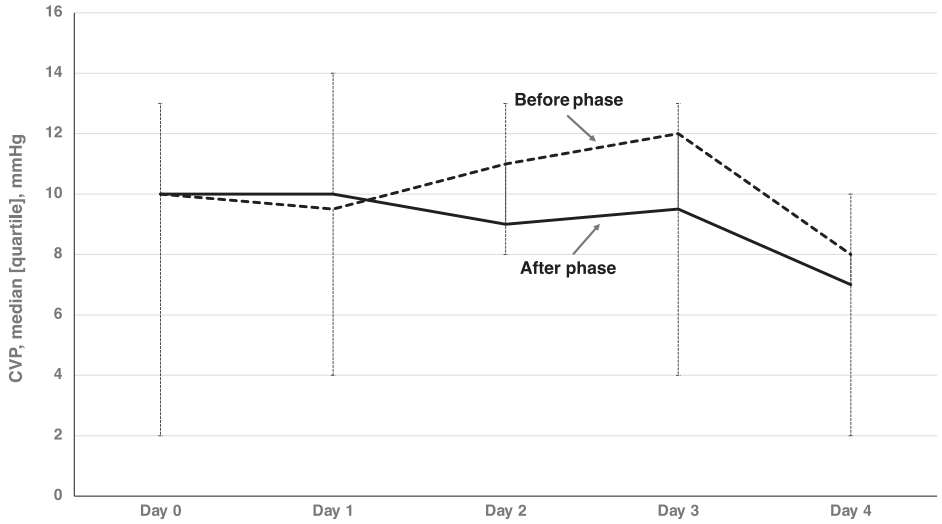

Fig. E2. Achieved CVP over study period in the two groups.

Table E1
Study inclusion and exclusion criteria.

***Inclusion criteria*:**

1. Aged 40 years or above
2. Within 48 h of admission to an intensive care unit
3. Either receiving or in imminent need of positive pressure ventilation (includes invasive or non-invasive ventilation or the use of high-flow nasal oxygen therapy)
4. Shock, which for the purpose of this study was defined as clinician-initiated vasopressor therapy for at least 4 h, supported by at least one of the following parameters:
   a. Lactate ≥2 mmol/l or base deficit ≥3 mmol/l,
   b. Central venous oxygen saturation ($ScvO_2$) ≤60%
   c. Urine output <0.5 ml/kg/h or < 40 ml/h for 2 h or acute elevation in serum creatinine level by >44 μmol/l
5. Patient has a central venous catheter (CVC) *in situ* or placement of a CVC is imminent as part of routine ICU management.

***Exclusion criteria*:**

1. Patients who are moribund, or deemed to have life expectancy of less than 6 months
2. Patients with renal failure requiring RRT, or in imminent need of RRT within the next 12 h in the opinion of treating clinician or increase in serum creatinine to 350 μmol/l or higher
3. End stage renal disease
4. Trauma is the main reason for the current ICU admission
5. Patients on extracorporeal support (ECMO, IABP, VAD).
6. Patient has already been included in the study.
7. Pregnancy, if known
8. Active bleeding (clinical suspicion or requiring >2 packed red blood cells within the last 24 h)
9. Potential contraindications to either higher or lower BP targets (including but not limited to):
   a. Cerebral perfusion pressure guided therapy *e.g.* intracranial hemorrhage or subarachnoid hemorrhage or traumatic brain injury
   b. Abdominal perfusion pressure guided therapy
   c. Aortic injury (*e.g.* dissection or post-operative)
   d. Post cardiac surgery
   e. Any other condition requiring higher or lower BP target specifically
10. Insufficient (<2) pre-illness blood pressure readings

Table E2
The pre-specified protocol to estimate pre-illness basal mean perfusion pressure.

Step 1: ***Find preferably up to five or at least two MAP (or BP) measurements[¶] from:***
1.1 MAP (or BP) recorded during nighttime ambulatory BP monitoring (*preferred*), outpatient or clinic visits, or pre-admission assessment before an elective procedure? *If unavailable, then*
1.2 MAP (or BP) recorded on the observation charts[#] from the last 48 h of a previous hospitalization.
Step 2: ***Derive pre-morbid basal MAP as follows:***
2.1 Convert BP readings that are recorded in SBP/DBP format to MAP[§].
2.2 Subtract 15% from daytime MA*P* values to estimate nighttime or basal MAP.
2.3 Consider the mean of available basal MAP values as pre-illness basal MAP.
Step 3: ***Derive pre-morbid basal CVP as follows:***
3.1 If a previous elective right heart catheterisation (RHC) report is available, the measured right atrial pressure (RAP) will be considered as basal CVP. *If unavailable, then*
3.2 Estimate CVP from a previous transthoracic echocardiography (TTE) study done in an outpatient setting, based on collapsibility of inferior vena cava (IVC) and IVC diameter (IVC_d), following standard ASE guidelines:

- CVP = 3 mmHg if $IVC_d \leq 2.1$ cm with >50% collapsibility on sniff (or stated as normal); or
- CVP = 15 mmHg if $IVC_d > 2.1$ cm with <50% collapsibility on sniff (or stated as dilated with minimal or reduced collapsibility); or
- For intermediate findings (*i.e.* normal IVC with reduced collapsibility, or dilated IVC with normal collapsibility),
  - If the report mentions diastolic flow predominance in the hepatic veins, then CVP = 15 mmHg
  - If the report mentions normal or systolic flow predominance in the hepatic veins, then CVP = 3 mmHg
  - If the report does not make any comment on hepatic vein flow pattern, then CVP = 8 mmHg

3.3 *If previous outpatient TTE is not available, then* estimate CVP = 8 mmHg if there is evidence of at least moderate valvular or cardiac dysfunction, or pulmonary hypertension, or raised filling pressures on any previous TOE or inpatient TTE study. *If not, or where no echocardiography report is available, then*
3.4 Assume basal CVP of 2 mmHg in patients with no heart disease[*], or 6 mmHg if there is any available evidence of pre-existing heart disease[**].
The basal MPP is the difference between basal MAP and basal CVP.

BP: Blood Pressure; MPP: Mean Perfusion Pressure; MAP: Mean Arterial Pressure; CVP: Central Venous Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.
[¶] Select MAP (or BP) measurements, recorded at least 12 h apart, starting with the most recent reading available within the last 3 years.
[#] If multiple BP readings are available, record the median BP of nighttime (2200–0600) BP readings within the last 24 h of hospital stay. Then, if available, record BP measurements that were done closest to the 12-h interval from this median BP reading.
[§] MAP = DBP + 1/3(SBP-DBP).
[*] In a spontaneously breathing adult without any heart disease, physiologists consider normal right atrial pressure (CVP) as 0 mmHg, equivalent to atmospheric pressure, and changes in body position usually do not affect the pressure measurement by more than 2 mmHg.
[**] In a previous study that analysed CVP from a large number of right heart catheterization studies in patients with mixed cardiovascular diseases, the mean CVP was 6 mmHg.

Table E3
Multivariate regression analyses – key outcomes *vs.* study exposure variables.

	Adjusted[#] Odds Ratio (95% Confidence Interval)	*P*-value
New Significant Acute Kidney Injury within 14 days		
MPP-deficit (time-weighted average), %	1.151 (1.021–1.297)	0.02
Time spent with >20% MPP-deficit, %	1.031 (1.001–1.062)	0.046
MAP-deficit (time-weighted average), %	1.13 (1.007–1.268)	0.04
Time spent with MAP<65 mmHg, %	1.025 (0.972–1.081)	0.36
Major Adverse Kidney Event within 14 days		
MPP-deficit (time-weighted average), %	1.069 (0.999–1.144)	0.05
Time spent with >20% MPP-deficit, %	1.018 (0.998–1.039)	0.08
MAP-deficit (time-weighted average), %	1.09 (0.996–1.192)	0.06
Time spent with MAP<65 mmHg, %	1.018 (0.968–1.069)	0.49

MPP- Mean Perfusion Pressure; MAP- Mean Arterial Pressure.
[#] *Adjusted on study site, APACHE III, and need for mechanical ventilation.*

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