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## Association between elevated mean arterial blood pressure and neurological outcome after resuscitation from cardiac arrest: results from a multicenter prospective cohort study

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### Abstract

**Objective:** Laboratory studies suggest elevated blood pressure after resuscitation from cardiac arrest may be protective; however, clinical data are limited. We sought to test the hypothesis that elevated post-resuscitation mean arterial blood pressure (MAP) is associated with neurological outcome.

**Design:** Pre-planned analysis of a prospective cohort study.

**Setting:** Six academic hospitals in the United States.

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The remaining authors have disclosed that they do not have any potential conflicts of interest.

**Patients:** Adult, non-traumatic cardiac arrest patients treated with targeted temperature management after return of spontaneous circulation (ROSC).

**Interventions:** MAP was measured non-invasively after ROSC and every hour during the initial six hours after ROSC.

**Measures and Main Results:** We calculated the mean MAP and *a priori* dichotomized subjects into two groups: mean MAP 70–90 and > 90 mmHg. The primary outcome was good neurological function, defined as a modified Rankin Scale (mRS)  $\leq 3$ . The mRS was prospectively determined at hospital discharge. Of the 269 patients included, 159 (59%) had a mean MAP > 90 mmHg. Good neurological function at hospital discharge occurred in 30% of patients in the entire cohort, and was significantly higher in patients with a mean MAP > 90 mmHg (42%) as compared to MAP 70–90 mmHg (15%) [absolute risk difference 27% (95% CI 17%–37%)]. In a multivariable Poisson regression model adjusting for potential confounders, mean MAP > 90 mmHg was associated with good neurological function, adjusted relative risk 2.46 (95% CI 2.09–2.88). Over ascending ranges of mean MAP, there was a dose-response increase in probability of good neurological outcome, with mean MAP > 110 mmHg having the strongest association, adjusted relative risk 2.97 (95% CI 1.86 – 4.76).

**Conclusions:** Elevated blood pressure during the initial six hours after resuscitation from cardiac arrest was independently associated with good neurological function at hospital discharge. Further investigation is warranted to determine if targeting an elevated MAP would improve neurologic outcome after cardiac arrest.

## Keywords

blood pressure; cardiac arrest; heart arrest; resuscitation

## Introduction

Cardiac arrest occurs in over 400,000 people each year in the United States alone.(1) Even among those who attain return of spontaneous circulation (ROSC) after cardiac arrest, in-hospital mortality remains over 50%, with a large proportion of survivors experiencing permanent and severe neurological disability.(2) After ROSC there is ongoing cerebral injury secondary to oxidant damage.(3, 4) Thus, finding new approaches to attenuate brain injury after resuscitation is a high priority for resuscitation science.

Brain injury secondary to cardiac arrest can result in disruption of normal cerebrovascular autoregulation.(5, 6) As a result, cerebral blood flow may become directly related to cerebral perfusion pressure.(6) Thus, an elevated mean arterial blood pressure (MAP) after resuscitation from cardiac arrest could improve cerebral blood flow through increased cerebral perfusion pressure, potentially attenuating ongoing cerebral injury. Current post-cardiac arrest guidelines recommend avoiding and immediately correcting post-resuscitation hypotension.(7, 8) However, there is currently insufficient evidence to recommend a specific blood pressure target. Our group previously published a single center prospective cohort study demonstrating an association between post-resuscitation MAP < 70 mmHg and poor neurological outcome at hospital discharge.(9) However, secondary to sample size

limitations we were unable to adequately test whether higher MAPs were associated with improved neurological outcome.

In this multi-center cohort study, our main objective was to test the association between elevated post-resuscitation MAP and neurological outcome among adult patients successfully resuscitated from cardiac arrest.

## Methods

### Setting

We performed a pre-planned analysis of a prospective cohort study across six hospitals in the United States. We prospectively compiled and maintained an Utstein style cardiac arrest registry.(10, 11) The Institutional Review Board at each participating institution approved this study. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.(12)

### Participants

Adult post-cardiac arrest patients who were comatose after ROSC between July 2013 and March 2017 were included. The inclusion criteria were: 1) age  $\geq$  18 years; 2) cardiac arrest, defined as a documented absence of pulse and the initiation of cardiopulmonary resuscitation (CPR); 3) ROSC  $>$  20 min; 4) unresponsive (i.e. Glasgow Coma Score motor less than 6) and mechanical ventilation after ROSC; and 5) clinician intent to perform targeted temperature management. We included patients with both in- and out-of-hospital cardiac arrest in order to allow for a pragmatic study from which results could be broadly applicable to as many cardiac arrest patients as possible. We excluded subjects with presumed etiology of arrest secondary to trauma, hemorrhage or sepsis; residents of a nursing home or other long-term care facility; pregnancy; prisoners; and known lack of commitment to aggressive support by next of kin. We excluded patients with persistent hypotension during the initial six hours after ROSC (defined as mean post-resuscitation MAP  $<$  70 mmHg).(9) We excluded these patients on the grounds that it has already been demonstrated that hypotension is associated with worse outcomes.(2, 9, 13, 14) Excluding these patients would permit us to focus the analysis on the association between elevations in MAP and neurological outcome.

### Data Collection

As part of our research protocol we measured MAP immediately after ROSC and hourly thereafter using a noninvasive blood pressure cuff for the first six hours after ROSC. We calculated the mean MAP over the initial six hours after ROSC. We chose the initial six hours as our time frame as it has previously been demonstrated to be the most critical time period for hemodynamic optimization after cardiac arrest.(15) We prospectively captured all the components of the Sequential Organ Failure Assessment (SOFA) score (i.e. respiratory, coagulation, hepatic, renal, cardiovascular, and neurological) during the first six hours after ROSC to assess severity of illness.(16) For calculation of the total SOFA score, we excluded the neurological component as described previously,(16–18) as well as the cardiovascular component given collinearity with MAP. We prospectively captured vasopressor

administration during the first six hours after ROSC and used the SOFA cardiovascular score to quantify vasopressor dosing. We abstracted clinical data from the medical record into Research Electronic Data Capture (REDCap, Vanderbilt University, TN), a secure, internet-based application designed to support data capture for research studies(19) and exported into Stata/SE 14.1 for Mac, StataCorp LP (College Station, TX, USA).

### Outcome measures

The primary outcome was good neurological function at hospital discharge, *a priori* defined as a modified Rankin Scale (mRS)  $\leq 3$ .(20, 21) The mRS was prospectively determined as part of our research protocol for each patient at the time of hospital discharge. All raters were trained and certified in mRS assessment(22) and used a structured questionnaire and interview, which have been shown to produce strong interobserver reliability.(23, 24) Secondary outcomes were survival to hospital discharge and good early neurological response, defined *a priori* as a Full Outline of UnResponsiveness (FOUR) score  $> 6$  at 72 hours after ROSC, based on previous literature.(25, 26)

### Data Analysis

We began the analysis with descriptive statistics. We displayed categorical data as counts and proportions, and continuous data as mean values and standard deviation (SD) or median values and interquartile range (IQR), based on distribution of data. Continuous variables were compared using student t-test or Wilcoxon rank-sum test, based on the distribution of the data and categorical variables were compared using the chi-square test

For our primary analysis we *a priori* grouped subjects into two categories: mean MAP 70–90 and  $> 90$  mmHg, based on previous literature.(15) For the primary outcome, we calculated relative risks (RR) using multivariable Poisson regression.(27) We entered candidate variables that were previously demonstrated to be strong predictors of poor outcome in post-cardiac arrest patients into the model (see Supplemental Methods for full description of the model). The same analyses were performed for the secondary outcomes.

For the primary outcome we performed multiple pre-planned subgroup analyses. We also tested if the dose of vasopressor administration modified the association between mean MAP and neurological outcome, as well as tested for a dose response between incremental increases in mean MAP and neurological outcome (detailed description of sensitivity analyses is discussed in Supplemental Methods). Finally, we performed two *post-hoc* sensitivity analyses: (1) we tested the association between the duration of exposure to MAP  $> 90$  mmHg and neurological outcome and (2) we tested the primary analysis among only patients who survived to hospital discharge. All models used robust standard error and allowed for intragroup correlations at the institution (i.e. site of enrollment) level.

### Results

Our prospective cohort consisted of 280 subjects (study flow diagram previous published). (28) Eleven (4%) subjects were excluded for a mean MAP  $< 70$  mmHg leaving 269 subjects in the final cohort. The mean (SD) mean MAP was 95 (15) mmHg for the entire cohort, and 101 (14) and 93 (15) mmHg for subjects with and without good neurological outcome at

hospital discharge respectively ( $p$ -value  $< 0.001$  using student  $t$ -test). One hundred fifty-nine (59%) subjects had a mean MAP  $> 90$  mmHg during the initial six hours after ROSC.

Table 1 displays baseline data for all subjects in the cohort, as well as subjects with a mean MAP 70–90 and  $> 90$  mmHg. We found that patients with a mean MAP 70–90 mmHg had a longer median (IQR) duration of CPR compared to those with a mean MAP  $> 90$  mmHg [17 (8–28) vs. 10 (6–20) min]. Four subjects (1%) had an unknown duration of CPR.

Supplemental Table 1 displays post-cardiac arrest data for all subjects. All subjects were mechanically ventilated after ROSC and received target temperature management. Several variables were statistically different at  $p < 0.10$  when comparing mean MAP 70–90 mmHg and  $> 90$  mmHg groups: vasopressor administration, Charlson co-morbidity index, and pre-existing congestive heart failure and malignancy.

Eighty-two (30%) subjects were found to have the primary outcome of good neurological function at hospital discharge among the entire cohort. Among subjects with a mean MAP 70–90 mmHg, good neurological outcome was observed for 15% compared to 42% among those with a mean MAP  $> 90$  [absolute risk difference 27% (95% CI 17% - 37%),  $p < 0.001$ ]. The proportion of subjects with each mRS score stratified by mean MAP is displayed in Figure 1.

In total, 218 subjects survived to 72 hours, and 81 (74%) vs. 137 (86%) survived to 72 hours among patients with a mean MAP 70–90 and  $> 90$  mmHg respectively ( $p = 0.01$ ). Among the entire cohort that survived to 72 hours the median (IQR) FOUR score was 8 (3–13). Patients with a mean MAP  $> 90$  mmHg had a higher median (IQR) FOUR score compared to patients with a MAP 70–90, [11 (5–13) vs. 6 (2–11),  $p < 0.001$  using Wilcoxon rank-sum test], as well as a higher proportion of good early neurological response [66% vs. 49%, absolute risk difference 17% (95% CI 4% - 30%),  $p = 0.013$ ].

One hundred and twenty-two subjects survived to hospital discharge. Compared to a mean MAP 70–90 mmHg, a MAP  $> 90$  mmHg was associated with increased survival to hospital discharge [28% vs. 57%, absolute risk difference 29% (95% CI 18% - 40%),  $p < 0.001$ ]. Survival to hospital discharge among patients with and without good early neurological response was 80% vs. 18% respectively, absolute risk difference 62% (95% CI 51% - 72%),  $p < 0.001$ . Of note a higher proportion of patients with a mean MAP 70–90 mmHg had withdraw of life sustaining therapy during hospitalization compared to MAP  $> 90$  mmHg [58% vs. 35% respectively,  $p < 0.001$ ].

Table 2 displays the results of the multivariable Poisson regression models for the primary and secondary outcomes. After adjusting for potential confounders, a mean MAP  $> 90$  mmHg was an independent predictor of good neurological function at hospital discharge, relative risk 2.46 (95% CI 2.09 – 2.88),  $p < 0.001$ , as well as survival to hospital discharge and early neurological response (see Supplemental Tables 2, 3, and 4 for full results of all regression models).

Figure 2 displays the results of the subgroup analyses. Mean MAP  $> 90$  mmHg was found to be associated with good neurological outcome among all subgroups. The association between mean MAP  $> 90$  mmHg and good neurological outcome was found to be stronger

among subjects with a previous diagnosis of hypertension compared to those without hypertension, relative risk 4.95 (95% CI 2.18 – 11.26) vs. 1.28 (95% CI 1.13 – 1.46) respectively.

We did not find evidence that the association between mean MAP > 90 mmHg and good neurological outcome differed as vasopressor dose increased (Supplemental Table 5). Figure 3 displays the proportion of good neurological outcome across ascending ranges of mean MAP. Entering mean MAP as a categorical variable into the original model we found a dose-response increase in the probability of good neurological outcome among all mean MAP ranges above 90 mmHg compared to the reference range of post-resuscitation MAP 70–80 mmHg (Supplemental Table 6). Mean MAP > 110 mmHg had the strongest association with good neurological outcome at hospital discharge, [adjusted relative risk 2.97 (95% CI 1.86 – 4.76),  $p = <0.001$ ]. We also found for every additional hourly blood pressure measurement with MAP > 90 mmHg there was a 15% increase in the probability of good neurological outcome [adjusted relative risk 1.15 (95% CI 1.11–1.18),  $p < 0.001$ ] (Supplemental Table 7). Among patients who survived to hospital discharge, 67% had good neurological outcome at hospital discharge. Mean MAP > 90 mmHg remained an independent predictor of good neurological outcome among survivors to hospital discharge, relative risk 1.36 (95% CI 1.08–1.72) (Supplemental Table 8).

## Discussion

In this multicenter prospectively compiled cohort, we tested the association between elevated MAP after resuscitation from cardiac arrest and neurological outcome. By excluding patients with persistent hypotension we were able to test if the association between arterial blood pressure and neurological outcome was driven by exposure to higher arterial blood pressure as opposed to exposure to arterial hypotension. In this cohort 59% of patients had a mean MAP > 90 mmHg during the initial six hours after ROSC. Compared to a mean MAP 70–90 mmHg, a MAP > 90 mmHg was independently associated with good neurological outcome at hospital discharge. Our results suggest a dose-response association between duration of exposure to MAP > 90 mmHg and good neurological outcome, as well as higher MAPs and good neurological outcome, with post-resuscitation MAP > 110 mmHg having the strongest association. In addition, we found an elevated MAP to be associated with good early neurological response as well as survival to hospital discharge. Good early neurological response was associated with survival to hospital discharge, suggesting that neurological injury was a major factor for mortality. Thus, it is reasonable to infer that the association between post-resuscitation MAP and mortality is mediated by early neurological injury. In summary, in this prospective, multicenter cohort, we found that elevated MAP during the early period after ROSC is associated with good neurological outcome.

In subgroup analyses we found the relationship between mean MAP > 90 mmHg and good neurological outcome was similar regardless of location of arrest, initial rhythm, or administration of vasopressor agent. Of note we found the association between mean MAP > 90 mmHg and good neurological outcome was stronger among subjects with a previous diagnosis of hypertension compared to among those without hypertension. The stronger association among subjects with a history of chronic hypertension may suggest an

underlying shift in the cerebral autoregulation curve resulting in these patients requiring a higher MAP to maintain adequate cerebral blood flow at baseline.(29, 30) Thus, patients with a history of hypertension may be more susceptible to additional brain injury when exposed to lower arterial blood pressure. These findings suggest that the optimal MAP may be patient dependent and that some patients may benefit from MAPs higher than the current recommendation of maintaining MAP > 65 mmHg.(7)

During the early post-ROSC period, shifts in arterial blood pressure could potentially put patients at risk for additional brain injury, and thus maintenance of an elevated MAP during this time may improve cerebral blood flow and confer neuroprotection. This hypothesis is supported by animal models, in which an induced hypertensive surge attenuates brain injury and improves outcomes.(31–34) Our group previously performed a single center prospective cohort study examining the association between elevated MAP and neurological outcome.(9) We found that a MAP less than 70 mmHg is associated with poor neurological outcome. While we did not observe an association with increasing MAPs above 90 mmHg and improved neurological outcome, this study was limited by a single center design, inclusion of only 12 patients with a MAP > 100 mmHg, and inconsistent use of targeted temperature management.

This current investigation has several advantages over previous studies that advance this area of investigation. First we prospectively collected MAP measurements and vasopressor utilization over the initial six hours after ROSC. Additionally, we obtained protocol directed assessments of neurological disability in real time, as opposed to abstracting this information through chart review. Furthermore, all subjects received consistent guideline-driven post-cardiac arrest care including targeted temperature management. Second, this study represented a larger multicenter population, with the majority of patients exhibiting a post-resuscitation MAP greater than 90 mmHg. In addition, we excluded patients with persistent post-resuscitation hypotension from our analyses to ensure our results were driven by elevated blood pressure as opposed to exposure to hypotension.

We acknowledge that this study has important limitations to consider. First, this was an observational study and thus we can only report association rather than infer causation. It is possible that post-resuscitation MAP > 90 mmHg reflects a patient population that is less ill in general and therefore has a higher likelihood to have good neurological outcome. However, we did not observe any significant differences in the post-resuscitation SOFA score, alveolar plateau pressure, or incidence of post-resuscitation percutaneous coronary intervention or hypoxia between the two groups, suggesting this was not the case. Compared to patients with a mean MAP > 90 mmHg, we found patients with a mean MAP 70–90 mmHg were less likely to have good early neurological response, as well as more likely to have withdraw of life sustaining therapy. However, we are unable to determine if lower MAP causes early neurological injury leading to withdraw of care, or if lower MAP is a marker for severity of illness influencing clinician decision to withdraw care. However, we found the association between mean MAP > 90 mmHg and good neurological outcome at hospital discharge remained statistically significant when limited to subjects who survived to hospital discharge, suggesting that the decision to withdraw life sustaining therapy did not confound our results. While we did observe patients with a mean MAP of 70–90 mmHg had a longer

duration of CPR compared to patients with a MAP > 90 mmHg, after adjusting all of our models for duration of CPR, mean MAP > 90 mmHg remained an independent predictor of good neurological outcome. Second, although we prospectively recorded MAP at least every hour, we did not require invasive blood pressure monitoring. However, the non-invasive blood pressure (cuff) measurement technique is accurate and ubiquitous in routine clinical practice. Thus our results are generalizable. Third, although all our clinicians aim to prevent exposure to hypotension as per current post-cardiac arrest guidelines,(7, 8) given there is equipoise as to the optimal target MAP, our protocol did not involve a standardized blood pressure target. Thus, blood pressure goals varied between treating clinicians. Of note, among patients with a mean MAP > 90 mmHg who were on vasopressors, 25/59 (42%) had exposure to hypotension during the initial six hours after ROSC. Thus, among these 25 patients it is possible that the higher MAPs were the result of a rebound in blood pressure while attempting to treat hypotension. However, it is likely that the remaining patients with higher MAPs who received vasopressors did so as a result of clinicians specifically targeting higher MAPs. Fourth, although we used multivariable Poisson regression analyses to adjust for cardiac arrest characteristics known to predict poor outcomes, there exists the potential of unmeasured confounders. Fifth, although we prospectively recorded administration of vasopressor infusion, and quantified the administered dose using the cardiovascular component of the SOFA score we did not collect data on number of vasopressor agents administered.

## Conclusion

Mean arterial blood pressure greater than 90 mmHg during the initial six hours after ROSC is associated with good neurological outcome at hospital discharge. This association was strongest among patients with a history of chronic hypertension, suggesting the association between arterial blood pressure and neurological outcome may be patient dependent. Further investigation is warranted to determine if interventions targeting an elevated arterial blood pressure would improve neurologic outcome after cardiac arrest and which patient populations may benefit.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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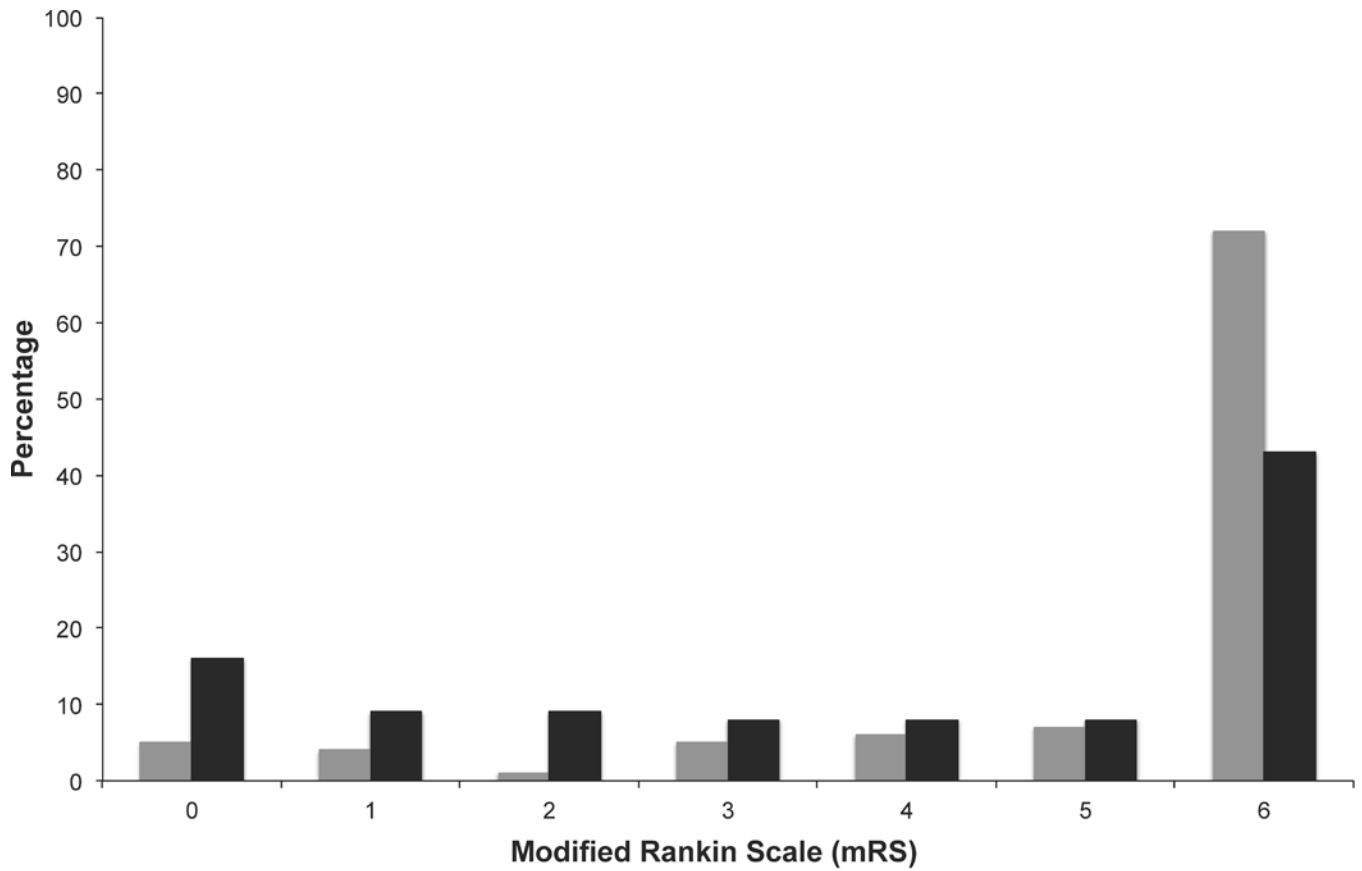


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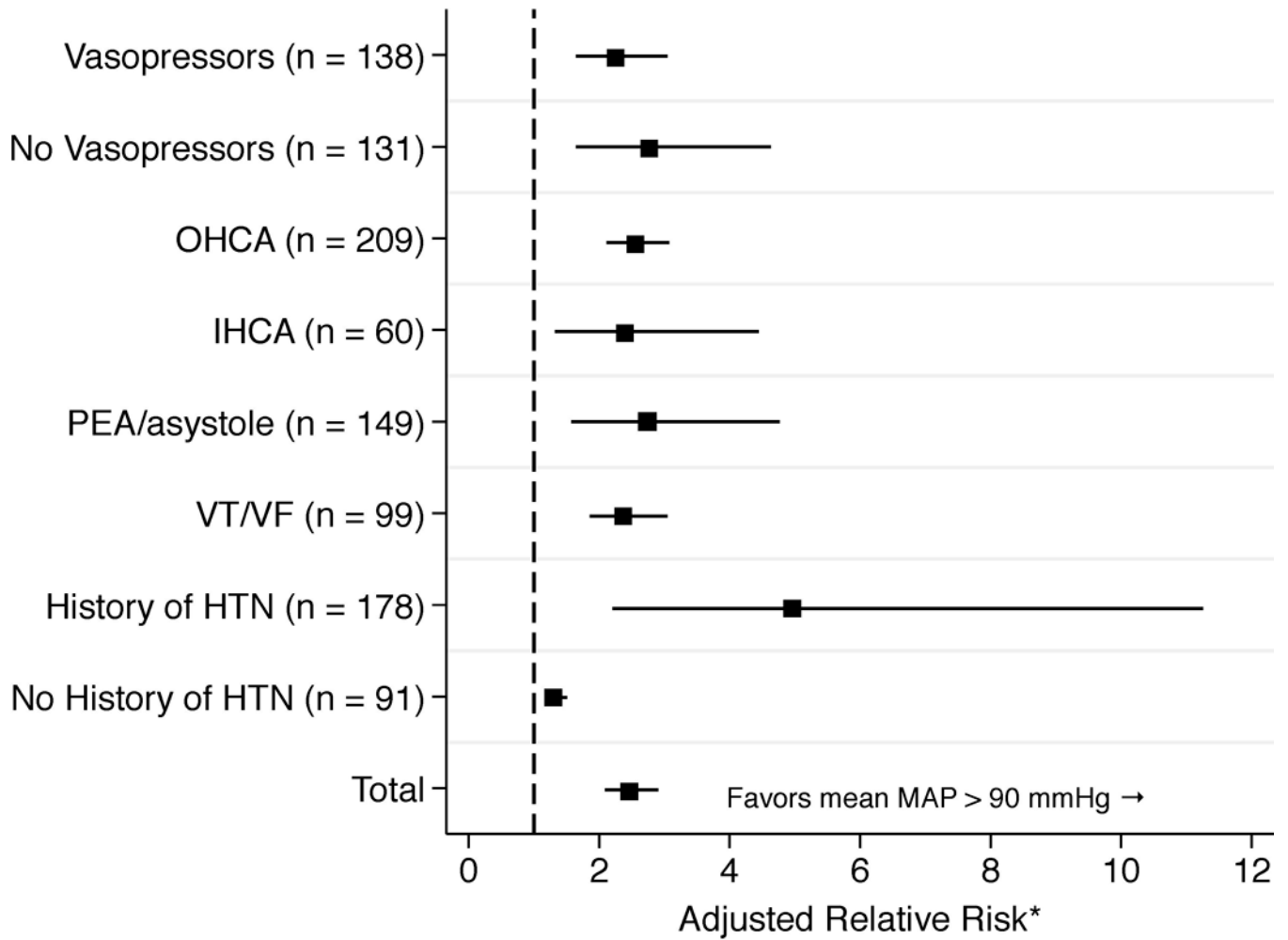
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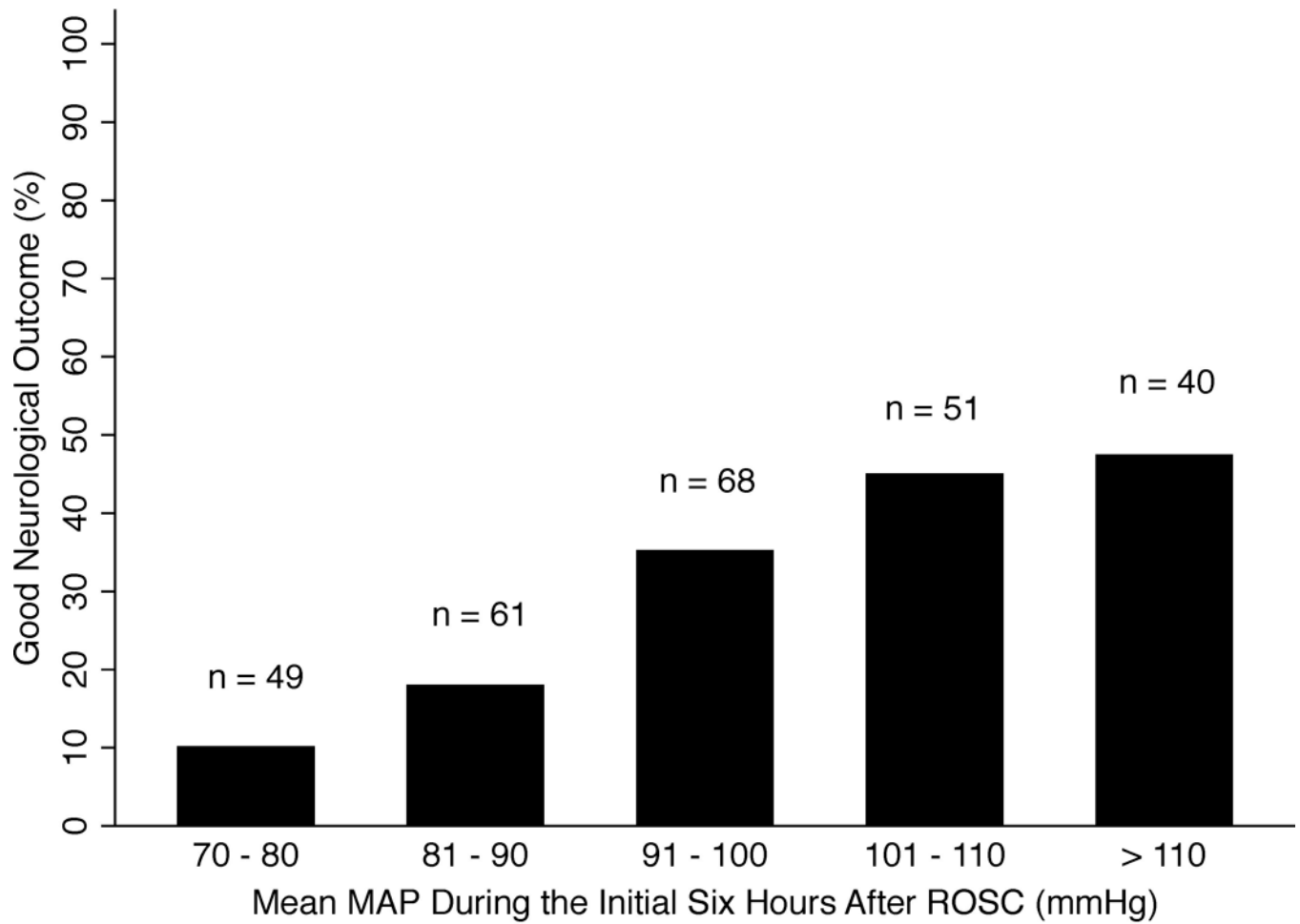


**Figure 1:** Modified Rankin Scale at hospital discharge stratified by mean MAP (mean arterial blood pressure) 70–90 mmHg (gray columns) and mean MAP > 90 mmHg (black columns). mRS: 0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderate severe disability; 5, severe disability; 6, death



**Figure 2:** Subgroup analyses: adjusted relative risks (squares) with 95% confidence intervals (horizontal lines) for the association between mean MAP (mean arterial blood pressure) > 90 mmHg (compared to 70–90 mmHg) and good neurological outcome (defined as a modified Rankin Scale (mRS) ≤ 3). We found mean MAP > 90 mmHg to be an independent predictor of good neurological outcome among all subgroups.

\*Relative risks were calculated using multivariable Poisson regression analysis (using a log link) adjusting for age, initial cardiac rhythm, and duration of cardiopulmonary resuscitation [initial cardiac rhythm was excluded from pulseless electrical activity (PEA)/asystole and ventricular tachycardia/ventricular fibrillation (VT/VF) analyses]. HTN, hypertension; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.



**Figure 3:**

Good neurologic function at hospital discharge (defined as a modified Rankin Scale (mRS) 3) in relation to mean MAP (mean arterial pressure) during the initial six hours after return of spontaneous circulation.

MAP; mean arterial blood pressure; ROSC, return of spontaneous circulation

**Table 1:**

Baseline data for all subjects at the time of cardiac arrest.

| Variable                           | All Subjects<br>n = 269 | Mean MAP*<br>70–90 mmHg<br>n = 110 | Mean MAP<br>> 90 mmHg<br>n = 159 | p - value |
|------------------------------------|-------------------------|------------------------------------|----------------------------------|-----------|
| Age [years (SD)]                   | 58 (15)                 | 61 (17)                            | 57 (13)                          | 0.037     |
| Female [n (%)]                     | 97 (36)                 | 38 (35)                            | 59 (37)                          | 0.667     |
| Pre-existing comorbidities [n (%)] |                         |                                    |                                  |           |
| Diabetes                           | 66 (25)                 | 25 (23)                            | 41 (26)                          | 0.567     |
| Known coronary artery disease      | 72 (27)                 | 30 (27)                            | 42 (26)                          | 0.876     |
| Hypertension                       | 178 (66)                | 71 (65)                            | 107 (67)                         | 0.639     |
| Malignancy                         | 18 (7)                  | 11 (10)                            | 7 (4)                            | 0.071     |
| Renal insufficiency                | 41 (15)                 | 19 (17)                            | 22 (14)                          | 0.441     |
| Pulmonary disease                  | 63 (23)                 | 28 (25)                            | 35 (22)                          | 0.512     |
| Cerebral vascular disease          | 24 (9)                  | 12 (11)                            | 12 (8)                           | 0.342     |
| Congestive heart failure           | 68 (25)                 | 35 (32)                            | 33 (21)                          | 0.040     |
| Charlson comorbidity score         | 1 (0–3)                 | 1 (0–3)                            | 1 (0–2)                          | 0.078     |
| Arrest location [n (%)]            |                         |                                    |                                  |           |
| Out-of-hospital                    | 209 (78)                | 78 (71)                            | 131 (82)                         |           |
| In-hospital                        | 60 (22)                 | 32 (29)                            | 28 (18)                          | 0.026     |
| Initial arrest rhythm [n (%)]      |                         |                                    |                                  |           |
| PEA/asystole                       | 149 (55)                | 69 (63)                            | 80 (50)                          |           |
| VF/VT                              | 99 (37)                 | 36 (33)                            | 63 (40)                          | 0.075     |
| Unknown                            | 21 (8)                  | 5 (5)                              | 16 (10)                          |           |
| CPR duration (min)                 | 15 (7–23)               | 17 (8–28)                          | 10 (6–20)                        | 0.006     |

\* Mean MAP (mean arterial blood pressure) over the initial six hours after return of spontaneous circulation. CPR, cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electrical activity; SD, standard deviation; VF, ventricular fibrillation; VT ventricular tachycardia

**Table 2:**

Adjusted relative risk for mean MAP (mean arterial blood pressure) > 90 mmHg (compared to reference 70–90 mmHg) for the primary and secondary outcomes.

| Outcome                                       | Relative Risk | 95% CI      | p-value |
|---|---------------|-------------|---------|
| Primary Outcome:                              |               |             |         |
| Good Neurological Outcome <sup>*</sup>        | 2.46          | 2.09 – 2.88 | <0.001  |
| Secondary Outcomes:                           |               |             |         |
| In-hospital mortality                         | 1.90          | 1.64 – 2.20 | <0.001  |
| Good early neurological response <sup>†</sup> | 1.36          | 1.17 – 1.58 | <0.001  |

<sup>\*</sup> Defined as modified Rankin Scale (mRS) = 3 at hospital discharge;

<sup>†</sup> Defined as a Full Outline of UnResponsiveness (FOUR) score > 6 at 72 hours after return of spontaneous circulation. CI, confidence interval. Results of the full models are displayed in the supplemental material.