SPONTANEOUS HYPOCAPNIA AFTER CARDIAC ARREST IS ASSOCIATED WITH 60-DAY MORTALITY

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by
Brian W. Roberts, MD
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Thesis Approvals:

Levent Dumenci, PhD, Thesis Advisor, Temple University, Department of Epidemiology, and Biostatistics

ABSTRACT

Background: Hypocapnia exposure after successful resuscitation from cardiac arrest has been previously demonstrated to be associated with poor clinical outcomes. During mechanical ventilation after return of spontaneous circulation (ROSC) it is unclear if spontaneous hyperventilation, as opposed high prescribed minute ventilation, is a common cause of hypocapnia. The objectives of this study were to determine the incidence of hypocapnia induced by spontaneous hyperventilation (spontaneous hypocapnia) among patients successfully resuscitated from cardiac arrest and to test if spontaneous hypocapnia is independently associated with 60-day mortality.

Methods: Pre-planned analysis of a prospective multi-center cohort. We included adult, cardiac arrest patients who were mechanically ventilated and received targeted temperature management after return of spontaneous circulation (ROSC). We excluded patients with cardiac arrest due to trauma or sepsis. Per protocol, partial pressure of arterial carbon dioxide ($PaCO_2$) was measured at one and six hours after ROSC. Hypocapnia was defined as a $PaCO_2$ < 35 mmHg. We defined spontaneous hypocapnia as hypocapnia plus a measured actual respiratory rate greater than the prescribed respiratory rate and induced hypocapnia as hypocapnia plus an actual respiratory rate not higher than the prescribed respiratory rate during the initial six hours after ROSC. The primary outcome was 60-day mortality. A multivariable Cox proportional hazards model was used to test the associations between spontaneous hypocapnia and 60-day mortality compared to induced hypocapnia and no hypocapnia exposure.

Results: Of the 280 patients included, 112 (40%) had exposure to hypocapnia; 89 vs. 23 spontaneous and induced hypocapnia, respectively. Sixty-day mortality occurred among 55% of patients in the entire cohort, and 47%, 57%, and 70% among patients with no, induced, and spontaneous hypocapnia respectively. Spontaneous hypocapnia was independently associated with 60-day mortality, hazards ratios 1.64 (95% CI 1.43-1.87)

compared to no hypocapnia exposure and 1.44 (95% CI 1.10-1.88) compared to induced hypocapnia.

Conclusion: Spontaneous hypocapnia is common during the initial six hours after return of spontaneous circulation and is independently associated with 60-day mortality.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Cardiac arrest is defined as the cessation of mechanical cardiac activity as evidenced by the absence of clinical signs of circulation (Roger et al., 2012). Sudden cardiac arrest is one of the leading causes of death in North America, (Berg et al., 2010) accounting for more than 400,000 deaths annually in the United States alone (Kong et al., 2011). It is estimated that over 82 million adults (>1 in 3) in the U.S. have one or more types of cardiovascular disease (Roger et al., 2011). Cardiac arrest is the most common lethal manifestation of cardiovascular disease and out-of-hospital cardiac arrest (OHCA) is often the first manifestation of cardiovascular disease, with two-thirds of arrests occurring without prior recognition of an underlying condition (Zheng, Croft, Giles, & Mensah, 2001). Despite advances aimed at improving successful return of spontaneous circulation (ROSC) and cardiac arrest survival, the mortality rate remains extraordinarily high, approaching 90% (Roger et al., 2012).

During cardiac arrest whole-body ischemia initially causes global tissue and organ injury, this is then followed by additional damage caused by reperfusion, which occurs during and after ROSC (Neumar et al., 2008). This ongoing injury is the result of a set of clinical manifestations collectively known as post-cardiac arrest syndrome (Neumar et al., 2008). Most deaths after ROSC (~70%) can be attributed to cerebral ischemia/reperfusion (I/R) injury (Laver, Farrow, Turner, & Nolan, 2004; Roberts, Kilgannon, Chansky, Mittal, Wooden, Parrillo, et al., 2013). A large U.S. multi-center cohort study of patients who survived to intensive care unit (ICU) admission following successful resuscitation from cardiac arrest found that 50% of patients did not survive to hospital discharge. Of those who did survive, the majority of patients were functionally

dependent, and more than half of these patients were discharged to a long-term care facility (Trzeciak et al., 2009).

Finding new means to attenuate I/R injury is of the utmost importance to resuscitation science. Changes in the partial pressure of arterial carbon dioxide ($PaCO_2$) can have profound changes to cerebral perfusion. Cerebral blood flow has been demonstrated to decrease approximately 3% for every 1 mmHg decrease in $PaCO_2$ in patients with traumatic brain injury (Cold, 1990). Historically, mechanical hyperventilation has been used to decrease the $PaCO_2$ and thus intracranial pressure (ICP) in patients suffering from cerebral injury, as CO_2 is a strong vasodilator. However, more recently hypocapnia (decreased $PaCO_2$ levels) has been postulated to be detrimental secondary to hypocapnia-induced cerebral vasoconstriction resulting in decreased cerebral blood flow and increased cerebral ischemia potentially exacerbating cerebral injury (Ausina et al., 1998; Buunk, van der Hoeven, & Meinders, 1997; Yundt & Diringer, 1997). In a recent prospective cohort study, our group reported an association between post-ROSC hypocapnia and poor neurological outcome among patients resuscitated from cardiac arrest (Roberts, Kilgannon, Chansky, Mittal, Wooden, & Trzeciak, 2013). In addition, in a systematic review performed by our group it was found that the preponderance of the current literature supports that hypocapnia is associated with increased mortality and poor neurological outcome among patients with cerebral injury including post-cardiac arrest syndrome (Roberts et al., 2015).

There are two major mechanisms by which patients with cerebral injury can develop hypocapnia. First, cerebral injury, including post-cardiac arrest syndrome, is one of the most common reasons critically ill patients require initiation of mechanical ventilation (Pelosi et al., 2011). During mechanical ventilation $PaCO_2$ levels are influenced by the

prescribed ventilator settings initiated by the treating clinician. As the clinician increases the set minute ventilation, the risk of developing hypocapnia increases (induced hypocapnia). Second, cerebral injury can result in an increased intrinsic respiratory drive (spontaneous hyperventilation) (Huang, Cook, & Lyons, 1963; North & Jennett, 1974). This spontaneous hyperventilation can lead to hypocapnia (spontaneous hypocapnia), and has been demonstrated to be associated with poor clinical outcomes among patients with several forms of cerebral injury (M. C. Lee, Klassen, & Resch, 1974; Rout, Lane, & Wollner, 1971; Williamson et al., 2015). However, it is unclear if spontaneous hypocapnia occurs in patients with ROSC after cardiac arrest, and if so, is it associated with worse clinical outcomes.

The objectives of this study were (1) to determine the incidence of spontaneous hypocapnia among patients successfully resuscitated from cardiac arrest and (2) to test if spontaneous hypocapnia is independently associated with 60-day mortality. We hypothesize that spontaneous hypocapnia is common and associated with 60-day mortality among patients successfully resuscitated from cardiac arrest. If spontaneous hypocapnia is found to be associated with 60-day mortality, then further investigation is warranted to test if prevention of spontaneous hypocapnia can improve clinical outcomes.

CHAPTER 2

METHODS

Setting

We analyzed a prospective protocol-directed cohort study across six academic hospitals in the United States. These analyses were planned prior to data collect. Each site utilized a 24-hour per day, 7-day per week alter system in order to identify post-cardiac arrest patients and begin data capture in real time. At each institution, an on-call investigator received the alert and responded to the cardiac arrest event to begin data entry. The Institutional Review Board at each participating institution approved this study.

Participants

We included both in- and out-of-hospital adult post-cardiac arrest patients who were comatose (defined as a Glasgow coma scale motor score < 6) after ROSC between 2013-2017. The inclusion criteria were: 1) age ≥ 18 years; 2) cardiac arrest, defined as a documented absence of pulse and cardiopulmonary resuscitation (CPR) initiated; 3) ROSC > 20 minutes; 4) mechanically ventilated after ROSC; and 5) clinician commitment to perform targeted temperature management. We excluded patients with presumed etiology of arrest secondary to trauma, hemorrhage or sepsis; resident of a nursing home or other long-term care facility; pregnancy; prisoners; and terminal illness with no reasonable expectation to survive to hospital discharge or known lack of commitment to aggressive support by next of kin. We also excluded patients who died prior to an arterial blood gas analysis being obtained.

Data Collection

As part of our protocol we obtained an initial arterial blood gas (ABG) one-hour after ROSC and a second ABG six hours after ROSC (plus or minus two hours). At the time of ABG collection we also recorded the plateau pressure during an inspiratory hold maneuver. We recorded all ventilator changes including tidal volume (TV) and prescribed respiratory rate (PRR), and the precise time of the adjustment. We monitored patients for over-breathing (i.e. spontaneous breaths above the PRR) during the first six hours after ROSC. We calculated a predicted body weight (PBW) for each patient using the following formulas:

Male patients: 50 + 0.91(centimeters of height - 152.4)

Female patients: 45.5 + 0.91(centimeters of height - 152.4) (Network, 2000)

We then calculated the initial prescribed minute ventilation (mL/min*Kg PBW) for each patient. Minute ventilation was calculated as equal to (prescribed TV/PBW) * PRR (Roberts, Kilgannon, Chansky, & Trzeciak, 2014). We abstracted demographics, comorbidities, and post-cardiac arrest interventions from the medical record. 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 24 hours after ROSC (Roberts, Kilgannon, Chansky, Mittal, Wooden, Parrillo, et al., 2013). For calculation of the SOFA score, we used the worst value for each component during the initial six-hour period after ROSC and excluded the neurological component (Roberts, Kilgannon, Chansky, Mittal, Wooden, Parrillo, et al., 2013; Trzeciak et al., 2007; Trzeciak et al., 2008). We entered all data into Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies (Harris et al., 2009) and exported into Stata/SE 14.1 for Mac, StataCorp LP (College Station, TX, USA) for analysis.

Outcome measures

The primary outcome was 60-day mortality. Survival time was defined as time from ROSC to death, or 60 days. If patients were discharged alive prior to 60-days, patients or their surrogate were contacted via phone to determine 60-day survival.

Data Analysis

We began the analysis with descriptive statistics, displaying 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. We used one-way analysis of variance (ANOVA) or Kruskal-Wallis rank test (or Wilcoxon rank sum) to compare continuous variables between hypocapnia groups, based on the distribution of the data, and chi-square test or Fisher exact test to compare categorical variables between hypocapnia groups.

For purposes of analysis we defined hypocapnia as exposure to a $PaCO_2$ < 35 mmHg during the initial six hours after ROSC. We chose these definitions based on the 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care definition of normocapnia (Callaway et al., 2015b). We defined spontaneous hypocapnia as hypocapnia plus over-breathing the PRR (actual respiratory rate greater than the prescribed respiratory rate), and defined induced hypocapnia as hypocapnia plus not over-breathing the PRR (actual respiratory rate not greater than the prescribed respiratory rate) during the initial six hours after ROSC. Kaplan-Meier survival estimates were graphed and the log-rank test was used to compare the three hypocapnia groups (no exposure, induced hypocapnia, and spontaneous hypocapnia).

Our primary analysis aimed to test the relationship between hypocapnia groups and 60-day mortality. Given three comparisons between groups we performed Bonferroni correction for multiple pairwise comparisons (i.e. for 3 groups, α level of .05 divided by 3 or 0.017). A multivariable Cox proportional hazards model was used to calculate hazard ratios with 95% confidence intervals (CI) for 60-day mortality among patients with induced and spontaneous hypocapnia compared to no hypocapnia exposure (Prentice & Kalbfleisch, 1979). Hazards ratios for 60-day mortality were adjusted for potential confounders, which were previously demonstrated to predict outcome in post–cardiac arrest patients: (1) age (decile); (2) initial cardiac rhythm [asystole or pulseless electrical activity (PEA) vs. ventricular fibrillation/ventricular tachycardia (VF/VT)] (Nadkarni et al., 2006); (3) metabolic acidosis (one or more recorded base deficit ≤ -6 during the initial six hours after ROSC) (Roberts, Kilgannon, Chansky, Mittal, Wooden, & Trzeciak, 2013); (4) arterial hypotension (mean arterial pressure < 70 mmHg during the initial six hours after ROSC) (Kilgannon et al., 2014); (5) pre-arrest comorbidities using Charlson comorbidities index (Murray, Bates, Ngo, Ufberg, & Shapiro, 2006); (6) prolonged duration of CPR (CPR duration > 20 min) (Hajbaghery, Mousavi, & Akbari, 2005); and (7) location of cardiac arrest (in- vs. out-of-hospital) (Gaul et al., 1996; Langhelle et al., 2003; Peberdy et al., 2003; Tok, Keles, Toprak, & Topcu, 2004). Given administration of neuromuscular blocking agents prevent spontaneous ventilations we also adjusted our model for administration of neuromuscular blocking agent during the initial six hours after ROSC (yes/no). Our model took into account the random effects at the institution (i.e. site of enrollment) level. A link test, which tests if the coefficient of the squared linear predictors is significant, was used to test model specification. We also tested the proportional-hazards assumption on the basis of Schoenfeld residuals after fitting a model.

CHAPTER 3

RESULTS

Two hundred and eighty patients meet all inclusion and no exclusion criteria (Site 1, 83; Site 2, 26; Site 3, 13; Site 4, 25; Site 5, 118; Site 6, 15). The majority of patients had a spontaneous respiratory rate greater than the prescribed ventilator respiratory rate [233/280 (83%)]. Among those over-breathing the prescribed ventilator respiratory rate, 38% (89/233) had hypocapnia exposure and 62% (144/233) had no hypocapnia exposure. Of the entire cohort, 40% (112/280) had exposure to hypocapnia, with the majority having spontaneous hypocapnia [89/280 (32%)] versus induced hypocapnia [23/280 (8%)]. **Table 1** displays the baseline data for all subjects in the cohort, as well as for subjects with no hypocapnia exposure, induced hypocapnia, and spontaneous hypocapnia. The most common type of cardiac arrest was out-of-hospital cardiac arrest with PEA/asystole as the initial rhythm [109/280 (39%)]. Patients with spontaneous hypocapnia had a longer median [interquartile (IQR)] duration of CPR compared to those with no hypocapnia exposure, 18 (10-26) vs. 11 (7-20) min respectively (Wilcoxon rank sum test $p = 0.021$). Otherwise, we found no differences in age, cardiac arrest characteristics, or comorbidities between groups.

Table 1: Baseline data for all subjects at the time of cardiac arrest.

Variable	All Subjects n = 280	No Hypocapnia* n = 168	Induced** Hypocapnia n = 23	Spontaneous† Hypocapnia n = 89	p-value
Age [years (SD)]	59 (15)	57 (14)	67 (15)	59 (16)	0.482
Female [n (%)]	101 (36)	58 (35)	9 (39)	34 (38)	0.801
BMI (kg/m^2 (SD)]	30 (8)	31 (8)	28 (8)	29 (8)	0.914
Pre-existing comorbidities [n (%)]					
Diabetes	68 (24)	43 (26)	4 (17)	21 (24)	0.679
Known coronary artery disease	75 (27)	48 (29)	6 (26)	21 (24)	0.690
Hypertension	183 (65)	101 (60)	17 (74)	65 (73)	0.078
Malignancy	20 (7)	11 (7)	2 (9)	7 (8)	0.885
Renal insufficiency	43 (15)	27 (16)	2 (9)	14 (16)	0.650
Pulmonary disease	65 (23)	46 (27)	4 (17)	15 (17)	0.129
Cerebral vascular disease	24 (9)	14 (8)	1 (4)	9 (10)	0.669
Congestive heart failure	69 (25)	42 (25)	5 (22)	22 (25)	0.944
Charlson comorbidity score(Murray et al., 2006) [median (IQR)]	1 (0-3)	1 (0-3)	1 (0-2)	1 (0-3)	0.780
Arrest location [n (%)]					
Out-of-hospital	216 (77)	127 (76)	17 (74)	72 (81)	
In-hospital	64 (23)	41 (24)	6 (26)	17 (19)	0.584
Initial arrest rhythm [n (%)]					
PEA/asystole	154 (55)	85 (51)	13 (57)	56 (63)	
VT/VF	103 (37)	67 (40)	10 (43)	26 (29)	0.201
Unknown	23 (8)	16 (10)	0	7 (8)	
CPR duration [median (IQR)]	15 (8-23)	11 (7-20)	15 (6-22)	18 (10-26)	0.066

* Hypocapnia was defined as a partial pressure of arterial carbon dioxide < 35 mmHg during the initial six hours after return of spontaneous circulation. ** Defined as actual respiratory rate not greater than the prescribed respiratory rate during the initial six hours after return of spontaneous circulation; † Defined as actual respiratory rate greater than the prescribed respiratory rate during 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 displays post-cardiac arrest data for all subjects. All patients were mechanically ventilated and received targeted temperature management after ROSC. Compared to those without hypocapnia exposure, patients with induced hypocapnia had a higher median (IQR) prescribed respiratory rate [16 (14-20) vs. 20 (17-22) breaths/min, Wilcoxon rank sum test p = 0.002] and minute ventilation, [121 (104-147) vs. 141 (131-164) cc/min*kg PBW, Wilcoxon rank sum test p = 0.003]. Patients with spontaneous hypocapnia exposure had a higher median (IQR) prescribed minute ventilation [130 (108-170) vs. 121 (104-147) cc/min*kg PBW, Wilcoxon rank sum test p = 0.043] and similar actual minute ventilation [148 (125-181) vs. 141 (118 - 168) cc/min*kg PBW, Wilcoxon rank sum test p = 0.084] compared to patients with no hypocapnia exposure. Patients with induced hypocapnia were more like to have received neuromuscular blocking agents compared to patients with spontaneous hypocapnia, 70% vs. 43%, Wilcoxon rank sum test p = 0.022. Spontaneous hypocapnia patients had a lower median (IQR) base excess compared to induced hypocapnia and no hypocapnia exposure, -10 (-13 - -6) vs. -7 (-12 - -3) and -6 (-10 - -2) respectively (Kruskal-Wallis rank test p <0.001), while induced hypocapnia had a higher pH compared to spontaneous hypocapnia and no hypocapnia, 7.34 (7.22-7.40) vs. 7.28 (7.19-7.36) and 7.26 (7.17-7.32) respectively (Kruskal-Wallis rank test p = 0.014). The majority of patients with spontaneous hypocapnia were found to have a metabolic acidosis 84%.

Table 2: Post-cardiac arrest data for all subjects.

Variable	All Subjects n = 280	No Hypocapnia* n = 168	Induced** Hypocapnia n = 23	Spontaneous† Hypocapnia n = 89	p-value
Ventilator parameters					
Prescribed respiratory rate (breaths/min)	17 (15-20)	16 (14-20)	20 (17-22)	18 (15-20)	0.005
Actual respiratory rate (breaths/min)	19 (17-22)	19 (17-22)	20 (17-22)	19 (18-22)	0.408
Tidal volume (cc/kg PBW)	7.4 (6.7-8.1)	7.3 (6.7-8.0)	7.4 (6.8-8.5)	7.6 (6.8-8.4)	0.147
Prescribed minute ventilation (cc/min*kg PBW)	125 (106-153)	121 (104-147)	141 (131-164)	130 (108-170)	0.004
FiO2	0.82 (0.66-0.97)	0.84 (0.66-0.99)	0.76 (0.64-0.90)	0.82 (0.67-0.96)	0.375
PEEP (cmH_2O)	5 (5-7)	5 (5-7)	5 (5-6)	5 (5-6)	0.272
Plateau pressure (cmH_2O)	20 (16-25)	21 (17-25)	18 (15-23)	19 (16-23)	0.135
Number of ABGs in first 6 hours	2 (2-3)	2 (2-3)	2 (2-4)	2 (2-3)	0.125
PaO_2/FiO_2 ratio	237 (145-337)	235 (118-309)	225 (151-402)	250 (160-362)	0.064
pH	7.27 (7.18-7.34)	7.26 (7.17-7.32)	7.34 (7.22-7.40)	7.28 (7.19-7.36)	0.014
Base excess	-8 (-11 - -3)	-6 (-10 - -2)	-7 (-12 - -3)	-10 (-13 - -6)	<0.001
Metabolic acidosis†† [n (%)]	202 (72)	112 (67)	15 (65)	75 (84)	0.008
MAP (mmHg)	94 (82-105)	94 (83-105)	88 (81-101)	93 (80-106)	0.508
Arterial hypotension‡ [n (%)]	142 (51)	83 (49)	15 (65)	44 (49)	0.348
Vasopressor infusion [n (%)]	150 (54)	87 (52)	15 (65)	48 (54)	0.478
Neuromuscular blockade [n (%)]	134 (48)	80 (48)	16 (70)	38 (43)	0.071
PCI [n (%)]	31 (11)	21 (13)	4 (17)	6 (7)	0.226
SOFA	7 (5-10)	8 (5-10)	7 (4-11)	7 (5-10)	0.800

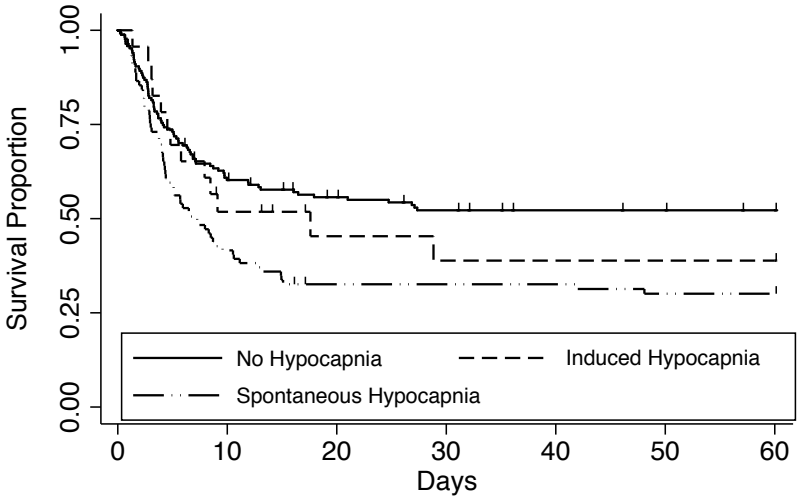
All values are median interquartile range unless otherwise noted.

* Hypocapnia was defined as a partial pressure of arterial carbon dioxide < 35 mmHg during the initial six hours after return of spontaneous circulation. ** Defined as actual respiratory rate not greater than the prescribed respiratory rate during the initial six hours after return of spontaneous circulation; † Defined as actual respiratory rate greater than the prescribed respiratory rate during the initial six hours after return of spontaneous circulation. †† Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡ Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation. ABG, arterial blood gas; FiO_2, fraction of inspired oxygen; MAP, mean arterial blood pressure; PaO_2, partial pressure of arterial oxygen; PBW, predicted body weight; PCI, percutaneous coronary intervention; PEEP, positive end expiratory pressure, ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment.

One hundred and fifty-four (55%) patients had the primary outcome of 60-day mortality. Among those who died the median (IQR) survival time was 4 (2-8) days. Patients with any exposure to hypocapnia had a higher 60-day mortality compared to those with no hypocapnia exposure [67% vs. 47%, absolute risk difference 20% (95% CI 8% - 31%), p = 0.001]. Patients with spontaneous hypocapnia had a higher incidence of 60-day mortality compared to those without hypocapnia exposure [70% vs. 47%, absolute risk difference 23% (95% CI 10% - 35%), p < 0.001]. We did not find a statistically significant difference in 60-day mortality between patients with spontaneous hypocapnia and induced hypocapnia [70% vs. 57%, absolute risk difference 13% (95% CI -9% - 36%), p = 0.232], or induced hypocapnia and no hypocapnia exposure [57% vs. 47%, absolute risk difference 9% (95% CI -12% - 31%), p = 0.393]. Among patients with no hypocapnia exposure, patients over-breathing the prescribed ventilator settings had a lower 60-day mortality compared to those who were not over-breathing the ventilator [43% (62/144) vs. 71% (17/24), absolute risk difference -28% (-48% - -8%), p = 0.012].

On Kaplan-Meier analysis, the 60-day survival fractions for both the spontaneous and induced hypocapnia groups diverge from no hypocapnia exposure (**Figure 1**). We found a statistically significant difference between the groups (log-rank test p = 0.003). However, after adjusting for potential baseline and post-cardiac arrest confounders, spontaneous hypocapnia, but not induced hypocapnia, was found to be an independent predictor of 60-day mortality, hazard ratios 1.64 (95% CI 1.43-1.87) and 1.14 (95% CI 0.84-1.54) respectively (**Table 3**). Using the same model we found spontaneous hypocapnia to have a higher risk of mortality compared to induced hypocapnia, hazards ratio 1.44 (95% CI 1.10-1.88), p = 0.007. The model was correctly specified (linktest, p = 0.810) and did not violate the proportional-hazards assumption (p = 0.369).

Figure 1: Sixty-day mortality between no hypocapnia exposure, induced hypocapnia, and spontaneous hypocapnia.



Number at risk				
No Hypocapnia	167	82	71	68
Induced Hypocapnia	23	7	6	6
Spontaneous Hypocapnia	89	26	26	24

Table 3: Multivariable Cox proportional hazards model with 60-day mortality as the dependent variable.

Variables	Hazard Ratio	95% CI	p-value
Hypocapnia*			<0.001
No exposure		Reference	
Spontaneous**	1.64	1.43 - 1.87	<0.001
Induced†	1.14	0.84 - 1.54	0.406
VT/VF	0.45	0.29 - 0.70	<0.001
Metabolic acidosis††	2.76	1.77 - 4.31	<0.001
Age‡	1.10	0.90 - 1.35	0.364
Arterial hypotension‡‡	2.00	1.33 - 3.00	0.001
Charlson co-morbidity index	1.27	1.09 - 1.47	0.002
In-hospital cardiac arrest	0.61	0.37 - 1.02	0.062
CPR duration (min)	1.01	1.00 - 1.02	0.008
NMB agent administration	0.96	0.63 - 1.47	0.855

* Hypocapnia was defined as a partial pressure of arterial carbon dioxide < 35 mmHg during the initial six hours after return of spontaneous circulation. ** Defined as actual respiratory rate greater than the prescribed respiratory rate during the initial six hours after return of spontaneous circulation; † Defined as actual respiratory rate not greater than the prescribed respiratory rate during the initial six hours after return of spontaneous circulation. †† Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡ Calibrated for a rise in 10 years. ‡‡ Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; CPR, cardiopulmonary resuscitation; NMB, neuromuscular blocking; VT/VF, ventricular tachycardia/ventricular fibrillation.

CHAPTER 4

DISCUSSION

In this multicenter study, we prospectively identified adult post-cardiac arrest patients, and determined the incidence of spontaneous and induced hypocapnia exposure during the first six hours after ROSC. Our objective was to test whether post-ROSC exposure to spontaneous hypocapnia was associated with 60-day mortality. Similar to our previous work (Roberts, Kilgannon, Chansky, Mittal, Wooden, & Trzeciak, 2013) we found that 40% of patients had exposure to hypocapnia. In this study we found the majority of hypocapnia exposure occurred in patients who had a spontaneous respiratory rate higher than the prescribed respiratory rate, suggesting that for the majority of patients with hypocapnia, hypocapnia was the result of the intrinsic respiratory drive as opposed to the prescribed ventilator settings. Using a multivariable Cox proportional hazards model we found spontaneous hypocapnia, but not induced hypocapnia, was an independent predictor of 60-day mortality. These findings further suggest that the association between hypocapnia and clinical outcome may be related to an intrinsic patient characteristic as opposed to the prescribed ventilator settings.

$PaCO_2$ is a major regulator of cerebral blood flow after brain injury. Hypocapnia has been postulated to exacerbate post-ROSC anoxic brain injury secondary to hypocapnia-induced cerebral vasoconstriction resulting in decreased cerebral blood flow and increased cerebral ischemia (Ausina et al., 1998; Buunk et al., 1997; Yundt & Diringer, 1997). Although it has been suggested that during this initial post-ROSC period the degree of vasoactive reactivity to $PaCO_2$ may be blunted, (Krep, Brinker, Pillekamp, & Hossmann, 2000; Nemoto, Snyder, Carroll, & Morita, 1975) recent literature suggests it remains intact (Buunk et al., 1997; Kagstrom, Smith, & Siesjo, 1983; Safar et al., 1996). Hypocapnia has also been suggested to worsen ischemic/reperfusion injury by

increasing cerebral oxygen demand through increased neural excitability, which could be deleterious in anoxic brain injury (Bergsholm, Gran, & Bleie, 1984; Huttunen et al., 1999).

Hypocapnia has been demonstrated to be associated with poor clinical outcomes in traumatic brain injury patients, mechanically ventilated preterm neonates, subarachnoid hemorrhage patients, and adult and pediatric post-cardiac arrest patients (Roberts et al., 2015). Also, a previous clinical study found ventilation titrated to maintain $PaCO_2$ 37.6 – 45.1 mmHg, as a part of a bundle with multiple other goals (including targeted temperature management, and oxygenation and blood pressure goals), was associated with increased survival in post-cardiac patients (Sunde et al., 2007). However, the independent effects of $PaCO_2$ control itself cannot be determined from this study.

Central neurogenic hyperventilation and subsequent hypocapnia has been demonstrated to occur is several forms of brain injury (Johnston, Singh, Ralston, & Gold, 2001; Nystad, Salvesen, & Nielsen, 2007; Takahashi, Tsunemi, Miyayosi, & Mizusawa, 2007; Williamson et al., 2015). It has been postulated that hyperventilation is induced in the setting of brain injury by disruption of cortical inhibition on the respiratory center of the brainstem, thus disinhibiting the brainstem respiratory centers and triggering hyperventilation (Leitch, McLennan, Balkenhol, Loudon, & McLaurin, 1979). A recent study found spontaneous hyperventilation is common in subarachnoid hemorrhage and is associated with delayed cerebral ischemia and poor neurological outcome (Williamson et al., 2015). It is possible that spontaneous hyperventilation and hypocapnia, resulting in ongoing cerebral ischemia, also occurs in post-cardiac arrest syndrome. However, as opposed to just being a marker for cerebral injury, over-breathing the ventilator among post-cardiac arrest patients may also be a compensative response to metabolic acidosis,

which is common after cardiac arrest (Roberts, Kilgannon, Chansky, Mittal, Wooden, & Trzeciak, 2013). Spontaneous respirations above the prescribed ventilator settings are consistent with some degree of respiratory center function and have been demonstrated to be predictive of better clinical outcomes compared to breathing at the ventilator rate or apnea (Nyam et al., 2017; Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005). In this study we found among patients without hypocapnia, breathing above the prescribed ventilator settings was associated with improved survival. However, over-breathing the ventilator resulting in hypocapnia exposure (i.e. spontaneous hypocapnia) was associated with 60-day mortality. In addition, the majority of the patients with spontaneous hypocapnia had a metabolic acidosis. Thus, it is possible that for the majority of post-cardiac arrest patients who over-breath the ventilator, hyperventilation may be a marker of an intact respiratory center compensating for metabolic acidosis, and thus a predictor of survival. However, when this response results in exposure to hypocapnia, it is possible reperfusion injury is exacerbated by the detrimental hypocapnia-induced mechanisms discussed above.

Current post-cardiac arrest guidelines recommend targeting normocapnia (i.e. $PaCO_2$ 35-45 mmHg) and avoiding hypocapnia during the initial post-ROSC period (Callaway et al., 2015a; Nolan et al., 2015). These recommendations are based on previous cohort studies (B. K. Lee et al., 2014; Roberts, Kilgannon, Chansky, Mittal, Wooden, & Trzeciak, 2013; Schneider et al., 2013) and it is currently unclear if hypocapnia is a marker for poor prognosis or if preventing hypocapnia exposure could improve clinical outcomes. To our knowledge this is the first report demonstrating that the majority of hypocapnia exposure is caused by intrinsic respiratory drive as opposed to prescribed ventilator settings. These results suggest that future clinical trials of $PaCO_2$ optimization likely will require administration of neuromuscular blocking agents to prevent

hyperventilation and hypocapnia exposure. However, benefits of administration of such agents must be weighed against the risks of worsening acidosis.

We acknowledge that this study has important limitations to consider. First, although we used a multivariable Cox proportional hazards model to adjust for potential confounders, there still exists the potential of unmeasured confounders. Second, it remains possible that spontaneous hypocapnia is a compensation for a more severe metabolic acidosis and reflects a patient population that is more ill and therefore has a higher likelihood to have 60-day mortality. However, spontaneous hypocapnia remained an independent predictor of 60-day mortality after adjusting our model for metabolic acidosis and duration of CPR. In addition, we did not observe any significant differences in the post-resuscitation SOFA score, or the incidence of post-resuscitation arterial hypotension or vasopressor administration between the three groups, suggesting this was not the case. Third, although we found a trend in higher mortality among patients with induced hypocapnia compared to no hypocapnia exposure (57% vs. 46%), this was not statistically significant. It is possible we did not find a statistically significant association secondary to the small number of patients with induced hypocapnia (n = 23). In addition, it is possible that some of the patients in the induced hypocapnia group would have over-breathed the ventilator had they been prescribed a lower minute ventilation or had a lower rate of neuromuscular blockade administration. However, if this were the case then an even higher proportion of patients would have been found to have spontaneous hypocapnia, further demonstrating that hypocapnia may be the result of intrinsic respiratory drive as opposed to the prescribed ventilator settings.

In conclusion, spontaneous hypocapnia is common during the initial six hours after return of spontaneous circulation and is independently associated with 60-day mortality.

Future randomized control trials are warranted to test if preventing exposure to hypocapnia improves clinical outcome.

BIBLIOGRAPHY

Ausina, A., Baguena, M., Nadal, M., Manrique, S., Ferrer, A., Sahuquillo, J., & Garnacho, A. (1998). Cerebral hemodynamic changes during sustained hypocapnia in severe head injury: can hyperventilation cause cerebral ischemia? *Acta neurochirurgica. Supplement, 71*, 1-4.

Berg, R. A., Hemphill, R., Abella, B. S., Aufderheide, T. P., Cave, D. M., Hazinski, M. F., . . . Swor, R. A. (2010). Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation, 122*(18 Suppl 3), S685-705. doi:10.1161/CIRCULATIONAHA.110.970939

Bergsholm, P., Gran, L., & Bleie, H. (1984). Seizure duration in unilateral electroconvulsive therapy. The effect of hypocapnia induced by hyperventilation and the effect of ventilation with oxygen. *Acta psychiatrica Scandinavica, 69*(2), 121-128.

Buunk, G., van der Hoeven, J. G., & Meinders, A. E. (1997). Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. *Stroke; a journal of cerebral circulation, 28*(8), 1569-1573.

Callaway, C. W., Donnino, M., Fink, E., Geocadin, R. G., Golan, E., Kern, K. B., . . . Zimmerman, J. L. (2015a). Part 8: Post-cardiac arrest care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation, 132*(Suppl 1), S465-S482. doi:10.1161/CIR.0000000000000262

Callaway, C. W., Donnino, M. W., Fink, E. L., Geocadin, R. G., Golan, E., Kern, K. B., . . . Zimmerman, J. L. (2015b). Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and

Emergency Cardiovascular Care. *Circulation, 132*(18 Suppl 2), S465-482. doi:10.1161/CIR.0000000000000262

Cold, G. E. (1990). Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. *Acta neurochirurgica. Supplementum, 49*, 1-64.

Gaul, G. B., Gruska, M., Titscher, G., Blazek, G., Havelec, L., Marktl, W., . . . Kaff, A. (1996). Prediction of survival after out-of-hospital cardiac arrest: results of a community-based study in Vienna. *Resuscitation, 32*(3), 169-176.

Hajbaghery, M. A., Mousavi, G., & Akbari, H. (2005). Factors influencing survival after in-hospital cardiopulmonary resuscitation. *Resuscitation, 66*(3), 317-321. doi:10.1016/j.resuscitation.2005.04.004

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

Huang, C. T., Cook, A. W., & Lyons, H. A. (1963). Severe Craniocerebral Trauma and Respiratory Abnormalities. I. Physiological Studies with Specific Reference to Effect of Tracheostomy on Survival. *Arch Neurol, 9*, 545-554.

Huttunen, J., Tolvanen, H., Heinonen, E., Voipio, J., Wikstrom, H., Ilmoniemi, R. J., . . . Kaila, K. (1999). Effects of voluntary hyperventilation on cortical sensory responses. Electroencephalographic and magnetoencephalographic studies. *Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale, 125*(3), 248-254.

Johnston, S. C., Singh, V., Ralston, H. J., 3rd, & Gold, W. M. (2001). Chronic dyspnea and hyperventilation in an awake patient with small subcortical infarcts. *Neurology, 57*(11), 2131-2133.

Kagstrom, E., Smith, M. L., & Siesjo, B. K. (1983). Cerebral circulatory responses to hypercapnia and hypoxia in the recovery period following complete and incomplete cerebral ischemia in the rat. *Acta physiologica Scandinavica, 118*(3), 281-291. doi:10.1111/j.1748-1716.1983.tb07272.x

Kilgannon, J. H., Roberts, B. W., Jones, A. E., Mittal, N., Cohen, E., Mitchell, J., . . . Trzeciak, S. (2014). Arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest*. *Critical care medicine, 42*(9), 2083-2091. doi:10.1097/CCM.0000000000000406

Kong, M. H., Fonarow, G. C., Peterson, E. D., Curtis, A. B., Hernandez, A. F., Sanders, G. D., . . . Al-Khatib, S. M. (2011). Systematic review of the incidence of sudden cardiac death in the United States. *Journal of the American College of Cardiology, 57*(7), 794-801. doi:10.1016/j.jacc.2010.09.064

Krep, H., Brinker, G., Pillekamp, F., & Hossmann, K. A. (2000). Treatment with an endothelin type A receptor-antagonist after cardiac arrest and resuscitation improves cerebral hemodynamic and functional recovery in rats. *Critical care medicine, 28*(8), 2866-2872.

Langhelle, A., Tyvold, S. S., Lexow, K., Hapnes, S. A., Sunde, K., & Steen, P. A. (2003). In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation, 56*(3), 247-263.

Laver, S., Farrow, C., Turner, D., & Nolan, J. (2004). Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive care medicine, 30*(11), 2126-2128. doi:10.1007/s00134-004-2425-z

Lee, B. K., Jeung, K. W., Lee, H. Y., Lee, S. J., Jung, Y. H., Lee, W. K., . . . Min, Y. I. (2014). Association between mean arterial blood gas tension and outcome in

cardiac arrest patients treated with therapeutic hypothermia. *Am J Emerg Med, 32*(1), 55-60. doi:10.1016/j.ajem.2013.09.044

Lee, M. C., Klassen, A. C., & Resch, J. A. (1974). Respiratory pattern disturbances in ischemic cerebral vascular disease. *Stroke; a journal of cerebral circulation, 5*(5), 612-616.

Leitch, A. G., McLennan, J. E., Balkenhol, S., Loudon, R. G., & McLaurin, R. L. (1979). Mechanisms of hyperventilation in head injury: case report and review. *Neurosurgery, 5*(6), 701-707.

Murray, S. B., Bates, D. W., Ngo, L., Ufberg, J. W., & Shapiro, N. I. (2006). Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 13*(5), 530-536. doi:10.1197/j.aem.2005.11.084

Nadkarni, V. M., Larkin, G. L., Peberdy, M. A., Carey, S. M., Kaye, W., Mancini, M. E., . . . Berg, R. A. (2006). First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA : the journal of the American Medical Association, 295*(1), 50-57. doi:10.1001/jama.295.1.50

Nemoto, E. M., Snyder, J. V., Carroll, R. G., & Morita, H. (1975). Global ischemia in dogs: cerebrovascular CO2 reactivity and autoregulation. *Stroke; a journal of cerebral circulation, 6*(4), 425-431.

Network, T. A. R. D. S. (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *The New England journal of medicine, 342*(18), 1301-1308. doi:10.1056/NEJM200005043421801

Neumar, R. W., Nolan, J. P., Adrie, C., Aibiki, M., Berg, R. A., Bottiger, B. W., . . . Vanden Hoek, T. (2008). Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation, 118*(23), 2452-2483. doi:10.1161/CIRCULATIONAHA.108.190652

Nolan, J. P., Hazinski, M. F., Aickin, R., Bhanji, F., Billi, J. E., Callaway, C. W., . . . Zideman, D. A. (2015). Part 1: Executive summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation, 95*, e1-31. doi:10.1016/j.resuscitation.2015.07.039

North, J. B., & Jennett, S. (1974). Abnormal breathing patterns associated with acute brain damage. *Arch Neurol, 31*(5), 338-344.

Nyam, T. E., Ao, K. H., Hung, S. Y., Shen, M. L., Yu, T. C., & Kuo, J. R. (2017). FOUR Score Predicts Early Outcome in Patients After Traumatic Brain Injury. *Neurocrit Care, 26*(2), 225-231. doi:10.1007/s12028-016-0326-y

Nystad, D., Salvesen, R., & Nielsen, E. W. (2007). Brain stem encephalitis with central neurogenic hyperventilation. *Journal of neurology, neurosurgery, and psychiatry, 78*(1), 107-108. doi:10.1136/jnnp.2006.094375

Peberdy, M. A., Kaye, W., Ornato, J. P., Larkin, G. L., Nadkarni, V., Mancini, M. E., . . . Lane-Trultt, T. (2003). Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation, 58*(3), 297-308.

Pelosi, P., Ferguson, N. D., Frutos-Vivar, F., Anzueto, A., Putensen, C., Raymondos, K., . . . Ventila Study, G. (2011). Management and outcome of mechanically ventilated neurologic patients. *Critical care medicine, 39*(6), 1482-1492. doi:10.1097/CCM.0b013e31821209a8

Prentice, R. L., & Kalbfleisch, J. D. (1979). Hazard rate models with covariates. *Biometrics, 35*(1), 25-39.

Roberts, B. W., Karagiannis, P., Coletta, M., Kilgannon, J. H., Chansky, M. E., & Trzeciak, S. (2015). Effects of PaCO2 derangements on clinical outcomes after cerebral injury: A systematic review. *Resuscitation, 91*, 32-41. doi:10.1016/j.resuscitation.2015.03.015

Roberts, B. W., Kilgannon, J. H., Chansky, M. E., Mittal, N., Wooden, J., Parrillo, J. E., & Trzeciak, S. (2013). Multiple organ dysfunction after return of spontaneous circulation in postcardiac arrest syndrome. *Critical care medicine, 41*(6), 1492-1501. doi:10.1097/CCM.0b013e31828a39e9

Roberts, B. W., Kilgannon, J. H., Chansky, M. E., Mittal, N., Wooden, J., & Trzeciak, S. (2013). Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation, 127*(21), 2107-2113. doi:10.1161/CIRCULATIONAHA.112.000168

Roberts, B. W., Kilgannon, J. H., Chansky, M. E., & Trzeciak, S. (2014). Association between initial prescribed minute ventilation and post-resuscitation partial pressure of arterial carbon dioxide in patients with post-cardiac arrest syndrome. *Ann Intensive Care, 4*(1), 9. doi:10.1186/2110-5820-4-9

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Adams, R. J., Berry, J. D., Brown, T. M., . . . Wylie-Rosett, J. (2011). Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation, 123*(4), e18-e209. doi:10.1161/CIR.0b013e3182009701

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2012). Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation, 125*(1), e2-e220. doi:10.1161/CIR.0b013e31823ac046

Rout, M. W., Lane, D. J., & Wollner, L. (1971). Prognosis in acute cerebrovascular accidents in relation to respiratory pattern and blood gas tensions. *British medical journal, 3*(5765), 7-9.

Safar, P., Xiao, F., Radovsky, A., Tanigawa, K., Ebmeyer, U., Bircher, N., . . . Stezoski, S. W. (1996). Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. *Stroke; a journal of cerebral circulation, 27*(1), 105-113.

Schneider, A. G., Eastwood, G. M., Bellomo, R., Bailey, M., Lipcsey, M., Pilcher, D., . . . Pilcher, J. (2013). Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation, 84*(7), 927-934. doi:10.1016/j.resuscitation.2013.02.014

Sunde, K., Pytte, M., Jacobsen, D., Mangschau, A., Jensen, L. P., Smedsrud, C., . . . Steen, P. A. (2007). Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation, 73*(1), 29-39. doi:10.1016/j.resuscitation.2006.08.016

Takahashi, M., Tsunemi, T., Miyayosi, T., & Mizusawa, H. (2007). Reversible central neurogenic hyperventilation in an awake patient with multiple sclerosis. *J Neurol, 254*(12), 1763-1764. doi:10.1007/s00415-007-0662-0

Tok, D., Keles, G. T., Toprak, V., & Topcu, I. (2004). Assessment of in-hospital cardiopulmonary resuscitation using Utstein template in a university hospital. *The Tohoku journal of experimental medicine, 202*(4), 265-273.

Trzeciak, S., Dellinger, R. P., Parrillo, J. E., Guglielmi, M., Bajaj, J., Abate, N. L., . . . Hollenberg, S. M. (2007). Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Annals of emergency medicine, 49*(1), 88-98, 98 e81-82. doi:10.1016/j.annemergmed.2006.08.021

Trzeciak, S., Jones, A. E., Kilgannon, J. H., Milcarek, B., Hunter, K., Shapiro, N. I., . . . Parrillo, J. E. (2009). Significance of arterial hypotension after resuscitation from cardiac arrest. *Critical care medicine, 37*(11), 2895-2903; quiz 2904.

Trzeciak, S., McCoy, J. V., Phillip Dellinger, R., Arnold, R. C., Rizzuto, M., Abate, N. L., . . . Hollenberg, S. M. (2008). Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive care medicine, 34*(12), 2210-2217. doi:10.1007/s00134-008-1193-6

Wijdicks, E. F., Bamlet, W. R., Maramattom, B. V., Manno, E. M., & McClelland, R. L. (2005). Validation of a new coma scale: The FOUR score. *Ann Neurol, 58*(4), 585-593. doi:10.1002/ana.20611

Williamson, C. A., Sheehan, K. M., Tipirneni, R., Roark, C. D., Pandey, A. S., Thompson, B. G., & Rajajee, V. (2015). The Association Between Spontaneous Hyperventilation, Delayed Cerebral Ischemia, and Poor Neurological Outcome in Patients with Subarachnoid Hemorrhage. *Neurocrit Care, 23*(3), 330-338. doi:10.1007/s12028-015-0138-5

Yundt, K. D., & Diringer, M. N. (1997). The use of hyperventilation and its impact on cerebral ischemia in the treatment of traumatic brain injury. *Critical care clinics, 13*(1), 163-184.

Zheng, Z. J., Croft, J. B., Giles, W. H., & Mensah, G. A. (2001). Sudden cardiac death in the United States, 1989 to 1998. *Circulation, 104*(18), 2158-2163.