Variation in Sedation and Neuromuscular Blockade Regimens on Outcome After Cardiac Arrest

A thesis submitted by

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in partial fulfillment of the requirements for the degree of

Master of Science

in

Clinical and Translational Science

Tufts University

Sackler School of Graduate Biomedical Sciences

February 2018

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Abstract

Sedation and neuromuscular blockade (NMB) protocols in patients undergoing targeted temperature management (TTM) after cardiac arrest address patient discomfort and manage shivering. These protocols vary widely between centers and may affect outcomes. Consecutive patients admitted to 20 centers after resuscitation from cardiac arrest were prospectively entered into the International Cardiac Arrest Registry between 2004-2016. Additional data about each center's sedation and shivering management practice was obtained via survey. Sedation and shivering practices (SP) were categorized as deep sedation and minimal or no NMB (SP1), moderate-deep sedation with continuous or scheduled NMB (SP2), or moderate-deep sedation with as-needed NMB (SP3). Good outcome was defined as cerebral performance category (CPC) score of 1 or 2. A logistic regression hierarchical model was created with two levels (patient-level data with standard confounders at level one and hospitals at level two) and sedation practice as a random effect at the hospital level. The primary outcome was dichotomized CPC at 6 months and the secondary outcome was dichotomized CPC at ICU discharge. A total of 4,267 patients were included, with mean age 62±15 years, 36% female, 77% out-of-hospital arrests, mean ischemic time was 24(±18) minutes, and good outcome at ICU discharge was 32% (1313 patients). The unadjusted odds ratio (OR) for good outcome at 6 months was 1.19 (0.88-1.42, p=0.07) and 1.65 (1.40-1.97, p<0.001) for SP2 and SP3 respectively, referenced to SP1. Adjusted odds ratio (for age, ischemic time, location of arrest, witnessed, initial rhythm, bystander CPR, and defibrillation, medical history and size of hospital) was 1.13 (0.74-1.73, p=0.56) and 1.45 (1.00-2.13, p=0.046) for SP2 and SP3 respectively, referenced to SP1. For the secondary endpoint of good outcomes at

discharge, the unadjusted odds ratio for SP2 and SP3 was 1.10 (0.90-1.34, p=0.34) and 1.69 (1.41-2.01, p<0.001), with adjusted odds ratios of 0.86 (0.55-1.35, p=0.52) and 1.46 (0.97-2.20, p=0.07), respectively. Cardiac arrest patients treated at centers using moderate-deep sedation and as-needed NMB had increased odds of good outcomes compared to centers using deep sedation and avoidance of NMB, even after adjusting for potential confounders. Using sedation alone to treat shivering associated with TTM could be harmful. These findings should be further investigated in prospective studies.

Acknowledgments:

I would like to firstly acknowledge my mentorship team: Dr. David Seder (primary mentor), Dr. Richard Riker (secondary mentor), Dr. David Kent (study design mentor) and Dr. Douglas Sawyer (career mentor) for their expertise, knowledge, and unwavering enthusiasm for this work and my future career. I would like to recognize the statistical support given by Christine Duarte, PhD who helped with the primary analysis and Farzad Noubary, PhD who served on the thesis committee. I thank Farzad and Jess Paulus for their education in statistical methods, study design, epidemiology and biostatistics, which have been incredibly valuable in shaping my future endeavors. I could not complete this work without the funding provided by the KL2TR001063, directed by Karen Freund, MD, MPH. In addition I would like to acknowledge the institutions that contributed data to INTCAR in their pursuit of better understanding this patient population. Lastly, I would like to thank my husband Kyle and daughter Josephine for their endless support.

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List of Abbreviations

ROSC	Return of Spontaneous Circulation
TTM	Targeted Temperature management
NMB	Neuromuscular Blockade
OHCA	Out of Hospital Cardiac Arrest
INHA	In Hospital Cardiac Arrest
PAD	Pain Agitation Delirium
ICP	Intracranial Pressure
HIE	Hypoxic Ischemic Encephalopathy
INTCAR	International Cardiac Arrest Registry
SP	Sedation Practice

Chapter 1: Introduction

Cardiac arrest is the third leading cause of death in the United States, following cancer and heart diseases[1]. Over the past several decades, the single most promising intervention for patients who obtain return of spontaneous circulation (ROSC) after cardiac arrest is the use of targeted temperature management (TTM). This involves decreasing the body temperature to 33 or 36 degrees for 12 to 24 hours after ROSC for any patient who shows signs of being encephalopathic [2]. This treatment, which has been internationally adopted, results in the need for sedation for comfort during cooling and various methods of shivering control, including sedative and analgesic medications along with neuromuscular blockade (NMB). NMB, when used, requires sedation to prevent patients awareness paralysis. However, the optimal dose, target, and duration of this treatment are unknown and may influence outcomes.

1.1 Unexplained variation in outcome by center

Among centers employing TTM following return of spontaneous circulation (ROSC), there is wide variation in outcomes. Studies have found that survival rates for out-of-hospital-cardiac-arrest (OHCA) range from 32% to 54% after for adjusting for age, ventilator status, and severity of illness[3]. The most cited reason for this is time to compressions, appropriate defibrillation by bystander or EMS personnel, the health of the patient, and the volume of the treating center although the extent to which each of these contribute has not well been studied. Risk-adjusted odds ratio for survival of in-hospital-cardiac-arrest (IHCA) varies by 42 percent among similar case-mixed hospitals after adjusting for 36 variables known to influence outcomes[4]. Inpatient management of these patients is not well standardized and may explain some of this variability. While the use

of TTM is recommended by international resuscitation guidelines[2], there is no recommendation for sedation and neuromuscular blockade (NMB) use in these patients. Sedation practices influence outcomes in the general ICU population and may explain some of the differences in cardiac arrest outcomes described above. Despite the substantial variation in outcome among hospitals and the known importance of sedation practices in the general ICU population, this topic is understudied in the cardiac arrest literature. When sedation is described, doses and targets of sedation and NMB vary widely[5].

1.2 Harms of sedation in medical/surgical ICU

Targeted sedation, along with sedation lightening protocols, has substantially improved outcomes of patients in the medical/surgical ICU. Light sedation (i.e., a patient who will waken to stimuli, communicate, and follow commands) was strongly recommended in the most recent guidelines for treating ICU pain, agitation, and delirium (PAD), published in 2013, due to improved outcomes of patients with lighter sedation when compared to deeper sedation[6-9]. Even brief deep sedation levels early in hospitalization have been shown to worsen 180-day mortality[10]. However, for patients receiving neuromuscular blockade (NMB), which is required to prevent or control shivering, deep levels of sedation (the patient is unresponsive to painful stimuli) are recommended to prevent the patient from being aware of paralysis. This conundrum must be investigated in the cardiac arrest population.

1.3 Benefits of sedation in the medical/surgical ICU

Continuous neuromuscular blockade, accompanied by deep sedation to prevent recall during paralysis, has been evaluated in acute respiratory distress patients and has been

shown to improve gas exchange, reduce pro-inflammatory cytokines measured directly from the lung, decrease ventilator free days and reduce adjusted 90-day mortality[11]. It is unknown whether this benefit is from the paralysis or deep sedation. High levels of sedation and NMB are also used in patients with elevated intracranial pressure (ICP). Here, propofol has been shown to reduce cerebral oxygen consumption and cerebral blood flow volume, which subsequently reduces ICP[12]. Cardiac arrest patients do not routinely have ICP monitors but a subset of patients experience brain inflammation and edema that can be recognized on radiographic imaging. The degree of potential ICP elevations and effect of sedative medications in this population is unknown.

1.4 Sedation can accumulate during TTM and affect prognostication

Some amount of sedation is required during TTM to prevent discomfort associated with a lower body temperature, but other considerations include lowering the hypothalamic shivering set-point to decrease systemic metabolic demands and cardiac strain, reduce cerebral oxygen demands, suppress or prevent seizures (that occur in up to 40% in cardiac arrest patients), and prevent awareness during NMB. The target of sedation needed to achieve these objectives varies from light to deep, depending on the goal at any particular time. However, the goals shift over the period of cooling and rewarming, when heavier sedation is needed early on for shivering control and comfort, but lighter sedation may be targeted at the end of rewarming to allow ventilator weaning and neuroprognostication. The most concerning complication is accumulation of drugs during TTM, which may confound the critical post-TTM neurological examination and influence the possibility of withdrawal of care. Although human studies are limited, midazolam plasma concentration can increase 5-fold during hypothermia in traumatic

brain injured patients, and propofol concentrations by 28% in hypothermic healthy adults[13,14]. The cytochrome-P450-3A system, which metabolizes many important ICU medications including midazolam, fentanyl, and propofol, decreases the clearance of these drugs by 7%-22% per degree Celsius below 37 degrees during cooling[15]. Organ dysfunction is also common after cardiac arrest and may be as high as 53%[16]. The liver and kidneys are largely responsible for metabolism and clearance of many of the medications and sedative drugs used during TTM. It is common for hypothermic patients after cardiac arrest to have reduced renal function that may or may not be reflected in the serum creatinine[17,18]. NMB can also accumulate during renal dysfunction, resulting in prolonged residual paralysis. Several published recommendations suggest that assessment of neurologic prognosis be delayed at least three days after cardiac arrest; however, the most recent American Heart Association and International Liaison Committee on Resuscitation 2015 favor delayed prognostication. The ideal timing for withdrawal of life support in the setting of a poor neurologic exam is unclear[2] and is confounded by both provider and family biases. Several reports of delayed wakening at 7 or more days after cardiac arrest have been reported[19] and are likely to be linked to the sedation regimens received during TTM.

1.5 Optimal shivering management is unknown

Very high dose of sedation and analgesia medications (that lower the shivering set point via action on the anterior hypothalamus) and neuromuscular blockade (which peripherally eliminates shivering, independent of the shivering set point) are routinely used for shivering control during TTM. Control of shivering can be achieved by high doses of sedation and avoiding NMB (SP1) or using continuous (SP2) or intermittent

(SP3) NMB to prevent or treat shivering with lower doses of sedation. However, there are few data to support or refute the risks or benefits of any specific approach, and addressing this knowledge gap is key to finding the best way to target sedation for these patients. Reports of protocols that try to utilize non-NMB methods of controlling shivering require levels of sedation that would be consistent with very-deep sedation (i.e., median propofol dose of 101mcg/kg/min with a median fentanyl dose of 47mcg/h)[20]. These doses are associated with higher incidence of complications in the general ICU population. Regarding NMB, many questions remain unanswered about the risks and benefits of continuous versus intermittent NMB versus no NMB, and also how to best target its use. A retrospective study of 123 adults treated with TTM after cardiac arrest compared continuous-infusion vecuronium in 80 patients with intermittent boluses of vecuronium in 43 patients. There was a shorter time to return of spontaneous respirations and extubation in the continuous infusion group[21]. This group also had improved survival when compared to the scheduled-intermittent group and also to those patients receiving no NMB. Another retrospective study evaluated 117 patients receiving continuous NMB for shivering compared to 27 patients without NMB[22]. ICU mortality was lower in patients treated with NMB but the difference was not significant after adjustment. Recent observations, suggest that patients with the most severe brain injury have less shivering[23-25] may partially explain the results above. However, this key treatment aspect remains unexplored in multicenter prospective data.

Chapter 2: Variation in sedation and neuromuscular blockade regimens on outcome after cardiac arrest[1]

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[1]May TL, Riker RR, Fraser G, Hirsch KG, Agarwal S, Friberg H, Soreid E, Patel N, Mooney M, McPherson J, Hand R, Kent D, Nielsen N, Seder DB Submitted to *Critical Care Medicine*, 11/2/2017.

2.1 Introduction

Targeted temperature management (TTM) may improve functional outcomes of patients with hypoxic ischemic encephalopathy (HIE) after cardiac arrest, and is recommended for these patients after the return of spontaneous circulation (ROSC)[26]. Sedative and analgesic infusions and neuromuscular blockade agents (NMB) are commonly used during TTM for comfort, suppression of shivering, and reduction of metabolic activity, but the optimal regimens are unknown, and dosing strategies vary widely[5,20,27,28]. During TTM, shivering increases the systemic metabolic rate[29], reduces brain oxygen levels[30], and increases intracranial pressure[31], each of which can worsen secondary neurologic injury. To counteract these effects, different strategies have been proposed, ranging from high dose of sedatives and analgesics without NMB, to much lower does with intermittent or continuous NMB[5,32,33].

Deeper sedation is associated with worse outcomes in other medical and surgical ICU populations [8,9,31,34-36]. During TTM, observational studies suggest that sedatives and analgesics accumulate due to impaired metabolism, which can delay wakening, confound neurologic assessment, and potentially result in inappropriate withdrawal of life support[15,27,32,37,38]. Deeper sedation also may induce more hypotension with or without lower cardiac index, which may also affect outcomes [39-42]. The approach to NMB during TTM also varies widely, from recommendations to avoid its use, to observational data that continuous use may improve outcome after cardiac arrest[5,22,27,32,33,43,44]. For these reasons, optimization of sedation is thought to be essential in the management of patients with critical illness[12], and the specific effects of sedation on cardiac arrest survivors undergoing TTM could be profound, but are unknown.

To address these controversies and inconsistencies, we evaluated sedation and shivering management practices in the International Cardiac Arrest Registry (INTCAR), a multicenter registry of patients that have been successfully resuscitated after in-hospital and out-of-hospital cardiac arrests.

2.2 Methods

2.2.1 Centers and Patients:

We included centers participating in the INTCAR registry between 2006 and 2017. The INTCAR registry consists of two iterations: a 1.0 dataset between the years of 2006-2011 and a 2.0 dataset between the years of 2011-2017. The core common variables were merged for this analysis. Centers enrolled consecutive adult patients admitted to an intensive care unit after in-hospital or out-of-hospital cardiac arrest. Only patients treated with TTM were included, and management varied according to local best practices. The database was maintained at Lund, Sweden on the Lytics© server. Centers participated in the registry on a volunteer basis, and there was no reimbursement for enrolling patients. The merging of the 1.0 and 2.0 iteration and the analysis below was competed in R software version 1.0.136[45].

2.2.2 Sedation Practices:

Patient-level sedation data was not part of the INTCAR database. Center-specific sedation practices (SP) were assessed using a Research Electronic Data Capture (REDCap) based survey hosted at Tufts University[46]. Surveys were sent by email to the investigators listed in the INTCAR system up to three times, on different days of the week. Centers that did not respond were then contacted directly by the administrators of INTCAR and asked to complete the survey. Two investigators independently assigned

centers into one of the three categories based on their survey results: SP1 indicated deep sedation and avoidance of NMB, SP2 indicated moderate or deep sedation with either scheduled or continuous NMB to prevent shivering, and SP3 indicated moderate or deep sedation with as-needed NMB in response to shivering. Only centers that enrolled at least 20 patients and completed the survey were included in the analysis.

2.2.3 Outcome:

The primary outcome was CPC at 6-month follow-up as a dichotomous variable, with good outcome defined as CPC of 1 or 2 and poor outcome as CPC of 3-5. Secondary outcome was CPC at ICU discharge. The 6-month CPC outcome was assessed with a review of medical records or telephone call to the patient or their proxy.

2.2.4 Predictors:

Candidate variables included in both INTCAR iterations were age, sex, number of prior medical conditions (CAD, CHF, arrhythmia, COPD, hypertension, CKD, neurologic disease, liver disease, malignancy, obesity, IDDM and NIDDM), location of arrest (in hospital vs. out-of-hospital), rhythm (shockable, non-shockable, and unknown), bystander CPR, witnessed CPR, volume of patients enrolled per year, number of beds at each center and country of center (European versus United States). These were extracted by chart review at the individual centers and uploaded into the Lytics© server. Continuous variables were tested for linearity assumptions.

2.2.5 Missing data:

Missing data was assessed and those with variables with greater than 10% missing data were estimated with multiple imputation. The imputation method was predictive mean metric, where a model is made for the missing data points. Then, coefficients from the distribution based on the model were used to make predictions. This was then

matched to predictions from five cases with non-missing data and a random value was drawn from those five cases. This was repeated 10 imputations and results pooled for the multivariate imputation by chained equations (mice) analysis.[47]

2.2.6 Statistical analysis methods:

Predictors were separated into patient-level and center-level sets. To account for shared variance between center, sedation use, and patient characteristics, a hierarchical model was used with two levels (patients at level one and centers at level two) with sedation practice as a fixed effect at center level. Explanatory variables were largely treated as dichotomous for yes/no variables and continuous variables were assessed for linearity with the logit of the outcome variables. Age was grouped by decade and time to ROSC was grouped by 5-minute intervals, referenced to the largest group. Past medical history consisted of a sum of relevant pre-arrest diagnoses listed above. Candidate variables were assessed in a univariate manner using logistic regression on the imputed dataset and variables were retained in the model if the p-value was < 0.20. The decision was made a-priori to force certain selected variables into the model, regardless of significance based on clinical importance (time to ROSC, rhythm, location, bystander CPR).

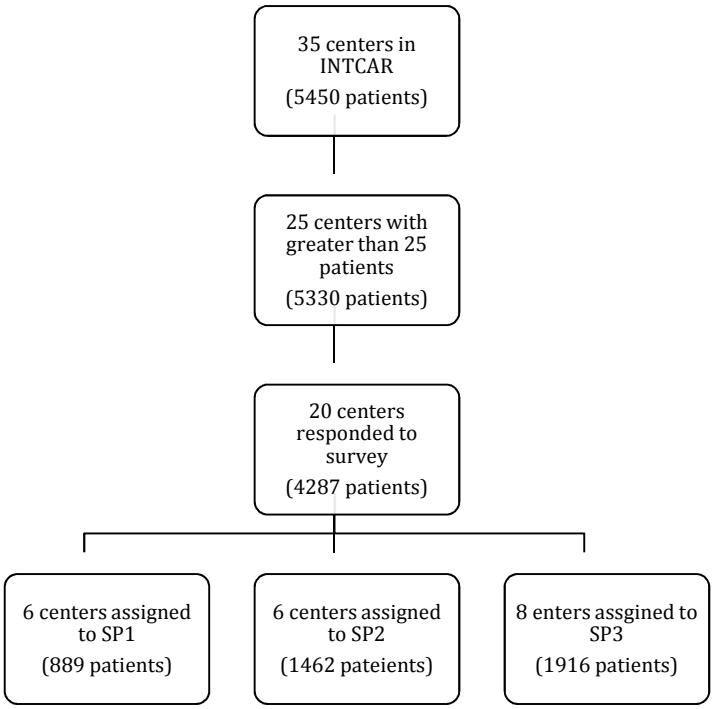
2.3 Results

2.3.1 Survey:

Thirty five eligible INTCAR centers were sent surveys and there were 25 centers who enrolled grater than 25 patients. Twenty (80%) of these eligible centers responded to the survey. Each center was assigned to one of the three categories based on their survey results without discrepancy between the assigners. Six centers were assigned to SP 1

practice, six centers were assigned to SP2 practice and eight centers were assigned to SP3 practice (Figure 2.1).

Figure 2.1: INTCAR centers and survey response



2.3.2 Patient population:

A total of 4,267 patients at 20 centers were included in the dataset. The mean age was 62 (± 15) years, 34% (n= 1432) were female and 77% (n=3256) were out of hospital arrests. There were similar rates of shockable and non-shockable rhythms and mean time to ROSC was 24 (± 18) minutes. Further characteristics are described in Table 2.1. At 6 month follow-up 1,349 (32%) had a good outcome, with similar results at ICU discharge (1,313 (31%)).

Table 2.1: Demographics, Clinical Characteristics and Outcome of All Cardiac Arrest Patients and by Sedation and Shivering Practices

Demographics and Clinical Factors	All INTCAR Centers	All Centers included in analysis	SP1	SP2	SP3
Centers (n,%)	35	20	6, 30	6, 30	8, 40
Number of Patients (n,%)	5450	4267	889, 21	1462, 34	1916, 45
Age (mean, SD)	62.0, 15	61.8, 15	65.4, 16	60.2, 15	61.2, 15
Female (n,%)	1792 (33)	1432 (34)	334, 38	509, 35	589, 30
Medical History Diagnosis (n, IQR)	2 1,3	2 2,2	2 2,2	2 2,2	2 2,2.25
Out-of-hospital (n,%)	4125, 76	3256, 77	634, 72	1183, 81	1439, 75
Witnessed (n,%)	4429, 82	3429, 81	710, 81	1161, 80	1558, 82
Rhythm: PEA/Asystole (n,%)	2478, 49	2050, 50	501, 60	675, 48	874, 47
Shockable (n,%)	2565, 49	1999, 49	320, 39	728, 51	951, 51
Unknown (n,%)	130, 2	64, 2	10, 1	15, 1	39, 2
Time to ROSC (mean, SD)	24, 18	24, 18	23, 18	26, 22	22, 15
Bystander CPR (n,%)	3718, 68	2008, 59	271, 57	715, 60	922, 60
Defibrillation (n,%)	3173, 59	2452, 59	422, 49	877, 61	1153, 61
European (n,%)	2449, 45	1365, 32	475, 53	245, 17	645, 34
ICU CPC1-2 (n, %)	1770, 32	1313, 32	225, 27	380, 28	780, 37
6 month CPC 1-2	1674, 31	1394, 35	224, 28	452, 32	718, 40

PEA: Pulseless electrical activity
Shockable: ventricular fibrillation/ventricular tachycardia
ROSC: Return of spontaneous circulation
SP: Sedation and shivering practice

2.3.3 Missing data:

At least one variable was missing from 23% of patients. 11% of patients had more than one variable with missing data. The most common variable with missing data was bystander CPR. Multiple imputation was performed with 10 imputations and pooled for the final analysis.

2.3.4 Model development:

Variables were selected a priori from existing literature describing outcome prediction after cardiac arrest. Using imputed data, the results of univariate analyses are shown in Table 4.1. Age and time to ROSC were changed from continuous variables to

intervals due to the nonlinear relationship of the raw variables with the outcome variables (Supplement figure 1,2). After model development, a priori interactions were tested. All variables were found to be significant and were retained in the model.

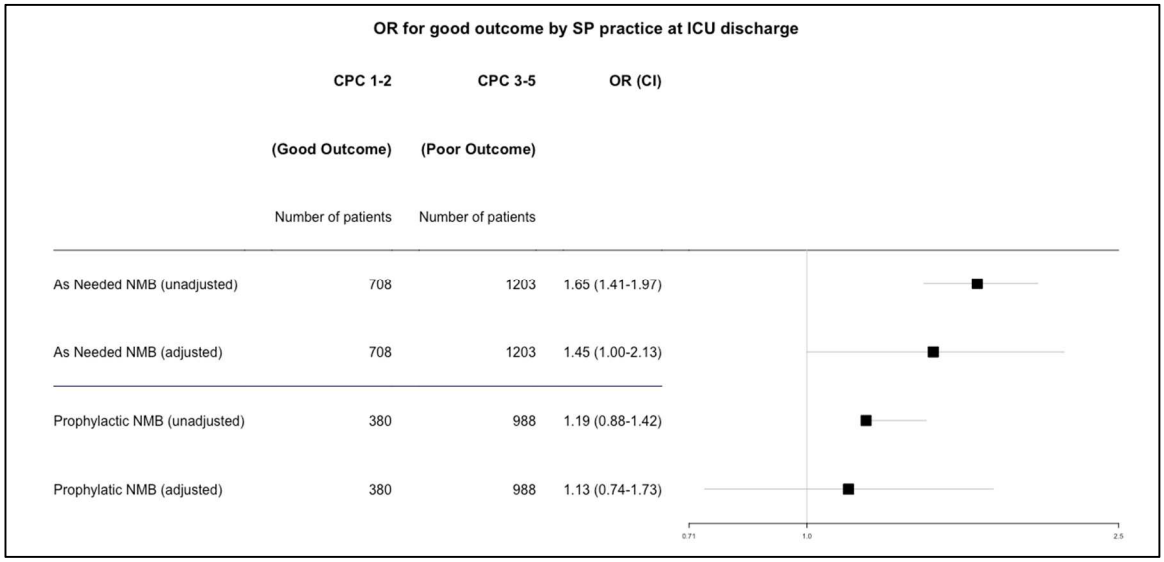
2.3.5 Model specification:

The full model is shown in Supplementary Table 1. Variables retained in the model included age, sex, arrest location, medical history, ischemic time, witnessed arrest, bystander CPR, rhythm, country, defibrillation, and hospital size.

2.3.6 Outcome by sedation category:

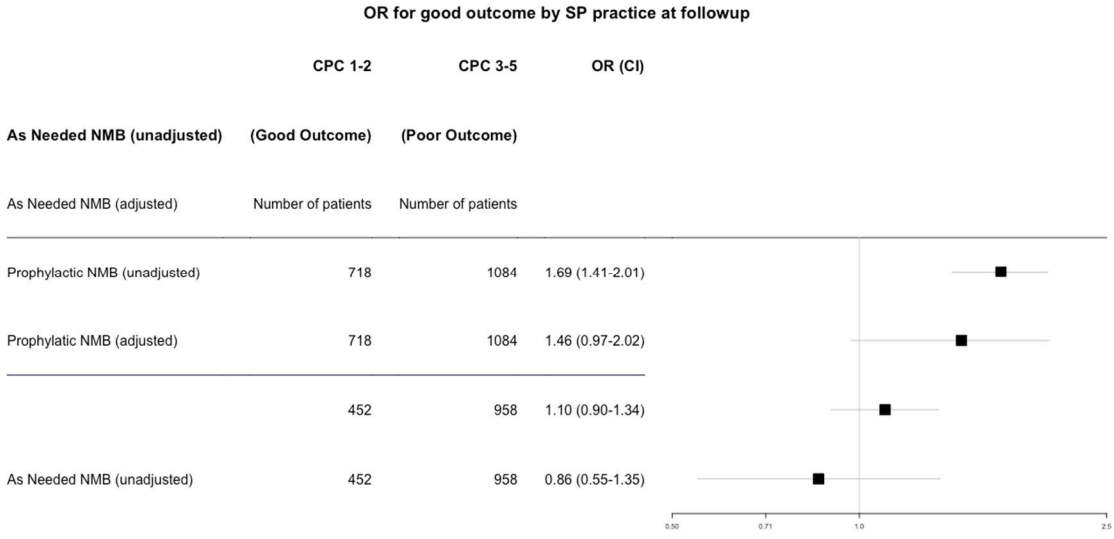
The overall F statistic for the three sedation practices, in the un-imputed data was 6.20, resulting in an F statistic of 0.002. This was then repeated for each separate imputed dataset and significant in each of the 10 cases. For the primary outcome of 6-month CPC referenced to SP1, the unadjusted odds ratios for good outcome were 1.19 (0.88-1.42, p=0.07) for SP2 and 1.65 (1.40-1.97, p<0.001) for SP3. The adjusted odds ratios were 1.13 (0.74-1.73, p=0.56) for SP2 and 1.45 (1.00-2.13, p=0.046) for SP3 (Figure 2.2). For the secondary endpoint of dichotomized ICU discharge CPC, the unadjusted odds ratios for good outcome were 1.10 (0.90-1.34, p=0.34) for SP2 and 1.69 (1.41-2.01, p<0.001) for SP3, and the adjusted odds ratio was 0.86 (0.55-1.35, p=0.52) for SP2 and 1.46 (0.97-2.20, p=0.07) for SP3, all referenced to SP1 (Figure 2.3).

Figure 2.2: Odds ratio for good outcome at 6 months of SP2 (prophylactic NMB) and SP3 (as needed NMB) referenced to SP1 (avoiding NMB).



CPC: Cerebral Performance Category

Figure 2.3: Odds ratio for good outcome at ICU discharge of SP2 (prophylactic NMB) and SP3 (as needed NMB) referenced to SP1 (avoiding NMB).



CPC: Cerebral Performance Category

2.4 Discussion

In patients receiving TTM after cardiac arrest, functional outcomes was associated with patients admitted to centers that used as-needed NMB with an adjunctive

sedation regimen compared to centers using deeper sedation and limiting NMB, including after adjustment for major confounders. This is the largest study to evaluate the impact of sedation and NMB on outcomes after cardiac arrest.

Current guidelines recommend "light" sedation (i.e. awake and responsive) in the general ICU population, which is associated with improved outcomes[9,48], but applying this approach to cardiac arrest patients undergoing TTM is inappropriate. Monitoring the depth of sedation has not been validated in brain-injured patients, as mental status changes may be secondary to brain injury rather than sedation. Finally, clearance of sedatives may be reduced in patients undergoing temperature management due to hypothermia, renal and hepatic dysfunction, and shock, leading to a prolonged coma state and confounded prognostication.

In addition to inconsistent sedation strategies during TTM, the use of NMB varies widely, and the benefits or risks are uncertain. A recent guideline for the use of NMB in the ICU made no recommendation regarding the use of NMB during TTM[49]. Several observational TTM studies have concluded that NMB administration was associated with improved outcome [22,43,44], yet some experts have recommended avoiding NMB during TTM[26,33]. Shivering itself is associated with good outcome after cardiac arrest,[23] possibly because the most severely injured brains do not mount a shivering response. Therefore requiring treatment for shivering with NMB may reflect a less severe brain injury and thus explain the association with better outcome. Our analysis, where sedation and shivering strategies were characterized at the hospital level, avoids this within-patient confounder and may be more generalizable to a center-treatment approach.

Worse outcomes associated with deeper sedation after cardiac arrest has several plausible explanations. The metabolism of many sedatives and analgesics decreases during hypothermia [50,51,15] likely resulting in accumulation of medication, which can confound neuroprognostication after cooling, resulting in inappropriate withdrawal of life support. Targeting a moderate depth of sedation and using NMB to treat shivering reduces the overall dose of sedatives, particularly for those who shiver vigorously, and appears to reduce the time to wakening after TTM. [27,52] Higher-doses of sedation to control shivering without NNB may also reduce blood pressure, known to influence outcome in animal cardiac arrest models[53,54] and retrospective human studies.[40,55] In addition, deeper sedation without NMB may incompletely control shivering or delay adequate suppression of shivering. This excess shivering may delay time to target temperature (TTM), elevate intracranial pressure, and lower brain oxygen levels. Sedation also has immunology effects,[56,57] which may increase the rate of infection, time on the ventilator, and prolong ICU course.[5,9]

Although this is the largest study to evaluate the effects of sedation on outcomes after cardiac arrest, several limitations warrant discussion. The INTCAR data were collected prospectively, but sedation and NMB doses were not collected at the patient level. However, every center had a sedation protocol, and although between-patient variability occurs within each center, it is unlikely for centers with established protocols to experience frequent and severe variations in treatment sufficient to confound these results. Next, the effect of similar sedation approaches within each center may not be consistent across all patients. Also, these effects on outcome may be due to variation in sedation protocols or from other unmeasured differences in practice.

Protocols for sedation and shivering management of patients undergoing TTM are variable (TTM) and there are no randomized trials to confirm one strategy is superior to another. Our data suggest that good outcome correlates with the use of a protocol that favors as needed NMB with basal sedation instead of increasing sedation to avoid NMB in response to shivering after cardiac arrest. Prospective study evaluating sedative and NMB use at the patient level, with outcomes adjusted for severity of illness, is warranted.

Chapter 3: Discussion

This work adds to existing knowledge of how sedation and shivering management in patients treated with TTM after cardiac arrest influences outcome, by studying the influence of 3 divergent protocols, by center. Current published literature has focused on single-center experiences and has found that patients who receive higher doses of paralytics have improved outcomes. Taking this into context of our understanding that patients who have an intact shivering response (from the hypothalamus to the periphery) also have a better outcome, it is difficult to extrapolate if these findings are a result of the treatment for shivering itself, or a need for more aggressive treatment as a result of intact shivering response. We were surprised to find that there was a nearly even distribution of the three types of protocols – reflecting different approaches to the treatment of shivering, between centers who responded to the survey. This supports the concept that there is variability in management between centers.

The findings in this study were that there was an increased odds ratio of a good outcome among those with as needed neuromuscular blockade (NMB) compared to centers that increase sedation in an effort avoid NMB. The odds ratio for good outcome with as-needed NMB (SP2) here was 1.45 (1.003-2.13, p=0.046) and the odds ratio of good outcome for prophylactic NMB (SP3) was 1.13 (0.74-1.73, p=0.56). Although the confidence interval for the SP2 group approaches 1, the ability for any one intervention or aspect of patient care to even show a trend toward improved outcomes in this incredibly complex group of patients with a high mortality rate at baseline is striking and warrants further investigation.

We found an overall trend for the highest rate of good outcome among centers that described using SP2 approach to treating shivering and sedation, followed by SP3 and SP1. The overall amount of NMB between the three groups is likely the smallest for SP1, followed by SP2 and the most for SP3. However, the total amount of sedation may not necessary trend in the same direction. As adequate sedation to ensure patients do not have recall when receiving NMB is recommended, the amount of total sedation given between the three groups is likely the highest for SP1 (very high doses are required for patients not receiving NMB who have an intact shivering response), followed by SP3 (where all patients will be on some amount of sedation, with the least in SP2 (where patients will only need deeper sedation when receiving NMB). Although this was not directly measured, it is possible that the trend in outcomes between SP2 and SP3 in relation to SP1 is driven by sedation level, rather than by total NMB dose.

This patient population is complex and there is a significant heterogeneity between the severity of injury and response to treatments. The next step in this evaluation is to assess how sedation levels affect patients individually. This will be done with prospectively collected data analyzed at the patient level. We are currently enrolling patients among 5 centers and have 250 patients enrolled to date. The analysis planned will be a mediation analysis; with the level of sedation as the mediator, the arrest and patient factors (combined) as the exposure, and the outcome of dichotomized hospital discharge CPC. Given the clinical heterogeneity of our patients and the direct relationship of very severe brain injury to less overall shivering, a subgroup analysis will be performed to evaluate this heterogeneity. The

patients will be sorted into three subgroups based on severity of brain injury; defined by the neurological examination and a combination of tests including neuron specific enolase levels, MRI findings, and somatosensory evoked potentials for those who do not immediately awaken (all available in prospective data source). The mediation analysis will be performed separately among those who awaken after therapy, those who do not awaken but have modest brain injury based on testing, and those who do not awaken and have severe brain injury based on testing. This may allow a better understanding of how sedation regimens may influence patients differently, based on severity of the underlying brain injury.

The risks and benefits of excessive or restricted amounts of sedation are described above and the most notable of these is that sedative medications used to provide comfort and treat shivering may also prevent or treat seizures in patients who are at risk. Inversely, those not at risk (with less severe brain injury) may have prolonged time to awakening and an increase other complications similar to what is seen with excessive sedation in the medical ICU. Seizures are common during TTM (20-40%) and currently there is no evidence for individualized treatment among this group of patients. Guidelines recommend that continuous EEG should be considered, when available, and that EEG should be performed in patients who do not awaken. It is unlikely that attempting to prevent seizures, through high levels of sedatives will benefit the entire population. To better understand this, there must first be a method of predicting which patients are at above-average risk of seizures during TTM. Once this is achieved, a prospective trial of various sedation and

shivering regimens, incorporating response to sedation based on severity of brain injury and risk of seizures can be executed

Chapter 4: Appendix

Supplement referenced in manuscript:

Table 4.1: Adjusted and unadjusted model: ICU CPC (good outcome)

Variable	Reference	Unadjusted OR (CI)	p-value	Adjusted OR (CI)	p-value
Age 18-28	58-68	1.20 (0.84- 1.70)	<0.001*	1.41(0.93-2.23)	<0.001*
Age 29-38	58-68	1.84 (1.34-2.52)		2.07(1.43-3.01)	
Age 39-48	58-68	1.43 (1.13-1.82)		1.34(1.02-1.65)	
Age 49-58	58-68	1.44 (1.19-1.73)		1.76(1.14-1.75)	
Age 69-78	58-68	0.60 (0.49-0.73)		0.62(0.49-0.77)	
79+	58-68	0.56 (0.44-0.71)		0.59(-.45-0.78)	
Female	Male	0.74 (0.64-0.85)	<0.001	0.01(0.77-1.07)	0.24
Medical History		0.69 (0.75-0.82)	<0.001	0.86(0.81-0.91)	<0.001
In-hospital arrest	Out-of-hospital	0.71 (0.61-0.83)	<0.001	0.56(0.50-0.67)	<0.001
Witnessed	Unwitnessed	2.26 (1.86-2.75)	<0.001	1.75 (1.41-2.19)	<0.001
Rhythm (Shockable)	PEA/asystole	3.91 (2.29-3.51)	<0.001	3.19(2.49-4.08)	<0.001
Rhythm (Unknown)	PEA/asystole	2.26 (2.03-5.56)	<0.001	2.78(1.58-4.88)	<0.001
Time to ROSC 0-5	11-15	1.29(1.097-1.80)	<0.001*	1.36(1.01-1.83)	<0.001*
Time to ROSC 6-10	11-15	1.12(0.8901.41)		1.10(0.84-1.42)	
Time to ROSC 16-20	11-15	0.77(0.60-0.98)		0.68(0.52-89)	
Time to ROSC 21-25	11-15	0.59(0.45-0.77)		0.51(0.38-0.68)	
Time to ROSC 26-30	11-15	0.39(0.29-0.52)		0.36(0.26-0.49	
Time to ROSC 31-35	11-15	0.34(0.24-0.50)		0.29(0.19-0.43)	
Time to ROSC 36-40	11-15	0.29(0.19-0.44)		0.24(0.15-0.37)	
Time to ROSC 41-45	11-15	0.34(0.22-0.51)		0.33(0.21-0.52)	
Time to ROSC 46-50	11-15	0.23(0.13-0.43)		0.21(0.11-0.41)	
Time to ROSC 51-55	11-15	0.26(0.12-0.52)		022(0.10-046)	
Time to ROSC 56-60	11-15	0.26(0.13-0.52)		027(-.13-0.56)	
Time to ROSC 61+	11-15	0.43(0.28-0.67)	<0.001	0.43(0.26-0.69)	<0.001
Bystander CPR	No Bystander CPR	1.29 (1.13-1.48)	0.003	1.30(1.08-1.55)	0.01
Defibrillation	No Defibrillation	1.84 (2.45-3.01)	<0.001	1.36(1.02-1.80)	0.04
Country (Europe)	United States	1.18 (1.03-1.36)	0.02	1.02(0.69-1.51)	0.91
Hospital size		0.99 (0.99-1.00)	0.002	1.00(1.00-1.00)	0.26
Sedation level	SP1 to SP2	1.10 (0.90-1.34)	0.34	0.86(0.55-1.35)	0.52
Sedation level	SP1 to SP3	1.69 (1.41-2.01)	<0.001	1.46(0.97-2.20)	0.07

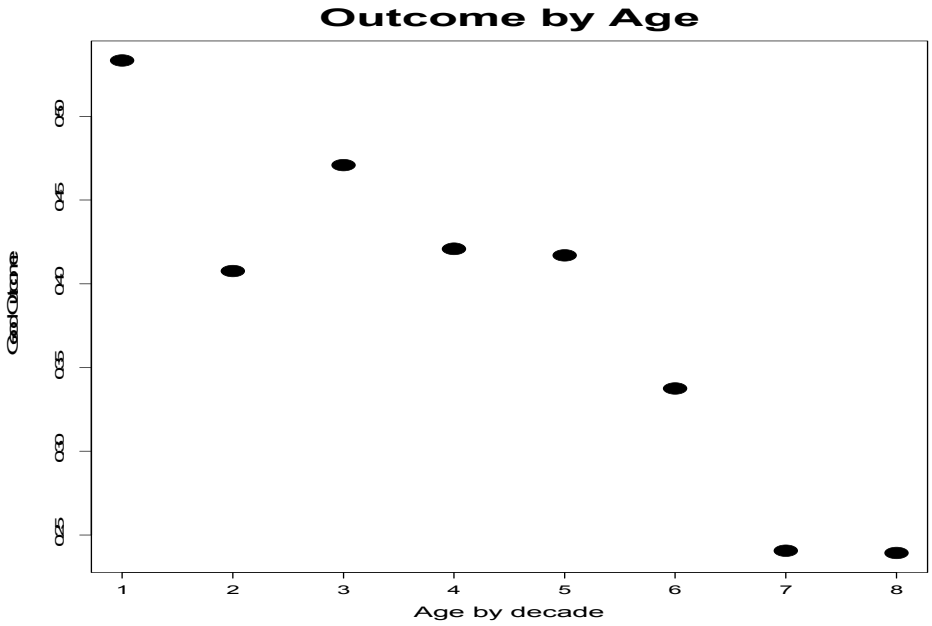
PEA: Pulseless electrical activity
Shockable: ventricular fibrillation/ventricular tachycardia
ROSC: Return of spontaneous circulation
Hospital size: per 10 beds
*Overall p-value based on F-statistic
**model intercept: 1.72

Table 4.2: Adjusted and unadjusted model: Follow-up CPC (good outcome)

Variable	Reference	Unadjusted OR (CI)	p-value	Adjusted OR (CI)	p-value
Age 18-28	58-68	0.96 (0.68-1.27)	<0.0018	1.05(0.6901.58)	0.001*
Age 28-38	58-68	1.63 (1.19-2.23)		1.95 (1.34-2.85)	
Age 38-48	58-68	1.41 (1.12-1.80)		1.43 (1.06-1.91)	
Age 48-58	58-68	1.39)1.161.67)		1.39 (1.12-1.74)	
Age 68-78	58-68	0.55 (0.460.67)		0.57 (0.46-0.72)	
78+	58-68	0.43 (-.34-0.55)		0.44(0.32-0.60)	
Sex	Male	0.61 (0.53-0.70)	<0.001	0.78 (0.67-0.92)	0.004
Medical History		0.76 (-.72-0.79)	<0.001	0.86 (0.81-0.91)	<0.001
In-hospital arrest	Out-of-hospital	0.89 (0.76-0.97)	0.39	0.86 (0.56-0.83)	<0.001
Witnessed	Unwitnessed	2.48 (2.06-3.00)	<0.001	1.86 (1.49-2.34)	<0.001
Rhythm (Shockable)	PEA/Asystoe	5.16 (4.47-5.95)	<0.001	3.27 (2.61-4.01)	<0.001
Rhythm (unknown)	PEA/Asystoe	6.14 (3.29-11.46)	<0.001	3.94 (2.18-7.14)	<0.001
Time to ROSC 0-5	11-15	1.31 (0.99-1.74)	<0.001*	1.39 (1.02-1.91)	<0.001*
Time to ROSC 6-10	11-15	1.23 (0.97-1.57)		1.32(0.99-1.75)	
Time to ROSC 16-20	11-15	0.94 (0.75-1.19)		0.89 (0.67-1.14)	
Time to ROSC 21-25	11-15	0.70 (0.53-0.91)		0.58 (0.42-0.81)	
Time to ROSC 26-30	11-15	0.45 (0.34-0.59)		0.39 (0.29-0.54)	
Time to ROSC 31-35	11-15	0.48(0.32-0.72)		0.39 (2.24-0.63)	
Time to ROSC 36-40	11-15	0.27(0.18-0.42)		0.20 (0.12-0.33)	
Time to ROSC 41-45	11-15	0.35(0.23-053)		0.33(0.21-0.56)	
Time to ROSC 46-50	11-15	0.26(0.14-0.48)		0.21 (0.10-0.43)	
Time to ROSC 51-55	11-15	0.22(0.09-0.52)		0.52(0.06-0.38)	
Time to ROSC 56-60	11-15	0.28(0.16-0.50)		0.27 (0.15-0.50)	
Time to ROSC 60+	11-15	0.44(0.28-0.69)		0.42(0.25-0.69)	
Bystander CPR	No Bystander CPR	1.50 (1.31-1.71)	<0.001	1.22 (1.03-1.44)	0.02
Defibrillation	No Defibrillation	3.80 (3.26-4.43)	<0.001	1.59 (1.24-2.02)	<0.001
Country (Europe)	United States	1.47 (1.29-1.69)	<0.001	1.69 (1.18-2.41)	0.004
Hospital size		0.999 (0.9-0.99)	<0.001	1.00(1.00-1.00)	0.45
Sedation level	SP1 to SP2	1.19 (0.88-1.42)	0.07	1.13 (0.74-1.73)	0.56
Sedation level	SP1 to SP3	1.65 (1.40-1.97)	<0.001	1.45(1.00-2.13)	0.046

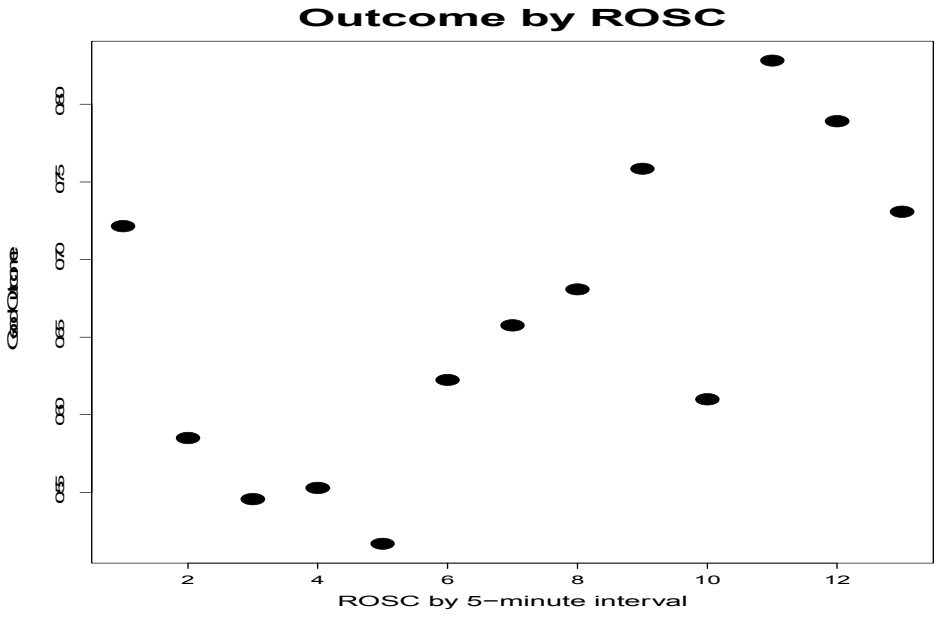
PEA: Pulseless electrical activity
Shockable: ventricular fibrillation/ventricular tachycardia
ROSC: Return of spontaneous circulation
Hospital size: per 10 beds
*Overall p-value based on F-statistic
**model intercept -1.53

Figure 4.1:



Odds of good outcome by age for total cohort

Figure 4.2:



Odds of good outcome by time to ROSC for total cohort

Additional Supplement:

Power calculation: Informed by outcome rates within the three available RCTs evaluating targeted temperature management, initial assumption of power calculation is that good functional outcome would range from 40% to 62% in high and low performing sedation practices. A simulation was created which accounted for within center patient correlation within the three groups using variance of inflation factor. As the correlation within a center was large, the power was largely driven by the number of centers rather than the number of patients within centers.

Table 4.3: Number of centers required with VIF of 29 and subsequent power to detect a difference

SP1	SP2	SP3	Alpha	power
8	7	8	0.05	80%
10	10	10	0.05	85%
14	14	14	0.05	95%

Missing data

Figure 4.3: Plot of missing data by fraction and number

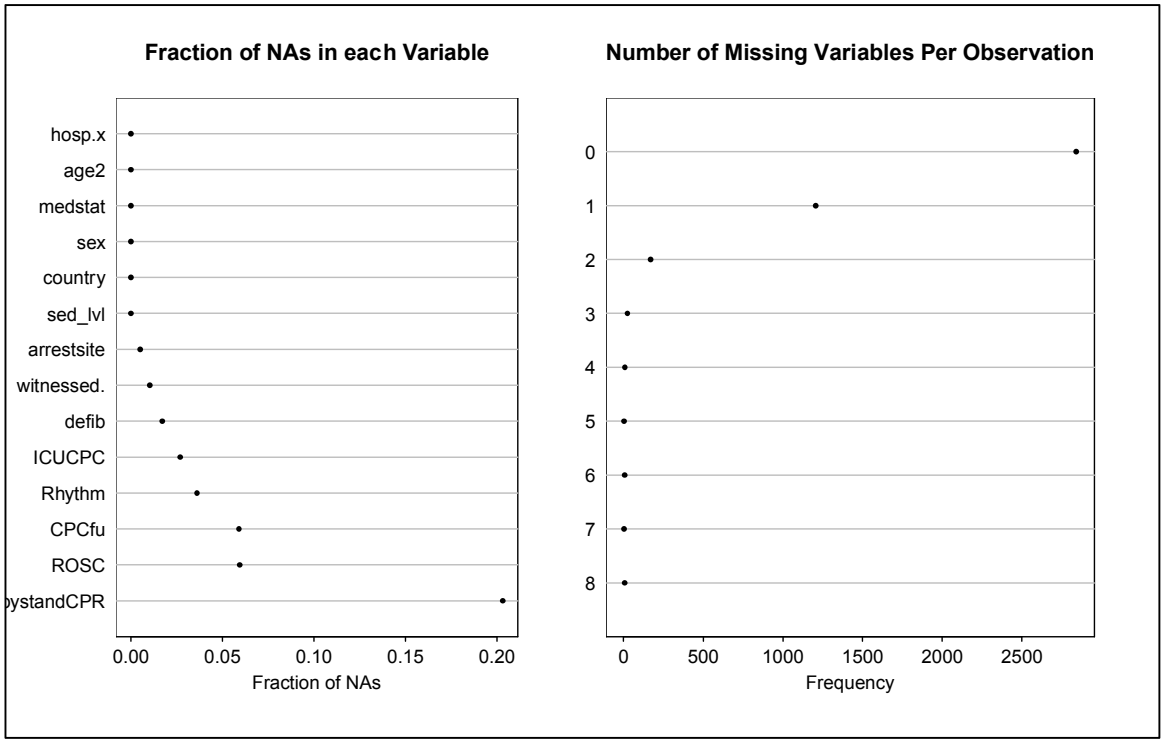
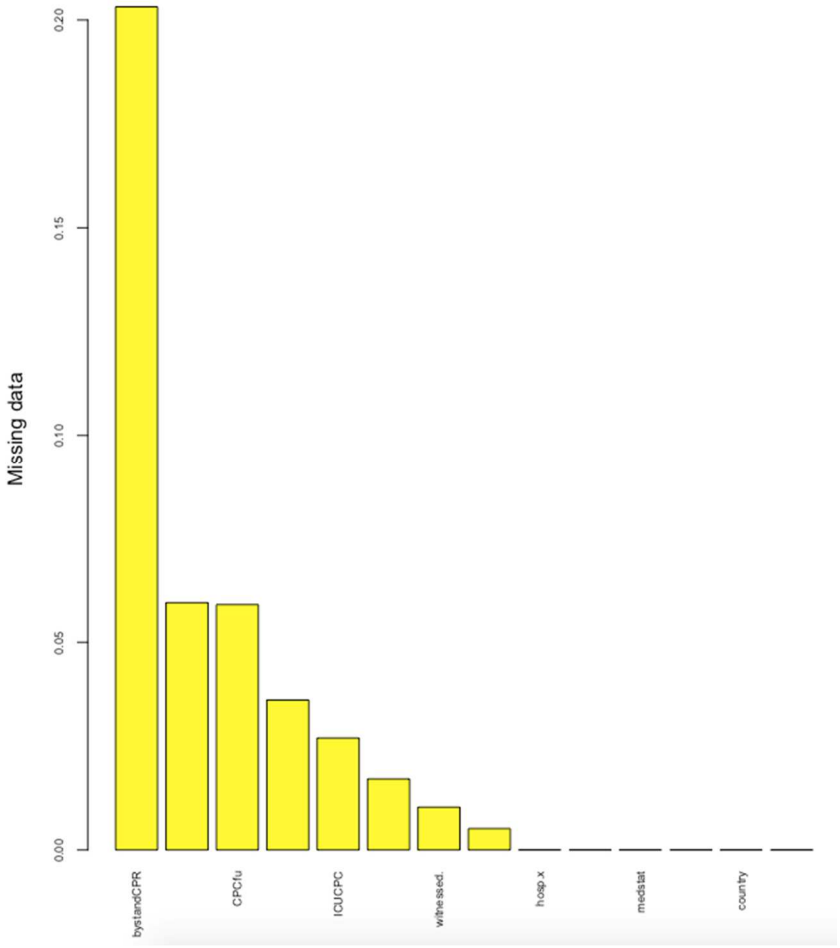


Figure 4.4: Plot of missing data by frequency



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