Clinical paper

Impact of sedation depth on neurological outcome in post-cardiac arrest patients – A retrospective cohort study

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ARTICLE INFO

ABSTRACT

Aims: Whether targeted temperature management (TTM) might improve neurologic prognosis in patients after cardiac arrest is currently under debate. Data concerning sedation depth during TTM is rare. This study aimed to compare the impact of different sedation depths on neurological outcomes in post-cardiac arrest patients undergoing TTM.

Methods: In this retrospective, before-and-after registry study, all patients receiving TTM on a medical ICU between 08/2016 and 03/2021 were included. This study evaluated the following sedation targets: RASS-target during TTM −5 until 08/2019 and RASS-target −4 since 09/2019. The primary endpoint was favorable neurological outcome at ICU discharge, defined as a Cerebral Performance Category (CPC) score of 1 or 2.

Results: 403 patients were included (RASS-target −5: N = 285; RASS-target −4: N = 118). Favorable neurological outcome was documented in 54/118 (45.8 %) patients in the group with a RASS-target of −4 compared to 111/285 (38.9 %) in the group with a RASS-target of −5. After adjustment for age, sex, initial shockable rhythm, bystander CPR, duration of CPR and mean arterial pressure 12 h after CPR, favorable neurological outcome was associated with RASS-target −4 (OR 1.82 (95 % CI: 1.02–3.23); p = 0.042). ICU survival was similar in both groups while 30-day survival was associated with RASS-target −4 (OR 1.81 (1.01–3.26); p = 0.047).

Conclusion: Lighter sedation strategies during TTM after cardiac arrest might improve outcome and should be further investigated.

Introduction

Whether targeted temperature management (TTM) after return of spontaneous circulation (ROSC) might improve neurologic prognosis in patients after cardiac arrest is currently under debate. While it was recommended in the ERC guidelines of 2015 and 2021, an updated ERC-ESICM guideline on temperature control after cardiac arrest in adults stated that there is insufficient evidence to recommend for or against temperature control at 32–36 °C.[1–3]

Although plenty data exists concerning hemodynamic management, ventilation and temperature control, only few data on sedation and analgesia exist.[1] Guidelines therefore offer sparse recommendations on drug selection, dosing, and specific sedation targets after ROSC.[4] In a 400 page long Institute of Medicine report on treatment of patients with and after cardiac arrest, 'sedation' is mentioned only twice, demonstrating the lack of knowledge nicely.[4,5]

For mechanically ventilated adults on the intensive care unit (ICU), clinical practice guidelines suggest light sedation, defined as RASS (Richmond Agitation-Sedation Scale) of –2 to + 1 range (or its equivalent using other scales), as this shortens time to extubation end reduces tracheostomy rate, although evidence is low.[6] However, this cannot be necessarily transferred to patients after cardiac arrest, since frequent

shivers and seizures, among other disorders, need to be considered after cardiac arrest.[7] Deeper sedation, in contrast, is associated with longer ICU stay and ventilation therapy, increases incidence of delirium, infection and delayed awakening.[4] Additionally, sedation hangover complicates neuroprognostication, potentially causing false assessments.[4].

As a result, there is considerable variation in the choice of drug, dosage, and sedation depth between different centers.[8] Although there are studies comparing different medication strategies, no studies comparing different sedation depth strategies exist.[9,10].

In our center, patients after cardiac arrest were treated with a very deep sedation strategy until August 2019. Due to the insufficient data and potential risks, we adopted a lighter sedation strategy in September 2019. We here present outcome data comparing sedation with a target RASS of −5 treated before 09/2019 to patients treated after 09/2019 with a target RASS of −4.

Our hypothesis was that reduced sedation would reduce sedation-associated complications and ultimately lead to better survival. Primary outcome of his study therefore was good neurological outcome defined as cerebral performance category (CPC) 1 or 2 at ICU discharge. Secondary endpoints were ICU and 30-day survival.

Methods

We conducted an investigator-initiated single-center retrospective before-and-after cohort study analyzing patients from the Freiburg CPR registry treated from August 2016 until March 2021. All patients with ROSC after cardiac arrest receiving TTM were included. Specifically, TTM was performed in all patients with cardiopulmonary resuscitation (CPR) for more than five minutes. In patients with CPR for less than five minutes, TTM was only performed in comatose patients (defined as Glasgow Coma Scale ≤ 7).

Exclusion criteria were death within the first 24 h and those undergoing extracorporeal CPR (ECPR). Patients with severe hypothermia were also excluded as these patients have different (good) chances of neurologic recovery with prolonged duration of CPR and thereby falsify time of CPR analysis.[11].

The analysis was blinded to patient identity and conducted under an ethics approval from the Ethics Committee of Albert-Ludwigs-University of Freiburg (file number 387/19). All methods strictly followed relevant guidelines and regulations, in full accordance with the principles of the Declaration of Helsinki. Since the study involved only retrospective data from an already completed therapy the ethics committee waived the requirement for informed consent.

Patient selection and data collection

All outcome variables were evaluated by manual case-by-case review of patient records. Since only data from the index hospital stay was evaluated, no patients were lost to a follow up. The registry was checked for data integrity and plausibility according to the RECORD recommendations for data clearing.[12].

Local policy on treatment of patients after cardiac arrest

All patients with cardiac arrest and cardiopulmonary resuscitation (CPR) for more than 5 min or a Glasgow coma scale of ≤ 7 after ROSC received target temperature management (TTM) for 72 h. Local standards advocate start of TTM as early as possible with a target temperature of 33 °C for 24 h followed by rewarming with 0.2 °C/hour. Within the 72 h of TTM, fever has to be strictly avoided. For TTM, either the Thermogard XP® temperature management system (Zoll Medical Corporation, Chelmsford, MA, USA) or the Arctic Sun® temperature management system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The management of vasopressors and fluid therapy is driven by clinical judgement of the intensivist in charge. A lung-protective

ventilation is advocated targeting a paCO₂ of 35–45 mmHg and a paO₂ of 70–80 mmHg.

For analgosedation, sufentanil and either isoflurane (1st choice) or propofol (2nd choice) were advocated. Sufentanil was used as the first-line opioid for analgesia. Co-analgesics could be administered when indicated by the physician in charge. Requirements for patients to be discharged from the ICU to a general ward included stable vital signs, adequate respiratory function, and the ability to use a call bell to alert nursing staff.

Change of local standard in September 2019

Until 09/2019, a target RASS of −5 was aimed for within the first 24 h after ROSC. With the updated standard operating procedure for post-resuscitation care 09/2019 we now aimed at a RASS of −4 within the first 24 h after ROSC. Deeper sedation was allowed in case of shivering or seizures. Neuromuscular blockade was not routinely utilized. After patients reached 36.5 °C, a wake-up attempt was advocated. A second significant change in post-resuscitation care at this time point was a lower mean arterial pressure (MAP) target from 80 mmHg to 65 mmHg within the first 24 h after ROSC.

Definitions

Neurologic outcome was defined by the CPC score at ICU discharge. In each post-CPR patient, attending physicians determined the CPC score based on their assessment of the patient's functional status at the end of the ICU stay. A score of one or two was defined as favorable outcome.[13] Mechanical ventilator-free days (VFD, absence of invasive mechanical ventilation) within 10 days after CPR and ICU free days 10 days after CPR were analyzed. VFD and ICU free days were counted as zero if the patient died within the first 10 days. If information on bystander CPR was unavailable, patients with a no-flow time of less than 2 min were assumed to have received bystander CPR. First spontaneous breathing was defined as either time of first assisted invasive ventilation (continuous positive airway pressure, proportional pressure support) for more than 30 min or first time without invasive or non-invasive mechanical ventilation. Duration of spontaneous breathing was defined as time with assisted invasive ventilation and time without invasive or non-invasive mechanical ventilation.

Statistical methods

All relevant data is given in standardized tables. For data analysis, SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY) and Prism (GraphPad Prism, Version 10.0.0 for Windows. San Diego, CA) were employed. For statistical analysis, Mann-Whitney *U* test was used for analysis of continuous variables. For categorical variables, Fisher's exact test was used when number of expected values was smaller than five, otherwise Pearson's Chi-squared test was performed. Two-way ANOVA was used when comparing two independent variables like RASS after CPR. A p-value of < 0.05 was considered statistically significant.

Adjustment for known predictors of the primary endpoint was performed by multivariate logistic regression using (SPSS) pre-defined variables (age, sex, initial shockable rhythm, bystander CPR, duration of CPR) and the mean arterial pressure (MAP) 12 h after CPR (since the MAP targets were also changed 09/2019).

Data are given as n (%), median and interquartile range (25th-75th) or odds ratio (OR) with 95 % confidence interval (CI) if not stated otherwise.

Results

Study population

From 08/2016 to 03/2021, 430 patients were included in the current research after cardiac arrest. Of these, 27 patients were excluded: 26 patients died during the first 24 h and one patient was excluded because of severe hypothermia with CPR-duration of 180 min (supplemental Fig. 1). Median age of the included 403 patients was 67 (57–77) years and 116/403 (28.8 %) of all patients were female. No differences were evident concerning baseline characteristics as age, sex and comorbidities between both groups. Both groups were also comparable concerning resuscitation characteristics such as shockable rhythm, no-flow-duration or duration of CPR (Table 1).

Target RASS

Of the 403 included patients, 285 were treated with a target RASS of −5, whereas 118 patients were treated with a target RASS of −4. RASS was slightly more positive in patients with a RASS target of −4 compared to those with a target of −5 (Fig. 1).

RASS −4 was achieved at least one time in the first 24 h after resuscitation in 79/285 (27.7 %) of the patients with target RASS −5 compared to 69/118 (58.5 %) in patients with a target RASS −4 (p < 0.001) (supplemental table 1).

Sedation

Dosage of sufentanil was significantly lower in the group with target RASS −4 (Fig. 2A). Within the first 24 h, 297/403 (73.7 %) patients were sedated with isoflurane. No differences were identified in both groups concerning isoflurane MAC 12 h after CPR, while MAC was lower in the group with target RASS −4 at 24 h after CPR (Fig. 2B). There were no differences in propofol dosage among patients receiving propofol

Table 1
Baseline characteristics and characteristics of cardiopulmonary resuscitation of all patients. CPR: Cardiopulmonary resuscitation; OHCA: Out-of-hospital cardiac arrest.

	Target RASS −5 (N = 285)	Target RASS −4 (N = 118)	p-value
Age	67 (57–77)	66 (58–77)	0.856
Female	85 (29.8 %)	31 (26.3 %)	0.473
Body mass index	24 (23–28)	24 (23–28)	0.905
Coronary heart disease	66 (23.2 %)	27 (22.9 %)	0.952
Pulmonary disease	68 (23.9 %)	24 (20.3 %)	0.444
Liver disease	17 (6.0 %)	8 (6.8 %)	0.758
Chronic kidney disease	46 (16.1 %)	22 (18.6 %)	0.541
Malignancy	10 (3.5 %)	5 (4.2 %)	0.774
Hematological disease	17 (6.0 %)	6 (5.1 %)	0.729
Peripherial artery disease	26 (9.1 %)	4 (3.4 %)	**0.046**
Neurological disease	44 (15.4 %)	17 (14.4 %)	0.793
Psychiatric disease	37 (13.0 %)	16 (13.6 %)	0.876
Alcohol abuse	28 (9.8 %)	15 (12.7 %)	0.393
Diabetes mellitus	57 (20.0 %)	29 (24.6 %)	0.308
Hypertension	132 (46.3 %)	56 (47.5 %)	0.834
SAPS2 at admission	49 (40–58)	50 (41–58)	0.893
Initial shockable rhythm	131 (46.0 %)	51 (43.2 %)	0.614
Cardiac cause	168 (58.9 %)	64 (54.2 %)	0.384
Noflow-time (min)	3 (0–8)	2 (0–7)	0.159
Bystander-CPR	129 (45.3 %)	57 (48.3 %)	0.577
CPR duration (min)	15 (10–23)	17 (10–25)	0.208
OHCA	235 (82.5 %)	94 (79.7 %)	0.510

p values < 0.05 are written in bold. Data are given as median and interquartile range (25th-75th) or number of patients (percent of all patients in group).

(supplemental table 1).

Mechanical ventilation

Ventilator-free days during the first 10 days after CPR (VFD10) and ICU-free days during the first 10 days after CPR (IFD10) did not differentiate comparing both groups. The first spontaneous breathing however was achieved earlier in case of target RASS −4 (2.2 (1.9–2.9) days versus 1.9 (1.8–2.2) days; p < 0.001) (Fig. 2C). Duration of spontaneous breathing was longer 48, 72 and 120 h after CPR in the group with target RASS −4 (Fig. 2D). For detailed outcome characteristics, see supplemental table 1.

Survival

Favorable neurological outcome was documented in 54/118 (45.8 %) patients in the group with a RASS-target of −4 compared to 111/285 (38.9 %) in the group with a RASS-target of −5 (absolute difference 6.8 %) (Fig. 3). No significant time trend of favorable outcome was identified within the two groups (supplemental table 2).

After adjustment, the odds ratio of favorable neurological outcome was 1.82 (1.02–3.23) for RASS-target of −4 (p = 0.042) (Fig. 4). ICU survival was similar in both groups while adjusted odds ratios were positive for RASS-target −4 (OR 1.81 (1.01–3.26); p = 0.047) for 30-day survival (Table 2).

Discussion

In this single-center, retrospective study we compared different sedation depth strategies in patients after cardiac arrest. After adjustment, favorable neurological outcome after CPR was better in the group of patients with a RASS-target of −4 compared to a target of −5. Similarly, 30-day survival, spontaneous breathing, and dosage of opiate were improved with a RASS-target of −4.

Approaches to sedation after cardiac arrest vary widely and no general recommendation exists. Different sedation protocols have been described, but are not detailed enough to be comparable.[14] Moderate-dose sedation regimen with a Riker Sedation-Agitation Scale target of ≤ 2 have been reported before as well tolerated and effective after cardiac arrest.[15] The sedation target of our less deep sedation strategy of target RASS −4 is comparable to the SAS target of the study of May et al, but so far, there has been no comparison of different sedation depth strategies.

In other medical and surgical ICU populations, deeper sedation strategies are associated with worse outcome, prolonged mechanical ventilation, ICU and hospital stays and increased delirium.[16] However, this cannot be easily transferred to the special population of patients after cardiac arrest receiving TTM. On the one hand, deep sedation can lower cerebral metabolic energy utilization, reduce cerebral ischemia and may reduce shivering and seizures potentially improving the outcome.[15,17] On the other hand, hypothermia increases plasma concentrations of medication as propofol (~30 %), and fentanyl (2-fold) compared to normothermic conditions persisting after rewarming. This may affect neurologic assessment, especially since many patients assigned for poor prognosis were still receiving sedation.[15,18–21] Our study indicates a higher rate of favorable neurological outcome using the less deep sedation approach. Additionally, adjusted odds ratios were positive for ICU survival (p = 0.118) and 30-day survival (p = 0.047). Although, differences between the groups are too small for concluding that less deep sedation improves survival, our results are promising and underscore the critical role of sedation depth in post-resuscitation care, a topic that has historically received limited attention. Analyzing the depth of sedation in larger, prospective studies could therefore be a meaningful approach to improve survival.

Mechanical ventilation is complicating the ICU stay and should therefore be as short as possibile.[22–24] The patients with less deep
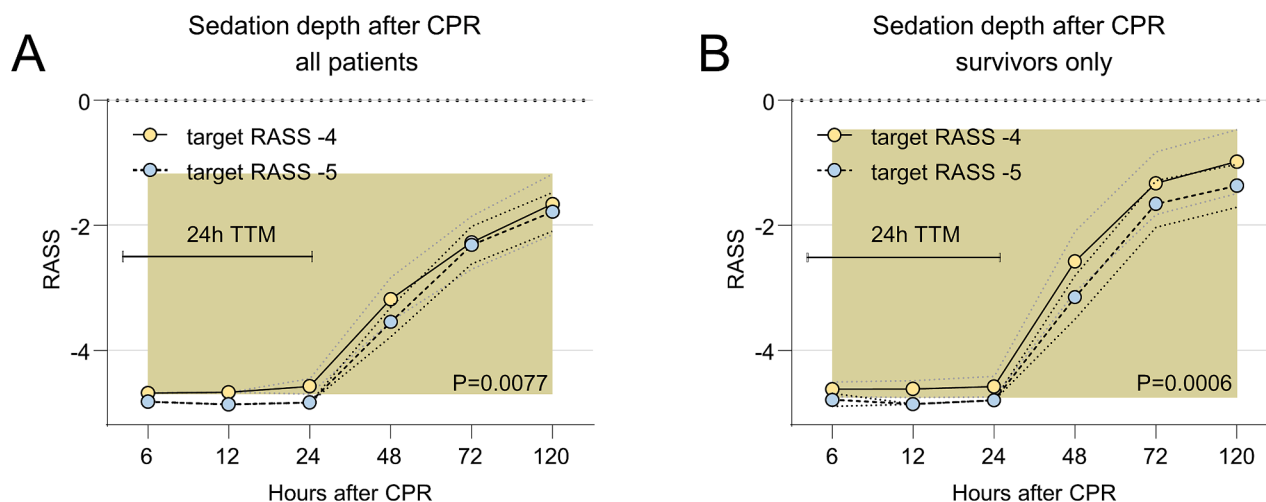
Fig. 1. Sedation depth after cardiopulmonary resuscitation (CPR). Two different sedation targets were investigated, either targeting RASS −4 (gold) or −5 (blue). Given are RASS values as mean with 95 % confidence interval either in all patients (A, N = 403) or in hospital survivors (B, N = 224). Significance is calculated by 2way ANOVA.
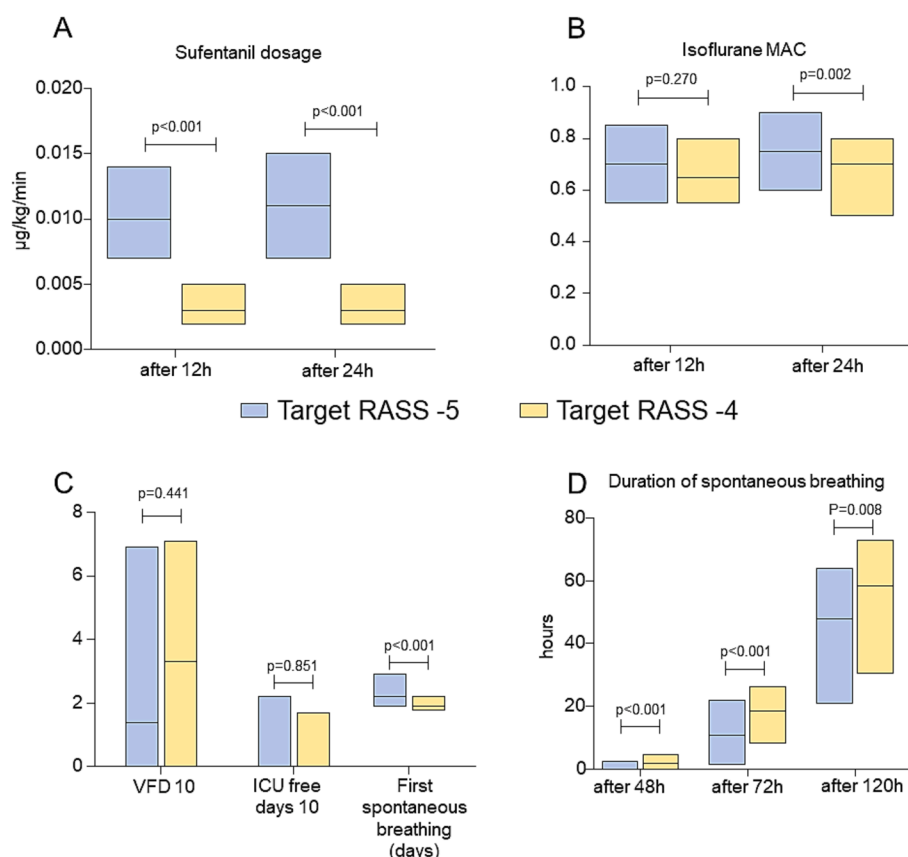

Fig. 2. Sedation and mechanical ventilation. Dosage of Sufentanil (A) and Isolfuran MAC (B) in patients with RASS-target −5 and −4 (MAC N = 297; RASS-target −5: N = 209; RASS-target −4: N = 88). Ventilator free days (VFD),Intensive care unit (ICU) free days 10 days after admission and time of first sponateous breating (C). Duration of spontaneous breathing (D).

sedation had longer duration of spontaneous breathing at various time points and earlier first spontaneous breathing. This may not come as a surprise, as this has already been described for other patient groups.[16,25,26] Nevertheless, this has not yet been proven for patients after cardiac arrest.

Limitations

When discussing the results presented in our study, some limitations have to be considered. We present single-center retrospective data. Therefore, our results should be considered hypothesis-generating only and have to be approved in larger trials. In addition, due to the before-and-after design of our study, we cannot exclude the possibility that
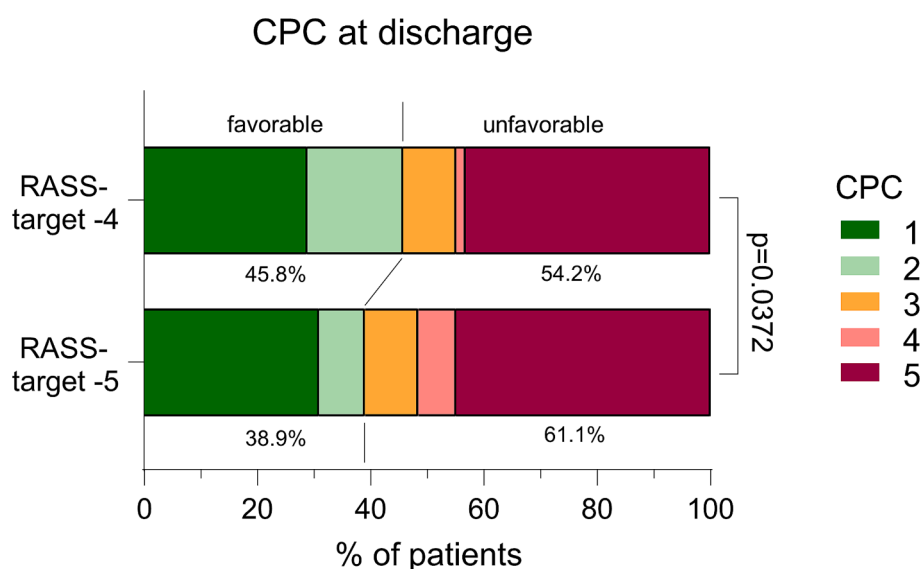
CPC at discharge

Fig. 3. Cerebral Performance Category (CPC) at ICU discharge. Significance is calculated by chi square test.
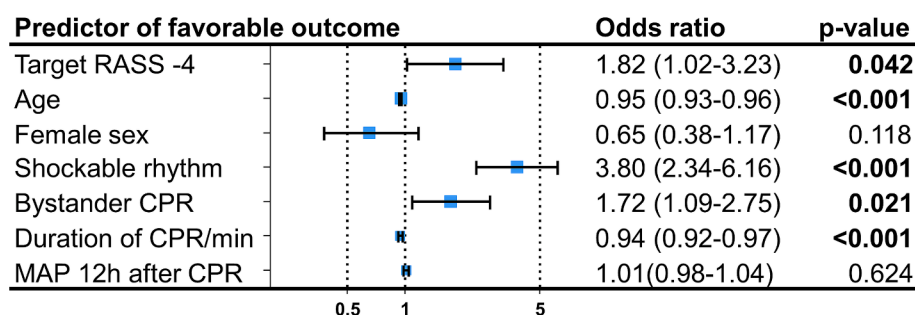

Fig. 4. Predictors of favorable Outcome Multivariable logistic regression analysis with odds ratio (95 % confidence interval) for predictors of favorable outcome. Odds ratios > 1 mark positive predictors, odds ratios < 1 negative predictors. Mean arterial pressure (MAP).

Table 2

ICU survival and 30-day survival of all patients. ICU: Intensive care unit; CPR: Cardiopulmonary resuscitation.

Outcome	Target RASS −5	Target RASS −4	Absolute difference	Odds ratio (95 % CI)	Odds ratio (95 % CI)*	p-value*
	(n = 285)	(n = 118)	(%)	Unadjusted	Adjusted*	Adjusted*
ICU survival	155/285 (54.4 %)	66/118 (55.9 %)	1.5	1.065 (0.691–1.639)	1.591 (0.888–2.850)	0.118
30-day survival	151/285 (53.3 %)	67/118 (56.8 %)	3.8	1.166 (0.757–1.796)	1.814 (1.009–3.263)	**0.047**
Favorable neurological outcome	111/285 (38.9 %)	54/118 (45.8 %)	6.8	1.323 (0.857–2.040)	1.818 (1.022–3.232)	**0.042**

p values < 0.05 are written in bold.

*Multivariate logistic regression model adjusted for age, sex, bystander CPR, shockable rhythm, CPR-duration, and mean arterial pressure 12 h after CPR. Positive odds ratios favor target-RASS −4.

other external factors or better treatment due to increasing experience may have influenced our results. However, a review of the existing literature shows that changes over time were minimal in the last decade. Survival after cardiac arrest showed no significant increase, according to a large Swedish registry.[27] Even more importantly, another large observational study demonstrated that the survival-to-discharge rate among all patients who achieved ROSC after in-hospital cardic arrest increased only minimally, from 30.3 % to 31.4 %, during the period from 2006 to 2018 (OR per year: 1.02).[28] Although we cannot completely rule out a time trend, the existing literature and the absence of a time trend within the two groups indicate that it is unlikely that a time trend significantly influenced our results.

The documented medical record rarely provides information about the exact time of events such as awakening, which therefore cannot be stated in our analysis. Additionally, we did not have follow up data of the patients discharged. As we defined the neurologic outcome at the time of ICU discharge, which is a very early time point for evaluation, it may still have changed during rehabilitation, especially in patients with an unfavorable outcome. However, although CPC evaluation at hospital discharge is better investigated, data exists showing that a good CPC at ICU discharge predicts a good long-term prognosis for two thirds of the patients.[29,30] Since we relied on routine medical record data rather than structured clinicial interviews, which provide a systematic and comprehensive way to assess the patients' medical data, it is possible that certain details may not have been fully documented, leading to potential underreporting of some variables. As this is a single-center experience, these results should be applied to other centers with caution.

Importantly, this study investigated a planned change in the RASS target, along with an independent adjustment in the blood pressure target. Data from the randomized trial by Kjaergaard et al. showed no

impact of blood pressure on outcome.[31] We therefore included the blood pressure in the adjustment of the primary endpoint and MAP did not predict outcome in our data. Nevertheless, we cannot completely rule out the possibility that MAP may have influenced our data.

Conclusion

A sedation after cardiac arrest with a RASS-target of −4 is associated with earlier spontaneous breathing and a more favorable outcome compared to a target of −5. Light sedation strategies after CPR might improve outcome and should be further investigated.

Ethics approval and consent to participate.

This retrospective study was approved by the ethics committee of the Albert Ludwigs University of Freiburg, file number 387/19.

Consent for publication

Not applicable.

Author contributions

Conceptualization: DLS, LH and MJ; Data curation: LH and MJ; Formal analysis: DLS, KK and MJ; Investigation: DLS, LH, AS, VZ and MJ; Methodology: DLS, AM, VZ and MJ; Supervision: DW and TW; Validation: PMB, AM, DW and TW; Visualization: DLS, JR, FAR and MJ; Roles/Writing – original draft: DLS and MJ; review and editing: LH, AM, JR, FAR, VZ, PMB, AS, TW, DW.

CRediT authorship contribution statement

Dawid Leander Staudacher: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Laura Heine:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Jonathan Rilinger:** Writing – review & editing, Visualization. **Alexander Maier:** Writing – review & editing, Investigation. **Felix A. Rottmann:** Writing – review & editing, Visualization. **Viviane Zotzmann:** Writing – review & editing, Methodology. **Klaus Kaier:** Writing – review & editing, Formal analysis. **Paul Marc Biever:** Writing – review & editing, Validation. **Alexander Supady:** Writing – review & editing, Investigation. **Dirk Westermann:** Writing – review & editing, Validation, Supervision. **Tobias Wengenmayer:** Writing – review & editing, Validation, Supervision. **Markus Jäckel:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

Open Access funding enabled and organized by Projekt DEAL

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110456.

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