Ventilatory settings in the initial 72 h and their association with outcome in out-of-hospital cardiac arrest patients: a preplanned secondary analysis of the targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2) trial

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Abstract

Purpose: The optimal ventilatory settings in patients after cardiac arrest and their association with outcome remain unclear. The aim of this study was to describe the ventilatory settings applied in the first 72 h of mechanical ventilation in patients after out-of-hospital cardiac arrest and their association with 6-month outcomes.

Methods: Preplanned sub-analysis of the Target Temperature Management-2 trial. Clinical outcomes were mortality and functional status (assessed by the Modified Rankin Scale) 6 months after randomization.

Results: A total of 1848 patients were included (mean age 64 [Standard Deviation, SD = 14] years). At 6 months, 950 (51%) patients were alive and 898 (49%) were dead. Median tidal volume (VT) was 7 (Interquartile range, IQR = 6.2–8.5) mL per Predicted Body Weight (PBW), positive end expiratory pressure (PEEP) was 7 (IQR = 5–9) cmH₂O, plateau pressure was 20 cmH₂O (IQR = 17–23), driving pressure was 12 cmH₂O (IQR = 10–15), mechanical power 16.2 J/min (IQR = 12.1–21.8), ventilatory ratio was 1.27 (IQR = 1.04–1.6), and respiratory rate was 17 breaths/minute (IQR = 14–20). Median partial pressure of oxygen was 87 mmHg (IQR = 75–105), and partial pressure of carbon dioxide was...
Introduction

Post cardiac arrest syndrome is characterized by high mortality and morbidity rates, and several strategies have been implemented with the aim to improve survival and neurological outcome [1]. Among these, research has focused on the optimization of respiratory function and the prevention of pulmonary complications, which are common in this population [1, 2].

Mechanical ventilation has the aim to provide appropriate gas exchange (arterial partial pressure of oxygen, PaO₂ and arterial partial pressure of carbon dioxide, PaCO₂), which can have important effects on the development of secondary brain damage, cerebral blood flow, and cerebrovascular dynamics, and patient’s survival rate [2]. The pathophysiology of cardiac arrest and its systemic effects, as well as the relationship between ventilatory settings and cerebral hemodynamics after resuscitation is complex and not completely elucidated [2]. The literature on the acute respiratory distress syndrome (ARDS) [3] and non-ARDS [4] population has highlighted the importance of the use of lung protective strategies (i.e. low tidal volume, low plateau pressure) to optimize patients’ outcome [4]. Only few and mostly small studies [5] have focused on the effect of mechanical ventilator settings on outcome after cardiac arrest, with no definitive conclusions [6]. Also, the role of parameters such as driving pressure (DP) and mechanical power (MP), which have shown to be potentially associated with ventilator-induced lung injury and worsened outcomes in the non-ARDS and ARDS population, has not been investigated so far in patients after cardiac arrest [7].

We performed a pre-planned secondary analysis of the Target Temperature Management-2 (TTM2) trial. The primary aim of this study was to describe the ventilator settings applied in a homogeneous population of adults after out of hospital cardiac arrest (OHCA) admitted to the intensive care unit (ICU). The secondary aim was to assess the association between ventilator settings and 6-month mortality and neurological outcome [8]. We hypothesized that patients after OHCA are ventilated using lung protective strategies and that some mechanical ventilator settings, in particular tidal volume, respiratory rate, plateau pressure, positive end expiratory pressure, driving pressure, mechanical power, and ventilatory ratio, would be associated with patients’ outcomes (mortality and neurological outcome).

Methods

The TTM2 trial (registered at clinicaltrials.gov NCT02908308) is an international trial randomizing 1861 mechanically ventilated post-cardiac arrest patients with 6-month follow-up. According to the TTM2 protocol, at ICU admission, patients were randomized to normothermia (931 patients, with the aim to maintain a temperature of 37.5 °C or less), and hypothermia (930 patients, target temperature 33 °C until 28 h after randomization, followed by rewarming to 37 °C in hourly increments in one third of a degree) [9, 10]. The Ethic Committees approved the TTM2 study in all participating centres and informed consent was obtained according to local regulations. No further ethical approval was necessary for this subanalysis. We performed a pre-planned analysis focusing on the mechanical ventilation strategies used in the first 72 h after hospital admission and the association between ventilator settings and 6-month mortality and neurological outcome [8]. We hypothesized that patients after OHCA are ventilated using lung protective strategies and that some mechanical ventilator settings, in particular tidal volume, respiratory rate, plateau pressure, positive end expiratory pressure, driving pressure, mechanical power, and ventilatory ratio, would be associated with patients’ outcomes (mortality and neurological outcome).

Conclusions: Protective ventilation strategies are commonly applied in patients after cardiac arrest. Ventilator settings in the first 72 h after hospital admission, in particular driving pressure and respiratory rate, may influence 6-month outcomes.

Keywords: Mechanical ventilation, Cardiac arrest, Outcome, Mechanical power, Driving pressure, Ventilator settings
Inclusion and exclusion criteria
The TTM2 trial included adult patients (18 years of age or older) admitted to the hospital after out-of-hospital cardiac arrest of presumed cardiac or unknown cause with a return of spontaneous circulation. Eligible patients experienced sustained return of spontaneous circulation (ROSC), were unconscious after ROSC, and required ICU admission and mechanical ventilation. Main exclusion criteria were an interval from ROSC to screening of more than 180 min, unwitnessed cardiac arrest with an initial rhythm of asystole, temperature on admission <30 °C, obvious or suspected pregnancy, intracranial bleeding at admission. Details regarding the inclusion and exclusion criteria are provided in the main manuscript and protocol [8–10]. We restricted this analysis to TTM-2 trial participants who had data pertaining to mechanical ventilation settings available from at least the first 24 h after hospital admission.

Objectives
The primary objective of this study was to describe the ventilatory settings/parameters used in mechanically ventilated patients included in the TTM2 trial. Among these, we focused on basic settings—tidal volume ($V_T$), positive end expiratory pressure (PEEP), Plateau pressure ($P_{plat}$), respiratory rate (RR)—and composite settings—driving pressure (DP), mechanical power (MP), and ventilatory ratio (VR). Secondary objectives were to evaluate the association of these parameters with patients’ 6-month mortality and neurological outcome.

Clinical outcome measures
Six months mortality and patients’ neurological status, assessed by the Modified Rankin Scale (mRS), were defined as clinical outcome measures. Binary 6 months mRS was used to define poor outcome (mRS = 4–6) and good outcome (mRS = 1–3), respectively. Additional clinical outcomes were ICU mortality, hospital mortality, hospital length of stay, duration of mechanical ventilation, ventilator free days at ICU discharge, and at 30 days. Further details on the study procedure and patients’ clinical management have been previously published [8, 10].

Study procedures and data collection
Data were collected at the time of enrollment, at hospital admission, during the ICU-stay, at ICU-discharge, at hospital-discharge, and at follow-up. Clinical, laboratory, and background data were collected from hospital records, relatives, and ambulance services. Data of the TTM2 trial used for this secondary analysis included patients’ demographic characteristics, pre-injury comorbidities (including Charlson comorbidity index [12]), and in particular cardiological issues, timing, type and management of cardiac arrest, clinical presentation, data regarding daily ventilator settings/parameters and respiratory mechanics ($V_T$, PEEP, RR, MP, DP, VR, Pplat, static respiratory system compliance (Crs)), arterial blood gases values ($pH_a$, $P_{O_2}$, $P_{CO_2}$, base excess) and outcomes.

For 6-month follow up, all responses were obtained by study personnel from patients or from a proxy (where impaired cognitive capacity prevented patient interview), during a face-to-face visit, by telephone interview, or by postal questionnaire. General Intensive Care Unit Care including ventilatory management were according to local care plans at the discretion of the treating physicians.

Ventilatory settings were collected from randomization every 4 h for the first 32 h, and then every 8 h until day 3 (72 h). $Cr_s$ was calculated as $V_T$ (ml)/($P_{plat}(cmH_2O) – PEEP(cmH_2O)$).

Mechanical power was estimated according to previously published evidence [13]. Ventilatory ratio was calculated according to the following formula [14]:

\[
\text{Minute ventilation (ml/min)} \times \frac{\text{PaCO}_2 (\text{mmHg})}{\text{Predicted body weight (kg)} \times 100 \times 37.5 (\text{expected PaCO}_2, \text{mmHg})}
\]

According to Costa et al. [7] we also tested the following formula as potential determinant of mortality and poor neurological outcome: $[(4 \times \text{Driving Pressure}) + \text{RR}]$.

Statistical analysis
Being a secondary analysis of a randomized trial and having a broad spectrum of exposures (all ventilatory settings), a formal sample size calculation could not be performed a priori for the present study. However, the achieved sample included 898 death events, allowing us to keep the ratio between events and covariates well above the conventional threshold of 10:1. Patient and ventilator characteristics, and arterial blood gases values were described by means± standard deviation (SD), or medians (interquartile range, IQR) when appropriate. Discrete variables were summarized as percentages. At baseline, the comparisons of means, medians, and frequencies among 6-month survival status were carried out using t-test, Wilcoxon–Mann–Whitney test, and chi-square test, respectively.

Six-month mortality.
The association between baseline ventilator settings and arterial blood gases with mortality was determined with Cox regression analysis. Overall, all regression models were built with variables chosen based on previous knowledge and aims of the study. Essentially, we built five models: (1) basic ventilatory markers, (2) a model for driving pressure; (3) a model for mechanical power; (4) a model for ventilatory ratio; and (5) a model for
respiratory system compliance. The basic ventilatory markers model was adjusted by the TTM2 randomization group (from the original randomized controlled trial), arterial blood gases values (pH, PaO2/FiO2, PaCO2, base excess), the basic ventilatory markers (V̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̊
Figure 1 and ESM Figure S3 show the longitudinal trajectories of the different parameters within the first 72 h in survivors and non-survivors.

All the ventilator strategies trajectories differed significantly over the 72 h studied according to survival status. Figure 2 and ESM Figure S4 present the relative distribution analysis assessing the best cut off point for mortality for each variable. Using PEEP as example, having a PEEP of 8 cmH2O (corresponding to a quantile 0.85 of the PEEP distribution in those alive) had a corresponding ratio of 1.3 (on the y-axis), thus suggesting that PEEP of 8 included 1.3 times the proportion of patients who died as compared with those who remained alive.

Association of ventilator parameters with 6 months mortality and neurological outcome

Among respiratory parameters, RR, driving pressure, MP, and VR were independently associated with mortality (omnibus p-values for the non-linear trajectories: $p<0.0001$, $p=0.026$, $p=0.029$, and $p=0.0003$, respectively) (Fig. 3a, b, ESM Table S6). Stratified analysis assessing the effect on mortality for driving pressure, MP, and RR according to elastance values are presented in ESM Figure S5. The Omnibus p-value for the three ventilator settings showed no difference according to elastance categories ($p=0.1703$, $p=0.3508$, $p=0.1887$, respectively). Driving pressure and RR were also associated with poor neurological outcome (OR $=1.015–1.525$, $p=0.048$ and OR $=1.035$, 95% CI $=1.003–1.068$, $p=0.030$, respectively), Table 2, ESM Table S7-8. Considering the formula $[(4\times \text{Driving Pressure}) + \text{RR}]$ from Costa et al. [7] we found a significant association with mortality (HR $=1.152$, 95% CI $=1.040–1.276$, $p=0.006$) and poor neurological outcome (OR $=1.244$, 95% CI $=1.015–1.525$, $p=0.036$) with a better performance compared to MP (ESM, Fig. S6, Table 2). Considering ventilator targets, PaCO2 values were not associated with 6 months mortality (HR $=1.089$, 95% CI $=0.993–1.195$, $p=0.069$); or poor neurological outcome (OR $=1.018$, 95% CI $=0.910–1.140$, $p=0.751$) (ESM Table S6; Table 2). PaO2 was independently associated with mortality (HR $=1.105$, 95% CI $=1.014–1.205$, $p=0.024$), but not with neurological outcome (OR $=1.009$, 95% CI $=0.993–1.024$, $p=0.273$) Additional results on arterial blood gases values are presented in ESM Table S7, 8. ESM Table S9 shows the Cox regression estimates of the basic ventilatory markers with stratification according to study center, and eliminating centers including less than ten patients. These results prove that our analysis is robust enough by no including the center effect in the model.

Discussion

In this pre-planned sub-study of the TTM2-trial, including 1848 patients after out of hospital cardiac arrest, we describe ventilation practice and the association of different mechanical ventilation settings with 6 months mortality and functional neurological outcome. Our results can be summarized as follows: (1) protective ventilation strategies are commonly used in this population during the first 72 h; (2) respiratory rate, driving pressure, mechanical power and ventilatory ratio were independently associated with 6-month mortality; (3) respiratory rate and driving pressure were also associated with 6-month functional outcome; (4) the formula $[(4\times \text{Driving Pressure}) + \text{RR}]$ [7] demonstrated to be significantly associated with mortality and poor neurological outcome.

To our knowledge, this is the largest study describing ventilatory settings applied in out of hospital cardiac arrest survivors and their association with 6-month mortality risk as well as functional outcome. In particular, this is the largest investigation to date on the potential effects on mortality and neurological outcome of ventilation settings, in particular driving pressure and respiratory rate, in a non-ARDS population.

The characterization of ventilator settings is fundamental in this group of patients, as mortality and poor outcome are still very high despite several medical interventions have been applied and implemented [2, 17–24]. The recent guidelines of the European Resuscitation Council and European Society of Intensive Care Medicine on post-resuscitation care do not provide specific recommendations on the optimal ventilator settings to be applied after cardiac arrest. It is just suggested to aim at a tidal volume of 6–8 mL/kg ideal body weight [25]. This is consequent to the availability of a limited number of studies for this specific population, and especially on the lack of data in literature of more advanced and specific parameters (such as driving pressure and mechanical power) [14], which have shown in other groups of patients to have a potential effect on outcome, but not in cardiac arrest [26–32]. Although recent literature has highlighted the importance of protective ventilation in ARDS and non-ARDS patients [33–35], some strategies may be potentially detrimental in patients after cardiac arrest; high PEEP might further aggravate cerebral edema by increasing intrathoracic pressure while reducing jugular outflow, and low tidal volume and consequent permissive hypercapnia can cause cerebral vasodilation [36, 37]. The appropriate target of PaCO2 needs to be better determined in this population [21, 38]; early cerebral hyperperfusion and impaired cerebrovascular autoregulation may make normal PaCO2 insufficient to achieve adequate cerebral perfusion and, consequently, cerebral oxygenation,
Table 1  Baseline patients’ characteristics, comorbidities, pre-hospital settings/interventions of the overall population and stratified according to 6 months survival status

|                                | Total  | Survivors | Non-survivors |
|--------------------------------|--------|-----------|---------------|
|                                | n = 1848 | n = 950 (51%) | n = 898 (49%) |
| **Baseline patients characteristics** |        |           |               |
| Age, years, mean (SD)          | 64 (14) | 59 (14)   | 68 (12)       |
| Gender (female), n (%)         | 379 (20) | 153 (16)  | 226 (25)      |
| Height, cm, mean (SD)          | 174 (9) | 176 (9)   | 173 (9)       |
| Weight, Kg, mean (SD)          | 83 (17) | 85 (16)   | 82 (19)       |
| BMI, Kg/m², mean (SD)          | 27.5 (5.7) | 27.3 (5.4) | 27.7 (6.1)    |
| **Comorbidities**              |        |           |               |
| Hypertension, n (%)            | 460 (35) | 289 (30)  | 351 (39)      |
| Diabetes, n (%)                | 336 (18) | 138 (14)  | 198 (22)      |
| Myocardial infarction, n (%)   | 291 (16) | 127 (13)  | 164 (18)      |
| Previous percutaneous coronary intervention, n (%) | 267 (14) | 121 (13)  | 146 (16)      |
| Coronary artery bypass graft, n (%) | 147 (8) | 62 (6)   | 85 (10)       |
| Heart failure, n (%)           | 181 (10) | 54 (6)    | 127 (14)      |
| Charlson comorbidity index, median (IQR) | 3 (1; 4) | 2 (1; 3)  | 4 (2; 5)      |
| **Pre-hospital settings/interventions** |        |           |               |
| Location of cardiac arrest, n (%) |         |           |               |
| Home                           | 971 (52) | 410 (43)  | 561 (63)      |
| Public place                   | 653 (35) | 402 (42)  | 251 (28)      |
| Other                          | 224 (12) | 138 (15)  | 86 (10)       |
| Witnessed cardiac arrest, n (%) | 1689 (91) | 881 (93)  | 808 (90)      |
| CPR performed bystander, n (%) | 1480 (80) | 806 (85)  | 674 (75)      |
| Type of rhythm, n (%)          |         |           |               |
| Not shockable                  | 486 (26) | 105 (11)  | 381 (42)      |
| Shockable                      | 1362 (74) | 845 (89)  | 517 (58)      |
| Time to return of spontaneous circulation (ROSC), min, median (IQR) | 25 (17; 40) | 20 (14; 30) | 31 (21; 46) |
| **TTM2: randomization treatment, n (%)** |         |           |               |
| Normothermia                   | 923 (50) | 485 (51)  | 438 (49)      |
| Hypothermia                    | 925 (50) | 465 (49)  | 460 (51)      |
| Shock diagnosis at hospital admission, n (%) | 529 (29) | 193 (20)  | 336 (37)      |
| STEMI diagnosis at hospital admission, n (%) | 742 (40) | 429 (45)  | 313 (35)      |
| **Ventilatory parameters at admission** |         |           |               |
| Positive end expiratory pressure, cmH₂O, median (IQR) | 6.90 (2.51) | 6.64 (2.31) | 7.18 (2.67) |
| Respiratory rate, breaths/min, median (IQR) | 17 (14; 20) | 16 (14; 19) | 18 (15; 20) |
| Plateau pressure, cmH₂O, median (IQR) | 20 (17; 24) | 20 (16; 23) | 21 (17; 25) |
| Tidal volume, mL, median (IQR) | 499 (441; 555) | 500 (450; 570) | 485 (429; 545) |
| Tidal volume, mL/kg per PBW, median (IQR) | 7.1 (6.3; 8.2) | 7.1 (6.3; 8.1) | 7.2 (6.4; 8.3) |
| Driving pressure, cmH₂O, median (IQR) | 13 (10; 16) | 13 (10; 16) | 14 (10; 17) |
| (4*Driving Pressure) + respiratory rate, median (IQR) | 69 (54;84) | 68 (54;83) | 74 (55;88) |
| Compliance of respiratory system, mL/cmH₂O, median (IQR) | 40 (31; 50) | 42 (33; 51) | 37 (28; 48) |
| Mechanical power, W/min, median (IQR) | 16.2 (12.5; 21.6) | 15.5 (12.6; 20.5) | 17.4 (12.5; 22.9) |
| FiO₂, %, median (IQR) | 60 (50; 90) | 60 (44; 80) | 60 (50; 98) |
| PaO₂/FiO₂ ratio, mmHg, median (IQR) | 173 (110; 256) | 192 (127; 282) | 151 (94; 230) |

Data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), numbers (n) and percentages (%) when not otherwise specified. BMI: body mass index; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; TTM2: Target Temperature Management; STEMI: ST-elevation myocardial infarction.
and mild hypercapnia has been suggested by some authors to optimize cerebral blood flow [39]. The ongoing TAME study (ClinicalTrials.gov: NCT03114033) is evaluating the effect of mild hypercapnia on patients’ outcome in this population.

Our results suggest that in a homogeneous population of patients after cardiac arrest, lung protective standards are often applied, similarly to the results of the PROVENT study [4], an observational study focusing on mechanical ventilation practices in a heterogeneous population of patients without ARDS, but not specifically including cardiac arrest patients.

Evidence have progressively demonstrated that low VT is associate with favorable outcome after cardiac arrest [37], and very low PEEP or zero PEEP (ZEEP) can aggravate the risk of atelectasis and lung damage [40, 41]. As consequence of this, over time, physicians are increasingly applying lower tidal volume and higher PEEP even in cardiac arrest patients [5, 42], and as well as in brain injured patients at risk of intracranial hypertension [43]. In a secondary analysis from a multicenter study in ICU patients receiving mechanical ventilation [44], Sutherasan et al. showed that in 1998 the mean tidal volume used in cardiac arrest patients was 8.9 mL/Kg, and mean PEEP was 3.5 cmH2O [5]. A sub-analysis of the TTM trial published in 2018 [6] demonstrated a median tidal volume = 7.7 mL/Kg PBW, and PEEP 6 cmH2O, and driving pressure of 14.7 cmH2O. In our cohort, we found even higher median values of PEEP, and lower median values of tidal volume and driving pressure, thus suggesting an increasing application of protective strategies in this population over years.

We found that mechanical power, driving pressure, and ventilatory ratio but not PEEP, plateau pressure of the respiratory system or tidal volume alone were independently associated with 6 months mortality. This suggests the importance of the titration of different settings taking in account intrathoracic pressure and ventilation to avoid ventilator lung injury rather than the application of only one single protective mechanical ventilation strategy. In particular, the fact that tidal volume “per se” is not associated with outcome, further supports the hypothesis that the most relevant parameter

**Fig. 1** Hourly trajectories of different ventilator settings/parameters according to survival status. Predicted values from a mixed regression analysis with random intercept. PEEP positive end-expiratory pressure; PBW predicted body weight; FiO2 fraction of inspired oxygen.
to be controlled is the tidal volume standardized for
the expected lung volume (i.e., estimated by respiratory
compliance), which in practical terms is identified by
the driving pressure (i.e., a bedside parameter measur-
ing the “dynamic” strain equal to tidal volume divided
the amount of aerated lung). Driving pressure, which
is a function of plateau pressure and PEEP, represents
the real stress applied to the respiratory system (of the
lung and chest wall combined) from end-inspiration to
end-expiration [45]. Similarly, mechanical power is the
mechanical energy which is transferred to the respira-
ry system in every respiratory cycle, multiplied with
each respiratory rate, and it is therefore considered as
a determinant of ventilator-induced lung injury (VILI)
[13, 46]. A recent experimental study showed that pul-
monary neutrophilic inflammation importantly corre-
lates with mechanical power [47]; similarly, mechanical
power has demonstrated to be related to radiological
signs of lung edema, and histological features of lung
injury [46]. In the clinical settings, mechanical power
was found to be associated with mortality in retro-
spective studies on critically ill patients [7, 26]. For the
first time, our results demonstrated in a prospectively
enrolled population of critically ill patients after cardiac
arrest, that mechanical power is independently associ-
ated with 6 months mortality, with a threshold similar

Fig. 2 Relative distribution analysis for the definition of the best cut-off associated with mortality for each parameter. Best cut-off point along the
continuum of the marker that separated survivors versus non survivors at the end of the follow-up. In this analysis, the quantile (or proportion)
distribution of the marker survivors (plotted on the x-axis plus the corresponding marker values at the top) is plotted against the proportion ratio of
the marker distribution for non survivors. PEEP positive end-expiratory pressure; PBW predicted body weight; FiO₂

Fig. 3 a,b Ventilatory markers and 6-month mortality. This regression model was adjusted by (1) clinical variables: TTM2 randomization group,
age (years), Charlson comorbidity index, cardiac arrest witnessed, ROSC (min), bystander performed CPR, shockable rhythm, cardiac arrest location
(home, public place, other), shock diagnosis on admission, and STEMI diagnosis on admission; (2) arterial blood gas values: arterial partial pressure
of oxygen (PaO₂) (mmHg)/Fraction of inspired oxygen (FiO₂) ratio, arterial partial pressure of carbon dioxide (PaCO₂) (mmHg), pH, and Base excess
(mEq/L); and (3) by the above markers among them. PEEP, positive end-expiratory pressure.
Fig. 3 (See legend on previous page.)
to other critically ill populations (Fig. 2) [7, 26]. We also found that the only basic ventilator setting associated with mortality is the respiratory rate, thus suggesting that this could be the major determinant of lung injury. This latter point is of extreme importance in cardiac arrest patients, as often high respiratory rates are used to precisely titrate PaCO₂ to modulate cerebral blood flow and vascular tone and avoid hypercapnia, cerebrovascular vasodilation and increase cerebral edema and may have a major role in non-ARDS patients as outcome determinant [6, 48, 49]. Consistently, this might also explain the relationship between ventilatory ratio, which depends on minute ventilation, and mortality. Indeed, ventilatory ratio is a relatively new bedside index able to detect impaired ventilation in ARDS and correlates well with pulmonary dead space fraction [14, 50]. However, stratified analysis assessing the effect on mortality for driving pressure, mechanical power, and respiratory rate according to classes of elastance, showed no difference. This is in contrast with a previous study from Goligher et al. [51], which showed that the mortality benefit in ARDS is greater in patients with high elastance and comparatively lower in patients with low elastance. However, it is important to highlight this study included only ARDS population, with importantly impaired respiratory mechanics, whereas in our study we included a homogeneous population of cardiac arrest patients with relatively healthy lungs, and therefore the effect of elastance may be less clear. Interestingly, we demonstrated that using the formula [(4*Driving Pressure) + RR] [7] previously applied only in patients with ARDS, the combination of driving pressure and respiratory rate has significant association with mortality and poor neurological outcome, and can be even more informative than mechanical power. This is the first study where this formula was applied in non-ARDS patients, and we believe that this is an unique result for clinicians, as this may guide ventilatory settings application: in particular, as this formula represents lung stress/strain and stress rate, lowering VT is beneficial only whether this yields a reduction in driving pressure of 1 cmH₂O with increases in respiratory rate not greater than 4 breaths/minute. Therefore, in the attempt to optimize ventilatory settings, first we should minimize the driving pressure, and secondly decrease the respiratory rate. This is of fundamental importance especially in the aim of optimize PaCO₂ and pH, through respiratory rate manipulations. Finally, we found an association between respiratory rate, driving pressure and neurological outcome. This suggests that these two parameters are fundamental not only to minimize patients’ mortality but also to reduce secondary brain damage, by modulating carbon dioxide values and ventilator-induced lung injury. However, as shown in our analysis, the effect observed on mRS is mainly related to the inclusion of mortality in this scale (mRS = 6), and this result should be taken with caution.

### Table 2: Regression estimates from the multivariable models for poor neurological outcome

| Ventilator settings                             | OR    | 95% Confidence Interval | p value |
|------------------------------------------------|-------|-------------------------|---------|
| **Model for basic ventilator markers**         |       |                         |         |
| Respiratory rate, per 10 breaths/min           | 1.035 | (1.003–1.068)           | 0.030   |
| Plateau pressure, cmH₂O                         | 1.016 | (0.964–1.068)           | 0.251   |
| Tidal volume, ml*kg⁻¹ per PBW                  | 0.971 | (0.898–1.051)           | 0.473   |
| PEEP, cmH₂O                                    | 1.023 | (0.968–1.081)           | 0.420   |
| PaCO₂, mmHg                                     | 1.018 | (0.910–1.140)           | 0.751   |
| PaO₂, mmHg                                      | 1.009 | (0.993–1.024)           | 0.273   |
| **Models for composite ventilator markers**    |       |                         |         |
| [4*Driving pressure]+RR                         | 1.244 | (1.015–1.525)           | 0.036   |
| Driving pressure FP21[-1], cmH₂O                | 1.005 | (1.001–1.036)           | 0.048   |
| Mechanical power, J/min                        | 1.012 | (0.990–1.034)           | 0.297   |
| Compliance of respiratory system, mL/cmH₂O     | 0.984 | (0.981–1.007)           | 0.597   |
| Ventilatory ratio                               | 0.867 | (0.640–1.174)           | 0.356   |

All regression models were adjusted by 1) Clinical variables: TTM2 randomization group, age (years), Charlson comorbidity index, cardiac arrest witnessed, return to spontaneous circulation, ROSC (min), bystander performed cardiopulmonary resuscitation, CPR, shockable rhythm, cardiac arrest location (home, public place, other), shock diagnosis on admission, STEMI diagnosis on admission, and arterial blood gases, ABG: PaO₂ (mmHg)/FiO₂, PaCO₂ (mmHg), pH, and Base excess (mEq/L)

OR odds ratio; PEEP positive end-expiratory pressure; TTM2 Target Temperature Management; ROSC return of spontaneous circulation; CPR cardiopulmonary resuscitation; STEMI ST elevation myocardial infarction; ABG arterial blood gases; PaO₂ arterial partial pressure of oxygen; FiO₂ fraction of inspired oxygen; PaCO₂ arterial partial pressure of carbon dioxide; RR respiratory rate
Limitations
This study presents several limitations. Firstly, this is an observational study, which therefore precludes to draw any causality conclusions from our results. Indeed, observational data do not fully describe if the underlying severity of patients explains the ventilator settings observed in patients with higher mortality, and results should be taken with caution. A randomized controlled trial would be needed to jump to strong conclusions. However, we used statistically robust models, which can provide information about the association between ventilator parameters and outcome and pave the way for the development of prospective randomized controlled trials to confirm these findings. Secondly, although this was a preplanned study, some information is lacking in eCRF (such as the Pittsburgh cardiac arrest score) and there are some missing data in the variables. Third, as per study protocol, paralysis was not routinely applied; this may have altered spontaneous breathing efforts respiratory rate and other ventilation data.

Conclusions
Cardiac arrest patients often and increasingly receive protective ventilation. Optimization of ventilator settings and limiting exposure to modifiable factors of mechanical ventilation and in particular to high respiratory rate, and driving pressure may improve patient's outcome after cardiac arrest.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06756-4.

Abbreviations
AUG: Arterial blood gas; ARDS: Acute respiratory distress syndrome; AUC: Area under curve; BMI: Body mass index; CI: Confidence interval; CO2: Carbon dioxide; COPD: Chronic obstructive pulmonary disorder; Crs: Respiratory system compliance; DP: Driving pressure; eCRF: Electronic case record form; ESM: Electronic supplemental material; GCS: Glasgow coma scale; HR: Hazard ratio; ICU: Intensive care unit; MP: Mechanical power; mRS: Modified Rankin Scale; OHCA: Out of hospital cardiac arrest; OR: Odds ratio; PaCO2: Arterial partial pressure of CO2; PaO2: Arterial partial pressure of oxygen; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; pH:A: Arterial pH; PI: Principal investigator; Ppeak: Peak pressure; Pplat: Plateau pressure; RCT: Randomized controlled trial; ROSC: Return of spontaneous circulation; RR: Respiratory rate; STEM: ST elevation myocardial infarction; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TTM2: Target Temperature Management 2 Trial; VR: Ventilator ratio; Vt: Tidal volume; ZEEP: Zero PEEP.

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Methods.

International study hypothesis (1).

The TTM2 trial was supported by independent research grants from nonprofit or governmental agencies (the Swedish Research Council [Vetenskapsrådet], Swedish Heart–Lung Foundation, and Ragna Gorbon Foundation, Knutsson Foundation, Laerdal Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, and Regional Research Support in Region Skåne) and by governmental funding of clinical research within the Swedish National Health Service. No further funding were requested for this subanalysis.

Ethical approval and informed consent

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Author contribution

CR: conception of the work, participation in data analysis and interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version to be published. All the authors: conception of the work, critical revision of the manuscript, final approval of the version to be published. PP and NN equally contributed.

Funding

Open access funding provided by Università degli Studi di Genova within the CRUI-CARE Agreement. The TTM2 trial was supported by independent research grants from nonprofit or governmental agencies (the Swedish Research Council [Vetenskapsrådet], Swedish Heart–Lung Foundation, and Ragna Gorbon Foundation, Knutsson Foundation, Laerdal Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, and Regional Research Support in Region Skåne) and by governmental funding of clinical research within the Swedish National Health Service. No further funding were requested for this subanalysis.

Declarations

Conflict of interests

MS, receiving consulting fees from Bard Medical; PJY, receiving lecture fees from Bard Medical, FST, receiving grant support from Bard Medical and ZOLL Medical, AN, receiving consulting fees from University College Dublin, from AM Pharma and grant support, paid to Monash University, from Baxter Healthcare; MSC, receiving lecture fees from Edwards Lifesciences; HF, receiving fees for academic advising from TEQCool; and NN, receiving lecture fees from Bard Medical and consulting fees from BrainCool. RB is supported by INCLIVA. No other potential conflict of interest relevant to this article was reported.

Ethical approval and informed consent

The Ethic Committees approved the TTM2 study in all participating centres and informed consent was obtained according to local regulations.

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Received: 12 March 2022 Accepted: 24 May 2022

Published: 2 July 2022

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