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Title: Practice of mechanical ventilation in cardiac arrest patients and effects of targeted temperature management: a substudy of the targeted temperature management trial

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Abstract

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Aims

Mechanical ventilation practices in patients with cardiac arrest are not well described. Also, the effect of temperature on mechanical ventilation settings is not known. The aims of this study were 1) to describe practice of mechanical ventilation and its relation with outcome 2) to determine effects of different target temperatures strategies (33°C versus 36°C) on mechanical ventilation settings.

Methods

This is a substudy of the TTM-trial in which unconscious survivors of a cardiac arrest due to a cardiac cause were randomized to two TTM strategies, 33°C (TTM33) and 36°C (TTM36). Mechanical ventilation data were obtained at three time points: 1) before TTM; 2) at the end of TTM (before rewarming) and 3) after rewarming. Logistic regression was used to determine an association between mechanical ventilation variables and outcome. Repeated-measures mixed modelling was performed to determine the effect of TTM on ventilation settings.

Results

Mechanical ventilation data was available for 567 of the 950 TTM patients. Of these, 81% was male with a mean (SD) age of 64 (12) years. At the end of TTM median tidal volume was 7.7 ml/kg predicted body weight (PBW)(6.4-8.7) and 60% of patients were ventilated with a tidal volume ≤ 8ml/kg PBW. Median PEEP was 7.7cmH$_2$O (6.4-8.7) and mean driving pressure was 14.6 cmH$_2$O (± 4.3). The median FiO$_2$ fraction was 0.35 (0.30-0.45). Multivariate analysis showed an independent relationship between increased respiratory rate and 28-day mortality. TTM33 resulted in lower end-tidal CO$_2$ (Pgroup=0.0003) and higher alveolar dead space fraction (Pgroup=0.003) compared to TTM36, while PCO$_2$ levels and respiratory minute volume were similar between groups.

Conclusions

In the majority of the cardiac arrest patients, protective ventilation settings are applied, including low tidal volumes and driving pressures. High respiratory rate was associated with mortality. TTM33 results in lower end-tidal CO$_2$ levels and a higher alveolar dead space fraction compared to TTTM36.

Introduction

Targeted temperature management(TTM) is the main treatment modality for survivors of a cardiac arrest[1]. Large scale studies on mechanical ventilation practice after cardiac arrest and during TTM are scant. Ventilation strategies such as low tidal volume ventilation can improve outcome in patients with acute lung injury[2] and possibly also in patients without lung injury[3, 4]. However implementation of lung protective ventilation strategies is difficult[5]·[6]. Recently, observational studies examined ventilation practices in ARDS[7], and non-ARDS[8], but these studies did not focus on cardiac arrest. Following the multi-center randomized target temperature management after cardiac arrest trial(TTM-trial)[9], the recommendation to control temperature between 32°C and 36°C[10] yielded variation in practice of TTM management[11]. The effect TTM on mechanical ventilation settings is largely unknown. In a retrospective study in cardiac arrest patients, application of 33°C was associated with improved gas exchange[12].

Studying mechanical ventilation practices in patients following cardiac arrest may lead to optimization of ventilation during TTM and may ultimately improve outcome of these patients. The TTM trial provides a unique opportunity to study mechanical ventilation practices in cardiac arrest and to study the effect of temperature on parameters of mechanical ventilation. Therefore, the aims of this study were the following:1) to describe practice of mechanical ventilation and its independent relation with outcome.2) to determine effects of different target temperatures on mechanical ventilation parameters. We hypothesized that TTM at 33°C would lower ventilation settings needed for a minute volume ventilation.

Methods

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Patients

This study is a retrospective substudy of the multi-centre, randomized, parallel-group, assessor-blinded TTM-trial. The TTM-trial included adult (≥18 years) unconscious patients (Glasgow Coma Scale <8) resuscitated from cardiac arrest of a presumed cardiac cause with return of spontaneous circulation during at least 20 minutes. Following informed consent according to the regulations as approved by local IRB, patients were included at 36 centres in Europe and Australia. Further details on the exclusion criteria, trial protocol and main results were published previously [9].

TTM protocol

The entire duration of the TTM-protocol was 36 hours, which started at randomization to either 33°C (TTM33) or 36°C (TTM36). The assigned target temperature was achieved as soon as possible after which patients were kept at their target temperature until 28 hours after randomization. After 28 hours, patients were gradually rewarmed to 37°C at a maximum speed of 0.5°C per hour. Sedation was mandatory for both groups during the entire TTM intervention. Patients were ventilated in either a pressure or a volume controlled mode.

Post-hoc survey

Participating centers of the TTM-trial were asked to complete an additional online case report form with data on mechanical ventilation at three time points: prior to the TTM intervention, after 24 hours of TTM (before rewarming) and after rewarming was completed (at the start of the normothermic phase). Collected data are tidal volume (V_T), positive end expiratory pressure (PEEP), plateau pressure of the respiratory system (Pplat), respiratory rate (RR) and end tidal CO_2 (etCO_2). Data on lactate, arterial PO_2 (PaO_2), arterial PCO_2 (PaCO_2), base excess, pHa and mean arterial pressure were derived from the original TTM-database. Blood gasses were measured alpha-stat. Respiratory minute volume (RMV) was calculated as the V_T x RR. Static compliance of the respiratory system (Cstat) was calculated as V_T / Pplat – PEEP. Driving pressure (ΔP) was calculated as V_T / Cstat. Alveolar dead space ventilation was calculated as (PaCO_2 - etCO_2) / PaCO_2 [13]. Supranormal arterial oxygen content was defined as a PaO_2 level >13.3 kPa [14].

Statistical Analysis

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All analyses were performed in R (version 3.1.1). Baseline differences and differences in mechanical ventilation parameters were assessed using either the students t-test or the Wilcoxon rank sum test depending on normality of the data. To study the relationship between mechanical ventilation on 28-day mortality, a logistic regression model was performed. A priori, age, SOFA score, asthma/COPD, time from cardiac arrest to ROSC, first measured body temperature, lactate and cardiovascular diseases were put into the model. Mechanical ventilation variables with a P-value below 0.2 were also included. Collinearity diagnostics were performed using the variance inflation factor to check for variable independence. Missing data was imputed using the "MICE" package [15]. A restricted cubic spline function was used for non-linear variables. Variables were sequentially removed from the model based on likelihood ratio tests.

LOESS regression with a polynomial regression of 1 and a span of 0.75 was used to visualize the relationship between mechanical ventilation variables and 28-day mortality. To study differences between target temperatures over time, continuous variables of interest were analyzed by repeated-measures mixed model. Overall differences between groups were measured using TTM group and time point as a fixed effect, expressed as β-coefficient, confidence interval and P value. Post-hoc analysis of estimates between time points were assessed with the interaction term TTM group and time point using the "LSmeans" package [16]. Normally distributed data was presented a mean ± (standard deviation). Non-parametric data was presented as median (25-75th percentile). P values < 0.05 were considered significant.

Results

Of the 950 patients randomized in the TTM-trial in 36 centers, mechanical ventilation data was available for a total 567 patients from 24 centers. The centers that were not able to submit data comprise of both academic and non-academic hospitals. Age, sex and mortality did not differ between the included and non-included patients.

Baseline characteristics

Baseline characteristics of included patients are shown in table 1. Patients were mostly male and frequently had cardiovascular risk factors. Of note, patients were hypothermic upon start of study. The number of patients with asthma or COPD Gold I-IV did not differ between survivors and non-survivors. Non-survivors had longer time from cardiac arrest to basic life support and higher incidence of circulatory shock compared to the survivor group [17].

Mechanical ventilation settings during TTM

Mechanical ventilation settings for patients are shown in table 2 and cumulative frequency distributions in figure 1. The median V_T was 7.7 ml/kg (6.4-8.7) predicted body weight (PBW) and in total, 60% of patients were ventilated with a V_T equal to or below 8 ml/kg (figure 1). Median PEEP was 6 cmH$_2$O (5-8) and mean driving pressure 14.7 cmH$_2$O ($\pm$ 4.2). More than half of patients were ventilated with > 5 mmHg of PEEP. Plateau pressure was above 30 cm H$_2$0 in 8% of patients and above 20 cm H$_2$O in 60% of patients. Compliance of the respiratory system, was below 50 mL/cmH$_2$O in the majority of patients (83%). The median FIO$_2$ fraction was 0.35 (0.30-0.45). In patients with a supranormal arterial oxygen content (> 13.3 kPa), 48% were ventilated with an FiO$_2$ $\geq$ 0.4.

Mechanical ventilation settings in hypoxemic vs. normoxemic patients

As a surrogate marker of pulmonary complications, hypoxemic patients (P/F ratio < 200 mmHg) were compared to normoxemic patients (P/F ratio $\geq$ 200 mmHg) (supplemental table 2). PEEP was significantly higher in hypoxemic patients compared to normoxemic patients as was Pplat driving pressure V_T and respiratory rate. Static compliance was lower in hypoxemic patients compared to normoxemic patients (34.3 mL/H$_2$O (

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Mechanical ventilation settings during TTM in survivors vs. non-survivors at 28-days

Baseline differences are given in table 1. V_T, PEEP, Pplat and driving pressure did not differ between groups (table 2). Static compliance of the respiratory system was significantly lower while respiratory rate was significantly higher in non-survivors compared to survivors.. Figure 2 shows the distribution of ventilation parameters plotted against V_T and PaO_2 levels. The distribution for survivors and non-survivors at 28-days was largely the same.

Figure 3 shows the relationship between mortality and ventilation settings using Loess regression curves. Mortality appears to be higher when driving pressures are above 20 cmH_2O and when plateau pressures are above 25 cmH_2O. Also, mortality is higher in patients with P/F ratios below 200 and in patients with low compliance. Of interest, high tidal volumes were not apparently related to mortality. Mechanical ventilation factors were included in a multivariable logistic regression model with a priori selected variables for disease severity and medical history to assess which factors were independently associated with mortality. In this analysis, with the exception of high respiratory rate, ventilator parameters were not associated with 28-day mortality (supplemental table 1).

The effect of different target temperature levels on mechanical ventilation parameters

At the end of the TTM period, patients kept at TTM33 had significantly lower $etCO_2$ when compared to patients kept at TTM36 (3.9 kPa ± 0.98 vs. 4.55 kPa ± 1.31, p<0.0001), whereas $PaCO_2$ levels and respiratory minute volume were similar between groups (supplemental table 3). In addition, alveolar dead space fraction was significantly higher in TTM33 vs. TTM36 (0.24 ± 0.19 vs. 0.15 ± 0.29, p=0.004). PEEP, V_T and Pplat did not differ between groups (supplemental table 3).

To study the effect of TTM on $etCO_2$ and $PaCO_2$ over time, we performed a mixed effects model (supplemental table 4, figure 4). $PaCO_2$ levels were significantly lower after 4 hours compared to baseline in both the TTM33 group (β = 0.41 kPa [95% confidence limit, 0.09 - 0.73 kPa]; p = 0.0014) and the TTM36 group (β = 0.63 kPa [95% confidence limit, 0.31 - 0.95 kPa]; p = <0.0001). However, there was no difference between groups in $PaCO_2$ levels. In contrast, $etCO_2$ levels were lower in the TTM33 group compared to the TTM36group, whereas alveolar dead space fraction was higher. These results were found at a similar respiratory minute volume between both groups. Metabolic acidosis was more pronounced in the TTM33 group, with lower pHa, lower base excess and increased lactate levels.

Discussion

In this substudy of the TTM-trial, we describe ventilation practice in patients after a cardiac arrest and the effects of different target temperatures on mechanical ventilation settings and parameters of gas-exchange. At the end of TTM (before rewarming), we found that patients are predominantly ventilated with low tidal volumes, equal or below 8 ml/kg. Oxygen was applied liberally, with 48% of patients with supranormal (>13.3 kPa) oxygenation receiving high FiO_2 levels. Non-survivors had lower oxygenation, higher respiratory rates, lower compliance, higher driving pressures and were ventilated with lower tidal volumes compared to survivors at 28-days.

In multivariate analysis, respiratory rate, but none of the other ventilation parameters, was independently associated with 28-day mortality. In studying the effect of different target temperatures on mechanical

ventilation, we found that TTM33 resulted in lower $etCO_2$ levels and higher alveolar dead space fraction compared to TTTM36 at similar minute ventilation.

This study suggests that a majority of cardiac arrest patients are ventilated according to lung protective standards. These results are similar to the PRoVENT study, an observational study focusing on mechanical ventilation practices in patients without ARDS [8]. In addition, a previous study in patients with cardiac arrest found that low V_T ventilation was increasingly applied in ICUs in 40 countries over a period of 12 years [6]. Of note, compliance of the respiratory system was low in the majority of patients and PEEP level was set at > 5 cm H_2O in more than half of patients. This may suggest that most of the patients may have had a pulmonary complication following cardiac arrest, such as lung contusion following chest compressions, pulmonary edema, atelectasis or aspiration. As a surrogate marker of pulmonary complications, we compared hypoxemic patients to normoxemic patients. In total, 105 patients out of 336 had a P/F ratio below 200, indicating that a relatively large portion of patients may have suffered from pulmonary complications. These patients were ventilated with markedly higher pressure levels. Unfortunately, we did not collect X-rays, so we cannot conclude with certainty about pulmonary conditions of patients. Of note, impaired circulation may also result in hypoxemia.

In the loess regression plots, both driving pressure > 20 cmH_2O as well as plateau pressure > 30 cmH_2O show a linear relation with mortality. Thereby, the relationship between ventilation settings and mortality following cardiac arrest appear follow similar trends as in ARDS, although in patients with ARDS the linear relation to proportion of deaths occurs at driving pressures > 10 cmH_2O and plateau pressures >20 cmH_2O [18]. Of note, V_T was not associated with mortality in this cohort of patients, likely due to the fact that the majority of them was already ventilated at relatively low V_T. In multivariate analysis, other ventilation factors were also not independently associated with outcome, as mortality was predominantly associated with non-respiratory factors. In ARDS patients, driving pressure is associated with adverse outcome [19]. The lack of a relationship between driving pressure and 28-day mortality in our cohort may be explained by a low effect size or a limited number of patients with high driving pressure. We are unsure how to explain the association between respiratory rate and 28-day mortality. An explanation may be that neurological damage may have driven the relation between hyperventilation and outcome. Of note, paralysis was not part of standard care. Alternatively, given that respiratory rate was increased

in the hypoxemic patients compared to normoxemic patients, increased respiratory rate may have been a consequence of lung injury or altered gas exchange, which may have had a negative interaction with outcome. The clinical relevance of this finding remains to be determined.

$PaCO_2$ levels decreased in both TTM groups, most likely due to sedation. In contrast, $etCO_2$ levels were lower in the TTM33 group compared to the TTM36 group. This coincided with a significantly higher alveolar dead space fraction in TTM33 compared to the TTM36 group. A possible explanation for this finding may be that TTM33 resulted in lower pulmonary perfusion due to increased vasoconstriction. This may be in line with the finding of higher lactate levels in TTM33 compared to TTM36.In ARDS, increased dead space in associated with increased mortality [20], and this finding could have implications for cardiac arrest patients at risk for lung injury. Taken together, although TTM33 does not result in reduced survival compared to TTM36 [9], we feel that decreased pulmonary perfusion with increased dead space fraction are unwanted effects, arguing against maintaining cardiac arrest patients at 33°C. Of note, blood gas was not corrected for temperature in this study. This means that $PaCO_2$ may have been lower in the TTM33 group, as the solubility of CO_2 increases at lower temperatures, Perhaps, correcting $PaCO_2$ levels for body temperature may have ultimately allowed for lower ventilation settings in the TTM33 group.

There are several limitations to this study. Although the study was predefined, several parameters were retrospectively collected through a post-hoc survey, and results should be considered within the limitations of this study design, including lacking data on cause of death. Also, data could not be obtained from all patients included in the original TTM trial. However, centers in whom patients were missing are both large and small centers, from all countries which contributed to the TTM trial. In comparing patients in this study to those that were left out, there was no difference between most baseline variables, nor in mortality. Also, several variables suffered from missing data, resulting in the necessity to impute data for the logistic regression model. However, running the model with and without imputed data did not alter the outcome, suggesting a stable model. We also lacked information about pulmonary complications. In addition to missing data, another limitation is that paralysis was not applied as per study protocol, which may have allowed for spontaneous breathing efforts, which in turn may have affected respiratory rate and other ventilation data.

IConclusions.

Cardiac arrest patients predominantly receive protective ventilation with low V_T and low driving pressures. Higher respiratory rate is associated with increased mortality. TTM33 resulted in decreased $etCO_2$ with increased alveolar dead space fraction compared to TTM36. Optimization of ventilator parameters and gas-exchange should be considered to improve outcome after cardiac arrest.

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Figure Legends

Figure 1. Cumulative frequency distributions of ventilation parameters during targeted temperature management.

Cumulative frequency distributions of tidal volume, PEEP, Pplat, Driving pressure, Static compliance, respiratory rate, PaO_2 and P/F ratio. The dotted line represents the proportion of patients reaching the cutoff value. Abbreviations: CFD, cumulative frequency distribution. PEEP, positive end-expiratory pressure. Pplat, plateau pressure.

Figure 2. The distribution of ventilation parameters at the end of targeted temperature management in survivors and non-survivors at 28-days.

Distribution of tidal volume against PEEP, Pplat, Driving pressure, Respiratory rate. In addition, the distribution of PaO_2 levels against FIO_2 fraction and PEEP. Abbreviations: PEEP, positive end-expiratory pressure. Pplat, plateau pressure.

Figure 3. Relationship between ventilation parameters at the end of targeted temperature management and 28-day mortality

LOESS regression plots showing the relationship between 28-day mortality and driving pressure, Pplat, tidal volume, respiratory rate, P/F ratio and static compliance respectively. Abbreviations: PEEP, positive end-expiratory pressure. Pplat, plateau pressure.

Figure 4. The effect of different target temperatures on mechanical ventilation.

Repeated-measures mixed model on the effect of target temperatures on mechanical ventilation. Circles represent estimates including error bars for 95% confidence limits from mixed effect modeling. Asterisks indicate a significant interaction between groups at each time point. Pgroup represents the overall difference between target temperature management (TTM) groups. Abbreviations: $etCO_2$, end-tidal CO_2. TTM33, TTM at 33°C. TTM36, TTM at 36°C
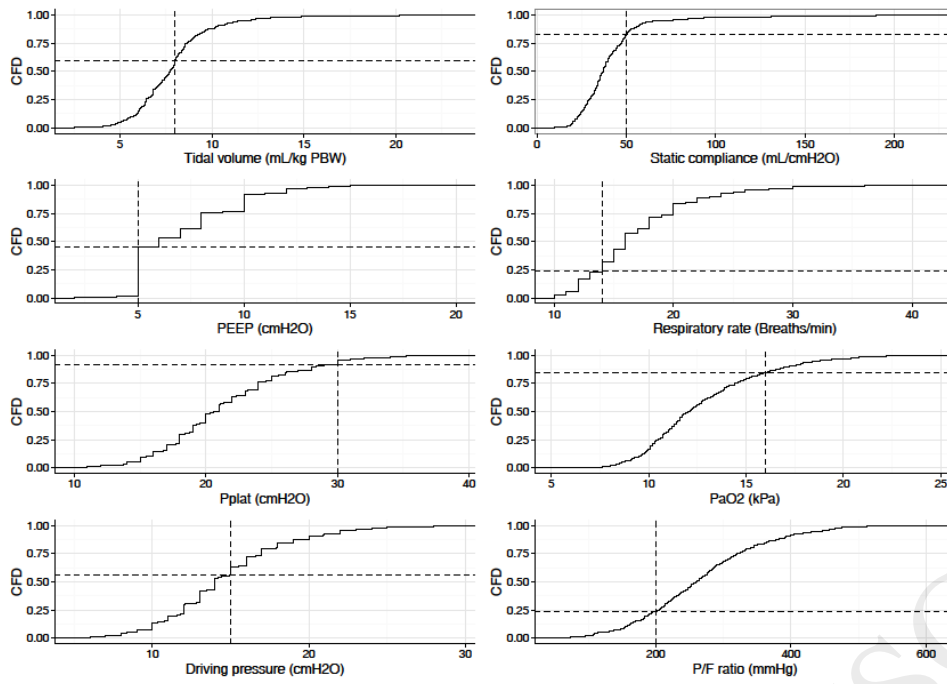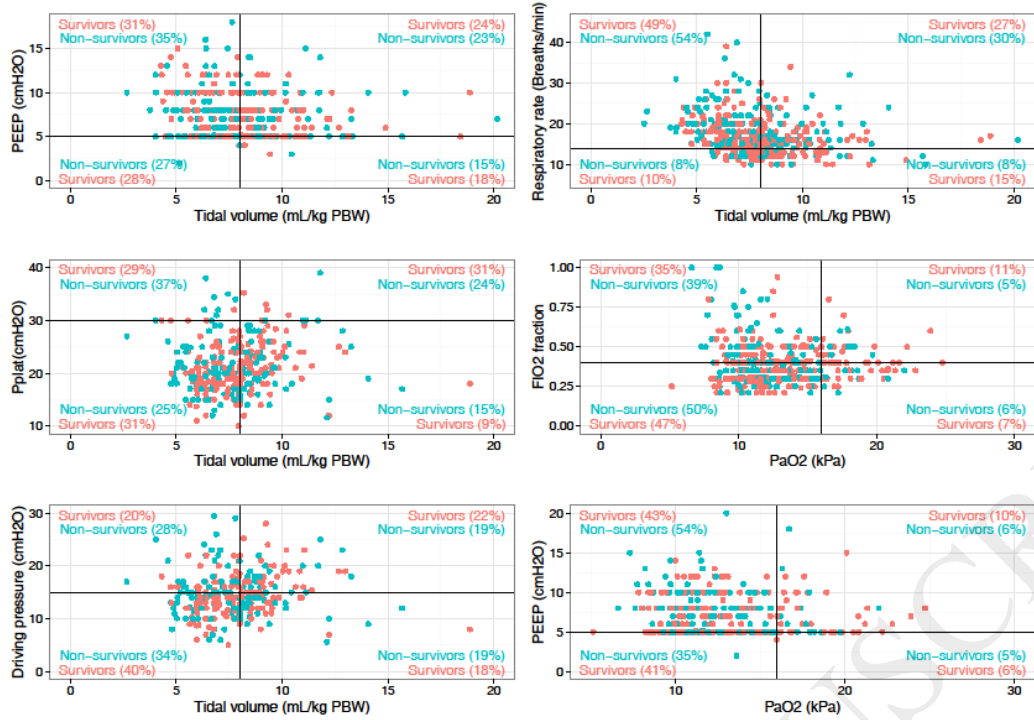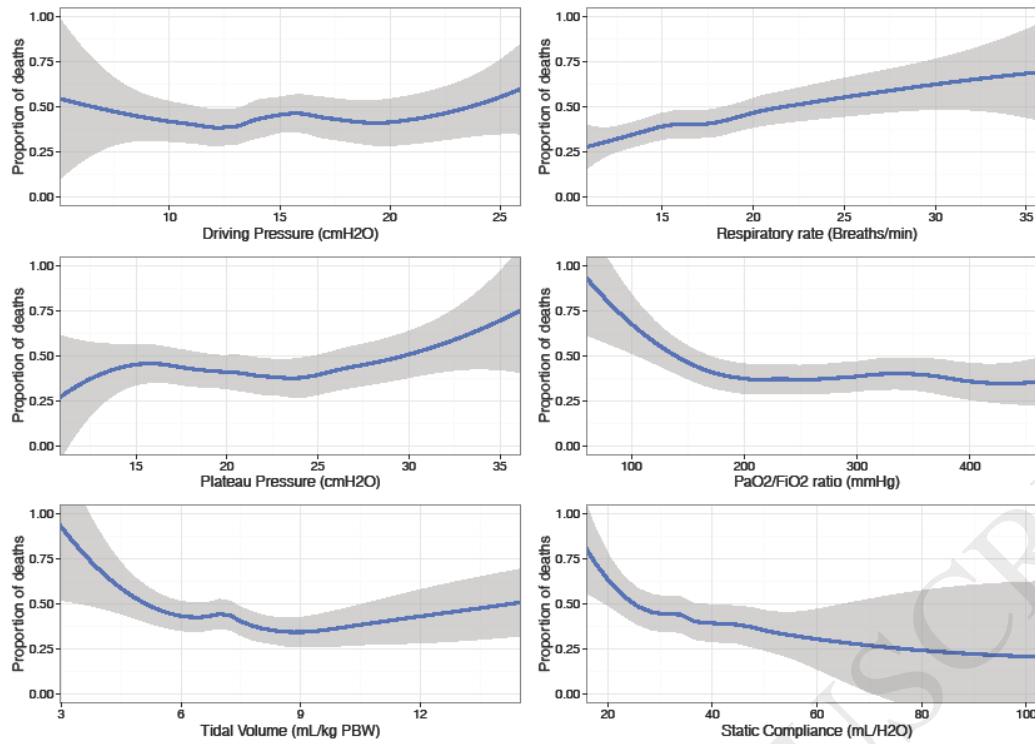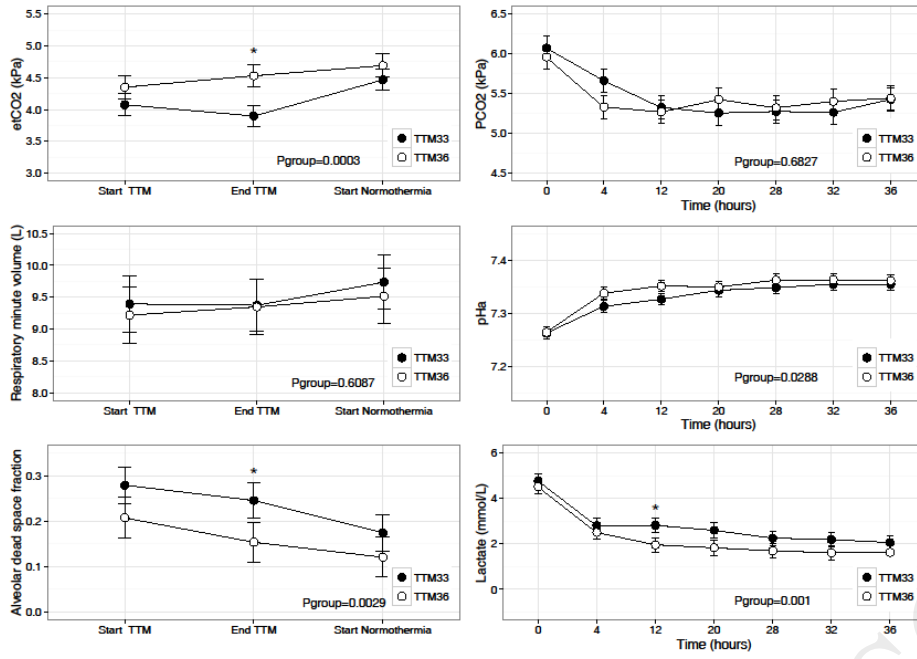
Table 1. Baseline patient characteristics in all patients and survivors vs. non-survivors at 28-days

	All N=567	Survivors N=328	Non-survivors N=239	P-value
Demographic characteristics				
Age (yr) - mean ±SD	64.1 ±12.3	60.9 ±12.4	68.4 ±10.8	<0.0001
Height (cm) - mean ±SD	175.1 ±8.5	176.2 ±7.9	173.6 ±9.2	0.001
Weight (kg) - mean ±SD	81.8 ±16.0	81.7 ±15.2	81.9 ±17.1	0.929
Male sex – no. (%)	460 (81)	273 (83)	187 (78)	0.175
Medical History - no.(%)				
Chronic heart failure	35 (6.2)	14 (4.2)	21 (8.7)	0.038
Previous AMI	125 (22.0)	58 (17.6)	67 (28.0)	0.004
Ischemic heart disease	163 (28.8)	85 (25.9)	78 (32.6)	0.077
Previous cardiac arrhythmia	93 (16.6)	43 (13.1)	51 (21.3)	0.01
Previous cardiac arrest	11 (1.9)	4 (1.22)	7 (2.93)	0.221
Arterial hypertension	220 (38.9)	117 (35.6)	103 (43.1)	0.081
TIA or stroke	41 (7.2)	13 (3.9)	28 (11.7)	<0.0001
Diabetes	86 (15.3)	37 (11.3)	49 (20.5)	0.003
Asthma or COPD	65 (11.5)	30 (9.1)	35 (14.6)	0.051
Characteristics of the cardiac arrest				
Bystander performed CPR - no. (%)	400 (71)	252 (77)	148 (62)	<0.0001
Time (min) from cardiac arrest to BLS - median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	0.071
Time (min) from cardiac arrest to ROSC - median (IQR)	25 (16.5- 40)	20 (14-31)	35 (23-51.5)	<0.0001
First monitored rhythm - no. (%)				<0.0001
Asystole - no. (%)	68 (12.0)	12 (3.6)	56 (23.4)	-
Non-perfusing VT - no. (%)	12 (2.1)	7 (2.13)	5 (2.09)	-
PEA - no. (%)	35 (6.2)	10 (3.0)	25 (10.4)	-
ROSC after bystander defibrillation - no. (%)	12 (2.1)	10 (3.0)	2 (0.84)	-
VF - no. (%)	428 (75)	284 (87)	144 (60)	-
Unknown - no. (%)	12 (2.1)	5 (1.5)	7 (2.9)	-
Clinical characteristics on admission				
First Body temperature (°C) - mean ±SD	35.3 ±1.1	35.4 ±1.0	35.2 ±1.2	0.039
Circulatory shock - no. (%)	57 (10.1)	22 (6.7)	36 (15.0)	0.001
SOFA score - mean ±SD	10.5 ±2.6	10.0 ±2.4	11.2 ±2.7	<0.0001

Abbreviations: AMI, acute myocardial infarction, BLS, basic life support, CPR, cardiopulmonary resuscitation, COPD, chronic obstructive pulmonary disease, IQR, interquartile range, PEA, pulseless electrical activity, ROSC, return of spontaneous circulation , SOFA, sequential organ failure assessment , TIA, transient ischemic attack, VT ventricular tachycardia, VF, ventricular fibrillation.

Table 2. Mechanical ventilation parameters and blood gas values at the end of targeted temperature management (T=28 hours)
in survivors at 28-days vs. non-survivors at 28-days

Variable (no. of patients)	All N=567	Survivors N= 328	Non-survivors N= 239	P-value
Tidal volume (mL/kg PBW) *(n=492)*	7.7 (6.4-8.7)	7.8 (6.5-8.7)	7.5 (6.4-8.7)	0.247
PEEP (cmH_2O) *(n=489)*	6 (5-8)	6 (5-8)	7 (5-8)	0.372
Pplat (cmH_2O) *(n=325)*	21.0 (18.0-24.0)	20.8 (18.0-24.0)	21.0 (18.0-25.0)	0.654
Respiratory rate (breaths/min) *(n=535)*	16 (14-20)	16 (13-18)	16.5 (15-20)	<0.0001
Driving pressure (cmH_2O) *(n=300)*	14.7 ±4.2	14.4 ±3.9	14.8 ±4.5	0.573
Static compliance (mL/H_2O) *(n=302)*	37.1 (29.2-47.1)	38.2 (31.5-48.8)	34.7 (27.4-44.7)	0.013
Respiratory minute volume (L/min) *(n=496)*	9.3 ± 3.3	9.2 ±3.3	9.4 ±3.3	0.588
End tidal CO_2 (kPa) *(n=307)*	4.2 ±1.2	4.2 ±1.1	4.2 ±1.3	0.725
Alveolar dead space fraction *(n=235)*	0.20 ±0.25	0.21 ±0.18	0.19 ±0.31	0.567
$PaCO_2$ (kPa) *(n=445)*	5.3 ±0.9	5.3 ±0.9	5.3 ±1.0	0.351
PaO_2 (kPa) *(n=442)*	12.8 ±3.1	13.0 ±3.4	12.3 ±2.9	0.019
FIO_2 fraction *(n=502)*	0.35 (0.30-0.45)	0.35 (0.3-0.42)	0.35 (0.3-0.45)	0.342
P/F ratio (mmHg) *(n=441)*	267 ±93	274 ±89	256 ±98	0.052
pHa *(n=444)*	7.36 ±0.1	7.36 ±0.1	7.35 ±0.1	0.051
Lactate (mmol/L) *(n=401)*	1.4 (1.0-2.1)	1.2 (0.9-1.8)	1.7 (1.1-2.7)	<0.0001
Base excess (mEq/L) *(n=442)*	-3.0 ±3.8	-2.5 ±3.4	-3.6 ±4.4	0.005

Abbreviations: PEEP, positive end-expiratory pressure, Pplat = plateau pressure of the respiratory system, P/F ratio, PaO_2/FIO_2 ratio Data is presented as mean ± standard deviation or median (interquartile range)