The effect of ventilation rate on outcome in adults receiving cardiopulmonary resuscitation

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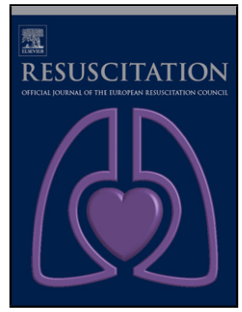

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Title

The effect of ventilation rate on outcome in adults receiving cardiopulmonary resuscitation

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Abstract

AIM: To investigate whether a ventilation rate ≤10 breaths min^{-1} in adult cardiac arrest patients treated with tracheal intubation and chest compressions in a prehospital setting is associated with improved Return of Spontaneous Circulation (ROSC), survival to hospital discharge and one-year survival with favourable neurological outcome, compared to a ventilation rate >10 breaths min^{-1}.

METHODS: In this retrospective study, prospectively acquired data were analysed. Ventilation rates were measured with end-tidal CO_2 and ventilation pressures. Analyses were corrected for age, sex, compression rate, compression depth, initial heart rhythm and cause of cardiac arrest.

RESULTS: 337 of 652 patients met the inclusion criteria. Hyperventilation was common, with 85% of the patients ventilated >10 breaths min^{-1}. The mean ventilation rate was 15.3 breaths min^{-1}. The corrected odds ratio (OR) of ventilating >10 breaths min^{-1} for achieving ROSC was 0.91 (95% CI: 0.49 – 1.71, p=0.78), the uncorrected OR of ventilating >10 breaths min^{-1} for survival to hospital discharge was 0.91 (95% CI: 0.30 – 2.77, p=0.78), and the uncorrected OR of ventilating >10 breaths min^{-1} for one-year survival with a favourable neurological outcome was 0.59 (95% CI: 0.19 – 1.87, p=0.32). A logistic regression with continuous ventilation rate showed no significant relation with ROSC, and a ROC curve for ROSC showed a poor predictive performance (AUC: 0.52, 95% CI: 0.46 – 0.58), suggesting no other adequate cut-off value for ventilation rate.

CONCLUSION: A ventilation rate ≤10 breaths min^{-1} was not associated with significantly improved outcomes compared to a ventilation rate >10 breaths min^{-1}. No other adequate cut-off value could be proposed.

Keywords: Cardiac arrest, CPR, neurological outcome, resuscitation, ROSC, tracheal pressure measurements, ventilation rate

Introduction

Cardiopulmonary resuscitation (CPR) and early defibrillation are the only therapies known to improve survival from sudden cardiac arrest [1, 2]. However, CPR quality can still be improved as survival rates are low [3]. For the ventilation of intubated patients in cardiac arrest, the latest ILCOR (International Liaison Committee on Resuscitation) recommendations from 2015 advocate the use of intermittent positive pressure ventilation (IPPV) with a ventilation rate of 8-

10 breaths min^{-1}, an inspiratory time of <1 second and a tidal volume of 7-8 ml kg^{-1} [4]. Observational studies, however, have documented varying degrees of hyperventilation during CPR, even when performed by professionals [5-13]. Aufderheide et al. showed in an observational study in 2004 an average ventilation rate of 30 ± 3.2 breaths min^{-1}, twice the rate recommended by the American Heart Association at that time [11]. In Belgium Maertens et al. showed that patients with cardiac arrest were ventilated two times faster than guidelines recommended [13]. Animal studies indicate that excessive ventilation rates during CPR may decrease survival [5, 11, 14-19]. Relative negative intrathoracic pressures, generated by the decompression phase of chest compressions may increase the return of venous blood to the heart [16, 18, 20, 21]. Increased mean airway pressures during positive pressure ventilation, however, seem to negate these beneficial effects of chest wall recoil and may decrease survival [18, 22, 23]. Even slow ventilation rates during CPR may still be sufficient to ensure adequate gas exchange [24]. A recent systematic review of the literature, including one observational study (concerning 67 humans) and ten animal studies (concerning 234 pigs and 30 dogs), concluded that a ventilation rate recommendation of 10 min^{-1} during adult CPR with a tracheal tube and no pauses for chest compression is a very weak recommendation based on very low quality evidence [25].

Methods

This study investigates the effect of ventilation rate on outcome in adults receiving cardiopulmonary resuscitation. The study question was whether a ventilation rate ≤10 breaths min^{-1} in adult cardiac arrest patients (both men and women) treated with tracheal intubation and chest compressions in a prehospital setting is associated with improved ROSC (primary outcome), survival to hospital discharge and one-year survival with favourable neurological outcome (secondary outcomes), compared to a ventilation rate >10 breaths min^{-1}.

Study population

Belgium has a two-tiered Emergency Medical Services (EMS) system. The first tier consists of an ambulance staffed by two emergency medical technicians who may defibrillate with an AED and who may provide bag-valve-mask ventilation, but who are not allowed to deliver drugs or to perform endotracheal intubation. The second tier consists of a doctor-car staffed by an consultant in emergency medicine (or a resident in training from the second year on) and an nurse specialised in emergency medicine. Whilst endotracheal intubation is only performed by the physician, the nurse establishes access for drug delivery. The emergency medical technicians assist with chest compressions and bag-valve-mask ventilation. A variable period of bag-valve-mask ventilation may precede endotracheal intubation. A supraglottic airway is only used in case endotracheal intubation fails.

The study was approved by the Ethics Committee of Ghent University Hospital using deferred consent. Prospectively acquired data were retrospectively analysed. Resuscitation events were studied among patients who were resuscitated in a prehospital setting by the medical staff of the Mobile Emergency Group of Ghent University Hospital in Ghent, Belgium. Data were collected between 1 March 2009 and 1 January 2015. Patients were excluded from analysis if they were younger than 18 years, did not receive continuous chest compressions, were not intubated, if no ventilation rate and/or compression rate and depth were measured, or if a technical problem prevented calculating the ventilation rate and/or compression rate and depth (e.g. a device not-connected, technical problems,…).

Measurements

During CPR a biphasic monitor-defibrillator (ZOLL E Series, ZOLL Medical Corporation, Massachusetts U.S.A.) was used. Patients were either manually ventilated using an adult 1600 ml self-inflating bag (Laerdal, Stavanger, Norway) or mechanically ventilated using a transport ventilator (Oxylog 3000, Dräger, Lübeck, Germany). To measure ventilation rate, both end-tidal CO_2 and ventilation pressures were used. End-tidal CO_2 was monitored via the monitor-defibrillator. Ventilation pressures were measured by a self-developed small two-channel recording device as described by Kalmar et al. [26]. To measure compression rate and compression depth an accelerometer was placed on the lower half of the sternum and connected to the monitor-defibrillator. This method was validated previously with a compression depth accuracy of 1.6 mm [27]. To evaluate the initial heart rhythm, the electrocardiogram from the monitor-defibrillator was used. The Modified Rankin Scale (MRS) [28] was used to evaluate neurological outcome by studying the patient's medical record or by personal interview.

Data processing

After each resuscitation event, the data from the defibrillator were uploaded to a computer using Code Review 5.5.4 (Zoll Medical Company, Chelmsford, USA) to determine end-tidal CO_2, compression rate, compression depth and initial heart rhythm. Data stored on the recording device were transferred to a personal computer using MSR Viewer 5.04 software (MSR, Seuzach, Switzerland) to determine ventilation pressures. A custom-developed Visual Basic for Applications (VBA) program was used to visualise and analyse the ventilation waveforms.

The first five minutes of CPR after intubation were analysed to determine CPR quality. Although most of the patients received CPR prior to intubation, we did not register its duration and quality. The first five minutes of CPR are presumed to be both clinically the most important [12] and the best rescuer effort based on studies regarding fatigue-induced deterioration in CPR performers [29]. Segments without registered ventilations and/or compressions were excluded from rate calculations in order not to lower rates artificially.

The ventilation rate was calculated based on end-tidal CO_2 or on ventilation pressures. If both end-tidal CO_2 and ventilation pressures were available, end-tidal CO_2 was used.

To determine initial heart rhythm, the electrocardiogram registered during CPR was analysed independently by two researchers (GV, CD). In case of any disagreement, a third researcher (KM) determined the rhythm. To determine the cause of cardiac arrest, medical records were studied. The following causes were considered as traumatic: traffic accidents, falls from height, penetrating wounds, injuries due to fire weapons, drowning, hanging, electrocution and burns. ROSC was defined as a return of spontaneous circulation for at least 30 seconds and characterised by more than one spontaneous breath, palpable pulse and/or visible arterial pulsation [30].

For analysing neurological outcome after one year, the MRS score was converted into a binary score: MRS scores 0 and 1 were classified as favourable neurological outcome, MRS scores 2 to 6 were classified as non-favourable neurological outcome.

Statistical analysis

For statistical analysis SPSS 23.0 (IBM Corporation, New York, U.S.A.) was used. Outcomes (ROSC, survival to hospital discharge and one-year survival) were compared for ventilation rates ≤10 and >10 breaths min^{-1} with a Chi-square test or a Fisher exact test where numbers were low. Corresponding odds ratios and 95% confidence intervals were calculated. Multiple logistic regression analysis was used for the outcome ROSC to correct for age, sex, compression rate, compression depth, initial heart rhythm, and cause of cardiac arrest. For survival to hospital discharge and one-year survival no adjustment for confounding covariates were performed due to the low number of events.

Additionally, ventilation rate was analysed on a continuous scale. A Mann-Whitney U test was performed to assess a difference in distribution of ventilation rates across patients with and without a positive outcome. Multiple logistic regression analyses were used to correct for age, sex, compression rate, compression depth, initial heart rhythm, and cause of cardiac arrest. Ventilation rate was log-transformed to improve normality. A Receiver Operating Characteristic

(ROC) curve was constructed to judge the predictive performance of ventilation rate with respect to ROSC by calculating area under the curve (AUC). $P<0.05$ was considered statistically significant.

Results

A total of 652 patients were resuscitated between 1 March 2009 and 1 January 2015. Seventy-one patients were excluded because no study registration form was completed. Eight patients were excluded because they were younger than 18. Ventilation rate was not registered correctly in 190 patients due to registration problems (e.g. secretions in the endotracheal tube, disconnection of the devices or attenuation of the signal). In the 383 patients with a successful registration of ventilation rate, ventilation pressure was used in 318 patients and end-tidal CO_2 in 65 patients. Forty-six patients were excluded due to a failure of compression rate and compression depth registration. Finally, 337 patients were included (Fig. 1).

Patient demographic and descriptive clinical data are shown in Table 1. The mean age was 65 years and 72.4% of the patients were men. The mean ventilation rate was 15.3 breaths min^{-1}. Mean compression rate and depth were 112 min^{-1} and 5.00 cm respectively. Cardiac problems were the most common cause of cardiac arrest (80.1%). A shockable initial heart rhythm was found in 21.1% (ventricular fibrillation: 19.6%; ventricular tachycardia: 1.5%). ROSC was achieved in 41.5% of all patients. Survival to hospital discharge and one-year survival with a favourable neurological outcome were 7.4% and 5.3% respectively.

CUT-OFF VALUE 10 MIN^{-1}

a) ROSC

Fifty patients (14.8%) were ventilated at a mean ventilation rate ≤10 breaths min^{-1}. Twenty-one of them (42.0%) achieved ROSC. Among the 287 patients ventilated at a rate >10 breaths min^{-1}, 119 patients (41.5%) achieved ROSC. The OR for achieving ROSC when ventilated at a rate

>10 breaths min^{-1} is 0.98 (95% CI: 0.53 – 1.80, p=0.94). When corrected for age, sex, compression rate, compression depth, initial heart rhythm, and cause of cardiac arrest, the OR for achieving ROSC when ventilated at a rate >10 breaths min^{-1} was 0.91 (95% CI: 0.49 – 1.71, p=0.78) (Table 2). There was a statistically significant effect of age (OR 1.02 (95% CI: 1.00 – 1.03, p=0.04)) and non-cardiac causes of cardiac arrest (OR 1.89 (95% CI: 1.06 – 3.37, p=0.03) on ROSC. The odds ratio for achieving ROSC for female patients was 1.63 (95% CI: 0.99 – 2.67, p=0.05) compared to male patients.

b) Survival to hospital discharge

Four patients (8.0%) ventilated at a rate ≤10 breaths min^{-1} achieved survival to hospital discharge. In the group ventilated at a rate >10 breaths min^{-1} 21 patients (7.3%) had survival to hospital discharge. The uncorrected OR for survival to hospital discharge when ventilated at a rate >10 breaths min^{-1} was 0.91 (95% CI: 0.30 – 2.77, p=0.78).

c) One-year survival with favourable neurological outcome

Eight percent (4 patients) of the group ventilated at a rate ≤10 breaths min^{-1} had one-year survival with a favourable neurological outcome. This was achieved by only 4.9% (14 patients) of patients ventilated at a rate >10 breaths min^{-1}. The uncorrected OR for one-year survival with a favourable neurological outcome when ventilated at rate >10 breaths min^{-1} was 0.59 (95%CI: 0.19 – 1.87, p=0.32).

DISTRIBUTION OF VENTILATION RATES

Hyperventilation was common in our study population, with 85.2% of the patients ventilated at a rate >10 breaths min^{-1}. However, Mann Witney U testing showed no significant differences in distribution of ventilation rates across patients with and without ROSC (p=0.48), survival to hospital discharge (p=0.71) or one-year survival with a favourable outcome (p=0.75) (Fig. 2). A logistic regression analysis with ventilation rate as a continuous variable shows no significant relation with ROSC (Table 3). The area under the ROC curve for ROSC (Fig. 3) showed a poor predictive performance of the ventilation rate, with a high confidence (AUC = 0.52, 95% CI: 0.46 – 0.58). This suggests that there is no other more adequate cut-off value for ventilation rate.

Discussion

Our study examined whether a ventilation rate of ≤10 breaths min^{-1} in adults with cardiac arrest and a secure airway, receiving CPR in a prehospital setting, was associated with improved outcome (ROSC, survival to hospital discharge and one-year survival with a favourable neurological outcome) compared to a ventilation rate >10 breaths min^{-1}.

The baseline characteristics and the rate of ROSC in our study were similar to data reported in other studies regarding cardiac arrest in adults [12, 31]. Our data confirmed that hyperventilation occurs frequently during CPR, as suggested by other studies [5-13]. However, the mean ventilation rate in our study was lower than the mean ventilation rates in previous studies. In our study 85.2% of the patients received ventilations at a rate >10 breaths min^{-1}, with a mean ventilation rate of 15.3 breaths min^{-1}. In 2005, Abella et al. showed that during 60.9% of the time patients were ventilated at a rate >20 breaths min^{-1} [12]. In 2012, Maertens et al. showed that 90% (manually ventilated) and 92% (mechanically ventilated) of their patients were ventilated at a rate >10 breaths min^{-1}, with a mean ventilation rate of 20 breaths min^{-1} [13]. Aufderheide et al. reported even a mean ventilation rate of 30 breaths min^{-1} [5].

Our study showed that a ventilation rate >10 breaths min^{-1}, compared to ventilation rates ≤10 breaths min^{-1}, was not associated with ROSC (OR 0.91, p=0.78). Moreover, no significant differences in survival to hospital discharge or one-year survival with favourable neurological outcome were observed. This may be due to the small number of survivors and the small number of patients that were ventilated at a rate <10 breaths min^{-1}.

Our study showed no differences in the distribution of ventilation rates across patients who had ROSC, survival to hospital discharge or one-year survival with favourable neurological outcome and patients who did not. Based on a literature review, we expected to find lower ventilation rates in patients with a positive outcome, since eight animal studies [5, 11, 15, 17, 32-35] and one observational study [12] suggested that a ventilation rate of 10 breaths min^{-1} improves ROSC compared to higher ventilation rates and that ventilation rates <10 breaths min^{-1} may even further improve ROSC, survival to hospital discharge and one-year survival with favourable neurological outcome. Yannopoulos et al. showed that reducing the ventilation rate during CPR in a porcine model by increasing the compression:ventilation (C:V) ratio from 15:2 to 15:1, resulted in improved perfusion pressures of the vital organs [16]. Hayes et al. also demonstrated improved haemodynamics in swine ventilated at a rate of 10 breaths min^{-1} compared to swine that were hyperventilated [32]. In other studies, however, reduced ventilation rates did not lead to haemodynamic improvements [33, 36].

Our study did not show an association between ventilation rate and outcome. Although the number of patients with a ventilation rate <10 breaths min^{-1} was rather small (50 patients), the observed difference between high and low ventilation rates in terms of ROSC was so small (41.5% versus 42%), that even in a large sample in the same population and under the same conditions, no clinically significant difference is to be expected. The same can be said about the predictive performance of the ROC curve for ROSC. With an AUC of only 0.52 (95% CI: 0.46 – 0.58), also in a larger sample no clear cut-off is to be expected and no specific ventilation rate is likely to be significantly associated with improved outcome.

Our study was performed with mean ventilation rates, as ventilation rate was not always constant during resuscitation. This might explain why some animal studies in a controlled setting and with a set ventilation rate showed an effect of ventilation rate on outcome whereas our study did not.

Study limitations

Our study has several limitations. It was a retrospective observational study that was performed at a single site. A large number of patients (41% of all patients ≥18 years) were excluded because of lack of ventilation rate registration and failure of compression depth/rate registration. During the study we experienced some practical and technical problems such as attenuation of the ventilation pressure signal due to blockage of the air-filled catheter by airway secretions or blood. In the future this may be solved by using electronic sensors inserted in the airway. There were very few patients with a ventilation rate <10 breaths min^{-1}, which diminishes the precision of the assessment of the effect of ventilation rates on outcome. We did not have information about the time interval between collapse and the start of CPR (the so called no flow time), what may influence outcome as well. No data was collected regarding witnessed cardiac arrest or whether bystander CPR was performed. The effect of the duration of CPR and the length of hospital stay were not taken into account. We did not take other ventilation variables such as tidal volume or inspiratory pressure into account. Ventilation rates were measured in two different ways (ventilation pressures and end-tidal CO_2 measurement). In this study we have included two different methods to assess ventilation rate, should we have restricted the inclusion to only one of both methods, fewer patients would have been available for analysis. The patient were usually ventilated with a bag-valve-mask device prior to endotracheal intubation, but we have not recorded how long it took to establish a definitive airway. The unknown time to intubation may be a confounder.

Conclusion

In 337 cardiac arrest patients, a ventilation rate ≤10 min^{-1} was not associated with significantly improved outcomes compared to higher ventilation rates. No specific ventilation rate was associated with significantly improved outcomes. A ventilation rate of >10 min^{-1} had no impact on ROSC, and in a small subset of patients it had no impact on survival to hospital discharge or one-year survival with favourable neurological outcome.

Conflicts of Interest statement

Gino Vissers (GV), Christophe Duchatelet (CD), Sofie A.M. Huybrechts (SH), Kristien Wouters (KW) Saïd Hachimi-Idrissi (SHI) and Koenraad G. Monsieurs (KM) have no conflicts of interest.

Author contributions

Study concept and design: KM. Performance of literature search: GV, CD. Analysis and interpretation of data: GV, CD, SH, KW, SHI, KM. Creating figures, tables and graphs: GV. Drafting the manuscript: GV. Critical revision of the manuscript: CD, SH, SHI, KW, KM. Study supervision: SHI, KM. All authors approved the final manuscript.

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Figure Legends

Figure 1. Patient selection

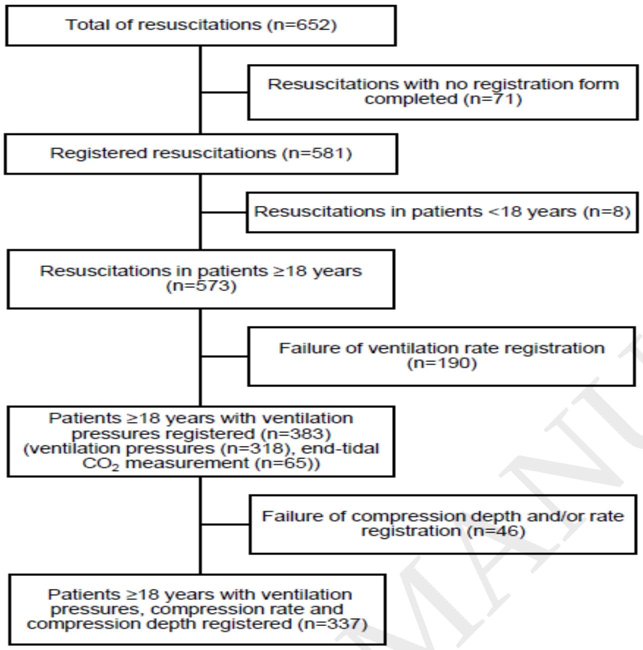

Figure 2. Distribution of ventilation rate for each outcome (n=337)

ROSC: Return of Spontaneous Circulation

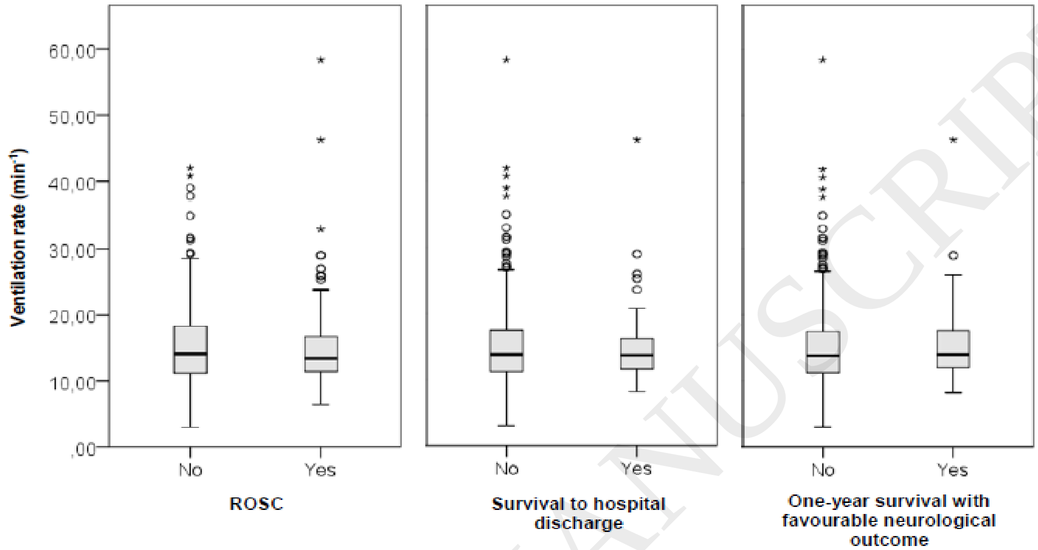

Figure 3. ROC Curve: ROSC by ventilation rate (log)

ROSC: Return of Spontaneous Circulation

The area under the curve is 0.52 (95% CI: 0.46 – 0.58).

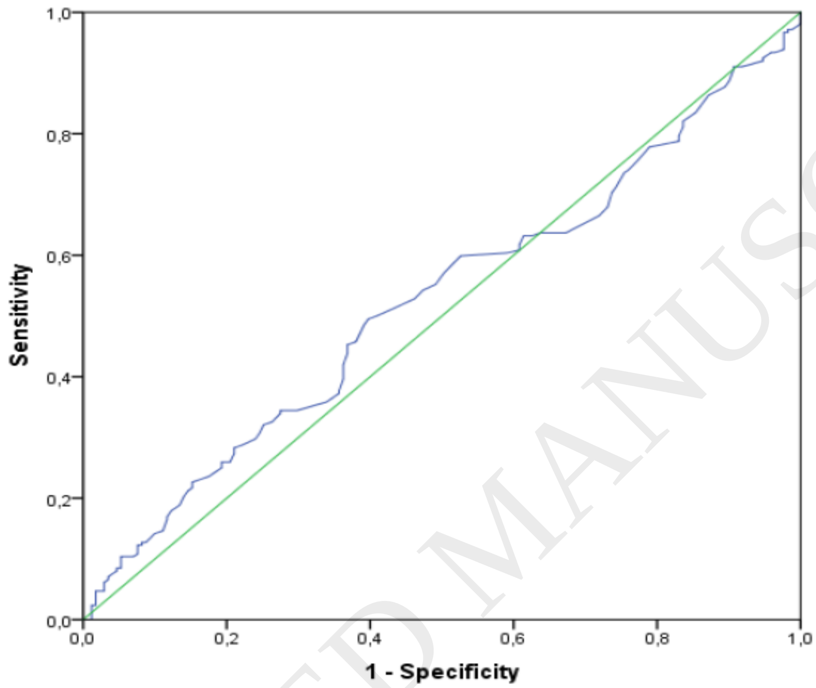

Table 1. Descriptive statistics for included patients (n=337)

	N (%)	**Minimum**	**Maximum**	**Mean**	**SD**
Age (years)	337 (100)	18	96	65.17	15.42
Sex					
Men	244 (72.4)				
Women	93 (27.6)				
Ventilation rate (min^{-1})	337 (100)	3.00	58.40	15.33	6.53
≤ 10 min^{-1}	50 (14.8)				
> 10 min^{-1}	287 (85.2)				
Compression depth (cm)	337 (100)	1.90	9.91	5.00	1.08
Compression rate (min^{-1})	337 (100)	16	163	112.23	13.16
Cause					
Cardiac	270 (80.1)				
Non-cardiac	67 (19.9)				
Initial heart rhythm					
Shockable	71 (21.1)				
Non-shockable	266 (78.9)				
Return of spontaneous circulation (ROSC)					
Yes	140 (41.5)				
No	197 (58.5)				
Survival to hospital discharge					
Yes	25 (7.4)				
No	312 (92.6)				
One-year survival with favourable neurological outcome					
Yes	18 (5.3)				
No	319 (94.7)				

SD: standard deviation

Table 2. Corrected odds ratios for ROSC in a multiple logistic regression with dichotomous ventilation rates ≤10 min^{-1} and >10 min^{-1}

	OR	95% CI	P-value
Ventilation rate >10 min^{-1}	0.91	0.49 – 1.71	0.78
Age (years)	1.02	1.00 – 1.03	0.04
Female sex	1.63	0.99 – 2.67	0.05
Compression depth (cm)	1.22	0.98 – 1.52	0.07
Compression rate (min^{-1})	0.99	0.97 – 1.01	0.32
Non-cardiac cause	1.89	1.06 – 3.37	0.03
Non-shockable rhythm	0.71	0.41 – 1.22	0.21
Constant	0.27		0.35

CI: confidence interval, OR: odds ratio

Table 3. Corrected odds ratios for ROSC in a multiple logistic regression with continuous ventilation rates.

	OR	95% CI	P-value
Ventilation rate (log) (min^{-1})	0.98	0.95 – 1.02	0.27
Age (years)	1.02	1.00 – 1.03	0.03
Female sex	1.61	0.98 – 2.64	0.06
Compression depth (cm)	1.24	0.99 – 1.54	0.06
Compression rate (min^{-1})	0.99	0.97 – 1.01	0.32
Non-cardiac cause	1.93	1.08 – 3.44	0.03
Non-shockable rhythm	0.69	0.40 – 1.19	0.19
Constant	0.31		0.40

CI: confidence interval, OR: odds ratio