Study Protocol:
Measurement of Airway Opening Index during Out-of-hospital cardiac arrest: The Lazarus AOI trial

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Abstract (English)

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide. Despite constantly improving resuscitation techniques, the chances of survival remain limited. During cardiopulmonary resuscitation (CPR), a closure of the airway may occur, impeding ventilation. This phenomenon also complicates the interpretation of the end-tidal CO2 (ETCO2) in the capnogram. The extent to which airway closure occurs is quantified by the Airway Opening Index (AOI). This can be calculated from the capnogram and is seen as a measure of the quality of CPR applied as well as a possible indicator to predict the outcome of CPR.

In this study, we analyse capnogram data from approximately 150 cases, collected during interventions for OHCA and logged in the Lazarus database (UZ Gent and AZORG) to answer three research questions below:
(1) What is the prevalence of AOI during CPR?
(2) Is there a correlation between AOI and return of spontaneous circulation (ROSC)?
(3) Does the application of positive end-expiratory pressure (PEEP) affect the AOI and ROSC?

A mathematical model for calculating AOI, based on a method from previous work by Bandhari et al. [1] will be developed. Using this model, the AOI will be calculated from the individual capnograms for all cases in the Lazarus database.

In addition, a multivariable regression model will be used to analyse whether AOI can be used to predict ROSC. Corrections will be made for relevant confounders such as age, gender, witnessed arrest and rhythm pattern.

Finally, it is investigated whether PEEP has a positive influence on AOI. This study aims to contribute to better insights into airway dynamics during CPR and the optimization of ventilation in OHCA.

Samenvatting (Dutch)

Hartstilstand buiten het ziekenhuis (OHCA) is wereldwijd een belangrijke doodsoorzaak. Ondanks steeds verbeterende reanimatietechnieken blijven de overlevingskansen beperkt. Tijdens cardiopulmonale reanimatie (CPR) kan een sluiting van de luchtweg optreden waardoor ventilatie wordt belemmerd. Ook bemoeilijkt dit fenomeen de interpretatie van de end-tidal CO2 (ETCO2) in het capnogram. De mate waarin sluiting van de luchtweg optreedt wordt gekwantificeerd door de Airway Opening Index (AOI). Deze kan worden berekend uit het capnogram en wordt gezien als een maat voor de kwaliteit van toegepaste CPR alsook een mogelijke indicator om de uitkomst van reanimatie te voorspellen.

In deze studie analyseren we capnogramgegevens van ongeveer 150 cases, verzameld tijdens interventies voor OHCA en bijgehouden in de Lazarus-database (UZ Gent en AZORG) om drie onderstaande onderzoeksvragen te beantwoorden:
(1) Wat is de prevalentie van AOI tijdens CPR?
(2) Is er een correlatie tussen AOI en terugkeer van spontane circulatie (ROSC)?
(3) Heeft toepassing van positieve eind-expiratoire druk (PEEP) invloed op de AOI en ROSC?

Een wiskundig model voor AOI-berekening, gebaseerd op een methode uit eerder werk van Bandhari et al. [1] zal worden ontwikkeld. Hiermee zal de AOI voor alle cases in de Lazarus database worden berekend, uitgaande van de capnogrammen van elke case.

Daarnaast zal een multivariabel regressiemodel worden gebruikt om de te analyseren of AOI kan worden gebruikt om ROSC te voorspellen. Hierbij zal worden gecorrigeerd voor relevante confounders zoals leeftijd, geslacht, witnessed arrest en ritmepatroon.

Tot slot wordt onderzocht of PEEP de AOI positief beïnvloedt. Deze studie beoogt bij te dragen aan betere inzichten in luchtwegdynamiek tijdens CPR en het optimaliseren van beademing bij OHCA.

1. Study Summary

IDENTIFIERS	
EC Reference No	
Full (Scientific) title	Measurement of Airway Opening Index during Out-of-hospital cardiac arrest: The Lazarus AOI trial.
Short title	The Lazarus AOI trial.
Dutch Title	Meting van de Airway Opening Index tijdens prehospitale hartstilstand: De Lazarus AOI-studie.
Health condition(s) or problem(s) studied	Cardiac arrest
Study Type	Retrospective observational trial
STUDY TIMELINES	
Expected Start Date	1/10/2025
Anticipated End date	31/08/2027
FUNDING & Other	
Funding	none

2. Roles and responsibilities

Role	Person	Responsibilities
Sponsor	Prof. Dr. S. Hachimi-Idrissi	Study sponsor, study design, data interpretation, writing – reviewing, decision to submit for publication, supervision
Investigator	Dr. T. Tackaert	Study design, methodology and management, formal analysis, interpretation of the data, report writing, project administration
Co-investigators	Ms. M. Van Den Berghe	Data management, formal analysis, interpretation of the data, report writing, project administration

3. List of abbreviations

AOI: airway opening index
CC: chest compressions
CFI: continuous flow insufflation
CPR: cardiopulmonary resuscitation
ETCO2: end-tidal expired CO2
FRC: functional residual capacity
OHCA: out-of-hospital cardiac arrest
PEEP: positive end-expiratory pressure
ROSC: return of spontaneous circulation.
SCA: Sudden cardiac arrest

4. Introduction

Sudden cardiac arrest (SCA) constitutes one of the most urgent and life-threatening medical emergencies, characterized by the abrupt of effective cardiac mechanical activity. It remains a leading cause of mortality worldwide. In Europe, approximately 84 per 100,000 individuals experience an out-of-hospital cardiac arrest (OHCA) annually, while in the United States, the figure exceeds 340,000 cases per year.[1]

Despite considerable advances in emergency medical services and improvements in cardiopulmonary resuscitation (CPR) techniques, overall survival rates remain low. These realities explain the critical need for continued research to optimize resuscitation practices and improve patient outcomes.

High-quality CPR is a cornerstone of successful resuscitation, with effective chest compressions and ventilation being its two essential components. While substantial progress has been made in optimizing chest compression strategies, ventilation during cardiac arrest has received comparatively less attention. Adequate ventilation is vital for maintaining oxygenation, facilitating carbon dioxide elimination, and supporting tissue viability during resuscitation efforts.

A factor that complicates ventilation during CPR is airway closure, a phenomenon wherein small airways, particularly bronchioles, collapse during expiration, leading to impaired airflow and severely compromised gas exchange. In contrast, chest compression causes limited passive ventilation with small tidal volumes when the airways remain open, producing characteristic oscillations in capnographic tracings. The degree of airway opening is quantified through the Airway Opening Index (AOI), an emerging parameter for assessing airway patency during CPR [3]. In their study, Bhandari et al. describe four models to calculate the AOI from a capnogram. Figure 1 below shows a capnogram with fluctuations in end-tidal CO_2

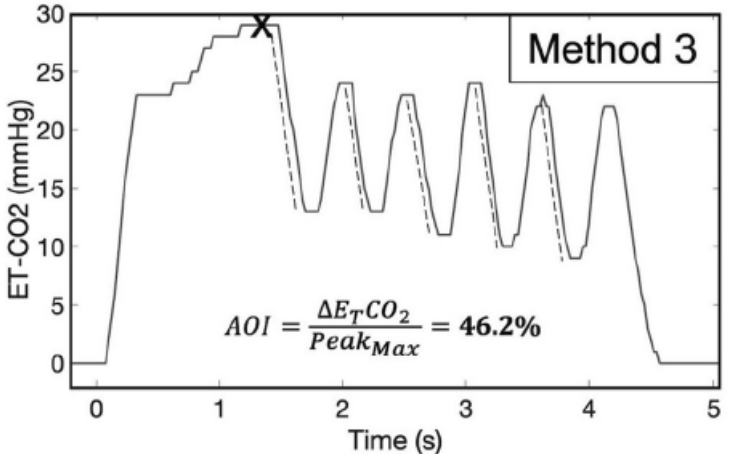

Figure 1: Capnogram showing fluctuations in end-tidal CO2.
Using the shown formula, the AOI can be calculated.

Several pathophysiological changes during cardiac arrest—including apnoea, hypoventilation, pulmonary oedema, reduced lung compliance, and mechanical effects of chest compressions can result in airway closure.

In experimental work by Cordioli et al. these mechanisms have been investigated. Using an advanced lung model, replicating cardiac arrest conditions, Cordioli demonstrated that lung volume progressively declines due to absent ventilation, chest wall deformation, and chest compressions. This progressive loss of aerated lung volume results in volumes falling well below functional residual capacity (FRC), thereby promoting airway closure. Notably, their findings indicated that lung volume recovery is only partial during interruptions in chest compressions, suggesting that airway closure may persist throughout much of the resuscitation effort [2]. They compared the combination of chest compressions (CC) with manual bag ventilation and continuous flow insufflation (CFI) to CPR with only chest compressions. It was found that the combination of CC with CFI significantly increases the alveolar ventilation. [2]

Further supporting the potential clinical significance of AOI, Bhandari et al. investigated its association with patient outcomes. In their retrospective analysis of 307 OHCA cases, higher AOI values were associated with an increased likelihood of return of spontaneous circulation (ROSC). These findings suggest that AOI may serve both as a marker of CPR quality and as a prognostic indicator for resuscitation success. [1]
Grieco et al. studied the impact of airway closure during CPR and its impact on ventilation by a quantitative analysis of the capnogram. They found that CCs induce oscillations in the capnogram, and that the magnitude of these oscillations depends on the degree of airway closure. In addition to that, they conclude that using PEEP positively influences delivered ventilation. As a method for quantifying capnogram oscillations and airway closure, the AOI is suggested. [3] The method used for this calculation differs from the four methods proposed by Bandhari.
In this study Grieco et al. demonstrate a relationship between the capnogram and airway closure in humans with cardiac arrest. Airway closure is found to have a major impact on delivered ventilation.

Clinical observations in five patients with OHCA, indeed confirmed that airway collapse was partially prevented by PEEP [2]. This can be explained by the fact that adding a small amount of pressure to the airway at the end of each exhalation, helps to keep the alveoli open, allowing them to participate in the gas exchange.

5. The rationale for this study

From earlier research [4,5] it is clear that the volume of expired CO2, measured by the ETCO2 is a sensitive measure of variations in pulmonary blood flow. As changes in the ETCO2 can help to identify sudden changes in the cardiac output, its monitoring during CPR is recommended to measure the efficacy of circulation. The evolution of ETCO2 is graphically represented in the capnogram.

However, Airway closure during chest compressions may cause variations in ETCO2 during CPR and as a result limit the interpretation and reliability of the End-tidal CO2. Therefore, the evolution of ETCO2 needs to be monitored.

As mentioned in the review on current literature, different methods to calculate the AOI are presented [1,3]. Based on these methods a mathematical model to quantify AOI will be developed in our study.

Bhandari et al showed in their study that a higher AOI correlates with ROSC but no correction for confounders was made. Grieco similarly describes this correlation and reports elevated AOI values in patients experiencing witnessed cardiac arrests and those presenting with a shockable rhythm.
Both studies mention that AOI can occur during CC but do not documenting prevalence. In the present study prevalence of AOI in our cohort will be documented and a multiple regression model will be developed, in which potential or identifiable confounders will be corrected for.

The current study will, based on the data available in the Lazarus database, test the hypothesis of correlation between high AOI and ROSC and asses the independent influence of AOI on survival outcomes adjusting for potential confounders such as age, sex, witnessed cardiac arrest and presence of shockable rhythm. As both above mentioned studies do not provide an exact quantification of a high AOI, the current study will try to establish an AOI threshold predictive of ROSC likelihood.

From the published studies it is not clear whether AOI is an intrinsic characteristic of patients, meaning that it is a non-modifiable variable, or whether AOI can be modified using different ventilation strategies. The current study will investigate whether PEEP during CPR can increase the AOI and as a result positively influence ROSC.

The current study will also be the first one in which the effect of PEEP on patients experiencing OHCA will be investigated.

Utilizing the database from the Lazarus Research group at Ghent University will add results from an additional cohort to the already existing literature.

This study should allow to better understand airway dynamics, parameters influencing it and the effect of PEEP during CPR. By doing so we want to contribute to the development of improved ventilation strategies that could enhance CPR effectiveness.

6. Study purpose and objectives.

In this study we will try to answer the three following research questions, based on the data from our cohort:

1. What is the prevalence of AOI during CPR in our cohort?
2. What is the correlation between AOI and ROSC?
3. What is the influence of PEEP during CPR on AOI?

As a first part of the study, , the Airway Opening Index (AOI) during CPR will be calculated based on the capnogram (i.e. the graphical representation of the measured concentration of carbon dioxide in exhaled air as a function of time). To this end, a mathematical model will be established in Phase 1 of the study, based on one of the methods described by Bandhari et al. [1]

In phase II of the study, the AOI will be calculated at the beginning, during and at the end of resuscitation or at spontaneous return of blood circulation, using the data from the Lazarus database. Based on this, the prevalence of AOI in cardiac arrest outside the hospital setting will be documented, answering our research question 1
In this phase, the hypothesis of Bandhari et al. [1] and Grieco et al. [2] will also be tested within the patient cohort. Both authors argue that the chances of survival in resuscitation are higher in the case of a high AOI, without quantifying it. The test will be done by quantitative comparison of the AOI in patients with and without spontaneous return of blood circulation. In addition, a sensitivity analysis will be used to try to determine a threshold value for AOI that can predict the probability of ROSC (research question 2).
Finally, using mixed model analyses, the independent influence of AOI on survival outcomes will be evaluated. Recognized prognostic factors such as the age of the patient, whether the cardiac arrest was observed, and whether a shockable heart rhythm was present will be considered.

In an attempt to answer question 3 of our research, the effect of positive end-expiratory pressure (PEEP) on AOI will be investigated in the third part of our study, as part of a secondary analysis of the Lazarus-PEEP RCT.

7. Study Design

Since 2017, the Lazarus research group at Ghent University has conducted systematic investigations into respiratory physiology during cardiac arrest, focusing on phenomena such as gasping patterns, reverse airflow dynamics from chest compressions, and the application of AOI during resuscitation.

The present research proposes a retrospective multicentric observational study and secondary analysis in order to further investigating the relationship between airway closure, as reflected by the AOI, the effect of PEEP and resuscitation outcomes during cardiac arrest.
The study will use anonymized clinical data, where no patient involvement is required, from the Lazarus database.

8. Study schedule

Phase I/II: UZ Ghent
Phase III: UZ Ghent and AZORG

9. Inclusion criteria

For this study, following inclusion criteria will be used:

- Adult (over 18 years old) patients with out-of-hospital cardiac arrest.
- Patients undergoing cardiopulmonary resuscitation (CPR).
- Patients who were intubated and had available capnogram recordings immediately after intubation.

10. Exclusion criteria

Will be excluded from the study:

- Patients that were not intubated
- Patients that did not receive CPR following intubation
- Cases with a technical challenge with the $ETCO_2$ measurement (i.e., issues with waveform data of the capnogram.

11. Data collection methods

In the context of this observational study, an analysis will be conducted on (a cleaned set of) data from the Lazarus database, which will be further supplemented with additional patient data as part of the project.

In all three phases of this research project a database, drawn up according to the Utstein guidelines, containing data from resuscitations performed by the medical team of UZ Gent, will be used.
For the study, this non-pseudonymized database, including identifiers, under the management of Professor Dr Said Hachimi-Idrissi, will be pseudonymized to a database without identifiers.
The resulting pseudonymized database, from which the principal investigator (PI) has removed all identifiable points, will be used by the research team for the study. If data from other research institutes will be used in this study, these data will be added to the Lazarus database after pseudonymization following the same procedure.

In phase three of the research project an additional database from AZORG will be used. This database will be pseudonymized by the PI before use by the research team.

The data relate to people who were victims of cardiac arrest outside the hospital environment and are collected by the medical team as part of the intervention.
These data include data taken from:

- the MUG sheets: data relating to the resuscitation itself
- the Electronic Patient Record (EPD): follow-up of the outcome of resuscitation
- Zoll: capnography data, automatically recorded by the Zoll x-series defibrillator during resuscitation.

The principal investigator is responsible for collecting these clinical cases.

12. Statistical methods

As described in the study purpose, this study consists of 3 three parts where for each part a different statistical approach will be applied.

The objective of the first phase is to document the presence of Airway Opening Index (AOI) in patients with out-of-hospital cardiac arrest (OHCA) and to compare these findings with prior descriptions in the scientific literature. To quantify AOI, a mathematical model will be developed based on Method 3 as described in the article by Bhandari et al.[1]. For model development, a sample of 10 to 20 datasets will be used. The AOI will be computed for each time segment - start, during, and end of CPR/ROSC- using this method. The resulting AOI values will be reported as continuous variables and described by the median, interquartile range (IQR), and range, or by the mean ± standard deviation (SD) if the distribution is approximately symmetric.

To support the analysis visually, a histogram or density plot will be generated to illustrate the distribution of AOI across the entire study population and to assess potential skewness or multimodality. The normality of the AOI distribution will subsequently be evaluated using the Shapiro-Wilk test, histograms, and Q–Q plots. The outcome of this assessment will determine whether parametric or non-parametric statistical methods will be applied in subsequent analyses.

Mean AOI values will be compared across clinically relevant subgroups, such as sex, age categories, witnessed arrest, and initial shockable rhythm. The choice of the appropriate statistical test will depend on the assumptions of normality and homogeneity of variances. For comparisons between two groups, an independent samples t-test will be applied if assumptions are met; otherwise, the non-parametric Mann–Whitney U test will be used. In analyses involving more than two groups, parametric analysis of variance (ANOVA) will be conducted or the non-parametric Kruskal–Wallis test. Levene's test will be used to assess the assumption of homogeneity of variances.

The second phase of the study investigates the correlation between the magnitude of the Airway Opening Index, a continuous variable, and the occurrence of Return of Spontaneous Circulation (ROSC), a binary outcome (yes/no). It is assumed that each patient has an outcome (ROSC achieved or not) and one or more measured AOI values during CPR. To quantify the correlation, one representative AOI measure per patient will be used for the analysis. In this respect the AOI at the end of CPR (or at the time of ROSC, if ROSC occurs) is considered the most clinically relevant.

To analyze the association between AOI and ROSC, a stepwise analytical approach will be followed:

1.The distribution of AOI values will be compared between patients with and without ROSC to determine the most appropriate statistical test. If the AOI values in both groups are normally distributed and the variances are comparable, an independent two-sample t-test will be used. If the assumption of normality is valid or if there is inequality of variances, the non-parametric Mann–Whitney U test will be used.

2. To investigate whether a threshold value for AOI allowing to predict ROSC can be identified, a ROC analysis will be performed with AOI as a continuous prediction score and ROSC as a binary outcome measure. In the resulting ROC curve, the sensitivity (true positive rate) is plotted against 1-specificity (false positive rate) for all possible threshold values of AOI. Based on this curve, the Area Under the Curve (AUC) is computed, representing the global discriminative value of AOI to distinguish patients with ROSC from patients without ROSC. An optimal threshold value for AOI is then determined, using the Youden index.

With the chosen threshold, diagnostic characteristics are reported, including sensitivity, specificity, positive predictive value and negative predictive value. These parameters provide insight into the clinical applicability of AOI as a predictor for ROSC.

3.After establishing a bivariate association between AOI and ROSC, a multivariable logistic regression model will be built to examine whether AOI is an independent predictor of ROSC, adjusted for relevant covariables. AOI constitutes the main variable of interest. In addition, covariates considered potentially confounding both from the literature and based on theoretical considerations are included:

- Age (in years) – continuous variable
- Gender (in years) – continuous variable
- Witnessed arrest (yes/no) – dichotomous variable (eyewitness present or not)
- Initial shockable rhythm (yes/no) – dichotomous variable (VF/VT vs PEA/asystole).

Eventually additional literature research might reveal other variables to be added.

The model has the following form:

$$logit\,(P(ROSC) = \alpha + \beta AOI \cdot AOI + \beta age \cdot (age) + \beta gender \cdot (gender) + \beta witnessed \cdot (witnessed) + \beta shockable \cdot (shockable) + \cdots$$

Covariables are stepwise added to the model to see their individual impact on the outcome of the model. The effect of each addition is assessed using the Akaike Information Criterion (AIC); a substantial decrease in the AIC indicates improved model performance. At the same time, multicollinearity is evaluated via the Variance Inflation Factor (VIF) for continuous variables. For VIF values > 5-10 (multicollinearity problem), removal or combination of variables is considered.

In addition, potential interactions between AOI and other covariables are evaluated. After modeling, model performance is assessed on three aspects:

1. Discrimination: The ability of the model to discriminate ROSC from non-ROSC is assessed with the C-statistic/AUC) based on the ROC curve. The multivariable model is expected to discriminate better than AOI alone.
2. Calibration: The match between predicted and observed probabilities is evaluated via the Hosmer-Lemeshow test or a calibration plot.
3. Model optimization: AIC and BIC are used to assess model complexity. A model comparison with and without AOI (e.g., via likelihood ratio test) determines whether AOI makes a significant independent contribution to ROSC prediction. A significant improvement ($p < 0.05$) and lower AIC would confirm AOI as an independent prognostic marker.

The third phase of the study investigates whether the application of PEEP during resuscitation is associated with differences in AOI. To address this, a secondary analysis will be performed using data from the Lazarus-PEEP randomized controlled trial. The analysis will compare AOI values between patients who received CPR with and without PEEP.

If only a single AOI value per patient is available, an independent samples t-test or Mann–Whitney U test will be used, depending on the assumptions of normality (Shapiro–Wilk test) and homogeneity of variances (Levene's test). If multiple time points per patient are available (e.g., start, middle, end of CPR), a linear mixed-effects model will be applied, with AOI as the dependent variable, PEEP as a fixed factor, time as a repeated measure, and patient as a random effect. Relevant covariates, such as age, witnessed arrest, and initial shockable rhythm, will be included where possible. Multicollinearity (VIF) and potential interaction effects will be assessed.

Missing data on AOI or PEEP will be described; if missing at random, a complete-case analysis will be conducted. Results will be summarized in tables including effect sizes, confidence intervals, and p-values,

and visually presented using boxplots or line graphs per group over time. This analysis aims to quantitatively assess the effect of PEEP on airway opening during CPR.

13. Ethical Considerations

Ethical Approval

The study protocol will be submitted to the Ethics Committee of Ghent University Hospital (UZ Gent) for central review and approval in August 2025. The EC of UZ Gent will serve as the central ethics board for this multi-centre study, coordinating the ethical oversight for all data-contributing sites. The study will be in coordination with previous studies who have included these patients in the past. Both studies have received EC approval: EC/2008/025/AM02 dd. 12/09/2022 and ONZ-2024-0496.

Waived Informed Consent

No new individual informed consent will be sought for this study, as it involves a retrospective analysis of existing data without any direct patient intervention. All data to be analysed were previously collected under Ethics Committee–approved research protocols, and thus participants' data were gathered with appropriate ethical safeguards in place. In particular, the dataset is derived from two prior studies: the Lazarus-PEEP trial (central EC file no. ONZ-2024-0496 AM, approved 27 March 2025) and a preceding investigation of intrathoracic pressures during CPR (EC reference EC/2008/025/AM02, approved 12 September 2022). Both studies received full ethical approval and implemented informed consent procedures or waivers as required for emergency research settings. For the present analysis, the relevant patient data will be reused in a fully pseudonymised form, meaning all identifying information has been removed prior to analysis. Given that no new data are being collected and patient privacy is protected, the requirement for additional informed consent is waived.

Confidentiality

Robust data protection measures are in place to ensure confidentiality and compliance with privacy regulations. All handling of study data will conform to the EU General Data Protection Regulation (GDPR) and relevant Belgian laws on personal data protection. As detailed in the protocol's GDPR plan, the source database has been pseudonymised: the principal investigator removed all direct patient identifiers, generating a coded dataset for analysis. The pseudonymised data are stored on secure, access-restricted servers and will be retained for at least 10 years in line with institutional policy. The University Hospital Ghent acts as the data controller for this project, and data processing is performed only by authorised research team members under the supervision of the principal investigator. The Data Protection Officer of UZ Gent is Ms. Katya Van Driessche, reachable at dpo@uzgent.be. Furthermore, any access to source medical records or identifiable information for audit or monitoring purposes will be strictly limited to authorised individuals (e.g. sponsor's representatives, auditors, or inspectors), all of whom are bound by professional confidentiality; such access is only permitted within the confines of applicable laws and regulations.

14. Declaration of interests

Person	Declaration of interests
Prof. Dr. S. Hachimi-Idrissi	Prof. Dr. S. Hachimi-Idrissi has previously received research grants from ZOLL Medical and the Laerdal Foundation to support academic studies related to ventilation strategies during cardiac arrest. These grants were unrestricted and had no influence on the design, conduct, data analysis, or reporting of those studies. Importantly, they exert no influence over the present study, which is conducted independently. There are no financial, commercial, or personal relationships that could be perceived as a potential conflict of interest in relation to this research. No industry funding or material support has been received for the execution of the current study.
Dr. T. Tackaert	Dr. Thomas Tackaert has previously received a research grant from the Laerdal Foundation to support academic studies related to ventilation strategies during cardiac arrest. This grant was unrestricted and had no influence on the design, conduct, data analysis, or reporting of those studies. Importantly, they exert no influence over the present study, which is conducted independently. There are no financial, commercial, or personal relationships that could be perceived as a potential conflict of interest in relation to this research. No industry funding or material support has been received for the execution of the current study.
Ms. M. Van Den Berghe	No relevant conflicts of interest to report.

15. References

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16. Appendices