

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 2244*

Exploring ventilation during cardiopulmonary resuscitation

Experimental and clinical insights

JOHAN MÄLBERG



ACTA UNIVERSITATIS
UPSALIENSIS
2026



UPPSALA
UNIVERSITET

Dissertation presented at Uppsala University to be publicly examined in H:son Holmdahlsalen, Akademiska sjukhuset ing 100, Dag Hammarskjölds väg 8, Uppsala, Friday, 8 May 2026 at 13:00 for the degree of Doctor of Philosophy. The examination will be conducted in Swedish. Faculty examiner: Professor Markus Skrifvars (Helsingfors universitet).

Abstract

Mälberg, J. 2026. Exploring ventilation during cardiopulmonary resuscitation. Experimental and clinical insights. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2244. 99 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2773-0.

Ventilation during cardiopulmonary resuscitation remains understudied with current guideline recommendations for the treatment relying on low level evidence and expert opinion. The aim of this doctoral project was to explore ventilation during cardiopulmonary resuscitation, both in the experimental and clinical setting.

Study I investigated whether a suction cup on a mechanical chest compression device intended to assist chest recoil affected the haemodynamics and ventilation in an experimental porcine model. No difference in EtCO₂, as a measurement of cardiac output, or ventilation could be found, although the suction cup increased the coronary perfusion pressure.

In study II, ventilation parameters, haemodynamics, blood gases and lung injuries were compared between ventilation during continuous chest compressions and ventilations given during a pause of the chest compressions (30:2) in an experimental porcine model. Continuous chest compressions were associated with higher peak inspiratory pressure, lower EtCO₂ and PaCO₂. No differences were found with regards to lung injuries between the groups.

Study III aimed to develop and test a novel algorithm designed to extract accurate ventilation parameters from ventilation waveform signals, gathered during experimental CPR, in the presence of chest compression artefacts in the signal, that otherwise interferes with the parameter extraction. The algorithm was tested with a pneumotachography device and with mechanical ventilators giving ventilation parameters with known values. The algorithm deviated only slightly from the ventilator settings and outperformed the standard software of the pneumotachograph.

Study IV was an observational multicentre study that aimed to describe ventilation parameters during cardiopulmonary resuscitation. Patients were included from five sites, four out of hospital and one in hospital. Included in the study were 241 patients and 28120 ventilations. The ventilations were heterogenous and varied with airway modality and ventilation mode. Bag-valve-mask ventilations were associated with large levels of leakage and asynchronous ventilations with endotracheal tubes with high airway pressures. No obvious signs of hyperventilation were found.

Future research on cardiopulmonary resuscitation should when possible include measurements of ventilation, in order to deduce if the varying ventilation parameters affects outcomes and to decide optimal ventilation strategies for survival.

Keywords: Cardiac arrest, cardiopulmonary resuscitation, ventilation, ventilation parameters, advanced life support

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ISSN 1651-6206

ISBN 978-91-513-2773-0

URN urn:nbn:se:uu:diva-581885 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-581885>)

To L

*Remember,
When tomorrow feels like a rainy day
That today was tomorrow yesterday
And that worked out too
– Povel Ramel
(freely translated)*

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. **Mälberg, J.**, Smekal, D., Marchesi, S., Lipcsey, M., Rubertsson, S. (2022) Suction cup on a piston-based chest compression device improves coronary perfusion pressure and cerebral oxygenation during experimental cardiopulmonary resuscitation. *Resuscitation Plus*, 12:100311
- II. **Mälberg, J.**, Marchesi, S., Spangler, D., Hadziosmanovic, N., Smekal, D., Rubertsson, S. (2023) Continuous chest compressions are associated with higher peak inspiratory pressures when compared to 30:2 in an experimental cardiac arrest model. *Intensive Care Medicine Experimental*, 11:75
- III. **Mälberg, J.**, van Eijk, J., Doeleman, L., Schober, P., van Schuppen, H., Smekal, D., Rubertsson, S., Spangler, D. (2026) A novel algorithm to determine ventilation parameters during cardiopulmonary resuscitation using pneumotachography waveform data. *Resuscitation Plus*, 28:101238
- IV. **Mälberg, J.**, Doeleman, L., van Eijk, J., Spangler, D., Hedberg, M., Ahlström, B., Bäckman, A., Johansson, S., Rodenburg, S., Schober, P., van Schuppen, H., Lagedal, R., Smekal, D., Rubertsson, S. CAvent: A Multicenter Observational Study on Manual Ventilation Parameters During Advanced Life Support in Cardiac Arrest. *Manuscript*

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Additional work

During the COVID-19 pandemic, the work on paper IV had to be paused and the devices in use in that study were instead used in another study, resulting in the following paper, which was outside the scope of this thesis.

Mälberg, J., Hadziosmanovic, N., Smekal, D. (2021) Physiological respiratory parameters in pre-hospital patients with suspected COVID-19: A prospective cohort study. *PLOS ONE*, 16:9.

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Abbreviations

ABG	Arterial blood gas
AED	Automated external defibrillator
ALS	Advanced life support
AP	Arterial pressure
ARDS	Acute respiratory distress syndrome
BLS	Basic life support
BVM	Bag-valve-mask
CCC	Continuous chest compressions
CCSV	Chest compression synchronized ventilation
CerPP	Cerebral perfusion pressure
CO	Cardiac output
CPR	Cardiopulmonary resuscitation
CRALE	Cardiopulmonary resuscitation associated lung oedema
CVP	Central venous pressure
ELV	Estimated lung ventilation
ET	Endotracheal tube
FRC	Functional residual capacity
Freq	Ventilation frequency
ICP	Intracranial pressure
IHCA	In-hospital cardiac arrest
IQR	Interquartile range
ITD	Impedance threshold device
ITV	Ideal tidal volume
LMA	Laryngeal mask airway
MCC	Mechanical chest compressions
Mve	Expiratory minute volume
Mvi	Inspiratory minute volume
OHCA	Out-of- hospital cardiac arrest
PaCO ₂	Partial pressure of arterial carbon dioxide
PALI	Post-arrest lung injury
PaO ₂	Partial pressure of arterial oxygen
PAW	Airway pressure
PBW	Predicted body weight

PEA	Pulseless electrical activity
PECO ₂	Peak expired carbon dioxide
PEEP	Positive end expiratory pressure
PIF	Peak inspiratory flow
PIP	Peak inspiratory pressure
Pplat	Plateau pressure
RCT	Randomized controlled trial
ROSC	Return of spontaneous circulation
SAD	Supraglottic airway device
SCA	Sudden cardiac arrest
Te	Duration of expiration
Ti	Duration of inspiration
Vdiff	Difference between inspiratory Vti and Vte
VF	Ventricular fibrillation
VT	Ventricular tachycardia
Vte	Expiratory tidal volume
Vti	Inspiratory tidal volume

Preface

Donald Rumsfeld (1932-2021), the former US secretary of defence, was a man who in his political life maybe did not do humanity that many favours (and is perhaps rarely mentioned in a thesis from the domain of medicine). He did, however, gift the world with one rather unforgettable quote during a hearing in 2002 on the lack of evidence of the Iraqi government supplying terrorist groups with weapons of mass destruction:

“...as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns—the ones we don't know we don't know...”¹.

This quote has stuck with me for quite some time while working on this thesis concerning ventilation during cardiac arrest. As one digs deeper into the subject, the sheer number of known unknowns can be overwhelming. It soon also dawns on you that with this many known unknowns, there must be many more unknown unknowns. All this leads to an important question: How can we know so little about something so fundamental in the treatment of what is arguably the most dramatic medical emergency there is, sudden cardiac arrest? Something that has been performed for centuries and to this day is highly prioritized during cardiopulmonary resuscitation.

This thesis aims not to answer all of these known unknowns, but hopefully turn some of them into known knowns, and perhaps, along the way, also discover some unknown unknowns, and by doing so transform them into known unknowns, to be explored further in the future.

Background

Sudden cardiac arrest

Pathophysiology

Sudden cardiac arrest (SCA) is a condition where the heart's ability to pump blood throughout the body suddenly ceases or is severely impaired. When this occurs, the blood pressure drops to inadequate levels, and there is insufficient cerebral circulation of blood and oxygen. Therefore, all of the brain's functions cease and with them the ability to maintain consciousness and control respiration, hence the cardinal symptoms of SCA: sudden loss of consciousness and abnormal or absent breathing².

Untreated SCA results in global cerebral ischemia with cell death occurring within a few minutes. If left untreated SCA almost always results in death due to irreversible brain damage.

The primary mechanism causing SCA in adults is cardiac arrhythmias³. In a healthy heart, the contraction of the heart is controlled by the cardiac conduction system. This system ensures that the heart contracts in a very specific and organized manner. The signal to start a contraction originates in the sinoatrial node (the pacemaker) in the right atrium of the heart. From there the signal spreads through both the right and left atrium, causing them to contract and subsequently fill the ventricles with blood. The signal then reaches the atrioventricular node, where it is shortly delayed in order to facilitate proper filling of the ventricles with blood. After this the signal goes through the bundle of His and into the Purkinje fibres in the walls of the ventricles, which causes them to contract and eject blood into the pulmonary and systemic circulation⁴. If parts of the heart are damaged, the myocardial cells can become hyperirritable and start producing their own pacing signals. This leads to the ventricles receiving multiple pacing impulses, leading to an electrical chaos in the heart. The ventricles start to quiver, or fibrillate, and a ventricular fibrillation (VF) has occurred. As there is no proper contraction of the ventricles, no, or very little, blood is being ejected and SCA ensues. On rarer occasions, the same mechanisms can instead lead to ventricular tachycardia (VT), where the

ventricles contract very rapidly. If the contractions become too rapid, the ventricles will not have the time to fill with blood, also leading to no or very little blood being ejected from the heart ⁵. If the VF/VT is not treated, it can lead to pulseless electrical activity (PEA), where there is electric activity in the heart, but no contractions ⁶, or to asystole, where there are no electrical signals in the heart and no contractions.

Another mechanism behind SCA is a decreased supply of oxygen to the heart muscle, either caused by insufficient oxygenation of the blood, or insufficient circulation. The culprit behind this can be lung diseases, asphyxia, trauma or internal bleeding. When the hearts consumption of oxygen exceeds the delivery, the contractions becomes slower (bradycardia). If nothing is done to reverse the underlying cause, PEA and eventually asystole ensues ⁷.

Epidemiology

When studying SCA, a distinction is usually made depending on where the SCA occurred: out-of-hospital cardiac arrests (OHCA) and in-hospital cardiac arrests (IHCA).

As SCA is not one uniform condition, the epidemiology is very varied. As there also exists some heterogeneity in definitions and reporting, the epidemiology comes with some uncertainty ⁸. However, among adults, the most common cause of SCA is heart disease. In Europe, 91% of all OHCA:s have a medical aetiology ⁸ and in Sweden, approximately 65% of all SCA:s are caused by heart disease ⁹. The most common heart disease causing SCA is coronary artery disease ¹⁰ In children up to 17 years old, the most common causes of SCA:s are hypoxia, cardiac related issues and drowning ¹¹. The leading non-medical causes of OHCA in Europe, in descending order, are trauma, asphyxia, drug overdose and drowning ¹².

The incidence of SCA varies throughout the world, and is more or less well known depending on the region. Some of the regions where the incidence of OHCA has been studied in greater detail is Europe and North America. Regions where it is less studied includes Asia and Africa ¹³. In Europe, OHCA is the third leading cause of death with an incidence rate of somewhere between 31 to 243 per 100 000 inhabitants in 2022 with approximately 65% being male and the median age being 67 years ¹⁴. In the United states, the incidence was 379 per 100 000 inhabitants in 2024 ¹⁵. Due to the inherent uncertainty of these figures, it is difficult to make direct comparisons between different regions ¹⁶.

Survival rates after OCHA also varies depending on the region. In Europe it is estimated to be between 8% and 12.7% with great variation between different countries ¹⁴. In the US 10.5% ¹⁵ and in Australia and New Zealand 12%. In a study of 7 Asian countries, a survival rate of less than 8% was found ¹⁷.

IHCA remains less studied than OHCA ¹⁸. The aetiology also differs from OHCA with pulmonary and cardiac aetiologies being comparable in frequency ¹⁹. The incidence in Europe is reported as 1.5 to 2.8 per 1000 admissions with a gender distribution comparable to OHCA but with a slightly higher median age. The survival rate is somewhere between 27-62% ²⁰⁻²².

Concerning risk factors; men are three to four times as likely to suffer a SCA compared to women. The risk also increases with higher age. As stated before, the most common cause of SCA is coronary artery disease which in turn is most commonly caused by smoking, diabetes, dyslipidaemia, obesity and hypertension. Other risk factors include heavy alcohol consumption, anxiety, depression and genetical factors such as a family history of SCA or specific genetical disorders of the heart ¹⁶.

Cardiopulmonary resuscitation

The treatment for SCA is cardiopulmonary resuscitation (CPR). As the body is without functional circulation and breathing during a SCA, the goal is to provide this in an artificial manner. This is done by oxygenating the blood and facilitating the removal of carbon dioxide via ventilation and establishing circulation with the help of chest compressions. This must continue until spontaneous circulation is restored, usually by the means of external defibrillation of the heart.

A brief history of CPR

The history of CPR is for the most part the history of ventilation. As SCA: s always has been present, various methods of resuscitating those who have suffered from it have emerged, regardless of how poorly understood the condition was. As unconsciousness and absence of breathing were the most obvious signs that something was seriously wrong, naturally people in different ages tried to do something about it.

As far back as the old testament, there are multiple examples of depictions of ventilations: God breathing life to Adam through his nostrils (Gen 2:7) ²³, the

prophets Elijah and Elisha resuscitating children with mouth to mouth breathing (1 Kgs 17:17-24, 2 Kgs 4:32-35)²³. The first scientifically sound study of ventilation seems to have been by the physician Galen in ancient Greece, who found that if you blew air through a reed down the throat of an animal, its chest expanded²⁴.

There have also been less (at least by today's standards) adequate ways of attempting resuscitation through the ages: Blowing tobacco up the rectum, rolling the person suffering a SCA over a barrel and flogging²⁵.

The first documented case of successful resuscitation by means of artificial ventilation was in 1732 when a Scottish surgeon, William Tossach used mouth to mouth breathing to resuscitate an apparently dead coal miner, who later made a complete recovery. Tossach later published an account of the episode²⁶.

Ventilation continued to be the primary focus of resuscitation until the 19th century. Different techniques were tried, among them rolling a prone patient up on its side and back again or raising and lowering the arms. The intended purpose was to expand and contract the chest in order to create ventilation²⁷. These techniques largely replaced mouth to mouth breathing in resuscitation. It was not until the 1950's that James Elam and Peter Safar demonstrated that mouth to mouth breathing was the superior way of achieving artificial ventilation²⁸.

Successful CPR with external cardiac massage was first described in 1892 by a German surgeon, Friedrich Maass²⁹ but was also not fully incorporated in resuscitation until the 1950's, when William Kouwenhoven, Guy Knickerbocker and James Jude demonstrated that by compressing the chest of a dog, they could get a femoral pulse and later proved that the method could successfully resuscitate humans with SCA³⁰.

CPR with chest compression and ventilation, as it is known today, was introduced in 1960 when both the above-mentioned teams presented their results at a medical conference.

Modern CPR

Modern CPR is usually divided into basic life support (BLS) and advanced life support (ALS) depending on how and by whom it is performed.

Basic Life Support

BLS represents the first line of defence during a SCA and should be started as soon as possible. The aim is to restore circulation and ventilation with little or no equipment. BLS is the reasonable level of care that can be provided by CPR-trained lay persons and professionals with basic training in health care, such as security guards, police and firefighters³¹. BLS consist of:

Chest compressions: administered by pushing down firmly on the middle part of the chest with both hands, roughly between the nipples. This should be done at a rate of 100-120 compressions a minute and with a depth of 5-6 cm (Fig 1.)³².



Fig 1. Correct hand placement when performing chest compressions. Source: Wikimedia commons, CC0

Rescue breaths: administered with mouth to mouth breathing, where the CPR provider pinches the nose of the person suffering an SCA and blows air mouth to mouth. The ventilation should take 1 second and produce a visible chest rise³² (Fig 2.) A face mask can also be used, which is placed over the patients mouth and nose, and used by either giving the rescue breath into the mask (often via a one-way valve) or in conjunction with a self-inflation bag (see below).



Fig 2. Mouth to mouth breathing. Source: Rama, via Wikimedia commons, licensed under CeCILL

Adult BLS CPR should be performed in the 30:2 mode: a repeating pattern of 30 compressions followed by a short pause during which 2 ventilations are performed. If the CPR-provider is not trained in rescue breaths, continuous chest compressions can be used, with no interruptions³².

The definitive treatment for SCA caused by VF/VT is external defibrillation. As such it should be included in the CPR-process as early as possible. In BLS this is usually done with an automated external defibrillator (AED), which automatically interprets the cardiac rhythm present and decides whether to defibrillate or not³². The function of a defibrillator is to deliver an electric shock to the heart with the goal to depolarize the cells in the myocardium in order to stop them from producing erroneous pacing signals and allowing the sinoatrial node to resume its normal pace-making function. It should be noted that the exact mechanism behind defibrillation terminating a VF/VT is not yet fully understood³³.

Advanced Life Support

ALS consists of the more advanced medical interventions that can be used as an adjunct to BLS. This is supplied by healthcare professionals with specific ALS training, such as doctors, paramedics and nurses. It includes manual (or sometimes mechanical) ventilation, advanced airway management, mechanical chest compressions (MCC), manual defibrillation and administration of drugs. In OHCA, ALS is usually performed by the Emergency medical service (EMS, or ambulance) and in IHCA by specialized emergency teams³⁴.

Ventilation: Manual ventilation is delivered with a self-inflating bag, with a one-way valve and often connected to a supply of oxygen. It is always connected to some form of airway management system. It can also be referred to as a resuscitator or, when used in conjunction with a mask, a bag-valve-mask (BVM).



Fig 3. Bag-valve-mask (BVM)

Advanced airway management:

Refers to different devices used to keep the patient's airway open in order to simplify ventilations and ensure adequate ventilation of the lungs. The most commonly used advanced airways are supraglottic airway devices

(SAD), which are inserted into the pharynx and can be inserted blindly. Of note is that there are many different types of SAD: s. One of the most common types, and used in the studies in this thesis, are laryngeal mask airways (LMA) which can be seen in Fig. 4. Endotracheal tubes (ET) are inserted in the trachea and require laryngoscopy to be placed properly. Inside the trachea, they are cuffed, meaning that an inflatable balloon fixates the tube and also blocks the airway (except for the tube itself, which runs through the balloon). ET is considered a safe airway as it protects the patient's airway to a larger extent from ingress of fluids, such as regurgitations or blood, compared to the other methods.



Fig 4. Endotracheal tube (left) and Supraglottic airway device, i-gel® (right)

Mechanical chest compressions: There are multiple devices in use today designed to perform manual chest compressions. This aims to ensure standardized compressions, lessen the impact of provider fatigue and enable high quality chest compressions to be performed in situations where it could otherwise be difficult, such as during transport ^{35,36}. The only MCC device used in the studies included in this thesis is the LUCAS (model 2 and 3) (Jolife AB/Stryker), which is a piston-based device equipped with a suction cup to enhance decompression.



Fig 5. LUCAS 3 attached to a CPR mannequin

Manual defibrillation: The defibrillators used in ALS are usually manual, meaning that the ALS provider is responsible for interpreting the cardiac rhythm present and deciding if a defibrillation is adequate or not. Therefore, manual defibrillators are equipped with a screen showing an electrocardiogram (ECG). Used correctly, manual defibrillators can shorten the pause of compressions during analysis and the charging of the defibrillator ^{37,38}. Many modern manual defibrillators can also perform capnography, measuring the end-tidal carbon dioxide (EtCO₂).



Fig 6. Manual defibrillator showing ventricular fibrillation

Drugs: The two drugs currently recommended in CPR guidelines are the vasopressor adrenaline and the antiarrhythmic amiodarone, both are administered intravenously or intraosseous. Adrenaline causes vasoconstriction which improves the coronary circulation of the heart, thereby increasing chances of return of spontaneous circulation (ROSC) ³⁹.



Fig 7. Pre-filled syringe with adrenaline and an ampule of amiodarone

Amiodarone is thought to increase the chances of terminating a VF/VT due to its antiarrhythmic properties ⁴⁰.

Concerning ventilation in modern CPR

Ventilation is a fundamental part of CPR during ALS. However, as will be discussed frequently in this thesis and the included studies, it remains insufficiently studied, and comparably less so than chest compressions and defibrillations. It should be noted though, that in recent years, there has been renewed interest in the field. As the practice of ventilation during CPR is very complex, with many distinct but intervening parts, finding direct correlations between

ventilation and outcomes can be challenging. Below is a brief overview of current clinical practices, their underlying scientific evidence and recommendations in CPR guidelines.

Airway management

How to manage the airway is perhaps the most well-studied part when it comes to ventilation during CPR, even though the evidence is inconclusive. There are numerous different ways to handle a patient's airways during CPR. For this overview, the focus will be on face masks, SAD:s and ET:S, which all comes with their advantages and disadvantages: A mask is relatively simple and quick to apply, but does not prevent regurgitation, leakage or gastric insufflation (where the air is ventilated into the stomach instead of the lungs) and it can be difficult to maintain a proper seal around the patients mouth and nose leading to leakage⁴¹. SAD: s requires a little more training, but are easier to use once in place. When used properly, they offer some protection against leakage^{42,43} gastric insufflation⁴⁴⁻⁴⁷ and regurgitation⁴⁸. ET is by far the most complicated method and requires significant training and special equipment, but once in place reduces the risk of regurgitation and leakage. How many attempts of endotracheal intubation that is needed before proficiency is achieved varies, but was found in a review to be around 50 before a 90% success rate within two attempts is achieved. However, this greatly increases with difficult airways⁴⁹. As opposed to masks and SAD: s, when inserting an ET, a pause of the chest compressions up to one minute might be necessary in order to be able to visualize the trachea⁵⁰, although this is not always needed⁵¹. This pause could potentially have a negative impact as interruptions in CPR and can lower the odds of survival^{52,53}.

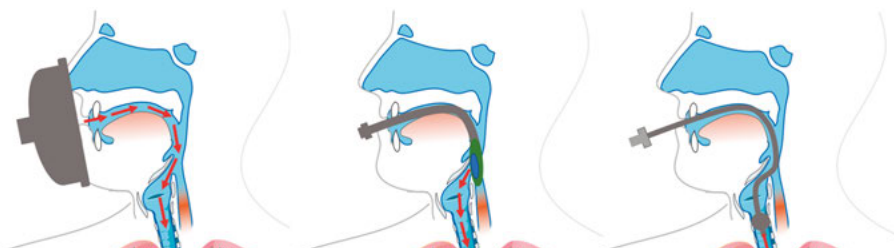


Fig 8. Schematic illustration of the mentioned airway devices and how they apply to the airways. From left to right: Facemask, supraglottic airway device (in this case a laryngeal mask airway, LMA) and endotracheal tube. The red arrows indicate where the airstream is supplied into the patient's airways by the device. Source: Wikimedia commons, CC0

A stepwise approach to handling the airway during CPR is usually recommended, where progressively more advanced methods are employed, according to the situation. This means that it is reasonable to start with the simplest method, a face mask, then switch to a SAD and lastly an ET, if the need arises. This could for example be due to airway complications, or circumstances surrounding the SCA necessitating a certain method, such as during transportation. According to this approach, it might not be necessary to use advanced airways if the more basic methods works well ³⁴.

If there is one particular type of airway management that is superior to others in terms of patient outcomes, such as ROSC, survival and favourable neurological outcome, is hotly debated, and the evidence is inconclusive. Many studies have looked into this in OHCA but consensus has not been reached. One large randomized controlled trial (RCT) compared rate of survival after 28 days with favourable neurological outcome between BVM and ET but found no difference between the methods (4.3% vs. 4.2%) ⁵⁴. In one cluster RCT, no difference was found in rates of ROSC when comparing a SAD with ET (25.8% vs. 26.9%) ⁵⁵. Another cluster RCT found no difference in neurological outcome when comparing SAD with ET ⁵⁶. One cluster RCT that compared ET with laryngeal tube (a type of SAD), did find a higher rate of survival after 72 hours in patients who received a laryngeal tube (18.3% vs. 15.4%) The difference was modest though and the failure rate of intubation was rather high ⁵⁷. Yet another cluster randomized trial found a higher rate of complications for laryngeal tubes compared to LMA (odds ratio (OR) 2.82) ⁵⁸, further complicating the picture. Numerous observational studies have been performed in the field, with very heterogenous results. Some studies found favourable results from using an advanced airway compared to more basic methods such as BVM ⁵⁹ while others found the opposite, favouring basic airway management over advanced methods ⁶⁰⁻⁶². Some found favourable results for SAD ^{63,64}, while others for ET ⁶⁵⁻⁶⁷ or no difference between the methods at all ^{68,69}. Due to differences in study design, the included measurements, and the risk of bias, comparing these observational studies and drawing conclusions in order to influence clinical practice is challenging ⁷⁰.

In IHCA there are very few studies on airway management. One large observational study found that the use of ET was associated with lower survival rates compared to not using ET (16.3% vs. 19.4%) ⁷¹.

Based on the current evidence when ventilating during ALS, the recommendations are to either use a BVM or an advanced airway (such as a SAD or an ET). If an advanced airway is used, it is only recommended to use an ET in

settings where the success rate of insertion is high, otherwise, a SAD should be used ^{34,72}.

Tidal volume

The tidal volume is the volume of gas (ambient air or air/oxygen mixture) given to the patient with every ventilation. A distinction is made between inspiratory volume (V_{ti}), which is the volume given to the patient and expiratory volume (V_{te}), which is the volume exhaled by the patient. V_{te} is thought to best represent the actual ventilation of the lungs, as parts of the V_{ti} can leak before reaching the lungs, for example due to insufficient airway seal ⁷³. The total volume given during one minute is called minute volume (MV). MV can also be divided into inspiratory (MV_i) and expiratory (MV_e) volumes ⁷⁴. Tidal volumes in ventilations during CPR is insufficiently studied and its effect on patients' outcomes is not fully understood. During mechanical ventilation in intubated patients in other severe conditions, such as acute respiratory distress syndrome (ARDS), a clear link has been found between large tidal volumes and increased mortality ^{75,76}. If this is also the case during CPR is unknown, although ARDS appears to be common after CPR ⁷⁷. On the other side of the tidal volume spectrum, low tidal volumes (less than 250 ml) or insufficient lung inflations seems to be connected to worse outcomes such as ROSC and survival ⁷⁸. The use of a smaller self-inflating bag was also found to have an adverse effect on ROSC in one study, possibly due to lower tidal volumes being administered ⁷⁹. This could be due to the dead space volume, which is the volume in the airways that does not participate in the gas exchange. During ventilation, this volume needs to be exceeded in order for oxygen-rich gas to reach the alveoli and for CO_2 to be effectively eliminated. Small tidal volumes could lead to retention of CO_2 , with potentially negative consequences ⁸⁰. The volume of anatomical dead space can be roughly estimated as 2.2 ml per kg bodyweight ⁸¹.

As such, current guidelines take a careful approach to tidal volume recommendations with the aim of neither giving to large nor to small volumes, although this is mostly based on expert opinions and not scientific evidence. European guidelines recommend a tidal volume delivered manually over 1 second producing a visible chest rise. For mechanical ventilation, their recommendations are 6-8 ml/kg⁻¹ predicted body weight ³⁴. The American guidelines recommend a tidal volume of 500-600 ml, or enough to produce a visible chest rise when ventilating manually and to avoid large tidal volumes. ⁸².

The tidal volumes actually given during CPR have long been unknown. There have been prior studies investigating this though. One pilot study found that the mean tidal volume given to intubated patients in the pre-hospital setting was 435 ml. The patients included were a mix of patients receiving CPR, already having achieved ROSC and those ventilated for other reasons ⁸³. A larger clinical observational trial measured tidal volumes in ventilation during 30:2 BLS CPR with BVM's and found V_{ti} in line with guideline recommendations (median 525 ml for the first ventilation and 531ml for the second). However, the V_{te} was significantly lower than the V_{ti} (median 273 ml for the first ventilation and 327 ml for the second), indicating issues with BVM's, either due to leakage or gastric insufflation ⁴¹.

Airway pressure

The pressure with which ventilations are given during CPR is not often measured and its interactions are poorly understood. As airway pressure is a central part in mechanical ventilation of sedated, intubated patients, there are numerous studies concerning the subject in that particular field. Findings from these studies are often discussed in the context of ventilation during CPR, but doing so comes with some caveats that are necessary to address. First, the studies are from patients suffering other conditions than SCA. Second, these patients are usually ventilated for hours or days, compared to a typical episode of CPR which is often well under one hour ^{84,85}. Third, ventilation during CPR is often performed manually and not mechanically, especially when not using an ET ⁸⁶. This distinction is important as many variables measured during mechanical ventilation cannot be measured (or simply are not present) in manual ventilation. Airway pressure measurements during CPR can also be further complicated by chest compression artefacts ⁷³ (discussed later under On the issue of measuring ventilation during CPR). Fig 9 illustrates pertinent differences in hypothetical curves of airway pressure over time in mechanical and manual ventilation, with important points of measurements annotated ^{83,87}.

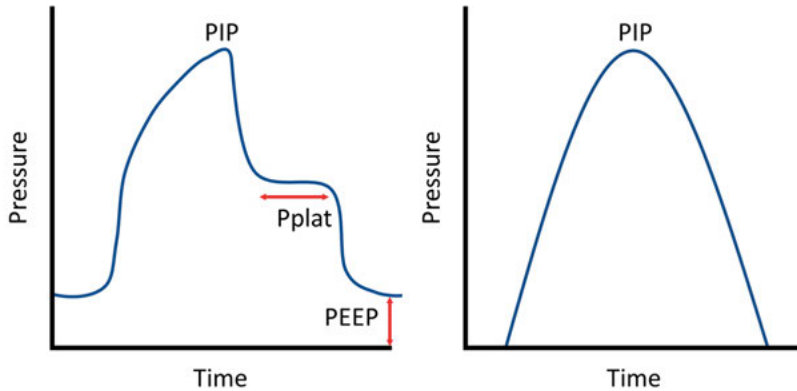


Fig 9. Pressure-time curves in mechanical (left) and manual (right) ventilation. PEEP: Positive end expiratory pressure; PIP: Peak inspiratory pressure; Pplat: Plateau pressure

PIP is the highest pressure during an inspiration, Pplat is the pressure measured during a pause directly following the inspiration when there is no flow, but the pressure remains and is allowed to equalize over the lungs and ventilatory circuit. This represents the alveolar pressure at the end of the inspiration. Measuring Pplat requires the ventilator to perform an inspiratory hold manoeuvre and is as such not measurable during manual ventilation. PEEP is the pressure maintained by the ventilator in the ventilatory circuit between ventilations. It serves to keep the alveoli in the lungs from collapsing (atelectasis)⁸⁷. PEEP can be achieved in manual ventilation with a PEEP-valve which retains a certain pressure in the airway during ventilation pauses.

Two of the most important studies on airway pressures were published around the turn of the 21st century and both found significantly better survival for ARDS patients in the intensive care unit ventilated with lower tidal volumes, Pplat and PIP, compared to higher. The first one found a Vti of 6ml/kg predicted body weight (PBW) and a PIP of <40 cmH₂O to be superior compared to a Vti of 12ml/kg PBW⁷⁶. The later, larger study found a Vti of 6ml/kg PBW and a Pplat of 30 cmH₂O superior to a Vti of 12ml/kg PBW and a Pplat of 45 cmH₂O⁷⁵. This lung protective strategy of ventilation has been in use ever since and has been shown to be beneficial in ventilation during other conditions and in other settings as well^{88,89}. These studies are often mentioned in the context of airway pressure (and tidal volumes) during CPR. The relevance of these studies for ventilation during CPR is unknown, due to the previously mentioned factors. However, they do serve as hypotheses generating for ventilation during CPR, namely, if high airway pressure is detrimental for the

patient or if it could in fact have some benefits, if applied at the right time during the compression/decompression cycle.

PEEP has been found to improve ventilation and reduce lung damage during CPR in animal studies^{90,91}, and some observational studies in humans have shown potential benefits of applying PEEP during CPR^{92,93}. No major RCT has to this day been performed on the subject.

The research on airway pressures during CPR is very limited. One small pilot study found that the PIP was higher in ventilations performed during chest compressions compare to ventilations when no chest compressions were given (absolute difference 32 cmH₂O)⁸³. There are currently no recommendations for airway pressure in neither the European nor the American CPR guidelines. Although of note is that the European guidelines did in their most recent (2025) edition include recommendations for mechanical ventilation where it is stipulated to use a PEEP of 0-5 cmH₂O and set a pressure alarm at 60 cmH₂O^{34,82}.

Ventilation rate

Along with airway management, ventilation rate has perhaps been the most discussed topic in ventilation during CPR. Due to ease of measuring (usually via a capnograph⁹⁴), the area is relatively well investigated, although without clear consensus. It was long feared that hyperventilation (meaning either to ventilate to fast, or with large tidal volumes, or a combination of both) was common during CPR, mainly due to two influential studies published in 2004 that found hyperventilating to be both common and detrimental to outcomes^{95,96}. The sample size and methodology of these studies have later been questioned. Newer studies have found hyperventilation to not be as prevalent as once thought⁹⁷⁻⁹⁹ and have failed to show clear effect on outcomes and also questioned the reliability of capnography as a mean to measure ventilation rate^{97,100,101}. One IHCA study on ventilation frequencies found that they were often above the recommendations, but also that higher ventilation rates (> 12/min) were associated with improved ROSC (45% compared to 24% for ventilation rates of 6-12/min)¹⁰². This study needs replication though as the results could be due to chest compressions being registered as ventilations in the capnography signal, further questioning the reliability of capnography to measure ventilation rate (at least in the absence of specialized tools for analyses of ventilation during CPR, as described later in this thesis).

The current recommendations for ventilation rates are 10/min when an advanced airway has been placed. When using BVM or rescue breaths, a 30:2

compression to ventilation ratio can also be used^{34,82}. If performing CPR with 110 compressions/min and utilizing a 3 second pause for ventilations, this equates to a ventilation rate of approximately 6/min.

Compression to ventilation ratio

Ventilations during CPR can be given asynchronous to chest compressions, meaning that the ventilations are given during ongoing continuous chest compressions. The other commonly used method is to perform ventilations synchronous to chest compressions. In practice, according to current guidelines, this means that 30 chest compressions are given, followed by a pause during which two ventilations are performed, afterwards the chest compressions are resumed. This pattern is then repeated. A large cluster randomized trial compared synchronous and asynchronous ventilations during CPR when using BVM and found no differences in survival or favourable neurological outcome (9.7% vs. 9.0% and 7.7% vs. 7.0% respectively). However, there were some per-protocol outcomes that favoured synchronous ventilations such as admission to hospital (25.9% vs. 24.6%) and hospital free survival days (1.5 vs. 1.3)¹⁰³. One perceived risk with asynchronous ventilations was previously that it could increase the rate of regurgitations. This was not found in this study. As such, in the American CPR guidelines, when using BVM, both methods are recommended⁸². The European guidelines are less specific about this³⁴ but both guidelines recommend using asynchronous ventilations when an advanced airway is placed unless there is excessive leakage leading to inadequate ventilation of the patients lung. What constitutes as excessive leakage and inadequate ventilation is not further specified. The rationale behind recommending advanced airways during continuous chest compressions can perhaps be questioned as the research directly informing this guideline was concerning BVM: s and not advanced airways, such as SAD: s or ET: s.

Physiological effects of CPR and ventilation

How chest compressions and ventilation affect the circulatory and respiratory systems, and the interaction between the two is very complex and not yet fully understood. As measuring pressure and flow in the circulatory system (haemodynamics) requires special equipment and invasive procedures, it is not often done in the field. Therefore, most of the research underlying the evidence comes from animal studies. To discuss the physiological effects of ventilation during CPR, some fundamental properties are worth highlighting:

- Ventilation during CPR is an example of positive pressure ventilation where air is delivered to the lungs by means of an external positive pressure as opposed to normal breathing, where air is drawn into the lungs by a negative pressure caused by the expansion of the thorax during inhalation.
- The purpose of ventilation during CPR is to oxygenate the blood and enable elimination of CO₂.
- Insufficient oxygen levels in the blood leads to ischemia in the brain, irreversible brain damage and death. It can also cause constriction of the pulmonary arteries, which inhibits blood flow in the pulmonary circulation^{104,105}, potentially reducing the blood flow to the left side of the heart and making chest compressions less effective due to decreased volumes of blood being ejected from the heart, or cardiac output (CO).
- Increased CO₂ levels causes the body to become acidic, which inhibits important vital functions like the binding of oxygen to haemoglobin. It can also negatively affect the success rate of defibrillations^{106,107}. Decreased CO₂ levels can cause constriction of arteries in the brain, with impaired cerebral circulation as a consequence¹⁰⁸.
- To enable adequate ventilation, the inspired oxygen must reach the alveoli where the gas exchange takes place, meaning that both the upper airways and the lower, smaller airways (such as the bronchioles and alveoli) needs to be open.
- The blood must be circulated, both in the pulmonary circulation, in order to reach the alveoli and participate in the gas exchange, and in the systemic circulation, in order to reach the tissues, oxygenate them and facilitate the removal of CO₂.
- During normal inhalation, the negative pressure in the thorax draws venous blood to the heart (increasing the venous return) and helps to ensure adequate CO.

Immediately following a SCA, the blood is already oxygenated to a certain degree (depending on the aetiology of the SCA). If this is enough to prevent ischemia in the brain with only chest compressions in the first few minutes after a SCA is debated with studies coming to different conclusions, some found chest-compression only CPR to be beneficial^{109–111} while others failed to detect a beneficial effect^{112,113}. Previous studies have also found that absence of ventilation can negatively affect the lung physiology, by increasing the formation of atelectasis^{114,115}.

If the SCA is not reversed quickly, ventilation becomes increasingly important as the oxygen levels drops and CO₂ levels increases.

Once ventilation starts during CPR, a complicated interaction takes place between the ventilations and the chest compressions. Traditionally, blood flow during CPR has been described by one of two theories, *the cardiac pump theory* and *the thoracic pump theory*, both of which relate to ventilation in different ways, mainly due to how ventilation alters the intrathoracic pressure.

- The cardiac pump theory postulates that the circulation is driven by the direct compression of the heart between the sternum and the spine, mimicking an actual contraction of the heart. During decompression (the up-stroke of a chest compression), the pressure inside the heart falls, allowing blood to fill it again ¹¹⁶.
- The thoracic pump theory arose when coughing during VF was found to prolong the duration of consciousness directly following the onset in a handful of patients undergoing angiography. The pressure in the aorta was found to be higher during a cough than what was achieved with chest compressions ¹¹⁷. As the heart was not directly compressed during the coughing, this cast doubt on the cardiac pump theory as the sole explanation for circulation during CPR. In the thoracic pump theory, it is the pressure inside of the thorax that is driving the circulation.

More modern interpretations see the two theories as not mutually exclusive, but both playing an important part in the understanding of circulation during CPR and being more or less relevant depending on the situation and patient at hand ^{118,119}. However, they do lead to different conclusions regarding the intrathoracic pressure (both caused by chest compressions and ventilations) and its effect on the circulation. If one solely relies on the cardiac pump theory, then an increased intrathoracic pressure due to ventilation could lower the venous return and thus lowering CO. Therefore, a high airway pressure (such as PIP) could lead to negatively affected haemodynamics if the pressure from the airway is transferred to the thorax (which is far from certain) ¹²⁰. An increased intrathoracic pressure according to the thoracic pump theory on the other hand, could if applied at the right moment in the compression/decompression cycle lead to a higher CO, due to more blood being pressed out of the thorax. Efforts have been made to implement ideas about altering intrathoracic pressure into clinical practice, such as with the impedance threshold device (ITD). It works by generating more negative intrathoracic pressure during decompression in order to improve the venous return (in line with the cardiac pump theory). The use of an ITD showed promising results in animal studies ^{121,122} but failed to

show any benefits in humans in a clinical randomized comparison of a large number of patients¹²³. Another more recent attempt at optimizing the intrathoracic pressure combining both of theories has been chest compression synchronized ventilations (CCSV) where a small, high pressure ventilation is given simultaneously with each chest compression with the aim of increasing the intrathoracic pressure only during compression to facilitate higher CO (thoracic pump theory) and maintaining a low intrathoracic pressure during decompression to facilitate higher venous return (cardiac pump theory). It requires specialized ventilators that use the increased airway pressure during chest compressions to trigger the ventilations¹²⁴. Initial animal testing showed positive results on oxygenation but a later animal study showed an increased risk of injuries (pneumothoraces)¹²⁵. Observational studies on CCSV in humans have failed to show survival benefits from CCSV, and have in fact displayed conflicting trends for ROSC when CCSV was compared to other ventilations modes, necessitating further investigation^{126,127}.

Further complicating the picture is the concept of intrathoracic airway closing. During normal respiration, there is a certain volume of air left in the lung at the end of the exhalation, the functional residual capacity (FRC). The function of this is to keep the small airways from collapsing in-between breaths. During CPR, as muscle tonus in the thorax is lost and due to chest compressions, the volume at the end of the expiration falls below the FRC, which can cause smaller airways to collapse¹²⁸. This can lead to the lungs being less aerated, impairing gas exchange, and to the formation of atelectasis, which can impair oxygenation¹²⁹ and increase pulmonary vascular resistance¹³⁰. The intrathoracic airway closing during CPR has also been found to limit the transmission of intrathoracic pressure to the pressure measure at the airways¹²⁸. This could in theory limit the effect of PIP on intrathoracic pressure and by extension effects on the haemodynamics. The clinical implications of this remain unknown. Applying PEEP has been proposed as a method to prevent intrathoracic airway closing, and has in experiments been shown to be effective¹³¹. The research on PEEP in CPR is inconclusive, as discussed before.

Capnography

Measuring EtCO₂ is one way to try to evaluate the physiological effects of CPR. EtCO₂ is the partial pressure of CO₂ in exhaled air measured at the end of expiration and reflects the cellular aerobic metabolism of perfused tissues. As such it can theoretically give insight into CO, the perfusion of tissues, pulmonary and systemic circulation, as well as the ventilation. A normal EtCO₂ is usually between 35-40 mmHg in healthy, spontaneously breathing adults

¹³². Capnography is commonly used in ALS CPR. Four main practical uses of capnography during CPR have been proposed:

- Assessment of CPR quality. This incorporates both the chest compressions, where studies have shown that increased chest compressions depth is associated with higher EtCO₂ ^{133,134} and measuring of the ventilation rate, in order to avoid hypo- and hyperventilation which has been discussed prior. It should be noted though that as capnography only measures the rate and not volume given, only ventilation rate-related hypo- and hyperinflation can be assessed.
- Detection of ROSC. Studies have found that EtCO₂ after ROSC can be higher than before ROSC, around 10 mmHg ^{135,136}. The timing of measurements and clinically usable levels remain unclear.
- Prognostication of outcome. As CO₂ is produced only by living cells, a very low (or absent) EtCO₂ should indicate widespread cell death. As such, a cut-off EtCO₂ value of 10 mmHg after 20 minutes has been proposed as a criteria for terminating CPR ¹³⁷. Later studies have found that survival is possible even with these low EtCO₂ values ¹³⁸. Capnography is also sensitive to other influences, such as airway potency, intrathoracic airway closure and chest compression quality. Therefore, it is not recommended to solely use capnography to prognosticate outcome during CPR
- Confirmation of ET placement in order to avoid oesophageal intubation. As EtCO₂ is produced in the lungs, even a low EtCO₂ indicates a tracheal intubation, and subsequently, no EtCO₂ readings indicates an oesophageal intubation. Although there are rare cases where there could be some CO₂ in the stomach, leading to false indications of tracheal intubation ¹³⁹, capnography is strongly recommended to use to confirm correct ET placement ¹⁴⁰.

On the issue of measuring ventilation during CPR

The art of measuring ventilation during CPR is a complicated and delicate procedure. First and foremost, it is a practical issue, SCA: are often very chaotic with many people involved in the various tasks surrounding the patient. This is especially evident in the beginning of the resuscitation process before the defibrillator has been set up, the airway managed, intravenous lines established and so on. To initiate an active registration of ventilation during this time is fraught with difficulties and is often (understandably) forgotten due to other more pressing tasks being prioritized. As such, measuring ventilation by

means of devices already in use during CPR is preferable. This probably serves as an explanation as to why capnography has been common for many years in SCA (as opposed to other ventilation associated measurements). As capnography is integrated in many modern manual defibrillators in use during ALS it can easily be incorporated in the standard CPR protocol. It should be mentioned though that there have been promising developments in this area in the last 10 years or so. One manual defibrillator on the market today comes equipped with an airflow sensor capable of measuring ventilation volume (Zoll X-series, Real BVM Help ©). A separate device for measuring volume and ventilation rate has also been developed and is available on the market, the (Archeon Medical EOLife). Devices like this could in theory enable measurements of volume to be included in standard CPR protocols the same way capnography is. If measuring ventilation is beneficial for the patient during CPR is unknown, but simulation studies have shown improvement in the ventilation while using ventilation feedback devices ¹⁴¹⁻¹⁴³. A clinical before and after study also found better compliance to pre-defined ventilation targets when using a feedback device ¹⁴⁴. More clinical research is needed and this is a developing area of research.

Once the ventilation data is collected, another issue arises when the data is analysed, namely the chest compression artefacts. For detailed analyses of ventilation parameters, they are often sampled at a high rate (>25 Hz) and compiled into a waveform for visual inspection. As the sensors measure flow, pressure and CO₂ changes in great detail, they are sensitive to changes in these. During a chest compression, air is pushed out of the chest, and during decompression, air is drawn in. This results in air going back and forth through the sensors at the rate of the chest compressions. This gives rise, to a varying degree, to sawtooth patterns in the waveform ⁷³ which can interfere both with the visual inspection of the waveform and make automatic extraction of individual parameters difficult, as the software designed to do this can struggle to identify the correct measuring points due to all the artefacts. The amplitude and frequency of the artefacts can vary due to airway seal and intrathoracic airway closure ¹³¹. Fig 10 shows an example of ventilation waveforms with and without chest compression artefacts. To extract accurate ventilation data, these artefacts need to be taken into consideration and be adjusted for.

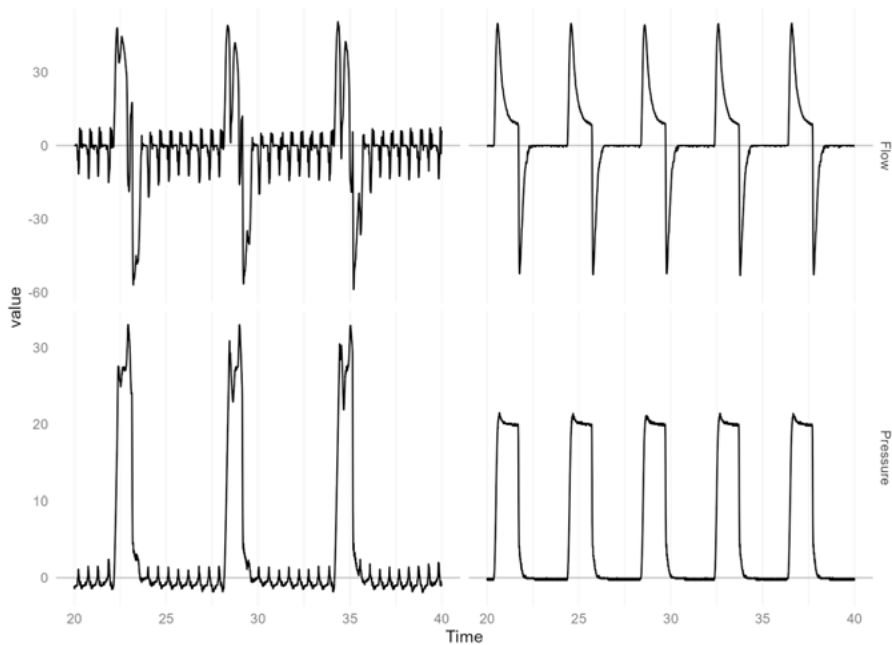


Fig 10. Ventilation waveforms signals of flow and airway pressure with compression artefacts (left) and without (right).

Animal models in CPR research

Due to the many inherent difficulties in performing prospective clinical CPR studies, especially those requiring invasive procedures, a large amount of the evidence that currently exists comes from pre-clinical studies in animal models. Some of the most seminal research in CPR concerning chest compressions and defibrillations were performed in animal models using dogs^{145,146}. In more modern CPR research, the most commonly used animal is the pig¹⁴⁷. The pig's internal anatomy shares many similarities with humans, making them suitable for use in experimental CPR research. The heart and lungs of the pig is very similar to humans with the coronary artery system being almost identical¹⁴⁸. In fact, the anatomy is so similar that transplants of heart and lungs from pigs to humans have been performed^{149,150}. There are differences of note in the context of CPR research, apart from the more obvious ones including the pigs body orientation, which is horizontal as opposed to human's vertical orientation. Regarding the respiratory anatomy and physiology, the pig's right lung has 4 lobes and the left three, compared to humans which have three lobes in the right lung and 2 in the left. Pigs also have an additional bronchus stemming from the trachea prior to where the trachea divides into the left and right main bronchi¹⁵¹. The thorax of the pig is also more triangular in shape, compared to that of humans which is flatter. The heart in pigs is as noted very similar to

humans, but with a slightly different shape, being more “heart shaped” compared to humans more trapezoidal shape, and with a more central and horizontal orientation in the thorax ¹⁵². As in all translational research, the differences between the species used in the research and their differences to humans are always important points of consideration.

Known unknowns

As is perhaps evident, there are many unanswered questions when it comes to ventilation during CPR. On the most fundamental level, it is unclear how ventilation is actually delivered during CPR; what tidal volumes are administered, and at what flow rates and pressure. The influence of chest compression on ventilation is also not fully understood, nor is the effectiveness of the given ventilations; do they reach the lungs and contribute to the gas exchange in a meaningful way. This thesis aims to explore these known unknowns and lay the foundation for future research to improve the treatment of patients suffering from SCA.

Unknown unknowns

Aims

The aim of this thesis was to explore and advance the understanding of ventilation during cardiac arrest and how it is measured. In the experimental setting by describing ventilation, haemodynamics and lung injuries in different ventilation modes, and in the clinical setting by measuring ventilation parameters during sudden cardiac arrest across different ventilation modes and airway methods.

The individual aims of the included studies in this thesis were as follows:

Study I: To investigate whether active decompression by means of a suction cup on a mechanical chest compression device aids chest recoil and improves haemodynamics and ventilation during CPR in an experimental porcine model.

Study II: To investigate differences in ventilation parameters, haemodynamics, blood gases and lung injuries in experimental CPR given as either continuous chest compressions and ventilations or 30:2 in a porcine model.

Study III: To develop and evaluate an algorithm to extract ventilation parameters from pneumotachography waveform data collected during ongoing simulated CPR.

Study IV: To present an extensive description of ventilation parameters during CPR given by ALS-providers and to compare them across different ventilation modes and airway modalities.

Methods

The measurements in study II-IV in this thesis share the same basis when it comes to ventilation parameters of interest and the devices used to capture these. They will be described below before the methodologies of the individual studies are addressed.

Ventilation parameters

A parameter is defined as: “*any of a set of physical properties whose values determine the characteristics or behaviour of something*”¹⁵³. In the included studies, the ventilation parameters are the quantification of the different measurements describing the ventilation. The definition of the included ventilation parameters can be seen in Table 1. Of note is that in this thesis, inspiratory refers to process of supplying gas to a subject (inhalation in normal breathing), and expiratory refers to gas coming from the subject (exhalation in normal breathing).

Table 1. Definitions of ventilation parameters

Parameter	Abbreviation	Unit	Definition
Inspiratory tidal volume	V _{ti}	ml	Total inspired volume during one ventilation
Expiratory tidal volume	V _{te}	ml	Total expired volume during one ventilation
Inspiratory minute volume	M _{vi}	ml	Total inspired volume during one minute
Expiratory minute volume	M _{ve}	ml	Total expired volume during one minute
Duration of inspiration	T _i	Sec	Duration of positive flow during one ventilation
Duration of expiration	T _e	Sec	Duration of negative flow during one ventilation
Peak inspiratory flow	PIF	L/min	Highest measured inspiratory flow during one ventilation

Peak inspiratory pressure	PIP	cmH ₂ O	Highest measured inspiratory pressure during one ventilation
Ventilation frequency	Freq	n/min	Number of ventilations per minute
Peak expired carbon dioxide	PECO ₂	mmHg	Highest measured CO ₂ during expiration

Pneumotachograph

The ventilation parameters in Study II-IV, with the exception of the PECO₂, were measured using a pneumotachograph (Fluxmed GrH, Mbmed, Buenos Aires, Argentina). A pneumotachograph is a differential pressure flowmeter and works on the principle of Hagen-Poiseuille's law, which states that in a fluid with laminar flow, the flow rate is proportional to the pressure drop over a resistive element. In practice, the pneumotachograph measures pressure during gas flow on different sides of a mechanical resistance in a hollow tube. By comparing these pressure readings, a calculation of flow can be made¹⁵⁴. The Fluxmed GrH uses a sample rate of 256 Hz, allowing for very precise measurements of flow and pressure over time. In this thesis, the tube (called flow sensor) was connected between the self-inflating bag and the airway device. A schematic illustration of the general workings of the flow sensor can be seen in Fig 11.

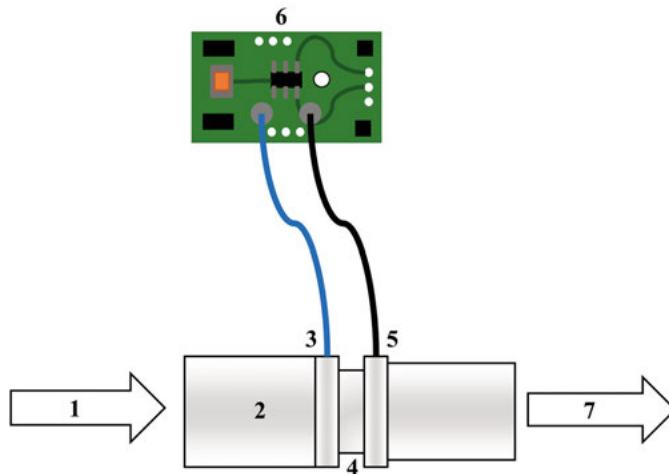


Fig 11. Schematic illustration of a pneumotachograph (not to scale). 1: Gas flow from self-inflating bag, 2: Flow sensor, 3: Pressure reading prior to resistance, 4: Resistance (narrowing of the tube), 5: Pressure reading after resistance, 6: Pressure sensors on a circuit board, 7: Gas flow to airway device

Capnograph

A capnograph measures the partial pressure of CO₂ (the proportion of total gas pressure that is exerted by carbon dioxide) based on the principle that CO₂ absorbs infrared light at a specific wavelength, 4.3 μm. By passing infrared light through expired air and measuring how much of it is absorbed before reaching a sensor, the concentration of CO₂ can be measured. This can be achieved in two ways, either by actively drawing a small volume of gas from the respiratory circuit into a sensor unit (side stream capnography) or by placing the sensor directly into the respiratory circuit, (mainstream capnography)¹⁵⁵, which was the method utilized in the studies of this thesis where the mainstream sensor was connected to the flow sensor of the pneumotachograph and placed between the self-inflating bag and the airway device.

In the included studies, the pneumotachograph and capnograph were connected to a portable computer, where numerical data of flow, pressure and CO₂ in 256 Hz was stored and could later be shown as waveforms. The assembled devices were housed in a bag to aid portability and ease of use. See Fig 12.

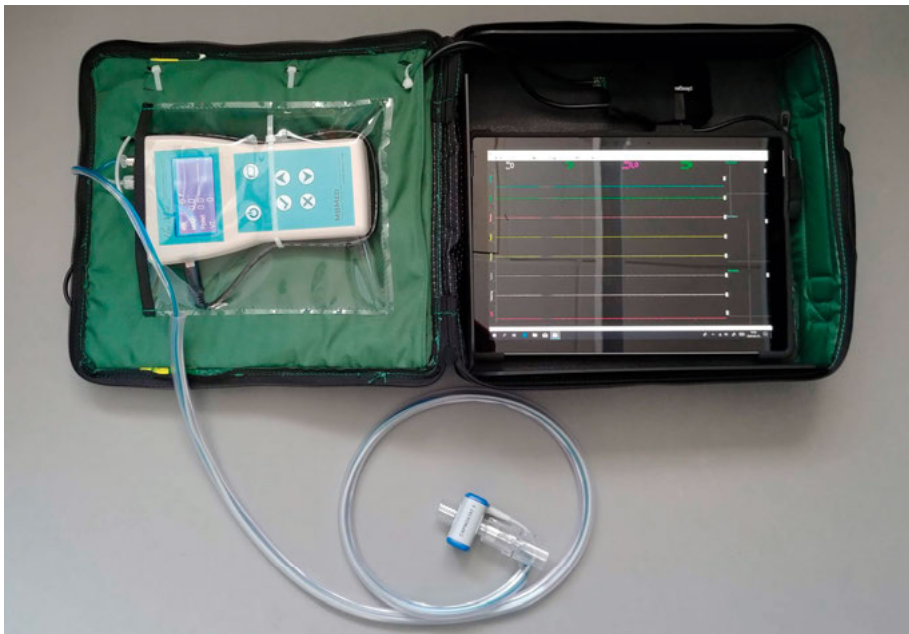


Fig 12. The setup of the devices used in the studies underlying this thesis

Individual study designs and methodologies

Study I and II

Study I and II were both experimental animal studies using pigs. Study I aimed to explore the effects of a suction cup on a mechanical chest compression device on haemodynamics and ventilation during experimental CPR. Study II aimed to compare ventilation and haemodynamics between CPR performed continuously or in the 30:2 mode. They shared the same ethical approval from the Animal Ethics Board in Uppsala, Sweden (Dnr. 5.8.18-05377/2021). They were conducted using the ARRIVE 2.0 guidelines and checklist ¹⁵⁶. Both studies were conducted at the Hedenstierna laboratory (Uppsala university, Sweden).

Animals

The pigs used were of the Norwegian landrace/Yorkshire/Hampshire mixed breed and aged 2-5 months. They were raised at a local, commercial pig farm which meant a relatively short transport from the farm to the laboratory. Prior to the start of the experiment, they were kept fasting for 12 hours with free access to water. All the pigs arrived in the morning to the laboratory.

Preparation

The preparation in both studies were the same. At arrival, the pigs were first weighed inside their transport box. After that they were anesthetized with a subcutaneous injection of tiletamine (6 mg/kg) and zolazepam (2.2 mg/kg). The pigs were left undisturbed for 5-10 minutes before checking that the anaesthesia was deep enough. If so, the pigs were placed supine on an operating table connected to ECG and SpO₂ monitoring and an ear vein was cannulated in order to first give a bolus of fentanyl (10-20 µg/kg) and then to maintain anaesthesia throughout the preparation and experiments. This was done with a continuous infusion of ketamine (30 mg kg⁻¹ h⁻¹), midazolam (0.1 mg kg⁻¹ h⁻¹) and fentanyl (3.75 mg kg⁻¹ h⁻¹). After ensuring that the anaesthesia was deep enough to prevent a response to painful stimuli, a bolus, followed by a continuous infusion, of rocuronium was administered (50 mg and by 0.15 mg kg⁻¹ h⁻¹). To prevent dehydration a continuous infusion of Ringer's acetate was administered at 30 ml kg⁻¹ h⁻¹. An incision was made to access the urinary bladder, in which a urinary catheter was placed.

The pigs were tracheotomized and an ET was inserted. During the preparation they were mechanically ventilated in volume-controlled mode with V_t 6-8 ml/kg, respiratory rate 25, inspiratory: expiratory ratio 1:2, FiO₂ 0.5 and PEEP 5 cmH₂O. After surgical preparations for the monitoring (described below)

was finished, the animals were left to rest for at least 30 minutes before the start of the experiment.

Monitoring

Study I: In order to facilitate aortic pressure (AP) measurement, a neck artery was dissected and a catheter was placed and advanced to the ascending tract of the aortic arch. On the same side a catheter was placed in the internal jugular vein for the purpose of central venous pressure (CVP) measurement. On the pig's forehead, the cranial parietal region was shaved and an incision was made to expose the parietal bone, where a hole was drilled to place an intracranial pressure (ICP) sensor. Lastly, defibrillator pads were placed.

Study II: Monitoring in study II was similar to study I, with the exception of ICP, and with the addition of a secondary femoral artery line to enable blood gas sampling without interfering with the AP measurement.

Protocol

Study I: The animals were randomized into two groups. One group received chest compressions with a LUCAS 3 chest compression device with suction cup (suction cup group) and the other group received chest compressions with the device without the suction cup (No-suction cup group). In the suction cup group, the edges of the cup were glued to the animal's thorax in order for it to stay adhered to the skin, as it does in humans. In the no-suction cup group, the compressions were done directly by the piston of the device, without a suction cup mounted.

To induce VF, two needles were placed subcutaneously on the chest, creating a line passing through the animal's heart. A device then delivered an alternating current (80 V-500 VA) through the heart. VF was verified by the absence of an AP and a VF on the electrocardiogram. The animals were left untreated for 3 minutes before CPR started. It was administered with 30:2 at a rate of 102/min. Ventilation was performed by the same person in all animals. Ventilation was done manually with a bag on the respiratory circuit which the animals remained connected to with 100% O₂. During the experiment, haemodynamics, NIRS, ICP, PbtO₂ and ventilation were sampled continuously. After 18 minutes an adrenaline bolus of 0.5 mg was administered and after 20 minutes a defibrillation with 150 J was given, followed by 2 minutes of CPR and then another defibrillation. If no ROSC was detected after 3 defibrillations the animal was declared dead. If ROSC was achieved the animal was observed and monitored for 60 minutes, followed by euthanasia by an injection of

potassium chloride. Autopsy was then performed to assess CPR related injuries. A trial flowchart with a timeline can be seen in Fig 13.

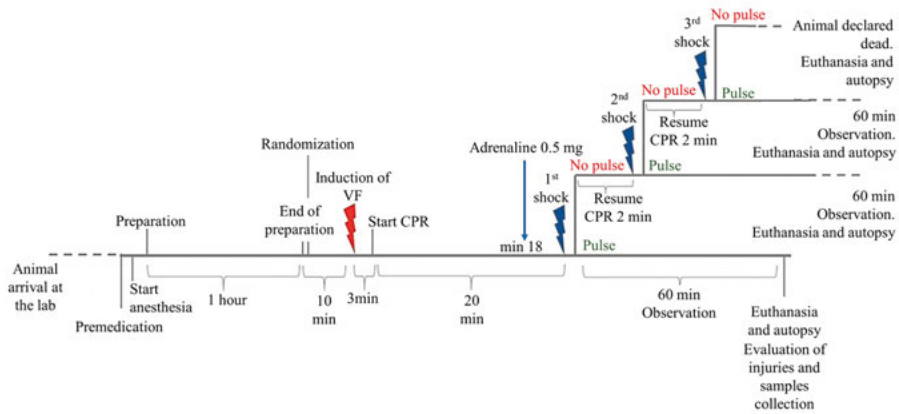


Fig 13. Timeline of the protocol. Abbreviations: CPR; cardiopulmonary resuscitation, VF; ventricular fibrillation

Study II: The animals were randomized into two groups. One received ventilations during CCC (CCC group) at 10/min. The other group received 30:2 CPR with two ventilations given during the pause of compressions. In the CCC group, a timer was used to give a signal every 6th second to indicate when the ventilation was to be given. Both groups received chest compressions from the LUCAS 3 device, in the CCC group it was set to continuous mode and in the 30:2 group to 30:2 mode. The compressions were given with a rate of 102/min. The suction cup’s edges were glued to the thorax of the animals. Before induction of VF a baseline blood gas sample was taken.

VF was induced the same way as in study I. After 3 minutes of VF CPR and ventilation was started according to the randomization and continued for 20 minutes. Ventilation was given manually with a self-inflating bag and Flux-med GrH was used both to record ventilation parameters and to guide the ventilation by providing real time information on the given tidal volume. The goal was for every ventilation to be as close to 8 ml/kg as possible. During the experiment, haemodynamics and ventilation was sampled continuously. Every 5th minute a blood gas sample was taken. After 20 minutes of CPR, the animals were euthanized with an injection of potassium chloride. Once the animals had been declared dead a post mortem analysis was performed. Injuries to the skin, airway and ribs were noted. This was followed by the removal of the heart and lungs in block. The lungs were visually inspected and the

occurrence of macroscopic signs of atelectasis, hyperinflation and haemorrhages were recorded. After this two samples were taken from 5 locations on each individual lung (left and right paracardiac region, upper ventral lobe, upper dorsal lobe, lower ventral lobe and lower dorsal lobe). The first set of samples were used to assess oedema by wet-dry ratio. The samples were weighed, then put in a 37 degrees oven for one week after which they were weighed again. The other set of samples were put in formaldehyde and sent to a pathologist at the National veterinary institute (SVA, Uppsala, Sweden) where they were analysed using microscopy. The pathologist graded the extent of atelectasis and hyperinflation and signs of oedema and microscopic haemorrhages. The timeline of the protocol can be seen if Fig 14.

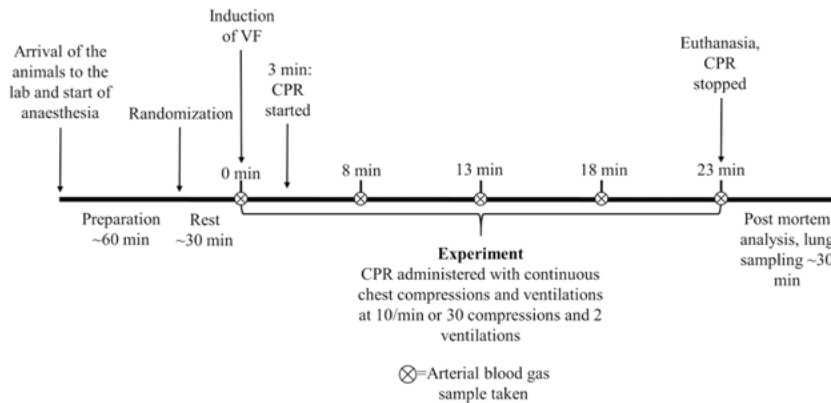


Fig 14. Timeline of the protocol. Abbreviations: CPR; cardiopulmonary resuscitation, VF; ventricular fibrillation

Collected data and data curation

Study I

- EtCO₂ – mmHg
- Aortic pressure (AP) – mmHg
- Coronary perfusion pressure (CPP) (calculated from aortic and venous pressure at the end of the decompression phase) – mmHg
- Cerebral perfusion pressure (CerPP) (calculated from aortic pressure and ICP at the end of the decompression phase) – mmHg;
- Compression and decompression (or peak and nadir) aortic pressure – mmHg;
- Central venous pressure (CVP) – mmHg
- Intracranial pressure (ICP) – mmHg
- Vti during CPR – ml

AP, CVP and ICP were sampled 100 times per second. Tidal volume and EtCO₂ were registered for each individual breath. For hemodynamic data, the experiment was divided into 4 timeframes and a mean value for each parameter was calculated for each individual timeframe.

AP, CVP and ICP were recorded at three different points of the curve at every compression/decompression cycle: peak pressure, nadir pressure and the end of decompression. The CPV and ICP pressure recorded at the end of decompression was used to calculate CPP and CerPP with the following formulas:
 $CPP = AP - CVP$ and $CerPP = AP - ICP$

Study II

- PIP
- Max and min Arterial pressure (maxAP, minAP)
- Max and min Central venous pressure (maxCVP, minCVP)
- Coronary perfusion pressure (CPP)
- V_{ti}
- T_i
- MV_i
- PECO₂
- PIF
- Arterial blood gases (ABG)
- Changes over time in haemodynamics, PECO₂ and ABG during the experiment
- Oedema assessed by wet-dry ratio
- Histopathological assessment of the lungs (atelectasis, oedema and hyperinflation)

For analysis of ventilation parameters from the waveform data from the Fluxmed GrH, a R-script was made to extract the peak value of these parameters for each ventilation, as well as the duration of the inspiration. MV_i was calculated as $V_{ti} * ventilations \cdot min^{-1}$. PECO₂ was used as a proxy for EtCO₂.

AP and CVP were recorded at 125 Hz. For these parameters, two timepoints were identified and the values there recorded using a Matlab script; Maximum compression (maxAP and maxCVP) and maximum decompression (minAp and minCVP). The values at maximum decompression were used to calculate CPP; $minAP - minCVP$. For both the ventilation parameters and

hemodynamic parameters, a mean value was calculated for each minute of the experiment (20 in total) and used for the statistical analysis.

Statistical analysis

Both studies used an online randomization tool to assign the animals to the different study groups¹⁵⁷.

Study I: Data analysis was performed using Prism 8.0 (GraphPad Software ©).

Normality was verified with the Shapiro-Wilks test and parametric data was presented with mean and standard deviation (SD). Non-parametric data was presented as median and range. Comparisons of the overall differences between groups was performed with a mixed model ANOVA for repeated measures. For comparisons of differences between the individual timeframes, multiple t-tests for parametric data and with Wilcoxon's test for non-parametric data was used. Multiple comparisons were adjusted using Bonferroni-Dunn correction. Correlations were investigated using Pearson's test with a correlation coefficient of 95% confidence interval (CI) and r being presented. A sample size of 16 was calculated as being sufficient to detect a 5 ± 1.6 mmHg difference in EtCO₂ between the groups (α error 0.05, β error 20%). A p-value of <0.05 was considered significant.

Study II: Statistical analysis was performed using SPSS 28.0 (IBM ©).

Baseline and post-mortem values were analysed using Mann-Whitney U test for continuous variables and Fisher's exact test for dichotomous variable. Descriptive statistics were presented as n for categorical variables and median and interquartile range (IQR) for continuous variables. The multiple comparisons of lung tissue samples were adjusted using Bonferroni correction.

Mean values throughout the experiment and changes over time were analysed using linear mixed models with time as a repeated measures and CPR mode, time and CPR mode-time interaction as fixed factors. First order ante dependence was chosen as the covariance structure as it gave the best model fit according to Akaike's information criterion (AIC) in a majority of the models. The mean values, confidence intervals and p-values presented were taken from the models estimates. Correlations were analysed using Pearson's test. A p value of <0.05 was considered significant.

Study III

Study III was an experimental algorithm development study with the aim of developing an algorithm capable of extracting accurate ventilation parameters

from ventilation waveform data in the presence of chest compression artefacts. A further aim was to achieve a robust enough algorithm that it could be used in the analyses of clinical data in Study IV. This was necessary as the proprietary software included with the Fluxmed GrH (Fluxreview, in Study III called the standard method) struggled due to the presence of chest compression artefacts in the waveforms. Two sets of ventilation data were used in the study to develop and evaluate the performance of the algorithm. The primary dataset came from an experimental setup and the secondary came from clinical data collected for Study IV. As such this data collection was approved under Swedish Ethical Review Authority approval Dnr. 2018/531 and the Medical Ethics Review Committee of Amsterdam UMC approval number 2023.0998.

Data collection

The primary dataset came from an experimental setup using ventilators (Maquet Servo-i or Maquet Servo-u, Getinge, Gothenburg, Sweden) connected via a respiratory circuit to a test lung (Smartlung Adult, IMT. Analytics, Buchs, Switzerland) with the Fluxmed GrH inserted between the ventilator and the test lung, see Fig 15.

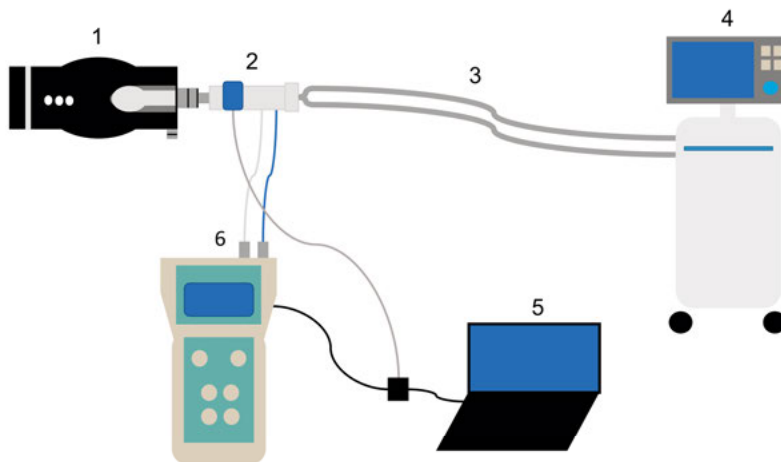


Fig 15. A schematic illustration of the experimental setup used (not to scale). 1: Test lung, 2: Flow sensor and capnograph, 3: Respiratory circuit, 4: Ventilator, 5: Portable computer, 6: Pneumotachograph device.

The ventilators were used to give ventilations with known V_{ti} , V_{te} , PIP and Freq. These ventilations were registered by the Fluxmed GrH, resulting in waveform signals on which the algorithm was tested and evaluated with the

aim of being able to extract values of the mentioned parameters matching the values of the ventilators as closely as possible. In order to evaluate a wide range of the included parameters, different settings were used on the ventilators. Tidal volumes between 177 and 612 ml, pressures between 12 and 45 cmH₂O and ventilation rates between 10 and 30 per minute. Both volume-controlled and pressure-controlled modes were used. In order to simulate chest compressions, the test lung was compressed at a rate of 110 compression per minute. To maintain the correct rate, a metronome was used. The test lung was compressed in such a way that the compression artefacts on the waveform signals visually resembled those observed in human data. Ventilations were either given asynchronous to the chest compressions or synchronous in the 30:2 mode. Airway leakage was also simulated with the built-in leakage regulator on the test lung.

The secondary dataset was used for manual fine tuning of the selected threshold parameters (described further down). As this data was taken from Study IV, the methodology of that data collection is described in detail under Study IV.

Algorithm development

For the development of the algorithm R v. 4.4.2. (R Foundation for Statistical Computing, Vienna, Austria) was used. The basis for the ventilation detection (meaning when to start the measuring of a ventilation) was sustained airway pressure over a given period of time. Fig 16 illustrates this as the red rectangle with the dimensions AB. These dimensions must be large enough to exclude compression artefacts and as small as possible as to not exclude smaller ventilations. As the pressure increase used for ventilation detection is not instantaneous, the start of the ventilation was defined as beginning slightly before the start of the red rectangle, in order to capture as much of the airflow as possible from the actual ventilation (line C in Fig 16.) To further prevent inclusions of compression artefacts as ventilations, the ventilation process was divided into two phases, an active and an inactive phase where the active phase represents when an actual ventilation is given, and the following expiration. The inactive phase represents when no active ventilation is given. In Fig. 16, the active phase is shown on the waveforms as turquoise and the inactive phase as red. The end of the active phase was defined as the first time point at which both the absolute flow rate, averaged over one second, was reduced below a given threshold, and the ventilation pressure was below the pressure threshold A (line D). As CPR causes absolute flow rates to be continually elevated, the absolute flow rate was calibrated by subtracting the minimum flow rate value, measured in the first 6 s after the start of the active ventilation (to prevent periods of CPR cessation in synchronous compression regimes

from being used as the baseline). To ensure complete capture of expiratory volume, the end of the active ventilation phase was extended by a fixed delay beyond point D (line E). Inspiratory volume was calculated as the sum of positive flow during the active phase and the expiratory volume as the sum of negative flow during the active phase.

In order to select a combination of values for the above-mentioned parameters that minimized the average standardized absolute deviation from the ventilator settings of V_{ti} , V_{te} , PIP and Freq, a grid search was performed across a range of potential of values. Each measure was weighted equally by standardizing the absolute deviation from the ventilator setting based on the standard deviation of the measure from all of the test runs. Based on visual inspection of the waveforms prior, a lower limit of ventilation duration was set at 0.3 seconds in order to prevent counting multiple chest compressions as ventilations within the active phase.

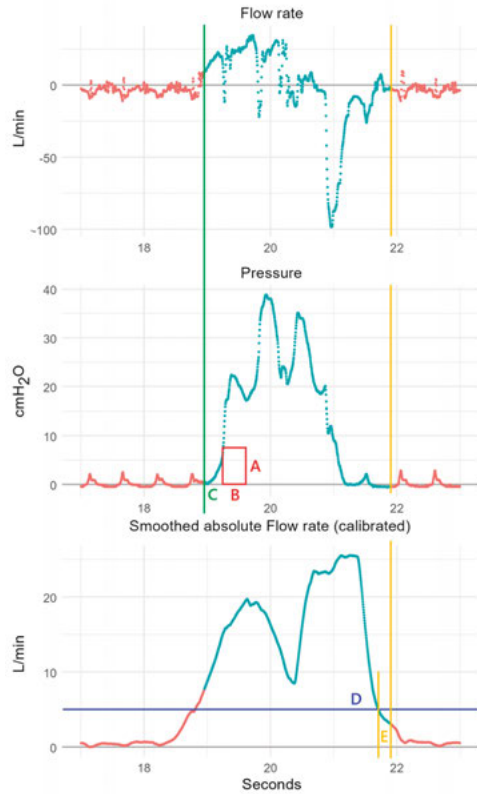


Fig 16. Ventilation waveform and algorithm parameters.

The parameters selected after the grid search was then applied to the dataset from Study IV and reviewed for face validity. Twenty randomly selected patients were reviewed. After this review it was evident that due to the apparent size of chest compression artefacts in the clinical data, the pressure threshold and the absolute flow threshold identified as optimal in the experimental data were too low. As such, a higher value of pressure and absolute flow threshold than those identified in the grid search were selected to be used in the evaluation of the algorithm. The evaluated parameters can be seen in Table 2 with corresponding letters in Fig 16.

Table 2. Parameters evaluated in the grid search

	Parameter name	Grid search parameter values	Optimized parameter values	Manually adjusted parameter values
A	Pressure threshold	1, 2, 5, 8, 10 cmH ₂ O	2	8*
B	Pressure duration	0.1, 0.2, 0.3, 0.4, 0.5 seconds	0.3	0.3
C	Ventilation lead	0, 0.1, 0.2, 0.3, 0.4, 0.5 seconds	0.1	0.3
D	Absolute flow threshold	-1 (no inactive phase), 1, 5, 10 litres per minute	1	5*
E	Inactive delay	0, 0.1, 0.2, 0.3 seconds	0.2	0.2

* Values held constant upon assessment of algorithm in clinical data set

Code to capture PECO₂ was also included in the algorithm, but not evaluated in the experimental dataset. PECO₂ is defined as the maximum value of CO₂ measured at any time during either the active or inactive phase. A delay parameter was included to prevent the final expired CO₂ to be attributed to the subsequent ventilation.

Statistical analysis

After the grid search and manual adjustments, the algorithm was evaluated compared to the known ventilator settings at the individual ventilation level. The clinical data, lacking known values, could not be used for the statistical evaluation. Median values, IQR and percentage error using the Bland-Altman method was used to describe differences between the algorithm and the ventilator settings. Visual comparisons were also made between the algorithm and the standard methods

Study IV

Study IV was a multicentre, observational cohort study (the Cardiac Arrest ventilation trial, CAvent) with the overall aim of describing how manual ventilation is given by ALS-providers during SCA and also to compare ventilation between different CPR modes and airway modalities. Ethical approval was granted by the Swedish Ethical Review Authority (Dnr. 2018-531) and the Medical Review Committee of Amsterdam UMC (approval number 2023.0998). The study was conducted in accordance to the declaration of Helsinki. In Sweden, informed consent was required for survivors of IHCA,

otherwise not. In the Netherlands no informed consent was required but deferred consent was obtained for demographic data.

Participants

Inclusion were performed in five different medical systems, shown in detail in Table 3. They all provided their service 24/7 in their respective area. Eligible participants for inclusion were adults > 18 years old with SCA treated with CPR by the ALS providers in the including medical systems. Exclusion criteria were obviously pregnant women. Staff in the including system were encouraged to include all SCA patients eligible for inclusion but it was up to them to decide if inclusion was feasible or not depending on the situation and available resources. Prior to the start of inclusions, the staff of the including systems were trained in the use of the study devices (as shown in Fig 12). Inclusions ran between May 2019 and August 2025.

Table 3. Including medical systems

Name and place	Population served (approx.)	Type and role	Staff
Uppsala EMS, Uppsala, Sweden	400 000	EMS. Primary care during OHCA	Two nurses or one nurse and one assistant nurse (usually one specialized nurse)
Capio AB rapid response cars, Stockholm Sweden	2 500 000	Non-transporting EMS vehicle. Support to regular EMS during all OHCA	Anaesthesiologist and specialized nurse
Ambulance Amsterdam EMS, Amsterdam, The Netherlands	896 000	EMS, primary care during OHCA	Nurse and driver
Lifeline 1, Amsterdam, The Netherlands	2 950 000	HEMS. Support to regular EMS during OHCA	Helicopter pilot, ambulance driver, HEMS nurse and HEMS physician
Falun hospital emergency team, Falun, Sweden	285 000	In-hospital emergency team. Support to regular staff at hospital wards during IHCA and	Medical physician, anaesthesiologist and nurse anaesthetist

Abbreviations: EMS; emergency medical services, HEMS; helicopter emergency medical services, IHCA; in hospital cardiac arrest, OHCA; out of hospital cardiac arrest

Data sources and management

Ventilation waveform data from each inclusion was visually reviewed by three of the study's authors. This was done in order to ensure inclusion of data of sufficient quality for further analysis and to exclude data with poor quality, such as due to sensor obstruction or device malfunction. The included cases were then checked for periods of ongoing CPR based on chest compression artefacts in the flow, pressure or CO₂ waveforms. These periods were then further divided into groups based on the ventilation mode used, asynchronous or synchronous. One minute of one mode was used as the minimum duration for inclusion into either group. Patients who received more than one ventilation mode were for, the patient characteristics data, assigned into the mixed group. If available, defibrillator data was also used to assist the group assignments. The ventilation waveform data was then analysed with the algorithm developed in Study III in order to extract the ventilation parameters of interest. This yielded flow, pressure and CO₂ based data.

Patient data and additional data concerning the SCA and the care given was acquired from case report forms, electronic medical records, the Swedish Cardiac Arrest Registry and the Amsterdam Resuscitation Studies registry.

Study variables

For analysis, ventilation mode (synchronous and asynchronous) as well as airway modalities (BVM, SAD and ET) were considered independent variables. Dependent variables were V_{ti}, V_{te}, difference between V_{ti} and V_{te} (V_{diff}), T_i, T_e, PIP, duration of airway pressure above 30 cmH₂O (PAW > 30 cmH₂O) PIF, PECO₂, Freq, MV_i and MVe. Additional calculated dependent variables used were ratio of V_{ti} and ideal tidal volume (V_{ti}/I_{tv}) where ideal tidal volume was calculated as 6 ml/ kg⁻¹ IBW^{158,159}, and estimated lung ventilation (ELV) which was defined as V_{te}-estimated anatomical dead space (2.2 ml/ kg⁻¹ IBW). All of the variables were measured per ventilation except Freq, MV_i and MVe which were measured per minute

Statistical analysis

The Statistical analysis was performed with SPSS 30.0 (IBM ©). Patient base-line characteristics were presented descriptively with categorical variables shown as frequencies (n) and percentages (%). Continuous variables were shown as medians and IQR.

A linear mixed effect model was used to analyse the ventilation parameters with ventilation mode and airway modality as fixed effects and patient as a random effect. Covariates were sex, age and BMI. Due to missing data in the covariates, multiple imputations were employed with five imputations being used. Mean values, confidence intervals and p-values were derived from the imputed models fixed effect estimates. For changes of ventilation parameters over time, overall time was divided into minutes and included in the model along with time*ventilation mode interaction as fixed effects. A p-value of <0.05 was considered significant. As the study had a descriptive approach, no power calculation was performed a priori.

Results

Study I

In study I, 16 pigs aged 2-3 month were included and randomized into equally sized groups (suction cup group and no suction cup group). The weight range of the included pigs were 27.2-32.8 kg. Due to technical difficulties, two animals had no EtCO₂ measurements. Prior to the start of the experiment, baseline values of hemodynamic and ventilation parameters were sampled and were found to be similar in the two groups.

EtCO₂ and ventilation

No differences between the groups were found in neither EtCO₂ (shown in Fig 17.) nor V_{ti} (292 ml in the suction cup group vs. 282 ml in the no suction cup group).

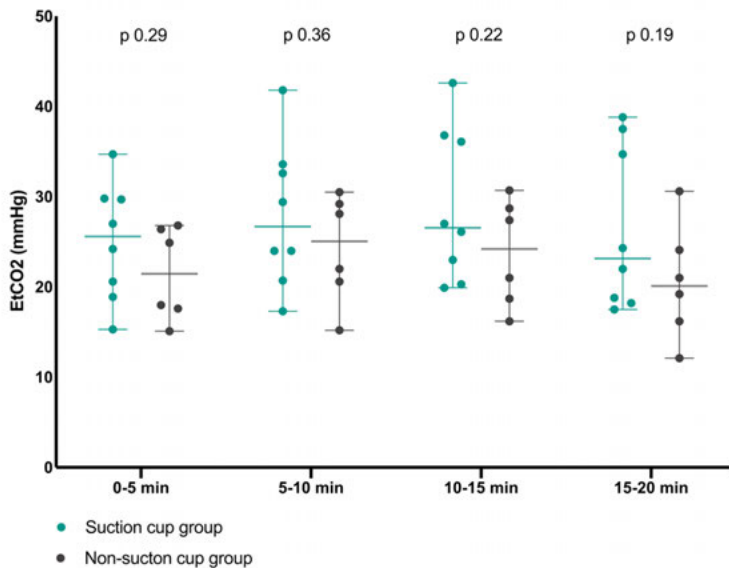


Fig 17. Differences in EtCO₂ between the groups in the different timeframes presented as means per individual in the different timeframes (dots), overall means (middle lines) and 95% CI (whiskers).

Passive Vti caused by the chest compressions were present in the ventilator waveform data, and it was similar in both groups with 40 ml/compression cycle in the suction cup group and 34 ml/compression cycle in the no suction group. Passive Vti correlated negatively with EtCO₂ when divided into the different timeframes (r=0.47, p=0.0004).

Haemodynamics

Measurements of AP, CVP and ICP at peak, nadir and end of decompression in the two groups and in the different timeframes are shown in Table 4. AP was higher at the end of decompression in the suction cup group in timeframe 0-5 minutes. Nadir CVP was lower in the suction cup group in all timeframes.

Table 4. Mean values ± standard deviation of AP, CVP and ICP at peak, nadir and end of decompression in the different groups and in the different timeframes

0-5 min			
	Suction cup	No suction cup	p-value
Peak AP	119 ± 63	94 ± 32	0.4
Nadir AP	11 ± 9	1 ± 14	0.13
End AP	31 ± 4	27 ± 4	0.04 *
Peak CVP	85 ± 96	126 ± 67	0.42
Nadir CVP	2 ± 4	6 ± 2	0.02 *
End CVP	10 ± 4	15 ± 2	0.06
Peak ICP	31 ± 5	26.7 ± 5	0.8
Nadir ICP	8 ± 5	8 ± 4	0.95
End ICP	10 ± 5	10 ± 4	0.63
5-10 min			
	Suction cup	No suction cup	p-value
Peak AP	100 ± 48	81 ± 25	0.38
Nadir AP	10 ± 9	2 ± 10	0.21
End AP	25 ± 9	23 ± 5	0.69
Peak CVP	65 ± 67	104 ± 47	0.27
Nadir CVP	0.3 ± 4	6 ± 2	0.01 *
End CVP	10 ± 5	13 ± 6	0.48
Peak ICP	26 ± 4	24 ± 4	0.56
Nadir ICP	6 ± 5	6 ± 7	0.9
End ICP	8 ± 5	11 ± 4	0.38

10–15 min			
	Suction cup	No suction cup	p-value
Peak AP	92 ± 44	74 ± 23	0.42
Nadir AP	8 ± 8	1 ± 11	0.22
End AP	23 ± 9	22 ± 6	0.77
Peak CVP	60 ± 60	95 ± 39	0.25
Nadir CVP	-2 ± 4	6 ± 2	0.003 **
End CVP	10 ± 5	12 ± 6	0.47
Peak ICP	24 ± 15	23 ± 16	0.89
Nadir ICP	5 ± 4	8 ± 2	0.06
End ICP	8 ± 5	11 ± 3	0.2

15–20 min			
	Suction cup	No suction cup	p-value
Peak AP	85 ± 42	74 ± 29	0.62
Nadir AP	8 ± 8	5 ± 10	0.54
End AP	23 ± 8	21 ± 6	0.75
Peak CVP	53 ± 49	86 ± 35	0.21
Nadir CVP	3 ± 3	7 ± 2	0.01 *
End CVP	9 ± 6	13 ± 6	0.31
Peak ICP	23 ± 18	22 ± 8	0.71
Nadir ICP	6 ± 5	9 ± 4	0.28
End ICP	8 ± 5	11 ± 3	0.19

* p-value <0.05, ** p-value <0.01. Unit of measurement mmHg. Abbreviations: AP; arterial pressure, CVP; central venous pressure, ICP; intra-cranial pressure

CPP was higher in the suction cup group during the first, second and fourth timeframe. CerPP was also higher in the fourth timeframe in the suction cup group as shown in Fig 18.

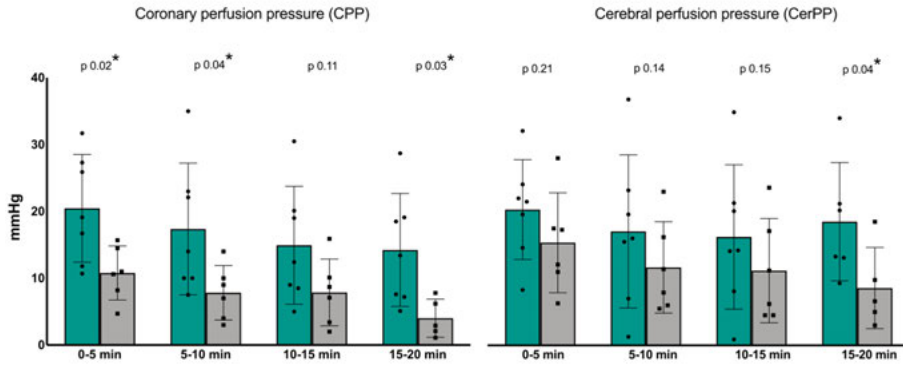


Fig 18. Differences of CPP and CerPP in the groups and different timeframes. Green: suction cup group, Grey, no suction cup group

Study II

Eighteen pigs were initially included and randomized into equally sized groups (CCC group or 30:2 group). Two animals, one in each group, experienced a total collapse of circulation early on during the experiment and was excluded. Autopsy later revealed rupture of the vena cava to be the cause of the bleeding in both the animals. Subsequently, eight animals in each group were included in the analysis. The included pigs were aged 3-5 months and their weight range was 28.7-41.8 kg and there were no differences in the baseline characteristics between the groups.

Ventilation parameters, haemodynamics and ABG

In the CCC group, PIF, PIP, MV and pH were higher while PECO₂ and PaCO₂ were lower compared to the 30:2 group. The full comparisons between the groups can be seen in Table 5.

Table 5. Comparisons of study parameters in the different groups

Parameters	CCC	30:2	Difference (95% CI)
	Mean (95% CI)	Mean (95% CI)	
PIF (L/min)	76.3 (72.2-80.5)	51.7 (47.6-55.9)	18.7-30.4
PIP (cmH₂O)	58.6 (54.7-62.5)	35.1 (31.2-38.9)	18.0-29.0
Vti (ml)	221.5 (206.8-236.3)	221.4 (206.6-236.2)	-20.8-21.0
Vti (ml/kg)	6.8 (6.5-7.2)	6.4 (6.1-6.8)	-0.1-0.9
MV (ml)	2190 (2061-2318)	1267 (1136-1398)	738.7-1106
PECO₂ (mmHg)	28.6 (22.3-34.8)	39.4 (33.1-45.6)	-19.7 -2.0

CPP (mmHg)	10.0 (2.5-17.4)	15.2 (7.7-22.6)	-15.7-5.3
maxAP (mmHg)	132.4 (94.9-170.0)	108.7 (71.2-146.3)	-29.4-76.8
minAP(mmHg)	-4.8 (-10.7-1.0)	-3.2 (-9.1-2.6)	-9.9-6.7
maxCVP (mmHg)	169.5 (146.3-192.7)	146.4 (123.3-169.5)	-9.6-55.9
minCVP(mmHg)	1.3 (-5.2-7.7)	5.0 (-1.3-11.3)	-12.7-5.3
PaO₂ (mmHg)	141.7 (86.2-196.8)	156.0 (103.4-208.6)	-90.4-61.8
PaCO₂ (mmHg)	50.2 (44.2-56.2)	61.1 (55.5-66.7)	-19.1--2.7
Lactate (mmol/L)	5.6 (5.0-6.3)	5.4 (4.8-6.0)	-0.7-1.1
pH	7.3 (7.2-7.3)	7.2 (7.2-7.3)	0.01-0.1

Abbreviations: AP; arterial pressure, CPP; coronary perfusion pressure, CVP; central venous pressure, MV; minute volume PaCO₂; partial pressure of arterial carbon dioxide, PaO₂; partial pressure of arterial oxygen, PECO₂; peak expired carbon dioxide PIF; peak inspiratory flow, PIP; peak inspiratory pressure, Vti: inspiratory tidal volume

PIP correlated positively with CVP ($r=0.546$, $p=0.029$) and PIP and PECO₂ correlated negatively ($r=-0.659$, $p=0.005$).

Changes over time

CPP, maxAP, maxCVP and pH decreased over time while PaCO₂ and lactate increased over time in both groups (all $p < 0.001$). The changes in PaO₂ during the experiment were not significant ($p=0.064$). When comparing the two groups, maxCVP decreased more over time in the 30:2 group. The changes over time and comparisons between the groups can be seen in Fig 19.

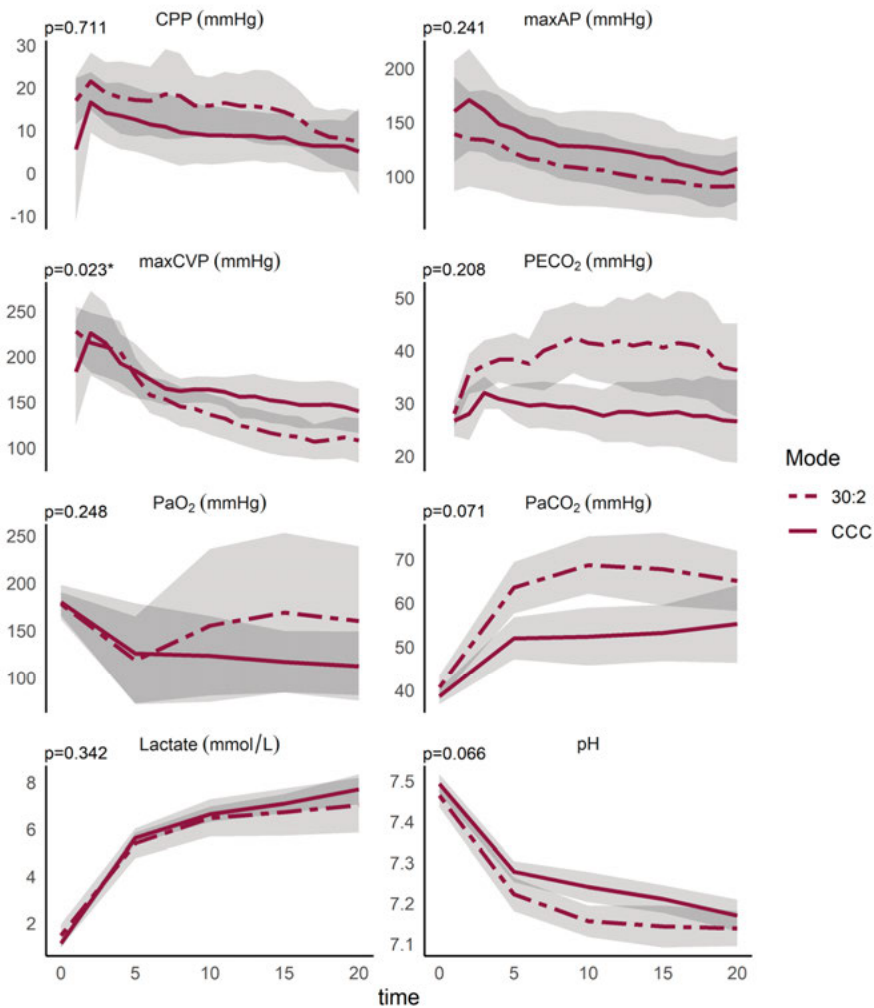


Fig 19. Changes over time in haemodynamics and blood gases. Shaded areas are 95% confidence intervals

Lung injuries

Injuries were present in all of the examined lungs, with atelectasis being the most prevalent and found in all of the pigs. Signs of hyperinflation were found in all of the pigs in the CCC group and in 7/8 pigs in the 30:2 group. When comparing the two groups, there were no differences in the lung injuries, neither by macroscopic inspection by the researcher nor microscopic inspection by the pathologist. There were no differences in oedema between the groups, neither in the pathologist’s assessment nor by wet-dry ratio. The extent of atelectasis and hyperinflation found in the lung samples in the microscopic examination can be seen in Fig 20.

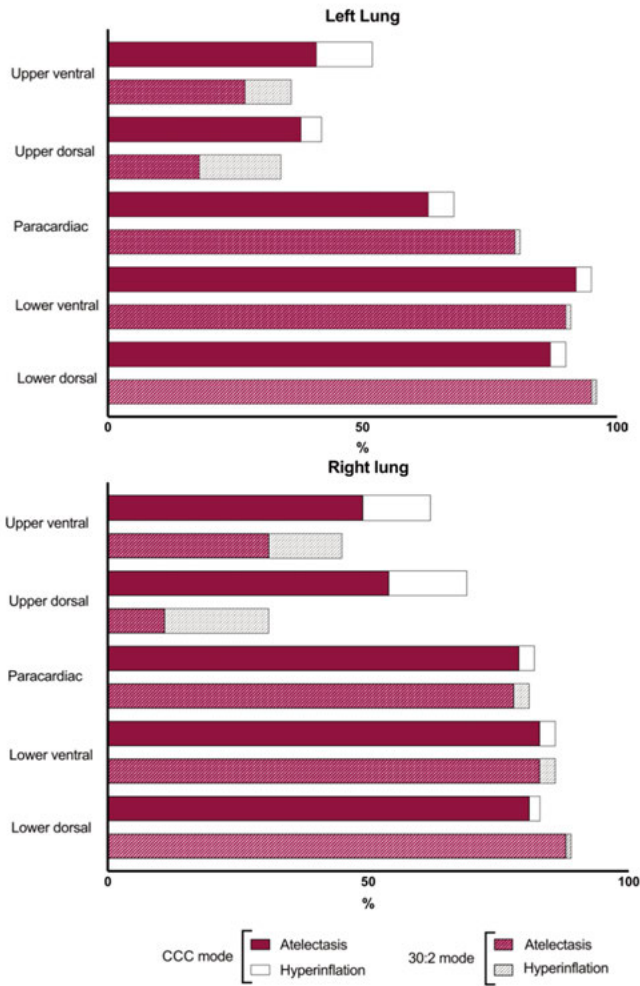


Fig 20. Extent of atelectasis and hyperinflation found in the lung tissue samples. Shown as percentages of the entire lung samples.

Study III

For evaluation of the algorithm, 37 runs, two minutes each, of simulated ventilation were performed. Both with and without ongoing, simulated, CPR. Table 6 shows the differences between ventilator setting and algorithm values.

Table 6. Comparisons of ventilator set and algorithm measured ventilation parameters

Ventilation type	N runs	N breaths *	Measure	Set value Median	Measured value Median	Difference Median (IQR)	Difference %**
Asynchronous	10	189	Vti (ml)	400	396	5 (-28 - 32)	1.1
		92	Vte (ml)	413	399	-8 (-43 - 68)	-1.6
		189	PIP (cmH ₂ O)	36	37.1	3 (0.3 - 5.8)	10.3
		189	Freq (per min)	10	10.0	0 (0 - 1)	0.1
No comparisons	20	637	Vti (ml)	500	445	-10 (-55 - 22)	-3.3
		637	Vte (ml)	399	388	-22 (-44 - 24)	-5.8
		637	PIP (cmH ₂ O)	23	22	0.1 (-1.4 - 0.5)	0.5
		637	Freq (per min)	20	20.0	0 (0 - 1)	0.1
Synchronous (30:2)	7	51	Vti (ml)	500	423	-46 (-76 - 10)	-13.5
		51	Vte (ml)	299	348	-5 (-30 - 28)	-0.8
		51	PIP (cmH ₂ O)	22	21.4	-1 (-1.9 - 0.2)	-4.9
		0	Freq (per min)	***	***	***	***

* Some runs excluded from evaluation of Vte due to measurement errors by the ventilation. ** Percentage difference is calculated as the difference between set and measured values divided by their average value. *** Synchronous ventilations were initiated manually and had no ventilator setting to compare with.

Compared to the ventilators, the largest differences between the ventilator values and those identified by the algorithm were a 10.3 % error of PIP in asynchronous ventilations, corresponding to 3 (0.3-5.8) cmH₂O and a 13.5% error of inspiratory volumes in synchronous ventilations, corresponding to -46 (-

76-10) ml. Freq deviated from ventilator settings with 0.1%. An example of the deviations from ventilator values of PIP in asynchronous ventilations can be seen in Fig 21. where chest compressions cause sawtooth patterns in the pressure curves with max values that visually are above the ventilator setting, something that the algorithm also measures.

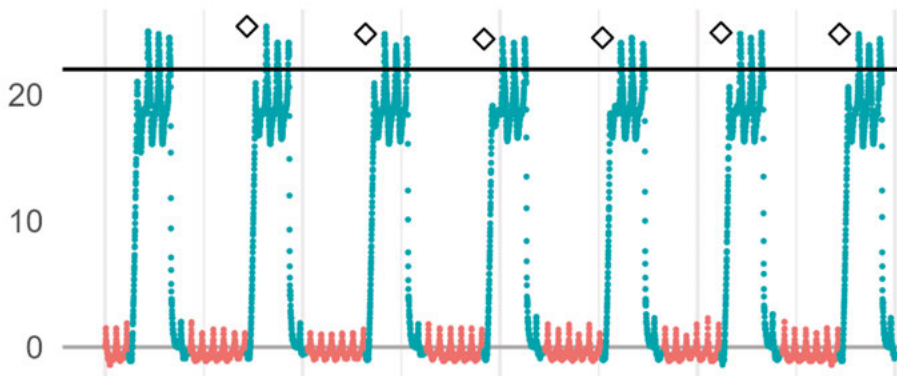


Fig 21. Example of pressure waveform from asynchronous ventilation during simulated chest compressions illustrating the differences between the ventilator setting (black line) and the algorithm identified value (highest point in the waveform between two black diamonds). Turquoise parts of the waveform indicate the active phase and red parts the inactive phase. Unit of measurement cmH_2O .

The performance of the algorithm compared to the standard model is illustrated in Fig 22. Both methods closely align with the ventilator settings in the absence of simulated chest compressions, but the standard models show larger deviations compared to the algorithm in the presence of simulated chest compressions. Especially in the measurements of PIP and Freq, where small, quick ventilations with low PIP caused by the simulated chest compressions are considered true ventilations and included as opposed to the algorithm where these are excluded.

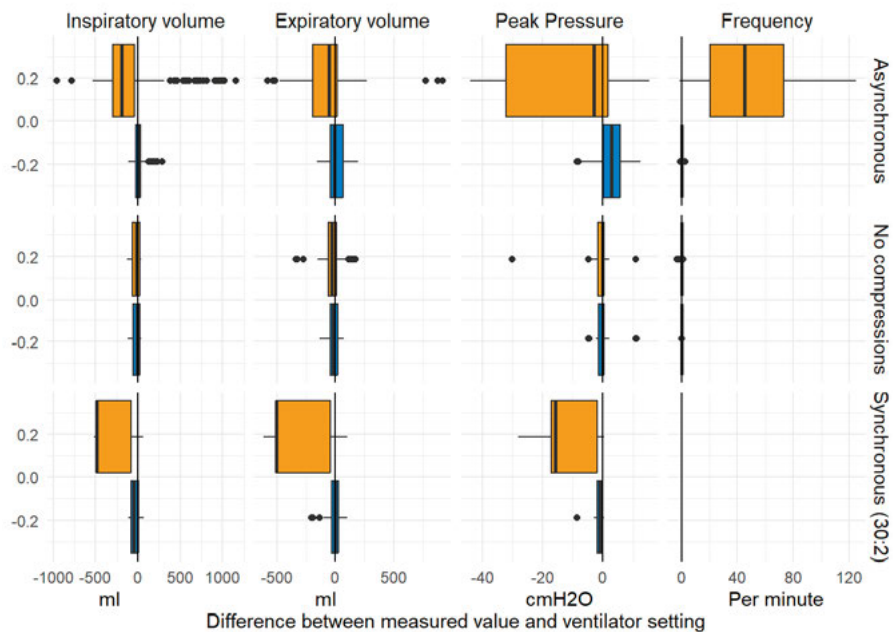


Fig 22. Boxplots of differences between the standard method and the algorithm compared to ventilator settings. Boxes represents IQR, black line in boxes represents medians and the whiskers represents extreme values within $IQR \times 1.5$. Dots are outliers. Black line: ventilator setting; Blue bars: Algorithm; Yellow bars: Standard method

Study IV

The CAvent trial included patients between May of 2019 and August of 2025. Inclusion attempts were performed in 340 patients of which 241 could be included in the study. This resulted in 28120 individual ventilations in 311 separate ventilation periods. The majority of exclusions ($n=52$) were due to device related issues, leading to no ventilation data being registered, such as failure to start the devices properly, disconnected cables or software issues. In 33 patients, there were issues with the flow signal, which had to be excluded, mainly caused by secretions from the patient blocking one of the two tubes of the flow sensor. Twenty-seven patients had issues with the CO_2 measurements, these were caused by either secretion blocking the sensor, software issues or improper management of the capnograph. The inclusion flow chart is shown in Fig 23.

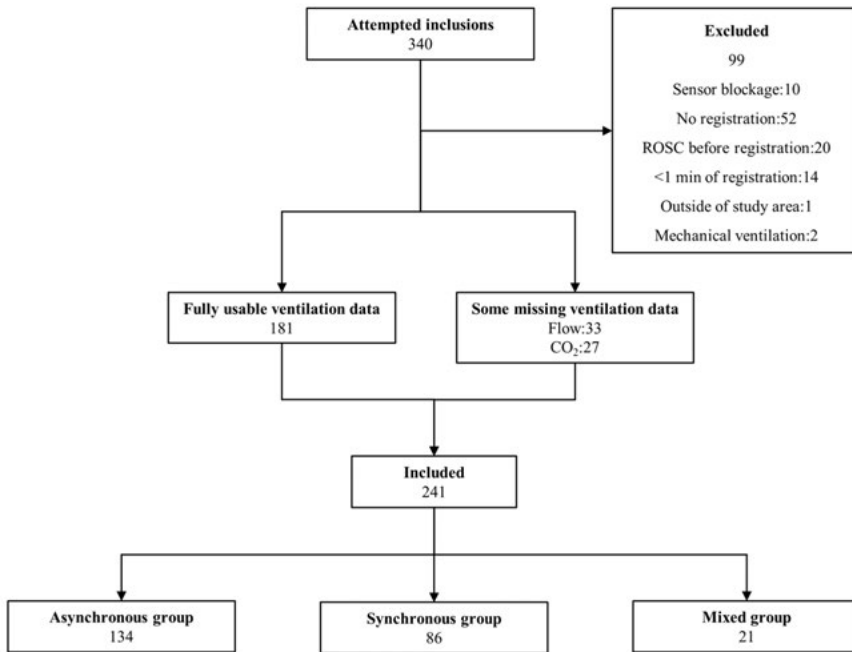


Fig 23. Inclusion flowchart

Of the included patients, 67% were male and the median age was 70 (IQR 56-78) years. The median duration of included ventilation periods during CPR was 554 (IQR 250-904) seconds and the median number of included ventilations were 61 (IQR 34-112) (%). A total of 15 patients had two different airway modalities and 1 had three different modalities during the included ventilation periods. The baseline characteristics of the patients can be seen in Table 7.

Table 7. Baseline characteristics of the included patients.

	Asynchronous (n=134)	Synchronous (n=86)	Mixed (n=21)	Missing n (%)
Male gender, n (%)	79 (69.3)	56 (65.1)	12 (60.0)	21 (8.7)
Age	68.0 (56.0-77.0)	70.0 (56.5-79.0)	72.5 (54.3-86.8)	23 (9.5)
Weight, kg (IQR)	80.0 (70.0-90.0)	80.0 (70.0-93.0)	88.0 (71.3-111.3)	67 (27.8)
Length, m (IQR)	1.75 (1.70-1.80)	1.74 (1.65-1.79)	1.70 (1.62-1.80)	52 (21.6)

BMI (IQR)	26.2 (24.2-29.4)	27.4 (23.6-30.8)	28.1 (24.3-35.3)	72 (29.9)
ITV, ml (IQR)	463 (396-520)	445 (388-495)	432 (358-451)	56 (23.2)
Anatomical dead space, ml (IQR)	156 (135-165)	150 (126-163)	147 (120-165)	56 (23.2)
Cause of arrest (%)				15 (6.2)
Medical	111 (92.5)	82 (95.3)	20 (100)	
Trauma	2 (1.7)	0	0	
Drug overdose	2 (1.7)	2 (2.3)	0	
Drowning	1 (0.8)	0	0	
Asphyxia	4 (3.3)	2 (2.3)	0	
Witnessed arrest, n (%)	58 (48.7)	50 (58.1)	14 (70.0)	44 (18.3)
Bystander CPR, n (%)	52 (45.2)	53 (63.1)	11 (57.9)	54 (22.4)
First recorded rhythm, n (%)				17 (7.1)
Asystole	45 (38.1)	43 (50.0)	6 (30.0)	
VF/VT	17 (14.4)	15 (17.5)	6 (30.0)	
PEA	12 (10.2)	13 (15.1)	3 (15.0)	
Bradycardia	6 (5.1)	5 (5.8)	2 (10.0)	
Unknown	38 (32.2)	10 (11.6)	3 (15.0)	
MCC, n (%)	56 (46.2)	68 (79.1)	18 (90)	28 (11.6)
ROSC, n (%)	38 (31.7)	30 (34.9)	6 (30.0)	20 (8.2)
Difficulties ventilating, n (%)	41 (34.7)	29 (33.7)	10 (50)	25 (10.4)
Duration of inclusion, sec (IQR)	434 (224-768)	561 (290-929)	1048 (724-1787)	
Number of ventilations, n (IQR)	88.5 (43.5-168)	48.0 (27.0-95.3)	160 (108-200)	

For categorical variables, data is shown as n and percentages for the non-missing within that group. For continuous variables data is shown as medians and IQR for the non-missing within that group.

Abbreviations: ALS, advanced life support; BMI, body mass index; CPR; cardiopulmonary resuscitation; ITV, ideal tidal volume; IQR, interquartile range; MCC,

mechanical chest compressions; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF/VT, ventricular fibrillation/ventricular tachycardia.

Ventilation parameters, ventilation modes and airway modalities

When compared overall between the ventilation modes, asynchronous ventilations yielded higher PIP, longer PAW > 30cmH₂O, Ti and Te and lower PIF and PECO₂ compared to synchronous ventilations. When calculated per minute, Freq was higher in asynchronous ventilation as were the minute volumes. The full comparisons can be seen in Table 8.

Table 8. Ventilation parameters and ventilation mode

Type of measurement	Asynchronous (95% CI)	Synchronous (95% CI)
Flow based (n*)	18564	6421
Vti (ml)	407 (378-437)	423 (388-459)
Vte (ml)	384 (353-415)	356 (319-394)
Vdiff (ml)	23.5 (-9.86-56.9)	64.4 (27.1-108)
Ti (sec)	0.84 (0.79-0.90)	0.70 (0.64-0.76)
Te (sec)	1.28 (1.20-1.35)	1.13 (1.04-1.21)
PIF (L/min)	56.8 (53.4-60.3)	64.5 (60.3-68.7)
Vti/Itv	0.94 (0.86-1.03)	0.93 (0.91-0.94)
ELV (ml)	224 (187-260)	209 (169-249)
Per minute (n#)	1512	1242
MVi (ml/min)	4447 (4121-4774)	2102 (1712-2494)
MVe (ml/min)	4465 (4071-4859)	1777 (1306-2249)
Pressure based (n*)	20597	7523
PIP (cmH ₂ O)	48.1 (46.3-50.0)	32.4 (30.2-34.6)
PAW > 30 cmH ₂ O (sec)	0.42 (0.39-0.46)	0.20 (0.16-0.24)
Per minute (n#)	1722	1462
Freq (n/min)	11.2 (10.6-11.8)	5.0 (4.3-5.7)
Capnography based (n*)	16486	6579
PECO ₂ (mmHg)	27.8 (24.9-30.7)	33.4 (30.0-36.8)

Abbreviations: ELV, estimated lung ventilation; Freq, frequency; Itv, ideal tidal volume; Mve, expiratory minute volume; Mvi, inspiratory minute volume; PAW, airway pressure; PECO₂, peak expired carbon dioxide; PIF, peak inspiratory flow; PIP, peak inspiratory pressure; Te, duration of expiration; Ti, duration of inspiration; Vdiff, Difference between Vti and Vte; Vte, expiratory tidal volume; Vti, inspiratory tidal volume.

There were no changes over time in Mvi, Mve, Freq and PIP nor did they change differently over time in asynchronous ventilation compared to synchronous ventilation.

Fig 23. Displays the ventilation parameters with both ventilation mode and airway modalities factored in. BVM ventilations area associated with large Vdiff while Asynchronous ventilations with ET shows the highest PIP and PAW >30 cmH₂O.

	BVM		SAD		ET	
	Async.	Sync.	Async.	Sync.	Async.	Sync.
Flow based (n*)	68	278	1292	5406	16 986	549
Vti (ml)	488 (291-684)	499 (402-596)	434 (363-504)	381 (351-424)	400 (371-430)	483 (331-635)
Vte (ml)	92.3 (-117-302)	179 (75.7-283)	332 (257-407)	361 (322-400)	404 (373-436)	511 (350-673)
Vdiff (ml)	396 (166-625)	322 (209-434)	101 (18.9-184)	26 (-16.6-68.8)	-3.7 (-38.5-31.0)	-27.2 (-204-150)
Ti (sec)	1.08 (0.72-1.44)	0.76 (0.61-0.92)	0.88 (0.76-1.01)	0.67 (0.61-0.73)	0.83 (0.78-0.88)	0.73 (0.47-0.98)
Te (sec)	0.60 (0.06-1.13)	0.91 (0.68-1.14)	1.13 (0.95-1.32)	1.13 (1.04-1.22)	1.32 (1.25-1.40)	1.24 (0.86-1.61)
PIF (L/min)	60.0 (34.6-85.4)	74.7 (62.2-87.2)	60.4 (51.3-69.5)	62.4 (57.7-67.1)	56.2 (52.4-60.1)	63.4 (43.7-83.0)
Vti/Itv	1.10 (0.60-1.60)	1.08 (0.83-1.33)	0.96 (0.75-1.16)	0.90 (0.80-1.00)	0.93 (0.84-1.01)	1.12 (0.74-1.50)
ELV (ml)	-77.3 (-283-128)	25.9 (-80.3-132)	189 (104-274)	212 (171-253)	237 (200-274)	356 (198-514)
Per minute (n*)	11	62	161	1056	1319	89
MVi (ml/min)	2847 (436-5258)	2060 (887-3232)	3637 (2776-4498)	1952 (1516-2387)	4683 (4325-5041)	2844 (1058-4629)
MVe (ml/min)	551 (-2278-3381)	851 (-254-2225)	2850 (1840-3861)	1784 (1271-2298)	4916 (4494-5337)	2855 (749-4962)
Pressure based (n*)	68	569	1347	6136	18 949	567
PIP (cmH ₂ O)	34.0 (20.6-47.5)	32.2 (26.4-38.0)	33.7 (29.0-38.3)	32.3 (30.0-34.6)	50.9 (49.0-52.9)	31.5 (22.0-40.9)
PAW > 30 cmH ₂ O (sec)	0.23 (-0.03-0.48)	0.20 (0.09-0.31)	0.21 (0.12-0.30)	0.20 (0.15-0.24)	0.47 (0.43-0.50)	0.20 (0.02-0.38)
Per minute (n*)	11	120	164	1524	1200	93
Freq (n/min)	6.0 (1.32-10.6)	4.2 (2.25-6.14)	9.4 (7.80-10.9)	5.1 (4.30-5.82)	11.7 (11.1-12.3)	5.4 (2.30-8.46)
Capnography based (n*)	5	363	1059	5478	15 353	549
PECO ₂ (mmHg)	4.40 (-32.6-41.4)	34.4 (23.3-45.5)	28.8 (20.7-37.0)	33.2 (29.4-37.0)	28.1 (24.9-31.3)	41.9 (25.6-58.1)

Fig 23. Heatmap of ventilation parameters with different airway modalities in the different ventilation modes. Mean values (95% CI) are shown. Colours represent per row-quartiles based on the highest in-row value with darker hues representing higher quartiles. *n Indicates number of ventilations included in the analysis. #n Indicates number of minutes included in the analysis. Abbreviations: BVM; bag-valve-mask, ELV, estimated lung ventilation; ET; endotracheal tube, Freq, frequency; Itv; ideal tidal volume; Mve, expiratory minute volume; Mvi, inspiratory minute volume; PAW, airway pressure; PECO₂, peak expired carbon dioxide; PIF, peak inspiratory flow; PIP, peak inspiratory pressure; SAD; supraglottic airway device, Te, duration of expiration; Ti, duration of inspiration; Vdiff, Difference between Vti and Vte; Vte, expiratory tidal volume; Vti, inspiratory tidal volume.

Discussion

The aim of this thesis was to explore and advance the understanding of ventilation during cardiac arrest. As there are so many known unknowns in the field, there is an urgent need for baseline research, which this thesis contributes to by investigating some fundamental characteristics of ventilation during cardiac arrest. This was accomplished by measuring ventilation parameters during CPR, both in the experimental and clinical setting, and investigating the effect different CPR modes and airway modalities had on these parameters. To facilitate this, a method to accurately measure ventilation parameters during CPR was also developed and employed in studies underlying this thesis.

Experimental insights

The first part of the work on this thesis consisted of Study I and II which aimed to, in detail not possible to achieve in humans suffering SCA, describe effects of different CPR modes on ventilation and haemodynamics. This was accomplished by using an animal CPR-model with invasive monitoring.

Study I focused on the effect of suction cup on a mechanical chest compression device and if it affected the haemodynamics and ventilation and found no difference in EtCO₂ (as a measure of CO) between the group where the suction cup was used and the group where it was not. The designed purpose of the suction cup is to aid the recoil of the chest during decompression, improving venous return to the heart and by extension CO. Suction cups has been employed for decades in CPR with one of the first comparisons to regular CPR being published in 1993¹⁶⁰. This active decompression has been explored previously, but then defined as lifting the chest wall above the neutral position as opposed to back to the neutral position, as was done in Study I. With the previously studied method, higher cerebral blood flow and CO was found in animal models^{161–163} and higher cerebral oxygenation in humans¹⁶⁴. While Study I did not detect any differences in EtCO₂ between the groups, there were other noteworthy findings. CPP was higher in the suction cup group, indicating potentially positive effects of the suction cup on the coronary circulation.

As the nadir CVP was lower in the suction cup group at all timeframes, a lower pressure in the right atrium could lead to better refilling of the heart, increasing CO and subsequently CPP. Although EtCO₂ (as a measure of CO) did not differ between the groups, there were trends indicating an increased EtCO₂ in the suction cup group. A larger group of animals could have shown this with significance. This remains speculative, but not unreasonable in conjunction with the higher CPP in the suction cup group. With regards to ventilation, there were no differences in V_{ti} nor the passive ventilation between the groups. Somewhat surprising is that the suction cup did not affect the passive ventilation more as a more pronounced, assisted, decompression could potentially increase the negative intrathoracic pressure more than an unassisted decompression and result in larger passive tidal volumes. There are multiple factors that could influence the passive ventilation, among them airway device seal and intrathoracic airway closure¹⁶⁵. The effect of passive ventilation has been studied prior and the overall evidence seems to point to the volumes being too small to have an actual contribution to the alveolar ventilation^{166,167}. While the volumes measured during the passive ventilation in Study I were below the dead space volume of the included pigs (when calculated as 2.2 ml/kg⁻¹), the passive ventilation did correlate negatively with EtCO₂, indicating a need to consider passive ventilation (and also active ventilation) when using EtCO₂ for prognostication and as a measure of CPR quality. If this change in EtCO₂ is caused by actual lowering of PaCO₂ or if it is due to dilution of the exhaled gas in the anatomical dead space remains unknown.

Study II investigated ventilation parameters and haemodynamics in asynchronous ventilations during continuous chest compressions and synchronous ventilations in 30:2 mode. The main finding in Study II was that asynchronous ventilations were associated with significantly higher PIP compared to synchronous ventilations. While a previous large clinical study found no differences in survival when comparing the two synchronous and asynchronous ventilations, no measurements of ventilation was actually performed in that study¹⁰³ necessitating the need for further studies on the ventilation itself in the two different modes. The theory behind the elevated PIP is that as asynchronous ventilations are given independently of the chest compressions, a ventilation will frequently be given at the same time as a chest compression. When the chest is compressed, the intrathoracic pressure increases, adding to the applied pressure of the ventilation. This higher PIP during chest compressions has also previously been shown in humans⁸³. The effect higher PIP has on the haemodynamics in humans is unknown. A constantly elevated PIP could be detrimental as it might decrease venous return. Due to both airway

device potency and intrathoracic airway closure, it is unknown how much of the PIP is actually transferred to the thorax, smaller airways and the alveoli. PIP is usually measured between the inflatable bag and the airway device, adding further complexity to the measurement. Other ways of quantifying the pressure caused by ventilations might yield more valuable information, but are much harder to measure, especially in the clinical setting, such as oesophageal pressure or Pplat. Although in Study II, a higher PIP correlated to a higher CVP, potentially implying better refill of the heart, a more reasonable interpretation of this result is probably that as this was the max CVP, it only represented the increased intrathoracic pressure during compression. Most studies indicate negative effects of high airway pressures, as discussed in the context of ARDS in the introduction, although if this is only due to the pressure is unknown, as tidal volumes and airway pressures are linked, higher pressure often mean higher tidal volumes and separating one from another could be difficult. The pressure being measured is also of importance, as previously discussed. One animal study did find a modest but significant correlation between Pplat and highest airway pressure, implying that PIP could be of clinical use. The study also found that lower airway pressures and Pplat led to higher CPP. However, this was in compressions only CPR, making it difficult to generalize the findings to ordinary CPR with ventilations ¹⁶⁸.

Another potentially important effect of a higher PIP is its effect on airway seal, especially when using a SAD. As mentioned prior, the current European CPR guidelines recommend using asynchronous ventilation when an advanced airway has been placed, such as a SAD, unless there is considerable leakage ³⁴. Although there are numerous different SAD models, the one recommended by the ERC, the i-gel[®], employs a mouldable, non-inflatable cuff that adapts to the anatomy of the pharynx to create airway seal. This is unlike an ET for example, which has an inflatable cuff that when inflated creates a mechanical pressure against the walls of the trachea that keeps it in place and prevents leakage (if applied correctly). Studies on SAD and the airway pressure at which they start to leak have shown that this occurs somewhere between 23-33 cmH₂O ¹⁶⁹⁻¹⁷³. With the higher PIP being generated during asynchronous ventilations, this could affect the seal of the SAD and potentially limit the alveolar ventilation due to excessive leakage. Estimating when airway leakage becomes an issue could be difficult in the field, for example due to high noises and low levels of lighting and difficulties to perceive if the chest rises caused by the ventilations are sufficient, especially during asynchronous ventilation.

PECO₂ and PaCO₂ was higher in the 30:2 group. While not surprising due to the higher ventilation frequency and higher minute ventilation in the CCC (asynchronous) group, which leads to more CO₂ being ventilated out of the lungs¹⁷⁴, the results from both Study I and II reinforces the notion that CO₂ measurements should not be considered in isolation during CPR as they can be dependent on both passive ventilation, ventilation rate and minute volumes, in addition to CPR quality and tissue perfusion.

Study II also included a detailed description of lung injuries after CPR. Although no differences were found between the ventilation modes, all of the examined lungs had significant injuries with widespread atelectasis being the most obvious one. These results indicate that CPR can have considerable effects on the lungs, even after 20 minutes. Even though the results were not statistically significant, there were interesting numerical differences with more atelectasis in parts of the lung, higher frequencies of micro bleedings and more inhomogeneous atelectasis patterns observed in the CCC group. As atelectasis was so prevalent in all of the lungs, a much larger sample size might have been required to see any differences between the CPR modes. This remains speculative though. Lung injuries post-CPR in humans is not fully understood, even though ARDS appears to be common⁷⁷ and concepts such as cardiopulmonary resuscitation-associated lung oedema (CRALE) and post-arrest lung injury (PALI) are receiving more interest^{175,176}. As with almost all things related to CPR, these conditions are multifaceted and probably not dependent on just one thing, such as the CPR mode, but on other factors during the treatment such as aspiration, physical trauma from the chest compressions, lung perfusion and barotrauma¹⁷⁷.

No major differences in the haemodynamics were found between the groups. As the chest compression in Study II (as well as in Study I) were given by a chest compression device in a highly standardized manner, this indicates that, at least in the experimental setting, CPR/ventilation mode has a limited impact on haemodynamics. A later, very similar study to Study II further reinforces this (as well as the higher PIP during asynchronous ventilations and absence of clear differences with regards to lung injuries between the CPR modes)¹⁷⁸. It is not inconceivable though, that in less optimized circumstances, such as with manual chest compressions of lesser quality, the effect of ventilation and CPR/ventilation modes on haemodynamics could be more pronounced.

The need for more sophisticated measurements of ventilation during CPR

During the time that Study I and II were performed, the inclusion for Study IV was also running. The ventilation waveforms gathered from all of these studies made it clear that the compression artefacts present in the waveform data required special consideration in order to extract accurate ventilation parameters. Initially it was planned to use the proprietary software that came included with the Fluxmed GrH-devices (the standard method). As more and more inclusions were made, it became clear that this was not feasible as the compression artefacts affected the results to such a degree that they could not be used to make meaningful interpretations of the ventilation (as can be seen Fig 22). As the standard method was not developed to be used during CPR, this was in hindsight unsurprising. The standard method used a flow threshold to detect ventilations, which meant that both small passive ventilations (caused by the chest compressions) as well as spontaneous gasping were included in the data. This generated tidal volumes that were too small, minute volumes that were too large as well as greatly exaggerated ventilation rates. As the aim in the included studies was to measure only active ventilations, this posed a problem. Therefore, the decision was made to develop an algorithm capable of processing the waveform data in a more adequate way in the context of ventilations during CPR, both because there was an apparent lack of a validated method to measure this, but also due to the necessity of having a well performing method to measure ventilation parameters in the CAvent trial (study IV).

An early version of the algorithm was developed and used in Study II with promising results. Further development and testing were later performed on the algorithm and described in study III. The developed algorithm had to accomplish two major goals: To detect only active ventilations, and to extract the ventilation parameters in an accurate way. This was accomplished by employing a set value of positive airway pressure over a certain amount of time for ventilation detection (8 cmH₂O >0.3 seconds). This dealt with the issue of spontaneous breathing being included (as this is associated with negative airway pressures) as well as excluding ventilations cause by the chest compressions, which are very short and generating a comparatively low airway pressure compared to true active ventilations. It is important to note though that if spontaneous breathing during CPR is of interest, the algorithm can be adjusted to only include these by altering the threshold parameters for the ventilation/breath detection. Furthermore, the ventilation episodes were divided into an active phase, during which the actual ventilation was performed, and an

inactive phase, which corresponded to the time in between individual ventilations. There are differing opinions as to if the expired tidal volume during the inactive phase should be included in the overall calculation of V_{te} ⁷³. In theory, the V_{ti} and V_{te} from the passive ventilation during the pauses of active ventilations (in study III referred to as the inactive phase) should cancel each other out. However, this was found to not always be the case. The reason for this is not entirely clear, but could be due to airway leakage and/or miscalibration of the measuring devices. It can also be argued that as the passive ventilation is usually below the dead space volume, it's contribution to the actual gas exchange should be negligible^{179,180}. Therefore, only the expired volume during the active phase was included for calculation of V_{te} in the algorithm, better representing the true expiration directly caused by the preceding inspiration.

During testing the algorithm performed well with only minor deviations from the ventilator settings, deviations that should not be clinically relevant. It also outperformed the standard method by a wide margin, especially evident during simulated chest compressions and performed at least as well, if not slightly better, during ventilations without simulated chest compressions, overall adding to the strength of the algorithm and making it suitable to be used in Study IV.

Clinical insights

Study IV, the CAvent trial, was both the start and the culmination of the work on this thesis, as it was the first to start and the last to end of the included studies. It presents one of the first extensive description of ventilation parameters during SCA and as such represents a step forward in the understanding of ventilation during CPR. It also builds upon the work performed simultaneously in the other studies included in this thesis with regards to the algorithm development as well as the experimental insights from the animal studies, which generated important new questions that Study IV could examine in the clinical setting.

One of the most obvious findings in the study is the great heterogeneity in the ventilation procedure, both in terms of ventilations, ventilation mode and airway modalities used, with many patients having both synchronous and asynchronous ventilations as well as both SAD and ET, and in one extreme case BVM, SAD and ET and both synchronous and asynchronous ventilations. As this was not an intervention study but an observational one, this probably gives a reasonably good approximation on how ventilation during CPR is performed in the clinical setting: often disorganized, especially in the beginning of the

procedure and many different interventions needed to achieve the intended goal. This infers that studying ventilation and its effect on outcomes such as survival can prove to be very difficult, due to the complexity of the situation at hand. To attempt to isolate the different factors during ventilation in CPR, Study IV presents the ventilation parameters overall, based on ventilation mode and on airway modality in the different ventilation modes.

As no known optimal ventilation parameters are known, there are no optimal values to compare the findings with. It can instead be valuable to compare the findings with the current CPR guidelines. Even though they are not based on best evidence at the moment, but rather expert opinion, they nevertheless represent the current best guide for clinical practice. The results from Study IV indicates that the V_{ti} given is usually below the recommended 500-600 ml^{34,82} with no obvious difference between the ventilation modes or airway modality. As the measurements of V_{ti} are performed between the inflatable bag and the airway device, it says a lot about the volume given by the ALS provider, but less about the actual volume reaching the patient's lungs and contributing to gas exchange. To evaluate this, V_{te} is a more adequate measure, as it also includes measurements of what happens distal to the airway device, such as leakage. In Study IV, this is further investigated by subtracting the estimated anatomic dead space volume from V_{te} (ELV), showing an approximation of the actual gas volume delivered to the lungs and contributing to the gas exchange. These measurements show a more complex picture, with choice of airway device being an important factor. Ventilations with BVM are associated with small V_{te} and large V_{diff} (as a measurement of leakage) indicating large amounts of leakage, perhaps due to difficulties in maintaining an adequate mask seal. While these results from Stud IV were based on few observations, a recent study measuring ventilation parameters such as V_{ti} and V_{te} in BVM ventilations also found worrying signs of large leakage⁴¹. This illustrates the complexity of maintaining a proper mask seal with BVM: s and perhaps also the fallacy of considering BVM as the first choice of airway device in the stepwise approach currently recommended. Further studies are needed to confirm these findings. It can perhaps be argued that i-gel® (or similar SAD: s) would be a better first option for airway management, even in some BLS-settings due to its ease of insertion and very little manual adjustment needed to maintain a good seal. The apparent low levels of leakage in SAD indicated by the results of Study IV, especially in synchronous ventilations seems to confirm this. It should be noted though that Study IV was exclusively in ALS settings, which makes direct generalisation of the results to BLS settings difficult.

Somewhat surprising is also the presence of non-guideline recommended ventilation strategies, asynchronous BVM ventilations and synchronous ET ventilations. The reasoning behind this can only be speculated, but could be due to miscommunication or confusion in an otherwise stressful environment. As these ventilations were comparatively few and the large majority of the ventilations were in accordance with guidelines, this does not appear to be a widespread problem.

The higher PIP during asynchronous ventilations found in Study II was also found in the clinical setting. However, it appears to mostly be associated with ventilations with an ET as the other airway modalities showed very similar PIP. Together with the very low levels of leakage in the ET groups, this indicates that a good airway seal is usually achieved with an ET, and as the airway is properly sealed, there is a much better environment for pressure to build up during simultaneous chest compressions and ventilations and for it to be registered by the sensors on top of the airway device. In asynchronous ventilations with a SAD or BVM, it is possible that, due to insufficient airway seal, the pressure diffuses to a larger extent before reaching the sensor. Something that can also be inferred by the larger amounts of leakage in asynchronous SAD and BVM ventilations compared to asynchronous ET ventilations. As previously mentioned, the effect of a high PIP during CPR is unclear, with both Study II and a similar animal study¹⁷⁸ showing no major differences in haemodynamics or lung injuries between asynchronous and synchronous ventilations, even though the PIP in the asynchronous groups was significantly higher. This remains to be evaluated in humans though. A high PIP could conceivably cause overdistention of the lung tissue, but coupled with comparatively low V_{ti} as found in Study IV, the occurrence of this is unknown. As PIP is just the highest measured airway pressure, it tells a limited picture of the overall pressure in the airway. Therefore, in Study IV, a measurement of total time within an individual ventilation spent over 30 cmH₂O was also included (PAW>30 cmH₂O). It also showed asynchronous ventilations with ET being associated with the highest values compared to the other airway modality/ventilation mode combination. The value of <30 cmH₂O was chosen as it is usually considered the limit for lung protective ventilation in mechanically ventilated patients. Considered together, PIP and PAW>30 cmH₂O gives a good approximation of the airway pressures. It is unclear if these relates to the actual intrathoracic pressures during CPR. There are better ways to measure the actual intrathoracic pressure, but much more difficult (perhaps even unrealistic) to perform in the clinical setting, especially in OHCA, such as directly measuring the intrapleural pressure or measuring the oesophageal pressure with an

oesophageal balloon¹⁸¹. Obvious effects of PIP on airway seal and subsequent leakage could not be found in SAD: s in Study IV. There were no significant differences in V_{te} or V_{diff} between synchronous and asynchronous ventilations with SAD with very similar airway pressures, which as stated above could be due to the pressure leaking at the mask part of the airway device or simply that without a hard, mechanical seal (as with a properly cuffed ET), pressure does not build up to the same extent.

As discussed previously, there has been a fear that hyperventilation is common during CPR, mainly due to two rather unfortunate studies^{95,96} which mainly showed the detrimental effect of a very pronounced, clinically improbable, hyperventilation. Later studies have failed to show that this is prevalent, and in Study IV there were no signs of hyperventilation, neither in terms of V_{ti} nor Freq. The risk of hyperventilation with regards to Freq is mainly present in asynchronous ventilations, as in synchronous ventilations, there are fixed pauses if the compression to ventilation ratio of 30:2 is used. Although there were extreme cases with up to 40 in Freq, these were very few and the mean Freq in asynchronous was rather close to the guideline recommended frequency of 10/min. The Freq in synchronous ventilations were also close to the predicted rate if the chest compressions are given at a rate of 100-120/min and the pause for ventilation is between three and five seconds (which equates to a Freq of between 5.2-6.0/min). This was probably aided by the use of the LUCAS device in many cases, which has a default compression rate of 102/min and a default ventilation pause of 3 seconds¹⁸².

While there were overall no dramatic deviations from reasonable ventilation parameters (at least according to the ventilation guidelines), there were signs that ventilation during CPR was not always effective, with leakage occurring, as well as high airway pressures (with at the moment unknown consequences). To optimize the ventilation during CPR, it should be measured in the field to a much greater extent than it is today. With new devices capable of measuring ventilations and new algorithms to process complicated ventilation data (such as the one presented in Study III), this is not unfeasible.

Ethical considerations

As this thesis includes both animal and human research, there are several important ethical considerations to be made, below divided into animal research and human research.

Animal Research

Before any animal experiment is performed, considerations of the three R's should always be made. They stand for Replace, Reduce and Refine¹⁸³.

- **Replace** asks the first important question in all animal research: is it necessary to include animals or can similar research be performed in other ways? In CPR research concerning ventilation, haemodynamics and other biological processes (such as evaluation of injuries), the answer is no. In Study I and II, the results could not be achieved in another way than with animals with pigs being the most appropriate species due to similarities with humans and also ease of acquisition.
- **Reduce** entails using as few animals as possible without making the research irrelevant and thus making it unethical to perform. It also means that as much data as possible should be acquired from each of the included animals. In Study I, a power calculation was made which gave a good estimation on the lowest number of animals needed. In Study II, due to its descriptive nature, no power calculation was made. The choice was made to include slightly more animals than in Study I to reach credible results without having to include an excessive number of animals. In both Study I and II, in order to maximize the gain from each animal and to keep the numbers needed low, multiple measures, both invasive and non-invasive, as well as multiple blood and tissue samples were obtained.
- **Refine** means designing the experiments in such a way that it minimizes pain, suffering and distress and enhances the animal's well-being. Both Study I and II were performed at an animal laboratory with long experience in animal experiments and with well-established routines. The pigs originally came from a pig farm approximately 30 minutes from the laboratory, meaning a relatively short time for transportation. Immediately upon arrival, the pigs were weighed in their transport boxes and then sedated with a subcutaneous injection. This was done in order to shorten the time the animals had to be awake in the laboratory, something that could otherwise cause significant stress. Once sedated, they were kept under anaesthesia with continuous infusion of analgesia until the experiment ended and euthanasia was performed. Compared to regular slaughter of pigs in Sweden using carbon dioxide, which has many issues from an animal-welfare standpoint¹⁸⁴, the protocol employed in Study I and II was most likely considerably less stressful for the pig.

Two additional ethical considerations are worth highlighting in the context of animal research using pigs. Firstly; what makes the pig a suitable animal for CPR research, its similarities to humans, also extends to their intelligence. Pigs are highly intelligent with a complex set of behaviours and requirements¹⁸⁵. This knowledge needs to permeate all animal research including pigs. Second is the issue affecting all animal research, namely the poor rate of translation into clinical trials and accepted interventions¹⁸⁶. Obviously, pigs, or mice for that matter, are not humans, and will, in many cases, yield different results from actual humans. This raises the question if animal research should be performed at all. In cardiac arrest research, there are very few alternatives though, as is perhaps shown in this thesis. Some of the most important milestones in CPR research also came from animal research, such as the development of chest compressions and defibrillations, which were tested first in animals^{30,146}. This shows that there is a place for animal research, at least in the field of CPR, but its usage should not be considered lightly.

Human research

Research in humans must follow rigorous ethical guidelines and mandatory ethical approval before the start of a study and informed consent should always be acquired prior to inclusion in a study. In CPR research, this presents an obstacle as consent cannot be acquired due to the person intended to be included usually being unresponsive and unable to give consent. According to article 28 and 30 of the declaration of Helsinki, which stipulates the ethical principles for human research, research on unconscious patients may only be performed if the condition that prevents them from giving consent is a necessary characteristic of the research, such as studying CPR in patients with SCA and if inclusion causes minimal risk or could potentially benefit the included patient. Informed consent should in such cases be acquired from a legally authorized representative. However, if no representative is present, and the research cannot be delayed, inclusions can be made if this has been described in the research protocol and has been approved by an ethical committee. Free and informed consent must be obtained as soon as possible after inclusion¹⁸⁷. Swedish law (act 2003:460 concerning the ethical review of research involving humans 20§, 21§, 22§¹⁸⁸) however, does not require explicit informed consent in these circumstances but rather infers that the researchers confer with the next of kin if they oppose the inclusion, when this is possible, if the participant in question cannot give informed consent on their own. This led to, for Study IV, that the Swedish ethical review committee waived the need for informed consent for patients out of hospital and requiring informed consent from patients surviving in-hospital, or if they were unable to give

informed consent, that the researchers conferred with the next of kin if they opposed the inclusion. None of the survivors declined to give informed consent. Further ground for this was that it was deemed unethical to confer with next of kin to deceased patients for this kind of observational study and also that the research did not alter or affect the standard treatment in any way. Not having informed consent is of course not ideal and ethically problematic (even if approved by an ethical committee). In CPR research though, there are so very few other options, especially out of hospital, where inclusions cannot wait and often has to be made on-site. As the survival rate after SCA is still so low, it can be argued (and often successfully is), that it would be more unethical to not perform this kind of research. Because without extensive research in the field, improvements in the survival rate after SCA is unlikely to happen.

Limitations

There are several limitations to the included studies, some of which are discussed throughout this thesis. Others will be highlighted here.

Study I and II were animal studies using pigs, meaning that the results cannot be directly transferred onto humans. Even if some results from the animal studies in this thesis, such as the higher PIP during asynchronous ventilations in Study II were also found in Study IV, there are numerous other variables from the animal studies with unclear implications for humans. While the results from Study I and II showed limited effects on haemodynamics and lung injuries by the different CPR and ventilation modes, it is far from certain that this is true in humans as well. Another important limitation for Study I and II is the context in which the research was performed, namely in a very controlled environment in the lab, with standardized CPR on young, healthy animals. This does not at all correspond to how, where and on whom CPR in humans is usually performed, especially out of hospital. A much more common CPR setting is instead rather disorganized and stressful for the providers and the patients receiving CPR is usually older with multiple comorbidities. Another limitation of Study I and II is the number of included animals. To be able to show differences with a high level of certainty, more animals might be needed, but due to ethical, economical and practical reason, this is not always preferable or even possible.

Study III carries some limitations and they are partly due to the lack of prior research into this very specific field. As such there was very little support from earlier research while designing the study. Study III also considered

ventilation parameters measured and given by two commercial ventilators to be the gold standard. While this was the best method available, ventilators suffer from the same issue as the standard method., They are not made to measure ventilation during CPR with constantly oscillating flow and pressures. There also might be a difference in the parameters generated by the ventilator and those measure by the Fluxmed GrH due to the location of the respective sensors in the respiratory circuit with the length of the tubing potentially affecting the flow and pressure.

Study IV was limited by not being a randomized study. Instead, the choice of which patient to include was up to the ALS providers in the including systems. This could lead to selection bias where the included patients do not accurately reflect the population as a whole, although this is a limitation in all non-randomized observation studies and not unique to Study IV. As previously mentioned, the Fluxmed GrH used in study IV (as well as in Study II and III) was not originally designed to measure ventilation during CPR (which necessitated the development of the algorithm in Study III). While pneumotachographs are capable of measuring flow and pressure in detail difficult to achieve with other devices, this sensitivity comes with some drawbacks. First is the issue of calibration, which is required frequently for a pneumotachograph. As this operation takes a few minutes on the Fluxmed GrH, it was not possible to do this prior to each inclusion. It was instead done after each inclusion when the devices were checked and restored by the researchers. This led to a number of inclusions having uncalibrated ventilation data. The developed algorithm from Study III incorporated a parameter to calibrate these signals post inclusion. While visually achieving this, there could possibly be some remaining issues in the calibrated values. The sensors were also very sensitive to obstructions, which were usually caused by secretions or blood from the patients' airways, this led to some loss of either flow signals or complete loss of ventilation data where the patient had to be excluded. The operation of the devices also caused some issue, especially in the beginning of the study where there were software issues that were later resolved as well as failures to start the devices properly while trying to include a patient. Even though this just required pressing two buttons, this can easily be forgotten during a SCA. Furthermore, the inclusion was started at different timepoints in the CPR procedure. Some were started immediately upon arrival of the ALS providers, while some started much later due to other parts of the treatment naturally being prioritized. This needs to be taken into consideration as it can affect how the measurements were done and that some factors may have changed during the CPR procedure. Finally, during the inclusion period, the covid-19 pandemic also struck, which severely

hampered the inclusions for almost two years, as the study was paused and the devices were used in other covid-19 related studies. A very long inclusion period (in the case of Study IV over six years) is not ideal, as treatments and routines can change during this time. Although there were no official changes in the CPR routines used, there could be other factors influencing how the ventilation is given over such a long period, such as new staff not fully trained with the devices. This is speculative but could play a part.

Conclusion

This thesis explored ventilation during SCA both experimentally and clinically, and increased the understanding of the procedure and its physiological effects by describing ventilation parameters and haemodynamics in different settings with different ventilation modes and airway modalities. Ventilation during CPR, and the measurement of it, is very complex, but can be achieved with the right equipment and data analysis tools and can give valuable insight into the procedure. Moving forward, ventilation during CPR should be measured more frequently to identify the optimal ventilation patterns associated with positive outcomes for patients suffering SCA. The study specific conclusions were:

Study I: In the experimental setting using a pig model, a suction cup on a mechanical chest compression device did not affect CO as measured by EtCO₂ or affect the ventilation.

Study II: In an animal model, asynchronous ventilations during continuous chest compressions resulted in higher PIP but otherwise did not produce markedly different haemodynamics or lung injuries compared to synchronous ventilations, although all included animals received significant lung injuries, mainly widespread atelectasis.

Study III: A novel algorithm capable of extracting ventilation data during ongoing CPR was developed, evaluated and found to be accurate. It was subsequently used on the clinical ventilation data in Study IV.

Study IV: In clinical practice, ventilation is inconsistently delivered, with tidal volumes often below guideline recommendations. PIP was significantly higher during asynchronous ventilations with an ET compared to all other combinations of ventilation mode and airway modality. Leakage was common during BVM ventilations

Future perspectives

The most important question when it comes to ventilation during CPR remains unanswered: What is the optimal way to perform ventilations in order to maximize the chance of survival. While this thesis did not aim to give an answer to this, it is of course the ultimate goal of this kind of research. What this thesis perhaps shows is that due to the heterogeneity of the ventilation and CPR procedure, it can indeed prove to be very complicated to reach consensus on this issue, but it should nevertheless be attempted. One obvious way to do this is to start measuring the ventilation during CPR more frequently than what is done today. Including tidal volumes, ventilation frequencies, airway pressures and EtCO₂. Devices capable of doing this already exists and will hopefully become more common in the future. This thesis shows what results from such measurements can look like. It also presents an algorithm to accurately measure ventilation parameters during CPR. This algorithm is open source and available for anyone interested to use. A natural next step would be to further validate the algorithm with other means besides that of a ventilator, to increase its accuracy and perhaps also incorporate it in more robust measurement devices. As the algorithm is not device based, there is no obstacle to use it on waveform data from other devices. With more clinical ventilation data from CPR, open questions from this thesis can perhaps be investigated further, such as if the high PIP during asynchronous ventilations with an ET is detrimental in any way and if the observed leakage during BVM ventilations is widespread. More clinical trials within the field are urgently needed. With the seemingly renewed interest in the field, and with the aid of thesis like this one, hopefully this can come to fruition in the not too distant future, turning more and more known unknowns into known knowns.

Populärvetenskaplig sammanfattning på Svenska

Plötsliga hjärtstopp fortsätter att vara en vanligt förekommande dödsorsak världen över. Behandlingen är hjärt-och lungräddning samt defibrillering. Trots att ventilering (dvs att med olika hjälpmedel ge den drabbade konstgjord andning) är en fundamental del av behandling och har genomförts i många hundra år (på mer eller mindre adekvata sätt) så saknas grundläggande forskning om hur ventilering ges samt vilka effekter ventilering har. Syftet med denna avhandling var att utforska hur ventilering ges under pågående hjärt-lungräddning (HLR) samt dess effekter och vad som kan påverka den, både experimentellt och kliniskt.

Studie I och II var experimentella djurstudier där grisar användes. I Studie I undersöktes om en sugkopp på en bröstkompressionsapparat påverkade blodcirkulationen och ventileringen. Inga tydliga skillnader fanns men hjärtats cirkulation var något bättre i gruppen som fick bröstkompressioner med sugkoppen jämfört med den grupp som fick utan. Studie II undersökte om det fanns skillnader i ventilering, blodcirkulation och lungskador om ventileringen gavs antingen kontinuerligt under pågående bröstkompressioner eller under pauser av bröstkompressionerna. Ventilering under pågående bröstkompressioner gav upphov till högre luftvägstryck samt lägre utandad koldioxid och lägre koldioxidhalt i blodet. Alla undersökta lungor uppvisade skador varav den vanligaste var sammanfallen lungvävnad. Det fanns inga skillnader mellan de olika ventileringsmetoderna.

I Studie III beskrevs utvecklingen och testningen av en algoritm för att kunna mäta ventilation under pågående hjärt-lungräddning. På grund av bröstkompressionerna uppstår störningar i signalerna från den uppmätta ventilationen. Algoritmen utvecklades för att kunna uppmäta korrekta värden även i närvaro av dessa störningar. Algoritmen testades mot mekaniska ventilatorer som kunde ge ventileringar med kända värden. Algoritmen presterade väl och användes i Studie IV.

I Studie IV studerades ventilering kliniskt genom att personal från ambulans, akutläkarbilar, ambulanshelikopter och ett akutteam på ett sjukhus mätte den ventilering de gav vid hjärtstopp. Resultaten visade att ventileringen som ges är väldigt olikartad med många olika kombinationer av hjärt-lungräddningsmetod och luftvägshantering. Precis som i Studie II var ventilering given under pågående bröstkompressioner (tillsammans med en endotrakealtub) förknippat med högt luftvägstryck. I övrigt var de givna volymerna något under de som rekommenderas i nuvarande HLR-riktlinjer. Ventilering med mask och blåsa var förknippat med stora läckage och ineffektiv ventilering. Tidigare har det funnits en rädsla att ventilering under hjärt-lungräddning ges för snabbt eller med för stora volymer. I Studie IV fanns inga tecken på detta, även om det förekom i enstaka fall.

I framtiden bör ventilering mätas i högre utsträckning under hjärt-lungräddning och algoritmer liknande den som utvecklades i Studie III implementeras i syfte att ytterligare öka förståelsen för ventilering under HLR, samt utröna hur ventileringen ska ges för att öka överlevnaden efter plötsliga hjärtstopp.

Acknowledgements

The road from a newly minted ambulance nurse, very much finished with all things academia and without a clear path in life, to writing the final lines of a thesis almost 11 years later, has been a long and trying one, but at the same time very fulfilling. The level of personal growth over the years has been rivalled only by the frustration and hair loss that comes from doing these kinds of things. For me this whole process also shows that the future is never certain and that life often takes you on journeys you could not possibly imagine from the start. I could, of course, never have done this by myself, and there were many good people who helped make this possible, and contributed in one way or another. To you I would like to extend my warmest gratitude.

To my main supervisors Sten and David, without you, none of this would have happened, and for that I am ever grateful. Thank you, David, for always being the research hotline I needed, and thank you Sten for being nothing less than the godfather of all things research (yes, I stole that one, but that doesn't make it any less true). You will leave a very big, Sten-shaped, hole at the institution and in the research group now that you retire.

To my office mate Douglas, the smartest person I know, without you, the studies we have now done would not have been possible, or at least would not have been nearly as good. My knowledge of statistics would also be severely lacking without the guidance you have given. But no, I will not learn R, and I'm still not exactly sure what a hierarchical model means. It will be a silent spring!

To Lotte and Jeroen, two of the brightest and most dedicated people I've ever met. You really came into the CAvent project when the outlook was the bleakest and you pretty much saved the whole thing! I really hope our collaboration can continue in the future, although preferably with less scrolling through ventilation waveforms hours on end and getting progressively more and more confused.

To my next-door office neighbours, Sara, Stefan, and Anna, for always being good looking, funny and constantly making me feel guilty for not hitting the gym enough.

To my old boss Per, who trusted me enough – without having much to go on – to hire me for this position back in the day.

To my present boss Hans, for understanding the importance of research and letting me prioritize it, and for the tip about whisky at ten o' clock during late night writing sessions.

To Jessica, for giving me the best possible start at the Uppsala EMS. I really wish you could have been here for this. You are dearly missed.

To Jonas, for always boosting the morale and being supportive.

To Silvia, for taking me under your wings when I had never even remotely done anything like an animal study. Your guidance into the “meatier” parts of the method was very much appreciated.

To the Uppsala EMS, who performed the actual the inclusions for the CAvent-study. It might have been reluctantly from time to time, but hopefully worth it in the end. And of course, for being my dear colleagues and helping Uppsala run the way it is supposed to.

To Magnus, for randomly coming up to me after a presentation and enrolling Akutläkarbilarna in Stockholm to participate in the CAvent-study, just like that.

To Rickard, who came in late as my supervisor but nevertheless helped make important decisions. At least we tried with the IHCA part.

To Joanna and Elin, for helping get all of this started.

To the staff at The Hedenstierna laboratory, for always being so helpful and always treating the animals in the best way possible.

To Fredrik Arnwald, for connecting us with the ARREST-team, and to Hans, for deciding that this was something that the ARREST-team was interested in.

To my parents, Eva and Tomas, for always being there.

To my kids Pelle and Ingrid, for making everything worth it.

And lastly, to my Linda, for being you!

References

1. Defense.gov Transcript: DoD News Briefing - Secretary Rumsfeld and Gen. Myers. Accessed January 23, 2026. <https://web.archive.org/web/20160406235718/http://archive.defense.gov/Transcripts/Transcript.aspx?TranscriptID=2636>
2. Kuller LH. Sudden death—Definition and epidemiologic considerations. *Progress in Cardiovascular Diseases*. 1980;23(1):1-12. doi:10.1016/0033-0620(80)90002-X
3. Zimmerman DS, Tan HL. Epidemiology and risk factors of sudden cardiac arrest. *Current Opinion in Critical Care*. 2021;27(6):613. doi:10.1097/MCC.0000000000000896
4. Padala SK, Cabrera JA, Ellenbogen KA. Anatomy of the cardiac conduction system. *Pacing and Clinical Electrophysiology*. 2021;44(1):15-25. doi:10.1111/pace.14107
5. Koplán BA, Stevenson WG. Ventricular Tachycardia and Sudden Cardiac Death. *Mayo Clin Proc*. 2009;84(3):289-297. doi:10.4065/84.3.289
6. Myerburg RJ, Halperin H, Egan DA, et al. Pulseless Electric Activity. *Circulation*. 2013;128(23):2532-2541. doi:10.1161/CIRCULATIONAHA.113.004490
7. Varvarousis D, Varvarousi G, Iacovidou N, D'Aloja E, Gulati A, Xanthos T. The pathophysiologies of asphyxial vs dysrhythmic cardiac arrest: implications for resuscitation and post-event management. *The American Journal of Emergency Medicine*. 2015;33(9):1297-1304. doi:10.1016/j.ajem.2015.06.066
8. Baldi E, Wnent J, Caputo ML, et al. European Resuscitation Council Guidelines 2025 Epidemiology in Resuscitation. *Resuscitation*. 2025;215. doi:10.1016/j.resuscitation.2025.110733
9. Jerkeman M, Sultanian P, Lundgren P, et al. Trends in survival after cardiac arrest: a Swedish nationwide study over 30 years. *Eur Heart J*. 2022;43(46):4817-4829. doi:10.1093/eurheartj/ehac414
10. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death. *Circulation*. 2018;137(25):2689-2700. doi:10.1161/CIRCULATIONAHA.117.033427
11. Katzenschlager S, Kelpanides IK, Ristau P, et al. Out-of-hospital cardiac arrest in children: an epidemiological study based on the German Resuscitation Registry identifying modifiable factors for return of spontaneous circulation. *Crit Care*. 2023;27(1):349. doi:10.1186/s13054-023-04630-3
12. Gräsner JT, Wnent J, Herlitz J, et al. Survival after out-of-hospital cardiac arrest in Europe - Results of the EuReCa TWO study. *Resuscitation*. 2020;148:218-226. doi:10.1016/j.resuscitation.2019.12.042

13. Nishiyama C, Kiguchi T, Okubo M, et al. Characteristics of out-of-hospital cardiac arrest from 2018 to 2021 across the world: third report from the International Liaison Committee on Resuscitation (ILCOR) research and registries committee. *Resuscitation*. 2025;217:110852. doi:10.1016/j.resuscitation.2025.110852
14. Baldi E, Wnent J, Caputo ML, et al. European Resuscitation Council Guidelines 2025 Epidemiology in Resuscitation. *Resuscitation*. 2025;215. doi:10.1016/j.resuscitation.2025.110733
15. Del Rios M, Bartos JA, Panchal AR, et al. Part 1: Executive Summary: 2025 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2025;152(16_suppl_2):S284-S312. doi:10.1161/CIR.0000000000001372
16. Zimmerman DS, Tan HL. Epidemiology and risk factors of sudden cardiac arrest. *Current Opinion in Critical Care*. 2021;27(6):613. doi:10.1097/MCC.0000000000000896
17. Wong CX, Brown A, Lau DH, et al. Epidemiology of Sudden Cardiac Death: Global and Regional Perspectives. *Heart, Lung and Circulation*. 2019;28(1):6-14. doi:10.1016/j.hlc.2018.08.026
18. Penketh J, Nolan JP. In-hospital cardiac arrest: the state of the art. *Crit Care*. 2022;26(1):376. doi:10.1186/s13054-022-04247-y
19. Lind PC, Risager BH, Gammelager H, et al. Why do patients develop in-hospital cardiac arrest? A prospective clinical observational study (WHY-IHCA). *Resuscitation*. 2025;216:110782. doi:10.1016/j.resuscitation.2025.110782
20. Silverplats J, Äng B, Källestedt MLS, Strömsöe A. Incidence and case ascertainment of treated in-hospital cardiac arrest events in a national quality registry – A comparison of reported and non-reported events. *Resuscitation*. 2024;195:110119. doi:10.1016/j.resuscitation.2024.110119
21. Bruchfeld S, Ullemark E, Riva G, Ohm J, Rawshani A, Djärv T. Aetiology and predictors of outcome in non-shockable in-hospital cardiac arrest: A retrospective cohort study from the Swedish Registry for Cardiopulmonary Resuscitation. *Acta Anaesthesiol Scand*. 2024;68(10):1504-1514. doi:10.1111/aas.14496
22. Yonis H, Andersen MP, Mills EHA, et al. Duration of resuscitation and long-term outcome after in-hospital cardiac arrest: A nationwide observational study. *Resuscitation*. 2022;179:267-273. doi:10.1016/j.resuscitation.2022.08.011
23. Bibeln.se - bibeln.se. Accessed January 13, 2026. <https://www.bibeln.se/>
24. Baker AB. Artificial respiration, the history of an idea. *Med Hist*. 1971;15(4):336-351.
25. History of CPR. cpr.heart.org. Accessed January 13, 2026. <https://cpr.heart.org/en/resources/history-of-cpr>
26. Medical essays and observations. *Medical Essays and Observations. Volume 5 (Part 2), 1744*. Edinburgh; 1744. Accessed November 6, 2023. <http://archive.org/details/s5id13407050>
27. Schäfer EA. Description of a Simple and Efficient Method of Performing Artificial Respiration in the Human Subject, especially in Cases of Drowning; to which is appended Instructions for the Treatment of the Apparently Drowned. *Med Chir Trans*. 1904;87:609-623.

28. Safar P, Escarraga LA, Elam JO. A Comparison of the Mouth-to-Mouth and Mouth-to-Airway Methods of Artificial Respiration with the Chest-Pressure Arm-Lift Methods. *New England Journal of Medicine*. 1958;258(14):671-677. doi:10.1056/NEJM195804032581401
29. *Berliner Klinische Wochenschrift 1892 29*. Accessed November 6, 2023. <http://archive.org/details/BerlinerKlinischeWochenschrift189229>
30. Kouwenhoven WB, Jude JR, Knickerbocker GG. CLOSED-CHEST CARDIAC MASSAGE. *JAMA*. 1960;173(10):1064-1067. doi:10.1001/jama.1960.03020280004002
31. Koster RW. Modern BLS, dispatch and AED concepts. *Best Practice & Research Clinical Anaesthesiology*. 2013;27(3):327-334. doi:10.1016/j.bpa.2013.07.005
32. Smyth MA, van Goor S, Hansen CM, et al. European Resuscitation Council Guidelines 2025 Adult Basic Life Support. *Resuscitation*. 2025;215:110771. doi:10.1016/j.resuscitation.2025.110771
33. Dossdall DJ, Fast VG, Ideker RE. Mechanisms of Defibrillation. *Annual Review of Biomedical Engineering*. 2010;12(Volume 12, 2010):233-258. doi:10.1146/annurev-bioeng-070909-105305
34. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2025 Adult Advanced Life Support. *Resuscitation*. 2025;215. doi:10.1016/j.resuscitation.2025.110769
35. Esibov A, Banville I, Chapman FW, Boomars R, Box M, Rubertsson S. Mechanical chest compressions improved aspects of CPR in the LINC trial. *Resuscitation*. 2015;91:116-121. doi:10.1016/j.resuscitation.2015.02.028
36. Alexander E, Katharina T, Verena F, et al. Comparison of different mechanical chest compression devices in the alpine rescue setting: a randomized triple crossover experiment. *Scand J Trauma Resusc Emerg Med*. 2021;29:84. doi:10.1186/s13049-021-00899-x
37. Perkins GD, Davies RP, Soar J, Thickett DR. The impact of manual defibrillation technique on no-flow time during simulated cardiopulmonary resuscitation. *Resuscitation*. 2007;73(1):109-114. doi:10.1016/j.resuscitation.2006.08.009
38. Iversen BN, Meilandt C, Væggemose U, Terkelsen CJ, Kirkegaard H, Fjølner J. Pre-charging the defibrillator before rhythm analysis reduces hands-off time in patients with out-of-hospital cardiac arrest with shockable rhythm. *Resuscitation*. 2021;169:23-30. doi:10.1016/j.resuscitation.2021.09.037
39. Perkins GD, Cottrell P, Gates S. Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest? *BMJ*. 2014;348:g2435. doi:10.1136/bmj.g2435
40. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine*. 2016;374(18):1711-1722. doi:10.1056/NEJMoa1514204
41. Lemoine F, Jost D, Lemoine S, et al. Manual bag-valve-mask ventilation during out-of-hospital cardiopulmonary resuscitation: a prospective observational study. *Resuscitation*. 2025;217. doi:10.1016/j.resuscitation.2025.110895
42. Theiler L, Gutzmann M, Kleine-Brueggeny M, Urwyler N, Kaempfen B, Greif R. i-gel™ supraglottic airway in clinical practice: a prospective observational multicentre study. *British Journal of Anaesthesia*. 2012;109(6):990-995. doi:10.1093/bja/aes309

43. Häske D, Schempf B, Gaier G, Niederberger C. Performance of the i-gel™ during pre-hospital cardiopulmonary resuscitation. *Resuscitation*. 2013;84(9):1229-1232. doi:10.1016/j.resuscitation.2013.04.025
44. Wahlen B m., Heinrichs W, Latorre F. Gastric insufflation pressure, air leakage and respiratory mechanics in the use of the laryngeal mask airway (LMATM)in children. *Pediatric Anesthesia*. 2004;14(4):313-317. doi:10.1046/j.1460-9592.2003.01213.x
45. Latorre F, Eberle B, Weiler N, et al. Laryngeal Mask Airway Position and the Risk of Gastric Insufflation. *Anesthesia & Analgesia*. 1998;86(4):867. doi:10.1213/00000539-199804000-00035
46. Helmy AM, Atef HM, El-Taher EM, Henidak AM. Comparative study between I-gel, a new supraglottic airway device, and classical laryngeal mask airway in anesthetized spontaneously ventilated patients. *Saudi Journal of Anaesthesia*. 2010;4(3):131. doi:10.4103/1658-354X.71250
47. Ye Q, Wu D, Fang W, Wong GTC, Lu Y. Comparison of gastric insufflation using LMA-supreme and I-gel versus tracheal intubation in laparoscopic gynecological surgery by ultrasound: a randomized observational trial. *BMC Anesthesiol*. 2020;20(1):136. doi:10.1186/s12871-020-01057-z
48. Stone BJ, Chantler PJ, Baskett PJF. The incidence of regurgitation during cardiopulmonary resuscitation: a comparison between the bag valve mask and laryngeal mask airway. *Resuscitation*. 1998;38(1):3-6. doi:10.1016/S0300-9572(98)00068-9
49. Buis ML, Maissan IM, Hoeks SE, Klimek M, Stolker RJ. Defining the learning curve for endotracheal intubation using direct laryngoscopy: A systematic review. *Resuscitation*. 2016;99:63-71. doi:10.1016/j.resuscitation.2015.11.005
50. Wang HE, Simeone SJ, Weaver MD, Callaway CW. Interruptions in Cardiopulmonary Resuscitation From Paramedic Endotracheal Intubation. *Annals of Emergency Medicine*. 2009;54(5):645-652.e1. doi:10.1016/j.annemerg-med.2009.05.024
51. Robinson AE, Driver BE, Prekker ME, et al. First attempt success with continued versus paused chest compressions during cardiac arrest in the emergency department. *Resuscitation*. 2023;186:109726. doi:10.1016/j.resuscitation.2023.109726
52. Cheskes S, Schmicker RH, Verbeek PR, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014;85(3):336-342. doi:10.1016/j.resuscitation.2013.10.014
53. Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. *Resuscitation*. 2006;71(2):137-145. doi:10.1016/j.resuscitation.2006.04.008
54. Jabre P, Penalzoza A, Pinero D, et al. Effect of Bag-Mask Ventilation vs Endotracheal Intubation During Cardiopulmonary Resuscitation on Neurological Outcome After Out-of-Hospital Cardiorespiratory Arrest: A Randomized Clinical Trial. *JAMA*. 2018;319(8):779-787. doi:10.1001/jama.2018.0156
55. Lee AF, Chien YC, Lee BC, et al. Effect of Placement of a Supraglottic Airway Device vs Endotracheal Intubation on Return of Spontaneous Circulation in Adults With Out-of-Hospital Cardiac Arrest in Taipei, Taiwan: A Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(2):e2148871. doi:10.1001/jamanetworkopen.2021.48871

56. Benger JR, Kirby K, Black S, et al. Effect of a Strategy of a Supraglottic Airway Device vs Tracheal Intubation During Out-of-Hospital Cardiac Arrest on Functional Outcome: The AIRWAYS-2 Randomized Clinical Trial. *JAMA*. 2018;320(8):779-791. doi:10.1001/jama.2018.11597
57. Wang HE, Schmicker RH, Daya MR, et al. Effect of a Strategy of Initial Laryngeal Tube Insertion vs Endotracheal Intubation on 72-Hour Survival in Adults With Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA*. 2018;320(8):769-778. doi:10.1001/jama.2018.7044
58. Chan JJ, Goh ZX, Koh ZX, et al. Clinical evaluation of the use of laryngeal tube versus laryngeal mask airway for out-of-hospital cardiac arrest by paramedics in Singapore. *Singapore Med J*. 2022;63(3):157-161. doi:10.11622/smedj.2020119
59. Comparison of supraglottic airway versus endotracheal intubation for the pre-hospital treatment of out-of-hospital cardiac arrest | Critical Care | Springer Nature Link. Accessed January 20, 2026. <https://link.springer.com/article/10.1186/cc10483>
60. Tanaka H, Ong MEH, Siddiqui FJ, et al. Modifiable Factors Associated With Survival After Out-of-Hospital Cardiac Arrest in the Pan-Asian Resuscitation Outcomes Study. *Annals of Emergency Medicine*. 2018;71(5):608-617.e15. doi:10.1016/j.annemergmed.2017.07.484
61. McMullan J, Gerech R, Bonomo J, et al. Airway management and out-of-hospital cardiac arrest outcome in the CARES registry. *Resuscitation*. 2014;85(5):617-622. doi:10.1016/j.resuscitation.2014.02.007
62. Association of Prehospital Advanced Airway Management With Neurologic Outcome and Survival in Patients With Out-of-Hospital Cardiac Arrest | Critical Care Medicine | JAMA | JAMA Network. Accessed January 20, 2026. <https://jamanetwork.com/journals/jama/fullarticle/1557712>
63. Prehospital Supraglottic Airway Was Associated With Good Neurologic Outcome in Cardiac Arrest Victims Especially Those Who Received Prolonged Cardiopulmonary Resuscitation - Park - 2017 - Academic Emergency Medicine - Wiley Online Library. Accessed January 20, 2026. <https://onlinelibrary.wiley.com/doi/abs/10.1111/acem.13309>
64. Honold J, Hodrius J, Schwietz T, et al. [Aspiration and pneumonia risk after preclinical invasive resuscitation: Endotracheal intubation and supraglottic airway management with the laryngeal tube S]. *Med Klin Intensivmed Notfmed*. 2015;110(7):526-533. doi:10.1007/s00063-015-0018-y
65. Kang K, Kim T, Ro YS, Kim YJ, Song KJ, Shin SD. Prehospital endotracheal intubation and survival after out-of-hospital cardiac arrest: results from the Korean nationwide registry. *The American Journal of Emergency Medicine*. 2016;34(2):128-132. doi:10.1016/j.ajem.2015.09.036
66. McMullan J, Gerech R, Bonomo J, et al. Airway management and out-of-hospital cardiac arrest outcome in the CARES registry. *Resuscitation*. 2014;85(5):617-622. doi:10.1016/j.resuscitation.2014.02.007
67. Wang HE, Szydlo D, Stouffer JA, et al. Endotracheal intubation versus supraglottic airway insertion in out-of-hospital cardiac arrest. *Resuscitation*. 2012;83(9):1061-1066. doi:10.1016/j.resuscitation.2012.05.018
68. Becker TK, Berning AW, Prabhu A, Callaway CW, Guyette FX, Martin-Gill C. An assessment of ventilation and perfusion markers in out-of-hospital cardiac arrest patients receiving mechanical CPR with endotracheal or supraglottic airways. *Resuscitation*. 2018;122:61-64. doi:10.1016/j.resuscitation.2017.11.054

69. Kajino K, Iwami T, Kitamura T, et al. Comparison of supraglottic airway versus endotracheal intubation for the pre-hospital treatment of out-of-hospital cardiac arrest. *Crit Care*. 2011;15(5):R236. doi:10.1186/cc10483
70. Granfeldt A, Avis SR, Nicholson TC, et al. Advanced airway management during adult cardiac arrest: A systematic review. *Resuscitation*. 2019;139:133-143. doi:10.1016/j.resuscitation.2019.04.003
71. Andersen LW, Granfeldt A, Callaway CW, et al. Association Between Tracheal Intubation During Adult In-Hospital Cardiac Arrest and Survival. *JAMA*. 2017;317(5):494-506. doi:10.1001/jama.2016.20165
72. 2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces | *Circulation*. Accessed January 20, 2026. <https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000734>
73. Segond N, Wittig J, Kern WJ, Orlob S. Towards a common terminology of ventilation during cardiopulmonary resuscitation. *Resuscitation*. 2025;207:110511. doi:10.1016/j.resuscitation.2025.110511
74. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *European Respiratory Journal*. 1993;6(Suppl 16):5-40. doi:10.1183/09041950.005s1693
75. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801
76. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a Protective-Ventilation Strategy on Mortality in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*. 1998;338(6):6. doi:10.1056/NEJM199802053380602
77. Johnson NJ, Caldwell E, Carlborn DJ, et al. The acute respiratory distress syndrome after out-of-hospital cardiac arrest: Incidence, risk factors, and outcomes. *Resuscitation*. 2019;135:37-44. doi:10.1016/j.resuscitation.2019.01.009
78. Idris AH, Aramendi Ecnarro E, Leroux B, et al. Bag-Valve-Mask Ventilation and Survival From Out-of-Hospital Cardiac Arrest: A Multicenter Study. *Circulation*. 2023;148(23):1847-1856. doi:10.1161/CIRCULATIONAHA.123.065561
79. Snyder BD, Van Dyke MR, Walker RG, et al. Association of small adult ventilation bags with return of spontaneous circulation in out of hospital cardiac arrest. *Resuscitation*. 2023;193:109991. doi:10.1016/j.resuscitation.2023.109991
80. Sinha P, Flower O, Soni N. Dead-space ventilation: a waste of breath! In: Pinsky MR, Brochard L, Mancebo J, Antonelli M, eds. *Applied Physiology in Intensive Care Medicine 2: Physiological Reviews and Editorials*. Springer; 2012:303-314. doi:10.1007/978-3-642-28233-1_29
81. Brewer LM, Orr JA, Pace NL. Anatomic dead space cannot be predicted by body weight. *Respir Care*. 2008;53(7):885-891.
82. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2020;142(16_suppl_2):S366-S468. doi:10.1161/CIR.0000000000000916

83. Yang BY, Blackwood JE, Shin J, et al. A pilot evaluation of respiratory mechanics during prehospital manual ventilation. *Resuscitation*. 2022;177:55-62. doi:10.1016/j.resuscitation.2022.06.003
84. Rohlin O, Taeri T, Netzereab S, Ullemark E, Djäv T. Duration of CPR and impact on 30-day survival after ROSC for in-hospital cardiac arrest—A Swedish cohort study. *Resuscitation*. 2018;132:1-5. doi:10.1016/j.resuscitation.2018.08.017
85. Adnet F, Triba MN, Borron SW, et al. Cardiopulmonary resuscitation duration and survival in out-of-hospital cardiac arrest patients. *Resuscitation*. 2017;111:74-81. doi:10.1016/j.resuscitation.2016.11.024
86. Cordioli RL, Brochard L, Suppan L, et al. How Ventilation Is Delivered During Cardiopulmonary Resuscitation: An International Survey. *Respiratory Care*. 2018;63(10):1293-1301. doi:10.4187/respcare.05964
87. Invasive Respiratory Support. In: *Cardiothoracic Critical Care*. Butterworth-Heinemann; 2007:419-436. doi:10.1016/B978-075067572-7.50032-1
88. Fuller BM, Mohr NM, Ablordeppey E, et al. The Practice Change and Clinical Impact of Lung-Protective Ventilation Initiated in the Emergency Department: A Secondary Analysis of Individual Patient-Level Data From Prior Clinical Trials and Cohort Studies. *Crit Care Med*. 2023;51(2):279-290. doi:10.1097/CCM.0000000000005717
89. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med*. 2005;31(7):922-926. doi:10.1007/s00134-005-2625-1
90. Levenbrown Y, Hossain MJ, Keith JP, Burr K, Hesek A, Shaffer T. The effect of positive end-expiratory pressure on cardiac output and oxygen delivery during cardiopulmonary resuscitation. *ICMx*. 2020;8(1):36. doi:10.1186/s40635-020-00330-2
91. Renz M, Müllejans L, Riedel J, et al. High PEEP Levels during CPR Improve Ventilation without Deleterious Haemodynamic Effects in Pigs. *Journal of Clinical Medicine*. 2022;11(16):4921. doi:10.3390/jcm11164921
92. Duchatelet C, Wolfskeil M, Vanwulpen M, Idrissi SH. Effect of positive end-expiratory pressure during cardiopulmonary resuscitation on short-term survival. *Resuscitation*. 2019;142:e7-e8. doi:10.1016/j.resuscitation.2019.06.029
93. Malinverni S, Wilmin S, de Longueville D, et al. A retrospective comparison of mechanical cardio-pulmonary ventilation and manual bag valve ventilation in non-traumatic out-of-hospital cardiac arrests: A study from the Belgian cardiac arrest registry. *Resuscitation*. 2024;199:110203. doi:10.1016/j.resuscitation.2024.110203
94. Aramendi E, Elola A, Alonso E, et al. Feasibility of the capnogram to monitor ventilation rate during cardiopulmonary resuscitation. *Resuscitation*. 2017;110:162-168. doi:10.1016/j.resuscitation.2016.08.033
95. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. Hyperventilation-Induced Hypotension during Cardiopulmonary Resuscitation. *Circulation*. 2004;109(16):1960-1965. doi:10.1161/01.CIR.0000126594.79136.61
96. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med*. 2004;32(9 Suppl):9 Suppl. doi:10.1097/01.ccm.0000134335.46859.09
97. Benoit JL, Lakshmanan S, Farmer SJ, et al. Ventilation rates measured by capnography during out-of-hospital cardiac arrest resuscitations and their association with return of spontaneous circulation. *Resuscitation*. 2023;182:109662. doi:10.1016/j.resuscitation.2022.11.028

98. Neth MR, Benoit JL, Stolz U, McMullan J. Ventilation in Simulated Out-of-Hospital Cardiac Arrest Resuscitation Rarely Meets Guidelines. *Prehospital Emergency Care*. 2021;25(5):712-720. doi:10.1080/10903127.2020.1822481
99. Wang HE, Jaureguibeitia X, Aramendi E, et al. Airway strategy and ventilation rates in the pragmatic airway resuscitation trial. *Resuscitation*. 2022;176:80-87. doi:10.1016/j.resuscitation.2022.05.008
100. Snyder BD, Van Dyke MR, Walker RG, et al. Association of small adult ventilation bags with return of spontaneous circulation in out of hospital cardiac arrest. *Resuscitation*. 2023;193:109991. doi:10.1016/j.resuscitation.2023.109991
101. Vissers G, Duchatelet C, Huybrechts SA, Wouters K, Hachimi-Idrissi S, Monsieurs KG. The effect of ventilation rate on outcome in adults receiving cardiopulmonary resuscitation. *Resuscitation*. 2019;138:243-249. doi:10.1016/j.resuscitation.2019.03.037
102. Jaffe IS, Ren Y, Tran L, et al. Higher ventilation rate is associated with increased return of spontaneous circulation in in-hospital cardiac arrest patients with advanced airways. *Resuscitation*. 2026;218:110885. doi:10.1016/j.resuscitation.2025.110885
103. Nichol G, Leroux B, Wang H, et al. Trial of Continuous or Interrupted Chest Compressions during CPR. *N Engl J Med*. 2015;373(23):23. doi:10.1056/NEJMoa1509139
104. Euler US v., Liljestrang G. Observations on the Pulmonary Arterial Blood Pressure in the Cat. *Acta Physiologica Scandinavica*. 1946;12(4):301-320. doi:10.1111/j.1748-1716.1946.tb00389.x
105. Bradford JR, Dean HP. The Pulmonary Circulation1. *The Journal of Physiology*. 1894;16(1-2):34-158. doi:10.1113/jphysiol.1894.sp000493
106. von Planta I, Weil MH, von Planta M, Gazmuri RJ, Duggal C. Hypercarbic acidosis reduces cardiac resuscitability. *Crit Care Med*. 1991;19(9):1177-1182. doi:10.1097/00003246-199109000-00014
107. Kerber RE, Sarnat W. Factors influencing the success of ventricular defibrillation in man. *Circulation*. 1979;60(2):226-230. doi:10.1161/01.CIR.60.2.226
108. Michenfelder JD, Sundt TMJ. The Effect of Paco₂ on the Metabolism of Ischemic Brain in Squirrel Monkeys. *Anesthesiology*. 1973;38(5):445. doi:10.1097/00000542-197305000-00006
109. T I, T K, K K, T K. Dissemination of Chest Compression-Only Cardiopulmonary Resuscitation and Survival After Out-of-Hospital Cardiac Arrest. *Circulation*. 2015;132(5). doi:10.1161/CIRCULATIONAHA.114.014905
110. Hallstrom A, Cobb L, Johnson E, Copass M. Cardiopulmonary Resuscitation by Chest Compression Alone or with Mouth-to-Mouth Ventilation. *New England Journal of Medicine*. 2000;342(21):1546-1553. doi:10.1056/NEJM200005253422101
111. SOS-KANTO study group. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet*. 2007;369(9565):920-926. doi:10.1016/S0140-6736(07)60451-6
112. Ong MEH, Ng FSP, Anushia P, et al. Comparison of chest compression only and standard cardiopulmonary resuscitation for out-of-hospital cardiac arrest in Singapore. *Resuscitation*. 2008;78(2):119-126. doi:10.1016/j.resuscitation.2008.03.012

113. Bohm K, Rosenqvist M, Herlitz J, Hollenberg J, Svensson L. Survival Is Similar After Standard Treatment and Chest Compression Only in Out-of-Hospital Bystander Cardiopulmonary Resuscitation. *Circulation*. 2007;116(25):2908-2912. doi:10.1161/CIRCULATIONAHA.107.710194
114. Markstaller K, Karmrodt J, Doebrich M, et al. Dynamic computed tomography: a novel technique to study lung aeration and atelectasis formation during experimental CPR. *Resuscitation*. 2002;53(3):307-313. doi:10.1016/s0300-9572(02)00031-x
115. Markstaller K, Rudolph A, Karmrodt J, et al. Effect of chest compressions only during experimental basic life support on alveolar collapse and recruitment. *Resuscitation*. 2008;79(1):125-132. doi:10.1016/j.resuscitation.2008.03.228
116. Georgiou M, Papanthanasoglou E, Xanthos T. Systematic review of the mechanisms driving effective blood flow during adult CPR. *Resuscitation*. 2014;85(11):1586-1593. doi:10.1016/j.resuscitation.2014.08.032
117. Criley JM, Blaufuss AH, Kissel GL. Cough-Induced Cardiac Compression: Self-administered Form of Cardiopulmonary Resuscitation. *JAMA*. 1976;236(11):1246-1250. doi:10.1001/jama.1976.03270120022018
118. Cordioli RL, Grieco DL, Charbonney E, Richard JC, Savary D. New physiological insights in ventilation during cardiopulmonary resuscitation. *Current Opinion in Critical Care*. 2019;25(1):37. doi:10.1097/MCC.0000000000000573
119. Chalkias A, Xanthos T. Timing positive-pressure ventilation during chest compression: the key to improving the thoracic pump? *European Heart Journal: Acute Cardiovascular Care*. 2015;4(1):24-27. doi:10.1177/2048872613516923
120. Kwon Y, Debaty G, Puertas L, et al. Effect of regulating airway pressure on intrathoracic pressure and vital organ perfusion pressure during cardiopulmonary resuscitation: a non-randomized interventional cross-over study. *Scand J Trauma Resusc Emerg Med*. 2015;23(1):83. doi:10.1186/s13049-015-0164-5
121. Lurie KG, Zielinski T, McKnite S, Aufderheide T, Voelckel W. Use of an Inspiratory Impedance Valve Improves Neurologically Intact Survival in a Porcine Model of Ventricular Fibrillation. *Circulation*. 2002;105(1):124-129. doi:10.1161/hc0102.101391
122. Yannopoulos D, Sigurdsson G, McKnite S, Benditt D, Lurie KG. Reducing ventilation frequency combined with an inspiratory impedance device improves CPR efficiency in swine model of cardiac arrest. *Resuscitation*. 2004;61(1):75-82. doi:10.1016/j.resuscitation.2003.12.006
123. Aufderheide TP, Nichol G, Rea TD, et al. A Trial of an Impedance Threshold Device in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine*. 2011;365(9):798-806. doi:10.1056/NEJMoa1010821
124. Kill C, Hahn O, Dietz F, et al. Mechanical Ventilation During Cardiopulmonary Resuscitation With Intermittent Positive-Pressure Ventilation, Bilevel Ventilation, or Chest Compression Synchronized Ventilation in a Pig Model*. *Critical Care Medicine*. 2014;42(2):e89. doi:10.1097/CCM.0b013e3182a63fa0
125. Kopra J, Mehtonen L, Laitinen M, et al. Chest compression synchronized ventilation during prolonged experimental cardiopulmonary resuscitation improves oxygenation but may cause pneumothoraces. *Resuscitation Plus*. 2025;22:100918. doi:10.1016/j.resplu.2025.100918

126. Hernández-Tejedor A, González Puebla V, Corral Torres E, et al. Comparison of ventilation modes in non-traumatic out-of-hospital cardiac arrest: SYMEVECA phase 2. *Resuscitation*. 2025;213:110655. doi:10.1016/j.resuscitation.2025.110655
127. Turowski P, Fetz K, Gräsner JT, Seewald S, Wnent J. Influence of different ventilation strategies during cardiopulmonary resuscitation on the return of spontaneous circulation in out-of-hospital cardiac arrest: a retrospective study from the German resuscitation registry. *Resuscitation*. 2025;215:110764. doi:10.1016/j.resuscitation.2025.110764
128. Charbonney E, Delisle S, Savary D, et al. A new physiological model for studying the effect of chest compression and ventilation during cardiopulmonary resuscitation: The Thiel cadaver. *Resuscitation*. 2018;125:135-142. doi:10.1016/j.resuscitation.2018.01.012
129. Bendixen HH, Hedley-Whyte J, Laver MB. IMPAIRED OXYGENATION IN SURGICAL PATIENTS DURING GENERAL ANESTHESIA WITH CONTROLLED VENTILATION. A CONCEPT OF ATELECTASIS. *N Engl J Med*. 1963;269:991-996. doi:10.1056/NEJM196311072691901
130. Benumof JL. Mechanism of decreased blood flow to atelectatic lung. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;46(6):1047-1048. doi:10.1152/jappl.1979.46.6.1047
131. Grieco DL, J. Brochard L, Drouet A, et al. Intrathoracic Airway Closure Impacts CO₂ Signal and Delivered Ventilation during Cardiopulmonary Resuscitation. *Am J Respir Crit Care Med*. 2019;199(6):728-737. doi:10.1164/rccm.201806-1111OC
132. Patel N, Panerai RB, Haunton V, et al. The Leicester cerebral haemodynamics database: normative values and the influence of age and sex. *Physiol Meas*. 2016;37(9):1485. doi:10.1088/0967-3334/37/9/1485
133. Gutiérrez JJ, Sandoval CL, Leturiondo M, et al. Contribution of chest compressions to end-tidal carbon dioxide levels generated during out-of-hospital cardiopulmonary resuscitation. *Resuscitation*. 2022;179:225-232. doi:10.1016/j.resuscitation.2022.07.009
134. Murphy RA, Bobrow BJ, Spaite DW, Hu C, McDannold R, Vadeboncoeur TF. Association between Prehospital CPR Quality and End-Tidal Carbon Dioxide Levels in Out-of-Hospital Cardiac Arrest. *Prehospital Emergency Care*. 2016;20(3):369-377. doi:10.3109/10903127.2015.1115929
135. Sandroni C, Ristagno G. End-tidal CO₂ to detect recovery of spontaneous circulation during cardiopulmonary resuscitation: We are not ready yet. *Resuscitation*. 2016;104:A5-A6. doi:10.1016/j.resuscitation.2016.05.018
136. Pokorná M, Nečas E, Kratochvíl J, Skřípský R, Andrlík M, Franěk O. A Sudden Increase in Partial Pressure End-Tidal Carbon Dioxide (PETCO₂) at the Moment of Return of Spontaneous Circulation. *The Journal of Emergency Medicine*. 2010;38(5):614-621. doi:10.1016/j.jemermed.2009.04.064
137. Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO₂) measurement to guide management of cardiac arrest: A systematic review. *Resuscitation*. 2018;123:1-7. doi:10.1016/j.resuscitation.2017.12.003
138. Smida T, Menegazzi JJ, Crowe RP, Salcido DD, Bardes J, Myers B. The Association of Prehospital End-Tidal Carbon Dioxide with Survival Following Out-of-Hospital Cardiac Arrest. *Prehospital Emergency Care*. 2024;28(3):478-484. doi:10.1080/10903127.2023.2262566
139. McCabe EB, Lukins M. Gastric Carbon Dioxide Insufflation Can Lead to Misleading Capnography Trace During Esophageal Intubation. *A&A Practice*. 2018;11(11):328. doi:10.1213/XAA.0000000000000898

140. Chrimes N, Higgs A, Hagberg CA, et al. Preventing unrecognised oesophageal intubation: a consensus guideline from the Project for Universal Management of Airways and international airway societies*. *Anaesthesia*. 2022;77(12):1395-1415. doi:10.1111/anae.15817
141. Khoury A, De Luca A, Sall FS, Pazart L, Capellier G. Ventilation feedback device for manual ventilation in simulated respiratory arrest: a crossover manikin study. *Scand J Trauma Resusc Emerg Med*. 2019;27:93. doi:10.1186/s13049-019-0674-7
142. You KM, Lee C, Kwon WY, et al. Real-time tidal volume feedback guides optimal ventilation during simulated CPR. *The American Journal of Emergency Medicine*. 2017;35(2):292-298. doi:10.1016/j.ajem.2016.10.085
143. Gould JR, Campana L, Rabickow D, Raymond R, Partridge R. Manual ventilation quality is improved with a real-time visual feedback system during simulated resuscitation. *Int J Emerg Med*. 2020;13:18. doi:10.1186/s12245-020-00276-y
144. Drennan IR, Lee M, Héroux JP, et al. The impact of real-time feedback on ventilation quality during out-of-hospital cardiac arrest: A before-and-after study. *Resuscitation*. 2024;204:110381. doi:10.1016/j.resuscitation.2024.110381
145. CLOSED-CHEST CARDIAC MASSAGE | JAMA | JAMA Network. Accessed February 9, 2026. <https://jamanetwork.com/journals/jama/fullarticle/328956>
146. KOUWENHOVEN WB. The Development of the Defibrillator. *Ann Intern Med*. 1969;71(3):449-458. doi:10.7326/0003-4819-71-3-449
147. Vognsen M, Fabian-Jessing BK, Secher N, et al. Contemporary animal models of cardiac arrest: A systematic review. *Resuscitation*. 2017;113:115-123. doi:10.1016/j.resuscitation.2017.01.024
148. Swindle MM, Makin A, Herron AJ, Clubb Jr FJ, Frazier KS. Swine as Models in Biomedical Research and Toxicology Testing. *Vet Pathol*. 2012;49(2):344-356. doi:10.1177/0300985811402846
149. Cooper DKC, Cozzi E. Clinical Pig Heart Xenotransplantation—Where Do We Go From Here? *Transpl Int*. 2024;37:12592. doi:10.3389/ti.2024.12592
150. Fieldhouse R. Pig lung transplanted into a person in world first. *Nature*. 2025;645(8079):20-20. doi:10.1038/d41586-025-02708-2
151. Anatomy and Bronchoscopy of the Porcine Lung. A Model for Translational Respiratory Medicine. *American Journal of Respiratory Cell and Molecular Biology*. Accessed February 9, 2026. <https://www.atsjournals.org/doi/10.1165/rcmb.2013-0453TR>
152. CRICK SJ, SHEPPARD MN, HO SY, GEBSTEIN L, ANDERSON RH. Anatomy of the pig heart: comparisons with normal human cardiac structure. *J Anat*. 1998;193(Pt 1):105-119. doi:10.1046/j.1469-7580.1998.19310105.x
153. Definition of PARAMETER. February 2, 2026. Accessed February 3, 2026. <https://www.merriam-webster.com/dictionary/parameter>
154. Gilbey JD, Wilson M. Measurement of gas flow and volume. *Anaesthesia & Intensive Care Medicine*. 2021;22(1):37-41. doi:10.1016/j.mpaic.2020.11.013
155. Ortega R, Connor C, Kim S, Djang R, Patel K. Monitoring Ventilation with Capnography. *New England Journal of Medicine*. 2012;367(19):e27. doi:10.1056/NEJMvcm1105237
156. Sert NP du, Ahluwalia A, Alam S, et al. Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0. *PLOS Biology*. 2020;18(7):7. doi:10.1371/journal.pbio.3000411

157. Research Randomizer. Accessed June 27, 2023. <https://www.randomizer.org/>
158. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST
159. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med.* 2017;43(3):304-377. doi:10.1007/s00134-017-4683-6
160. Cohen TJ, Goldner BG, Maccaro PC, et al. A Comparison of Active Compression-Decompression Cardiopulmonary Resuscitation with Standard Cardiopulmonary Resuscitation for Cardiac Arrests Occurring in the Hospital. *New England Journal of Medicine.* 1993;329(26):1918-1921. doi:10.1056/NEJM199312233292603
161. Steinberg MT, Olsen JA, Eriksen M, et al. Haemodynamic outcomes during piston-based mechanical CPR with or without active decompression in a porcine model of cardiac arrest. *Scand J Trauma Resusc Emerg Med.* 2018;26(1):31. doi:10.1186/s13049-018-0496-z
162. Moore JC, Holley J, Segal N, et al. Consistent head up cardiopulmonary resuscitation haemodynamics are observed across porcine and human cadaver translational models. *Resuscitation.* 2018;132:133-139. doi:10.1016/j.resuscitation.2018.04.009
163. Ryu HH, Moore JC, Yannopoulos D, et al. The Effect of Head Up Cardiopulmonary Resuscitation on Cerebral and Systemic Hemodynamics. *Resuscitation.* 2016;102:29-34. doi:10.1016/j.resuscitation.2016.01.033
164. Berve PO, Hardig BM, Skålhegg T, Kongsgaard H, Kramer-Johansen J, Wik L. Mechanical active compression-decompression versus standard mechanical cardiopulmonary resuscitation: A randomised haemodynamic out-of-hospital cardiac arrest study. *Resuscitation.* 2022;170:1-10. doi:10.1016/j.resuscitation.2021.10.026
165. Intrathoracic Airway Closure Impacts CO2 Signal and Delivered Ventilation during Cardiopulmonary Resuscitation. *American Journal of Respiratory and Critical Care Medicine.* Accessed February 13, 2026. <https://www.atsjournals.org/doi/full/10.1164/rccm.201806-1111OC>
166. Vanwulpen M, Wolfskeil M, Duchatelet C, Hachimi-Idrissi S. Do manual chest compressions provide substantial ventilation during prehospital cardiopulmonary resuscitation? *The American Journal of Emergency Medicine.* 2021;39:129-131. doi:10.1016/j.ajem.2020.09.037
167. Deakin CD, O'Neill JF, Tabor T. Does compression-only cardiopulmonary resuscitation generate adequate passive ventilation during cardiac arrest? *Resuscitation.* 2007;75(1):53-59. doi:10.1016/j.resuscitation.2007.04.002
168. Kwon Y, Debaty G, Puertas L, et al. Effect of regulating airway pressure on intrathoracic pressure and vital organ perfusion pressure during cardiopulmonary resuscitation: a non-randomized interventional cross-over study. *Scand J Trauma Resusc Emerg Med.* 2015;23(1):83. doi:10.1186/s13049-015-0164-5
169. Shin WJ, Cheong YS, Yang HS, Nishiyama T. The supraglottic airway I-gel in comparison with ProSeal laryngeal mask airway and classic laryngeal mask airway in anaesthetized patients. *European Journal of Anaesthesiology | EJA.* 2010;27(7):598. doi:10.1097/EJA.0b013e3283340a81

170. ORIGINAL ARTICLE: Comparison of guided insertion of the LMA ProSeal™ vs the i-gel™ - Gasteiger - 2010 - Anaesthesia - Wiley Online Library. Accessed February 16, 2026. <https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/10.1111/j.1365-2044.2010.06422.x>
171. Comparison of the Proseal LMA and intersurgical I-gel during gynecological laparoscopy. Accessed February 16, 2026. <https://ekja.org/journal/view.php?doi=10.4097/kjae.2012.63.6.510>
172. Van Zundert TCRV, Brimacombe JR. Similar oropharyngeal leak pressures during anaesthesia with i-gel, LMA-ProSeal and LMA-Supreme Laryngeal Masks. *Acta Anaesthesiol Belg*. 2012;63(1):35-41.
173. Hayashi K, Suzuki A, Kunisawa T, Takahata O, Yamasawa Y, Iwasaki H. [A comparison of the single-use i-gel with the reusable laryngeal mask airway Proseal in anesthetized adult patients in Japanese population]. *Masui*. 2013;62(2):134-139.
174. Gazmuri RJ, Ayoub IM, Radhakrishnan J, Motl J, Upadhyaya MP. Clinically plausible hyperventilation does not exert adverse hemodynamic effects during CPR but markedly reduces end-tidal PCO₂. *Resuscitation*. 2012;83(2):259-264. doi:10.1016/j.resuscitation.2011.07.034
175. Endo Y, Aoki T, Jafari D, et al. Acute lung injury and post-cardiac arrest syndrome: a narrative review. *J intensive care*. 2024;12(1):32. doi:10.1186/s40560-024-00745-z
176. Marchese G, Bungaro E, Magliocca A, et al. Acute Lung Injury after Cardiopulmonary Resuscitation: A Narrative Review. *Journal of Clinical Medicine*. 2024;13(9). doi:10.3390/jcm13092498
177. Mai N, Miller-Rhodes K, Knowlden S, Halterman MW. The post-cardiac arrest syndrome: A case for lung–brain coupling and opportunities for neuro-protection. *J Cereb Blood Flow Metab*. 2019;39(6):939-958. doi:10.1177/0271678X19835552
178. Olasveengen TM, Skåre C, Skjerven-Martinsen M, et al. Lung tissue injury and hemodynamic effects of ventilations synchronized or unsynchronized to continuous chest compressions in a porcine cardiac arrest model. *Resuscitation Plus*. 2024;17:100530. doi:10.1016/j.resplu.2023.100530
179. Vanwulpen M, Wolfskeil M, Duchatelet C, Hachimi-Idrissi S. Do manual chest compressions provide substantial ventilation during prehospital cardiopulmonary resuscitation? *The American Journal of Emergency Medicine*. 2021;39:129-131. doi:10.1016/j.ajem.2020.09.037
180. Deakin CD, O'Neill JF, Tabor T. Does compression-only cardiopulmonary resuscitation generate adequate passive ventilation during cardiac arrest? *Resuscitation*. 2007;75(1):53-59. doi:10.1016/j.resuscitation.2007.04.002
181. Piquilloud L, Beitler JR, Beloncle FM. Monitoring esophageal pressure. *Intensive Care Med*. 2024;50(6):953-956. doi:10.1007/s00134-024-07401-y
182. LUCAS 3, v3.1 chest compression system. Accessed February 18, 2026. <https://www.stryker.com/us/en/emergency-care/products/lucas-3.html>
183. Matthiessen L, Lucaroni B, Sacher E. Towards responsible animal research. *EMBO Rep*. 2003;4(2):104-107. doi:10.1038/sj.embor.embor745
184. Jerlström J, Berg C, Wallenbeck A. Unnecessary suffering during the slaughter of cattle and pigs: mapping stun quality and associations to stun-to-stick intervals. *Front Anim Sci*. 2025;6. doi:10.3389/fanim.2025.1633616
185. Positive welfare: What does it add to the debate over pig welfare? In: *Advances in Pig Welfare*. Woodhead Publishing; 2018:415-444. doi:10.1016/B978-0-08-101012-9.00014-9

186. Ineichen BV, Furrer E, Grüniger SL, Zürrer WE, Macleod MR. Analysis of animal-to-human translation shows that only 5% of animal-tested therapeutic interventions obtain regulatory approval for human applications. *PLoS Biology*. 2024;22(6):e3002667. doi:10.1371/journal.pbio.3002667
187. WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants. Accessed February 18, 2026. <https://www.wma.net/policies-post/wma-declaration-of-helsinki/>
188. Lag (2003:460) om etikprovning av forskning som avser människor. Accessed February 18, 2026. https://www.riksdagen.se/sv/dokument-och-lagar/dokument/svensk-forfattningssamling/lag-2003460-om-etikprovning-av-forskning-som_sfs-2003-460/

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