Ventilation during advanced cardiopulmonary resuscitation in out-of-hospital and in-hospital cardiac arrests – an observational study.

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1. Summary/Abstract

The aim with this descriptive multicentre study is to examine the quality of the ventilation given by pre-hospital Emergency Medical Service (EMS) personnel and emergency team personnel in-hospital during cardiopulmonary resuscitation (CPR). It will consist of two parts. One examining the ventilation in Out-of-hospital cardiac arrests (OHCA) and one examining the ventilation in In-hospital cardiac arrests (IHCA).

Primary endpoint is the ventilation quality measured as ventilation frequency, peak airway pressure, tidal volume, and minute ventilation.

In OHCA: s this will be studied in patients receiving either 30:2 CPR with a supraglottic airway (SGA) or CPR with continuous ventilations with an endotracheal tube (ET) given during ongoing chest compressions.

In IHCA:s this will be studied in patients receiving continuous ventilations with an ET given during ongoing chest compressions.

The inclusion of patients in the OHCA part will be performed at multiple sites: Uppsala, Dalarna County, Västmanland county, Stockholm metropolitan area; Sweden and Amsterdam and Utrecht; The Netherlands). OHCA patients will receive standard care according to current CPR guidelines using manual or mechanical chest compressions.

Inclusion of patients in the IHCA part will be performed at Uppsala University Hospital in Uppsala, Karolinska University Hospital in Stockholm, and Falun County Hospital in Falun. IHCA patients will also receive standard care according to current CPR guidelines.

1.2 Criteria for inclusion

Out of hospital cardiac arrest treated with cardiopulmonary resuscitation performed by the emergency medical services and in hospital cardiac arrest treated with cardiopulmonary resuscitation performed by emergency team personnel.

1.3 Criteria for exclusion

- Patient age < 18 years.
- Known pregnancy.

2. List of abbreviations and definitions of terms

CABG	Coronary Artery Bypass Grafting
CPR	Cardiopulmonary Resuscitation
CPC	Cerebral Performance Categories
CRF	Case Report Form
EMR	Electronic Medical Records
EMS	Emergency Medical Service
ET	Endotracheal tube
etCO2	End Tidal Carbon Dioxide
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GOS-E	Extended Glasgow Outcome Scale
I-Gel	Supraglottic Airway device
ICD	Implantable Cardioverter Defibrillator
IHCA	In-hospital cardiac arrest
LUCAS	Mechanical Chest Compression System
mRS	Modified Rankin Scale
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous Coronary Intervention
ROSC	Return of Spontaneous Circulation
SGA	Supraglottic airway
SCA	Sudden Cardiac Arrest

3. Background

In Europe approximately 500 000 people per year are affected by sudden cardiac arrests (SCA) and it is one of the leading causes of death (1). CPR with external chest compressions, has been the standard resuscitative measure since the beginning of the 1960´s (2). Despite progress in research and interventions most patients do not survive an OHCA (3), although the 30 days survival, in Sweden, after a SCA under the last decade has doubled resulting in a survival rate at 11% in 2017 (4). An analysis of OHCA outcome in 27 countries in Europe presented rates of Return of Spontaneous Circulation (ROSC) from less than 10.0% up to 50.0% and hospital survival ranging from less than 5.0% up to 30.0%. The cause of this variance may be due to different EMS structures, CPR standards or due to differences in how the occurrence of ROSC has been perceived and registered in different regions in Europe (5).

The survival rate for IHCA is significantly higher, with 37% of the patients alive after 30-days in Sweden 2019. This in part because ICHA: s receives CPR much earlier than OHCA: s. In 90% of the cases in Sweden 2019, CPR was started within 1 minute of the cardiac arrest (6).

The field of IHCA has received considerably less attention than OHCA, and most of the patients affected still do not survive (7). Many variables in the treatment in IHCA therefore remains unexplored and in need of investigation, among them the ventilation.

High quality CPR is crucial for maximizing survival and several studies have displayed the importance of early defibrillation, high quality chest compressions and minimizing interruptions of chest compressions but not only the quality of these components but also the timing is vital. Since 2010 the gold standard of the ratio between compressions and ventilations has been 30:2 although when a SGA or an ET have been inserted the patient can be ventilated at a rate of 10 breaths/min with continuous chest compressions at the rate of 100-120/min (8-11). One concern is the theoretical risk that during periods of continuous chest compressions the ventilation might be compromised, a higher intrathoracic pressure generated by chest compressions may impede airflow to the lungs and when combined with a SGA leading to a higher risk for air leakage (12).
During ongoing CPR, there are not many ways to measure the efficacy of CPR. It has been postulated that end tidal carbon dioxide ($etCO_2$) could serve as a pseudo marker for the quality of CPR due to its correlation with pulmonary blood flow and cardiac output (13). Measurement of $etCO_2$ is therefore a validated method but due to lack of definitive data on the best form of ventilatory support and technological restrictions to collecting valid $etcCO_2$ during cardiac arrest one should be cautious when using the data in clinical situations (12). It has never been elucidated how the different CPR techniques (i.e., mechanical chest compressions versus manual chest compressions or continuous ventilation versus ventilation during pauses) affects the ventilation quality or $etCO_2$ and therefor the primary goal of this descriptive study is to evaluate the ventilation achieved during CPR performed by EMS personnel.

4. Primary and secondary endpoints

4.1 Primary endpoint

Primary endpoint is the ventilation quality measured as the ventilation frequency, peak airway pressure, tidal volume, and minute ventilation.

4.2 Secondary endpoints

The secondary endpoints are values or measurements that could be connected or affected by ventilation quality including:

- $etCO_2$ variation in relation to different modes of compression/ventilation (30:2 and ventilation during ongoing compressions).
- Variances in inspiration time.
- Fraction of dead space ventilation.
- Differences in the above-mentioned parameters between OHCA and IHCA
- Differences in the above-mentioned parameters between intubated patients with ventilation during ongoing compressions and patients with a supraglottic airway with 30:2 CPR.

5. Study population

The study population will be patients who have suffered an OHCA with CPR started by EMS personnel in Uppsala, Dalarna County, Västmanland County, and Stockholm metropolitan area; Sweden and

Amsterdam and Utrecht; The Netherlands and patients who have suffered an IHCA in Uppsala; Sweden, Stockholm; Sweden and Falun; Sweden.

5.1 Timetable

- OHCA part start Q1 2019.
- IHCA part start Q4 2022
- End of inclusion Q4 2024

5.2 Criteria for inclusion

OHCA treated with CPR performed by EMS personnel and IHCA treated with CPR performed by emergency team personnel.

5.3 Criteria for exclusion

- Patient age < 18 years.
- Known pregnancy.

6. Method

The study will be a prospective descriptive multicentre study where measurement of ventilation data will be sampled during CPR.

The study will consist of two parts. One with OHCA: s and one with IHCA: s.

The first part will include OHCA patients treated by the EMS service staffed by registered nurses and where CPR using the 30:2 method with an SGA variant called I-GEL is used. It will also include OHCA patients treated by an EMS rapid response unit staffed with anaesthesiologists where an ET is used, and ventilations are given continuously during ongoing chest compressions. The second part will include IHCA patients treated by emergency teams consisting of anaesthesiologists and nurse anaesthesiologists where an ET is used, and ventilations are given continuously during ongoing chest compressions.

Data regarding care during and after the cardiac arrest will be obtained from the Swedish CPR registry.

Data regarding hospital care and standard laboratory tests related to ventilation quality will be obtained from the patient medical journal systems. Outcome measures will be any ROSC, survival, and neurological outcome (CPC) measured at hospital discharge, 30 days and at 6 months.

The inclusion will run until the end of 2024. If the goal of 400 patients in the OHCA part and 200 in the IHCA part is reached before the end of 2024, the inclusion will stop by that time.

The study has been preceded by a trial period to solve any logistic and technical problems and will be registered at Clinicaltrials.gov before its initiation.

6.1 Setting

The inclusion of patients for the OHCA part will be performed at multiple sites (Uppsala, Dalarna County, Västmanland County, Stockholm metropolitan area; Sweden and Amsterdam and Utrecht; The Netherlands), all of the sites have the LUCAS device in their protocol for cardiac arrest and have implemented a specific algorithm, order of priority, while working with the LUCAS device. The algorithm which is in accordance with current guidelines will be presented as an attachment to the study.

The inclusion of patients for the IHCA part will be performed at Uppsala University Hospital in Uppsala, Sweden, Karolinska University Hospital in Stockholm, Sweden and Falun County Hospital in Falun, Sweden.

6.1.1 Uppsala

Uppsala is the capital of Uppsala County and the fourth largest city in Sweden. Uppsala has approximately 210 000 residents (2017). The EMS service of Uppsala County has 13 ambulances covering 24 hours a day, seven days a week. Six of these are based in the city of Uppsala. Additionally, five ambulances are in service during office hours on weekdays. The EMS personnel in all ambulances consists of at least one nurse, in most cases (90%) a specialized nurse with additional education in emergency and ambulance care, anaesthesia or intensive care. The city of Uppsala has about 80 employees consisting of nurses, specialized nurses, and assistant nurses.

6.1.2 Utrecht, the Netherlands

Utrecht is the fourth largest city in The Netherlands and the city of Utrecht is the capital of the Utrecht Province. The Utrecht province has app. 1.3 million residents (2017). EMS provides 24/7 prehospital care for all inhabitants in the Utrecht province. The public can call the dispatch centre via telephone number 1-1-2 in case of any emergencies. There is 1 dispatch centre and there are 11 Ambulance-stations for 46 Ambulances, 15 fast responder Cars and 6 fast responder Motor bikes. The EMS personnel in all ambulances consists of one driver and one nurse, all the nurses are specialized nurses with additional education in emergency and ambulance care, anaesthesia, or intensive care. Utrecht has about 160 specialized nurses and 130 ambulance drivers.

6.1.2 Ambulance Amsterdam, the Netherlands

Amsterdam is the capital city of the Netherlands, situated in the province of North-The Netherlands. Amsterdam city has approximately 896 000 residents (2023). Ambulance Amsterdam provides all prehospital care as emergency medical service for all inhabitants, 24/7. The public can call the dispatch center via national telephone number 1-1-2 in case of any emergency. There is 1 regional dispatch center and there are 8 EMS stations. The station on the west side of the city center is the most centrally positioned station in Amsterdam, and attends the highest rate of OHCA of all Ambulance Amsterdam stations of Ambulance Amsterdam. It provides care with 7 advanced life support ambulances. The EMS personnel in all ambulances consists of one driver and one nurse, all the nurses are specialized nurses with additional education in emergency and ambulance care, anesthesia or intensive care. Ambulance post West employs about 60 specialized ambulance nurses.

6.1.3 Dalarna County

Dalarna County has a population of approximately 280 000. There are two larger cities in the county, Borlänge and Falun where roughly 40 % of the population lives. The EMS service in Dalarna consist of 11 stations with 18 ambulances in service 24/7. They are staffed with at least one nurse, often specialized in emergency and ambulance care, anesthesia or intensive care.

6.1.4 Västmanland County

Västmanland county has around 280 000 inhabitants with Västerås being the largest city where approximately 56% of the county's population lives. The EMS service in Västerås county consists of 4 stations and 16 ambulances in service 24/7. They are staffed with at least one nurse, often specialized in emergency and ambulance care, anesthesia, or intensive care.

6.1.5 Stockholm metropolitan area

Stockholm is the capital of Sweden with approximately 2.5 million inhabitants in the metropolitan area. The area is served by over 80 ambulances as well as two helicopters and three non-transporting

rapid response units staffed by physicians (specialized in anesthesiology or emergency medicine) and nurse anesthetists. Of these, one is in service 24/7. These special units mainly respond to serious conditions such as cardiac arrests and major trauma.

6.1.6 Uppsala University Hospital

Uppsala university hospital is one of Sweden's largest hospitals with 8000 employees and approximately 940 beds. The emergency teams that respond to cardiac arrest alarms consist of anaesthesiologists and nurse anaesthesiologists.

6.1.7 Karolinska University Hospital

Karolinska University Hospital in Solna, Stockholm, Sweden is one of Stockholm's five metropolitan hospitals. It has 550 beds and 6000 employees. The emergency teams that respond to cardiac arrest alarms consist of anaesthesiologists and nurse anaesthesiologists.

6.1.8 Falun County Hospital

Falun county hospital is the county hospital of Dalarna County. It has 3300 employees and 500 beds. The emergency teams that respond to cardiac arrest alarms consist of anaesthesiologists and nurse anaesthetists.

6.2 Training

All EMS and emergency team personnel (Sweden) are obliged to participate in annual CPR training sessions per standards of Swedish CPR council. All Dutch EMS personnel are obliged to participate in at least three CPR training sessions per standards and guidelines of Dutch CPR council.
All personnel responsible for the inclusion of patients will undergo a theoretical and practical training program to ensure that they can perform measurements of ventilation markers in a secure and correct way. The personnel, that have been working with the Flux Med device prior to the study, have received individual instructions in how to use the equipment.

6.3 Equipment

The Flux Med device with the ability to measure ventilation parameters will be used in the study. In complement to the Flux Med a computer (Microsoft surface) will be connected to collect and save ventilation values. The equipment will be carried in a special bag appropriated for the prehospital setting. A routine for maintaining and configurating the equipment has been created. A description of the device and routine for application and configuration will be presented as an attachment to the study. The device has been implemented in the clinical setting and has therefore been in use prior to the start of the study.

7. Implementation

In the OHCA part the FluxMed device and the computer, will be carried in a special bag by the EMS personnel in complement with the other equipment used when performing CPR. In OHCA the EMS personnel carrying the Flux Med device will oversee the airway management. The personnel will follow the current standards for CPR and priority order while working with the LUCAS device. When either the SGA is successfully placed or the patient is intubated with an ET, the FluxMed will be started and a mainstream sensor, placed between the SGA/ET and bag valve mask, will automatically sample ventilation parameters. All OHCA patients will receive care according to current guidelines, which includes chest compressions, ventilation, defibrillation, and the use of Epinephrine and Amiodarone.

The standard compression to ventilation ratio used in the prehospital setting is 30:2. In the cases where the patient is intubated by the rapid response unit ventilations will be given continuously during ongoing compressions.

In the IHCA part, the FluxMed device and the computer will be carried in a special bag by the emergency teams that responds to cardiac arrest alarms inside the hospital. The bag will be mounted on a bike that the personnel use to get to the patient. When they reach the patient, they will continue the CPR that the ward staff has already started. They will then perform an endotracheal intubation and connect the FluxMed to the tube. When the intubation is done, the CPR will continue with continuous chest compressions and 8-10 ventilations per minute.

7.1 Documentation of patient data & CRF

The personnel will use the current electronic medical record (EMR) system available in the ambulance organizations and in the hospitals for documenting and keeping patient records. In addition, they will also use a case report form (CRF). All the questions in the CRF must be answered, if the question can´t be answered the alternatives ND=not done, NA=not applicable or NK=Not known can be used.

7.2 Patient monitoring

Monitoring of OHCA patients included in the study will be performed by the responsible investigator. Monitoring will be performed by obtaining data from the Swedish CRP registry and by checking the patient records for ROSC, post cardiac arrest care, survival rate including neurologic outcome measured using CPC and mRS at discharge, 30 days and at 6 months using GOS-E.
Monitoring of post cardiac arrest treatment will also be conducted, and we will check for eventual implantable cardioverter defibrillator (ICD) insertions, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and treatment with targeted temperature management.

8. Safety

No safety risks have been acknowledged while using the Flux Med prior to the planning of the study. Eventual deviations that are brought to attention, while using the Flux Med device, regarding patient safety will be reported to responsible investigators and reported according to current regulations stipulated in the respective ambulance organizations.

9. Monitoring

Monitoring of data will be performed by the responsible sponsor and performed by research nurses employed at Uppsala University Hospital and personnel from Uppsala Clinical Research according to Good Clinical Practice (GCP).

An independent monitor shall ensure that:

- The protocol is followed according to set standards.
- The recruitment and inclusion of patient follows the study plan.
- The correct data are collected for the CRF which been assembled for the study.
- The needed resources are available for implementation of all parts to answer the study's endpoints.

The principal investigator shall ensure that the independent monitor have access to CRF, patient records and blood samples/laboratory data originals etc. to ensure that the correct data are documented for the study, without any risk for the patient's integrity.

9.1 Source data

Data in the CRF will be controlled so that the patient data are confirmed with the data documented in the patient records.

10. Data Collection

A database will be established and maintained by the responsible investigators in this study. Principal investigator is Sten Rubertsson.
The included patients name, and social security number will be replaced in the database with a code. A keycode will be kept protected to ensure that the patients' identities are protected from unauthorized persons. All documents related to this study will be kept in such a way that information regarding included patients is safe from unauthorized persons and controlled according to the general data protection regulation (GDPR) which purpose is to ensure that all EU citizens data privacy are protected. The Dutch general data protection regulation is followed in The Netherlands and quite similar to the Swedish regulations.

11. Ethical considerations

There are several reasons why the patients who suffered from a SCA are to be included in scientific examinations. The mortality is, in defiance to new guidelines and research, still high and therefore there is humanitarian as well as scientific reasons to continue to pursue ways to improve survival. Otherwise, there is a risk that this group of patients are excluded from the possibility to a better outcome which can be considered unethical.

12. Statistical considerations

As this study will be a descriptive study no power analysis has been performed.
Continuous variables will be reported as means and SDs or medians and IQRs and categorical variables as proportions. Dichotomous outcomes will be compared using χ^2 tests or Fisher's exact test when appropriate. Continuous outcomes will be compared with independent samples using the *t* test or the non-parametric Mann-Whitney *U* test if variables are not normally distributed. We will use the Kaplan-Meier method and log-rank test to compare survival curves from inclusion until 30 days.

13. Insurance of patients included in the study

Subjects in the study in Sweden are covered by the Swedish Patient Insurance. In other countries a similar insurance system will be applicable as in the Netherlands patient insurance is also mandatory.

14. Publication policy

After completion of the study, the statistical analyses will be performed by the investigators. Based on these data, the investigators, will prepare manuscripts intended for publication in medical/scientifical journals.

15. Steering committee

Sten Rubertsson MD, PhD, Professor, Uppsala, Sweden

David Smekal MD, PhD, Uppsala, Sweden

Johan Mälberg, RN, PhD student, Uppsala, Sweden

Hans van Schuppen, MD, PhD, Amsterdam, the Netherlands

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