Diploma Thesis

Mechanical Ventilation during External Chest Compressions

Observation of Tidal Volumes during Chest Compressions in the Thiel Human Cadaver Model

submitted by

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Affirmation

I hereby declare that the submitted diploma thesis was created by myself only, without external aid, no other sources but the cited sources were used, all sources were cited properly and clearly in the present document.

Graz, 31.03.2022 *Johannes Ulrich Wittig eh.*

Acknowledgments

Above all, I would like to thank my mother, Johanna Winands-Wittig, who continues to support me and is the reason why I have always felt free to pursue my aspirations. I believe Ulrich would have been happy and proud to see how we carried on.
My grandmother, Elisabeth Ritzerfeld, and my aunt, Maria Ritzerfeld-Bockstegers, have supported me ever since I can remember – Thank you for getting me so far.
To my partner, Cornelia Laserer – I am grateful for your love and unwavering support.

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This research project was possible because people decided to donate their bodies to science. Their noble decision helped to educate me during my anatomical studies and enabled this research project to contribute to the safety of the sickest patients' medical treatment. My gratitude goes out to them.

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Abbreviations

ALS	Advanced Life Support	
BLS	Basic Life Support	
BVM	bag-valve-mask	
CO_2	carbon dioxide	
CPR	cardiopulmonary resuscitation	
C_{stat}	static compliance	in ml/mbar
EMS	emergency medical services	
EuReCA	European Registry of Cardiac Arrest	
f	(ventilation) frequency	in min^{-1}
F_iO_2	fraction of inspired oxygen	in % or decimal
FRC	functional residual capacity	
ID	identification	
IHCA	in-hospital cardiac arrest	
ILCOR	International Liaison Committee on Resuscitation	
IPBW	ideal predicted bodyweight	in kg
IPPV	intermittent positive pressure ventilation	
i.o.	intraosseous	
i.v.	intravenous	
I:E	inspiratory to expiratory ratio	
O_2	oxygen	
OHCA	out-of-hospital cardiac arrest	
PEA	pulseless electrical activity	
PEEP	positive end-expiratory pressure	in cmH_2O
P_{max}	maximum pressure limit	in cmH_2O
P_{start}	starting pressure	in cmH_2O
P_{top}	top pressure	in cmH_2O
PV	pressure-volume (diagram or loop)	
VT	ventricular tachycardia	
ROSC	return of spontaneous circulation	
SCA	sudden cardiac arrest	
SCD	sudden cardiac death	
$t_{maneuver}$	time of recruitment maneuver	in s

t_{pause}	time of pause of recruitment maneuver	in s
VC-CMV	volume-controlled continuous mandatory ventilation	
VF	ventricular fibrillation	
V_t	tidal volume	in ml

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Abstract (German)

Einleitung

Die Herzdruckmassage und Beatmung sind Grundpfeiler der kardiopulmonalen Reanimation. Allerdings werden bei manueller Beatmung wiederholt exzessive Beatmungsfrequenzen beobachtet. Exzessiven Beatmungsfrequenzen während der Reanimation sind mit reduzierten Überlebenschancen assoziiert. Gleichzeitig lassen Blutgasanalysen während der Reanimation vermuten, dass Hypoventilation häufig vorkommt. Der Einsatz von mobilen Beatmungsgeräten ist eine Möglichkeit exzessive Beatmungsfrequenzen zu vermeiden. Unbekannt ist, in welchem Ausmaß die eingestellten Tidalvolumina durch die Herzdruckmassage beeinflusst werden. Diese Diplomarbeit war Teil einer Studie in der hinterfragt wurde, ob mobile Beatmungsgeräte für den Gasaustausch relevante Tidalvolumina unter Herzdruckmassage generieren können.

Material und Methoden

Als Reanimationsmodelle dienten sechs Thiel‘sche Leichen. Drei mobile Beatmungsgeräte wurden in einem randomisierten Cross-over Design simulierter Reanimation beobachtet. Die Modelle wurden über einen Endotrachealtubus in volumenkontrolliertem Beatmungsmodus und mit einem Tidalvolumen von 6 ml/kg idealem Körpergewicht beatmet. Es kamen die Beatmungsgeräte „MEDUMAT Standard^2“, „Oxylog 3000 plus“ und „Monnal T60“ unter kontinuierlicher Herzdruckmassage zum Einsatz.
Dabei wurden Gasfluss, Atemwegsdruck und Ösophagusdruck aufgezeichnet. Abgeleitete Tidalvolumina und deren Abweichung vom eingestellten Tidalvolumen wurden berechnet und verglichen. Analysen der Volumenabweichung, des Spitzenflusses und des Spitzendrucks wurden anhand von gemischt-linearen Modellen durchgeführt.

Ergebnisse

Es wurden 715 Beatmungen in die Analyse inkludiert. Das eingestellte Tidalvolumen lag im Median bei 390 (40, [290; 410]) ml. Das mediane inspiratorische Tidalvolumen ergab 275 (68, [47; 464]) ml. Die mediane Abweichung vom eingestellten Tidalvolumen betrug −21.2 (19.6, [−87.9; 25.8]) %, was ein Tidalvolumen von 4.75 (1.2, [0.7; 7.6]) ml/kg idealem Körpergewicht entsprach. Die mediane Abweichung für den “MEDUMAT Standard^2” war −31.5 (16.6, [−56.5; −14.8]) %, für den “Oxylog 3000 plus” −22.7 (22.1, [−70; −12.3]) % und für den ‘Monnal T60’ −8.3 (20.5, [−87.9; 25.8]) %. Schätzwerte des gemischt-linearen

Modell ergaben −31 [95%-CI: −38.9; −23] % ($p < 0.0001$) für den ‘MEDUMAT Standard^2’, −30.6 [95%-CI: −38.6; −22.6] % ($p < 0.0001$) für den ‘Oxylog 3000 plus’ und −14.5 [95%-CI: −22.5; −6.5] % ($p = 0.0004$) für den ‘Monnal T60’.

Konklusion

Mobile Beatmungsgeräte können unter kontinuierlicher Herzdruckmassage Tidalvolumina generieren, welche den Totraum überschreiten und damit zum Gasaustausch beitragen. Allerdings weichen die applizierten Tidalvolumina deutlich von den voreingestellten Parametern ab. Während der Reanimation sollten Tidalvolumina kontinuierlich gemessen werden.

Abstract

Introduction

Chest compressions and artificial ventilation are cornerstones of cardiopulmonary resuscitation (CPR). However, excessive manual ventilation frequencies can be observed during resuscitation. Excessive ventilation frequencies are associated with reduced survival chances. In contrast, blood gas analyses indicate that hypoventilation is common during CPR. Transport ventilators offer an opportunity to control ventilation frequency. It is unknown how chest compressions impact tidal volumes. This diploma thesis was part of a study investigating whether transport ventilators can produce tidal volumes relevant to gas exchange during continuous chest compressions.

Materials and Methods

Six human cadavers, embalmed using the Thiel method, served as resuscitation models. Three transport ventilators were studied in a randomized cross-over design of simulated CPR. The models were intubated and received volume-controlled ventilation with a tidal volume of 6 ml/kg ideal predicted bodyweight. During continuous chest compressions, the transport ventilators 'MEDUMAT Standard^2', 'Oxylog 3000 plus', and 'Monnal T60' were assessed. Airflow, airway pressure, and esophageal pressure were recorded. Derived volumes and their deviation from the preset tidal volume were calculated and compared. Volume deviation, peak airflow, and airway pressure were analyzed in a linear mixed model.

Results

715 ventilations qualified for analysis. The median preset tidal volume was 390 (40, [290; 410]) ml. Median inspiratory tidal volume was 275 (68, [47; 464]) ml. The median deviation from preset tidal volume was −21.2 (19.6, [−87.9; 25.8]) %, corresponding to 4.75 (1.2, [0.7; 7.6]) ml/kg ideal predicted bodyweight. For the 'MEDUMAT Standard^2' median deviation was −31.5 (16.6, [−56.5; −14.8]) %, −22.7 (22.1, [−70; −12.3]) % for the 'Oxylog 3000 plus' and −8.3 (20.5, [−87.9; 25.8]) % for the 'Monnal T60'. Population estimates of the mixed-linear model were −31 [95%-CI: −38.9; −23] % ($p < 0.0001$), −30.6 [95%-CI: −38.6; −22.6] % ($p < 0.0001$), −14.5 [95%-CI: −22.5; −6.5] % ($p = 0.0004$) for the 'MEDUMAT Standard^2', 'Oxylog 3000 plus' and 'Monnal T60' respectively.

Conclusion

During continuous chest compressions, transport ventilators can provide tidal volumes that exceed dead space ventilation and therefore contribute to gas exchange.

However, delivered tidal volumes significantly deviate from preset values. Hence, tidal volumes should be continuously monitored during CPR.

Declaration of Prior Publication

Multiple publications were generated from the time the laboratory experiment was conducted to the realization of this diploma thesis document. The publications are stated below.

In these publications, significant aspects of the current knowledge regarding ventilation during the advanced treatment of cardiac arrest were discussed, and the relevant literature was critically appraised. Most importantly, an *original publication* was published in a peer-reviewed journal that described the major aspects and results of the laboratory experiment. The contributions of the authors to the original publication are stated in the original publication. The publication can be found in the Appendix of this document. It was published under a Creative Commons License (CC BY 4.0);
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JW (Johannes U. Wittig) contributions to the original publication include conceptualization, methodology, investigation, data curation, writing of the original draft, visualization. The contributions included the following aspects. Before the laboratory experiment, JW was involved in planning the laboratory experiment and the preceding logistics. JW compiled the experiment workflow and experiment documentation process based on the original proposal. During the laboratory experiment, JW was responsible for ensuring the precise execution of the study protocol, conducting and overseeing the documentation process, keeping a laboratory journal, facilitating experimental logistics, and assisting with the study execution. Following the experiment, JW was responsible for data filing, data digitalization, and curation. JW was involved in the data preparation and data export for external statistical analysis. After data analysis, JW was involved in the preparation of the original manuscript, which included a literature review and writing as well as discussions of the manuscript with the lead author throughout the submission and revision processes.

Furthermore, extensive literature research was conducted, which led to two further publications in the form of short communications/letters. The generated datasets and software visualization tool were made available in a data repository.

This diploma thesis embeds the original investigation and its results in the ongoing debate of ventilation during cardiac arrest, summarizes the current and relevant literature, and

describes the laboratory investigation as well as its results in detail. Modified tables and figures from the original publication are identified as such.

Publications in peer-reviewed journals:

1. **Wittig J**, Orlob S, Prause G. Ventilation During Cardiac Arrest and After Return of Spontaneous Circulation: Like Father, Like Son? Respir Care. 2021 Mar;66(3):538-539. Doi: 10.4187/respcare.08791. PMID: 33632792.

2. Orlob S, **Wittig J**, Tenhunen J, Wnent J FERC, Gräsner JT FERC, Prause G. Never quite there? – Hyperventilation in cardiopulmonary resuscitation. Resuscitation. 2021 Aug;165:138-139. Doi: 10.1016/j.resuscitation.2021.05.040. Epub 2021 Jun 21. PMID: 34166742.

3. Orlob S, **Wittig J**, Hobisch C, Auinger D, Honnef G, Fellinger T, Ristl R, Schindler O, Metnitz P, Feigl G, Prause G. Reliability of mechanical ventilation during continuous chest compressions: a crossover study of transport ventilators in a human cadaver model of CPR. Scand J Trauma Resusc Emerg Med. 2021 Jul 28;29(1):102. Doi: 10.1186/s13049-021-00921-2. PMID: 34321068; PMCID: PMC8316711.

Publications in data repositories:

1. Orlob, Simon; Hobisch, Christoph; **Wittig, Johannes**; Auinger, Daniel; Honnef, Gabriel; Touzil, Otto; Schindler, Otmar; Metnitz, Philipp; Feigl, Georg; Prause, Gerhard (2020), "Data for: Do emergency ventilators deliver preset tidal volumes? – Mechanical ventilation in a human cadaver model of asynchronous cardiopulmonary resuscitation.", Mendeley Data, V1, doi: 10.17632/vh4tdsscns.1

2. Orlob, Simon; Hobisch, Christoph; **Wittig, Johannes** (2021), "ThielViewer – an interactive visualization tool for: Do emergency ventilators deliver preset tidal volumes? – Mechanical ventilation in a human cadaver model of asynchronous cardiopulmonary resuscitation.", Mendeley Data, V3, doi: 10.17632/43h7zzp67k.3

1 Introduction

1.1 Sudden Cardiac Arrest

1.1.1 Definition

Cardiac arrest is defined by the cessation of mechanical cardiac activity. (1) In clinical medicine, an unconscious person without normal or absent breathing is presumed to be in cardiac arrest. (2,3)

The term "Sudden Cardiac Arrest" (SCA) is commonly used to underscore the acute and often unpredictable nature of cardiac arrest. "Sudden Cardiac Death" (SCD) describes events where cardiac arrest leads to death and is not successfully treated by a lifesaving intervention.

Depending on the environment of SCA, it is referred to as out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA). (4)

1.1.2 Epidemiology

OHCA is estimated to be the third leading cause of death and a leading cause of morbidity in the United States of America. (5,6) In Europe, OHCA affects approximately 730,000 inhabitants every year. (7) More recent investigations estimate the incidence of OHCA attended by medical professionals in Europe at 84.0 per 100,000 inhabitants per year, with a range of 28.0 to 160.0 between countries. Austrian registry data suggest an incidence of cardiac arrest of 55.0 per 100,000 inhabitants per year. (8)

When recognized, bystanders do not always immediately treat cardiac arrest with cardiopulmonary resuscitation (CPR). This is reflected in bystander CPR rates. The recent European Registry of Cardiac Arrest (EuReCa) TWO study reports an overall bystander CPR rate of 58.0 % across Europe, ranging from 13.0 % to 82.0 % in between reporting nations. In Austria, bystander rates are estimated to fall just below the European average at 57 %. (9)

In Europe, the mean rate of return of spontaneous circulation (ROSC) lies between 28.6 % and 33 %. The likelihood of achieving ROSC in Austria is on average at 35.2 %. (9) ROSC is defined by a sustained perfusing rhythm that generates signs of life such as breathing, coughing, movements, a palpable pulse, or measurable blood pressure. (10)

Survival after SCA varies between nations and patient populations. Relevant subgroups are patient populations with initial shockable rhythms and initial non-shockable rhythms. Patients who are found to have ventricular fibrillation or pulseless ventricular tachycardia are treated with electrical defibrillation during CPR. Thus, this group is considered to have a shockable rhythm, while patients with asystole or pulseless electrical activity have non-shockable rhythms. Shockable rhythms are associated with better patient outcomes and a greater likelihood of survival. (11) In the EuReCa TWO study, OHCA patients had an initial shockable rhythm in 20 % of all recorded cases, while the proportion of initial shockable rhythms was above 25 % in Austria. (9)

Resuscitation is attempted at virtually all ages. The average patient receiving CPR is likely to be older (66.5 to 67.6 years) and likely male. (8,9)

Overall survival to hospital discharge after OHCA varies markedly between 0 % and 18 % across Europe. In Austria, overall survival can be estimated below 10 % on average. (9)

1.1.3 Etiology

The etiology of adult cardiac arrest is separated into medical and traumatic causes, drug overdose, drowning, electrocution, and asphyxia by consensus reporting guidelines. (12) In most cases, a medical cause is responsible for cardiac arrest. Traumatic cardiac arrest is rare compared to all medical causes of cardiac arrest. (8,9,13)

Medical causes of cardiac arrest subsume a broad spectrum of life-threatening conditions.

In general, cardiac disease accounts for the majority of medical etiologies. (14) The most prevalent cause of cardiac arrest is due to coronary artery disease. (15–17) Patient groups at high risk for SCA suffer from coronary artery disease, including previous or acute myocardial infarction and heart failure with low left ventricular ejection fraction. (18–21)

The potentially reversible causes of cardiac arrest include hypoxia, hyper-/hypokalemia, other metabolic disturbances, hyper-/hypothermia, hypovolemia, tension pneumothorax, cardiac tamponade, intoxication, pulmonary or coronary thrombosis. During cardiac arrest treatment, all potentially reversible causes should be explored and, if detected, treated. (22,23)

1.1.4 General Pathophysiology of Cardiac Arrest

The mechanisms leading to cardiac arrest are manifold and influence the initial pathophysiological process that follows the cessation of organized cardiac activity. Special circumstances for cardiac arrest that significantly impact pathophysiology after cardiac

arrest are hypothermia, major trauma, hypovolemia, electrical injury, asphyxia, and drowning. (22)

The description of the general pathophysiologic process of cardiac arrest can be started with the cessation of organized cardiac activity. Organized cardiac activity should consist of an electrical rhythm that is sufficiently conducted throughout the heart and results in ventricular contractions that produce a life-sustaining cardiac output. During cardiac arrest, unorganized, electrical cardiac activity is present that is unable to produce meaningful ventricular contractions. Electrocardiographic findings of the cardiac rhythm during cardiac arrest are pulseless ventricular tachycardia, ventricular fibrillation, pulseless electrical activity, or asystole. (24,25)

Without meaningful cardiac contractions, blood flow to vital organs is discontinued. Therefore, oxygenated blood is no longer pumped to vital organs, and their demand of continuous oxygen is no longer met, resulting in global ischemia. Cellular processes that depend on continuous oxygen supply become severely disturbed. Cellular energy metabolism is impacted as the mitochondrial function becomes severely reduced. The process of global ischemia also impacts the continuous removal of metabolites. Especially carbon dioxide removal is inhibited, leading to respiratory acidemia. These processes are reinforced by the absence of blood flow into the pulmonary vessels and the cessation of spontaneous breathing, which would otherwise enable gas exchange across the alveolar blood-gas barrier. (26,27)

Following cardiac arrest, consciousness is lost rapidly, along with the loss of muscle tone and spontaneous respiration as blood flow to the brain halts. In some cases, a temporary myoclonic state can be observed, resulting from anoxic cerebral conditions. Additionally, agonal breathing is present at times, but it does not produce air movements above dead space ventilation and therefore is inconsequential to pulmonary gas exchange. Apart from absent breathing, the upper airway can be obstructed due to the loss of muscle tone. The absence of protective reflexes reinforces this and increases the risk of pulmonary aspiration. (28–32)

Overall, hemodynamic collapse and respiratory arrest result in critically insufficient oxygen supply and carbon dioxide removal with subsequent derangements of acid-base-balance and cellular metabolism. Cellular and systemic homeostasis collapse, and cell death progresses. Secondary processes can further impact electrolyte balance or lead to mixed acidemia due to respiratory and metabolic acidosis under hypoxic conditions. (33)

Also, different tissues show variation in temporal tolerance of ischemic conditions. The most vulnerable organ to hypoxia and ischemia is the central nervous system due to the constantly

large substrate demand for the brain's metabolism. Permanent damage to brain cells can be observed within minutes after circulatory arrest. This observation is reflected by neurological impairment after successful cardiopulmonary resuscitation. (34–36)

1.1.5 Time in Cardiac Arrest Pathophysiology

Weisfeldt and Becker proposed *"A 3-Phase Time-Sensitive Model"* for resuscitation after cardiac arrest in 2002. (37) This model builds on basic research, animal models for cardiac arrest, and clinical observations. The authors introduce the factor of time from circulatory arrest as a determining variable for the efficiency of resuscitation interventions. The emerging physiological model of cardiac arrest of patients with ventricular fibrillation entails the *electrical phase*, the *circulatory phase,* and the *metabolic phase*. All phases have an overlap in pathophysiology and time frame as pathologies progress with time from circulatory arrest.

The first phase after cardiac arrest is the *electrical phase*. The authors estimate it to last for approximately four minutes. During this phase, electrical therapy by defibrillation should be the primary treatment approach as this intervention is likely to restore an organized cardiac rhythm with meaningful cardiac output and, therefore, sufficient organ perfusion. The treatment effect of time-sensitive defibrillation is illustrated by the effectiveness of implantable cardioverter defibrillators (38) and early defibrillation programs that apply rapid automated external defibrillator use in OHCA. (39,40) These interventions improve survival after cardiac arrest and are recommended throughout current guidelines. (23,41)

The second phase is the *circulatory phase,* where chances for successful defibrillation as a primary therapeutic approach are decreased. (42,43) The authors argue that chest compressions combined with ventilations should be prioritized before defibrillation is attempted. Current scientific consensus statements by the International Liaison Committee on Resuscitation (ILCOR) do not follow this rationale. (44) Additionally, advanced interventions that are an integral part of recommended Advanced Life Support (ALS) treatment algorithms might be beneficial during this phase. (23) Experimental animal studies and clinical observation support this approach. (45) Although, estimating time from cardiac arrest to initiation of treatment is not feasible in patients with unwitnessed collapse. This phase is estimated to last from four to ten minutes after cardiac arrest and transitions to the third phase.

The third and final phase is the *metabolic phase* and entails resuscitation physiology after ten minutes of cardiac arrest. During this phase, pathophysiologic effects of prolonged global

ischemia and reperfusion phenomena could dominate the disease process. Driven by these two central mechanisms, irreversible cell death progresses, even when global reperfusion is established. (46) Some interventions, such as artificial hypothermia during and after resuscitation, appear to yield protective effects. (47–50) Although, therapeutic hypothermia after ROSC has been challenged repeatedly. (51,52) Standard interventions, such as chest compressions, defibrillation, and artificial ventilation, appear to offer dwindling effects as time from cardiac arrest increases. Some standard interventions might even worsen chances for survival, as observed in late administration of adrenalin. (53)

This theoretical model for cardiac arrest highlights the challenge of rapid intervention to improve survival, the dependency on the timing of established interventions, and the need for individualized treatment during cardiopulmonary resuscitation.

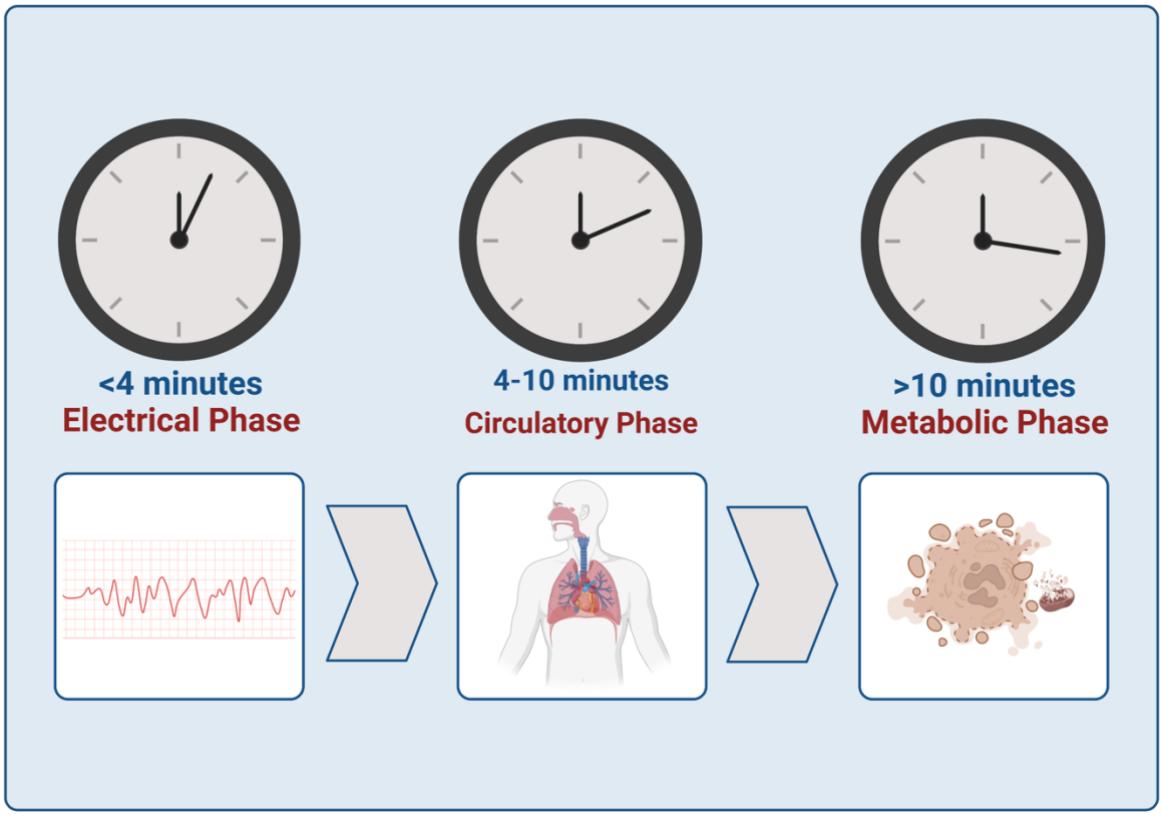

Figure 1 'A 3-Phase Time-Sensitive Model'

Illustration of the pathophysiological model of cardiac arrest from Weisfeldt and Becker (37). Figure created with BioRender.com.

1.2 Cardiopulmonary Resuscitation

1.2.1 Overview of Pathophysiological Treatment Concepts

Once organized cardiac activity stops, blood flow and consequently oxygen supply to vital organs ceases. Additionally, the respiratory removal of carbon dioxide is discontinued. This

state is followed by homeostatic collapse and cellular dysfunction, damage, or cell death.(54,55)

Artificial blood flow, generated by chest compressions, is the most essential, immediate intervention to attenuate this detrimental process. Chest compressions should be viewed as a bridge to definitive therapy as chest compressions alone rarely restore an autonomous cardiac rhythm capable of organ perfusion. (56)

Chest compressions can be performed continuously or interrupted by artificial ventilation. In adult patients, this is performed in a 30:2 ratio, as 30 chest compressions are followed by two ventilation attempts, and then chest compressions are immediately resumed.

Artificial ventilation primarily seeks to increase oxygen supply but also removes accumulated carbon dioxide in the process.

As alluded to in the '3-Phase Model' for resuscitation after cardiac arrest, treatment priorities might shift during the time course of a resuscitation attempt. More advanced interventions, represented by the ALS treatment algorithm, routinely include advanced airway management, artificial ventilation with high concentrations of inspired oxygen, and drug administration but always build on the treatment fundamentals displayed in the Basic Life Support (BLS) algorithm, namely chest compressions, defibrillation and artificial ventilation. (23,37)

1.2.2 Treatment Concept: Chest Compressions

In most cardiac arrest scenarios, cardiac massage is understood to be achieved by external chest compressions or closed-chest cardiac massage. (2,57) When the chest must be opened for cardiothoracic surgery or is opened during a traumatic cardiac arrest, direct cardiac massage becomes feasible. (58)

Chest compressions in adult patients are performed by placing both hands on top of each other at the middle of the chest above the lower half of the sternum to compress the chest vertically downwards. Thereby, the heart is compressed between the sternum and vertebral bodies. Compressions are followed by immediate release to allow complete chest wall recoil. This sequential process is repeated with a frequency of 100 to 120 compressions per minute. (2,44,59)

The quality of chest compressions is essential, as chest compressions quality can be correlated to generated blood flow parameters and ultimately improved clinical outcomes. (60) The first hallmark of chest compression quality is the correct **hand position** as described above. Although, current methods of chest compression point discrimination can

potentially lead to compression of the left cardiac outflow tract and, therefore, insufficient cardiac output. (61–63)

The second hallmark of chest compression quality is **compression depth**. Chest compression depth should at least be five cm and at most be six cm. Shallow chest compressions do not compress cardiac chambers enough to produce sufficient cardiac output and organ perfusion, while excessive chest compression depth increases the risk of organ injury without obvious benefit. (64–68)

The third quality hallmark is complete and immediate **chest wall recoil** after chest compression. The chest wall recoil is necessary to reduce intrathoracic pressure and permit expansion of the compressed organs, especially the cardiac chambers, to allow venous return. Incomplete chest wall recoil causes a reduction of cardiac filling and subsequently cardiac output and organ perfusion. This includes coronary perfusion as a constantly compressed heart does not have a timeframe nor coronary perfusion pressure for oxygenated blood to reach myocardial cells. (69,70)

The fourth hallmark of chest compression quality is the **rate of compressions**. Chest compressions should be performed at a constant rate between at least 100 and at most 120 times per minute. Slower and accelerated chest compression rates were found to reduce the chance for ROSC and survival after cardiac arrest. (71–73)

Another hallmark of chest compressions is the **reduction of pauses** of chest compressions. While indicated pauses are necessary during rhythm analysis, synchronized ventilation, or shock delivery, chest compression pauses should be limited as increasing the chest compression fraction appears to improve chances of survival. (74–76)

Chest compressions can be performed manually, which is usually the case when first responders or witnesses perform CPR. Another option are mechanical chest compressions performed by automated chest compression devices.

1.2.2.1 Forward Blood Flow: Cardiac and Thoracic Pump Concepts

Two major physiological concepts for the chest compression mechanisms generate forward blood flow during resuscitation. (64,77)

The *cardiac pump* concept poses that the direct compression of the heart between the anterior chest wall and spine causes forward-directed blood flow, given that the heart valves are competent to restrict retrograde flow. (57) External compression of the cardiac chambers increases intracardiac pressures that force the aortic and pulmonary heart valves to open, allowing blood to enter the systemic and pulmonary circulation, respectively. During

decompression of the chest, the heart chambers can passively refill with blood from the venous circulation. (78–81)

The *thoracic pump* concept assumes that the compression of the thorax causes intrathoracic pressure to increase, which then forces forward blood, while valves in the large thoracic veins hinder retrograde blood flow. (82–84) In this concept, the heart itself is regarded as a central, passive conduit for blood flow. (85)

Regardless of the true hemodynamic mechanism of chest compressions, blood flow generated by effective chest compressions is the primary driver for oxygen delivery to vital organs during cardiac arrest. (86–88) However, it should be considered that chest compressions generate only a fraction of pre-arrest cardiac output. (80,89)

1.2.3 Treatment Concept: Artificial Ventilation

Spontaneous breathing ceases in case of cardiac arrest. Depending on cardiac arrest etiology, respiratory arrest or severe respiratory compromise can precede circulatory arrest.

Regardless of arrest etiology, artificial ventilation is part of all standard CPR attempts and gains of importance after the first initial minutes of cardiac arrest. (2,90) The latter is more likely true when breathing was not significantly impaired before cardiac arrest. (91) An explanation for a reduced need for artificial ventilation within the first minutes of cardiac arrest is that oxygenated blood is present in the vessels and lungs at the moment of circulatory arrest. (92) Animal studies show that oxygen concentrations in the arterial circulation remain acceptable for minutes following cardiac arrest. (92,93) The remaining oxygen reserves allow for the passive process of gas exchange across the alveolar membranes to continue, but this is limited by blood flow in the capillary bed surrounding the alveoli. (94) Chest compressions can restore some blood flow to the pulmonal-capillary vessels and therefore contribute to gas exchange as long as a sufficient partial pressure gradient is present. Once oxygen in the alveoli is depleted and the partial pressure gradient resolves, no gas exchange can happen, and chest compressions alone become insufficient. (95)

As circulation stops, blood cannot reach the peripheral tissue anymore, and oxyhemoglobin is unable to donate oxygen to peripheral cells. Once chest compressions are started, oxygenated blood is moved more gradually to peripheral tissue.

Both residual mechanisms are unable to compensate for the vital oxygen demand, especially as time from cardiac arrest progresses and the necessity for artificial ventilation grows. (37)

A further consideration of artificial ventilation is the elimination of carbon dioxide that appears to impact resuscitation outcomes as well as oxygenation. (96)

1.2.3.1 Artificial Ventilation: Oxygenation

During untreated cardiac arrest, oxygen supply to all tissue diminishes and leads to global cellular impairment and cell death. In order to retain basic cellular function, oxygen supply to vital organs must be restored but might lead to secondary injury. (97)

As cardiac arrest causes loss of protective airway reflexes and muscle tone, the route of supplying oxygen for gas exchange is interrupted by airway obstruction. (28) Additionally, spontaneous breathing is absent during cardiac arrest regardless of airway patency. This stops the supply of fresh air to the gas-blood-barrier for gas exchange. A reduction of lung volume below functional residual capacity (FRC) can also be observed during CPR, contributing to the decrease in oxygenation. (98)

Oxygenation in cardiac arrest can be achieved by artificial ventilation. For this to be successful, the airway must be opened or secured by an advanced airway device, and air must be forced into the lungs by positive pressure ventilation. In order to achieve this, rescue breathing, manual ventilation with a bag-valve(-mask) system, or mechanical ventilation with a mechanical ventilator can be applied. (2)

To achieve oxygenation of peripheral tissue, pulmonary gas exchange and oxygen delivery through blood flow are dependent on cardiac output and fresh air supply to the lungs.

Therefore, chest compressions are required to move deoxygenated blood into the pulmonary vasculature for gas exchange to happen and further drive blood flow of oxygenated blood to peripheral tissue in demand.

1.2.3.2 Artificial Ventilation: Carbon Dioxide Elimination

Carbon dioxide continuously arises from cellular energy metabolism and leads to respiratory acidemia if not removed. As cells continue to produce carbon dioxide after cardiac arrest, but blood flow to the lungs for gas exchange is halted, carbon dioxide accumulates. Once chest compressions are able to restore some degree of pulmonary blood flow, gas exchange can occur passively across the alveolar blood-gas-barrier as long as a partial pressure gradient is present. (99,100)

When carbon dioxide arises from cellular metabolism and is not removed by ventilation, buffer systems are overwhelmed, and the accumulation of carbon dioxide causes acidemia.

While metabolic and respiratory acidosis are prevalent during cardiac arrest and are associated with poor outcomes, the necessary degree of carbon dioxide elimination during cardiac arrest remains uncertain. (101,102)

1.2.4 Interaction of Chest Compressions and Ventilation

Chest compressions and artificial ventilation are cornerstones of cardiopulmonary resuscitation. They can be carried out in a synchronized fashion, which means that sets of 30 chest compressions are alternated with two ventilation attempts. An alternative, asynchronous strategy is comprised of continuous chest compressions and up to ten ventilation attempts over each minute of CPR. The latter is recommended during ALS when an advanced airway is in place. (23) The rationale behind continuous chest compressions is to keep forward blood flow going, increasing oxygen delivery to organs. As chest compressions and positive pressure ventilation both result in an increase of intrathoracic pressure, their combined effects on hemodynamics and ventilation need to be considered.

Venous return can be impaired as both interventions increase intrathoracic pressure, which in turn can lead to markedly decreased cardiac output likely due to insufficient cardiac preload. (82,103) Increasing the frequency of artificial ventilation increases the time proportion of positive intrathoracic pressure and could also reduce venous return, which might otherwise be facilitated by low to negative intrathoracic pressure during decompression of the chest. (104)

During CPR, a decrease in lung compliance and volume has been observed and is known to increase pulmonary vascular resistance due to collapsed vessels. (105–107) Therefore, insufficient ventilation would minimize efforts to restore a degree of pulmonary circulation by chest compressions.

On the other hand, large lung volumes can compress pulmonary capillaries, subsequently increasing pulmonary vascular resistance. Although not independently proven for the state of cardiac arrest, pulmonary vessels constrict due to hypercapnic conditions and hypoxic conditions, which can both be present during cardiopulmonary resuscitation and further limit pulmonary blood flow by increasing pulmonary vascular resistance. (108–110)

Pulmonary and chest wall compliance determine the required inspiratory airway pressure to drive inward airflow, but both are impacted by external compression of the chest. (111) During artificial ventilation, the interaction with chest compressions can be observed in derangements of airflow. Ongoing chest compressions cause fragmentation of airflow and lead to reversed airflow as the pressure generated by external chest compression force

exceeds inspiratory driving pressure. (112,113) Hence, simultaneous chest compression and inspiratory positive pressure ventilation can be viewed as counteracting forces on the airflow that can drastically limit tidal volumes. Positive airway pressure during artificial ventilation is additionally increased by external chest compressions and further impairs low-flow hemodynamics. (114,115)

When no artificial ventilation is attempted, which might be the case during the first minutes of CPR by bystanders, chest compressions can cause a limited degree of ventilation. This is explained by an increase of intrathoracic pressure above atmospheric pressure causing airflow out of the lungs during compression of the chest. Once the chest is decompressed, the chest wall recoils and negative intrathoracic pressure causes inward-directed airflow. Nevertheless, chest compression-induced ventilation is dependent on an open airway and only results in tidal volumes, which have an insufficient impact on gas exchange. (29,30,116,117)

1.2.5 Cardiac Arrest Treatment: Advanced Life Support

ALS is performed by specialized medical personnel trained in advanced emergency medical procedures and are outfitted with special equipment. In OHCA, this is achieved by emergency medicine services (EMS) personnel. In Austria, cardiac arrest is always treated by an emergency physician on site.

The ALS treatment algorithm builds on the core elements of the BLS algorithm. Hence, high-quality chest compressions, early defibrillation, and adequate ventilation take priority. (2) Once chest compressions are started, the underlying cardiac rhythm should be analyzed immediately. A non-shockable or shockable rhythm can be diagnosed, and the latter treated with defibrillation. In ALS, the cardiac rhythm also determines the prioritization of vascular access and medication administration. When a shockable rhythm is diagnosed, chest compressions are resumed during defibrillator charging and only stopped for defibrillation. When a non-shockable rhythm is present, chest compressions are resumed immediately. The subsequent analysis of the cardiac rhythm occurs after a two-minute interval of CPR. This procedure is continued and repeated for the entire resuscitation scenario.

After the first rhythm analysis, ventilation and airway management should be prioritized in case the airway is not already secured. Under normal circumstances, the airway is secured using an advanced airway device. Artificial ventilation is initially provided using a bag-valve system with the highest achievable inspiratory oxygen fraction. Once the airway is secured

with an advanced airway device, continuous chest compressions with asynchronous ventilation are recommended.

Current guidelines recommend that vascular access must be acquired to administer adrenalin and, in case of a shockable rhythm, to give antiarrhythmic drugs.

Potentially reversible causes of cardiac arrest need to be diagnosed and treated if identified. (23)

This ALS algorithm continues until return of spontaneous circulation (ROSC) is achieved, post-arrest care can be initiated, or a decision is reached to terminate resuscitation. (118,119)

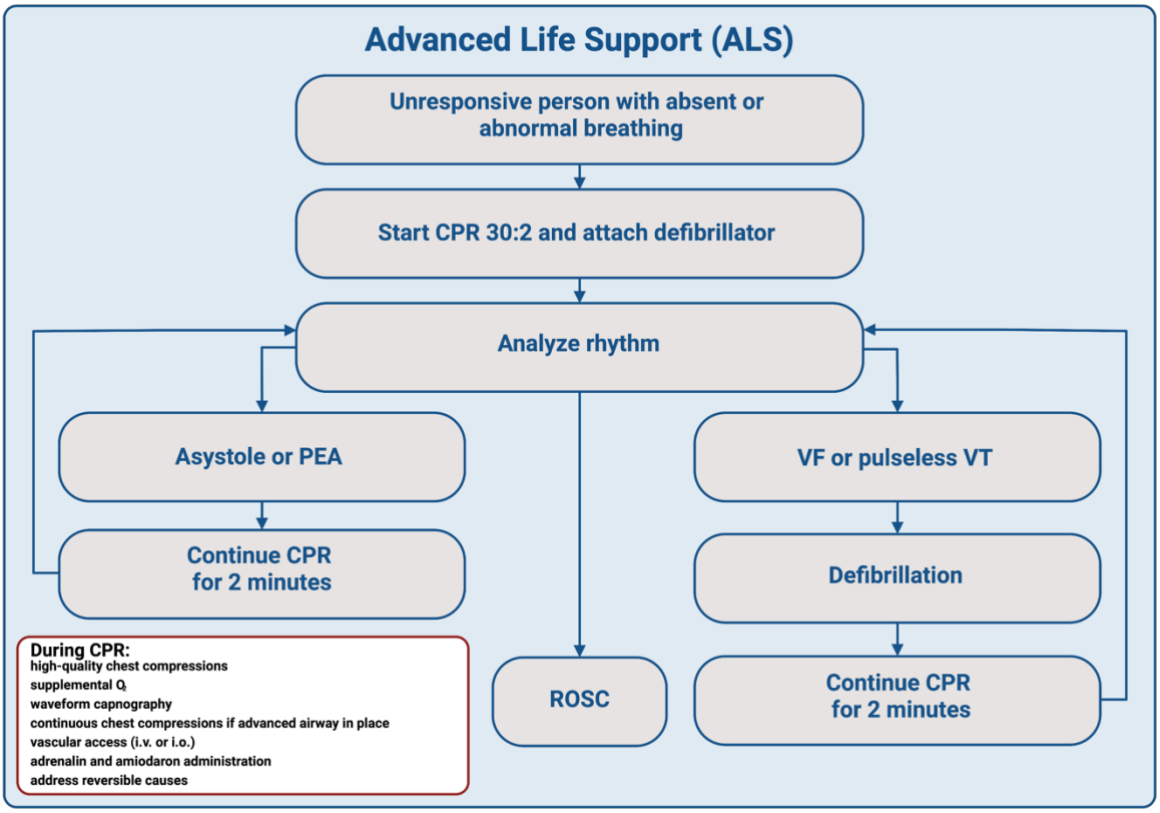

Figure 2 Advanced Life Support (ALS) Algorithm

Modified and redrawn from Figure 3 ***(23)****. Figure created with BioRender.com.*

1.2.5.1 Basic Life Support Foundation

The availability of EMS and prehospital emergency physicians provides the foundation for complex treatment interventions and addressing the potentially reversible causes of cardiac arrest immediately. However, all ALS interventions build on continuing BLS measures, such as high-quality chest compressions, early defibrillation, and artificial ventilation. The efforts of specialized emergency medicine teams are likely of little to no consequence if the patient has not received early, high-quality BLS in the time from cardiac arrest to EMS arrival. The

importance of BLS measures is upheld during advanced treatment phases of cardiac arrest and regularly takes priority over ALS measures. (120–122)

1.2.6 Minimally Interrupted Chest Compressions

Limiting pauses during which no chest compressions are performed is a major quality metric of high-quality CPR, along with correct hand placement, compression depth, complete chest recoil, and an adequate chest compression frequency. (2,23,74,75,123)

The rationale behind minimally interrupted chest compressions is that no blood flow and organ perfusion are present once chest compressions are stopped. Interrupting chest compressions is unavoidable during the analysis of cardiac rhythm and defibrillation. Nevertheless, limiting this interruption by performing chest compressions during defibrillator charging time to deliver an electrical shock was shown to be beneficial. (124,125)

Additionally, chest compression generated cardiac output increases only after the first number of chest compressions. This is also reflected in coronary perfusion pressure that increases as chest compressions are commenced and reaches a plateau as long as chest compressions are performed but drops once they are stopped. As coronary perfusion pressure is related to coronary blood flow, keeping this at a constantly increased level appears beneficial. (56,126)

However, the concept of blood pressure instability caused by brief interruption of chest compressions has been challenged by a more recent clinical investigation. (127) (56,126)

Consequently, providing continuous chest compressions with asynchronous ventilation appears to offer a hemodynamical advantage as chest compressions do not need to be paused for synchronized ventilation attempts.

1.2.7 Automated Chest Compressions

Manual chest compressions are laborious and exhaust providers within minutes. This is resembled by decreasing the quality of chest compressions during prolonged resuscitation activity. Chest compression quality is essential for good resuscitation outcomes, and providers are advised to alternate every two minutes to allow for providers to rest. Especially during prolonged resuscitation attempts, the application of an automated chest compression device seems advantageous. (128,129)

Another opportunity to use automated chest compressions devices is during patient transport. This allows providers to safely travel and perform other essential tasks while resuscitation continues. (130)

Manufacturers have come up with a variety of automated chest compression devices that provide chest compressions differently. Piston devices were introduced early and provided chest compressions with a vertically moving piston above the chest. An alternative chest compression method can be observed in devices that use load-distributing bands. (131)

In theory, automated chest compression devices should provide close to ideal chest compression rate, depth, recoil without performance affected by fatigue or psychological factors as observed in manual chest compressions. However, no clear benefit for increased survival in conjunction with good neurological outcome of automated chest compression devices over manual chest compressions has been established to this date. (132)

The current guidelines advise to consider automated chest compression devices when high-quality chest compressions are not practically feasible or have a negative impact on provider safety. (23)

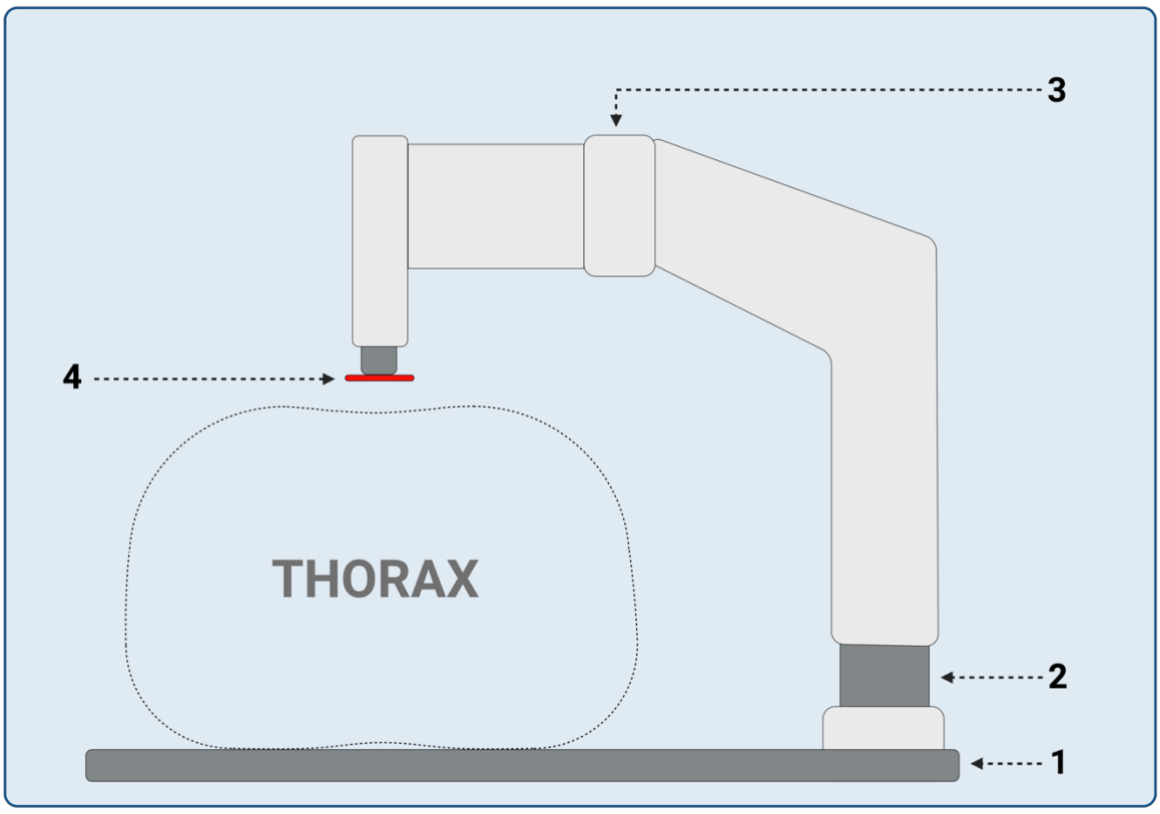

Figure 3 Exemplary Automated Chest Compression Device

[1] board [2] horizontally adjustable stand [3] vertically adjustable hinge [4] stamp connected to piston; simplified depiction of the automated chest compression device 'corpuls cpr' (GS Elektromedizinische Geräte G. Stemple GmbH, Kaufering, Germany). Figure created with BioRender.com.

1.2.8 Advanced Airway

Supraglottic airway devices, such as laryngeal masks or laryngeal tubes and endotracheal tubes, are considered advanced airway devices.

The necessity to insert an advanced airway device is based on the loss of muscle tone and absence of protective airway reflexes during cardiac arrest. Additionally, a correctly placed advanced airway device allows for more reliable artificial ventilation attempts compared to bag-valve-mask (BVM) ventilation. (133,134)

Under most circumstances, placement of an advanced airway is considered the standard of care for securing an airway during a medical emergency. In adult cardiac arrest, endotracheal intubation is considered the gold standard for airway management. Performing endotracheal intubation safely and quickly during an active resuscitation effort is an attainable but challenging skill. (135,136)

Methods to place an endotracheal tube during cardiac arrest include oral insertion by direct laryngoscopy, by video-assisted laryngoscopy, or surgically by emergency cricothyroidotomy. (137,138)

Once the tube's cuff is placed below the vocal cords, it can be inflated. Correct tube placement must always be confirmed. During CPR, the use of waveform capnography is recommended. Endotracheal tubes need to be mechanically secured to avoid dislocation, resulting in loss of airway control or accidentally deep intubation with unilateral lung ventilation. (23,139)

Once the cuff is inflated, a correctly placed endotracheal tube offers airway protection and protection from aspiration. Additionally, ventilation through an endotracheal tube reduces the risk of accidental gastric inflation. (32,140–142) Endotracheal intubation allows to ventilate and perform chest compressions simultaneously and is recommended by the most recent resuscitation guidelines. Compared to supraglottic airway devices, higher airway pressure is tolerated by the endotracheal tube seal with less risk of air bypassing the system. Ventilation can be provided using manual bag-valve systems directly connected to the endotracheal tube. Alternatively, mechanical ventilators can be connected to the endotracheal tube and used to ventilate the patient during ongoing CPR. (58,143)

1.2.9 Artificial Ventilation

The priority of artificial ventilation during resuscitation of adult cardiac arrest patients was changed and repeatedly discussed in the past two decades. (93,144)

Artificial ventilation, including oxygenation and carbon dioxide removal, are also treatments for two of the potentially reversible causes of cardiac arrest — hypoxia and severe metabolic disturbances, such as acidemia. However, all BLS and ALS treatment algorithms include artificial ventilation. Ventilation can be performed in a 30:2 fashion with chest compressions or asynchronously during continuous chest compressions once an advanced airway is in place. When a cardiac arrest patient is artificially ventilated, it is advised to administer the maximum amount of supplementary oxygen available. Additionally, waveform capnography should be used to monitor ventilation, CPR quality, and correct airway placement. (2,22,23)
Bag-valve systems can be used in conjunction with a mask or advanced airway devices to provide ventilation and oxygenation. Other options for ventilation and oxygenation in an emergency are mechanical ventilation devices. Depending on the environment of a cardiac arrest, the devices are mobile mechanical transport ventilators or stationary devices such as intensive care ventilators.

1.2.9.1 Manual Ventilation

Bag-valve systems can be used with an advanced airway or face mask to provide manual ventilation.
A bag-valve system is composed of an air-filled, self-inflating bag connected to an oxygen source. The volume of the air-filled bag depends on the model. (145)
The bag can be directly attached to a face mask or advanced airway device via an adapter that includes a built-in valve restricting airflow towards the bag system. During passive expiration, exhaled gas can exit through an exhalation port. The adapter can be fitted with a positive end-expiratory pressure (PEEP) valve.
To achieve manual ventilation with a BVM system, providers must place the mask over the person's mouth and nose with a tight seal and open the airway with one hand. The second hand is used to squeeze the air-filled bag. An advanced airway should be inserted during ALS to provide synchronized ventilations more reliably during chest compression pauses. One provider should give ten ventilations per minute if the asynchronous ventilation to chest compression method is chosen. This provider is unlikely able to perform other tasks in-between manual ventilations. (23)
Manual compression of a self-inflating bag needs to be controlled regarding ventilation frequency and tidal volume. During OHCA, providers have limited options to monitor manual ventilation. Waveform capnography is an available method that can confirm correct airway device placement and monitor ventilation frequency. (23) Recently developed

devices offer feedback for manual ventilation during cardiac arrest in regard to frequency and tidal volume. (146) In the absence of such equipment, health care providers are advised to give ventilations every five to six seconds during asynchronous CPR or in case of synchronized CPR to give two ventilations that cause a visible chest rise. (147)

1.2.9.2 Mechanical Ventilation

Once an advanced airway device is in place, manual ventilation with a self-inflating bag can be continued or taken over by a mechanical ventilator. During CPR, especially in OHCA, mobile transport ventilators are used. (58,148)

Transport ventilators are also used during intra- or inter-hospital transports in emergency departments and serve as backup equipment. Stationary but technologically more sophisticated respirators are available in operating rooms and intensive care units. These advanced devices offer different ventilation modes, detailed measurements of ventilation parameters, and a clear graphic depiction of these parameters. The ventilation parameters such as airway pressure, airflow, end-tidal CO_2, inspiratory and expiratory volumes are plotted in real-time.

Transport ventilators have the advantage of functioning autonomously but are limited by battery power and mobile oxygen supply. Many transport ventilators are dependent on compressed oxygen and therefore consume large quantities of oxygen during emergency usage. Alternatively, turbine-driven ventilators consume less oxygen to operate.

Transport respirators offer only reduced ventilation measurements and graphic depictions. Often, only standard ventilation modes are available. Parameters that can be altered depend on the respective ventilation mode. A simplified and exemplary depiction of a transport ventilator user interface is shown below in Figure 4 to illustrate the adjustable device settings.

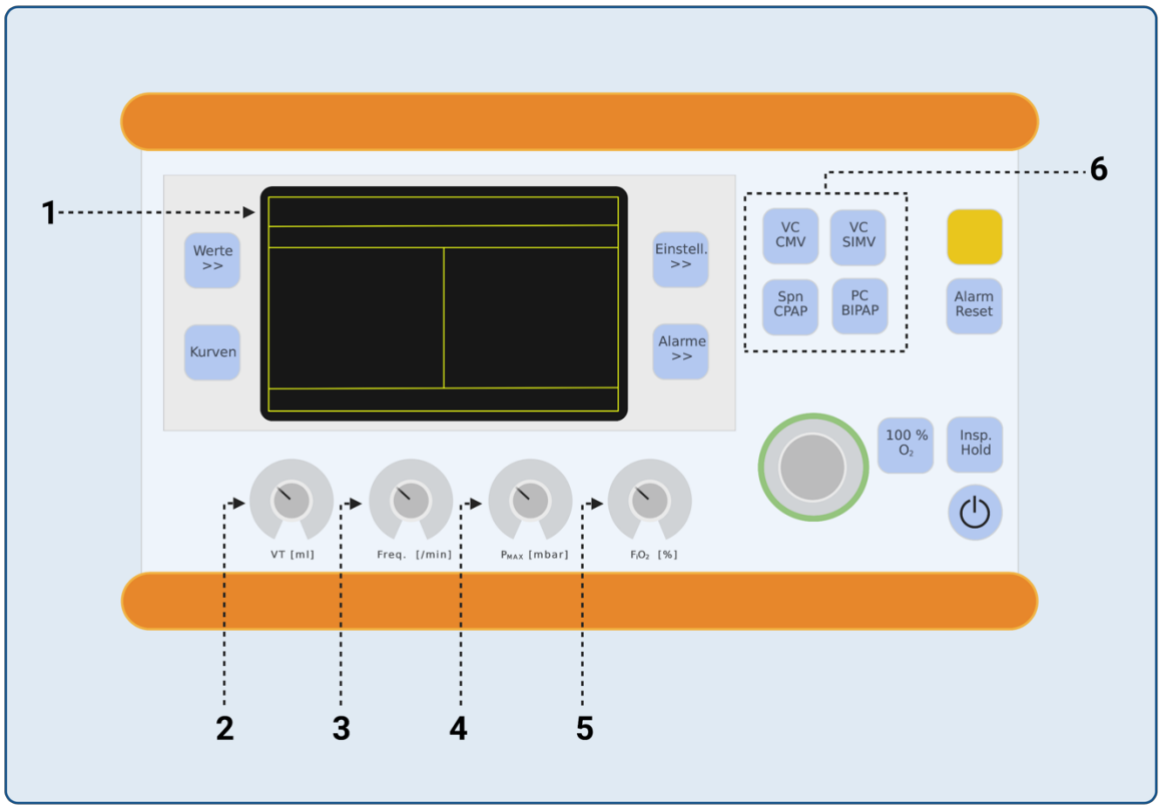

Figure 4 Exemplary Transport Ventilator User Interface

[1] display [2] control knob tidal volume [3] control knob ventilation rate [4] control knob maximum pressure limit [5] control knob fraction of inspired oxygen [6] selection of ventilation modes; simplified depiction of the ventilator model 'Oxylog 3000 plus' (Drägerwerk Ag & Co. KGaA, Lübeck, Germany). Figure created with BioRender.com.

In contrast to physiologic breathing, where airflow is generated by intrathoracic negative pressure by expansion of the thoracic structures, artificial ventilation is driven by positive pressure that forces air into the lung and subsequently results in expansion of the lung tissue. (149,150)

Standard ventilation modes use positive pressure and can be controlled either by a predetermined volume or inspiratory pressure as the fixed variable.

During volume-controlled ventilation, the machine aims to give a predetermined volume with each breath. The pressure needed to provide the given volume varies when counteracting forces must be overcome. The device operator must limit the inspiratory pressure to avoid barotrauma from high inspiratory pressures. (151,152)

In pressure-controlled ventilation, the machine operates on a predefined inspiratory pressure that generates a variable volume depending on the counteracting forces met with each artificial ventilation. As large ventilation volumes can cause lung strain or volutrauma, the inspired volume must be limited. (153,154)

Multiplied by ventilation frequency, tidal volumes result in minute ventilation. The device operator can also alter ventilation frequency.

During artificial ventilation, PEEP valves are used to retain a positive pressure within the respiratory tract at the end of expiration. PEEP improves oxygenation and facilitates ventilation at lower inspiratory pressures but increases intrathoracic impedance, which is disadvantageous during defibrillation. The safe usage and benefit or harm of PEEP during CPR remains unclear. (155–157)

The ratio of inspiratory to expiratory time (I:E) can also be determined by the machine operator and is often set to 1:2 as in spontaneously breathing adults but can be altered to therapeutic need.

The composition of inspiratory gas fractions depends on the supplemental oxygen given. When no supplemental oxygen is given, room air is inspired with an inspiratory oxygen fraction of 21% (F_iO_2 of 0.21). During CPR, the F_iO_2 is set to 1.0, meaning a 100 % oxygen concentration is given with each ventilation. (134,143)

International resuscitation guidelines offer no clear guidance for mechanical ventilation during asynchronous CPR. Practice handbooks suggest using a volume-controlled ventilation mode with tidal volumes at 6 to 7 ml/kg ideal predicted bodyweight (IPBW) and a ventilation frequency of ten per minute. It is also advised to monitor system leakage when using a supraglottic airway device and mechanical ventilation during asynchronous CPR. If significant leakage is present synchronized CPR should be prioritized as insufficient ventilation becomes likely. (23,158)

1.3 The Hyperventilation Controversy

Asynchronous chest compressions and ventilations are advised once an advanced airway is in place. The change away from alternating 30 chest compressions with two consecutive ventilations allows for continuous chest compression and aims for improved chest compression hemodynamics. (23) However, it was observed that providers who manually ventilate patients tend to hyperventilate patients during resuscitation. It was also observed that excessive hyperventilation can negatively impact survival and hemodynamics. (115,159,160)

This was first shown by Aufderheide et al. in 2004. They observed hyperventilation in a series of consecutive cases of OHCA with excessive manual ventilation rates, but no tidal volumes were measured. None of the 13 patients survived. These findings prompted an experimental animal study to investigate the impact of hyperventilation during resuscitation. Pigs received 12, 20, and 30 ventilations per minute. Notably, the ventilation device provided a constant flow rate of 160 l/min resulting in tidal volumes approaching 2.7 l. The study

found that survival in pigs ventilated at higher frequencies was markedly reduced compared to pigs that received lower ventilation frequencies. Additionally, hemodynamic measurements revealed corresponding adverse effects on blood flow during higher ventilation frequencies. Following this landmark publication by Aufderheide et al., resuscitation guidelines adopted the message to warn of inadvertent hyperventilation caused by excessive manual ventilation (115,123,161,162)

However, hyperventilation is determined by tidal volume and ventilation frequency. O'Neill et al. further investigated hyperventilation in clinical human resuscitation attempts and found that hyperventilation was primarily driven by excessive ventilation frequencies rather than high tidal volumes. (159)

Gazmuri et al. further investigated the effects of hyperventilation and its components, ventilation frequency, and tidal volume on resuscitation outcomes. They found that clinically plausible hyperventilation did not yield the same detrimental effects on resuscitation hemodynamics as shown previously with excessive tidal volumes and ventilation frequencies. Additionally, end-tidal carbon dioxide levels were dependent on tidal volumes. (163)

As hyperventilation causes hypocapnia, and if excessive should cause respiratory alkalemia, arterial blood gas investigations should be able to reveal prevalent, inadvertent hyperventilation during cardiac arrest. However, arterial blood gas analyses acquired during CPR attempts of OHCA patients showed that hypocapnia was rare and that the contrary process, acidosis leading to acidemia, was prevalent. (33,164)

An important caveat of hyperventilation during CPR and the interpretation of arterial blood gases is introduced by the factor of clinically unknown hemodynamics, especially in the pulmonary circulation during resuscitation. Low blood-flow, ventilation-perfusion mismatch and subsequent right-left shunt could impair the expected impact of hyperventilation on arterial blood gases.(165,166)

Therefore, the questions remain how prevalent hyperventilation in OHCA treatment is and how ventilation should be optimized during CPR attempts to avoid hyper- as well as hypoventilation. Ultimately, these questions need to be answered in the context of hemodynamic variables during CPR.

Treatment guidelines advise to ventilate patients at a rate of ten per minute. Clinical evidence on tidal volumes is lacking, but recommendations exist to limit tidal volumes to 6 to 7 ml/kg IPBW. (123,161,167)

To mitigate hyperventilation caused by excessive manual ventilation frequencies, mechanical ventilators could be used as they provide a reliably fixed ventilation rate. (168) But the impact of continuous chest compressions on tidal volumes delivered by transport ventilators remains uncertain. (112,169)

This study aimed to explore how continuous chest compressions impact asynchronous mechanical ventilation parameters delivered by transport ventilators.

2 Materials and Methods

2.1 Workflow Overview

The experiment was conducted in three consecutive phases. Phase 0 (depicted in blue; see Figure 5) was done to prepare the human cadaver model and achieve standardization. At the end of Phase 0, it was determined whether a prepared cadaver met any exclusion criteria. After inclusion, the emergency ventilator sequence for Phase 2 was randomly assigned to the individual human cadaver. During Phase 1 (depicted in green; see Figure 5), the mechanical properties of the human cadaver model were measured. This phase included measurements of ventilation only, mechanical chest compressions only, and a combination of both. Phase 2 (depicted in yellow; see Figure 5) was carried out in a cross-over design and consisted of three periods, each assessing a different emergency ventilator's performance during continuous mechanical chest compressions over two two-minute simulated CPR cycles. The experiment's workflow is depicted in Figure 5. Individual phases are described in detail below.

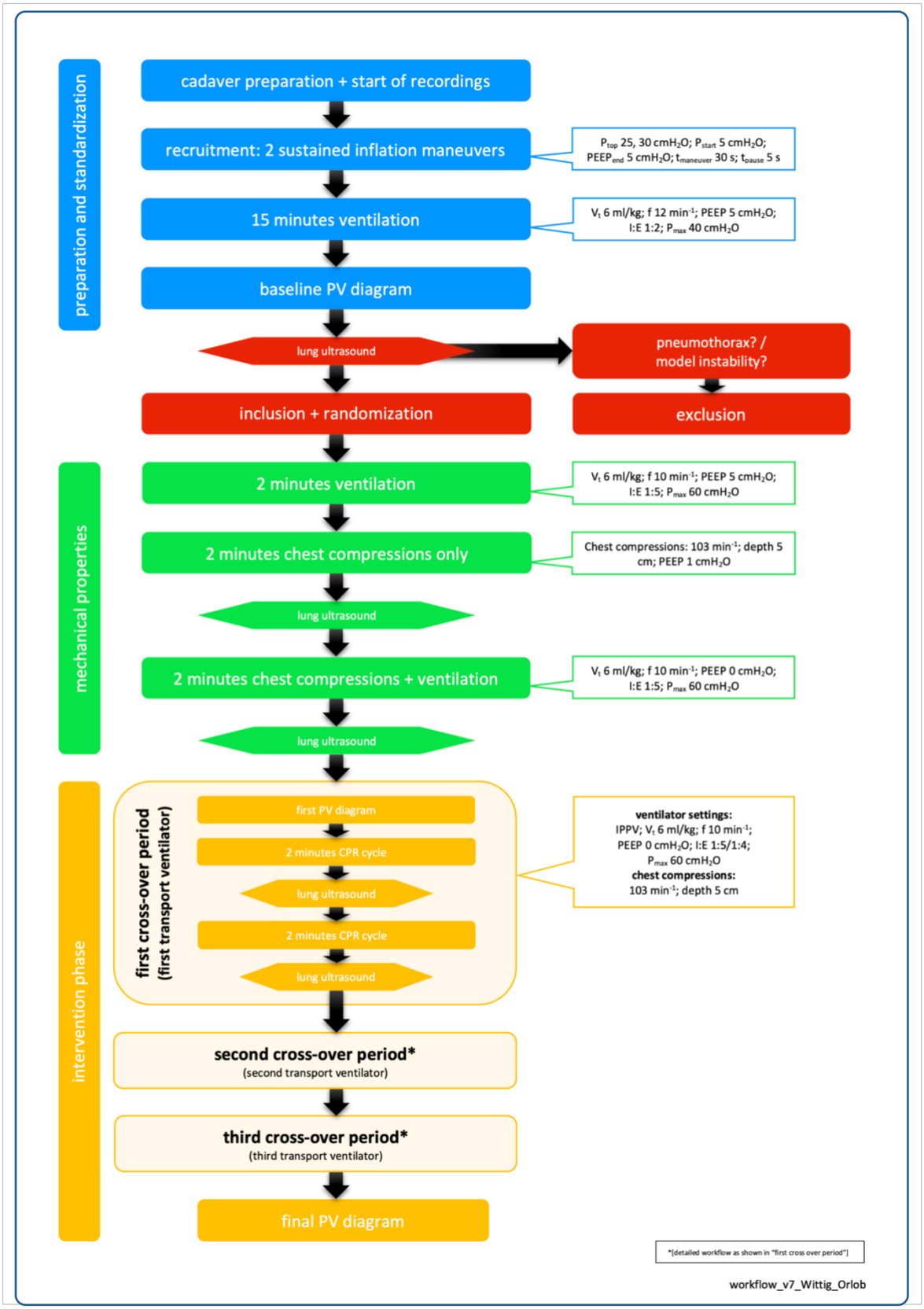

Figure 5 Flowchart of the Experiment

Phase 0 is depicted in blue, Phase 1 in green and Phase 2 in yellow, the inclusion/exclusion process is highlighted in red, the detailed steps of the first cross-over period apply to all other cross-over periods; Colored, rectangular boxes show device settings; A modified version was published by Orlob et al. as Additional file 1(170). Figure created with BioRender.com.

2.2 Thiel Human Cadaver Model

The Thiel cadavers have been successfully used as a model for CPR to study ventilation mechanics. (171,172) The Thiel embalming method was developed by Walter Thiel in 1992 and is known to preserve close to life-like biomechanical properties of the human tissue. The fixation of the cadavers is performed over nine months by submersion of the bodies in the Thiel embalming solution. (173,174)

The bodies are donated to the Chair of Macroscopic and Clinical Anatomy of the Medical University of Graz. The regulations under the Styrian burial law for scientific purposes apply. Therefore, no further guidance by the local ethics committee was sought.

The cadavers were stored at ambient room temperature (23 °C) and randomly selected for this experimental study.

2.2.1 Model Stability

To detect model instability and to record unexpected observations, all Thiel human cadaver models were continuously assessed during the experiment. According to the study protocol, model stability had to be evaluated at defined stages in-between the investigational cycles regardless of continuous observations. This included pressure-volume diagrams at defined steps of the experiment and lung ultrasound to screen for pneumothorax.

All observations were fitted with time stamps and annotated if any further action was taken. In case of signs for model instability, it was decided in advance to complete an ongoing interventional cycle before further investigation.

Model instability was considered in case of unexpected sensory readings of airway pressure, tidal volume, and esophageal pressure. Additionally, visually evolving abnormalities in human cadaver models that would raise concerns during real CPR scenarios were investigated. Investigators were instructed to evaluate changes in chest wall movements, which could indicate rip cage fractures that could result in pneumothorax. Events of accumulation of liquid residue in the endotracheal tube were resolved by suction after the respective two-minute cycle was concluded.

Visual observation, continuous assessment of sensory readings, lung ultrasound, and five performed pressure-volume diagrams were undertaken to monitor model stability.

2.2.1.1 Detection of Pneumothorax

Injuries related to cardiopulmonary resuscitation attempts are quite common. Typical findings include rib fractures, sternal fractures, and soft tissue injuries resulting in

pneumothorax. The most likely cause of these injuries is external manual or mechanical chest compressions. (175,176)

In positive pressure ventilation, pneumothorax can quickly evolve into a condition where large parts of lung tissue are replaced by trapped air inside the chest cavity. (151) Subsequently, this results in difficulty to properly ventilate a patient. Ventilator signs of relevant pneumothorax are an increase of peak airway pressure, while at the same time, tidal volumes can decrease. Additionally, this has a detrimental hemodynamic effect on patients. Nevertheless, this can be disregarded; hence there are no circulation measurements attempted in the human cadaver model.

Therefore, investigators were instructed to be vigilant of any signs of rip fracture, subcutaneous emphysema, or unexpected changes in the ventilation measurements. The effort was made to screen for pneumothorax using bilateral lung ultrasound investigations after every cycle that included chest compressions and before the decision was made to include a human cadaver model into the study. (177,178)

A bilateral thoracostomy was performed to screen for undetected accumulation of air in the pleural spaces at the conclusion of Phase 2. Pneumothorax was assumed if an air discharge was notable upon opening the chest wall.

2.2.1.2 Pressure-Volume Diagrams

Five pressure-volume diagrams were performed on each cadaver model throughout the experiment to account for model stability and reasonable post hoc comparability between cardiac arrest patients and the human cadaver model.

The pressure-volume diagrams were acquired employing the P/V Tool® of the 'HAMILTON-C6' (Hamilton Medical Inc., Bonaduz, Switzerland) intensive care ventilator connected to the endotracheal tube. Sensor readings and raw data recordings were used to plot pressure-volume curves. Static lung compliance was calculated as the maximum slope of the pressure-volume curve's inspiratory leg. All pressure-volume diagrams were additionally recorded using the screenshot function of the 'HAMILTON-C6', and the picture file was saved to a secure digital memory card for data transfer.

2.3 Documentation and Study Protocol

One investigator (JW) was tasked to ensure adherence to the study protocol, take time, photograph technical setups, note findings, and cross off completed steps on a paper protocol throughout the experiment. The age of the cadaver models was added after the completion

of the investigation. Paper protocols included model identification, utilizing a code that consisted of the recording number given out by the computer system and the alphanumeric code assigned by the Institute for Macroscopic and Clinical Anatomy at the Gottfried Schatz Research Center of the Medical University of Graz. This code was later used to match paper protocols with the digital data collected from sensory systems. Sensory readings were transmitted via a secure wireless local area network within the human cadaver laboratory.

A second investigator was responsible for handling ventilators, observing the monitor readings, and supervising the airway and the connected sensor probes.

A third investigator ensured the correct function of the mechanical chest compression device and gathered sonographic lung imaging in accordance with the study protocol. This person assisted the second investigator during preparation and standardization, including airway placement, video bronchoscopy, and alveolar lavage.

Further investigators assisted during the experiment and rotated with one of the above investigators to ensure an uninterrupted workflow.

Experimental data was documented by filling in paper protocol sheets and by the continuous digital collection of sensor readings. Collected raw data points were saved on a receiving laptop and secure external hard drive.

2.4 Phase 0: Preparation and Standardization

Phase 0 was undertaken to prepare all six human cadaver models and gain a baseline assessment of the bodies. The steps below were carried out to achieve comparability with cardiac arrest patients regarding bio-mechanic lung and chest wall properties. Phase 0 is depicted in blue in the study flowchart (Figure 5).

2.4.1 Technical and Laboratory Setup

The study was conducted over three days at the Institute for Macroscopic and Clinical Anatomy at the Gottfried Schatz Research Center of the Medical University of Graz. The laboratory was set up in one of the institute's dissecting rooms.

On the first day, the human cadaver models were placed on their backs on steel dissecting tables to account for flat solid support, which is the recommended position for conventional CPR. Due to the necessity to set up all technical equipment, establish a feasible workflow, and gain experience in handling the Thiel human cadaver model, the first day of the three-day experiment was entirely used for these purposes. On the following two days, the actual experiment was performed in accordance with the study protocol.

Three sensor probes were prepared to measure esophageal pressure (differential pressure sensor; 'DLVR-L60D', All Sensors Corporation, Morgan Hill, California), airway pressure (differential pressure sensor; 'DLVR-L60D', All Sensors Corporation, Morgan Hill, California), and airflow rate (mass flow meter; 'SFM3000', Sensirion AG, Staefa, Switzerland). Every sensor was connected to one of three single-board computers ('Raspberry Pi 3 B+', Raspberry Pi Foundation, Cambridge, United Kingdom). The sample rate was 500 Hz for the differential pressure sensors and 200 Hz for the flow meter. A graphical overview of the laboratory setup is provided below in Figure 6.

During the experiment, a live plotting of the collected data on the laptop screen was available.

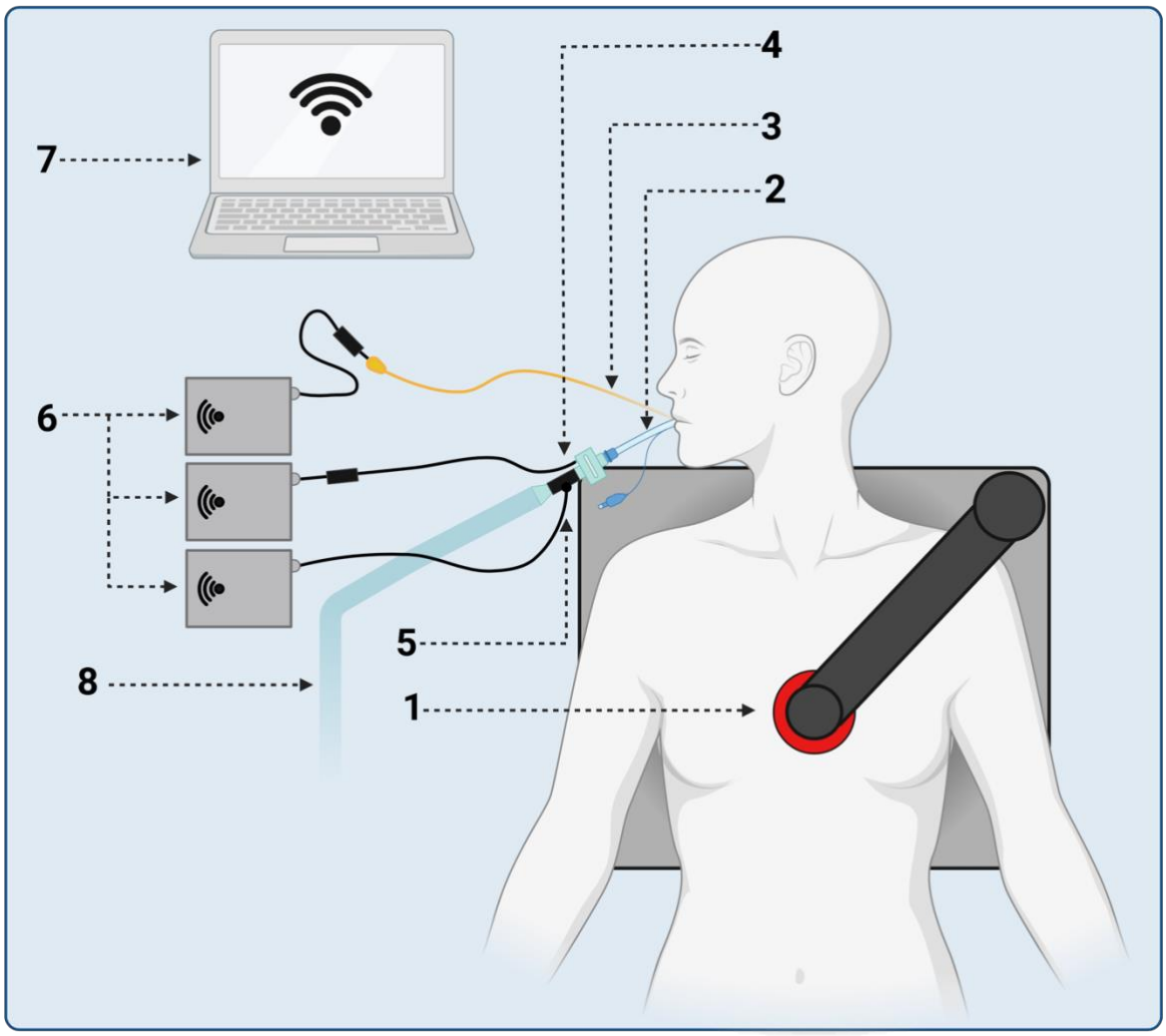

Figure 6 Laboratory Setup

[1] automated chest compression device [2] endotracheal tube [3] esophageal balloon catheter connected to a differential pressure sensor [4] differential pressure sensor connected to the heat-moisture exchange port of the endotracheal tube [5] mass flow meter installed in the ventilation circuit [6] three single board computers connected to the sensors and to a data-receiving laptop [7] laptop running 'MATLAB' for live plotting [8] flexible tubing connected to the ventilator circuit. Figure created with BioRender.com.

2.4.2 Human Cadaver Model Preparation

Model preparation was started by initiating the documentation process, in which starting time, alphanumeric identification code of human cadaver models, and investigator names were noted. Additionally, gender (male/female) and body height (cm) were documented along with the investigator consensus decision whether a subject was estimated to be visibly overweight.

IPBW was derived using a modified Broca's formula. (179) Target tidal volumes minimum and maximum were calculated for the range of 6 and 8 ml/kg IPBW.

Along with the investigator tasked to document the investigation, two other investigators inspected the bodies for visible signs of injury, which could have impeded further experimentation. Thoracic, cervical, and abdominal injuries were considered to impact the study viability. Any such abnormalities were noted on the documentation sheet.

Following the external examination, cadaver models were intubated orally by direct laryngoscopy, and subsequently, video bronchoscopy was performed ('aScope^{TM} 4 Broncho Large', Ambu^{TM}, Ballerup, Denmark). Correct endotracheal tube placement was confirmed by bronchoscopy and lung auscultation. Two investigators commenced to inspect and clear the airway of any debris and embalmment liquid by bronchoalveolar lavage with isotonic 0.9 % sodium chloride solution as well as pneumatic suction. The differential pressure sensor for airway pressure was connected to the side port of the endotracheal tube's heat and moisture exchanger. The differential pressure sensor for esophageal pressure was connected to the esophageal balloon catheter, in accordance with manufacturer recommendations.

Additionally, lung ultrasound was used to screen for pleural effusion and pneumothorax. Following tube fixation, adequate cuff pressure was measured. The subsequent step was the oral, esophageal pressure probe placement with an insertion depth of 30 cm. Probe fixation by suturing was necessary to avoid dislocation under mechanical chest compressions. The airway pressure and airflow sensors were connected to the artificial airway system. All sensors were connected to receiving single-board computers.

From this point onwards, all sensor readings were continuously recorded.

2.4.3 Lung Recruitment

The initial aeration maneuvers were carried out using the intensive care ventilator, which was connected to the endotracheal tube at all times. If the artificial airway had to be disconnected from a ventilator at any point of the experiment, it was blocked at a pressure

of 20 cmH_2O to minimize alveolar collapse. This was not feasible when the airway had to be cleared of debris or liquid by suction.

Two subsequent recruitment maneuvers were performed using quasi-static inflation maneuvers upon connection to the ventilator. During both maneuvers, start/end PEEP was 5 cmH_2O, plateau pause time was five seconds, and overall time to perform the maneuver was 30 seconds. For the first maneuver, adjustments were applied as mentioned, and targeted maximum airway pressure was set to 25 cmH_2O, whereas in the second maneuver, the targeted maximum airway pressure was adjusted to 30 cmH_2O.

Following the two recruitment maneuvers, 15 minutes of volume-controlled continuous mandatory ventilation (VC-CMV) was carried out, and the calculated tidal volume of 6 ml/kg IPBW was applied. The subjects were ventilated at a rate of 12/min, with an I:E ratio of 1:2. During this timeframe, PEEP was adjusted to 5 cmH_2O, and positive pressure was limited to 40 cmH_2O.

2.4.4 Inclusion and Randomization

After the initial 15 minutes of ventilation, the baseline pressure-volume diagram was obtained. Subsequently, lung ultrasound was performed to screen for pneumothorax.

Model stability was assessed using the obtained pressure-volume loops and sonographic findings. In the case of sonographic signs of a large pneumothorax, it was predefined to exclude the respective cadaver model from the study. It was also defined to exclude cadaver models with baseline pressure-volume diagrams showing signs of model instability. Once the threshold for model stability was passed and no signs of a clinically relevant pneumothorax were present, a cadaver model could be included in Phase 1 and Phase 2 of the study, provided that the mentioned criteria were sustained throughout the experiment.

Randomization was carried out at the point of inclusion by one investigator, who randomly drew one of six sealed envelopes, which had been prepared in advance by another investigator. Each of the closed envelopes contained a printed note with one of the possible permutations of ventilator sequences. Therefore, none of the sequences were alike, and every ventilator was applied to a different cadaver model as the first, second, and third device twice. This was done to account for model degeneration over the cross-over period of Phase 2 and achieve comparability between mobile emergency ventilators. The first standardized ultrasound investigation, inclusion process, and randomization are depicted in red in the study flowchart (Figure 5).

2.5 Phase 1: Mechanical Properties

Phase 1 consisted of three consecutive two-minute-long intervention to assess mechanical properties of the human cadaver models during ventilation, chest compressions, and the combination of both. Phase 1 is depicted in green in the study flowchart (Figure 5). The aforementioned intensive care ventilator was used for artificial ventilation during the entire phase. To provide standardized chest compressions, a mechanical chest compression piston device was used ('corpuls cpr', GS Elektromedizinische Geräte G. Stemple GmbH, Kaufering, Germany). The resuscitation board was placed under the thorax before the first two-minute cycle was started.

During the first two-minute-long intervention, ventilation was provided for two consecutive minutes. Ventilator adjustments were set to VC-CMV mode, with a tidal volume at 6 ml/kg IPBW, a ventilation rate of 10/min, an I:E ratio of 1:5, a PEEP of 5 cmH_2O, and a maximum pressure of 60 cmH_2O.

In the second two-minute-long intervention, chest compressions were applied while the ventilator was connected to the endotracheal tube to maintain a PEEP of 1 cmH_2O. The automated chest compression device had been set up in advance. The piston position of the device was adjusted to ensure a mid-chest compression point in accordance with applicable guideline recommendations. (123,161) The compression rate was set to 103 compressions per minute, and a compression depth of five cm was selected. The compressions rate was chosen to prevent ventilation-compression synchronization at later experiment stages when asynchronous CPR was commenced. After two minutes of continuous chest compressions, the intervention was discontinued. It must be noted that the automated chest compression device regularly interrupts continuous chest compressions to correct the vertical piston position automatically.

At the end of this intervention, lung ultrasound was performed to screen for newly developed pneumothorax.

For the third two-minute-long intervention, the automated chest compression device was set up in the same way as in the previous study cycle. Mechanical ventilator adjustments remained unchanged from the first study cycle except for PEEP, which was set to 0 cmH_2O. Asynchronous automated chest compressions and mechanical ventilation were provided for two consecutive minutes. This was followed by the third ultrasound screening for pneumothorax.

2.6 Phase 2: Intervention Phase

Phase 2 of the experiment was conducted in a randomized cross-over design to assess the performance of three commonly used mobile transport ventilators during asynchronous CPR. This phase was the core investigation, while the preceding phases were conducted to prepare the respective cadaver models and obtain data for model stability. Phase 2 is depicted in yellow in the study flowchart (Figure 5).

The three emergency ventilators 'MEDUMAT Standard^2' (WEINMANN Emergency Medical Technology GmbH + Co. KG, Hamburg, Germany), 'Oxylog 3000 plus' (Drägerwerk Ag & Co. KGaA, Lübeck, Germany) and 'Monntal T60' (Air Liquide Medical Systems, Antony Cedex, France) were applied together with the automated chest compression piston device in the human cadaver model of CPR.

This investigation continuously assessed air volumes, airflow, airway pressure, and esophageal pressure.

Phase 2 consisted of three consecutive cross-over periods, each employing one of the three transport ventilators. The order in which the ventilators were applied was determined upon inclusion by randomization. Every cross-over period was identical, apart from the applied ventilator.

The respective transport ventilator was set to a volume-controlled ventilation mode (VC-CMV) with a tidal volume at 6 ml/kg IPBW, a ventilation rate of 10/min, an I:E ratio of 1:5, a PEEP of 0 cmH_2O, and a maximum pressure of 60 cmH_2O. In some devices, the exact tidal volume as calculated was not allowed by the device, and the closest to calculated but allowed settings were selected instead. For the 'MEDUMAT Standard^2', an I:E of 1:4 was the maximum allowed ratio and therefore selected. The inspiratory period was set to 1 second in all devices. The automated chest compression device was handled and fitted with the same settings as in the two study cycles in Phase 1.

The respective transport ventilator was started together with the chest compression device and stopped after the first two-minute cycle of asynchronous CPR. A sonographic screening for pneumothorax was performed before the second two-minute cycle of asynchronous CPR with the same device was started. At the conclusion of the first cross-over period, another sonographic pneumothorax screening was conducted.

After the first cross-over period, the second transport ventilator was connected to the endotracheal tube after the third pressure-volume diagram was recorded using the intensive care ventilator. The second and third cross-over periods were conducted identically to the

first cross-over period. Over three cross-over periods, six two-minute cycles of asynchronous CPR, six ultrasound investigations, and three pressure-volume loops were performed. After the third cross-over period was concluded, a fifth and final pressure-volume diagram was obtained. A bilateral thoracostomy concluded each human cadaver study to screen for undetected pneumothorax.

2.7 Data Processing and Statistical Analysis

Sensor data was transmitted via the single-board computers to a laptop and securely stored for data processing. Raw data was processed and visualized using 'MATLAB', which allowed for interactive exploration and manual annotation of the measured signals. The interactive tool and data set were published in a cloud-based data repository. (180,181)

Ventilation parameters of interest were derived from raw data measurements.

Gas volumes were derived from flow signals of all ventilation cycles individually. This included *inspiratory tidal volume* [in ml], defined as net gas inflow; *expiratory tidal volume* [in ml], defined as net gas outflow; *cumulative inspiratory volume* [in ml], defined as the total gas inflow over the entire ventilation cycle. Therefore, the cumulative inspiratory volume included gas movements produced by chest compression.

The reverse airflow phenomenon was defined as the volume of gas moved in the opposite direction of the ventilation phase, resulting in reversed airflow during the inspiratory phase and reversed airflow during the expiratory phase.

Missed inspiratory tidal volume [in %] was calculated as the fraction deviation of inspiratory tidal volume from the preset tidal volume.

Peak airflow [in ml/min] was defined as the inspiratory maximum of each inspiratory phase of the respective ventilation cycle.

Peak airway pressure [in mbar] was defined as the measured maximum pressure during decompression of the chest of a respective ventilation cycle.

Two investigators (Simon Orlob and Johannes Wittig) independently reviewed the visualized data set to exclude ventilations during incomplete chest compressions. Incomplete chest compressions were defined as chest compressions that incompletely covered a ventilation cycle or could not reach the preset five cm compression depth. The excluded ventilations were not included in the subsequent analysis.

Esophageal pressure [in mbar] was primarily used to detect chest compressions within the interactive visualization tool reliably.

Exported data were analyzed using standard statistic software ('IBM SPSS Statistics for Macintosh', Version 26.0, IBM Corp., Armonk, New York, United States of America; SAS 9.4', SAS Institute, Cary, North Carolina, United States of America; 'R 3.6.1.', R Development Core Team).

For *missed inspiratory tidal volume*, *peak airflow* and *peak airway pressure* linear mixed models were calculated having the respective human cadaver model as the random factor. The human cadaver model's height, sex, the transport ventilator type, cross-over period, and sequential ventilation number within each cross-over period were applied as covariates in the linear mixed models.

The presented data analyses are reported as appropriate as mean ± standard deviation or median with interquartile range, minimum and maximum (IQR, [Minimum; Maximum]). 95%-confidence intervals are indicated with the effect estimates. Parametric and non-parametric statistical testing was performed as specified. A significance level of 0.5 was selected.

3 Results

3.1 Human Cadaver Model Characteristics

This experimental study included six human cadaver models, composed of three female and three male cadaver models.

The median height was 168 (5, [154; 172]) cm and median IPBW was 64.6 kg (5.4, [48.6; 67.5]) kg. Two of the cadaver models were estimated to be overweight.

All measured model characteristics and derived values are depicted in Table 1.

Model ID	Sex [female/male]	Age [years]	Height [cm]	IPBW [kg]	Overweight [yes/no]	Calculated V_t [ml] for 6 ml/kg IPBW	Calculated V_t [ml] for 8 ml/kg IPBW
G73	female	89	166	59.4	no	356	475
G84	male	81	171	67.5	no	405	540
G87	female	90	172	64.8	no	389	518
G88	male	74	168	64.6	yes	388	517
G74	male	83	166	62.7	no	376	502
G83	female	81	154	48.6	yes	292	389

Table 1 Human Cadaver Model Characteristics and Calculations

*IPBW (ideal predicted body weight), V_t (tidal volume); This modified version was originally published by Orlob et al. as Table 1**(170)**.*

3.2 Human Cadaver Model Stability

For each human cadaver model, nine sonographic screenings for pneumothorax were conducted, five pressure-volume diagrams were generated, and from each pressure-volume loop, static compliance (C_{stat}) [ml/mbar] was derived.

Across all cadaver models the median baseline C_{stat} was 30.1 (11.9, [25; 51.5]) ml/mbar. At the beginning of the first cross-over period, median C_{stat} had increased significantly to 38.8 (19.8, [32.5; 70.3]) ml/mbar ($p = 0.028$) and increased further over the subsequent pressure-volume measurements, while the incremental C_{stat} increase between the second and third measurement was significant ($p = 0.046$). The median C_{stat} of the pressure-volume diagrams before the second cross-over period was 43.1 (14.6, [31.3; 67.1)] ml/mbar and 48.5 (21.9, [34.8; 76.3]) ml/mbar before the third cross-over period. The median C_{stat} of the fifth and final pressure-volume diagrams was 49.7 (22.2, [34.7; 70.8]) ml/mbar. The C_{stat} increase over five measurements was significant ($p = 0.002$).

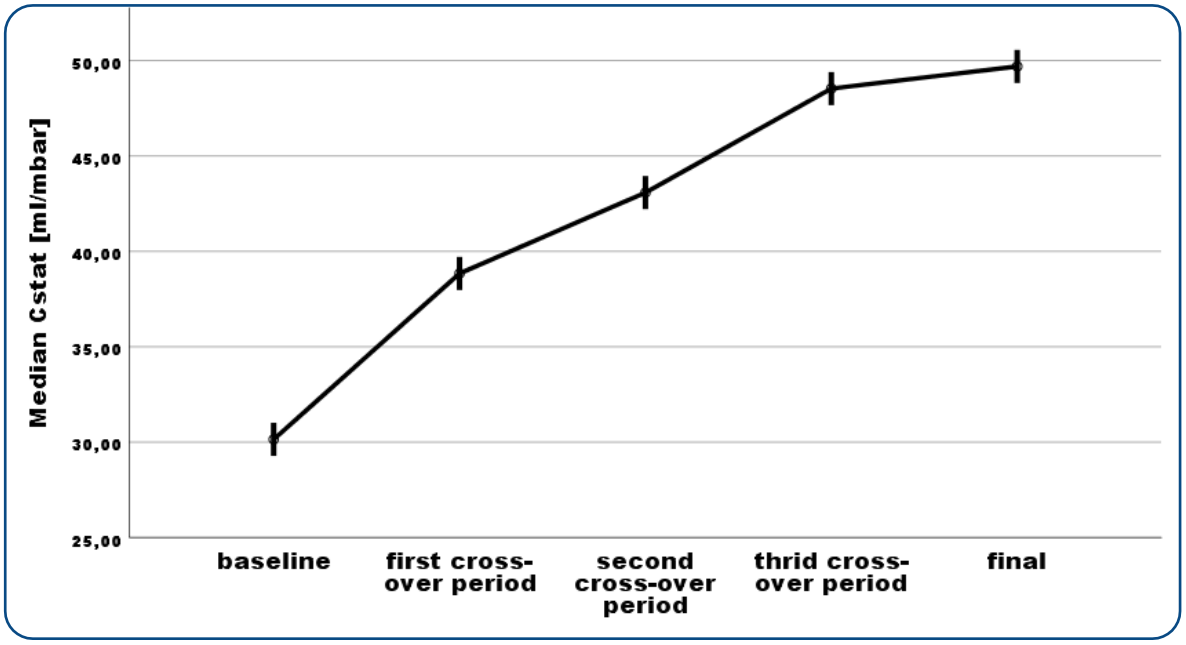

Figure 7 Static Compliance Changes

Shown are median static compliances (C_{stat}) [ml/mbar] of all cadaver models, grouped by predefined measuring points over the course of the experiment. Created with 'IBM SPSS Statistics for Macintosh'.

The sonographic screenings revealed unilateral pneumothorax in three cadaver models (cadaver ID: G73, G84, G87). Two of the three unilateral pneumothoraxes were left-sided, and all were detected after the second period of the cross-over study (Phase 2). As all pneumothoraxes were considered by investigator consensus to be minor, sufficient model stability was assumed, and the experiment continued.

3.3 Transport Ventilator Performance

During the three cross-over periods, each of the six human cadaver models received six segments of asynchronous CPR. This accumulated in 36 CPR segments, during which 757 ventilations were recorded. 42 (5.5 %) of the 757 were excluded due to incomplete chest compressions, resulting in 715 (94.5 %) ventilations included in the analysis.

The preset tidal volumes based on the tidal volumes calculated for 6 ml/kg IPBW are presented in Table 2 for each human cadaver model and transport ventilator. The median preset tidal volume was 390 (40, [290; 410]) ml.

Model ID	Preset Vt [ml] 'MEDUMAT Standard2'	Preset Vt [ml] 'Oxylog 3000 plus'	Preset Vt [ml] 'Monnal T60'
G73	350	360	360
G84	400	410	410
G87	400	390	390
G88	400	390	390
G74	400	380	380
G83	300	290	290

Table 2 Ventilator Volume Settings

A modified version was published by Orlob et al. as Table 1 ***(170)****.*

3.3.1 Tidal Volume

Median inspiratory tidal volume was 275 (68, [47; 464]) ml, and median expiratory tidal volume was 275 (72, [53; 451]) across all devices. The median deviation between inspiratory and expiratory tidal volumes was 1.14 (8.68, [−24.5; 35.4]) ml.

When the inspiratory tidal volume was normalized for IPBW, the median volume was 4.75 (1.2, [0.7; 7.6]) ml/kg IPBW.

The median missed inspiratory tidal volume across all transport ventilator devices was −21.2 (19.6, [−87.9; 25.8]) %.

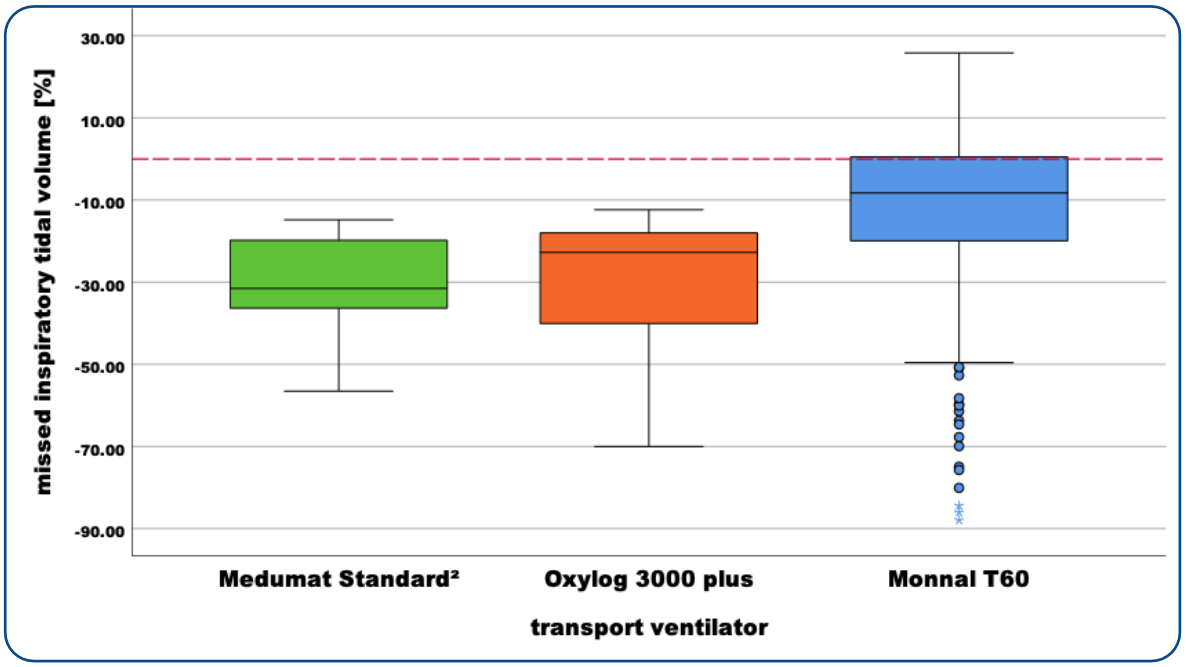

Figure 8 Missed Inspiratory Tidal Volume of Transport Ventilator Models

Boxplots of missed inspiratory tidal volume [%] are shown for each transport ventilator model. The dotted red line indicates no deviation from preset tidal volume. Created with 'IBM SPSS Statistics for Macintosh'.

The median missed inspiratory tidal volume for the 'MEDUMAT Standard²' was −31.5 (16.6, [−56.5; −14.8]) %, for the 'Oxylog 3000 plus' the median deviation was −22.7 (22.1, [−70; −12.3]) % and −8.3 (20.5, [−87.9; 25.8]) % for the 'Monnal T60' turbine ventilator.

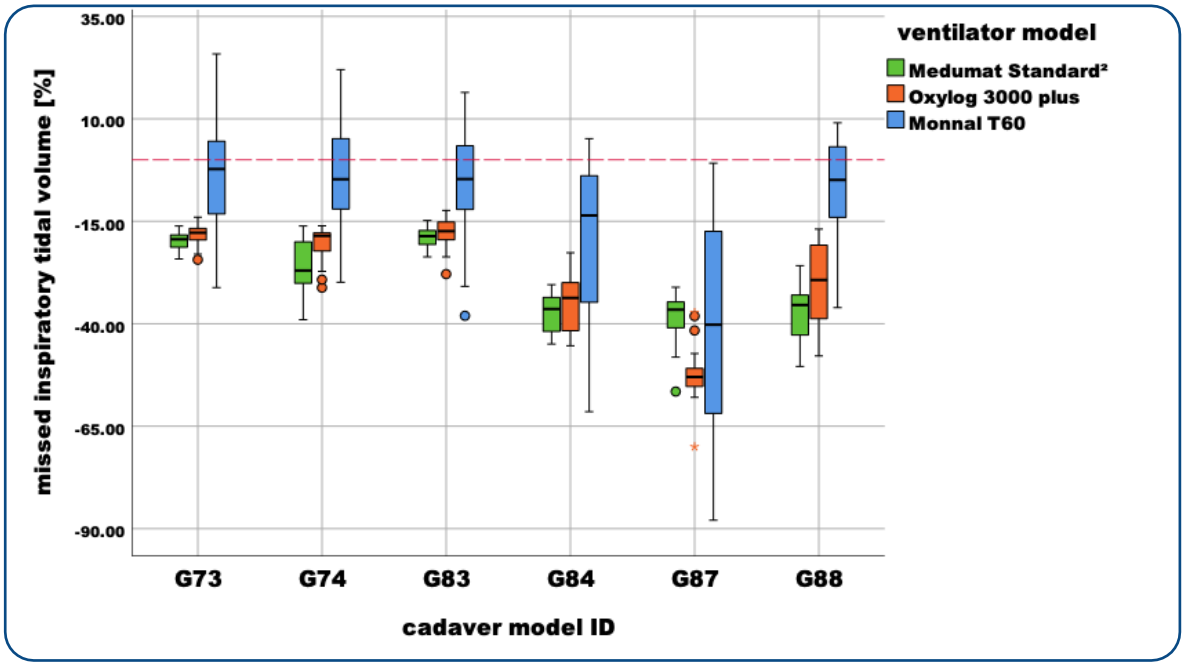

Figure 9 Missed Inspiratory Tidal Volume of Transport Ventilator Models per Cadaver Model

Boxplots of missed inspiratory tidal volume [%] are shown for each transport ventilator model and cadaver model. The dotted red line indicates no deviation from preset tidal volume. Created with 'IBM SPSS Statistics for Macintosh'. A modified version was published by Orlob et al. as Figure 2 ***(170).***

Mean population estimates for missed inspiratory tidal volume were −31 [95%-CI: −38.9; −23] % ($p < 0.0001$) for the 'MEDUMAT Standard²', −30.6 [95%-CI: −38.6; −22.6] % ($p < 0.0001$) for the 'Oxylog 3000 plus' and −14.5 [95%-CI: −22.5; −6.5] % ($p = 0.0004$) for the for the 'Monnal T60' turbine ventilator, according to a mixed linear model.

Transport ventilator device, the cross-over period, and height of the human cadaver model were statistically significant factors for missed inspiratory tidal volume, while female gender was found to be not significant.

3.3.2 Airflow and Airflow Phenomena

Median peak airflow was 45.9 (15.8, [20.65; 93.03]) l/min across all transport ventilators. For the 'MEDUMAT Standard²' median peak airflow was 43.5 (8.1, [31.2; 54.9]) l/min, 44.4 (11, [27.9; 57.9]) l/min for the 'Oxylog 3000 plus' and 68.5 (23.6, [20.7; 93]) l/min for the 'Monnal T60'.

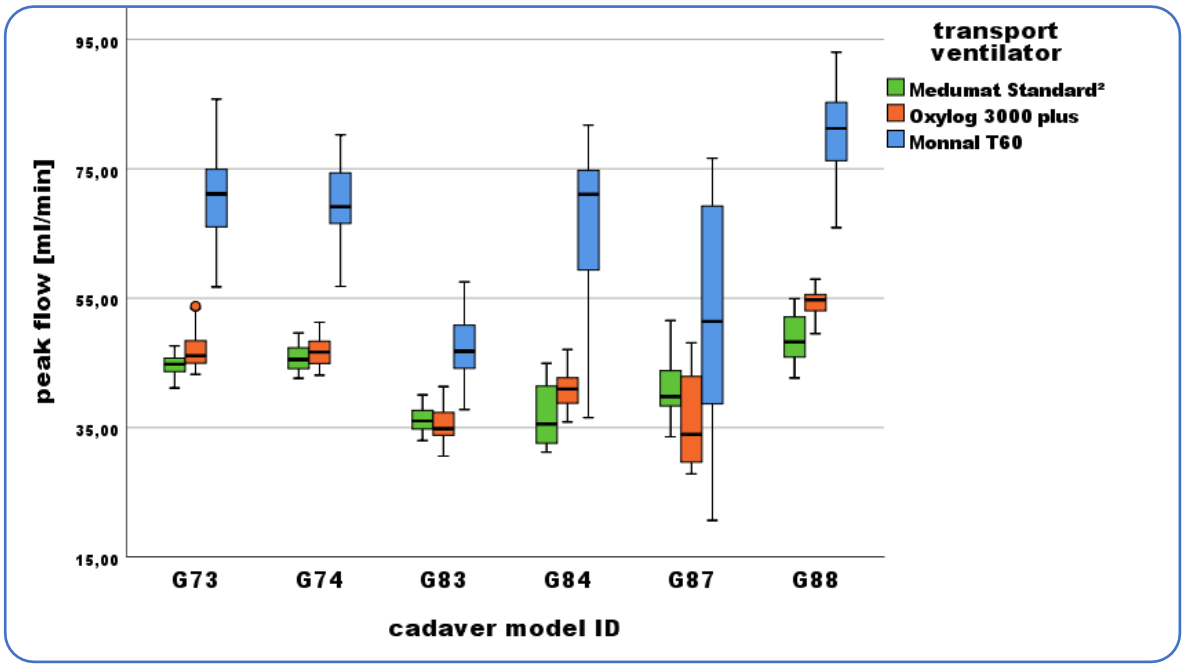

Figure 10 Peak Flow of Transport Ventilator Models per Cadaver Model

Shown are boxplots of peak airflow for each transport ventilator model and cadaver model. Created with 'IBM SPSS Statistics for Macintosh'.

The effect estimates of the ventilator devices on peak airflow were significantly different for the 'Monnal T60' ($p < 0.001$) compared with the 'MEDUMAT Standard²' and 'Oxylog 3000 plus'. The same comparison between 'MEDUMAT Standard²' and 'Oxylog 3000 plus' was not significant in a linear mixed model.

Fragmented and reversed airflow could be observed in inspiratory and expiratory phases of ventilation cycles. During inspiration, the median number of reversed airflow episodes was

1 (0, [0; 2]), and during expiration, the median number of reversed airflow episodes was 7 (1, [0;9]). Reversed airflow episodes were counted when they exceeded 1 ml of derived volume. The median volume of reversed airflow was 0.95 (0.96, [0.05; 2.87]) ml/kg IPBW. The largest volume of measured reversed airflow was 45.6 ml, which was 0.7 ml/kg IPBW.

3.3.3 Airway Pressure

Median peak airway pressure during chest compression and decompression was 64.6 (15.2, [47.3; 79.5]) mbar for the 'MEDUMAT Standard²', 63.7 (14.4, [44.2; 77.9]) mbar for the 'Oxylog 3000 plus' and 52 (13.5, [33.2; 70.3] mbar for the 'Monnal T60'.

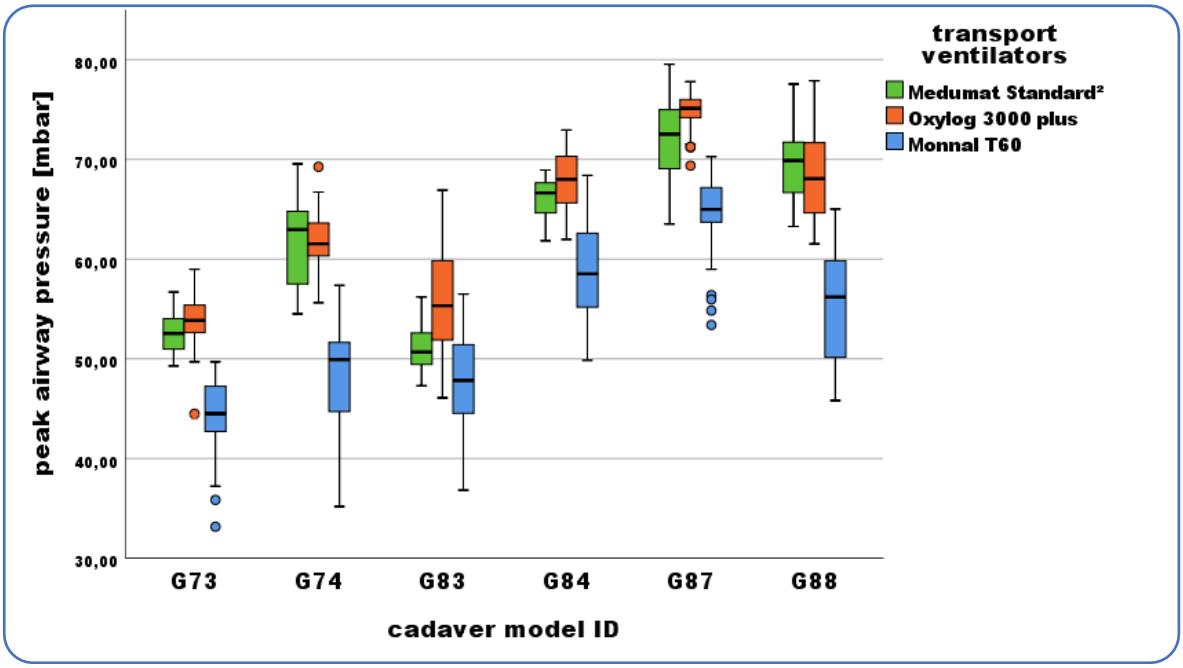

Figure 11 Peak Airway Pressure of Transport Ventilator Models per Cadaver Model

Boxplots of peak airway pressure are shown for each transport ventilator model and cadaver model. Peak airway pressure was evaluated regardless of chest compression phase. Created with 'IBM SPSS Statistics for Macintosh'.

Median peak airway pressure during decompression of the chest was 48.5 (14.4, [27; 73.3]) mbar for the 'MEDUMAT Standard²', 55.5 (12.6, [27.9; 66]) mbar for the 'Oxylog 3000 plus' and 46.6 (10.7, [30.2; 64.4] mbar for the 'Monnal T60'.

In a linear mixed model, the effect estimates of the three transport ventilators on airway pressure were all significantly different when compared with each other ($p < 0.001$).

4 Discussion

4.1 Study Insights

The present study supports the use of transport ventilators during continuous chest compressions because all devices were able to provide tidal volumes that exceeded dead space ventilation. This means that transport ventilators can provide ventilation that contributes to pulmonary gas exchange when a volume-controlled continuous mandatory ventilation mode with a preset tidal volume of 6 ml/kg IPBW is applied.

However, severely reduced tidal volumes were observed across all devices. The median tidal volume reduction differed between devices and depended on the respective device. The turbine-driven 'Monnal T60' ventilator performed best and showed hints of a compensatory mechanism as volume overshoots repeatedly followed reduced tidal volumes. For the same device, a relative superiority to rapidly increase peak airflow can be inferred from the reported observations. It can be speculated that the device makes use of an internal corrective algorithm to compensate for changing respiratory system mechanics to satisfy preset ventilation parameters. Differences in ventilation device technology must be considered when transferring the study findings into practice.

Inspiratory tidal volumes were used to calculate the most important study metric — deviation from preset tidal volume during chest compressions. The usage of inspiratory tidal volume should be explained as it is contrary to advisable clinical practice. The respiratory resting position is more affected by chest compressions which in turn impacts expiratory volumes. Therefore, inspiratory volumes were preferred for the subsequent analysis.

However, it seems more advisable to observe expiratory volumes in clinical practice closely. Expiratory tidal volumes reflect air volumes for alveolar ventilation more reliably because inspiratory tidal volumes could overestimate the volumes relevant for pulmonary gas exchange as downstream system leakage is falsely incorporated. The observed expiratory and inspiratory volumes in this study were almost identical, which is explained by a tightly sealed ventilation system.

Consequently, using an endotracheal tube, which allows for a sealed ventilation circuit with a broader tolerance of high airway pressure, is significant to prevent leakage. Therefore, the study's findings are limited to mechanical ventilation during asynchronous CPR in conjunction with cuffed endotracheal tubes. This study does not allow any conclusions on mechanical ventilation in conjunction with supraglottic airway devices.

Airflow phenomena produced by the interaction of artificial ventilation and chest compressions are known as reversed airflow and fragmentation of airflow. (112,113) Both phenomena were observed in this investigation as well. Reversed airflow did not exceed anatomical dead space, limiting its ability to impact pulmonary gas exchange. The volumes produced by reversed airflow explain the considerable difference in actual inspiratory tidal volume and cumulative tidal volume. It is important to separate the various measurable volumes as only tidal volumes contributing to alveolar ventilation can facilitate gas exchange.

4.2 Lessons and Limitations of The Thiel Model

The International Liaison Committee on Resuscitation (ILCOR) concludes that there is limited evidence to either refute or support the use of automated ventilation during CPR. (58,143) Although the present investigation provides experimental data from a human cadaver model of CPR, the findings broaden the understanding of devices already in use during critical clinical scenarios.

The Thiel human cadaver model has been successfully used to study ventilation mechanics during CPR before. (171) It has also received comparative appraisal to other human cadaver models of cardiac arrest. (172) The results from this study add to the evidence that the Thiel model is suitable to study lung and thoracic properties during resuscitation. The present results also indicate satisfactory model stability for the observed study duration but also show signs of model deterioration. This was represented by small but detectable pneumothoraxes in half of the models during Phase 2. Additionally, observed static lung compliance was comparable to previous studies of lung compliance after cardiac arrest but significantly increased throughout the experiment. (105,182) That the occurrence of pneumothorax and change in static lung compliance is exclusive to the Thiel model cannot be safely assumed but warrants to consider it as a model limitation. Therefore, statistical compensation was attempted for model deterioration in the linear mixed models.

An obvious advantage of the Thiel model is that animal sacrifice is not necessary, while actual human airway and thoracic anatomy can be studied. Many experimental approaches to resuscitation require animal sacrifice but must deal with the drawback of differences in airway anatomy. (183,184) Nevertheless, the Thiel human cadaver model cannot provide answers about hemodynamics, actual gas exchange, or any patient-relevant outcomes. (172) Alternatively, respiratory and chest wall mechanics have been studied in specialized manikin

models of CPR. (169,185) The investigation by Speer et al. observed a comparable reduction of tidal volumes in a manikin model.

However, the transfer of knowledge gained from experimental models should be attempted with caution as no model of CPR realistically resembles resuscitation efforts in human patients.

Further limitations of the present study are the small group size that did not allow to compensate for carry-over effects and the missing past medical history of the human cadaver models. To reduce the impact of an unknown pathology on the study, all individual cadaver models were considered random factors in the linear mixed models.

4.3 Implications for Clinical Practice

While considering the limitations, the presented investigation offers opportunities and insights for clinical practice.

The use of transport ventilators to avoid excessive ventilation frequencies seems reasonable as long as expiratory tidal volumes are closely monitored. The observation of reduced tidal volumes during chest compressions also provides a possible explanation for prevalent signs of hypoventilation from blood gas analyses acquired during CPR. (33,164)

The landmark publication by Aufderheide et al. that ignited the hyperventilation debate needs to be critically assessed regarding its applicability to modern resuscitation practice. (115,162) It needs to be considered that the tidal volumes applied by Aufderheide et al. were markedly larger than the tidal volumes common in modern practice and investigated in this study. Gazmuri et al. already revealed that reducing tidal volumes to clinically plausible levels reverses detrimental outcomes. (163) Recent simulation studies further suggest that not manual hyperventilation but hypoventilation might be an emerging problem in modern resuscitation practice. (186) This is supported by studies based on real-world resuscitation data on manual ventilation quality that show that ventilation quality is lacking and that insufficient ventilation negatively impacts survival. (187,188) Combining the heterogenous evidence on ventilation during cardiac arrest is challenging. Consequently, reliable guidance is unlikely. (167,168) Clinicians and researchers need to be cautious to avoid the conflation of readily available evidence on post ROSC ventilation and intra-arrest ventilation, for which evidence is scarce, as the need for artificial ventilation might differ greatly between the two patient populations. (189)

Therefore, the question remains which tidal volumes and minute ventilation are needed during CPR. Additionally, it is uncertain which ventilation mode and device should be used

to deliver these tidal volumes. (190) Ultimately, the ventilation-perfusion mismatch during resuscitation should be addressed. Special ventilation modes that aim to facilitate gas exchange and support hemodynamics present a promising opportunity for future ventilation practice but currently lack clinical evidence. (191,192)

Another opportunity to move ventilation forward is the development of ventilation feedback devices. These devices measure ventilation frequency and tidal volume while simultaneously giving feedback on manual ventilation during clinical CPR. (146) This presents two opportunities. First, best clinical practice and guideline adherence could be supported. Second, ventilation parameters during resuscitation have not been broadly available for scientific analysis. If these devices were used to record and analyze ventilation, insights into the need for ventilation during CPR could be gained.

The present investigation underscores that resuscitation practitioners and researchers should follow the recommendation by Ornato et al. and measure tidal volumes during CPR, instead of blindly hoping for sufficient ventilation – be it delivered by human or machine. (182)

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5 Appendix

5.1 Template for Experiment Documentation

Beobachtung der Beatmungsvolumina unter Thoraxkompressionen an der Thiel'schen Leiche - Orlob, Wittig, Feigl, Prause

Dokumentationsblatt **__ __ . 06. 2018**

Durchführende/r	
Protokollführer/in	
Startzeit	

Leiche ID/ Versuchnummer		❒ männlich ❒ weiblich
Körpergröße (cm)		
Adipositas	❒ ja ❒ nein	
ideales Körpergewicht (kg)		*Frauen: Ideales KG [kg] = Körpergröße [cm] - 100cm - 10%* *Männer: Ideales KG [kg] = Körpergröße [cm] - 100cm - 5%*
Tidalvolumen (V_t) 6ml/kg KG		*V_t = 6ml/kg ideal. Körpergewicht*
Tidalvolumen (V_t) 8ml/kg KG		*V_t = 8ml/kg ideal. Körpergewicht*
Anmerkungen		

Vorbereitung:

❒ orotracheale Intubation ❒ Cuffdruck-Kontrolle ❒ bronchoskop. Lagekontrolle
❒ Tubusfixierung ❒ Absaugen ❒ bronchoalveoläre Lavage

❒ Ösophagusdrucksonde verbunden mit Drucksensor
❒ Ösophagusdrucksonde verbunden mit Respirator (Hamilton-C6S)
❒ Ösophagusdrucksonde fixiert
❒ Ösophagusdrucksonden-System geschlossen (3-Wege-Hahn)
❒ Atemwegsdrucksensor
❒ Flowsensor
❒ Ultraschalluntersuchung
❒ Fotodokumentation
❒ Aufzeichnung starten (ab hier werden P_{es}, P_{aw}, Flow kontinuierlich aufgezeichnet)

Alle Tubusklemmungen werden mit 20 cmH2O durchgeführt

Initiale Recruitmentphase	Zeit:	
Aufzeichnungs-ID		*Vom Computer generiert*
❒ Recruitmentmanöver ❒ 15 Min. Ventilation ❒ 1. P/V-Diagramm ❒ Screenshot	 Start: Stopp: C_{stat} = ❒ Stabil ❒ Instabil	***P_{max} 40 cmH_2O*** ***V_{max} 8ml/kg iKG*** ***errechnetes V_t f 10/min, PEEP 5 cmH_2O, I:E 1:2, IPPV, P_{max} = 60 cmH_2O*** *P/V Screenshot* *C_{stat} = Tidalvolumen/(endinsp. Druck - endexsp. Druck) wird errechnet aus Aufzeichnung*
[❒ Bronchoskopie] [❒ Lungenultraschall] [❒ Pneumothorax] [❒ Wiederholung Recruitment] [❒ P/V-Diagramm]	[❒ Intervention + Zeit] [C_{stat} = ❒ Stabil ❒ Instabil]	*[im Fall von Instabilität des Modells/ signifikanten Schwankungen der Compliance]*
Anmerkungen:		
Studieneinschluss	❒ ja ❒ nein	*C_{stat} >20ml/cmH_2O und stabiles Modell*
Randomisierung	❒ Kuvert öffnen	*Respiratoren Reihenfolge/Nummer auf Kuvert vermerken*

❒ Sensorenkontrolle

Messung mechanischer Eigenschaften	Zeit:	
Ventilation ❒ 120 Sekunden	Start: Stopp:	***errechnetes V_t, f 10/min, PEEP 5 cmH_2O, I:E 1:5), IPPV, P_{max} = 60 cmH_2O, kont. Flow*** *Ermittlung von C_{stat} via Aufzeichnung* *C_{stat} = Tidalvolumen/(endinsp. Druck - endexsp. Druck)*
Anmerkungen		
Thoraxkompression ❒ 120 Sekunden	Start: Stopp:	***PEEP 1 cmH_2O*** *Platzierung corpuls cpr* *Start der kontinuierlichen Kompressionen* ***(103/min, 5cm Drucktiefe)*** **Thoraxkompressionskraft wird durch Reanimationshilfe corpuls cpr aufgezeichnet*
Anmerkungen		
Thoraxkompression-Ventilation Interaktion ❒ 120 Sekunden	Start: Stopp:	*Stopp der Reanimationshilfe* *Respirator rekonnektieren* ***PEEP 0, T_{insp} 1s, I:E 1:5*** ***kont. Flow, P_{max} = 60 cmH_2O***
Anmerkungen		

Primäre Interventionsphase	Zeit:	
❒ Pneumothorax Ausschluss ❒ 2. P/V-Diagramm ❒ Screenshot		*mittels Hamilton-C6s* *C_{stat} = Volumen/(Plateaudruck-PEEP)* *Ermittlung von C_{stat} via Aufzeichnung*
❒ 1. Respirator	❒ Medumat Standard[2] ❒ Oxylog 3000 ❒ Monnal T60	***errechnetes V_t (6ml/kg i,KG), f 10/min, PEEP 0 cmH_2O, T_{insp} 1s, I:E 1:5, IPPV, P_{max} = 60 cmH_2O, kont. Flow***

Respiratoreinstellungen	V_t =	*Tatsächliche Einstellungen am Respirator, daher wenn gerundet werden muss*
❒ Thoraxkompression + Ventilation 4 Minuten	Start: Stopp: ❒ Pneumothoraxausschluss Start: Stopp:	*2 Zyklen simulierte CPR bei kontinuierlichen Kompressionen* ***(103/min, 5cm Drucktiefe)*** **Thoraxkompressionskraft wird durch Reanimationshilfe corpuls cpr aufgezeichnet*
[❒ Lungenultraschall]	[❒ Intervention + Zeit]	*[im Fall von Instabilität des Modells/ signifikanten Schwankungen der Compliance, Lekage, Dislokation Reanimationshilfe]*
Anmerkungen		

Sekundäre Interventionsphase	Zeit:	
❒ Pneumothorax Ausschluss ❒ 3. P/V-Diagramm ❒ Screenshot		*mittels Hamilton-C6s* *C_{stat} = Volumen/(Plateaudruck-PEEP)* *Ermittlung von C_{stat} via Aufzeichnung*
❒ 2. Respirator	❒ Medumat Standard[2] ❒ Oxylog 3000 ❒ Monnal T60	***errechnetes V_t (6ml/kg i,KG), f 10/min, PEEP 0 cmH_2O, T_{insp} 1s, I:E 1:5, IPPV, P_{max} = 60 cmH_2O, kont. Flow***
Respiratoreinstellungen	V_t =	*Tatsächliche Einstellungen am Respirator, daher wenn gerundet werden muss*

❒ Thoraxkompression + Ventilation 4 Minuten	Start: Stopp: ❒ Pneumothoraxausschluss Start: Stopp:	*2 Zyklen simulierte CPR bei kontinuierlichen Kompressionen* ***(103/min, 5cm Drucktiefe)*** **Thoraxkompressionskraft wird durch Reanimationshilfe corpuls cpr aufgezeichnet*
[❒ Lungenultraschall]	[❒ Intervention + Zeit]	*[im Fall von Instabilität des Modells/ signifikanten Schwankungen der Compliance, Lekage, Dislokation Reanimationshilfe]*
Anmerkungen		

Tertiäre Interventionsphase	Zeit:	
❒ Pneumothorax Ausschluss ❒ 4. P/V-Diagramm ❒ Screenshot		*mittels Hamilton-C6s* *C_{stat} = Volumen/(Plateaudruck-PEEP)* *Ermittlung von C_{stat} via Aufzeichnung*
❒ 3. Respirator	❒ Medumat Standard[2] ❒ Oxylog 3000 ❒ Monnal T60	***errechnetes V_t (6ml/kg i,KG), f 10/min, PEEP 0 cmH_2O, T_{insp} 1s, I:E 1:5, IPPV, P_{max} = 60 cmH_2O, kont. Flow***
Respiratoreinstellungen	V_t =	*Tatsächliche Einstellungen am Respirator, daher wenn gerundet werden muss*
❒ Thoraxkompression + Ventilation 4 Minuten	Start: Stopp: ❒ Pneumothoraxausschluss Start: Stopp:	*2 Zyklen simulierte CPR bei kontinuierlichen Kompressionen* ***(103/min, 5cm Drucktiefe)*** **Thoraxkompressionskraft wird durch Reanimationshilfe corpuls cpr aufgezeichnet*

[❒ Lungenultraschall]	[❒ Intervention + Zeit]	*[im Fall von Instabilität des Modells/ signifikanten Schwankungen der Compliance, Lekage, Dislokation Reanimationshilfe]*
Anmerkungen		

Abschluss:

❒ 5. P/V-Diagramm
❒ Screenshot
❒ Endzeitpunkt: _____

❒ Vollständigkeit der Arbeitsschritte & Daten kontrollieren
❒ Sicherung der elektronisch erfassten Daten
❒ Sicherung der Fotos
❒ Scannen der Dokumentationsblätter (4)

5.2 Prior Publications

5.2.1 Reliability of mechanical ventilation during continuous chest compressions: a crossover study of transport ventilators in a human cadaver model of CPR

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Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

ORIGINAL RESEARCH Open Access

Reliability of mechanical ventilation during continuous chest compressions: a crossover study of transport ventilators in a human cadaver model of CPR

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Abstract

Background: Previous studies have stated that hyperventilation often occurs in cardiopulmonary resuscitation (CPR) mainly due to excessive ventilation frequencies, especially when a manual valve bag is used. Transport ventilators may provide mandatory ventilation with predetermined tidal volumes and without the risk of hyperventilation. Nonetheless, interactions between chest compressions and ventilations are likely to occur. We investigated whether transport ventilators can provide adequate alveolar ventilation during continuous chest compression in adult CPR.

Methods: A three-period crossover study with three common transport ventilators in a cadaver model of CPR was carried out. The three ventilators 'MEDUMAT Standard^2', 'Oxylog 3000 plus', and 'Monnal T60' represent three different interventions, providing volume-controlled continuous mandatory ventilation (VC-CMV) via an endotracheal tube with a tidal volume of 6 mL/kg predicted body weight. Proximal airflow was measured, and the net tidal volume was derived for each respiratory cycle. The deviation from the predetermined tidal volume was calculated and analysed. Several mixed linear models were calculated with the cadaver as a random factor and ventilator, height, sex, crossover period and incremental number of each ventilation within the period as covariates to evaluate differences between ventilators.

Results: Overall median deviation of net tidal volume from predetermined tidal volume was − 21.2 % (IQR: 19.6, range: [− 87.9 %; 25.8 %]) corresponding to a tidal volume of 4.75 mL/kg predicted body weight (IQR: 1.2, range: [0.7; 7.6]). In a mixed linear model, the ventilator model, the crossover period, and the cadaver's height were significant factors for decreased tidal volume. The estimated effects of tidal volume deviation for each ventilator were − 14.5 % [95 %-CI: −22.5; −6.5] ($p = 0.0004$) for 'Monnal T60', − 30.6 % [95 %-CI: −38.6; −22.6] ($p < 0.0001$) for 'Oxylog 3000 plus' and − 31.0 % [95 %-CI: −38.9; −23.0] ($p < 0.0001$) for 'MEDUMAT Standard^2'.

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Conclusions: All investigated transport ventilators were able to provide alveolar ventilation even though chest compressions considerably decreased tidal volumes. Our results support the concept of using ventilators to avoid excessive ventilatory rates in CPR. This experimental study suggests that healthcare professionals should carefully monitor actual tidal volumes to recognise the occurrence of hypoventilation during continuous chest compressions.

Keywords: Cardiac arrest, Artificial respiration, Ventilators, mechanical, Cardiopulmonary resuscitation, Tidal volume, Reversed airflow, Out-of-hospital cardiac arrest

Background

Sudden cardiac arrest is the third leading cause of death in Europe [1]. Out-of-hospital cardiac arrest (OHCA) has an annual incidence of approximately 89 per 100,000 inhabitants, resulting in more than 400,000 resuscitation attempts by emergency medical services every year in Europe and an overall survival rate of roughly 10 % [2, 3]. OHCA itself is a clinical condition that can be caused by several aetiologies. The predominant cause is of cardiac origin with underlying coronary disease. Cessation of organised cardiac contractions immediately leads to collapse of circulation with global ischemia, hypoxia, and global cell death.

To restore spontaneous circulation, cardiopulmonary resuscitation (CPR) strives to provide minimal perfusion with subsequent oxygen delivery to cells, predominantly of the heart and brain. Therefore, chest compressions and artificial ventilation have been a bundle of care in modern cardiac arrest treatment [4].

In recent years the role of ventilation has been comprehensively discussed [5, 6]. A major caveat in this debate has been the risk of hyperventilation in CPR [7]. As such, previous studies have posed that hyperventilation occurs commonly in CPR, mainly due to excessive ventilation frequencies, especially when a manual valve bag is used [8]. Nevertheless, apart from ventilation frequencies, actual tidal volumes (Vt) and minute volumes have been measured rarely in clinical CPR [8–11]. Ventilation during CPR can be synchronised with a compression-ventilation ratio of 30:2, or asynchronous with ventilations during continuous chest compressions [12]. While the synchronous ventilation strategy limits excessive manual ventilation frequencies, asynchronous manual ventilation does not. Still, continuous chest compressions may provide increased hemodynamic benefits regarding coronary perfusion pressure and limit no-flow time [13, 14]. Therefore, continuous chest compressions are recommended by international guidelines once the airway is secured [15].

Nevertheless, chest compressions are a counteracting force to positive pressure ventilation and may limit inspiratory volumes [16]. The risk of hypoventilation in CPR has been recently illustrated by Duchatelet et al. [11]. According to their study, chest compressions can impair tidal volumes, resulting in dead space ventilation without sufficient gas exchange.

Usage of mechanical ventilation in CPR might be a valid strategy to limit the respiratory rate and prevent tachy-ventilation during continuous chest compressions [6]. Whether common portable ventilators can provide relevant alveolar ventilation during continuous chest compressions is unknown. We sought to investigate the effect of continuous chest compressions on delivery of Vt, using transport ventilators in adults.

Methods

A three-period crossover study with three common transport ventilators in a cadaver model of CPR was conducted. The three ventilators 'MEDUMAT Standard²' (WEINMANN Emergency Medical Technology GmbH + Co. KG, Hamburg, Germany), 'Oxylog 3000 plus' (Drägerwerk AG & Co. KGaA, Lübeck, Germany) and 'Monnal T60' (Air Liquide Medical Systems, Antony Cedex, France) represent three different interventions providing volume-controlled continuous mandatory ventilation (VC-CMV) under continuous automated chest compressions. The latter of the three ventilators was a turbine-driven ventilator. Preparation, measurements and interventions have been conducted following an exact study protocol [see flowchart, Additional file 1].

In 1992, Walter Thiel (Graz, Austria) developed an embalming process for human cadavers preserving their natural mechanical properties, known as Thiel's method [17, 18]. Using this method, fixation is carried out over nine months by submersion of cadavers in basins of an embalming solution. Due to the close to in-vivo texture of the tissue, these cadavers are used in surgical training. More recently, they have also been used to study respiratory mechanics in models of resuscitation [19, 20].

All bodies were donated to the Chair of Macroscopic and Clinical Anatomy of the Medical University of Graz, under the strict rules of the anatomical donation program according to the Styrian burial law for scientific purposes. Hence, no additional approval by the local ethical board was required. For the present study, cadavers were randomly selected from the conservation basins and stored at ambient room temperature of 23 °C.

Cadavers were intubated orally by direct laryngoscopy. Tube positioning was verified by bronchoscopy ('aScope™ 4 Broncho Large', Ambu™, Ballerup, Denmark). Intrapulmonary fluid collections were suctioned through the bronchoscope's working channel; the residue of the embalming process was removed by lavage.

A differential pressure sensor ('DLVR-L60D', All Sensors Corporation, Morgan Hill, California) was installed to the sideport of a heat and moisture exchange filter connected to the endotracheal tube. The sensor was zeroed to the atmospheric pressure. A mass flow meter ('SFM3000', Sensirion AG, Staefa, Switzerland) was placed distal to the filter, in line with the artificial airway.

Each sensor was connected to an individual small single-board computer ('Raspberry Pi 3 B+', Raspberry Pi Foundation, Cambridge, United Kingdom), recording raw signals. The sample rate of the flow meter was 200 and 500 Hz for the differential pressure sensor.

Ventilatory strategy

The height of the cadaver was measured, and predicted body weight (PBW) was calculated using an adjusted Broca's formula [21]. Ventilatory settings were chosen in accordance with the applicable guidelines [22, 23]. Throughout the experiment, volume-controlled ventilation was used. The target tidal volume was calculated as 6 mL/kg PBW. Tidal volumes were set to the closest possible values of the respective ventilator (Vt_{set}). For sequences of chest compressions, a ventilatory frequency of 10/min, no positive end-expiratory pressure (PEEP), a pressure limit (P_{max}) of 60 cmH_2O with the shortest possible inspiratory period was used - being an inspiratory-expiratory-ratio of 1:5 for 'Monnal T60' and 'Oxylog 3000 plus', and 1:4 for 'MEDUMAT Standard²'. The inspiratory period was set to the recommended inflation duration of 1 s.

Chest compressions

Standardised chest compressions were performed using an automated chest compression piston device ('Corpuls CPR', GS Elektromedizinische Geräte G. Stemple GmbH, Kaufering, Germany). To avoid synchronisation of the chest compression phase and respiratory cycle, as given by a frequency of 100/min and 10/min, a chest compression frequency of 103/min and a compression depth of 5 cm was used.

Study protocol

Respiratory mechanics were monitored by repeated pressure-volume curves (P/V loop) with an intensive care ventilator ('HAMILTON-C6', Hamilton Medical Inc., Bonaduz, Switzerland). Static compliance (C_{stat}) was derived as the maximum slope of the inspiratory leg. Pneumothorax was ruled out by sonography after every two-minute cycle of chest compressions.

The initial aeration of the lung was carried out with the previously mentioned intensive care ventilator. Two quasi-static inflation manoeuvres were performed using a top pressure of 25 and 30 cmH_2O. This was followed by a 15-minute sequence of ventilation (VC-CMV: Vt 6 mL/kg PBW, f 12/min; PEEP 5 cmH_2O, I:E 1:2, P_{max} 40 cmH_2O) [s. blue segment of flowchart, Additional file 1].

Lung and thoracic properties were assessed utilising three separate sequences, lasting two minutes each. During the first sequence only ventilation was provided, followed by chest compressions only, concluding with a combined sequence of chest compressions and ventilation [s. green segment of flowchart, Additional file 1].

The three transport ventilators were tested in a three-period crossover design. Each period consisted of two, two-minute-long segments of simulated CPR [s. yellow segment of flowchart, Additional file 1]. The possible permutations of ventilator orders were calculated in advance and randomly assigned to the individual cadaver using sealed envelopes.

In this publication, the results of the three-period crossover study are presented.

Data processing & statistical analysis

Raw signals were processed with 'MATLAB' (MathWorks, Natick, Massachusetts, United States). Tidal volumes were derived from the flow signal for every single respiratory cycle. Cumulative inspiratory volume was calculated as the volume of the total inward-directed airflow over the whole respiratory cycle ($V_{insp-sum}$); thus, air movements due to chest compressions are also included. Inspiratory tidal volume was calculated as maximal inspiratory volume (Vt_{insp}), therefore as the volume of net air inflow (s. Figure 1). Correspondingly, the same volumes were calculated for expiratory flow. Reverse airflow was calculated as the volume of opposite directed airflow to the respiratory phase - hence outward-directed airflow during the inspiratory phase and inward-directed airflow during the expiratory phase.

Missed inspiratory tidal volume ($Vt_{insp-missed}$) was calculated as the deviation in percentage of inspiratory net tidal volume from Vt_{set}. Peak flow was directly derived as inspiratory maxima for each respiratory cycle. Peak airway pressure was derived as maxima during the decompression phase for each respiratory cycle.

Two investigators (J.W. and S.O.) reviewed each ventilation separately and excluded ventilations without continuous chest compressions to the full depth of 5 cm in the inspiratory phase from further analysis.

Standard statistic software was used ('IBM SPSS Statistics for Macintosh', Version 26.0, IBM Corp., Armonk, New York, United States; 'SAS 9.4', SAS Institute, Cary,

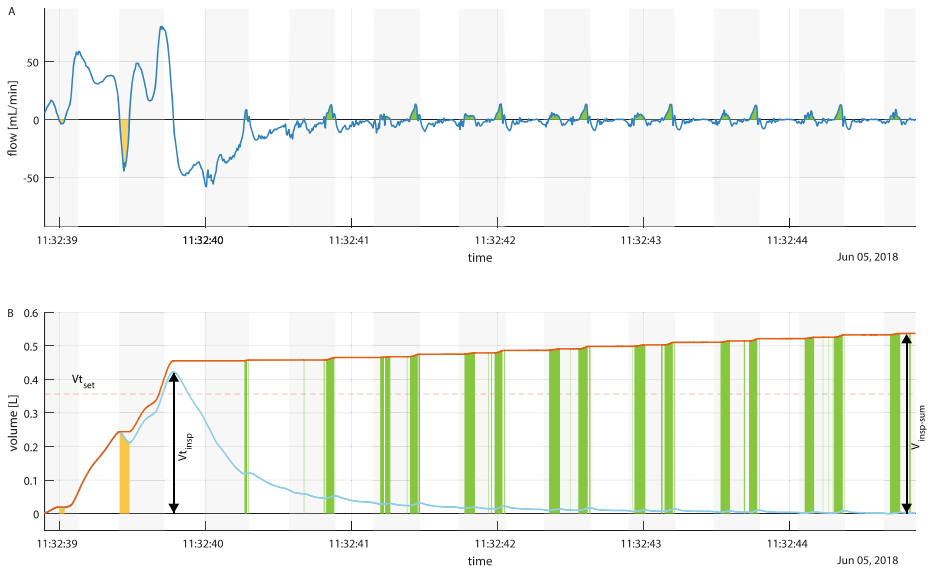

Fig. 1 Flow (top) and derived volumes (below) of a single respiratory cycle under ongoing chest compressions. The light blue line represents net tidal volume, while the orange line represents cumulative inspiratory volume. Grey rectangles indicate intervals of chest compression. Yellow areas highlight reversed airflow in the inspiratory phase, while green areas highlight phases of expiratory reversed airflow. Vt_{set} is plotted as a broken red line. Arrows indicate derived values of volume

North Carolina, United States; 'R 3.6.1'., R Development Core Team) for analysis. Parametric and non-parametric tests were conducted as indicated. Linear mixed models were calculated for $Vt_{insp-missed}$, peak flow and peak airway pressure, each with the cadaver as the random factor and ventilator, height, sex, crossover period and incremental number of each ventilation within the period as covariates. The model specification allowed for different variances for each device. All data are reported as mean ± SD or median (IQR, [Minimum; Maximum]), as appropriate. Estimates are presented with their 95 %-confidence interval.

Results

Model characteristics

Six cadavers (three female, three male) were included in the study. Characteristics of cadavers and derived values are shown in Table 1. All measurements are available as raw data in a repository [24]. An executable plotting tool is available from another repository to review these ventilatory tracings [25].

Median C_{stat} was 30.1 (11.9, [25; 51.5]) mL/mbar before chest compressions were started and increased with the first set of chest compressions up to 38.8 (19.8, [32.5; 70.3]) mL/mbar ($p = 0.03$). Further increase of static compliance was more subtle over the course of the experiment (2nd P/V loop: 43.1 (14.6, [31.3; 67.1]) mL/mbar, 3rd P/V loop: 48.5 (21.9, [34.8; 76.3]) mL/mbar, final P/V loop: 49.7 (22.2, [34.7; 70.8]) mL/mbar ($p = 0.042$) [s. Additional file 2].

Tidal volumes

Within the 36 segments of simulated CPR, 757 single ventilations were recorded, of which 715 were valid for further analysis.

Inspiratory and expiratory tidal volumes differed in median by + 1.14 (8.68, [– 24.5; 35.4]) mL.

Overall, the delivered median Vt_{insp} was 274.8 (68.3 [47; 463.6]) mL. Normalized for body weight a median Vt_{insp} of 4.75 (1.2[0.7; 7.6]) mL/kg PBW.

$Vt_{insp-missed}$ - meaning the percentage deviation of Vt_{insp} from the predetermined tidal volume (Vt_{set}) - was – 21.2 (19.6, [– 87.9; 25.8]) %. For each ventilator $Vt_{insp-missed}$ was in median – 8.3 (20.5, [–87.9; 25.8) % for 'Monnal T60', – 22.7 (22.1, [–70; – 12.3]) % for 'Oxylog

Table 1 Characteristics and calculated ventilatory settings of individual cadavers

ID	sex	age [years]	height [cm]	PBW (calculated) [kg]	C_{stat} initial [mL/mbar]	Vt_{opt} (calculated 6 mL/kg) [mL]	Vt_{set} [mL]			Pneumothorax
							'Monnal T60'	'Oxylog 3000 plus'	'MEDUMAT Standard²'	
G73	female	89	166	59.4	34.6	356	360	360	350	left, post 2nd period
G84	male	81	171	67.5	35.2	405	410	410	400	right, post 2nd period
G87	female	90	172	64.8	70.3	389	390	390	400	left, post 2nd period
G88	male	74	168	64.6	42.5	388	390	390	400	none
G74	male	83	166	62.7	32.5	376	380	380	400	none
G83	female	81	154	48.6	48.5	292	290	290	300	none

3000 plus' and − 31.5 (16.6, [−56.5; − 14.8]) % for 'MEDUMAT Standard²'.

In a mixed linear model ventilator, crossover period and height were significant factors for $Vt_{insp-missed}$ [s. Additional file 3]. The estimated population means of $Vt_{insp-missed}$ for ventilator models were − 14.5 [95 %-CI: −22.5; −6.48] % ($p = 0.0004$) for 'Monnal T60', − 30.6 [95 %-CI: −38.6; −22.6] % ($p < 0.0001$) for 'Oxylog 3000 plus' and − 31 [95 %-CI: −38.9; −23] % ($p < 0.0001$) for 'MEDUMAT Standard²'.

Cumulative inspiratory volume ($V_{insp-sum}$) - meaning the total volume of inward-directed airflow over a single respiratory cycle - deviated from predetermined volume in median by + 20.1 (29.4, [− 72.9; 58.6]) % for 'Monnal T60', − 9.1 (25.6, [− 54.8; 9.4]) % for 'Oxylog 3000 plus' and + 0.4 (19.3, [− 36.9; 22.7]) % for 'MEDUMAT Standard²' (s. Figure 2).

Inspirations and expirations were fragmented by chest compressions. Per respiratory cycle of reversed airflow episodes, exceeding 1 mL of volume, occurred in median 1 (0, [0; 2]) time in inspiratory phase and 7 (1, [0; 9]) times in expiratory phase. Reversed airflow resulted in a median volume of 0.95 (0.96, [0.05; 2.87]) mL/kg PBW over the whole respiratory cycle, of which in median 0.05 (0.1, [0; 0.7]) mL/kg PBW occurred during inspiration and 0.87 (0.79 [0; 2.48]) mL/kg PBW during expiration. Maximal volume of a single episode of reversed airflow was 0.7 mL/kg PBW, corresponding to 45.6 mL.

Flow and airway pressure

Median peak flow was 68.5 (23.6, [20.7; 93]) L/min, 44.4 (11, [27.9; 57.9]) L/min, 43.5 (8.1, [31.2; 54,9]) L/min for 'Monnal T60', 'Oxylog 3000 plus' and 'MEDUMAT Standard²', respectively. In a mixed linear model, we found that the differences of estimated effects by ventilators on peak flow between 'Oxylog 3000 plus' and 'Monnal T60' as well as between 'MEDUMAT Standard²' and 'Monnal T60' were significant ($p < 0.001$).

The median peak airway pressure during decompression phase was 46.6 (10.7, [30.2; 64.4]) mbar for 'Monnal T60', 55.5 (12.6, [27.9; 66]) mbar 'Oxylog 3000 plus' and 48.5 (14.4, [27; 73.3]) mbar Medumat Standard². According to the linear mixed model, the differences between the estimated effects of ventilator models on airway pressure were significant ($p < 0.001$).

Discussion

Our main finding is that all ventilators were able to provide tidal volumes exceeding anatomical deadspace under ongoing chest compressions with volume-controlled mandatory ventilation and a ventilatory frequency of 10/min. Thereby, all ventilators were able to deliver tidal volumes required for alveolar ventilation and gas exchange.

However, we also found all tested ventilators to provide substantially smaller tidal volumes than preset. Interestingly, the extent to which the tidal volumes were diminished was dependent on the ventilator model. While we found the turbine-driven ventilator to perform best, both pneumatic ventilators missed the preset tidal volume by almost a third. This compares to the results of a manikin study [16] and corresponds to the suspicion of hypoventilation in our previous clinical studies of blood gases in OHCA [26, 27]. These found that contrary to the common perception of hyperventilation in CPR, hypocapnia leading to alkalosis was not observed at all. Instead, most patients were found to be hypercapnic.

Oxygenation and decarboxylation are perceived as cornerstones of resuscitation efforts. Excessive hyperventilation has been shown to have detrimental effects on haemodynamics and resuscitation outcomes in an animal study [7]. In a trial with clinically more realistic tidal volumes, those results were not reproducible [28]. It is to be noted that the tidal volumes used in our experiment were substantially smaller than those used by Aufderheide and Gazmuri [7, 28, 29].

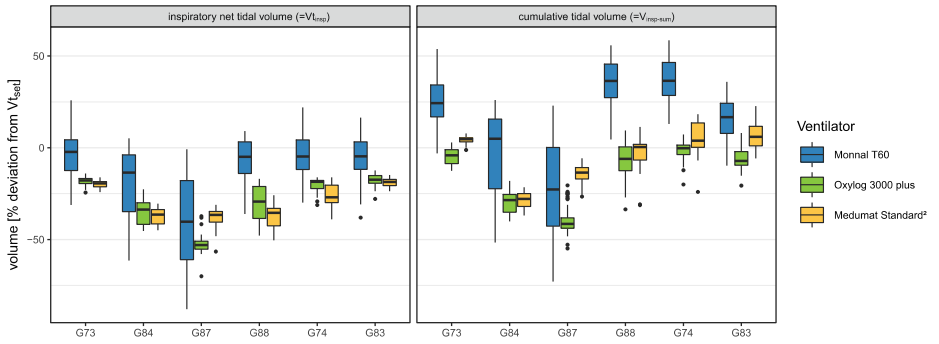

Fig. 2 Deviation of net tidal volume from Vt_{set} for every single ventilation (=$Vt_{insp-missed}$) as scatter plot separated for each ventilation crossover period. Colour represents the ventilator model. Marker shape represents individual cadavers. Trend lines are plotted for each two-minute-long segment of CPR and each particular cadaver separately

We observed a periodical overshoot in net tidal volume in the turbine-driven ventilator, which indicates an internal control mechanism to compensate for diminished tidal volumes (s. Figure 3). This is a clinically relevant finding, as it implies that ventilators - although operating in the same mode - behave substantially different under ongoing chest compressions. The higher peak flow of the turbine-driven ventilator may suggest this device can deliver inspiratory flow more instantaneously during decompressions with less peak airway pressure.

We used endotracheal intubation as the airway gold standard with continuous chest compressions as recommended by the current guidelines [30]. The respiratory system was sealed, without a difference between inspiratory and expiratory tidal volumes. Clinically the focus should be on expiratory volumes, as they characterise alveolar ventilation more reliably due to possible leakage. For statistical analysis, we used the inspiratory volumes to quantify ventilation, as expiratory tidal volumes are influenced more by volatile changes of respiratory resting position due to chest compressions.

Chest compressions fragment ventilation through the occurrence of opposite directed airflow, known as reversed airflow. Compared to the observations by Duchatelet [11], we observed smaller volumes of reversed airflow and even episodes of opposite directed airflow in the expiratory phase. None of our observed reversed airflow episodes exceeded anatomical dead space. Thus, reversed airflow did not contribute to alveolar ventilation in our experiment but explains the difference between cumulative and net tidal volume. The distinction between cumulative and net tidal volumes is relevant. Total inspiratory airflow ($V_{insp-sum}$) might suggest sufficient ventilation, while alveolar ventilation could be substantially less or even insufficient. Since we did not record displayed volumes of the ventilators, we cannot report the accuracy of their internal measurements and calculations. However, our results emphasise that the internal algorithm of the ventilators to calculate tidal volumes in CPR is of importance. Furthermore, our observations suggest that ventilatory volumes in CPR need to be reported and discussed in a more differentiated manner. Due to leakage and reversed airflow several varying tidal volumes can be calculated for a single ventilation. This should be acknowledged in clinical research to grant comparability of results, but also in clinical practice as only volumes contributing to gas exchange are meaningful.

Usage of human cadavers to study airflow phenomena might be advantageous over animal models as animals have substantial differences in the airway and thoracic configuration [31]. However, cadaver models are not suitable to observe haemodynamics, gas exchange or metabolic processes during resuscitation. In our experiment, static compliance was comparable to those observed previously in Thiel-embalmed cadavers [19] and immediately after termination of CPR [32].

The embalming process enriches the corpses with fluid. This might have contributed to the effect of increasing compliance with the application of chest compressions, possibly forcing fluid out of the parenchyma. Although the observed changes of static compliance were within a clinically plausible range, this might indicate deterioration of the model over time. Breakdown of endothelial function and the fluid load of the corpse are substantial limitations of this model.

Statistically, we compensated for deterioration effects over the course of the experiment. Due to the small sample size, we could not compensate for any carry-over effects in this crossover study. We have no

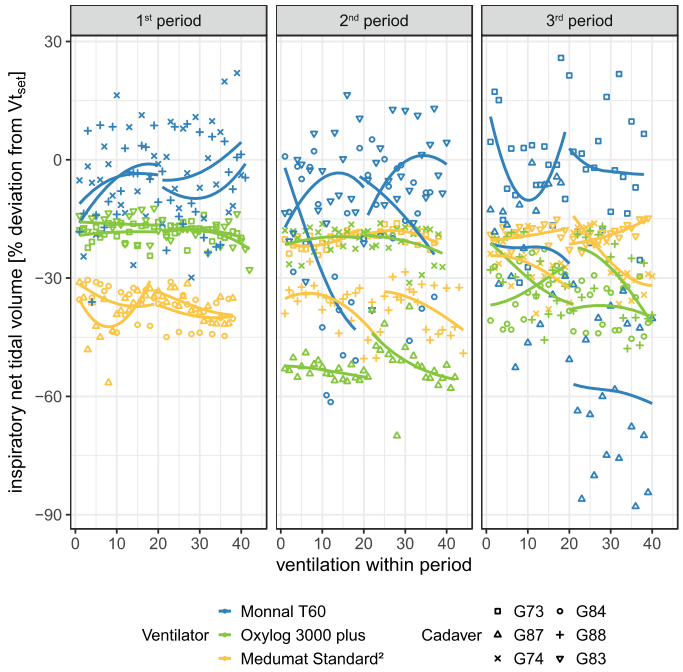

Fig. 3 Deviation of the net (left) and cumulative (right) tidal volume from Vt_{set} as boxplot for each ventilator model grouped by individual cadavers. Colour represents the ventilator model. Note that due to standardization of the y-axis, Vt_{insp} resembles $Vt_{insp\text{-}missed}$

comprehensive medical history of the body donors; therefore, pre-existing pulmonary conditions might have had an impact on cadaver-specific properties. This was considered in our statistical modelling with the cadavers as a random factor.

We used volume-controlled ventilation, as chest compressions increase airway pressure and thereby disturb pressure-controlled ventilation. This procedure is also recommended by recent guidelines [33]. Volume-controlled mode is standard in all ventilators but is more prone to cause barotrauma. When airway pressure exceeds P_{max}, the expiratory valve is opened to reduce airway pressure. In CPR, peak airway pressure occurs during the compression phase. It has to be emphasised that this is the result of an extrapulmonary pressure increase and is as such not a cause for barotrauma per se, as transpulmonary pressure is not elevated [34]. In the present paper we are reporting peak airway pressure during the relaxation phase of chest compressions.

We chose a ventilatory strategy in accordance with the previous guidelines [22, 23]. These ventilatory settings also meet the 2021 guideline recommendations [30, 33], especially regarding the ventilatory mode, $P_{max,}$ and ventilatory frequency. Even more, our approach lines up well with recently published ventilatory strategies for CPR [35, 36]. Nevertheless, we chose a conservative tidal volume of 6 mL/kg PBW, which is at the lower spectrum of the recommended 6–7 ml/kg PBW in the 2015 guidelines [22] and 2 ml/kg PBW less than recommended in the "Six-dial Strategy" [36]. Equally conservative, we decided to not use PEEP, although this is a controversial topic [37, 38]. While our settings avoided high airway pressures due to large tidal volumes and PEEP, both may have contributed to airway closure and atelectasis.

During CPR, atelectasis is common in dorsal lung areas with cyclic recruitment [39]. The increased ventilation in ventral lung areas implies the risk for volutrauma in those areas, while atelectotrauma occurs in the dorsal regions. As per protocol, we monitored for pneumothoraces. Those found by sonography were minor, did not reduce lung compliance and resulted in no air discharge upon thoracostomy at the end of the experiment.

In CPR, a severe ventilation-perfusion mismatch is present. Yet finding optimal ventilatory strategies is still

an unsolved problem. Capnography as a sole concentration measurement of carbon dioxide is influenced by pulmonary blood flow and cannot quantify ventilation alone [40]. As in the present study, measurement of expiratory tidal volumes should become a clinical standard, as already demanded by Ornato et al. in 1983 [9]. Recent advances in technology made this readily available for manual ventilation as well [11, 41]. Furthermore, the nexus of capnography with tidal volumes as volumetric capnography might be a field of future developments in individualised, goal-directed CPR [42, 43].

Conclusions

Our findings support the concept of using transport ventilators to limit the ventilation rate. Nevertheless, we also observed ventilations with severely low tidal volumes. Therefore, healthcare providers should closely monitor expiratory tidal volumes when using mechanical ventilation during continuous chest compressions without relying on preset values.

Due to reversed airflow, ventilations are fragmented in CPR, with a significant portion of airflow presumably not contributing to alveolar ventilation. Therefore, tidal volumes have to be considered in a much more differentiated way under ongoing chest compressions in clinical research to grant comparability of results, but also in clinical practice as only volumes contributing to gas exchange are meaningful. Future clinical studies are needed to confirm our findings.

Abbreviations

95%-CI: 95 % confidence interval; $aADCO_2$: Arterio-alveolar carbon dioxide gradient; CPR: Cardiopulmonary resuscitation; C_{stat}: Static compliance; IQR: Interquartile range; OHCA: Out-of-hospital cardiac arrest; P/V loop: Pressure-volume loop; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; P_{max}: Pressure limit; VC-CMV: Volume controlled continuous mandatory ventilation; $V_{insp-sum}$: Cumulative inspiratory volume (volume of the total inward-directed airflow for a respiratory cycle); Vt: Tidal volume; Vt_{insp}: Inspiratory net tidal volume; $Vt_{insp-missed}$: Missed inspiratory tidal volume (difference of Vt_{insp} and Vt_{set}); Vt_{set}: Preset tidal volume

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13049-021-00921-2.

Additional file 1. Experiment flowchart. Colour represents the phase of the experiment. Detailed ventilator and chest compression settings are given within the text balloons. Note that the yellow segment illustrates the crossover study, and the iterative workflow is only provided for the first period in detail.

Additional file 2. Repetitive pressure-volume loops over the course of the experiment for each cadaver obtained by quasi-static inflation-deflation manoeuvres. Colour represents the chronological order of P/V loops.

Additional file 3. Contrasts and coefficients of the three presented mixed linear models

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Authors' contributions

Conceptualisation SO, JW, GP; Methodology SO, JW, CH, DA, GH, OS, GF, GP; Software SO, CH; Formal analysis SO, TF, RR; Investigation SO, JW, CH, DA, GH, GP; Data Curation SO, JW, CH; Writing- Original Draft SO, JW, TF; Writing - Review & Editing DA, RR, OS, PM, GF, GP; Visualization SO, JW, CH, TF; Project administration SO, GP; Resources PM, GF; Supervision PM; Funding acquisition SO. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are available in the Data Mendeley repository, https://doi.org/10.17632/vh4tdsscns.1.
An interactive visualisation tool to review the data is available from Data Mendeley repository, https://doi.org/10.17632/43h7zzp67k.3 (operating system: Windows; other requirements: MATLAB Runtime; license: CC BY 4.0).

Declarations

Ethics approval and consent to participate

All bodies were donated to the Chair of Macroscopic and Clinical Anatomy of the Medical University of Graz, under the strict rules of the anatomical donation program according to the Styrian burial law for scientific purposes. Hence, no additional approval by the local ethical board was necessary.

Consent for publication

Not applicable.

Competing interests

SO has received a grant to fund this study (s. above). GP has given a talk at a national symposium, invited by RWM Medizintechnik GmbH. All other authors have no personal conflict of interest.
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