Mechanical Ventilation Management During Mechanical Chest Compressions

Daniele Orso, Luigi Vetrugno, Nicola Federici, Matteo Borselli, Savino Spadaro, Gianmaria Cammarota, and Tiziana Bove

Ventilation during chest compressions can lead to an increase in peak inspiratory pressure. High inspiratory pressure can raise the risk of injury to the respiratory system and make it challenging to deliver the required tidal volume. The utilization of mechanical devices for chest compression has exacerbated this challenge. The aim of this narrative review was to summarize the different mechanical ventilation strategies applied during mechanical cardiopulmonary resuscitation (CPR). To this end, we searched the PubMed and BioMed Central databases from inception to January 2020, using the search terms "mechanical ventilation," "cardiac arrest," "cardiopulmonary resuscitation," "mechanical cardiopulmonary resuscitation," and their related terms. We included all studies (human clinical or animal-based research studies, as well as studies using simulation models) to explore the various ventilation settings during mechanical CPR. We identified 842 relevant articles on PubMed and 397 on BioMed Central; a total of 38 papers were judged to be specifically related to the subject of this review. Of this sample, 17 studies were conducted on animal models, 6 considered a simulated scenario, 13 were clinical studies (5 of which were retrospective), and 2 studies constituted literature review articles. The main finding arising from the assessment of these publications is that a high F_{IO_2} must be guaranteed during CPR. Low-grade evidence suggests turning off inspiratory triggering and applying PEEP $\geq$ 5 cm H_2O. The analysis also revealed that many uncertainties persist regarding the ideal choice of ventilation mode, tidal volume, the ventilation rate setting, and the inspiratory:expiratory ratio. None of the current international guidelines indicate the "best" mechanical ventilation strategy to apply during mechanical CPR. We propose an operating algorithm worthy of future discussion and study. Future studies specifically addressing the topics covered in this review are required. *Key words: mechanical CPR; mechanical ventilation; peak inspiratory pressure; out-of-hospital cardiac arrest*. [Respir Care 2021;66(2):334–346. © 2021 Daedalus Enterprises]

Introduction

International guidelines recommend ensuring effective ventilation for cardiac arrest patients;[1,2] however, a "best" invasive ventilation strategy for cardiopulmonary resuscitation (CPR) has yet to be established. The European Resuscitation Council guidelines suggest a protective ventilation approach derived from the management of other types of critically ill patients, such as patients with ARDS or acute respiratory failure,[2] but the conditions that arise during cardiopulmonary resuscitation can be very different from the clinical models investigated to date. Following cardiac arrest, the thoracic system's compliance declines, leading to an increase in pressure against the mobilized volumes.[3] Furthermore, asynchronous ventilation during the delivery of chest compressions can increase the risk of a rise in peak inspiratory pressure.[4] In addition to increasing the potential risk of injury to the respiratory system, it may also make it challenging to deliver the required tidal volume (V_T). A recent retrospective study reported that nonsurvivors of cardiac arrest had received a higher mean plateau pressure and higher driving pressure, which suggests that ventilation plays a central role in determining survival following a cardiac arrest.[5] The continued development of mechanical devices for chest compression and the rapid spread of their use underscore the uncertainty that continues to exist in this area. Although mechanical CPR has not been proven superior to manual CPR, the former seems to be useful, particularly when maintaining high-quality chest compressions is difficult (eg, during ambulance transport or a coronary angioplasty procedure).[6] The adoption of mechanical chest compressions in clinical practice has led to problems in the management of invasive mechanical ventilation, and the guidelines have yet to address this issue adequately.

Our narrative review aims to summarize the different strategies of mechanical ventilation presented in the literature. In particular, we discuss the following topics: the choice of ventilation mode; the challenge of achieving the predetermined V_T; the PEEP setting and ventilation rate; the role of the inspiratory-expiratory ratio and the most appropriate inspiratory trigger threshold; and adequate F_{IO_2}. Finally, future and advanced perspectives are addressed.

Search Strategy and Study Selection

We searched the MEDLINE (PubMed) and BioMed Central databases, from inception to January 2020, in accordance with the PRISMA guidelines, using following the search terms: "mechanical ventilation," "cardiac arrest," "cardiopulmonary resuscitation," and "mechanical cardiopulmonary resuscitation," as well as their possible variations or other closely related terms. We also searched actual citations of relevant primary and review articles. We included a wide range of study types, including those on human or animal models or simulation models, as well as literature review articles and observational studies. Studies conducted within the hospital setting as well as out-of-hospital cardiac arrest scenarios were included. We excluded studies that considered pediatric subjects only, mechanical ventilation after the return of spontaneous circulation, extracorporeal cardiopulmonary resuscitation, case reports, conference abstracts, and articles in languages other than English. Although we considered a broad spectrum of different study designs, our review attempts to classify the evidence collected: meta-analyses before randomized clinical trials, followed by observational studies, and finally animal or preclinical studies.

The articles were screened and read independently by three authors (DO, LV, NF). Each author made an independent judgment regarding the degree of relevance of the study in question. These judgments were compared, and a majority criterion was used to include the research in the review.

Data Extraction and Synthesis

The following data were extracted from the selected studies: year of publication, study design, ventilation variable(s) studied, clinical context, the aim of the study, measured parameters, and the main findings. Because the included studies were all very different from each other in terms of design and aims, we summarized the results in the

Dr Orso, Mr Vertrugno, Dr Federici, and Ms Bove are affiliated with the Department of Medicine, University of Udine, Udine, Italy. Mr Vertrugno and Ms Bove are affiliated with the Department of Anesthesia and Intensive Care Clinic, ASUFC University Hospital Santa Maria della Misericordia, Udine, Italy. Dr Borselli is affiliated with the Department of Emergency Medicine, Azienda Usl Toscana Sud-Est, Grosseto, Italy. Mr Spadaro is affiliated with the Department of Morphology, Surgery and Experimental Medicine, Intensive Care Unit, Sant'Anna Hospital, Ferrara, Italy. Ms Cammarota is affiliated with the Department of Anaesthesia and General Intensive Care, "Maggiore della Carità" University Hospital, Novara, Italy.

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Correspondence: Luigi Vetrugno, Department of Anesthesia and Intensive Care Clinic, ASUFC University Hospital "Santa Maria della Misericordia," p. le S. Maria della Misericordia 15, 33100 Udine, Italy. E-mail: luigi.vetrugno@asufc.sanita.fvg.it.

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form of a narrative review according to the following scheme: ventilation mode, V_T, PEEP, ventilation rate set, inspiratory/expiratory time ratio, F_{IO_2}, and new research directions.

Literature Review

We identified 842 articles on PubMed and 397 on BioMed Central; of these, 38 were judged to be related to the subject of this review (see Fig. 1 and the search strategy section in the supplementary materials at http://www.rcjournal.com). Seventeen articles were conducted on animal models, 6 were considered a simulated scenario, 13 were clinical studies (5 of which were retrospective), and 2 constituted literature review articles.

Ventilation Modes

The ventilation mode chosen during CPR is not irrelevant in determining the outcome. In pressure control continuous mandatory ventilation, the provider can control the pressure level applied, but this modality runs the risk of not achieving sufficient V_T. By contrast, in volume control continuous mandatory ventilation, the volume delivered by the ventilator is established a priori, but this runs the risk of exceeding safe peak inspiratory pressure levels. The main problem in administering high inspiratory pressures is related to the risk of overdistention of the alveolar structures (ie, barotrauma).[7] Depending on the mechanical ventilation settings used, asynchronous ventilation combined with chest compressions may result in high positive pressure and rapid changes in chest wall compliance secondary to chest compressions. Furthermore, it is not possible to preset the maximum pressure limit on all transport ventilators, so achieving the target volume can be challenging. Additionally, positive pressure mechanical ventilation causes some alterations in hemodynamic physiology, the most relevant of which is the reduction in venous return and, therefore, the reduction in ventricular preload.[8,9]

A recent survey reported that the most commonly used ventilation mode is volume control continuous mandatory ventilation.[10] However, no clinical studies have yet defined the "best" mode of invasive ventilation to use during mechanical CPR. Only experimental bench simulation studies have been proposed to evaluate the effects of different mechanical ventilation modes during mechanical CPR. Speer and colleagues[11] compared pressure modes with volumetric modes and established that both permitted adequate V_T to be achieved without increasing the peak inspiratory pressure.

Some alternative strategies to administering oxygen with positive pressure without the risk of high peak pressures have been studied in the literature. These approaches are discussed in the section on future and advanced perspectives, given their limited diffusion in clinical practice.

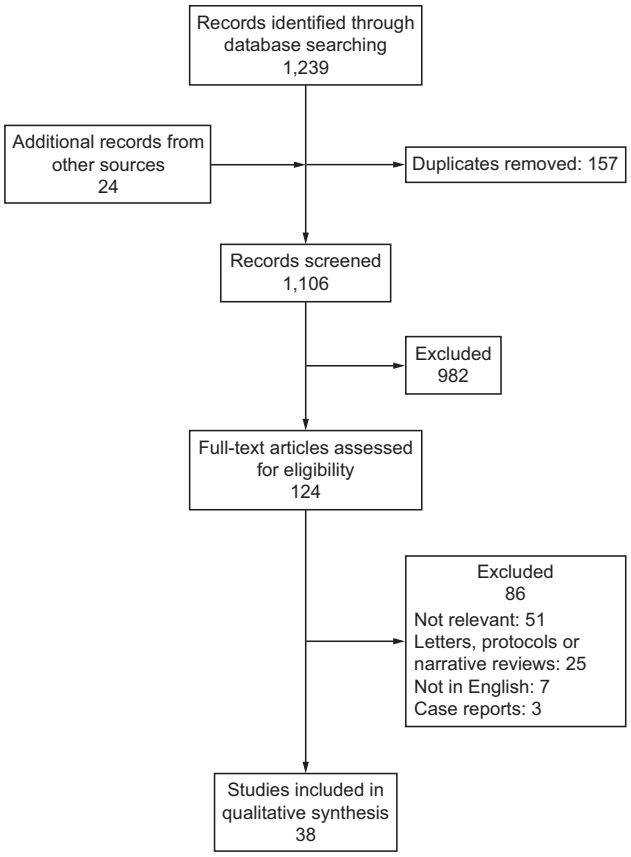

Fig. 1. Flow chart.

Tidal Volume

The V_T range most frequently cited as being administered in actual practice is 6–8 mL/kg[10]; however, it is essential to note that the studies contributing to the deduction of this range mainly concern protective ventilation in patients with ARDS. Indeed, the debate about the best V_T remains very much open. For example, although the evidence correlating the magnitude of V_T with the probability of spontaneous recovery of circulation tends to be weak,[12] V_T has been shown to correlate positively with the level of neurological recovery in the context of in-hospital cardiac arrests.[13] Moreover, a reasonable V_T value might never be established in cardiac arrest patients, especially if the patient is subjected to mechanical chest compressions. Mechanical chest compression devices can deliver compressions in "synchronous" mode (ie, 30 compressions alternating with 2 ventilations) or in "asynchronous" mode (ie, continuous compressions that are not synchronized with ventilation). The latter method allows the pauses between compressions to be minimized, and the reduction in the pause time between one compression and another is a known factor associated with better survival.[1,2] However, how this mode affects the delivery of an adequate V_T is

uncertain. In fact, a recent retrospective study reported that the asynchronous mode, and not the synchronous mode, correlated with a higher survival rate.[14] However, it is difficult to determine whether this correlation is related to more effective chest compression or to better ventilation in terms of V_T. Moreover, in the survey conducted by Cordioli et al,[10] the most frequently observed complications of invasive mechanical ventilation during cardiopulmonary resuscitation were activation of the high-pressure alarm and delivery of an insufficient V_T. Thus, the broad range of possible intrathoracic pressure changes and the compliance of the respiratory system make it difficult to predict the behavior of a cardiac arrest patient's ventilatory system during chest compressions.[10]

Moreover, the only direct evidence available has been derived from animal studies. One recent study reported favorable consequences following the use an ultra-low V_T (ie, 2–3 mL/kg) in terms of both adequate ventilation and a reduced risk of iatrogenic damage.[15] By contrast, another study demonstrated a high V_T ventilation strategy (ie, 10 mL/kg vs 7 mL/kg) to increase the probability of return of spontaneous circulation.[12] Further studies are required to define the most appropriate V_T to apply in different clinical contexts.

PEEP

The application of PEEP can bring about different effects. First of all, PEEP is known to improve oxygenation by increasing the V_T and keeping the alveoli open (the so-called "open the lung and keep it open" concept).[16] A recent Canadian study on cadavers showed that changes in intrathoracic pressure are related to the PEEP levels applied rather than the inspiratory pressure (at least within certain limits). Moreover, the authors were able to establish that while intrathoracic pressure is generally stable during CPR, the pressure in the airway can vary, even dropping below the alveoli closure limit. This effect has important implications in terms of oxygenation during cardiac arrest.[17] The same group also reported that end-tidal CO_2 influences proper alveolar ventilation, as it decreases in cases of alveoli closure despite a satisfactory hemodynamic effect of chest compressions.[18] On the other hand, PEEP increases the risk of dynamic hyperinflation (and is associated with important hemodynamic effects); this can, in turn, cause a reduction in venous return and, therefore, cardiac output (under conditions of preload-dependent cardiac stroke).[19]

As long ago as 1980, Babbs and co workers noted that applying positive airway pressure during chest compressions increased oxygenation without deteriorating cardiac function.[20] Data gathered from animal models seem to point in the same direction: the application of PEEP brings about an improvement in survival independently of other parameters.[21,22] Considering the actual evidence, application of at least 5 cm H_2O PEEP seems to be beneficial; however, the optimal PEEP still needs to be adequately investigated. Excessive PEEP may worsen the outcome of cardiopulmonary resuscitation, but more evidence is required to establish the validity of this statement. For instance, Van der Touw et al[23] pointed out that, during conditions of hyperinflation, the increase in intrathoracic pressure resulting from chest compressions reduces the cardiac output and the mean arterial pressure.

Ventilation Rate

In a small case study, Maertens et al[24] reported that subjects in cardiac arrest, even when intubated, are ventilated at a higher frequency than prescribed by the guidelines (ie, 10–12 breaths/min). Vissers and colleagues[25] systematically reviewed the literature to investigate whether the optimal set ventilation rate during cardiopulmonary resuscitation was indeed $\sim$ 10 breaths/min. Their results were inconclusive, as was the issue of whether rates lower or higher than 10 breaths/min are able to influence outcomes (Table 1). Note that rates $<$ 10 breaths/min run the risk of not achieving the target minute volume, whereas higher rates are more likely to cause dynamic hyperinflation and bring about a deterioration in hemodynamic parameters. In an animal model, a high ventilation rate was associated with a reduction in coronary perfusion.[26] However, a recent prospective observational study reported that subjects who reached the return of spontaneous circulation received faster ventilation compared to subjects who did not get the return of spontaneous circulation.[14] The effect caused by the ventilation frequency is probably indirect and related to changes in the patient's intrathoracic pressure, volume state and the normal range for the patient's body structure. However, studies specifically aimed at this issue are required to obtain clearer data.

Inspiratory-Expiratory Ratio

The relationship between inspiratory time and expiratory time is fundamental for the complete replacement of the respiratory system's anatomical deadspace. If the expiratory time is not long enough, the phenomenon of dynamic hyperinflation can occur, causing an increase in intrinsic PEEP. The mechanisms through which this generates hemodynamic impairments have been clearly demonstrated in the literature.[27,37] Fitz-Clarke[28] highlighted the relationship between target V_T and the duration of the inspiratory phase by means of a physiological model. The model showed that the length of the inspiratory phase correlates inversely with the pressure regime, such that an inspiratory time that was too short could result in gastric insufflation. However, this study was conducted using an unprotected airway model. Von Goedecke et al,[29] considering a bag-mask ventilation simulation model, assessed the possibility

Table 1. Summary of the Reviewed Studies

Study	Study Type	Study Design	Aim	Main Findings
Ventilation mode				
Speer et al[11]	Manikin model study	Intermittent PPV, bi-level ventilation, and chest compression synchronized ventilation were applied in a randomized order 19 times.	To verify whether 3 ventilation modes with the same target parameters did not exceed a tolerance range concerning airway pressure.	Chest compression synchronized ventilation works best without exceeding the upper pressure preset during simulated CPR.
Tidal volume				
Moskowitz et al[13]	Prospective observational study	185 IHCA subjects	To investigate the association between tidal volume and neurologic outcome following IHCA.	Found no relationship between tidal volume and neurologic outcome following IHCA (vs OHCA).
Ruemmler et al[15]	Animal model study	30 pigs randomized to intermittent PPV, CPAP, or a novel ultra-low tidal volume ventilation regime.	To verify if an ultra-low tidal volume ventilation regime is as effective as intermittent PPV or CPAP.	Ultra-low tidal volume ventilation provided sufficient oxygenation while demanding lower intrathoracic pressures ($P < .001$).
Tan et al[12]	Animal model study	32 pigs randomized to 2 ventilation modes: 10 mL/kg or 7 mL/kg	To verify if the 2 tidal volume regimes were comparable.	Low tidal volume resulted in better ventilation ($P < .01$), oxygenation ($P < .01$), acid/base balance ($P < .01$), and higher ROSC compared to the guideline-recommended ventilation at 8 min ($P < .05$).
PEEP				
Charbonney et al[17]	Cadaver model study	11 cadavers + 9 OHCA subjects	To compare a bench model and an in vivo model.	Transmission of changes in intrathoracic pressures at the airway opening was significantly affected by PEEP (as in vivo model).
Grieco et al[18]	Observational study + bench model + cadaver model	89 OHCA subjects	To understand the impact of airway closure during CPR and the relationship between the capnogram shape, airway closure, and delivered ventilation.	During chest compressions, intrathoracic airway patency greatly affects the delivered ventilation. The expired CO_2 signal can reflect CPR effectiveness but is also dependent on airway patency.
Babbs et al[20]	Animal model study	5 dogs, invasively ventilated during CPR	To verify if positive-pressure ventilation determines a decrease in hemodynamic parameters.	Increased positive-pressure ventilation did not decrease cardiac output during CPR ($R^2 = .07$) or MAP ($R^2 = .01$).
Hevesi et al[21]	Animal model study	18 pigs randomized to receive conventional intermittent ventilation with or without CPAP	To verify if a PEEP regime can improve arterial blood gases compared to a no-PEEP scheme.	CPAP decreased P_{aCO_2} (55 ± 28 vs 100 ± 16 mm Hg) and increased S_{aO_2} (0.86 ± 0.19 vs $0.50 \pm 0.18\%$, $P < .001$).
McCaul et al[22]	Animal model study	Unspecified number of rats randomized to receive 5 cm H_2O or zero PEEP	To verify if a PEEP regime can improve the survival rate compared to a zero PEEP regime.	Administration of 5 cm H_2O PEEP (F_{IO_2}, 1.0 and 0.21) was associated with improved survival compared with zero PEEP (7 of 9 and 6 of 6 vs 0 of 9, $P < .01$ and $<.001$, respectively).
Van der Touw et al[23]	Animal model study	7 dogs, invasively ventilated during CPR	To verify if positive-pressure ventilation determines a decrease in hemodynamic parameters.	The decrease in cardiac output due to mechanical ventilation with pulmonary hyperinflation was exacerbated by rib cage compression ($P < .001$).

(Continued)

Table 1. Continued

Study	Study Type	Study Design	Aim	Main Findings
Ventilation rate set				
Maertens et al[24]	Prospective observational study	98 subjects (57 with and 41 without cardiac arrest)	To measure the ventilation rate using tracheal airway pressures in prehospitally intubated subjects with and without cardiac arrest.	During mechanical ventilation, 35 of 38 (92%) had ventilation rates > 10 compressions/min.
Vissers et al[25]	Systematic review	67 pooled subjects and 264 pooled animal models	To evaluate whether a ventilation rate of 10 compressions/min, compared to any other rate during CPR, improves outcomes in adults with cardiac arrest and a secure airway (tracheal tube).	A ventilation rate of 10 compressions/min during adult CPR with a tracheal tube and no pauses for chest compression is a very weak recommendation based on very low-quality evidence.
Aufderheide et al[26]	Retrospective observational study + animal model	13 OHCA subjects + 9 pigs	To quantify the degree of excessive ventilation in humans and to determine if comparable excessive ventilation rates during CPR in animals significantly decrease coronary perfusion pressure and survival.	Excessive ventilation rates resulted in significantly increased intrathoracic pressure ($P < .001$) and markedly decreased coronary perfusion pressures and survival rates ($P = .006$).
Sanson et al[14]	Prospective observational study	285 OHCA subjects	To verify the quality of CPR and to compare synchronous vs asynchronous ventilation modes.	Ventilation rate provided for the duration of CPR was an independent predictor for a good neurological outcome (odds ratio 3.795, $P = .005$).
Inspiratory-expiratory time ratio				
Woda et al[27]	Manikin model study	Bench model	To verify the effect of ventilatory factors on auto-PEEP.	Auto-PEEP can be generated to substantial levels depending on the methods of ventilation performed.
Fitz-Clarke[28]	Manikin model study	Bench model of a simulated unprotected airway	To study how inflation time affects the division of gas flow between the lungs and esophagus.	Breath duration with an unprotected airway should be 1 s to minimize gastric inflation.
Von Goedecke et al[29]	Manikin model study	Bench model of a simulated unprotected airway	To evaluate if inspiratory time can be decreased from 2 s to 1 s at different lower esophageal sphincter pressure levels during ventilation with a bag-valve-mask device.	Breath duration of 1 s resulted in a higher peak airway pressure and peak inspiratory flow ($P < .001$), while tidal volumes at all lower esophageal sphincter pressure levels were clinically comparable.
Inspiratory trigger				
Tan et al[30]	Animal model study	18 pigs in 3 groups at different triggering sensitivities	To verify if several triggering values were of any benefit for gas exchange and hemodynamics.	Ventilation with pressure- or flow-triggering tends to induce hyperventilation ($P < .05$) and deteriorating gas exchange ($P < .05$) and hemodynamics during CPR ($P < .05$) compared with no triggering.
F_{IO_2}				
Nelskylä et al[31]	Animal model study	19 pigs: one group ventilated at F_{IO_2} 0.50, and one group at 1.0	To verify if the use of 50% compared to 100% oxygen maintains cerebral oxygenation.	ROSC was achieved in 6 pigs in the 50% group and 8 pigs in the 100% group.
Ebner et al[32]	Prospective observational study	869 OHCA subjects	To test the association of hyperoxemia and hypoxemia with poor neurological outcome.	Hyperoxemia and hypoxemia were not significantly associated with poor neurological outcome after 6 months.
Oh et al[33]	Retrospective observational study	792 IHCA subjects	To study whether early hyperoxemia is associated with a poor post-ROSC outcome.	Postresuscitation hyperoxemia was not associated with survival or neurological outcome.

(Continued)

Table 1. Continued

Study	Study Type	Study Design	Aim	Main Findings
Spindelboeck et al[34]	Retrospective observational study	145 OHCA subjects with an arterial blood analysis performed during CPR	To investigate the impact of P_{aO_2} on the rate of survival to hospital admission.	The high F_{IO_2} group achieved a high hospital admission rate (83.3% vs 18.8% vs 50.6%, $P < .001$ high group vs low, $P = .004$ high group vs intermediate).
Patel et al[35]	Retrospective observational study	167 IHCA subjects	To verify the association between intra-arrest P_{aO_2} levels with rates of ROSC and survival to hospital discharge.	Subjects with higher intra-arrest P_{aO_2} levels had progressively higher rates of ROSC (58% vs 71% vs 72% vs 79% vs 100%, $P = .02$) and survival to discharge (16% vs 23% vs 30% vs 33% vs 56%, $P = .031$).
Patel et al[36]	Systematic review + meta-analysis	241 pooled OHCA subjects	To investigate the association between hyperoxia and mortality in adults with cardiac arrest.	Hyperoxia is associated with lower mortality compared to normoxia (odds ratio 0.25, 95% CI 0.12–0.53, $P < .001$).

PPV = positive-pressure ventilation
CPR = cardiopulmonary resuscitation
OHCA = out-of-hospital cardiac arrest
IHCA = intrahospital cardiac arrest
ROSC = return of spontaneous circulation
MAP = mean arterial pressure

of reducing the inspiratory time from 2 s to 1 s. They reported that, although the target V_T was continuously met, it was detrimental to peak inspiratory pressure, which increased.[29] However, the comparability of this simulated model to invasive mechanical ventilation of a patient during mechanical CPR is debatable. No clinical studies have investigated the inspiratory-expiratory ratio in the invasive ventilated patient during cardiac arrest.

Inspiratory Trigger

One of the most frequently encountered problems during mechanical cardiopulmonary resuscitation is the auto-triggering or the inappropriate activation of ventilator delivery due to the incorrect setting of the ventilator's inspiratory trigger.[38] Ventilation with pressure- or flow-triggering can lead to hyperventilation and deteriorating gas exchange and hemodynamics during CPR. Indeed, the results obtained from small animal model studies have encouraged physicians to turn the inspiratory trigger off during CPR (or to increase the threshold to at least 20 cm H_2O).[30]

F_{IO_2}

Guidelines regarding cardiac arrest patients usually recommend F_{IO_2} close to 1.0 to improve oxygen delivery.[2] However, this physiological assumption has never been proven. Furthermore, the harmful role of hyperoxemia in the development of post-cardiac arrest syndrome is being increasingly acknowledged.[39-41] For example, a 2017 study using an animal model investigated whether F_{IO_2} significantly < 1.0 (in this case, 0.50) would permit comparable cerebral oxygenation and reduce mitochondrial oxidative stress.[31] The results obtained were not straightforward: on the one hand, a F_{IO_2} of 0.50 resulted in a reduction in cerebral oximetry values compared with those achieved with F_{IO_2} values nearing 1.0; on the other hand, invasive methods of measuring cerebral oxygenation showed no significant differences[31] (Table 1). However, how hyper- and hypoxemia affect survival and neurological outcomes is controversial.[32,33,42] A recent meta-analysis, which pooled the data of the only 2 clinical studies present in the literature,[34,35] concluded that whereas hyperoxemia in the post-arrest period is associated with a worse outcome, during CPR it appears to be related to a higher rate of return of spontaneous circulation.[36] The effects induced by hyperoxemia seem to correlate with the timing of the pathological process, rather than a simple on/off effect.[43,44]

Future and Advanced Perspectives

This review has focused on the problems primarily encountered when invasively ventilating a patient in cardiac arrest with mechanical CPR. However, other strategies

Table 2. Summary of the Reviewed Studies for Future and Advanced Perspectives

Study	Type of Study	Study Design	Aim	Main Findings
Deakin et al[45]	Prospective observational study	17 OHCA patients	To verify if passive ventilation during compression-only CPR provides adequate gas exchange.	Median tidal volume per compression was considerably less than measured dead space in all patients.
Wang et al[46]	Animal model study	6 pigs randomized to continuous load-distributing band CPR without rescue ventilation (C-CPR), load-distributing band 30:2 CPR (A-CPR), load-distributing band CPR with continuous rescue breathing (V-CPR), or manual 30:2 CPR	To compare the hemodynamics and ventilation during and after the load-distributing band CPR vs the manual CPR, and to investigate the influence of ventilation rescue.	Coronary perfusion pressure of the V-CPR group was significantly lower than the C-CPR group ($P < .01$), but higher than the manual CPR group. Cerebral performance categories were better in the A-, C-, and V-CPR groups compared with the manual CPR group ($P < .001$).
Hayes et al[47]	Animal model study	36 pigs randomized to 3 groups: standard ventilation vs hyperventilation vs passive insufflation of oxygen	To verify if continuous oxygen insufflation would be as effective as PPV for 24-h, neurologically intact survival.	No significant difference (standard: 2 of 12, hyperventilation: 2 of 12, insufflation: 4 of 12; $P = .53$).
Wolf et al[48]	Animal model study	10 pigs treated with oxygenation only vs oxygenation + CPR	To determine whether intrabronchial oxygenation would provide adequate gas exchange.	Mean p_{O_2} decreased from 426 mm Hg (95% CI: 273–579) to 130 (92–168) after 28 min, $P < .001$.
Steen et al[49]	Animal model study	16 pigs randomized to 2 groups to receive intratracheal continuous insufflation of oxygen vs intermittent PPV	To compare the efficacy of intratracheal continuous insufflation of oxygen vs intermittent PPV.	Arterial oxygen tension ($P < .05$) and coronary perfusion pressure ($P < .01$) were significantly higher in the group receiving continuous insufflation of oxygen.
Saïssy et al[50]	Open-label randomized controlled trial	95 OHCA patients randomized to 2 groups receiving standard ventilation vs continuous insufflation of oxygen	To verify if continuous insufflation of oxygen is as effective as intermittent PPV.	P_{aCO_2} was significantly lower in the continuous insufflation of oxygen group (35.7 ± 2.1 compared with 72.7 ± 7.4 mm Hg, $P < .05$).
Bobrow et al[51]	Retrospective observational study	1,019 OHCA patients	To compare the adjusted neurologically intact survival between an initial passive ventilation and a bag-valve-mask ventilation strategy.	Adjusted neurologically intact survival to hospital discharge higher passive ventilation group (adjusted odds ratio 2.5, 95% CI 1.3–4.6).
Bertrand et al[52]	Open-label randomized controlled trial	944 OHCA patients randomized to 2 groups: standard ventilation vs passive insufflation of oxygen	To verify if continuous insufflation of oxygen is as effective as intermittent PPV.	No difference in outcomes regarding return to spontaneous circulation, hospital admission, or ICU discharge.
Kjærgaard et al[9]	Animal model study	22 pigs randomized to no ventilation vs standard ventilation vs constant oxygen flow vs apneic oxygenation	To test different modes of ventilation during mechanical CPR for a prolonged period (60 min).	Except for the free airway group, the other methods resulted in $P_{aO_2} > 10$ kPa and P_{aCO_2} of 3.8–12.3 kPa after 1 h.
Hu et al[53]	Animal model study	20 pigs randomized to 3 groups: manual ventilation using a manual resuscitation bag vs an automatic ventilator at low pressure vs the same at high pressure	To verify if ventilation with a pneumatically powered, automatic ventilator can provide adequate ventilation.	The device-specific setting of Ox20/30 ventilation yielded higher P_{aO_2} and a lower arterial–alveolar gradient than manual ventilation ($P < .001$).
Winkler et al[54]	Manikin model study	A simulation model study	To evaluate the tidal volumes and airway pressures achieved during CPAP–CPR.	Tidal volumes during CPAP–CPR were higher than during compression-only CPR without positive airway pressure.

(Continued)

Table 2. Continued

Study	Type of Study	Study Design	Aim	Main Findings
Kill et al[55]	Animal model study	24 pigs randomized to intermittent PPV (control group), bi-level, or chest compression synchronized ventilation group	To investigate the influence of intermittent PPV, bi-level ventilation, and the novel chest compression synchronized ventilation mode.	Chest compression synchronized ventilation elicited the highest mean arterial pressure ($P < .02$), and best oxygenation at 4 min ($P < .001$).
Kill et al[56]	Animal model study	20 pigs receiving intermittent PPV or chest compression synchronized ventilation	To investigate the influence of intermittent PPV and chest compression synchronized ventilation.	All patterns of chest compression synchronized ventilation led to higher P_{aO_2} ($P = .001$) and avoided an arterial blood pressure drop ($P < .001$).
Soltesz et al[57]	Animal model study	20 pigs stratified in 2 groups: continuous intratracheal insufflation of oxygen vs phase-controlled intermittent insufflation of oxygen	To compare phase-controlled intermittent insufflation of oxygen vs continuous intratracheal insufflation of oxygen during mechanical CPR.	The phase-controlled intermittent insufflation of oxygen group showed a higher coronary perfusion pressure ($P < .01$).

PPV = positive-pressure ventilation
CPR = cardiopulmonary resuscitation
OHCA = out-of-hospital cardiac arrest

that permit respiratory homeostasis to be maintained in cardiac arrest patients subjected to mechanical ventilation have been explored in the context of clinical research (Table 2). Data in the literature suggest that ventilation involving air solely mobilized by the mechanical chest compressor is not sufficient to meet the organism's metabolic needs. Deakin and colleagues[45] observed that the volume of air mobilized by an automatic device for chest compressions was $\sim$ 40 mL/breath. This value cannot meet the metabolic needs of an adult patient of standard size; indeed, the eliminated CO_2 quota was well below the regular quota (only 20 mL/min were observed vs the standard value of $>$ 150 mL/min).

Some research groups have explored the possibility of not ventilating cardiac arrest patients at all but only oxygenating them; this is known as "apneic oxygenation," which exploits the displacement of air caused by the chest compressions themselves.[46,58] Both animal and clinical studies seem to demonstrate the feasibility of this oxygenation strategy.[47,48] Steen et al,[49] using an animal model, reported a higher coronary perfusion pressure in the group of animals treated with continuous passive oxygenation compared with the group treated with standard intermittent ventilation. In the early 2000s, Saïssy et al[50] conducted a clinical study involving subjects in out-of-hospital cardiac arrest. The authors noted better oxygenation levels and significantly more CO_2 elimination in the group treated with passive oxygenation alone.[50] However, the size of the study was not adequate to detect a statistically significant difference in terms of survival rate. Bobrow and colleagues,[51] in their case history, reported that passive oxygen insufflation is superior to bag-valve-mask ventilation in terms of survival outcome and hospital discharge with preserved neurological status. Bertrand and colleagues[52] found the application of a passive oxygen flow of $\sim$ 15 L/min to be associated with the same survival rates as obtained with conventional invasive ventilation.

It is essential to distinguish between passive oxygen insufflation, achieved mainly using dedicated devices (such as the Boussignac tube), and pure apneic oxygenation, in which the complete denitrogenation of the alveoli is sought through the administration of pressure flow (usually 20 cm H_2O). From a theoretical point of view, this distinction is essential for determining the risk of atelectasis from oxygen reabsorption; however, from a practical point of view (at least in relation to the studies conducted on animal models), no substantial difference has been identified between the 2 methods in terms of side effects, or between these methods and invasive ventilation performed at zero PEEP.[9,53,54]

Although, from a theoretical point of view, the application of PEEP seems to be beneficial for achieving an adequate oxygenation target (see the section on PEEP), other clinical studies have focused on more specifically adapting ventilation to the patient, even during the inspiratory phase. Indeed,

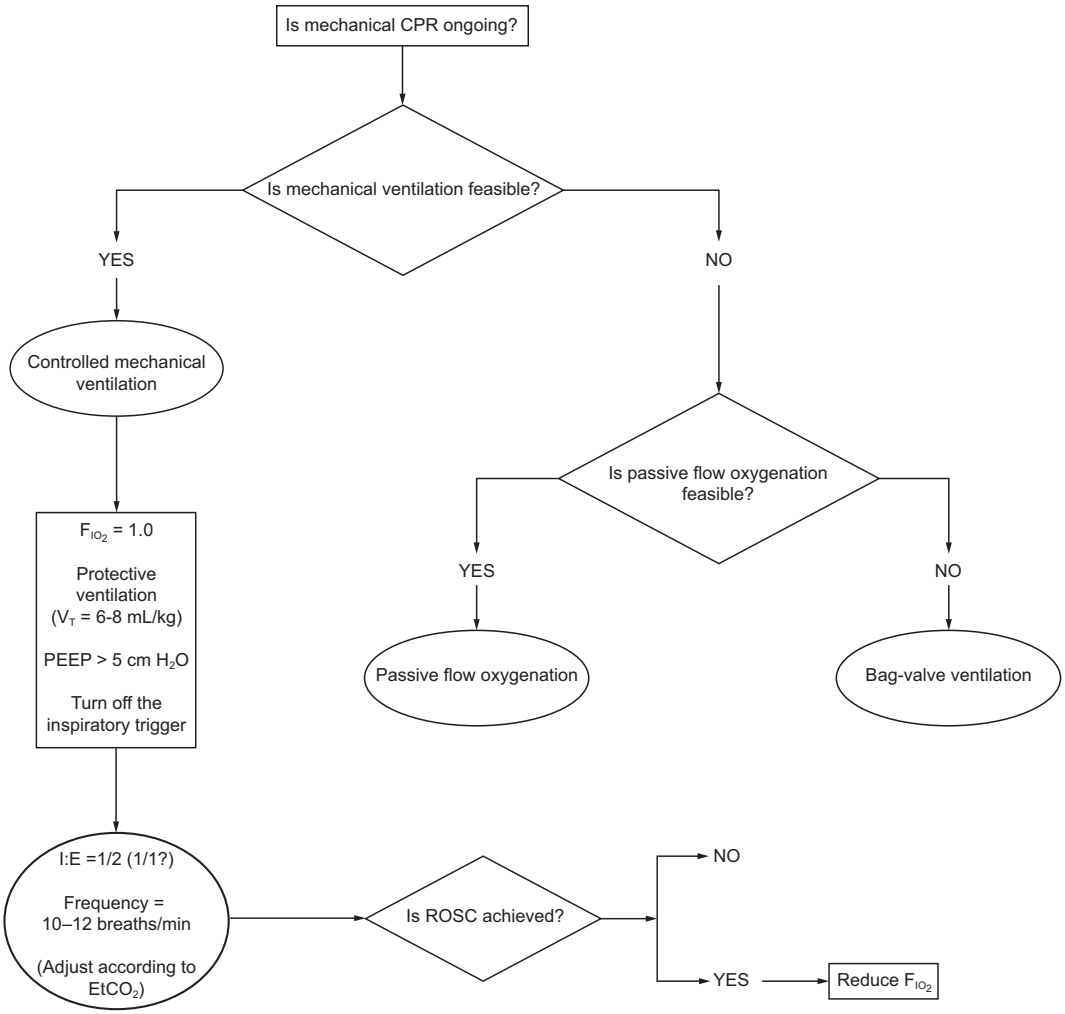

Fig. 2. Proposed operating algorithm for invasive mechanical ventilation during mechanical CPR. CPR = cardiopulmonary resuscitation; V_T = tidal volume; I:E = inspiratory-expiratory ratio; ROSC = return of spontaneous circulation; P_{ETCO_2} = end-tidal carbon dioxide pressure.

the risk of barotrauma during ventilation occurring simultaneously with chest compressions is well documented in the literature.[59] The arrival of new portable ventilator devices in the market capable of activating flow delivery through reverse inspiratory triggers (which work when the airway pressure rises fast enough above an absolute threshold after a minimal time of expiration) has opened a new line of research into intermittent ventilation synchronized with chest compressions. Animal studies have shown greater efficiency in terms of achieving (and maintaining) certain threshold levels of P_{aO_2}, with beneficial effects also on the hemodynamic conditions (eg, maintenance of adequate mean arterial pressure) and acid/base homeostasis (Table 1).[55,56] However, as previously mentioned, the studies conducted to date have only involved animal models. Thus, no conclusions can yet be drawn about such devices in terms of achieving return of spontaneous circulation or better neurological performance.

Therefore, 2 opposing strategies exist: passive oxygenation versus the synchronization of ventilation with chest compressions. Until now, the only study to compare these 2 strategies in an animal model is that by Soltsez and colleagues.[57] They found a higher coronary perfusion pressure and compression phase aortic pressure when positive-pressure ventilation was applied.

Limitations

The priority of this review was to consider all of the literature assessing mechanical ventilation during mechanical CPR. In doing so, we have been largely inclusive, as demonstrated by the wide variety of study designs involved. Most investigations are preclinical studies (animals or laboratory models), so their direct relevance to clinical practice is limited. In addition, the literature contains controversial results regarding the need for ventilation during cardiopulmonary

resuscitation.[60-64] Indeed, doubts persist regarding the need to intubate cardiac arrest patients at all[65-68]; although a discussion of this issue is beyond the scope of our review, we can affirm that the benefits of protecting the airways and mechanical ventilation continue to be widely recognized and prioritized.[69,70] This review has only addressed the evidence regarding mechanical ventilation during mechanical CPR. Any evidence that relates to data gathered outside this time frame (including after return of spontaneous circulation) has not been covered. The reader is instead referred to the recent publication by Holmberg and colleagues,[71] which discusses oxygenation and ventilation targets after cardiac arrest.

Summary

Research into the optimal way to ventilate a patient in cardiac arrest using mechanical chest compressions is ongoing. At present, very few clinical studies have explored the best ventilation strategy for cardiac arrest patients during mechanical CPR. According to the evidence published to date, a high F_{IO_2} during CPR must be guaranteed in these patients. Low-grade evidence suggests deactivating the inspiratory trigger and applying PEEP (at least 5 cm H_2O). Uncertainties remain about the ideal ventilatory mode, V_T, the ventilation rate setting, and the inspiratory-expiratory ratio. Current international guidelines do not provide any indications about the "best" mechanical ventilation strategy to use during mechanical CPR. Here, we put forward an operating algorithm based on the current state of knowledge (Fig. 2). Studies specifically addressing the topics covered in this review would be required to investigate its validity.

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