Ventilation and Oxygenation During and After Adult Cardiopulmonary Resuscitation: Changing Paradigms

Ahmed I Algahtani, J Brady Scott, and Jie Li

Cardiac arrest (CA) remains a major cause of death despite advancements in cardiopulmonary resuscitation (CPR), post–resuscitation care, and international efforts to develop evidence-based guidelines. Effectively managing ventilation and oxygenation during and after CPR is vital for patient survival and neurological outcomes, yet it remains a challenging task. This review examines current strategies for ventilation and oxygenation during and after CPR, focusing on evidence-based guidelines, the balance between ventilation effectiveness and risks, and proposed methods for monitoring ventilation quality. It emphasizes the need to provide adequate ventilation and oxygenation during and after CPR while avoiding hyperventilation and hypoventilation, which can negatively impact resuscitation and post-CA outcomes. The review also explores mechanical ventilation as an alternative to manual methods and the use of feedback devices. The impact of post-CA ventilation and oxygenation on patient outcomes and recommended management strategies are discussed. Finally, the review highlights current gaps in the literature and the need for more well-designed large clinical studies, such as the impact of different ventilation variables (tidal volume and breathing frequency) on the return of spontaneous circulation and long-term outcomes. *Key words: advanced life support; basic life support; cardiac arrest; resuscitation; ventilation; oxygenation*. [Respir Care 2024;69(12):1573–1586. © 2024 Daedalus Enterprises]

Introduction

Cardiac arrest (CA) is a serious, life-threatening medical emergency that claims thousands of lives each year.[1,2] The incidence of CA, both in and out of hospital, is a significant challenge for the health care community regarding meaningful recovery and survival.[2] Although there have been significant advances in CA care, survival rates remain modest, particularly survival with intact neurological function. This underscores the need for improvement in both cardiopulmonary resuscitation (CPR) and post–resuscitation care.

Global collaboration to enhance the quality of CPR and post–resuscitation care has been ongoing for decades.[3] As a result, international CPR and post–resuscitation clinical practice guidelines have been published and frequently updated.[3] For patients who experience in-hospital CA (IHCA), adherence to these guidelines has been shown to enhance the quality of CPR, increase the likelihood of survival, and improve neurological function.[4] Whereas it is encouraging that guideline adherence improves important outcomes, survival rates after IHCA are still low.[4,5]

An essential part of the guidelines is the focus on providing safe and effective ventilation and oxygenation during CPR and after the return of spontaneous circulation (ROSC). Yet, most of the recommendations for ventilation and oxygenation are based on a relatively narrow body of evidence, most of which was derived from animal and observational studies.[3,6] Some recommendations have remained unchanged over time simply due to the lack of large, well-designed clinical trials.[7,8] This review examines current recommended strategies for ventilation and oxygenation during CPR and post-CA and techniques for monitoring delivery to optimize care and patient outcomes. Additionally, areas where additional research could potentially enhance patient outcomes following CA will be identified.

Ventilation and Oxygenation During CPR

Proper ventilation and oxygenation during CPR involve providing optimal gas exchange while minimizing harm.[9,10] Excessive ventilation, either by high breathing frequencies, large tidal volumes (V_T), or both, can lead to dynamic lung hyperinflation. Dynamic hyperinflation can lead to increased intrathoracic pressures, adversely affecting hemodynamics by decreasing venous return and ultimately diminishing coronary and cerebral perfusion.[8,11,12] Also, dynamic hyperinflation increases pulmonary vascular resistance, limiting blood flow to the pulmonary circulation and worsening gas exchange.[13] Furthermore, hyperventilation lowers blood CO_2 levels, leading to cerebral vasoconstriction and reducing blood flow to the brain.[8,13] Excessive V_T delivered during bag-mask ventilation (BMV) may lead to gastric inflation and abdominal distention. Gastric inflation and abdominal distention can also increase intrathoracic pressure; however, it is unclear if this impacts ROSC.[14,15] Overall, it appears that hyperventilation may impair or delay ROSC and reduce the chance of survival with intact neurological function.[8,11-13] Hypoventilation may also be detrimental, as it can lead to hypoxemia, hypercapnia, and acidemia.[8,13]

Oxygen is essential in sustaining life for all living beings, yet its role in resuscitation is nuanced. Oxygen is necessary for mitochondrial aerobic respiration, facilitating the adenosine triphosphate production, and generating reactive oxygen species.[16,17] Adenosine triphosphate provides the energy required for the body to function, while reactive oxygen species play a role in immune responses.[16,17] However, high levels of reactive oxygen species can be toxic, leading to direct lung damage, coronary vasoconstriction, reperfusion injury, and poor gas exchange.[17] Despite these risks, correcting hypoxia during CPR is crucial, as a high P_{aO_2} appears to enhance the likelihood of ROSC and survival with meaningful neurologic function.[18] Also, low blood oxygen levels lead to vasoconstriction of the pulmonary vasculature, limiting blood flow into the pulmonary circulation and left heart, which may reduce the effectiveness of chest compressions.[13] In contrast, hyperoxia should be avoided after ROSC as it is associated with increased in-hospital mortality.[19]

Current Evidence-Based Guidelines and Recommendations

Airway management during CPR. The most recent updates on airway management during CPR include recommendations supported by evidence varying in strength and certainty (see Table 1).[3,9,10,20-31] Current CPR guidelines prioritize chest compressions over airway management and ventilation to improve resuscitation outcomes.[9,21,25] For basic airway management, the head tilt–chin lift technique is recommended for airway opening in adults unless a cervical spine injury is suspected, in which case a jaw thrust without head extension is preferred.[9,21] If the jaw thrust is insufficient for adequate ventilation, the head tilt–chin lift may be used carefully, considering the risk of spinal injury.[9,21]

Further recommendations include considering BMV or advanced airway interventions for adults in CA. For out-of-hospital CA (OHCA), a supraglottic airway (SGA) is recommended over tracheal intubation for providers with less experience or who have had a low success rate with tracheal intubation.[22,26] Conversely, for those with extensive experience and competence with the placement of artificial airways, using either SGA or endotracheal tube is advised, including in IHCA situations.[22,26] Waveform capnography is strongly recommended for verifying proper tracheal tube placement and continuous monitoring.[10,27] The American

Mr Algahtani is affiliated with Department of Cardiopulmonary Sciences, Division of Respiratory Care, College of Health Sciences, Rush University, Chicago, Illinois; and Department of Pediatrics, Pediatric Respiratory Care Division, Prince Sultan Military Medical City, Riyadh, Saudi Arabia. Drs Scott and Li are affiliated with Department of Cardiopulmonary Sciences, Division of Respiratory Care, College of Health Sciences, Rush University, Chicago, Illinois.

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Correspondence: J Brady Scott PhD RRT RRT-ACCS AE-C FAARC, Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University. 600 S. Paulina Street, Suite 751, Chicago, IL. 60612. E-mail: Jonathan_B_Scott@rush.edu.

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Table 1. Summary of Present Evidence-Based Guideline Recommendations for Ventilation and Oxygenation During Cardiopulmonary Resuscitation

Guideline, Year	Recommendation	Strength of Recommendation	Level of Evidence	Last Reviewed
Airway Management				
AHA, 2020[21]	Opening the airway during BMV			
	The head tilt–chin lift technique (no cervical spine injury is suspected).	Strong*	Weak, expert opinion*	2010
	The use of oropharyngeal and/or nasopharyngeal (in unconscious patients)	Moderate*	Weak, expert opinion*	2010
	The jaw thrust without head extension when cervical spine injury is suspected; if the airway cannot be opened, use head tilt–chin lift, oropharyngeal, and/or nasopharyngeal	Strong*	Weak, expert opinion*	2010
ILCOR CoSTR,2019[26]	BMV and advanced airway placement			
	BMV or advanced airway may be considered based on the situation and skill set of providers	Weak†	Low to moderate†	2019
	During OHCA, SGA can be used for low tracheal intubation success rates and less experienced providers	Weak†	Low†	2019
	During OHCA, SGA or tracheal intubation can be used by expert providers	Weak†	Very low†	2019
	During IHCA, SGA or tracheal intubation are suggested	Weak†	Very low†	2019
Ventilation and Oxygenation				
AHA, 2015, 2019,2020[9,21,22]	Ventilation			
	V_T of 500–600 mL or enough to produce a visible chest rise	Moderate*	Weak, limited data*	2010
	Deliver the breath over 1 s	Weak*	Weak, expert opinion*	2010
	During BMV it is reasonable to apply C/V ratio of 30:2	Moderate*	Moderate*	2017
	Before advanced airway placement, breathing frequency of 10 breaths/min (a breath every 6 s) during CCC	Weak*	Moderate*	2017
	After advanced airway placement, breathing frequency of 10 breaths/min (a breath every 6 s) during CCC	Weak*	Weak, limited data *	2017
	Health care providers should avoid excessive ventilation (too many breaths or too large a volume)	Strong (harm)*	Weak, limited data *	2010
AHA, 2015;[20] ILCOR CoSTR, 2021, 2022[3,27]	Oxygenation			
	Administering the highest possible inspired oxygen concentration	Weak†	Very low†	2015
	Recommend against the routine use of passive ventilation (passive oxygen insufflation)	Weak†	Very low†	2022
Feedback and Monitoring				
AHA, 2015 part 7, 2015 part 4, 2020;[10,20,21] ILCOR CoSTR, 2020[30,31]	Continuous waveform capnography (P_{ETCO_2}) for confirming and monitoring ETT placement	Strong*	Weak, limited data *	2015
	If waveform capnography is not available, non-waveform CO_2 detector is recommended for confirming and monitoring ETT placement	Strong*	Low*	2015
	Recommends against P_{ETCO_2} cutoff value alone as a mortality predictor	Strong†	Low†	2015
	Suggests that a P_{ETCO_2} of ≥ 10 mm Hg after tracheal intubation or after 20 min of CPR effort may be a predictor of ROSC	Weak†	Low†	2015
	Suggests that a P_{ETCO_2} of ≥ 10 mm Hg after tracheal intubation or ≥ 20 mm Hg after 20 min of CPR effort may predict survival to discharge	Weak†	Moderate†	2015

(Continued)

Table 1. Continued

Guideline, Year	Recommendation	Strength of Recommendation	Level of Evidence	Last Reviewed
	It may be reasonable to use audiovisual feedback devices during CPR to optimize CPR performance	Weak*	Moderate*	2020
	Physiological parameters such as arterial blood pressure or end-tidal CO_2 may be reasonable to use when feasible to monitor and optimize CPR quality	Weak*	Weak, limited data*	2020
	Routine measurement of arterial blood gases during CPR has uncertain value	Weak*	Weak, expert opinion*	2010

*Based on American Heart Association cardiopulmonary resuscitation guidelines.
†Based on International Liaison Committee on Resuscitation Consensus on Science with Treatment Recommendations cardiopulmonary resuscitation guidelines.
AHA = American Heart Association
BMV = bag-mask ventilation
ILCOR = International Liaison Committee on Resuscitation
CoSTR = Consensus on Science with Treatment Recommendations
OHCA = out-of-hospital cardiac arrest
SGA = supraglottic airway
IHCA = in-hospital cardiac arrest
V_T = tidal volume
C/V ratio = compression/ventilation ratio
CCC = continuous chest compression
P_{ETCO_2} = end-tidal CO_2
ETT = endotracheal tube
CPR = cardiopulmonary resuscitation
ROSC = return of spontaneous circulation

Heart Association (AHA) emphasizes the need for regular retraining for providers performing intubation alongside implementing continuous quality improvement initiatives.[22] These measures are intended to mitigate complications associated with advanced airway management techniques, such as SGA placement and intubation, and improve success rates.[22]

The 2019 International Liaison Committee on Resuscitation (ILCOR) Consensus on Science with Treatment Recommendations (CoSTR) for Advanced Life Support (ALS) Task Force identified notable gaps in airway management during CPR. Key areas lacking clarity include the optimal airway management technique for adults with IHCA and the impact of various airway management strategies on oxygenation, ventilation, and no-flow time during CPR.[26] Additionally, the task force has emphasized the need for additional research on the impacts of using SGA or tracheal intubation, aside from BMV, on CPR outcomes.[26] They also noted a need for further investigation into the clinical training and experience required to achieve and maintain expertise across airway management techniques.[26]

Ventilation during CPR. Ventilation during CPR is a dynamic process requiring careful attention to technique, rate, and volume to be effective.[21,22] Recently updated guidelines on ventilation during CPR include recommendations of varying strengths, ranging from very low to moderate certainty.[3,9,10,20-25] Recommendations vary between providers (layperson or trained health care provider), settings (OHCA or IHCA), and if the cardiac event was witnessed or unwitnessed. For example, CPR guidelines recommend that laypersons provide chest compressions and rescue breaths but only if trained and willing.[25] If the laypersons are not trained or willing, the guidelines support compression-only CPR for all patients in CA.[25] Recommendations for ventilation by health care providers during CA are (1) V_T between 500–600 mL or to ensure visible chest rise, (2) 1-s inspiratory times, and (3) ventilation rates of 10 breaths/min when an advanced airway device is inserted.[3,20,21,25] Despite these and other recommendations, a significant gap in clinical research persists regarding the direct impact of these strategies on ROSC and other favorable outcomes.[3,20] For example, the optimal V_T and ventilation rate during CPR remain unknown.[20]

Oxygenation during CPR. AHA and ILCOR CoSTR recommend administering the highest possible oxygen concentration during CPR.[20,27] This approach aims to maximize oxygen delivery and reduce risks associated with systemic hypoxemia.[20,21] However, specific arterial and tissue oxygen targets and the reliability of ways to monitor and control oxygen targets remain unclear.[20] These areas are recognized as significant knowledge gaps, driven at least partially by the limited clinical trials investigating various oxygen concentrations during CPR.[20]

The AHA and ILCOR guidelines address other oxygenation techniques like passive oxygen insufflation (passive ventilation) and extracorporeal CPR.[3,26,27] Currently, the routine use of passive oxygen is not advised for adults undergoing CPR in either the out-of-hospital or in-hospital setting.[3] The only exception is emergency medical services systems using bundles of care, which include minimally interrupted cardiac resuscitation strategy or continuous chest compression.[9,24,25] Current guidelines suggest that extracorporeal CPR can be considered a rescue intervention when conventional CPR is failing and where its rapid implementation by experienced and skilled providers is possible.[3,22,29]

The Conundrum of Adequate Ventilation: Rate and Tidal Volumes

The ongoing conundrum over ventilation (rate and V_T) during CPR centers on the balance between providing effective ventilation and avoiding hypoventilation and hyperventilation, both of which are harmful during CPR and associated with poor outcomes.[11,12,32-35] Several clinical studies, mostly experimental animal studies, have assessed the effect of different ventilation rates during CPR and their impact on outcomes (see Tables 2 and 3).[11,12,33-46] Ventilation rates that are too low may lead to poor ventilation, resulting in inadequate blood oxygenation and hypoventilation.[32,33] Atelectasis, hypoxemia, compromised CPR hemodynamics, and decreased cerebral oxygenation and perfusion are also possible if positive-pressure ventilation is not provided during CPR (eg, chest compressions-only CPR) or when ventilation rates are too low.[34,35]

Conversely, several observational clinical studies have demonstrated that delivering high ventilation rates leading to hyperventilation is common during CPR in all settings.[11,12,36-40] In 2004, Aufderheide et al[11,12] conducted a clinical observation study and an experimental animal study to quantify excessive ventilation during out-of-hospital CPR in humans and its effects on coronary perfusion pressure and survival in pigs. The clinical study observed an average ventilation rate of 30 ± 3.2 breaths/min delivered during CPR on 13 adult subjects, none of whom survived.[11,12] The animal study, which included 2 protocols involving a total of 30 pigs, found that a higher ventilation rate of 30 breaths/min was significantly associated with increased intrathoracic pressure ($P < .001$), decreased coronary perfusion pressure ($P = .03$), and reduced survival rates ($P = .006$).[11,12] Other experimental animal studies have reported similar hemodynamic findings associated with higher ventilation rates.[41-43] One study reported a significant association between the reduction of ventilation rates and a higher rate of ROSC.[42] In contrast, 2 experimental animal studies have shown that a reduction in ventilation rates was not associated with an improved rate of ROSC, nor did the reduction demonstrate any improved hemodynamic effects during CPR.[44,45] In 2 observational studies on human subjects, researchers found no significant differences in ventilation rates delivered during CPR between subjects who achieved ROSC and those who did not.[38,39] In 2023, results from a randomized controlled trial (RCT) on subjects with CA indicated that a ventilation rate of 20 breaths/min versus 10 breaths/min during out-of-hospital CPR increased minute ventilation significantly; however, there was no significant difference in the CO_2 washout, acidemia, oxygenation, or the rate of successful ROSC.[46]

Ventilation rate is not the only component of ventilation that clinicians need to consider. V_T, inspiratory time, airway pressures, and the interaction between chest compressions and ventilation are also considerations.[47] The current understanding of the interplay of these factors is limited, underscoring the need for further research.[47] O'Neill and Deakin[36] conducted one of the first human clinical studies reporting ventilation variables delivered during adult CPR, which included V_T. They reported a median delivered V_T of 618.5 mL with volumes ranging from 374–923 mL. They also reported median peak inspiratory pressures of 60.6 cm H_2O, ranging from 46–106 cm H_2O.[36] The authors concluded that hyperventilation was common but more from a high ventilation rate than a high V_T.[36]

As stated previously, the current recommended V_T during CPR is 500–600 mL. The rationale behind this recommendation in CPR guidelines is that ventilation in this range is usually appropriate to produce visible chest rise and maintain gas exchange in apneic patients in CA. These volumes also help to avoid excessive airway pressures and gastric overdistention.[48-50] It is notable that the current recommendations are supported by RCTs conducted more than 20 years ago, and no evidence since then has been able to convincingly refute these V_T targets.[49,50] The current V_T recommendations are also supported by physiological models of respiratory gas exchange that have shown that V_T of 600 mL via BMV was enough to maintain appropriate gas exchange when ventilation rates were maintained at 12 breaths/min.[51] Notably; however, Ruemmler et al[52] used an experimental animal study to demonstrate that ultra-low V_T (2–4 mL/kg) during resuscitation promotes lung protection and positive neurological outcomes due to decreased inflammation.[52] At present, the optimal ventilation rate and V_T that contribute to favorable outcomes such as ROSC, meaningful neurological recovery, and survival across diverse patient populations remain unknown. To address this critical gap, further research, particularly through large-scale human clinical trials, is necessary.

Oxygen: How Much?

A critical consideration in CPR is whether ventilation with 100% oxygen, as opposed to lower oxygen concentrations, is necessary. During CA, the body experiences a state

Table 2. Summary of Outcomes From Included Human Studies on Ventilation and Oxygenation During Cardiopulmonary Resuscitation

Author, Year	Design	Sample Size	Groups/Aim	Outcomes			Implications
				ROSC	Survival, %	Neurological Status	
Ventilation							
Hessulf et al,[6] 2018	Retrospective observational study	18,069	Factors of importance to 30-d survival after IHCA in Sweden	N/A	28.5*/28.3†/25.0‡	CPC score 1–2 (93%)	30-d survival after IHCA is associated with the time of the event, the etiology of the CA, and the degree of monitoring
Aufderheide et al,[11,12] 2004	Clinical observational study	13	Quantify the degree of excessive ventilation	Not reported (if any)	No subject survived	N/A	Excessive ventilation was common (ventilation rate 30 ± 3.2 breaths/min, range 15.0–49.0)
Naito et al,[15] 2023	Retrospective observational study	446	Effect of gastric inflation on ROSC	120 (27)	N/A	N/A	Gastric distention did not prevent ROSC.
O'Neill and Deakin,[36] 2007	Prospective observational study	12	Observe ventilation variables during CPR	None	None	N/A	Hyperventilation was common mostly due to high ventilation rates (median 21 breaths/min, range 7.0–37.0 breaths/min).
Maertens et al,[37] 2013	Prospective observational study	98	Measure ventilation rate using tracheal airway pressures	N/A	N/A	N/A	Cardiac arrest patients were ventilated 2 times faster than the recommended rate (overall median 20, min 4, max 74).
Vissers et al,[38] 2019	Retrospective observational study	337	Comparing ventilation rates of ≤ 10 breaths/min to > 10 breaths/min during CPR	21/50 (42) vs 119/287 (41.5), $P = .48$	4/50 (8) vs 21/287 (7.3), $P = .71$*	4/50 (8) vs 14/287 (4.9), $P = .75$§	Hyperventilation was common 287/337 (85.2). No significant difference was observed between ventilation rates ≤ 10 breaths/min compared to > 10 breaths/min during CPR.
Abella et al,[39] 2005	Prospective observational study	67	Measure CPR parameters of IHCA and adherence to CPR guidelines	27/67 (40.3)	7/67 (10.4)	N/A	Ventilation rates were > 20 breaths/min (60.9), and they were not significantly different between subjects with or without ROSC ($P = .17$).
Prause et al,[46] 2023	RCT	46	Assess the effects of ventilatory rate 10 breaths/min (group 1) vs 20 breaths/min (group 2)	12/23 (52) vs 11/23 (48), $P = .77$	N/A	N/A	Ventilation rates did not significantly impact ROSC, which may be due to the study's small sample size.
Tangpaisarn et al,[76] 2023 (CPR-VENT)	RCT	60	Assess the effects of manual bag-valve ventilation (group 1) vs mechanical ventilation (group 2) on gas exchange during CPR and the impact on CPR outcomes	13/30 (43) vs 15/30 (50), $P = .77$	3/30 (10) vs 5/30 (17), $P = .71$*	0/30 (0) vs 2/30 (7), $P = .49$§	No differences in CPR outcomes for subjects in both groups, including ROSC, survival to admission, 24-h survival, 28-d survival, and survival with good neurological outcomes.
Oxygenation							

(Continued)

Table2. Continued

Author, Year	Design	Sample Size	Groups/Aim	Outcomes			Implications
				ROSC	Survival, %	Neurological Status	
Spindelboeck et al,[55] 2013	Retrospective cohort study	145	Investigate the association between P_{aO_2} during CPR and OHCA outcomes. Group 1: low (P_{aO_2} 0–60 mm Hg) vs group 2: intermediate (P_{aO_2} 61–300 mm Hg) vs group 3: high (P_{aO_2} > 300 mm Hg)	7/32 (21.8) vs 47/83 (56.6) vs 25/30 (83.3), $P < .001$	6/32 (18.8) vs 42/83 (50.6) vs 25/30 (83.3), $P < .001$‖	1/32 (3.1) vs 11/83 (13.3) vs 7/30 (23.3), $P = .062$§	Higher P_{aO_2} during OHCA CPR was associated with higher ROSC rates and a positive but not statistically significant, trend toward better neurological outcomes.

Data are presented as *n*, *n* (%), or *n*/*n* (%) unless otherwise noted.
* Survival to hospital discharge.
† 30-d survival.
‡ One-y survival.
§ One-y survival with favorable neurological outcomes or (cerebral performance category score 1–2).
‖ Survival to hospital admission.
ROSC = return of spontaneous circulation
IHCA = in-hospital cardiac arrest
CPC = cerebral performance category
CPR = cardiopulmonary resuscitation
RCT = randomized controlled trial
OHCA = out-of-hospital cardiac arrest

of low blood flow, significantly reducing oxygen delivery to tissues and depleting intracellular oxygen reserves.[53] High oxygen concentrations (eg, 100% oxygen) during CPR are thought to be needed to restore intracellular oxygen levels and avoid hypoxia and its detrimental impacts on outcomes. In a low-flow state, it is unlikely that oxygen delivery will exceed demand or that elevated P_{aO_2} will result in hyperoxia, which theoretically underlies the increased oxidative injury observed during reperfusion.[10,53] However, after the restoration of blood flow and adequate oxygen delivery to tissues, high oxygen concentrations may lead to hyperoxia, which is thought to be harmful.[53] For example, a retrospective observational study by Kilgannon et al[54] showed that post-ROSC hyperoxia was significantly associated with higher in-hospital mortality rates.[54]

Two observational studies assessing P_{aO_2} during OHCA showed that a high P_{aO_2} during CPR (due to high concentrations of oxygen being delivered during CPR) was associated with improved survival rates to hospital admission.[55,56] Interestingly, the harmful effects of hyperoxia post ROSC do not appear to be an issue for high P_{aO_2} values measured during CPR (see Tables 2 and 3), suggesting that providing the highest oxygen concentration possible during CPR is safe and effective.[55,56] However, questions remain regarding how high of an oxygen concentration is actually needed. For example, in an animal study, 50% oxygen delivered during CPR was compared to 100% oxygen.[57] The authors reported no significant differences in clinical outcomes, such as ROSC and time to ROSC; however, the administration of 50% oxygen did not alleviate the disturbances in mitochondrial respiration.[57] At present, CPR guidelines suggest that clinicians administer the highest possible oxygen concentration during CPR when supplemental oxygen is available.[10,20,21] It appears that the harmful effects of hyperoxia are not as profound during the low-flow state of CPR. In the early post-CA period, guidelines suggest that it is reasonable to provide the highest oxygen percent available until oxyhemoglobin saturations can be measured. Further prospective clinical studies are needed to determine whether an optimal oxygenation level exists during CPR and, if so, how clinicians can monitor oxygen in real-time to make necessary adjustments to improve outcomes.[10,20,21]

Monitoring Quality and Effectiveness

Capnography. Capnography during CPR provides critical feedback on the quality of chest compressions, ventilation, and endotracheal tube placement.[20,21,30,31] Guidelines suggest that low or decreasing end-tidal CO_2 (P_{ETCO_2}) levels may indicate the need to reassess CPR quality.[21] They suggest that a P_{ETCO_2} value of more than 10 mm Hg or a sudden and sustained increase after intubation or 20 min of CPR may predict ROSC.[20,21,30,31] They also suggest that P_{ETCO_2} values of 10–20 mm Hg during CPR may predict

Table 3. Summary of Outcomes From Included Randomized Experimental Animal Studies on Ventilation and Oxygenation During Cardiopulmonary Resuscitation

Author, Year	Sample	Groups Control and Comparison	Outcomes			
			ROSC	Survival Rates	CPP (mm Hg)	CerPP (mm Hg)
Ventilation						
Aufderheide et al,[11,12] 2004	Pigs, 21	12 breaths/min/100% O_2*	6/7 (85.7)	N/A	23.4 ± 1.0	N/A
		30 breaths/min/100% O_2	1/7 (14.3)		19.5 ± 1.8	
		30 breaths/min/5% CO_2/95% O_2	(14.3), $P = .006$		16.9 ± 1.8, $P = .03$	
Yannopoulos et al,[33] 2005	Pigs, 8	C/V ratio 15:2*	N/A	N/A	10.1 ± 4.5	7.7 ± 6.2
		C/V ratio 15:1			19.3 ± 3.2, $P = .007$	14.5 ± 5.5, $P = .008$
Lurie et al,[35] 2008	Pigs, 22	10 breaths/min/100% O_2*	N/A	N/A	17.6 ± 9.3	16.0 ± 9.5
		2 breaths/min/100% O_2			14.3 ± 6.5, $P = .20$	9.3 ± 12.5, $P = .25$
Yannopoulos et al,[41] 2004	Pigs, 32	C/V ratio 5:1*	6/8 (75)	N/A	14 ± 1	N/A
		C/V ratio 10:1	6/8 (75), NS		17.8 ± 1.2, $P < .05$	
Yannopoulos et al,[42] 2006	Pigs, 18	C/V ratio 15:2*	1/9 (11.1)	N/A	18 ± 1	16 ± 3
		C/V ratio 30:2	6/9 (66.7), $P < .03$		25 ± 2, $P = .04$	18 ± 3, $P = .07$
Hayes et al,[43] 2007	Pigs, 36	10 breaths/min/V_T 10 mL/kg/ 100% O_2*	3/12 (25)	3/12 (25)	7.2 ± 2	N/A
		35 breaths/min/V_T 20 mL/kg/ 100% O_2	5/12 (41.7)	4/12 (33.3)	7.2 ± 2	
		Nasal cannula 10 L/min	5/12 (41.7), $P = .62$	4/12 (33.3), $P = .88$†	13 ± 3, $P < .05$	
Hwang et al,[44] 2008	Dogs, 30	C/V ratio 15:1	8/10 (80)	6/10 (60)	5.8 ± 1.2	N/A
		C/V ratio 15:2	8/10 (80)	6/10 (60)	7.0 ± 1.9	
		C/V ratio 30:2	8/10 (80), $P > .99$	7/10 (70), $P = .87$‡	3 ± 1.6, $P = .78$	
Gazmuri et al,[45] 2012	Pigs, 16	10 breaths/min/V_T 6 mL/kg*	No statistical associations	N/A	23 ± 1	32 ± 3
		10 breaths/min/V_T 18 mL/kg			17 ± 6	23 ± 8
		33 breaths/min/V_T 6 mL/kg			18 ± 6	30 ± 12
		33 breaths/min/V_T 18 mL/kg			21 ± 2, NS	31 ± 3
Ruemmler et al,[52] 2018	Pigs, 30	10 breaths/min/V_T 8–9 mL/kg/ 100% O_2*	6/10 (60)	N/A	N/A	N/A
		O_2 10 L/min/PEEP = 5 cm H_2O	6/10 (60)			
		50 breaths/min/V_T 2–3 mL/kg/ 100% O_2	8/10 (80), $P = .36$			
Oxygenation						
Nelskylä et al,[57] 2017	Pigs, 19	F_{IO_2} 1.0*	8/10 (80)	N/A	N/A	N/A
		F_{IO_2} 0.50	6/9 (67), $P = .51$			

Data are presented as *n* or *n*/*n* (%) unless otherwise noted.
*Control group.
†24-h survival.
‡2-h survival.
ROSC = return of spontaneous circulation
CPP = coronary perfusion pressure
CerPP = cerebral perfusion pressure
C/V ratio = compression/ventilation ratio
NS = not significant
V_T = tidal volume

an increased chance of survival to discharge (see Table 1).[20,21,30,31] However, guidelines do not recommend using P_{ETCO_2} values alone to make decisions regarding the continuation or termination of resuscitative efforts or to predict mortality.[20,21,30,31] Studies have reported that the sensitivity and specificity of P_{ETCO_2} for detecting ROSC varies, and in fact, the P_{ETCO_2} values associated with ROSC detection remain unclear.[58-60] For example, a retrospective case-control study of 108 OHCA subjects reported an abrupt increase in P_{ETCO_2} ($\geq$ 10 mm Hg) had an 80% sensitivity and 41% specificity for detecting ROSC.[59] Whereas, Lui et al,[60] in a cross-sectional study of 178 OHCA subjects, reported that a rise in P_{ETCO_2} value ($\geq$ 10 mm Hg) had 33% sensitivity and 97% specificity for detecting ROSC.

When utilizing waveform capnography during CPR to monitor ventilation rates and quality, clinicians must consider other confounding factors that may impact its applicability.[57] Artifacts caused by chest compressions and the impact of certain drugs, such as sodium bicarbonate or adrenaline, as well as chest compression quality and ventilation pattern variations, may affect capnography and P_{ETCO_2}.values.[58] P_{ETCO_2} is recognized as an indicator of cardiac output in low-flow states. During CA, the body is in a low-flow state, limiting pulmonary circulation and compromising gas exchange, resulting in limited C_{O_2} clearance and low P_{ETCO_2}.[61] With high-quality chest compressions during CPR, blood flow and gas exchange are improved, and P_{ETCO_2} increases.[61] In a multi-center cohort study that assessed 583 OHCA and IHCA subjects, a significant association was found between higher P_{ETCO_2} values and increased chest compression depth, as well as a significant correlation between higher ventilation rates and lower P_{ETCO_2}.values.[61] Leturiondo et al[62] showed that the presence of chest compression artifacts decreased sensitivity and positive predictive value of waveform capnography to well below 80%, in addition to a 50% reported error in the ventilation rate measurement.[62] Given the perceived importance of P_{ETCO_2} monitoring, efforts are being directed toward developing innovative techniques and algorithms capable of delivering more accurate, real-time ventilation feedback.[63,64] Two experimental studies of automated algorithms incorporated with capnography have improved the overall sensitivity and positive predictive value for detecting ventilation rates during chest compression.[63,64] Hopefully, these algorithms or others can provide valuable information that will improve the capabilities of capnography.

A knowledge gap exists regarding the use of capnography during CPR, including confounding factors, clinical applicability, and prognostic values.[20] Specifically, the impact of CA etiology, chest compressions, and ventilation rates on capnography values during CPR is not fully understood.[20] Cutoff values for predicting short- or long-term outcomes after CA have not been established.[20] Despite practical limitations and the multiple confounding factors that limit capnography's applicability, it is commonly used during CPR.[65] Clinicians need to be aware of the current limitations of the technology; thus, clinical education initiatives should focus on the capabilities and limitations of capnography in an effort to optimize its use during CPR. More research and a clearer understanding of its use are needed to optimize this technology.

Real-time ventilation feedback systems/devices. In practice, ventilation during CPR is provided without feedback, and clinicians often rely on their perception of adequacy based on visual observation on chest rise. In a 2019 survey of Canadian emergency medical physicians, only 12% utilized CPR feedback devices, whereas 41.2% relied only on visual observation to assess CPR quality.[66] Studies continue to demonstrate that variables such as V_T delivered during CPR are often not within the recommended ranges.[67,68] In a cross-sectional study evaluating the delivery of V_T and ventilation rates during simulated resuscitation, Scott et al[68] found a significant variation in V_T delivered by clinicians during manual ventilation. Fewer than half of the participants delivered V_T within the recommended range of 5–8 mL/kg of predicted body weight (PBW) for the simulated subject. However, the participants could meet the target ventilation rate of 10 breaths/min.[68] To improve CPR quality, guidelines suggest using feedback devices is reasonable.[21,22,30]

Commercially available ventilation feedback devices offer real-time guidance, monitoring, and corrective feedback on ventilation rates and volumes during CPR. Ventilation feedback device technology ranges from basic audiovisual ventilation rate timers to real-time feedback devices equipped with sensors that measure V_T and ventilation rates during CPR.[69-74] Modern devices are small, portable, easy to use, and connected between the resuscitation bag and ventilation interface.[72-74] Simulation-based studies have shown that real-time ventilation feedback devices improve ventilation (eg, reducing hypoventilation and hyperventilation) delivery during CPR and increase adherence to CPR guidelines.[69-74] Ongoing efforts are being made to improve these devices' accuracy, usability, and integration. Innovations such as wireless connectivity for remote monitoring and data analysis, machine learning algorithms for improved decision support, and automated CPR devices that adjust ventilation based on physiological feedback have been described.[69-74] However, whereas promising, there remains a lack of human clinical studies that have assessed the impact of utilizing these devices on patient outcomes.[21,30]

Mechanical Ventilation as an Alternative to Manual Ventilation During CPR

The use of mechanical ventilation, as an alternative to manual ventilation, during CPR has been proposed.[75,76] In a

2018 international survey, 46% (223/490 respondents) reported using mechanical ventilators during CPR for intubated patients. Seventy-two percent of surveyed clinicians reported using volume controlled modes when using a mechanical ventilator.[65] Sahu and colleagues[75] proposed a "six-dial" strategy for using mechanical ventilation during CPR for patients who were already intubated. Their strategy includes using volume controlled ventilation with (1) PEEP of 0 cm H_2O, (2) V_T of 8 mL/kg with an F_{IO_2} at 1.0, (3) ventilation rate of 10 breaths/min, (4) maximum peak inspiratory pressure alarm of 60 cm H_2O, (5) switching OFF of the trigger sensitivity, and (6) inspiratory-to-expiratory-time ratio (I-E) of 1:5.[75] This proposed strategy was based on clinical application experience in one hospital emergency department and settings similar to established CPR guidelines.[75] However, it is important to note that this method has not been evaluated in large clinical trials to establish its safety and effectiveness.[75] In 2023, an RCT (CPR-VENT) compared the efficacy of mechanical ventilation to BMV ventilation during CPR in subjects in emergency departments.[76] Sixty CA adult subjects receiving CPR were randomized into 2 groups, 30 subjects in each.[76] The control group received BMV during CPR, whereas the intervention (mechanical ventilation) group received ventilation via a Hamilton-C1 ventilator (version SW 2.2.x, Hamilton Medical, Bonaduz, Switzerland) right after intubation.[76] The ventilator was set on volume control, with a V_T of 6–7 mL/kg, ventilation rate 10 breaths/min, PEEP 0 cm H_2O, inspiratory time of 1 s, I:E ratio of 1:5, and F_{IO_2} of 1.0. For subjects with unknown ideal body weights, the V_T was set at 500 mL for males and 400 mL for females.[76] Ventilation parameters in this RCT were similar to the ventilation strategy Sahu and colleagues proposed and recommended ventilation values by CPR guidelines.[75,76] The result showed no significant difference in P_{aO_2} values between the control group (36.5 mm Hg, interquartile range [IQR] 14–70 mm Hg) and the intervention group (29 mm Hg, IQR 15–70 mm Hg, $P = .88$).[76] The resuscitation outcomes and complications of subjects between the control and intervention groups were not significantly different, ROSC (13, 43% vs 15, 50%, respectively, $P = .80$), survival to hospital admission (10, 33% vs 11, 37%, respectively, $P > .99$), survival to hospital discharge (3, 10% vs 5, 17%, respectively, $P = .71$), survival with good neurological outcome (0 vs 2, 7%, respectively, $P = .49$), and pneumothorax was not observed even though not all subjects received chest radiography.[76] Whereas no differences in outcomes were noted, this RCT did demonstrate the feasibility and safety of mechanical ventilation during CPR in intubated subjects with CA.[76]

Currently, it is unclear if using a mechanical ventilator offers any real advantage over manual ventilation during CPR. Whereas it appears safe, the optimal mechanical ventilation strategy during CPR is not yet known, and further research is needed.

Ventilation and Oxygenation Post–Cardiac Arrest

Ventilation and oxygenation, if not managed carefully post CA, may lead to detrimental pathophysiological consequences. After CA, the body may undergo a systemic inflammatory state known as post-CA syndrome.[77] The syndrome is characterized by 4 primary components: brain injury, myocardial dysfunction, systemic response to ischemia/reperfusion, and persistent precipitating pathology.[77,78] The main pathophysiological features of post-CA syndrome involve oxidative stress, coagulation abnormalities, and extensive inflammation, all contributing to multi-organ failure.[77,79]

Hyperventilation may lead to cerebral vasoconstriction and secondary ischemic brain injury, especially during the early stage after ROSC, due to cerebral vasculature sensitivity to P_{aCO_2} and impaired cerebral autoregulation. Hypoventilation may result in cerebral vasodilation, increasing blood flow to the brain, which could result in cerebral edema and reperfusion injury.[77-81] Prolonged administration of high F_{IO_2} may lead to hyperoxia, resulting in increased reactive oxygen species production, worsened oxidative stress, mitochondrial dysfunction, neuronal injury, and organ failure.[77,78,82-84] Hypoxia may worsen the existing ischemic injury, permanent cellular injury, and organ dysfunction.[77,78,82-84]

ARDS is common in patients post CA.[78,85,86] Two clinical studies reported that 48–72% of intubated post-CA subjects developed ARDS within 24–48 h after ROSC, which is associated with increased mortality.[85,86] Thus, several recommendations have been made regarding the pulmonary management of patients who are post CA.

Recommended Clinical Management Strategies for Patients Post–Cardiac Arrest

Current recommendations for mechanical ventilation post CA include implementing a strategy aimed at lung protection and adequate gas exchange.[21,58,78] In general, recommendations suggest that clinicians should target normal P_{aO_2} and P_{aCO_2} while avoiding hyperoxia and hypercarbia.[21,58,78] A lung-protective strategy in intubated patients post CA is particularly important given the high incidence of ARDS post CA.[78,85,86] Lung-protective strategies include (1) V_T of 4–8 mL/kg PBW, (2) plateau pressure < 30 cm H_2O and driving pressure < 15 cm H_2O, and (3) titrating PEEP and F_{IO_2} to achieve normoxia.[78] Recent observational studies associated targeting normocapnia for ventilated subjects post CA with better neurological outcomes.[87,88] Some studies have reported an association between hypercarbia and poor neurological function and increased in-hospital mortality after OHCA.[89,90] However, the evidence is somewhat conflicting. In 2023, an RCT (the TAME study) included 1,700 subjects from 63 ICUs in 17 countries,

compared targeted mild hypercapnia (P_{aCO_2} of 50–55 mm Hg) to normocapnia (P_{aCO_2} of 35–45 mm Hg).[91] The authors reported no significant differences between the mild hypercapnia group and the normocapnia group in terms of favorable neurological outcomes (43.5% vs 44.6%; relative risk 0.98 [95% CI 0.87–1.11], $P = .76$, respectively) and 6 months mortality (48.2% vs 45.9%; relative risk 1.05 [95% CI 0.94–1.16], respectively).[91]

As for oxygenation, AHA guidelines recommend titrating F_{IO_2} to target S_{pO_2} values of 92–98%.[21] However, recommendations suggest that F_{IO_2} should not be titrated post CA until a reliable assessment of blood oxygen saturation is available, such as pulse oximetry or arterial blood gases.[21] A 2018 systematic review and meta-analysis assessed the effect of hyperoxia on mortality and reported an association between post-CA hyperoxia and higher mortality compared to normoxia (odds ratio 1.34 [95% CI 1.08–1.67], $P = .008$, respectively).[18] In contrast, 3 RCTs, including the ICU-ROX study, reported no significant difference in neurological outcomes and mortality between liberal (hyperoxia) and conservative (normoxia) oxygen strategies.[92-94] However, the sum of the evidence suggests that conservative oxygen management is the best for patients after ROSC.[18,92-94]

In 2022, Battaglini et al[82] proposed 10 rules for optimizing mechanical ventilation and targets post CA. They suggest that protective and personalized mechanical ventilation is warranted even in patients without ARDS and after CA.[82] For ventilation, they proposed V_T of 6–8 mL/kg of PBW, ventilation frequency of 8–16 breaths/min, targeting P_{aCO_2} of 35–50 mm Hg, maintaining plateau pressures $\leq$ 20 cm H_2O, driving pressures $<$ 13 cm H_2O, and a mechanical power $<$ 17 J/min.[82] For oxygenation, they suggest PEEP $\geq$ 5 cm H_2O and the titration of F_{IO_2} to achieve normoxia (P_{aO_2} values of 70–100 mm Hg).[82] Whereas literature recommendations on ventilation and oxygenation post CA may vary slightly, it is generally agreed that clinicians should prioritize lung protection and aim for relatively normal targets for P_{aCO_2} and P_{aO_2}.

Summary

Effective ventilation and oxygenation are critical components of CPR, requiring careful attention to technique and adherence to evidence-based guidelines. Excessive ventilation and inadequate ventilation may negatively impact patient outcomes. Similarly, hypoxia and hyperoxia can also lead to adverse outcomes, emphasizing the need for optimal oxygenation levels during and after CPR. Real-time feedback devices and mechanical ventilation show promise, but further research is needed to establish their efficacy. Post-CA care should focus on lung protection strategies to mitigate the risk of ARDS and other complications. Continuous clinical research, updates to guidelines, and training for health care providers are essential to improve patient outcomes in CPR.

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