



Personalized physiology-guided resuscitation in highly monitored patients with cardiac arrest—the PERSEUS resuscitation protocol

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Abstract

Resuscitation guidelines remain uniform across all cardiac arrest patients, focusing on the delivery of chest compressions to a standardized rate and depth and algorithmic vasopressor dosing. However, individualizing resuscitation to the appropriate hemodynamic and ventilatory goals rather than a standard “one-size-fits-all” treatment seems a promising new therapeutic strategy. In this article, we present a new physiology-guided treatment strategy to titrate the resuscitation efforts to patient’s physiologic response after cardiac arrest. This approach can be applied during resuscitation attempts in highly monitored patients, such as those in the operating room or the intensive care unit, and could serve as a method for improving tissue perfusion and oxygenation while decreasing post-resuscitation adverse effects.

Keywords Resuscitation · Physiology-guided treatment · Pathophysiology · Cardiac arrest · Monitoring

Introduction

Since 2000, resuscitation guidelines remain uniform across all cardiac arrest patients, focusing on the delivery of chest compressions to a standardized rate and depth and algorithmic vasopressor dosing [1]. The widespread implementation of this algorithmic approach was responsible for the impressive improvements in survival in recent years. However, evidence has shown that intra-arrest optimization of coronary perfusion pressure (CPP), diastolic arterial pressure (DAP), and/or end-tidal carbon dioxide (ETCO₂) may improve the quality of cardiopulmonary resuscitation (CPR) and outcome [2–4]. This is feasible in highly monitored settings, such as the operating room or the intensive care unit, in which titration of resuscitation efforts to an individual patient’s physiologic response may improve survival while decreasing post-resuscitation adverse effects [5]. In this context, several

studies have demonstrated the efficacy of hemodynamic-directed CPR for improving rates of survival with favorable neurologic outcomes [6, 7].

Research on resuscitation made early gains, but recent progress has been slow due to the dispersion of the researchers to other aspects than elucidating the physiology and pathophysiology of cardiac arrest and resuscitation. Addressing the unique needs of our patients by assessing their individual response in real time to interventions and titrating our therapies seems the only way for improving outcome and pursuing methods of CPR that are based on patient physiology should be the “holy grail” of resuscitation science.

Although the concept of goal-directed hemodynamic optimization as a treatment strategy to improve clinical outcome in critically ill patients has been tested since the 1980s, no human study has established that prospectively targeting hemodynamics during CPR improves outcomes until now [8]. Nevertheless, individualizing resuscitation to the appropriate hemodynamic and ventilatory goals rather than a standard “one-size-fits-all” treatment seems a promising new therapeutic strategy that can be applied during resuscitation attempts in highly monitored patients.

The PERSEUS protocol is a new approach to the resuscitation of highly monitored patients with cardiac arrest. It has been developed based on our experience and the observation that the most important determinant of survival is the optimization of all the available physiological parameters and the full exploitation of both the “cardiac pump” and “thoracic pump.”

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The aim of this review is to present the PERSEUS protocol and the related rationale and methodology for physiology-guided CPR.

Physiological and pathophysiological aspects of cardiac arrest

Cardiac arrest interval

Immediately after the abrupt loss of effective blood flow, the hypotension-induced baroreflex withdrawal with the net increase in the vascular resistance maintains an impaired antegrade and pulmonary blood flow [9]. The systemic and pulmonary blood flow continue for at least 30–60 s, until the pressure gradient between the aorta and the right side of the heart, as well as between the pulmonary artery and the left atrium, has been completely dissipated, resulting in a rapid increase in the volume of the right ventricle and the extrapericardial component of the pulmonary veins. When arterial and systemic venous pressures reach equilibrium, the mean systemic filling pressure (Pmsf) is approximately 6–12 mmHg [10]. The coronary blood flow declines to zero, but CPP remains positive because of the retrograde coronary flow. However, this diminishes the removal of norepinephrine from the interstitial spaces, which together with the formation of cardiac edema prolongs vasoconstriction and enhances myocardial hypoperfusion and hypoxia.

At the same time, cerebral perfusion decreases while the damage of fatty acids of the neuronal cell membrane by reactive oxygen species leads to a progressive increase in membrane permeability and severe derangements of intracellular electrolytes, resulting in cell swelling and brain edema formation [10]. This, together with venous congestion, increases intracranial pressure (ICP) and damages the neuropil and synaptic structures and/or contacts.

Cardiopulmonary resuscitation

Myocardial blood flow is a major determinant of resuscitation success. With the onset of CPR, chest compressions result in forward blood, but even during optimal CPR, the cardiac output is between 25 and 40% of pre-arrest values while the coronary arteries receive 5–15% of this amount [9]. During the relaxation phase of CPR, CPP (the difference between DAP and right atrial pressure - RAP) is generated as blood passively flows from the aorta into the coronary arteries. The peak systolic arterial pressure ranges between 60 and 80 mmHg, while the mean pulmonary artery pressure is approximately 40 mmHg. This, together with the hypoxic pulmonary vasoconstriction, may increase RAP and aggravates venous return and CPP. Even though the coronary blood flow may be low and cannot maintain aerobic myocardial metabolism, it may be sufficient

enough to promote the deleterious effects of reperfusion, which has been initiated by the onset of CPR.

In the brain, blood flow is partially restored by the onset of CPR. During optimal chest compressions, the brain receives 30% of the compression-related cardiac output [10]. During the compression phase, ICP is increased probably due to changes in intrathoracic pressure transduced through the paravertebral venous/epidural plexus and spinal fluid to the intracranial compartment, which in turn increases resistance to cerebral perfusion [11, 12]. On the contrary, ICP decreases during chest recoil based on the same pressure mechanisms that increase ICP during the compression phase [13]. In addition, the activation of blood coagulation after the onset of reperfusion leads to the formation of microthrombi, while the activated neutrophils and platelets accumulate in microvessels [10]. These impair cerebral microvascular blood flow which may further be compromised by the α 1-adrenergic agonist action of endogenous and/or exogenous adrenaline which reduces capillary blood flow and increases arterial lactate levels.

Despite the significant research efforts during the last decades, the physiology of cardiac arrest and resuscitation remains only partially understood. Although much discussion takes place worldwide regarding the mechanisms of blood flow during CPR, it is widely recognized that increased emphasis should be given on the optimal performance of chest compressions. The mechanism of blood flow during CPR seems to be dependent on the stage and momentum of compression or decompression, without forgetting that the effect of ventilation, as well as that of compression force and rate, may vary during CPR [6, 14]. However, chest compression depth has been inversely associated with survival, while the depth necessary to generate forward blood flow is not uniform between individuals [5]. Therefore, compression depth should be actively titrated to a targeted physiologic arterial blood pressure goal in highly monitored patients.

The effectiveness of chest compressions is also dependent on venous return, which is proportional to the pressure gradient between Pmsf and central venous pressure (CVP). If chest compression rate and depth remain within currently recommended limits, venous return will be mainly maintained by the pressure gradient between Pmsf and CVP [15]. As the systemic vascular resistance is highly affected by the patient's condition and previous administration of anesthetic agents, it is extremely important to preserve Pmsf, especially in mechanically ventilated patients with cardiac arrest. Considering that the venous system has a large vascular capacitance and a constant compliance, large fluid volume infusion may rapidly increase right filling pressures while exerting a minimal effect on Pmsf, thus diminishing venous return, especially if administered via a subclavian or internal jugular vein. At the same time, fluid infusion is important for increasing systemic pressures and tissue perfusion.

Therefore, optimization of venous return is crucial in order to increase the compression-related cardiac output and in this context, vigilant ventilation and fluid administration, as well as earlier small doses of vasopressors, could optimize Pmsf and venous return.

Improving microcirculatory blood flow

At the microcirculatory level, arterioles are richly adrenergically innervated, thus responding to adrenergic stimulation causing vasoconstriction. Following sympathetic stimulation, the A1 and A2 arterioles show the greatest percentage of change in diameter values and remain constricted for long periods of time, whereas the A3 and A4 arterioles respond initially via constriction, but return to their initial diameter in a short period of time [16]. Vasodilatation of the smallest distal arterioles may assist with the maintenance of adequate tissue perfusion when larger arterioles are constricted.

During CPR, arterial blood pressure may correlate only poorly with microcirculatory flow and normalization or elevating blood pressure with vasopressors may result in unpredictable effects on microcirculatory and capillary perfusion, despite reaching initial resuscitation endpoints, such as DAP and/or ETCO₂ [17, 18]. As prolonged resuscitation leads to accrual of ischemic injury and results in ischemic contracture of the heart that inevitably becomes unresponsive to defibrillation and resuscitation efforts [9], a CPR method that provides higher tissue perfusion may lead to better outcomes by delaying ischemic cardiac contracture and decreasing neurological injury.

Nitroglycerin has a favorable hemodynamic profile which promotes forward blood flow and has been associated with increased rates of resuscitation and improved post-resuscitation outcome [19]. It can diffuse through all membranes, including the blood-brain barrier, and it is a potent cerebrovasodilator that increases cerebral blood flow through the release of nitric oxide (NO) from the endothelium [20]. Nitroglycerin also improves the endothelial function and the vascular tone of cerebral vessels and inhibits platelet aggregation and neutrophil adhesion simultaneously, improving macro- and microcirculatory blood flow and ameliorating ischemic damage [21, 22]. In addition to the primarily vascular activity, it may also have antioxidant effects through the release of NO, which is a potent antioxidant and is capable of rendering neuroprotection against oxidative stress-induced neurotoxicity [23]. Besides nitroglycerin, sodium nitroprusside-enhanced CPR has been shown to improve myocardial, carotid, and cerebral blood flow, post-resuscitation left ventricular global function, and 24-h survival with good neurological function in porcine models of cardiac arrest [24, 25]. Also, the addition of inhaled NO to

hemodynamic-directed CPR may improve short-term survival and intra-arrest hemodynamics [26].

Ventilation during cardiopulmonary resuscitation

Tracheal intubation and mechanical ventilation

Although it is widely believed that positive-pressure ventilation during CPR is bad for the circulation, proper timing of compression and ventilation may actually improve the circulation. Indeed, increasing evidence from large cohorts and a meta-analysis suggest that early insertion of endotracheal tube and positive-pressure ventilation may increase immediate survival [27–29]. During positive-pressure ventilation, blood flow may be promoted by the “thoracic pump,” but by the beginning of the expiratory phase (ventilator pause), the “thoracic pump” effect decreases as the “cardiac pump” begins to take over, reaching a peak effect by the end of ventilator pause and just before the inspiratory phase [6].

Of note, ventilation during CPR by using currently recommended chest compression rates has been reported to take place entirely below functional residual capacity and is associated with negative intrathoracic pressures during decompression [30], while the severe lung de-recruitment and atelectasis observed in chest compression-only CPR are not expected in mechanically ventilated patients in whom sufficient ventilation has preceded the onset of cardiac arrest, even with low pressures [14]. Consequently, each positive-pressure breath inflates the lungs, facilitates O₂ delivery, and opens up the pulmonary arterial and venous vasculature, allowing for respiration and transpulmonary circulation [13, 14, 30, 31]. However, a positive-pressure breath increases intrathoracic pressure, which may decrease right ventricular preload while increasing right ventricular afterload and ICP, thereby decreasing cerebral perfusion pressure (CerPP) [13]. Therefore, achieving the correct balance between too little and too much ventilation is of major importance for optimizing survival, and there must be an intrathoracic pressure limit for each patient at which the effect of “thoracic pump” should be maximal. Above this limit, intrathoracic pressure would be deleterious, while under this limit, ventilation may not provide adequate blood oxygenation due to small airway closure, increasing pulmonary vascular resistance and impairing gas exchange [6, 14, 31]. Our group has recently showed an association between mean airway pressure and outcome of CPR in mechanically ventilated patients, with a value of 42.5 mbar being associated with return of spontaneous circulation (ROSC) [14]. Ventilatory parameters were intermitted positive-pressure ventilation mode, tidal volume 6 ml/kg, respiratory rate 10 min⁻¹, I:E 1:2, PEEP 0 cm H₂O, and fraction of inspired oxygen (FiO₂) 100%. In this study, we found no

difference in ETCO_2 between survivors and non-survivors probably due to the maintenance of flow in small airways and the improvement in minute-volume ventilation during CPR [30–32].

How much oxygen during cardiopulmonary resuscitation?

Although current guidelines recommend giving the maximum feasible inspired oxygen during CPR [1], the optimal oxygen requirement remains uncertain, as too little or too much could be harmful. Considering that ROSC may be more likely with high FiO_2 , as well as it may not result in cerebral hyperoxia, it seems prudent to continue to provide 100% oxygen during CPR or maintaining an arterial oxygen saturation of > 94% in patient with hemoglobin (Hb) levels of > 10 g/dl and a central venous oxygen saturation (ScvO_2) of 65–80%.

Capnography and end-tidal carbon dioxide

During CPR, changes in ETCO_2 parallel the changes in pulmonary blood flow and thus cardiac output, provided that other factors that regulate ETCO_2 are constant [33]. Taking into consideration that blood flow and CPP during CPR depend on the quality of chest compressions [34], capnography and ETCO_2 monitoring can be a valuable asset, serving as an indicator of systemic and pulmonary blood flow and reflecting the effects of CPR on cardiac output and stroke volume index [33].

On the other hand, it should be noted that many potential confounding factors may affect the levels of ETCO_2 , such as the cause of the arrest, hypercapnia, the initial heart rhythm, the early onset of CPR, the rescuer fatigue, and the administration of epinephrine, sodium bicarbonate, or other drugs [33, 35, 36]. In mechanically ventilated patients, the simultaneous positive-pressure ventilation in time with each chest compression may prevent a loss of intrathoracic pressure via the airway and maintain air flow in small airways, improving minute-volume ventilation and maintaining stable or even reducing ETCO_2 [31–33]. Therefore, low or decreasing ETCO_2 levels during CPR may not necessarily indicate poor prognosis in mechanically ventilated patients.

Neuroprotection during cardiopulmonary resuscitation: brain tissue oxygen saturation

Maintaining sufficient cerebral perfusion during CPR is strongly associated with survival and favorable neurologic outcome in animals [37–39], and cerebral oximetry is a non-invasive technology that uses near-infrared light to measure brain tissue perfusion [40, 41]. Until now, however, no general threshold has been set at which ROSC will be achieved. In a study of in-hospital cardiac arrest, patients with sustained

ROSC had higher overall brain tissue oxygen saturation (rSO_2) during CPR, while patients who survived to hospital discharge with a favorable neurologic outcome had higher rSO_2 than those who did not survive to hospital discharge [42]. Also, an rSO_2 values less than 30% has been negatively correlated with ROSC [8, 41, 43]. Furthermore, there is evidence that rSO_2 can play a role in predicting neurologic outcome 1 week after cardiac arrest or at hospital discharge [41].

Considering that cerebral perfusion during CPR is critical for neurologically intact survival, enhancing cerebral vein drainage will lead to decreased ICP thereby promoting forward cerebral flow. Interestingly, it has been reported that an increase in intrathoracic pressure may not reduce internal jugular vein drainage, but actually it may increase intracranial venous volume in healthy individuals in the upright posture [44]. As the decompression-induced negative intrathoracic pressure is not affected by ventilation, optimizing intrathoracic pressure during incline CPR may allow venous return and enhance cerebral vein drainage and oxygenation [14, 30, 45]. This may be facilitated with the use of Head Up CPR (HUP-CPR), which uses gravity to enhance venous return from the head and paravertebral plexus, further reducing ICP and increasing CerPP [46]. In a swine study, CerPP remained significantly higher in the HUP-CPR pigs, especially when an impedance threshold device was used [47]. These physiological changes were recently replicated in deceased human cadaver models; HUP-CPR resulted in decreased ICP and increased CerPP , further supporting its use in patients in cardiac arrest [48]. Nevertheless, the compression-related cardiac output may be impaired during human HUP-CPR due to pooling of blood in the lower extremities.

Blood pressure-directed cardiopulmonary resuscitation versus end-tidal carbon dioxide-directed cardiopulmonary resuscitation

Until now, numerous randomized-controlled animal studies have established that hemodynamic-directed targeted CPR results in superior outcomes compared to standard CPR [8], while animal data regarding ETCO_2 -directed CPR are not as convincing [49, 50]. Mean DAP > 34 mmHg was reported to be a superior discriminator of survival than mean ETCO_2 in porcine models of in-hospital cardiac arrest [5]. In this study, DAP values during the final 2 min of CPR preceding the first defibrillation attempt were substantially higher among survivors compared with non-survivors, but the concomitant ETCO_2 measurements did not differ between survivors and non-survivors.

As stated before, a number of factors may influence ETCO_2 , including minute ventilation, pulmonary pathology, and the ventilation/perfusion defects that occur with

vasopressor administration [5]. It is important to remember that ETCO_2 primarily reflects pulmonary blood flow rather than myocardial blood flow, while cardiac output does not always correlate with DAP and its downstream effects on myocardial blood flow. Of note, the main determinant of Pmsf, venous return, and DAP adequacy (and therefore myocardial flow) is systemic vascular resistance [5].

Targeting intra-arrest hemodynamics compared to standard CPR has been reported to improve both short- and long-term survival with favorable neurologic outcomes [5, 51, 52]. Besides the evidence, it can be easily understood that inability to obtain an adequate DAP is highly predictive of death and patient-centric titration of CPR to hemodynamics may improve survival rates.

The PERSEUS personalized physiology-guided resuscitation protocol

Recognizing cardiac arrest in highly monitored areas can be more difficult than in other hospital areas, such as the ward. Considering that the vast majority of alarms from sensors are false alarms [53], cardiac arrest should be recognized and confirmed by the combined assessment of the rhythm, the arterial blood pressure and waveform, the abrupt decrease of ETCO_2 , and the loss of carotid pulse. Once cardiac arrest is confirmed, CPR should be initiated without delay with high-quality chest compressions according to the recent resuscitation guidelines (Fig. 1) [1]. However, the effectiveness of chest compressions is depending on the venous return, which

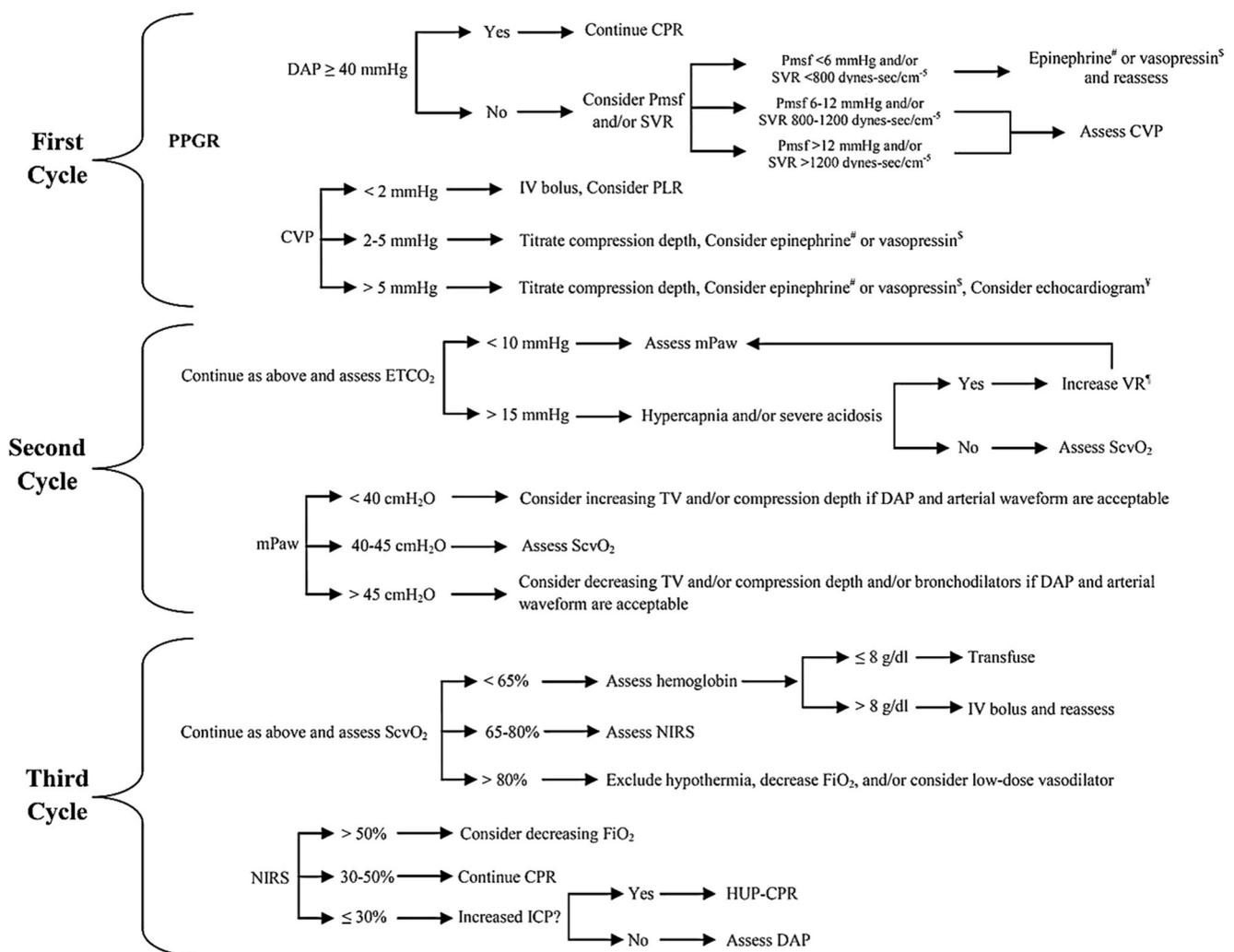


Fig. 1 Our stepwise approach to the management of cardiac arrest in highly monitored patients. PPGR, personalized physiology-guided resuscitation; CPR, cardiopulmonary resuscitation; DAP, diastolic arterial pressure; Pmsf, mean systemic filling pressure; SVR, systemic vascular resistance; CVP, central venous pressure; PLR, passive leg raising; ETCO_2 , end-tidal carbon dioxide; mPaw, mean airway pressure; VR, ventilation rate; ScvO₂, central venous oxygen saturation; TV, tidal

volume; NIRS, near-infrared spectroscopy; FiO₂, fraction of inspired oxygen; ICP, intracranial pressure; HUP-CPR, head up cardiopulmonary resuscitation at 30°. [#] Epinephrine 100–1000 mcg IV, may repeat/consider epinephrine infusion. [§] May replace 1 dose of epinephrine with 4–40 U of Vasopressin IV. [†] Consider inhaled nitric oxide in known or suspected increased pulmonary hypertension. [‡] Up to 50% or less if necessary to maintain DAP ≥ 40 mmHg

is proportional to the pressure gradient between Pmsf and CVP, and particular attention is needed by the rescuers to determine Pmsf within the first 5–7.5 s of cardiac arrest and prior to the onset of chest compressions [54, 55]. The Pmsf is a quantitative measurement of the patient's volume status and represents the tone of venous reservoir [56], indicating the pre-arrest “vasoreactivity” status of the patients. Therefore, optimizing Pmsf during CPR is paramount for increasing survival rates.

During the first cycle of CPR, the resuscitation efforts must maintain a relaxation DAP of ≥ 40 mmHg (calculated at the time of full chest decompression) [3–5]. In patients with a lower DAP, administration of epinephrine or vasopressin should be based on the pre-arrest value of Pmsf and/or systemic vascular resistance (SVR) and is anticipated to be beneficial in those with Pmsf < 6 mmHg and/or SVR < 800 dynes-sec/cm⁻⁵, enhancing volume recruitment from the unstressed compartment and increasing the stressed volume [57–59]. In all other patients, the vasoreactivity will be maintained for some time provided that intravascular volume and chest compressions are sufficient. Therefore, circulatory volume should be increased in patients with a pre-arrest CVP < 2 mmHg using a fluid bolus and/or the passive leg-raising maneuver. However, it should be noted that rapid and liberal fluid administration during CPR may lead to an excessive increase in RAP, aggravating venous return and CPP, especially when administered via a jugular or subclavian central venous catheter. At the onset of cardiac arrest, ventilatory parameters should be changed to tidal volume 6 ml/kg, respiratory rate 10 min⁻¹, I:E 1:2, PEEP 0 cm H₂O, and FiO₂ 100% [1, 14]. During this cycle, all other treatment efforts must follow current recommendations for standard CPR [1].

After the onset of the second cycle of CPR, the resuscitation efforts should be continued as above while assessing ETCO₂. As stated previously, ventilation during CPR by using currently recommended chest compression rates may take place entirely below functional residual capacity and may not provide adequate blood oxygenation due to small airway closure, increasing pulmonary vascular resistance and impairing gas exchange [6, 14, 30, 31]. Therefore, mean airway pressure should be maintained 40–45 cmH₂O in patients with DAP ≥ 40 mmHg and ETCO₂ < 10 mmHg to facilitate gas exchange. On the contrary, all patients with DAP > 40 mmHg and ETCO₂ > 15 mmHg should be assessed for hypercapnia, and if present, they should be treated by increasing the ventilatory rate by up to 50% (or less if necessary to maintain DAP ≥ 40 mmHg). Also, severe acidosis should be treated immediately because it causes vasodilatation which may decrease venous return and CPP.

During the third cycle of CPR, the resuscitation efforts should be continued as above while assessing ScvO₂, which should be maintained 65–80%. In patients with ScvO₂ $< 65\%$, transfusion of red blood cells should be initiated when Hb is ≤ 8 g/dl to

improve oxygen delivery. In patients with Hb > 8 g/dl, a fluid bolus should be given to improve circulatory flow provided that DAP is maintained ≥ 40 mmHg. In patients with DAP ≥ 40 mmHg and a ScvO₂ value of $> 80\%$, hypothermia should be excluded and treated aggressively if present, the FiO₂ should be decreased in case of hyperoxemia (PaO₂ > 200 mmHg), and a low-dose vasodilator may be considered when microcirculatory shunting and loss of hemodynamic coherence between macro- and microcirculation can be directly assessed or possible (e.g., DAP ≥ 40 mmHg, Hb > 8 g/dl, PaO₂ > 200 mmHg, ScvO₂ $> 80\%$, and mixed venous oxygen tension ≤ 26 mmHg (if available), with or without hyperlactatemia). In patients with normal ScvO₂, trend cerebral oxygenation monitoring (near-infrared spectroscopy - NIRS) should be used because it focuses more on the amount of change from the pre-arrest baseline cerebral oxygenation value. Decreasing FiO₂ until PaO₂ is 200 mmHg can be considered when NIRS is $> 50\%$ of the pre-arrest value, while HUP-CPR (30°) should be considered in patients with NIRS $\leq 30\%$ of the pre-arrest value and signs or known increased intracranial pressure. The resuscitation efforts may be considered as adequate in patients who have reached the pre-defined targets and have a NIRS of 30–50% of the pre-arrest value, and should be continued by repeating the approach from the beginning. Finally, extracorporeal CPR should be considered after 8–10 cycles of CPR.

Conclusion

Although outcomes after cardiac arrest remain poor more than 50 years, increasing evidence suggest that physiology-guided resuscitation may increase both short- and long-term survival. The PERSEUS CPR is a new approach to the resuscitation of highly monitored patients with cardiac arrest and could serve as a treatment strategy to titrate chest compressions, ventilation, and vasopressor dosing to physiological parameters.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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