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Review

The pathophysiologies of asphyxial vs dysrhythmic cardiac arrest: implications for resuscitation and post-event management ☆

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ABSTRACT

Background: Cardiac arrest is not a uniform condition and significant heterogeneity exists within all victims with regard to the cause of cardiac arrest. Primary cardiac (dysrhythmic) and asphyxial causes together are responsible for most cases of cardiac arrest at all age groups. The purpose of this article is to review the pathophysiologic differences between dysrhythmic and asphyxial cardiac arrest in the prearrest period, during the no-flow state, and after successful cardiopulmonary resuscitation.
Methods: The electronic databases of PubMed/Medline, Scopus, and Cochrane were searched for relevant literature and studies.
Results/Discussion: Significant differences exist between dysrhythmic and asphyxial cardiac arrest regarding their pathophysiologic pathways and affect consequently the postresuscitation period. Laboratory data indicate that asphyxial cardiac arrest leads to more widespread postresuscitation brain damage compared with dysrhythmic cardiac arrest. Regarding postresuscitation myocardial dysfunction, few studies have addressed a comparison of the 2 conditions with controversial results.
Conclusions: Asphyxial cardiac arrest differs significantly from dysrhythmic cardiac arrest with regard to pathophysiologic mechanisms, neuropathologic damage, postresuscitation organ dysfunction, and response to therapy. Both conditions should be considered and treated in a different manner.

1. Introduction

Cardiac arrest (CA) is a clinical syndrome defined as the "cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation" [1]. Cardiac arrest and sudden cardiac death (SCD) are terms used usually to describe primary (cardiogenic) or dysrhythmic CA of cardiac origin. Asphyxial causes of CA are less common in adults and include all processes that critically reduce cellular availability and use of oxygen. Cardiac arrest may be sudden, but unlike cardiac causes, it is not immediate and follows a "prearrest" period characterized by tissue hypoxia and progressive cardiopulmonary dysfunction. However, evidence suggests that CA is not a uniform condition and significant differences exist in the postresuscitation period after CA due to asphyxia or due to cardiac causes with regard to neurologic recovery, myocardial dysfunction, and outcome.

The aim of the present study is to review the literature to summarize and illustrate the differences between asphyxial and dysrhythmic CA concerning pathophysiologic mechanisms in the prearrest period, during CA, and the after the resuscitation period.

2. Cardiac arrest causes and epidemiology

Cardiac arrest is a leading cause of death with major socioeconomic implications; it affects more than 400 000 individuals annually with poor prognosis and with survival to hospital discharge not exceeding 11% and neurologic status of the survivors not always being optimal [2,3]. The true incidence of CA/SCD remains unclear, and definitions of CA and SCD are still not standardized.

Cardiac causes of CA are predominant in adults. Ventricular fibrillation (VF) and pulseless ventricular tachycardia account for most of primary sudden CA cases of cardiac origin [2,3]. These arrhythmic events are triggered by myocardial ischemia, cardiac channelopathies, electrolyte disturbances, and a variety of other diseases affecting the heart and usually lead to an immediate no-flow state.

On the other side, noncardiac causes far outnumber cardiac causes in younger ages, children, and neonates [4]. Asphyxial, respiratory, or "secondary" CA has different causes. Although the Greek term *asphyxia* literally refers to pulselessness, it represents an inability to breathe

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normally and failure of gas exchange leading to severe hypoxemia and tissue hypoxia. Different mechanisms are included in asphyxial CA such as impaired alveolar ventilation due to pulmonary diseases, airway obstruction, neuromuscular, or other causes. There are often overt clinical signs prior to cardiac standstill, and thus, in settings of witnessed CA, it is usually possible to distinguish between CA of cardiac origin and asphyxia. Although the true incidence of asphyxial CA is difficult to be estimated, summary data indicate that 20% to 40% of out-of-hospital CA (OHCA) are of noncardiac origin [5,6].

Finally, there is a third category of causes including hypovolemia, hemorrhage, and circulatory shock that also lead to CA and death, although their incidence is lower in comparison to cardiac and respiratory causes, which represent most OHCA causes.

3. Differences in pathophysiologic mechanisms

Asphyxial CA is characterized by a prolonged time course and an important prearrest period where *hypoxia* (defined as critical reduction in arterial oxygen saturation or arterial oxygen tension), and *hypercapnia* (defined as increases in arterial carbon dioxide tension), progressively advance along with maintained but gradually deteriorating cardiopulmonary function (Fig. 1) [7–10].

As asphyxia progresses, bradycardia, as a sign of decompensation, and hypotension, in part due to myocardial impairment, develop, terminating in CA and no-flow state. Bradyarrhythmias in the prearrest period typically progress to pulseless electrical activity (PEA) or asystole rather than VF [11]. The marked effect of hypoxia/ischemia and acidosis to the cardiac pacemaker and electrical conduction system may explain the cardiac depressant activity along with the unstable myocardial electrical state and the not infrequent rhythm alternations, although the exact mechanisms are still unclear [11,12].

Contrary to asphyxial, dysrhythmic CA leads to sudden and complete cessation of blood flow (Fig. 2). VF, the predominant mechanism in dysrhythmic CA, follows the 3-phase time-sensitive model described by Weisfeldt and Becker [13]. In the first electrical phase lasting 4 to 5 minutes, the most important intervention is prompt electrical therapy. Although the myocardium is continuously fibrillating, neither its energy stores have been depleted, nor serious cellular damage has been developed, and this period is therefore considered as the time when defibrillation is most likely to be successful. However, other cardiac rhythms can also occur in OHCA of cardiac origin as bradyarrhythmias and asystole, although, especially in unwitnessed settings, it is uncertain whether bradyarrhythmia represents the arresting cardiac rhythm or rhythm deterioration due to prolonged VF [14].

Although VF is a lethal tachyarrhythmia often associated with underlying cardiac disturbances and considered to be the immediate cause of CA, it can also occur during the asphyxial process. Ventricular fibrillation in this setting is uncommon, but not rare [15]. Asphyxia-induced or secondary VF has different underlying pathophysiologic mechanisms with regard to myocardial bioenergetics and electrophysiology [16]. The findings of different studies generally indicate that hypoxia and hypercapnia can lower the threshold for VF occurrence and the tendency of the heart to ventricular ectopy [17]. Hypoxemia is known to cause VF by shortening the duration of the cardiac action potential [18]. Ventricular fibrillation during the course of an asphyxial event occurs gradually, is associated with significant tissue hypoxia and severe depletion of myocardial cellular energy stores [19]. Probably therefore, VF can be refractory to defibrillation and hypercapnia can be associated with refractory VF [17]. In this case, one can assume that

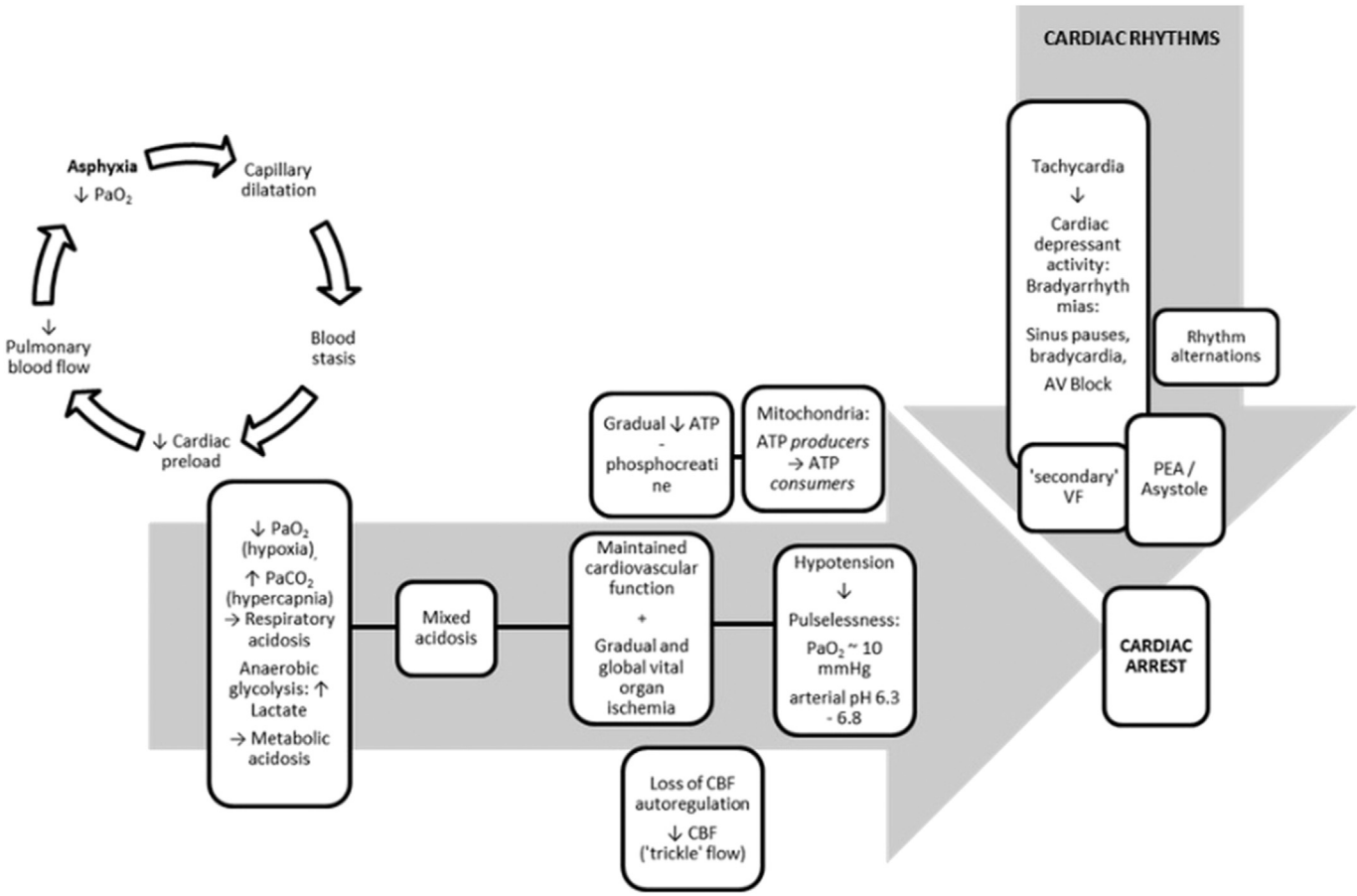

Fig. 1. Typical pathophysiologic disorders and associated cardiac rhythm disturbances during asphyxial CA, where severe global hypoxia precedes cardiac standstill. Pa_{O_2}, arterial oxygen tension; Pa_{CO_2}, arterial carbon dioxide tension; AV block, atrioventricular block; CBF, cerebral blood flow.

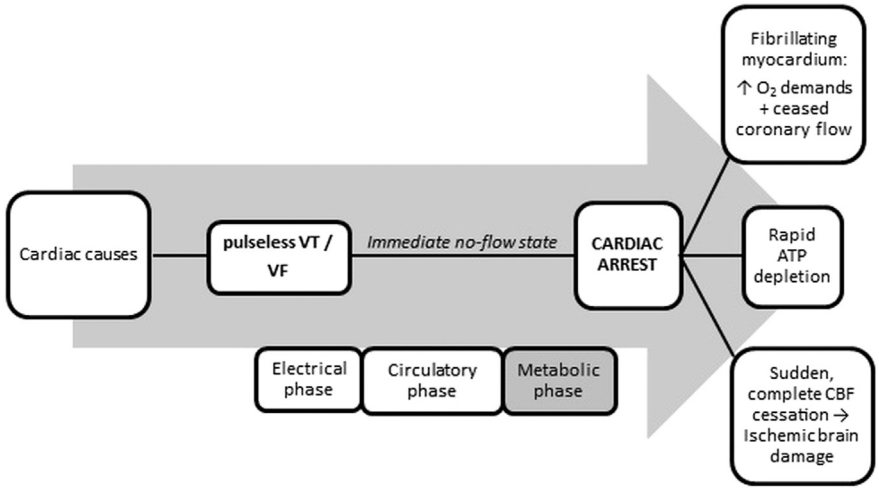

Fig. 2. Main pathophysiologic characteristics of dysrhythmic CA. VT, ventricular tachycardia; CBF, cerebral blood flow.

during resuscitation efforts, other interventions often need to be delivered prior to electrical therapy. The conversion of PEA and nonshockable rhythms to shockable during asphyxia is an interesting phenomenon and it seems that outcomes after asphyxial CA with asystole/PEA with subsequent VF are worse than after asystole/PEA without subsequent VF [20]. This is probably attributed to the fact that subsequent VF might be a marker of more severe myocardial dysfunction.

The impaired cerebrovascular autoregulation that occurs during asphyxia contributes to the decreased cerebral blood flow (CBF) that consecutively follows the changes in mean arterial pressure prior to its cessation. The induced brain hypoxia and ischemia in this period lead, via glutamate release, calcium cell entry, complex changes in membrane function, and cytotoxic edema, to neuronal damage, mimicking neonatal hypoxic-ischemic-encephalopathy lesions [21]. Hickey and Painter [7] addressed this issue and assumed that low CBF during asphyxia may be even worse than no flow. Based on a previous animal study where worse postresuscitation cerebral reperfusion had been observed after controlled resuscitated VF than untreated VF [22], they proposed the detrimental effect of "trickle" cerebral flow combined with hypoxemia that characterizes the prearrest asphyxial period. They suggested that prolonged delivery of substrates during anaerobic metabolism to the brain along with platelets and coagulation factors may impair microcirculation and subsequently alter postresuscitation cerebral reperfusion.

At cellular level, sudden CA of cardiac origin causes an immediate no-flow state with global ischemia, where high-energy phosphates are depleted rapidly. Especially in the brain, adenosine triphosphate (ATP) depletion is thought to occur within a few minutes [23]. On the contrary, asphyxial CA is characterized by progressive and global hypoxia with incomplete ischemia and results in gradually with the length of asphyxia ATP and phosphocreatine reduction. If ATP is depleted during hypoxia, necrosis occurs because of mitochondria transmembrane potential disruption, leading to cell swelling and ultimately to apoptosis and necrosis [24,25]. Depletion of cellular energy initiates biochemical cascades that lead to cell damage and death prior to the no-flow state [21]. This was also supported by the findings of a recent laboratory study by Wu et al [26], who focused on the greater myocardial mitochondrial damage and lower levels of cyclic adenosine monophosphate, cyclic guanosine monophosphate, and phosphodiesterase in resuscitated animals after asphyxial CA, indicating a higher degree of energy depletion compared with dysrhythmic CA.

Finally, maintained cardiovascular function during asphyxia prior to cardiac standstill results in CO_2 tissue production and accumulation in the alveoli, as there is no alveolar gas exchange. There are at least 5 laboratory studies that showed different patterns of end-tidal carbon dioxide ($ETCO_2$) levels during cardiopulmonary resuscitation (CPR) between asphyxial and dysrhythmic CA. Levels of $ETCO_2$ were initially high after asphyxial CA before they decreased [27–31]. On the contrary, after dysrhythmic CA, $ETCO_2$ levels decrease abruptly with onset of the no-flow state, reflecting zero cardiac output [32]. No study showed any prognostic value and correlation between high initial $ETCO_2$ levels and return of spontaneous circulation (ROSC) after asphyxial CA. Two human studies also confirmed the higher $ETCO_2$ levels after OHCA due to asphyxial causes compared with dysrhythmic CA and suggested that $ETCO_2$ could be useful in differentiating the cause of CA in the prehospital setting [33,34].

4. Postresuscitation period

Successful CPR attempts and ROSC are the first step toward the goal of complete recovery from CA. The term *postcardiac arrest syndrome* is related to the pathophysiologic process after the whole-body intense ischemia during prolonged CA and the subsequent reperfusion injuries after successful resuscitation [35]. Important factors that affect prognosis include the duration of untreated CA (no-flow phase), the duration and quality of CPR (low-flow phase), the use of vasopressors, and the possible persistent precipitating underlying disease [35]. It is reasonable to assume that the cause of CA, cardiac or asphyxial in origin, may also play a key pathophysiologic role. In particular, organ perfusion with hypoxemic blood during asphyxia prior to complete circulatory collapse may contribute to a different degree of reperfusion injury after ROSC compared with sudden dysrhythmic CA, affecting overall prognosis. Not surprisingly, Hang et al [36] using a swine CA model found worse kidney postresuscitation dysfunction after asphyxial compared with dysrhythmic CA, attributing it to the detrimental effect of prolonged global hypoxia to vital organs, including kidneys, during the prearrest period.

4.1. Differences in brain injury

Postresuscitation brain injury constitutes a leading cause of morbidity and mortality among patients who are successfully resuscitated from CA [35]. Its pathophysiology is only partially understood, but it seems that most of the damage occurs not during ischemia but during reperfusion, although the 2 processes work sequentially. Oxygen free radical–triggered injury cascades lead to lipid perioxidation and DNA/RNA fragmentation; they are exacerbated by reduced cardiac output and local circulatory impairment due to altered blood-brain barrier permeability, complement activation, coagulation factors, and platelet and white blood cell aggregation and adhesion [35]. Mitochondrial damage

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is caused by several additional factors that activate intrinsic and extrinsic pathways leading to programmed cell death (apoptosis).

In general, data from laboratory animal studies agree and suggest that resuscitated normothermic CA due to untreated VF of 3 to 4 minutes duration can lead to complete functional neurologic recovery and that histologic ischemic neuron damage development requires a period of at least 5 minutes of untreated VF [37,38]. On the contrary, in asphyxial CA, it seems that prompt reversal of asphyxiation prior to cardiac standstill results in complete neurologic recovery, whereas after pulselessness permanent brain injury and deficit can develop even after few minutes [38–41].

Although both asphyxial and dysrhythmic CAs lead to brain damage through global ischemia, it seems that significant histopathologic differences exist between the 2 conditions. Both injuries demonstrate selective vulnerability of brain regions, as the hippocampus, the reticular thalamus, the cerebellum, and neocortex [38,40–42]. Characteristic ischemic lesions include shrunken injured neurons, with eosinophilic cytoplasm and pycnotic or absent nuclei [39,43]. It appears that additional scattered brain microinfarcts, relatively more injury to basal ganglia, and more edema are observed after resuscitated asphyxial opposed to dysrhythmic CA [7,39].

Few studies have addressed a direct comparison of asphyxial and dysrhythmic CA with regard to postresuscitation brain damage (Table 1). First, Vaagenes et al [39] in various experiments, after inducing asphyxial and dysrhythmic CA, concluded that asphyxial CA of 7 minutes no-flow duration causes worse morphologic ischemic brain damage than dysrhythmic CA of 10 minutes duration, although there were found no differences in functional neurologic deficit. All experiments included in the study though were not fully concurrently randomized. Moreover, the vasopressor agents use during CPR, based on the study protocol, differed significantly between the 2 groups (double initial dose of adrenaline for the asphyxial CA and the observed PEA, defined by mean arterial pressure <25 mm Hg); unequal durations of untreated CA in the 2 groups were used, explaining the higher ROSC rates (100%) in the asphyxia group with concurrent shorter CPR duration required until ROSC. Previous experiments on analogous animal CA models by the same group of investigators had led to similar findings after asphyxial CA of different durations compared with dysrhythmic CA [43].

Lin et al [44] compared the neurologic deficit and the histopathologic lesions at a later time point after resuscitated CA in a rodent model and also concluded that asphyxial CA appears more injurious morphologically to the brain than dysrhythmic CA. Despite that no-flow duration was equal, time until ROSC was significantly shorter in the asphyxial CA group, which may have accounted for the fact that there were no differences in relevant functional brain damage.

Moreover, animal studies have shown that postresuscitation cerebral perfusion, both after asphyxial or dysrhythmic CA, is characterized by a transient hyperemia; this is probably inadequate though to meet the microcirculation demands of this period, before CBF decreases to subnormal levels and generalized hypoperfusion occurs, in part due to the 'no-reflow' phenomenon [39,45]. Drabek et al [46] tested the hypothesis that CBF reperfusion patterns would differ between resuscitated asphyxial and dysrhythmic CA. The investigators concluded that regional differences exist between the 2 conditions, especially in the early post-ROSC cerebral hyperperfusion, and suggested early cerebral hyperperfusion and delayed hypoperfusion as potential therapeutic targets.

Nevertheless, animal studies have important limitations, such as healthy baseline status and anatomical and functional differences compared with human brain; furthermore, there are differences regarding study design, CPR quality, and nonintervention intervals (untreated CA duration) used [47,48]. However, in a clinical study with OHCA patients, Morimoto et al [49] used brain computer tomography scanning and also reported significantly increased prevalence of brain swelling in comatose patients after successful resuscitated asphyxia compared with dysrhythmic CA. In summary, all available data support the assumption that the ischemic degree and final brain damage are greater and more severe after asphyxial CA than after dysrhythmic CA. Pathophysiologic pathways regarding the complexity of postresuscitation brain injury need to be elucidated in depth, before potential therapeutic targets are identified.

4.2. Differences in postresuscitation myocardial dysfunction

Myocardial dysfunction after resuscitated CA is a well-recognized and described component of the post-CA syndrome [16]. Myocardial "stunning" and cardiogenic hemodynamic instability are major causes of mortality and occur usually within the first hours after ROSC. Although the pathophysiologic picture remains still incomplete, it is thought to mimic ischemia/reperfusion injuries.

In addition to the duration of untreated CA and the duration of the resuscitation efforts, other important factors that contribute to myocardial injury include the underlying myocardial state prior to CA and the delivery of electrical shocks when indicated, which has been associated with worse myocardial function [50,51]. Moreover, the use of vasopressor agents during CPR has also been linked to intensified ischemia and worse postresuscitation myocardial dysfunction [52]. However, compelling evidence suggests that the cause of CA, asphyxial or primary cardiac in origin, plays a key role for the extent of myocardial dysfunction.

Ventricular fibrillation is known to be an energy-consuming arrhythmia [53]. The high oxygen demand of the fibrillating heart after CA of cardiac origin, combined with the ceased coronary flow, creates a severe imbalance after the onset of VF [54]. The decrease in oxygen supply results in a rise of intracellular calcium followed by left ventricular diastolic and systolic dysfunction, a situation often observed in pseudo-PEA. Further depletion of energy stores leads to progressive left ventricular wall thickening and "ischemic contracture." Moreover, Kette et al [55] highlighted the increase in myocardial CO_2 tension that is observed during VF anyway. While the fibrillating myocardium continues to perform work, CO_2 is produced, but not removed, as coronary flow has ceased, resulting in an intramyocardial increase of CO_2 concentration that impairs contractility.

Table 1
Laboratory studies that have addressed a direct comparison of postresuscitation brain injury after asphyxial and dysrhythmic CA

Study	Year	Animal CA model	Non-intervention interval	Results
Vaagenes et al [39,43]	1997	Canine models—various experiments	Unequal durations	More widespread histopathologic brain damage after ACA compared with VFCA. No differences in functional brain damage after 96 h
Lin et al [44]	2013	Rat model	Equal duration (6 min)	More histopathologic lesions after ACA compared with VFCA at 1, 3, and 7 d. No differences in functional neurologic deficit
Drabek et al [46]	2014	Rat model	Equal duration (8 min)	Regional and temporal differences in postresuscitation CBF between ACA and VFCA, measured using ASL-MRI. More pronounced early cerebral hyperperfusion in the cortex and thalamus after ACA

ACA, asphyxial CA; VFCA, ventricular fibrillation–induced CA; ASL-MRI, arterial spin-labeling magnetic resonance imaging.

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The initial anticipation of a less marked energy imbalance in the minimally active myocardium during nonfibrillatory CA, in case of asystole or PEA due to asphyxial causes, was based on laboratory studies [56]. Nevertheless, increasing evidence suggests that asphyxial CA causes myocardial damage by a different mechanism. Asphyxiated myocardium undergoes complex pathophysiologic disturbances that are possibly reflected in cardiac rhythm alternations. In particular, prolonged hypoxia and hypercapnia during the period before cardiac standstill can have deleterious effects on the myocardium. The negative inotropic effect of hypoxia and hypercapnia has been outlined in several laboratory studies [57,58].

First, Vaagenes et al [39] using various canine CA models had assumed, among other findings, that dysrhythmic CA causes relatively more severe postresuscitation myocardial dysfunction than asphyxial CA, although the group's experiments did not focus on myocardial dysfunction per se. Given the fact that postresuscitation myocardial reperfusion injury follows ischemic processes of different degree, after asphyxial or dysrhythmic CA, few experimental studies have attempted a direct comparison of post-ROSC myocardial dysfunction between those 2 conditions (Table 2).

Kamohara et al [56] in a laboratory study concluded that resuscitated asphyxial CA leads to less impairment of myocardial function than dysrhythmic CA. The investigators controlled the duration of untreated CA between both study groups and the number of electrical shocks delivered; they attributed the differences observed to the higher myocardial metabolic demands during VF. Limitations of the study, though, include the animal species used and the short nonintervention interval applied. Although the rodent asphyxial CA model is an established model for evaluating brain injury, rats have hearts with significant differences from human heart [59]. The relatively short duration of untreated CA (4 minutes), combined with short asphyxia duration, considering that asphyxial CA (PEA) was defined by mean aortic pressure less than 30 mm Hg, might also explain the shorter CPR duration until ROSC that was observed in the asphyxia group (on average 77 seconds vs 174 seconds for dysrhythmic CA); consequently, it might be responsible, at least in part, for the differences in myocardial dysfunction observed. The findings are in agreement with the conclusions of Chen et al [60], who used autopsy materials and observed lower atrial and brain natriuretic peptides messenger RNA expressions in ventricular walls after asphyxial than dysrhythmic CA, suggesting differences in myocardial processes during CA with greater acute terminal myocardial impairment after dysrhythmic compared with asphyxial CA.

In contrast to the aforementioned data are the findings of another experimental study by Tsai et al [61]. They reported worse and more diffuse myocardial injuries after asphyxial compared with dysrhythmic CA of equal no-flow and CPR duration. The authors highlighted the mitochondria change from ATP producers to strong ATP consumers that is accomplished due to prolonged hypoxia during asphyxia.

A recent study by Wu et al [62] also provided evidence that asphyxia exerts additional negative effects on myocardial dysfunction after ROSC. The investigators clearly suggested worse postresuscitation cardiac dysfunction after asphyxia compared with dysrhythmic CA and attributed it to the greater degree of global hypoxia and acidosis during asphyxia causing severe metabolism disturbances [26]. Pulseless electrical activity during asphyxial CA was defined by systolic aortic pressure less than 30 mm Hg, but contributing factors to the reported results might have been the CPR duration in the asphyxia group, which was significantly longer than that in the VF group, along with the differences in inotropic agents use between both groups.

Xanthos and Chalkias [63] also mentioned the difference in postresuscitation myocardial dysfunction between asphyxial and dysrhythmic CA, possibly attributed to the effect of prolonged hypoxia that characterizes asphyxia prior to cardiac standstill. They emphasized the potential role of diffuse microcirculation disturbances and enzyme deactivation during asphyxia that can lead to more severe myocardial injury due to inability of the myocardium to use the offered oxygen in the postresuscitation period.

Bringing it all together, differences in study design, in parameters measured, and in nonintervention intervals used make an overall analysis of all performed laboratory studies difficult. It is, however, reasonable to assume that the cause of CA most likely plays a significant role in the subsequent postresuscitation myocardial dysfunction, although it is not clear whether asphyxia or VF causes more damage to the myocardium. Besides, during clinical practice, dysrhythmic CA usually accompanies coronary artery disease and asphyxial CA usually intoxication, trauma, respiratory diseases, or central nervous system diseases. All these complex clinical conditions render a more careful interpretation of laboratory findings when extrapolated into clinical practice. Further well-designed studies are needed to clarify the pathophysiologic mechanisms involved in myocardial dysfunction after resuscitated CA of cardiac or noncardiac origin.

5. Therapeutic considerations

Overall differences that exist between asphyxial and dysrhythmic CA result to a different response to therapy. Treatment implications for each of the 2 entities during resuscitation and after ROSC are summarized in Table 3.

The initial steps in CPR followed A-B-C (airway-breathing-circulation), a noteworthy and easy to recall acronym that highlights the importance of delivering rescue breaths to the CA patient. However, as outlined above, most of adults found in CA do not collapse due to primary respiratory failure and efforts to provide oxygenation without circulation could be considered as loss of valuable moments. This is a significant reason why the sequence A-B-C in basic life support was questioned and finally changed to C-A-B, regarding adult patients with witnessed OHCA or with low likelihood of noncardiac or asphyxial CA, indicating the need to maintain adequate circulation with high-quality chest compressions (CCs) and minimize interruptions [64], Estimation of the cause of the collapse in settings of unwitnessed CA can often be very challenging [65]. However, in the context of simplifying interventions by bystanders in adult OHCA, differential diagnosis was de-emphasized.

Table 2
Summary of experimental studies on animal CA models that have primarily attempted a comparison between asphyxial and dysrhythmic CA with regard to postresuscitation myocardial dysfunction

Study	Year	Animal CA model	Non-intervention interval	Parameters measured	Results
Kamohara et al [56]	2001	Rat model	Equal durations (4 min)	CI, $\pm dP/dT_{40}$, LVEDP	Greater impairment postresuscitation after VFCA compared with ACA
Tsai et al [61]	2012	Rat model	Equal durations (5 min)	Histopathologic findings, mitochondrial swelling rate, complex activities	Diffuse myocardial injury, more severe mitochondrial damage, faster mitochondrial swelling rate after ACA vs regional damages after VFCA
Wu et al [62]	2013	Swine model	Equal durations (8 min)	LVEF by Echo, SPECT, $\pm dP/dT_{max}$, histopathologic findings	More severe postresuscitation myocardial dysfunction after ACA compared with VFCA

ACA, asphyxial CA; VFCA, ventricular fibrillation–induced CA; LVEDP, left ventricular end-diastolic pressure; CI, cardiac index; LVEF, left ventricular ejection fraction; SPECT, single-photon emission computer tomography; Echo, echocardiography; $+dP/dT_{40}$, rate of left ventricular pressure rise at left ventricular pressure of 40 mm Hg; $-dP/dT$, rate of left ventricular pressure decline.

Table 3
Treatment priorities for asphyxial versus dysrhythmic CA during resuscitation and post-ROSC

	Asphyxial CA	Dysrhythmic CA
Resuscitation		
Basic life support	A-B-C Rescue breaths	C-A-B Chest compression–only CPR Early defibrillation
Advanced life support	Standard CPR Early airway management Adequate oxygenation—ventilation efforts	"Cardiocerebral resuscitation"
Post-ROSC		
Controlled reoxygenation	Data lacking—"Permissive hypoxia" or 100% oxygen administration + antioxidants	Oxygen administration based on So_2 target of 94%-98% (in the first hours)
Pharmacologic approach	Different vasopressor response (possibly increased requirements)	
Therapeutic hypothermia	RCT needed	Beneficial

RCT, randomized controlled trials.

"Chest compression–only CPR" and "cardiocerebral resuscitation" are relatively recent terms and approaches introduced and proposed for the treatment for CA patients due to primary cardiac causes, meaning adults with witnessed, unexpected collapse without prior symptoms [66,67]. Their basis is the well-described 3-phase time-sensitive model of CA due to VF and the principles of restoring tissue oxygenation through CC and augmenting the possibilities of successful defibrillation [13]. At the onset of primary VF, pulmonary veins, the left side of the heart, and the entire arterial system are filled with oxygenated blood. Animal studies suggest that acceptable po_2/pco_2 levels can be maintained for several minutes after dysrhythmic CA without rescue breathing. In these circumstances, oxygen delivery is limited more by blood flow rather than oxygen content. Besides, CCs themselves and "gasping" are additional factors contributing to some gas exchange during the arrest period [68]. The 2010 resuscitation guidelines clearly de-emphasize initial ventilation efforts and suggest that CC-only CPR might be preferable than standard CPR during the first minutes in witnessed adult OHCAs or with low likelihood of noncardiac origin [64].

On the contrary, CA patients with high likelihood of asphyxial cause as the mechanism of collapse suffer from significant hypoxemia, making the need for rescue breaths and efforts for correction of the underlying hypoxemia of utmost importance for favorable outcome. The benefits of standard CPR (CC combined with rescue breaths), concerning ROSC rates and neurologic recovery, have clearly been demonstrated in animal asphyxial CA models. Berg et al [68] induced asphyxia in piglets by clamping the tracheal tubes until CA, defined by systolic arterial pressure less than 50 mm Hg. Piglets were randomized to simulated bystander CPR with rescue breaths, CC alone, rescue breaths alone, and no CPR. As expected, ROSC rates and 24-hour survival were clearly superior in the group with CC combined with rescue breaths. Similarly, in another animal study performed by the same investigators, asphyxia continued until complete loss of aortic pulsations and CC with assisted ventilations resulted in superior outcome compared with bystander CC alone [69]. Not surprisingly, clinical evidence by an important and large observational study also supported the benefits of additional rescue breaths during bystander CPR in OHCAs of noncardiac origin [70]. Asphyxial CA is characterized by severe hypoxia and acidosis, depleted pulmonary reservoir, and worse metabolic reserve prior to the resuscitation efforts compared with dysrhythmic CA, necessitating oxygenation and ventilation as critical components of successful CPR.

During advanced life support, concerns regarding reoxygenation of the resuscitated patient in the immediate and late post-ROSC period have raised the question of the ideal arterial blood oxygen saturation (So_2) target. "Controlled reoxygenation" with a So_2 target of 94% to 98% in the first hours after ROSC may not apply for dysrhythmic and asphyxial CA, as these values might be considered as "relative hyperoxia" for the latter. Whether 100% oxygen administration plus antioxidants is superior to oxygen administration based on ideal So_2 or if "permissive hypoxia" is beneficial after resuscitated asphyxial CA, needs to be addressed in future well-designed studies [63].

Furthermore, regarding pharmacologic approach, a different metabolic state has to be expected in adult patients after asphyxial compared with dysrhythmic CA, although, when the latter enters its metabolic phase, metabolism has shifted to anaerobic pathways as well. Differences in metabolic status and endogenous stress hormone levels between asphyxial and dysrhythmic CA possibly reflect different vasopressor vasculature response.

Finally, the beneficial role of therapeutic hypothermia after sudden CA of cardiac origin has been proven [71]. After asphyxial CA, it is thought to be more controversial, although compelling clinical evidence suggests neuroprotective actions of hypothermia in hypoxic-ischemic encephalopathy [21]. These neuroprotective properties have been highlighted in several animal studies, by modulating some of the key biochemical and metabolic pathways in brain that occur during asphyxia, no-flow state, and reperfusion [72]. However, it is still questionable whether therapeutic hypothermia should be implemented routinely after asphyxial CA before the results of high-quality randomized controlled trials.

6. Conclusions

As outlined in this review, asphyxia-induced CA differs significantly from primary CA of cardiac origin with regard to pathophysiologic mechanisms, neuropathologic damage, postresuscitation organ dysfunction, and response to therapy. Advances in our understanding of CA and organ injury require high-quality basic research and clinical trials, possibly on a multicenter basis due to infrequent occurrence of asphyxial CA. Better illustration of pathophysiologic mechanisms involved in the process of ischemic and postischemic injury will eventually allow the opportunity for developing new and individualized resuscitation therapies. "One size does not fit all" and it seems that asphyxial CA must be considered and treated in a different way from primary dysrhythmic CA.

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