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EDITORIAL

Oxygen and carbon dioxide targets during and after resuscitation of cardiac arrest patients

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Introduction

The goal of cardiopulmonary resuscitation (CPR) may be summarized as an effort to rapidly restore spontaneous circulation and to prevent hypoxic ischaemic brain injury (HIBI) [1]. The key determinant of tissue oxygenation during CPR is high quality chest compressions [2]. With ventilation the aim is to increase oxygen content of arterial blood whilst decreasing arterial carbon dioxide ($paCO_2$), alleviating respiratory acidosis. On the other hand, reactive oxygen species play an important part in the development of HIBI, thus avoiding extreme hyperoxia seems intuitive [3]. The relationship between arterial and tissue oxygenation and ventilation during CPR is complex. Conclusive evidence of optimal oxygen or carbon dioxide targets are scarce, but taking into account the pathophysiological changes may guide clinical practice (Fig. 1). In the current commentary we discuss what is known about the optimal oxygen and carbon dioxide targets during and immediately after cardiac arrest (CA) and how we may achieve them.

Changes in oxygen and carbon dioxide in cardiac arrest

Cardiac arrest causes an abrupt cessation in the delivery of oxygen, and while many organs may survive hours with ischemia, the brain´s survival is measured in minutes. With high metabolic rates and limited energy stores, the heart and brain deplete their tissue oxygen within seconds [4], and glucose and glycogen reserves within minutes [5]. There are limited observations of blood and tissue oxygenation and carbon dioxide levels during untreated CA in humans, but these levels are likely influenced by the pre-arrest factors that determine oxygen supply and demand. An asphyxial arrest is expected to cause lower tissue oxygenation and hypercapnia compared to an arrest from a sudden arrhythmia, as tissue metabolism has continued with decreasing oxygen supply. Conversely, conditions with decreased oxygen demand, i.e. hypothermia, will likely yield higher initial tissue oxygenation and lower carbon dioxide compared to a normothermic arrest.

In the first minutes after CA patients may have abnormal brainstem mediated breathing, commonly referred to as "agonal breathing". Prospective studies have reported agonal breathing in about a third of witnessed out-of-hospital cardiac arrests (OHCA), and found it to be associated with improved survival [6]. This phenomenon has also been observed in animal experimental studies, where this agonal respiration has been shown to produce both forward blood flow and ventilation [7]. Although the effectiveness of agonal breathing is uncertain, consistent observations that gasping patients have better outcomes suggest positive effects on circulation and/or gas exchange during CA.

Oxygen and carbon dioxide during cardiopulmonary resuscitation

Two elegant studies by Spindelboeck and colleagues investigated oxygen and carbon dioxide levels in arterial blood during CPR in patients ventilated with 100% oxygen, describing different oxygen levels ranging from hypoxia to hyperoxia [8, 9]. The study showed that patients with hypoxia had lower survival than those

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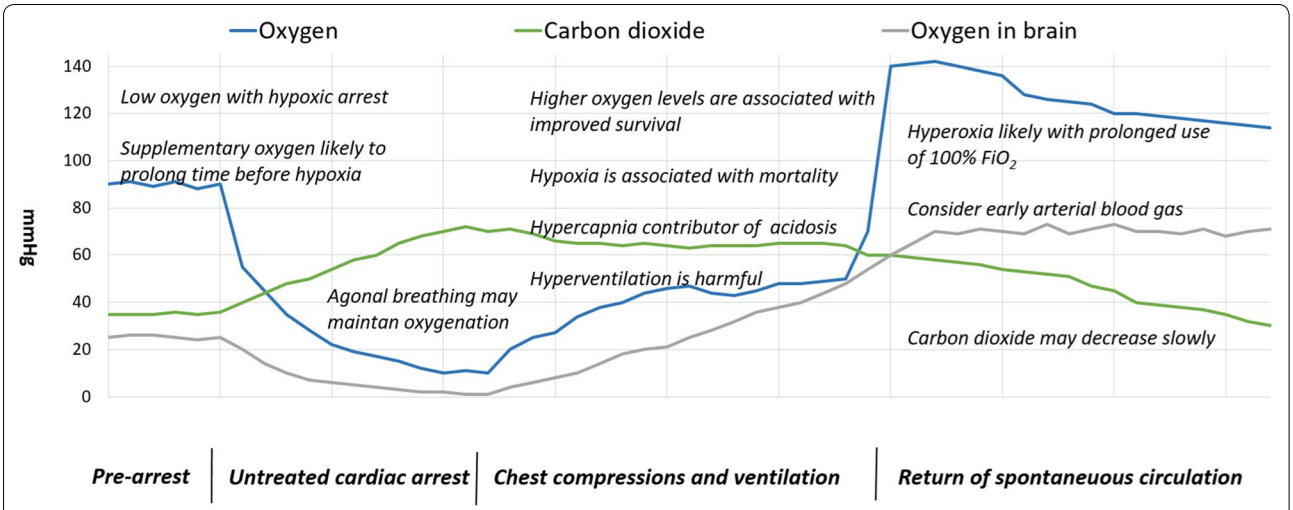

Fig. 1 An approximate depiction of changes in oxygen and carbon dioxide in the arterial blood as well as oxygen in brain tissue before with management aspects, during and immediately after cardiac arrest

with normoxia or hyperoxia, but they could not find any association between oxygenation and bystander CPR or delay from collapse to CPR. Neither did they show any link between extreme intra-arrest hyperoxia and worse outcomes. Animal data, on the other hand, suggest that ventilation with 50% oxygen may be enough to correct hypoxia and result in similar levels of brain tissue oxygen compared to 100% oxygen [10]. Theoretically, such a practice could decrease the rate of extreme hyperoxia and should be studied further. One problem is the lack of means to monitor intra-arrest oxygenation, since obtaining an arterial blood gas (ABG) reading appears feasible only in the intensive care unit (ICU) and in some selected pre-hospital systems. It may also be argued that venous samples could be more reflective of tissue oxygenation than arterial samples. Recent studies have addressed intra-arrest brain oxygenation monitoring with near infrared spectroscopy (NIRS). Thus far, the evidence does not suggest any role for NIRS for tailoring oxygen use during CPR.

The studies by Spindelboek also showed that most patients are hypercapnic during CPR and have severe respiratory acidosis [8, 9]. They did not, however, find any association between the severity of hypercapnia or acidosis with outcome. Severe acidosis causes negative inotropy and vasodilatation which intuitively appears harmful. Ventilation with higher minute volumes can decrease $paCO_2$ quicker and normalize pH but this has inadvertent effects. An important study by Aufderheide and colleagues showed that hyperventilation during CPR increases intra-thoracic pressure, decrease coronary perfusion pressure and worsens outcome [11]. By decreasing the frequency of ventilations, cardiac output and pulmonary blood flow may be increased without compromise of arterial oxygen content or acid–base balance [12]. Thus, the recommendation to ventilate cardiac arrest patients with 100% oxygen with a ventilation rate of 12 and tidal volume of 500 ml appears justified, and in many OHCA cases this will correct the hypoxia; the effect on $paCO_2$ appears variable.

Oxygen and carbon dioxide targets immediately after ROSC

A sharp increase in mean arterial blood pressure immediately after ROSC after CA has been commonly reported. This will also increase oxygen levels in brain tissue. The goal at this stage is to monitor oxygenation and to target normoxia [13]. In the majority of patients, the percentage of inspired oxygen (FiO_2) can be decreased. Prolonged ventilation with a FiO_2 of 100% is a common cause of extreme hyperoxia [14]. Even though conclusive evidence does not exist, there is little reason not to avoid extreme hyperoxia at this stage. In the only randomized study conducted to date, Kuisma and colleagues showed an increase in neuron specific enolase (biomarker of brain injury) in one subset of patients ventilated with 100% compared to 30% [15]. Monitoring oxygenation is difficult in the pre-hospital setting, though a small pilot trial using peripheral oxygen saturation to titrate oxygen found this strategy resulted in frequent hypoxia [16]. Thus, there is a need for obtaining an arterial blood gas reading as soon as possible.

In most cases, $paCO_2$ is elevated after ROSC. This will correct itself over the first hour and there is little need to speed up this process; some clinical data even suggest associations between moderate hypercapnia and

improved outcome [17]. Indeed $paCO_2$ is an important regulator of cerebral blood flow and moderate hypercapnia can, according to experimental studies and one clinical pilot study, increase cerebral oxygenation and attenuate ischaemia-reperfusion injury due to mitigation of oxidative stress [18, 19]. Animal data also suggest antiepileptic effects with moderate hypercapnia and potential reduction in the excitotoxicity induced by high levels of excitatory neurotransmitters such as the amino acid glutamate [20]. Two ongoing large RCTs, one on oxygen use during tranportation of OHCA patients (the EXACT trial, NCT3138005) and one on targeting mild hypercapnia during the first 24 h of ICU care (the TAME trial, NCT3114033) are ongoing and are likely to provide more conclusive evidence. Until conclusive clinical data are made available, the current recommendation is to aim for normoventilation with a paO_2 of 4.5–6.0 kPa [13].

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Compliance with ethical standards

Conflicts of interest
Markus Skrifvars has received a lecture fee from Covidien (Invos).

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