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The Role of Oxygen in Cardiac Arrest Resuscitation

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ABSTRACT

The heart is incapable of storing significant oxygen or substrates and thus is entirely dependent on a continuous delivery of flow in order to support its high metabolic state. Following cardiac arrest, myocardial tissue oxygen tension falls rapidly and aerobic production of ATP ceases. Without re-oxygenation of the ischemic myocardium, return of spontaneous circulation (ROSC) cannot be achieved. The oxygen paradox which has been described regarding other ischemia-reperfusion conditions seems to have application in cardiac arrest. It is clear that some level of oxygenation is necessary to achieve ROSC, however post ROSC there appears to be increased toxicity associated with hyperoxia. The optimal conditions for re-oxygenation in the setting of cardiac arrest remain ill defined at present.

Keywords: cardiac arrest, oxygen, myocard, oxygen delivery, Adenosine-5'-triphosphate (ATP), mitochondria, measurement of tissue oxygen, oxygen paradox

Introduction

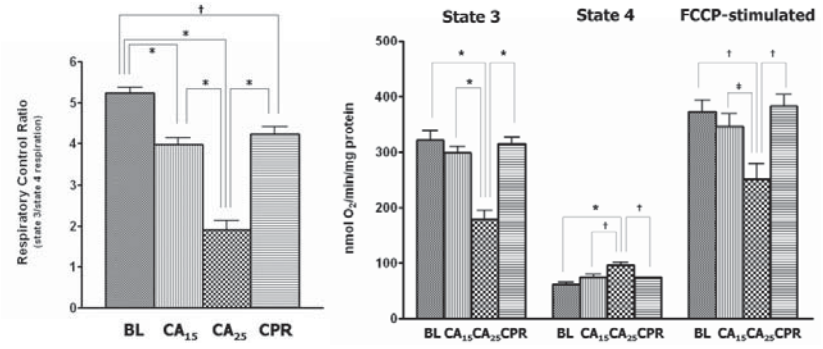
At the onset of cardiac arrest all perfusion ceases and consequently oxygen delivery is terminated. For many organs and tissues, oxygen stores and metabolic requirements allow survival to be measured in hours. For the heart and the brain however, survival without ongoing oxygen delivery is measured only in minutes, due to the high metabolic rate and the absence of significant stores of oxygen and substrate.

CPR Oxygen requirement for resuscitation

To achieve restoration of spontaneous circulation (ROSC) following cardiac arrest, re-oxygenation of the myocardium is necessary. Following relatively short periods of ventricular fibrillation (VF), defibrillation alone may be sufficient to restore cardiac contractility anallow reperfusion of the myocardium. However, the incidence of ventricular fibrillation as the initial rhythm during out-of-hospital cardiac arrest is decreasing, while asystole and pulseless electrical aciticity (PEA), rhythms for which cardioversion is ineffective and which require initial re-oxygenation dependent on chest compression generated blood flow are increasing in number. (1,2) If flow generated by chest compressions is low, the likelihood of successful resuscitation diminishes rapidly with time. The exact myocardial oxygen requirement for initial restoration of spontaneous circulation is not known and is likely dynamic dependent upon a number of factors associated with cardiac arrest including; duration of ischemia, temperature, pre-arrest coronary artery occlusion, and preceding anoxia. Recent animal work highlights the importance of oxygen delivery to the myocardium independent of flow. In a rat KCl (pottassium chloride) cardiac arrest model, after 8 minutes of arrest, cardiopulmonary resuscitation (CPR) was initiated with ventilation of either 100% O_2, 21% O_2 or 0% O_2 (100% N_2) for the first 3 minutes and then all animals received 100% O_2. Only 10% of the N_2 ventilated animals achieved ROSC, compared with 80% in the other two groups. Despite similar CPR generated flow as determined by similar perfusion pressure, the absence of ventilation with oxygen for 3 minutes during CPR precluded successful ROSC. (3) In contrast CPR coupled with room air or higher oxygen levels resulted in a high rate of ROSC. In the absence of intrinsic cardiac output, perfusion is dependent on extra-cardiac support which for most out-of-hospital cardiac arrest consists of CPR. CPR generated myocardial oxygen delivery is primarily constrained by two factors: 1) flow of < 20% of normal and 2) a lower oxygen content level due to the de-oxygenated state of the hemoglobin. The resultant low flow state leads to continued loss of the bioenergetic state, anaerobic metabolism and accumulation of metabolic by-products which eventually shut off what little metabolism exists. With the onset of cardiac arrest, there is a dramatic and rapid loss of high energy phosphates within the heart. Using Phosphorus-31 NMR nuclear magnetic resonance (^{31}P NMR), in a large animal (swine) VF arrest model, we note the immediate loss of creatine phosphate and the more gradual loss of cellular Adenosine-5'-triphosphate (ATP). With

full reperfusion, creatine phosphate is rapidly regenerated, often with a baseline overshoot, however repletion of ATP is a much slower process requiring hours to days. Using closed chest cardiopulmonary bypass to determine the minimum flow necessary to preserve myocardial cellular ATP stores, we noted that 60% of normal flow to the heart provided immediately at the onset of VF cardiac arrest was insufficient to maintain myocardial ATP levels in the normal range. This loss of ATP was not homogeneous within the heart and was noted primarily in the epicardium with sparing of the endocardium. In a separate set of experiments, perfusion of the in vivo fibrillating heart with 70% normal flow was capable of maintaining a normal creatine phosphate:adenotriphosphate ratio (CP/ATP) ratios within both the endocardium and epicardium. (4) These data emphasize the high relative flow (and thus oxygen delivery) required by the heart for preservation of myocardial high energy phosphates and highlights the limitations for sustaining the bioenergetic state of the myocardium over time, even with good quality CPR.

Within the myocardium, the primary site of oxygen utilization and energy production is the mitochondria. Cardiomyoctyes differ from myocytes of skeletal muscle in their relatively large density of mitochondria. Mitochondria are thought to be progressively damaged with ongoing ischemia and may be further injured with reperfusion. (5) However, very little is known about heart mitochondrial function during CPR. We have recently demonstrated a benefit of CPR at the mitochondrial level. Following cardiac arrest of 15 minutes in the rat, heart mitochondria were harvested and respiratory function determined and compared to mitochondria harvested after 25 min of cardiac arrest or 15 min of cardiac arrest plus 10 minutes of CPR. CPR was noted to preserve mitochondrial respiratory function and prevent the further decline in mitochondrial function seen after 25 minutes of cardiac arrest (figure 1). (6) Of note, despite the limitations of CPR, this work does demonstrate for the first time a limited CPR benefit at the subcellular level.



BL, basic level; CA, cardiac arrest; CA_{15}, cardiac arrest of 15 min; CA_{25}, cardiac arrest of 25 min; FCCB, carbonyl cyanide p-(tri-fluromethoxy)phenyl-hydrazone; RCR, respiratory control ratios.

Figure 1. Respiratory control ratio (ratio of state 3 and state 4 respiration) are shown at baseline, after CA of 15 min (CA15), after CA of 25 min (CA25) and after CA of 15 min + 10 min of CPR. The CA25 group had the lowest RCR while the CPR group, not different from the CA15 group, had a higher RCR than the CA25. FCCP was used to measure mitochondrial respiration under conditions of uncoupling and was preserved in the CPR group compared with CA25 group. Yeh ST, Lee HL, Aune SE, Chen CL, Chen YR, Angelos MG. Perseveration of mitochondrial function with cardiopulmonry resuscitation in prolonged cardiac arrest in rats. J Mol Cell Cardiol 2009;47:789-97.

Measurement of Tissue Oxygen and Best approximation of oxygen requirement

Measurement of oxygenation under in vivo conditions has significantly limitations. With normal perfusion, peripheral pulse oximetry is frequently used as an overall guide to total body oxygenation. However under cardiac arrest conditions, this technique fails due to the disassociation of peripheral (extremity) oxygenation from core tissue oxygenation. Likewise, arterial blood gases are frequently used to gauge tissue oxygenation during cardiac arrest, but these also poorly reflect the state of oxygenation. Arterial blood gases measure oxygen levels in the arterial blood but are far removed from the actual site of oxygen utilization, the mitochondria. In the body, oxygen moves down a steep gradient from the lungs to the mitochondria, with oxygen tension typically in the range of 150 torr in the lungs to 2-5 torr in the mitochondria. As the upstream gradient decreases, oxygen delivery to the mitochondria diminishes and ultimately stops. During cardiac arrest, arterial blood gases provide an even less precise gauge of tissue oxygenation and primarily reflect oxygen tension of the static blood located in the large arteries which have relatively small metabolic requirements relative to the ischemic capillary beds. Measurement of tissue Partial Pressure of Oxygen (PO_2) gives a much closer approximation of cellular and mitochondrial PO_2. Currently, there are experimental methods to measure tissue PO_2 which can be used in vivo or ex vivo in pre-clinical models. One such method is electron paramagnetic resonance (EPR) oximetry, in which tissue oxygen tension can be measured continuously using oxygen sensitive spin probes implanted in the heart with spectral properties which can be measured using EPR spectroscopy. (7-9) The EPR probe yields a sharp straight line, the width of which is highly sensitive to oxygen tension. A continuous EPR signal is obtained and the peak-to-peak width of the EPR spectrum is used to calculate PO_2 using a standard calibration curve.

These methods provide experimental tools to better approximate re-oxygenation conditions in the ischemic and reperfused heart.

Oxygen Paradox

Although it is clear that restoration of oxygen is necessary for cardiac resuscitation, the re-introduction of oxygen itself causes injury. This has been termed the oxygen paradox and suggests that to optimize re-oxygenation of the ischemic tissue, initial oxygen delivery must be controlled. Indeed a number of animal and isolated heart ischemia-reperfusion studies suggest that initial control of oxygen delivery via either controlled flow or controlled oxygenation can improve recovery of cardiac function. (10-12) In these pre-clinical studies, strategies have included using a gradual increase in the perfusion rate and intracoronary pressure over the first few minutes of reperfusion, which has been associated with a reduction in myocardial necrosis and tissue edema. In the setting of cardiac arrest resuscitation, controlled re-oxygenation is much more difficult. As opposed to reperfusion from regional cardiac ischemia, reperfusion and re-oxygenation in cardiac arrest occurs in two stages. In the first stage, initial re-oxygenation is driven by the low flow generated by chest compressions and CPR. This is followed by increased myocardial reperfusion flow if ROSC is achieved. It is with full reperfusion, immediately after ROSC, that controlled re-oxygenation may be possible and may improve outcome. There is good pre-clinical, and now some clinical data, in support of early controlled oxygenation to improve outcome following resuscitation from cardiac arrest. It has long been assumed that hyper-oxygenation increases reactive oxygen species (ROS) formation. Support for this concept is found in work using cultured cardiac fibroblasts. Cells cultured in a high O_2 environment (hyperoxia) had higher levels of reactive oxygen species production than cells cultured in mild hypoxia. (13) The brain seems to be particularly sensitive to hyperoxia. A series of studies utilizing a ventricular fibrillation, open-chest dog CPR model have demonstrated that hyperoxia during the first hour after ROSC impairs cerebral aerobic energy metabolism and causes more neuronal damage in the hippocampal CA1 region. (14,15) In the same cardiac arrest model, controlled post-ROSC oxygenation using a pulse oximeter to control O_2 saturation to 94-96% resulted in improved neurologic outcome compared with ventilation using 100% O_2. (16) In a recent clinical review, 6326 post cardiac arrest ICU patients were divided into 3 cohorts; hyperoxia defined as partial arterial pressure of O_2 (PaO_2) > 300 mm Hg (18%), hypoxia defined as a PaO_2 < 60 mm Hg (63%) and normoxia (63%) based on at least one arterial blood gas obtained within 24 hours of arrival to the intensive care unit (ICU). The hyperoxia group had significantly higher hospital mortality compared with the normoxia and the hypoxia groups (figure 2). (17) These clinical data add more evidence in support of controlled re-oxygenation. To date the role of post-ROSC hyperoxia on other organ function, including the heart is less defined than the central nervous system (CNS) effects.

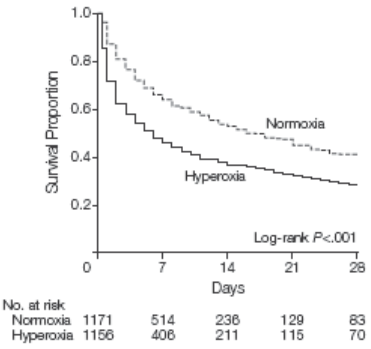


Figure 2. In-hospital death between hyperoxia and normoxia (Referens 17.).

SUMMARY

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