

Stroke, Oxygen and Prehospital Care: A Commentary on Current Treatments and Opportunities for Improvement

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Introduction

Stroke is a common and very serious illness where timely evaluation and intervention can have dramatic effects on patient outcomes. Approximately 795,000 patients will experience a stroke each year [1]. The great majority of these strokes will be ischemic (87%) but a considerable portion will also be hemorrhagic strokes seen as intracerebral hemorrhage (10%) and subarachnoid hemorrhage (3%) [1]. Encouragingly, stroke mortality has been decreasing and stroke is now the fifth leading cause of mortality in the United States [1]. Part of the declining mortality of stroke has been attributed to stroke systems of care [2]. Emergency Medical Service (EMS) plays an important role in the transport of acute stroke patients to the closest, most appropriate stroke center to initiate evaluation and treatment as rapidly as possible [3]. In addition to transport, some treatments initiated by EMS can impact acute stroke patients' care in the emergency department and inpatient units and may impact their overall outcome.

Oxygen is one such treatment [4]. Nearly ubiquitous and easily applied, oxygen is commonly used by EMS providers of all levels of training, but its effect is highly complex. Since stroke impairs oxygen delivery to affected brain tissue, providing excess oxygen as a treatment is attractive intuitively [5]. In fact, hypoxia, defined as oxygen saturation <94% as has been shown to be harmful to acute stroke patients [6]. Yet the role of excess oxygen or hyperoxia, defined as supplemental oxygen applied to patients with normal oxygen saturation, is more controversial, possibly offering benefit and harm. Conflicting evidence indicates oxygen treatment may offer benefit if given early in acute

ischemic stroke, but excess oxygen may also cause harm [5,7-9]. Hyperoxia is thought to cause harm via neuronal injury through vasoconstriction, and free-radical formation causing apoptosis, and hypoperfusion [9,10]. The frequency of hyperoxia associated with treatment by EMS providers in acute stroke care may be underappreciated, and its etiology is understudied.

Examining oxygen therapy in stroke and cardiac arrest clarifies the role of oxygen as a neuroprotective therapy. Coupling this understanding with a review of the current structure and resources of EMS and EMS' uses of oxygen in acute stroke patients offers insights into future studies and routes to optimize prehospital stroke care.

The Inadequacies of Modern Acute Ischemic Stroke Therapies and the Concept of Neuroprotection

Emergent intracranial large vessel occlusion causes brain tissue to be hypoperfused, which may rapidly progress to irreversible ischemic injury without timely reperfusion, based on the well-validated penumbra model [11]. In the penumbral model, irreversibly damaged ischemic core is surrounded by the ischemic penumbra, which is defined as the severely hypoperfused, physiologically stunted but still potentially viable brain tissue. Penumbral model of ischemia has been investigated extensively in the animal model of middle cerebral artery occlusion and human PET studies. Modern endovascular therapies are highly effective in achieving that reperfusion, improving clinical outcomes in nearly half the patients. The benefits of acute stroke therapies such as intravenous thrombolysis and

mechanical thrombectomy, however, are time-dependent and wane beyond 4.5 hours from stroke onset for the former and approximately 7 hours for the latter, despite the expanded 24-hour consideration window [12-14]. Limited access to endovascular therapies in the United States, wherein an estimated half of the population resides outside the critical “golden” hour’s distance from an endovascular-capable hospital, presents an additional challenge [15].

Approaches that preserve the at-risk penumbral tissue, increasing the therapeutic window and enhancing the beneficial effects of reperfusion, are consequently essential. Mechanistically, these therapies either improve oxygen delivery to the penumbra by increasing oxygen transport or reduce the brain tissue’s oxygen demand [16]. Nonpharmacological interventions that could be easily and safely administered in the prehospital setting – oxygen, for example – are especially valuable. Saver et al. demonstrated the feasibility of such a strategy, in which neuroprotective therapy was delivered in the field within 45 minutes after stroke symptom onset [17]. Unfortunately, neuroprotection as a monotherapy in the treatment of acute ischemic stroke has a long and disappointing history, and direction of research has now shifted to specifically consider neuroprotection as an adjuvant to reperfusion, potentially extending the time window for intervention or reducing consequences of reperfusion injury [18].

Oxygen as a Neuroprotectant

One such attractive neuroprotectant under investigation is oxygen. Common in the early period after acute ischemic stroke, hypoxia is associated with increased risk of deterioration, greater mortality, and decreased functional independence [19,20]. Outcomes improve with continuous monitoring, and adverse consequences decrease when the desaturations of less than 90% are identified and aggressively treated [21,22]. The use of supplemental oxygen has been proposed to prevent hypoxia and secondary brain injury, considering its safety, wide availability, and permeability through the blood brain barrier [23,24].

Oxygen can be administered through a face mask or a nasal canula at normal atmospheric pressure – the so-called normobaric oxygen therapy (NBO) – which is more accessible than hyperbaric oxygen therapy (HBO) that delivers 100% oxygen at environmental pressures exceeding one atmosphere. HBO requires a specialized airtight chamber and is likely not feasible in the acute setting [25]. Its practicality has established NBO as a well-studied nonpharmacological approach of preserving the penumbra in animal studies. In the transient middle cerebral artery occlusion rodent model of ischemia, NBO

more than doubled penumbral oxygen and arrested infarct growth when administered early, reducing the final infarct volume. The “time is brain” mantra additionally held true, as the benefit of oxygenation dissipated when middle cerebral artery occlusion lasted beyond 180 minutes, highlighting the importance of treatment timing. Equally important is the safety aspect, and oxygen had no obvious detrimental side effects in combination with tissue plasminogen activator (tPA) [26,27]. Despite the promising animal data, the benefits did not successfully translate to human subjects [28].

Normobaric Supplemental Oxygen

Stroke Oxygen Study (SO2S) was the largest study of acute oxygen supplementation [29]. In this single-blind randomized multicenter United Kingdom-based trial conducted from 2008 to 2015, 8003 adults with acute stroke were randomized within 24 hours of hospital admission to receive 72 hours of low-dose oxygen (2 to 3 liters/minute depending on baseline O₂ saturation of greater than or less than or equal to 93%). Oxygen was supplemented via nasal cannula nocturnally, continuously, or as a treatment of hypoxia. Nocturnal supplementation was hypothesized to be beneficial owing to the more frequent occurrence of hypoxia at night, while preserving the patients’ daytime mobility. Efforts were made to monitor compliance, and oxygen saturations in the treated groups were significantly higher than in the control group. Unfortunately, among non-hypoxic patients with acute stroke, routine prophylactic use of low-dose oxygen supplementation – whether continuous or nocturnal – did not reduce death or disability at 3 months. Subgroup analysis also failed to yield positive results even in groups for which benefit was most anticipated, such as patients enrolled early (within 3 to 6 hours after stroke onset), those with lower baseline oxygen saturation, severe strokes, or a history of heart failure or lung disease.

While the authors concluded that their findings did not support low-dose oxygen supplementation for acute ischemic or hemorrhagic stroke patients, a closer examination of patient selection may help contextualize the observed results. This pragmatic study included patients with a clinical diagnosis of acute stroke, and nearly one fifth enrolled participants were diagnosed with intracerebral hemorrhage or lacked imaging confirmation of ischemia. Patients had mild strokes with a median National Institutes of Health Stroke Scale score of 5 (interquartile range of 3 to 9) and were randomized late with a median time of over 20 hours from stroke onset. Only 15 to 17% of this patient population received thrombolysis, and recanalization status was uncertain. Despite what essentially could be considered conservative management, over 50% of the enrolled patients achieved independence

by 90 days, likely obscuring any potential positive effects of oxygen therapy. Nevertheless, the 2019 American Heart Association/American Stroke Association guidelines for the management of patients with acute ischemic stroke echoed the authors conclusions, recommending supplemental oxygen use only in hypoxic patients to maintain oxygen saturation above 94% [28].

Hyperoxia may be associated with increased mortality, and recent prospective and retrospective observational studies highlighted a concerning trend, especially in the ventilated critically ill patients with severe strokes. The Stroke Oxygen Study, on the other hand, showed no evidence of increased stress levels (higher heart rates, blood pressures, and the need for sedation) or higher rates of infections (higher temperatures or the need for antibiotic therapies), albeit in a patient population with lower illness acuity [5,30].

To address a major concern with prior neuroprotectant research, Penumbral Rescue by Normobaric Oxygen Administration in Patients With Ischaemic Stroke and Target Mismatch Profile (PROOF) randomized controlled trial was launched in 2017 in the European Union. This international multicenter randomized phase II proof-of-concept trial adopts insights from preclinical research and specifies NBO as a rapidly administered adjuvant to reperfusion therapy in a patient population with emergent large vessel occlusions. The active intervention was 100% oxygen at high flow (≥ 40 L/min) inhaled via a sealed non-rebreather face-mask or via endotracheal tube (where clinically required). The oxygen was rapidly administered within 20 minutes after baseline brain imaging and within 3 hours of stroke symptom onset. To avoid respiratory adverse effects, supplementation was continued until the completion of endovascular intervention but no longer than four hours. The control group was treated with guideline-specified oxygen supplementation of 2-4 L/min, as needed, to maintain $SpO_2 > 94\%$. The primary outcome is ischemic core growth within the initial 24 hours after stroke onset. Secondary outcomes include familiar acute stroke trial measures, such as early neurological deterioration as well as 90-day survival and disability. Estimated study completion is June 2021 [31,32].

Optimal duration and route of administration of normobaric oxygen remain undetermined. Mask-administered normobaric oxygen may be a more suitable option for stroke patients, as cohorts oxygenated via mask who derived benefits from oxygenation were more frequent than cohorts receiving oxygen via nasal cannula, according to a recent meta-analysis involving 11 randomized controlled trials [24]. Although animal studies addressed the timing and duration of oxygenation, no reasonable conclusions can yet be drawn for human subjects, given the variability and scarcity of evidence [33-35].

Guidelines for Emergent Oxygen Treatment in Acute Stroke

The 2018 guidelines from the American Heart Association and American Stroke Association make three recommendations regarding emergent oxygen therapy in acute stroke patients and reflect the important balance between hypoxia and hyperoxia [36]. Regarding emergency oxygen therapy, the first recommendation is to offer airway and ventilatory support for acute stroke patients with altered mental status or bulbar dysfunction that compromises their airway. The second recommendation is to provide supplemental oxygen to maintain oxygen saturation above 94%. Finally, the third recommendation is that supplemental oxygen is not recommended in “non-hypoxic” patients.

Hyperoxia During EMS Transport

While national guidelines should help to standardize prehospital oxygen therapy in stroke, it seems a considerable portion of acute stroke patients transported by EMS are subject to hyperoxia [37]. In a single center retrospective analysis of adult stroke patients over four years, Dylla et al. found that 26% of patients received oxygen despite normal oxygen saturations (hyperoxia) [38]. Interestingly, patients treated with oxygen appeared to have more severe disease with higher National Institute of Health Stroke Scale (NIHSS) scores and lower Glasgow coma scores (GCS). While patients treated with oxygen had higher respiratory complications, neurologic outcomes (modified Rankin Scale and ambulatory status) were similar between hyperoxia, hypoxia and no oxygen patient groups. Analyzing the same data examining hyperoxia's effect on blood pressure, Dylla et al. found a five percent decrease in MAP in acute stroke patients treated with hyperoxia pre-hospital, but still no change in neurologic outcomes [39]. In another single center retrospective analysis, Chan et al. examined oxygen delivery prehospital and in the emergency department (ED) in acute stroke patients over a five-year period and examined which patients had adverse events. The investigators did not look at hyperoxia specifically but found 98% of patients received high flow oxygen with EMS and as a result they could not examine level of oxygen treatment prehospital and instead only examined oxygen levels in the ED. Subjects were divided into no oxygen (38%), low (47%), and high-flow (15%) oxygen and subjects were examined for any adverse events. The frequency of adverse events was lower in the high-flow oxygen group. Adverse events and oxygen treatment were found to be associated with diagnoses of intracerebral hemorrhage, encephalopathy, and seizure but not with amount of oxygen delivered [40]. Thus, neither Dylla et al. nor Chan et al. found oxygen treatment to be associated with neurologic harm and both found disease severity and final diagnosis to be drivers of oxygen treatment. These

data would suggest that sicker patients tend to be treated with oxygen despite normal oxygen saturations. However, the rationale for EMS administering hyperoxia is often not known.

Structure of EMS and Guidelines for Oxygen Treatment in Stroke

An additional factor resulting in EMS hyperoxia in acute stroke patients may be the complexity and diversity of guidelines regarding oxygen treatment. While evidenced based national guidelines exist to optimize emergency oxygen therapy in acute stroke patients, unfortunately, some recommendations can inadvertently result in hyperoxia. For example, the American Heart Association and American Stroke Association's three recommendations regarding oxygen therapy in acute stroke patients offer a glimpse into the complexity of acute stroke patients' needs [36]. The first and second recommendations both recommend giving oxygen (for altered mental status and if oxygen saturation < 94%). But, the third recommendation is to avoid oxygen in "non-hypoxic" patients. Taking all three of these recommendations together, it's possible to understand the goal is to avoid both hypoxia and hyperoxia in caring for acute stroke patients. However, if a provider considers only the first and second recommendations from the American Heart Association and American Stroke Association then providers could be misled in providing hyperoxia and still believe they are following the established recommendations.

Additionally, the first recommendation addressing altered mental status in the acute stroke patient pertains to an especially difficult clinical scenario for the EMS provider. Altered mental status can be a presenting sign of many illnesses other than stroke – substance abuse, hypoglycemia, even hypoxia itself [41]. So, in a patient with altered mental status the EMS provider will initiate treatment without knowing the diagnosis, often starting with applying oxygen, then checking the blood sugar and physical exam findings to determine the etiology of the patient's altered mental status. So, the EMS provider will sometimes have treated a patient with oxygen for several minutes or longer before determining the diagnosis of stroke. Regardless, by initiating supplemental oxygen the EMS provider could equate their care with supporting the patient's airway in adherence to the American Heart Association and American Stroke Association recommendation and be clinically appropriate but at the same time cause hyperoxia.

The National Association of State EMS Officials (NASEMSO) also provide national guidelines for oxygen therapy in acute stroke patients for EMS providers that are more succinct than the 2018 American Heart Association and American Stroke Association Guidelines [42]. In their

protocol for "Suspected Stroke/Transient Ischemic Attack" NASEMSO recommends EMS providers "administer oxygen as appropriate with a target of achieving 94-98% saturation." While these recommendations are more specific and should protect against hyperoxia, EMS providers are still faced with two different national guidelines that are both evidence-based yet offer different guidance.

In addition to multiple national guidelines regarding oxygen therapy, there is further complexity and diversity from the fragmented system of prehospital care. The prehospital environment overlaps between health care, public health and public safety [43]. As a result, EMS providers are ultimately guided by their local protocols which can vary widely rather than national guidelines [4]. For example, comparing oxygen treatment guidelines in acute stroke patients for EMS providers from the state with the lowest stroke mortality based on 2018 data (New York (USA)) and highest stroke mortality (Mississippi (USA)) is revealing [44]. Mississippi (USA) uses the NASEMSO Guidelines [42], recommending oxygen titrated to 94-98%. New York (USA) Statewide BLS Adult and Pediatric Treatment Protocols make no explicit mention of oxygen therapy under the Stroke section of their guidelines but, under a separate section titled, "Oxygen" under "Key Points and Considerations", there is an advisory: "Oxygen should be titrated to maintain saturation at or just above 94% and/or to treat signs of dyspnea. If there is a situation in which the patient may be unstable and hypoxia might be missed (such as major trauma), it is acceptable to place the patient on high flow oxygen" [45].

Beyond state-to-state variation in practice guidelines, there is considerable variation by region even within individual states. For example, in California (USA) there are 33 different EMS agencies each with a variation in clinical practice guidelines [4]. EMS protocols also vary to account for levels of training, skills and available treatment resources. Protocols are different between highly trained advanced life support (ALS) providers equipped with pulse oximeters to monitor oxygen saturations in addition to skills to start intravenous (IV) catheters, administer medications, perform intubations and basic life support (BLS) providers with variable training who can provide oxygen but no other medication, and may or may not carry equipment to monitor oxygen saturation and cannot provide titrated oxygen. Additional protocol differences also can be seen when considering volunteer versus professional BLS agencies and first responders from police and fire departments.

Thus, standardizing prehospital care for acute stroke patients presents a tremendous challenge in educating and creating protocols with universality across the diverse landscape of EMS providers, training, and resources.

Interestingly, in acute stroke standardizing protocols might be more feasible since the large majority of patients are transported by ALS providers who are the most highly trained. Dylla et al. found 96% and Collins et al. found 91% of acute stroke patients were transported by ALS [37,38].

Nonetheless, the considerable number of acute stroke patients treated with hyperoxia shows EMS' use of oxygen is an area of prehospital care that requires investigation. Currently there is no sufficient evidence to change recommendations regarding emergency oxygen treatment in acute stroke in regard to hyperoxia [4]. Yet investigations of hyperoxia in cardiac arrest may be instructive for stroke and indicate an urgent need to better understand hyperoxia in prehospital stroke care.

Cardiac Arrest and Oxygen as Neuroprotective Therapy

Despite obvious differences in pathophysiology between cardiac arrest and stroke, oxygen therapy recommendations for patients post cardiac arrest care offer a useful comparison to acute stroke. Cardiac arrest represents a state of whole-body ischemia with profound shock. Global tissue hypoxia produces an inflammatory reaction that collects in hypoperfused tissues during arrest and then is distributed upon reperfusion. Reactive oxygen species and inflammatory mediators cause endothelial damage, microvascular thrombosis and multi organ failure [46]. This highly complex cascade of events has been described as post cardiac arrest syndrome with four key components: brain injury, cardiac dysfunction, systemic ischemic/reperfusion response, and persistent precipitating pathology [47].

The syndrome reflects how sensitive the brain is to ischemic injury and neuroprotective therapies have been extensively studied and implemented in cardiac arrest. Some treatments like targeted temperature management have limited overlap with stroke treatment, however neuroprotective oxygen therapy has substantial overlap with stroke care.

Hypoxia has been broadly accepted to be harmful in both cardiac arrest and stroke, however hyperoxia has only convincingly been associated with harm in cardiac arrest [36,48,49]. The harm associated with hyperoxia in cardiac arrest can be seen remarkably early. Roberts et al. demonstrated that early hyperoxia with PaO₂ > 300 on blood gas analysis at one and six hours post cardiac arrest were associated with worse neurologic outcomes. Thus, in cardiac arrest the negative impact of hyperoxia can be seen as early as one-hour post arrest. Additionally, the harm of hyperoxia appeared to be dose related with each hour of exposure resulting in three percent worsening neurologic outcome [50].

Current guidelines for cardiac arrest treatment incorporate evidence of the harm of hyperoxia and recommend a balance between hypoxia and hyperoxia. The 2020 American Heart Association guideline for post cardiac care advise avoiding hypoxemia and hyperoxia titrating oxygen when accurate measure of blood oxygen saturation is available to maintain saturations between 92-98% [51].

Roberts et al.'s findings of harm at one-hour post arrest would seem to highlight the potential importance of EMS care in cardiac arrest outcomes – providing immediate post arrest care in out of hospital arrest. Unfortunately, efforts to study prehospital titrated oxygen delivery in post cardiac arrest have been unsuccessful. Young et al. attempted a prehospital multi-center, randomized single blind trial comparing titrated and standard oxygen treatment in adults with return or spontaneous circulation after ventricular fibrillatory or ventricular tachycardic arrest. Their primary end point was the prehospital median oxygen saturation. Unfortunately, the trial was stopped early due recurrent hypoxia in the group treated with titrated oxygen and the authors concluded that prehospital titrated oxygen in cardiac arrest is not feasible [52].

Interestingly, the 2015 American Heart Association guidelines described that oxygen saturation measurements may be inaccurate in cardiac arrest due to vasoconstriction [49]. Roberts et al. also found poor correlation between PaO₂ values and oxygen saturation readings in their post cardiac arrest population. So while Young et al. concluded that prehospital titrated oxygen treatment in cardiac arrest is not feasible, it's possible that using oxygen saturation to measure oxygen titration in their study design may have been flawed in post cardiac arrest patients. If a more accurate prehospital measure of PaO₂ were available, it's possible their results may have been different.

Moreover, cardiac arrest is not the only context where inaccuracy in pulse oximeters is seen. Sjoding et.al found differences in pulse oximetry accuracy based on the patient's race [53]. In their study of adult patients receiving oxygen who had paired pulse oximetry and arterial blood gas measurements, pulse oximetry missed hypoxia saturations <88% in 11.4% of Black patients compared to 3.6% of White patients. If oxygen levels cannot be accurately measured, resultant incorrectly titrated therapy may magnify downstream treatment effects and contribute to outcome disparities.

Conclusion

Oxygen therapy in stroke is complex. Current guidelines reflect the understanding that hypoxia is harmful and oxygen saturations should be maintained >94%. Evidence regarding hyperoxia's effect is conflicting. Current

evidence does not support routine continuous normobaric supplementation in patients with acute ischemic stroke. Adjuvant neuroprotection with oxygen in patients with acute ischemic stroke is an attractive strategy for preserving the at-risk penumbral tissue and reducing reperfusion injury. The results of the PROOF study are eagerly anticipated to determine if early hyperoxia may offer a benefit for patients with large vessel occlusions. However, experience with cardiac arrest indicates hyperoxia could be harmful very early after an ischemic event. Despite the challenges in the prehospital care system and clinical environment, there is urgent need for greater understanding of EMS providers' motivation in applying oxygen to patients with normal oxygen saturation (hyperoxia). More accurate tools are needed to assess PaO₂ and oxygen saturation for improved patient care and understanding of oxygen therapy's impact. Currently optimal dosing, duration, and mode of administration of oxygen in acute stroke are yet to be defined. EMS plays a critical role in acute stroke care and optimizing EMS's use of oxygen offers an area worthy of further investigation for potential improvement in treatment of the acute stroke patient.

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