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Effects of perfluorocarbon emulsions on microvascular blood flow and oxygen transport in a model of severe arterial gas embolism

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ABSTRACT

Background: Arterial gas embolism (AGE) is a clinical problem that occurs directly in cardiopulmonary bypass machines in open-heart surgeries, or indirectly (through cardiac or pulmonary right to left shunts) in dive accidents, resulting in serious morbidity and even death. Perfluorocarbon (PFC) emulsions have been used for the treatment of AGE in an animal model. We hypothesized that PFC emulsions enhance microvascular blood flow, speed bubble resolution, and oxygenation in AGE compared with saline in a model of cremaster muscle from anesthetized rats.

Materials and methods: AGE was induced by direct air injection into the femoral artery ipsilateral to the studied cremaster muscle. Microhemodynamics, microvascular, and tissue oxygenation were determined before and after treatment with two different commercial PFC emulsions ($C_{10}F_{20}$, Oxycyte; Oxygen Biotherapeutics, Inc and $C_{10}F_{18}$, PHER-O_2; Sanguine Corporation, Inc) compared with saline in real time using brightfield and phosphorescence microscopy.

Results: Blood pressure and heart rate remained unchanged. Systemic PO_2, oxygen (O_2) content, and glucose were higher in PFC groups, whereas hematocrit dropped in all groups. Arteriolar blood flow went up 85% and 80% of baseline after $C_{10}F_{20}$ and $C_{10}F_{18}$ treatments, respectively, *versus* 11% after saline treatment. Arteriolar and tissue PO_2, and O_2 delivery were higher in PFC groups compared with the control group. There was an increase in arteriolar blood flow, reduction in diffusional resistance of O_2 in the plasma, and improved tissue oxygenation.

Conclusions: Administration of PFC emulsions in AGE is superior to saline primarily because of surfactant properties along with air bubble reabsorption.

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1. Introduction

For a century, we have understood that a principal function of the microcirculation is delivery of oxygen (O_2) to tissues [1–3]. O_2 transport depends on convective delivery and diffusion of O_2 from red blood cells (RBCs) to tissues. Although the O_2-carrying capacity of the RBC mass is large, plasma offers a resistance to O_2 diffusion to tissue target mitochondria [1–3]. An interruption in blood flow occurs in many medical conditions: heart attack and stroke, organ transplantation and replantation, and different types of embolism (air, fat, and thrombotic) [4].

Arterial gas embolism (AGE) is a potentially lethal event seen in cardiopulmonary bypass, organ transplantation, orthopedic, neurologic, and gynecologic surgery [5–10]. Data regarding the consequences of cardiopulmonary bypass AGE are that 35%–83% of patients suffer a neuropsychiatric event immediately afterward and in 35% of patients this becomes permanent [5]. In battlefield blast injury, it is thought to be an immediate threat to life because of lung rupture [10–13]. AGE can arise directly, from venous gas embolism moving through a patent *foramen ovale* or from intrapulmonary vascular shunts [4]. In dive accidents, AGE may result from primary lung barotraumas or because of decompression sickness (DCS). Spinal cord and central cerebral for AGE are one of the most feared complications of a spectrum of dysbaric complications. During AGE, microbubbles may interrupt the blood flow downstream (decreased convective delivery) in a vessel network. The danger is greatest when AGE lodges in the coronary arteries, lung, or brain leading to severe immediate organ dysfunction, impairment, or death [3,4,14]. Hyperbaric compression therapy is an existing but complex treatment for AGE because chambers are limited in availability and are not readily transportable. In surgical AGE, time is the essence and it is rare to be able to get a victim to a hyperbaric chamber ensuing positive outcome. Today other than supportive therapy (intravenous colloids/volume expansion, ventilator, and catecholamine therapy), there are no definitive easy alternative interventions [4,14,15]. The danger may be mitigated by using PFC emulsions.

Perfluorocarbons (PFCs) are fluorinated, inert organic compounds coated with an emulsifier and a stabilizer that dissolve large volumes of respiratory gases such as O_2 and carbon dioxide (CO_2) [16]. The amount of O_2 dissolved in plasma by PFC is linearly related to the local PO_2. The PFC may not only facilitate O_2 transport but act by shrinking air bubbles, thereby reestablishing blood flow [3,17,18]. There would be many clinical applications of PFCs if it was further demonstrated that enhanced O_2 diffusion could occur in the face of reduced convective movement (embolic blockade of microvasculature) [3].

Our previous work provides quantitative data to support a mechanism by which PFC may improve tissue blood flow after massive AGE (increase large air bubbles breakup, decrease air bubble length and volume, and increase air bubbles slide to smaller microvessels) [18]. Thus, it is not known whether PFC supports tissue oxygenation under normobaric normoxia. We hypothesize that PFC restores tissue oxygenation as per the enhancement of microvascular blood flow because of its surfactant effect, compared with saline. In the present work, we assess for the first time the O_2 transport and *in vivo* microhemodynamics simultaneous to systemic measurements in a self-perfused muscle model of AGE using two different PFC emulsions. To exclude the effects of hyperbaric O_2 or hyperoxia on the microcirculation, animals were kept spontaneously breathing room air ($F_iO_2 = 0.21$) throughout the experimental protocol.

2. Methods

This study was performed in 14 male Sprague-Dawley rats (225 ± 10 g of body mass). Animal handling and care was approved in advance by the Institutional Animal Care and Use Committee of Virginia Commonwealth University Health System and follows the Guide for the Care and Use of Laboratory Animals of the National Research Council and the American Physiological Society's Guiding Principles in the Care and Use of Animals. Rats were anesthetized with isoflurane (2%), followed by constant infusion (0.24–0.36 mg/kg/min) of alfaxalone (Alfaxan; Jurox, Worcestershire, UK) through the femoral vein. Acute cannulas were implanted into the carotid artery and femoral vein to measure arterial pressure, collect arterial blood gas samples, and to inject (venous) prewarmed PFC emulsion or saline, respectively. Core temperature was monitored by a rectal thermometer and maintained at 37°C with a heating pad.

2.1. Animal preparation

An incision was made in the left scrotum, and the testis and surrounding cremaster muscle were exposed, as previously described [18]. The cremaster was carefully dissected away from the surrounding connective tissue and positioned flat on a thermostatically controlled transparent viewing platform [19]. During surgery, the suffusion of the muscle was done by warm Krebs–Henseleit solution. To prevent dehydration and gas exchange with the ambient air, the muscle was covered with an impermeable film (Saran Wrap; Dow Chemical Co, Midland, MI). Animal was then moved to the microscope to initiate the protocol.

2.2. Systemic parameters

Recordings of arterial pressure and heart rate (HR) were obtained using a data acquisition system (Biopac Systems, Goleta, CA). Pulse pressure (PP) and mean arterial pressure (MAP) were calculated from the original digitized traces of arterial pressure. Arterial blood was collected in heparinized capillary tubes (35-μL volume; Readacrit Centrifuge, Clay Adams, NJ) for hematocrit (Hct) and fluorocrit (Fct). Fct, expressed as percentage, represents the length of PCF emulsion in the centrifuged capillary tube relative to the entire length of the whole blood. Total hemoglobin concentration (tHb) and hemoglobin O_2 saturation (S_aO_2) were analyzed in arterial blood (OSM3; Radiometer, Westlake, OH), and P_aO_2, P_aCO_2, lactate, base excess, and pH_a (ABL 700 series;