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Regulation of exercise blood flow: Role of free radicals

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ABSTRACT

During exercise, oxygen and nutrient rich blood must be delivered to the active skeletal muscle, heart, skin, and brain through the complex and highly regulated integration of central and peripheral hemodynamic factors. Indeed, even minor alterations in blood flow to these organs have profound consequences on exercise capacity by modifying the development of fatigue. Therefore, the fine-tuning of blood flow is critical for optimal physical performance. At the level of the peripheral circulation, blood flow is regulated by a balance between the mechanisms responsible for vasodilation and vasoconstriction. Once thought of as toxic by-products of in vivo chemistry, free radicals are now recognized as important signaling molecules that exert potent vasoactive responses that are dependent upon the underlying balance between oxidation–reduction reactions or redox balance. Under normal healthy conditions with low levels of oxidative stress, free radicals promote vasodilation, which is attenuated with exogenous antioxidant administration. Conversely, with advancing age and disease where background oxidative stress is elevated, an exercise-induced increase in free radicals can further shift the redox balance to a pro-oxidant state, impairing vasodilation and attenuating blood flow. Under these conditions, exogenous antioxidants improve vasodilatory capacity and augment blood flow by restoring an "optimal" redox balance. Interestingly, while the active skeletal muscle, heart, skin, and brain all have unique functions during exercise, the mechanisms by which free radicals contribute to the regulation of blood flow is remarkably preserved across each of these varied target organs.

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1. Introduction

Despite the continual discovery of potent vasoactive molecules such as nitric oxide (NO), prostaglandins, endothelium derived hyperpolarizing factor (EDHF), adenosine triphosphate (ATP) [1–4], the identification of the mechanisms essential to the regulation of blood flow during exercise in humans has proven to be a difficult and arduous task [5]. Indeed, concurrent inhibition of multiple vasodilatory pathways during exercise has yielded significant, albeit modest, changes in blood flow [6–8]. Additionally, limitations in the ability to target specific enzymatic isoforms and pharmacologically dissect vasodilatory pathways during exercise in humans may be contributing to these disparate findings [9–12]. Based on these findings it may be concluded that either the underlying mechanism of exercise hyperemia has yet to be identified or adequately inhibited during in vivo human experimentation or that the regulation of blood flow during exercise involves the complex interaction of numerous compensatory and redundant pathways that control the balance between vasodilation and vasoconstriction in the human vasculature.

Much attention has been focused on elucidating specific mechanisms regulating blood flow, with the ultimate goal of identifying a "master regulator". When considering that blood flow is determined by the integration of central (cardiac output, mean arterial pressure) and peripheral hemodynamics (vascular conductance or resistance) and the multitude of factors that regulate these processes during exercise, it is unlikely that a single molecule will encompass the properties of a master regulator. Indeed, thus far, this notion is supported by many elegant investigations utilizing pharmacological dissection of specific vasodilatory pathways [6–8,13–18]. However, when considering the overall goal of increased blood flow during exercise, to match oxygen delivery and oxygen demand, it becomes evident that even minor modifications in blood flow in the intact human may have significant consequences in terms of physical performance [19]. The impact of these alterations is likely to be most relevant during high intensity aerobic exercise or during exercise under conditions of compromised vascular function such as with aging and disease.

Active skeletal muscle demands a large increase in blood flow during exercise, increasing by 100-fold compared to resting values

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[20,21]. As such, the skeletal muscle vascular bed is arguably the most important vascular bed in terms of the regulation of blood flow during exercise. The regulation of blood flow to this "sleeping giant" is important to maintain adequate oxygen and nutrient delivery to meet the energetic demands of the skeletal muscle during exercise [22], as inadequate oxygen delivery compromises exercise performance and accelerates the development of fatigue [23]. Importantly, minor changes in oxygen delivery have profound consequences in human performance, especially in conditions where components of the oxygen cascade are operating at near maximal capacity or have been altered by disuse, aging, or disease [24–28]. However, blood flow to other vital organs, including the brain and the heart, is of critical importance and small alterations in oxygen and nutrient delivery can have a profound impact on function and performance. Additionally, the skin, second only to the active skeletal muscle in regards to vasodilatory capacity, participates in critical thermoregulatory processes that are directly linked to exercise performance. Clearly, the regulation of blood flow during exercise requires a coordinated and integrated approach to adequately deliver oxygen and nutrient rich blood throughout the body.

The ubiquitous nature and potential vasoactive properties of free radicals is becoming increasingly appreciated. Indeed, NO, first identified 35 years ago as endothelium-derived relaxing factor by Furchgott and Zawadzki [1] and later determined to be NO by Ignarro et al. [2], is actually a reactive nitrogen species (RNS) or free radical. NO certainly has potent vasodilatory properties and has, in fact, been a strong contender for the title of "master regulator" of blood flow. However, although still commonly discussed, the source and complex role of NO in vascular function and blood flow regulation is not the focus of this review and the reader is directed to several excellent reviews on this topic [29–31]. Instead, this review will focus on the regulation (or modification) of blood flow during exercise by other RNS and reactive oxygen species (ROS) such as peroxynitrite ($ONOO^-$), superoxide (O_2^-), hydroxyl radical (OH^-), and lipid radicals that promote oxidative stress. Ultimately this depends on several factors including the free radical species, the interaction of the free radical with vasodilators (or vasoconstrictors), possible direct effects of the radical on the vasculature, and the underlying redox balance. Here, the interaction of these factors will be addressed as they relate to the regulation of blood flow during exercise in health, aging, and disease as it appears that the underlying redox status dictates how an exercise-induced increase in free radicals promote or impair vasodilation (Fig. 1).

When information regarding the exercise associated regulation of blood flow is limited, free radical regulation of basal blood flow will be reviewed. Furthermore, to gain additional mechanistic insight into the possible regulatory roles of free radicals during exercise, investigations evaluating the control of isolated blood vessels will be discussed. Additionally, this review will extend beyond blood flow control in skeletal muscle as important insight may be gained from understanding how free radicals contribute to blood flow regulation in the vasculature of the heart, skin, and brain. As a complete overview of the factors that regulate blood flow during exercise is beyond the scope to this review, the reader is referred to the many excellent reviews on this topic [32–37].

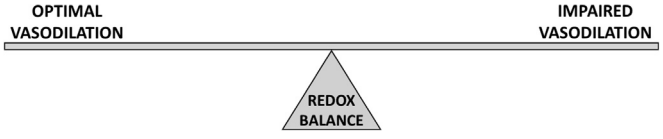

Fig. 1. A conceptual schematic of the proposed critical link between redox balance and the regulation of blood flow by free radicals during exercise. Shifting the underlying redox status such that an imbalance is created may determine whether free radicals promote or impair vasodilation in the vasculature. Optimal vasodilation is defined as the precise matching of oxygen delivery and oxygen demand coupled with the appropriate pressor response to adequately perfuse the active tissue.

2. Sources of free radicals

Over the last 30 years, our understanding and appreciation of free radical biology has changed a great deal. Indeed, these highly reactive molecules, characterized by an unpaired electron, were originally viewed as toxic by-products of in vivo chemistry, but are now considered critical regulators of cell signaling and play essential roles in facilitating the damage and adaptations that accompany exercise [38–45]. Importantly, the production of free radicals is augmented during exercise in proportion to the severity of exercise intensity. Seminal work by Davies et al. [46] provided the first electron paramagnetic resonance (EPR) spectroscopic evidence of increased free radical production during exhaustive exercise in animals [46]. These findings have been translated to humans in a series of innovative studies by Bailey and colleagues [47,48] utilizing isolated knee extension exercise and ex-vivo spin trapping of blood and skeletal muscle (Fig. 2). The production of free radicals is clearly augmented during exercise; however, the source(s) of these free radicals remains equivocal.

Early investigators proposed that skeletal muscle mitochondria were the primary source of free radical production during exercise [46]. It was estimated that during exercise 2–5% of oxygen consumed during oxidative phosphorylation was converted to O_2^- during the transfer of electrons through the complexes of the electron transport chain (ETC) [42,49–52]. This hypothesis centered on the notion that during state 3 mitochondrial respiration, when electron flux through the ETC is maximized, the potential for electrons to bypass the respiratory complexes and aberrantly reduce oxygen, producing O_2^-, would also be maximized [53,54]. Contrary to this concept, it has recently been documented that ROS production is actually lowest during state 3 respiration, as the coupling of electron transfer to ATP production is optimized [55,56]. Thus, the early estimates that 2–5% of oxygen consumed is converted to ROS have been re-evaluated, and it is now more commonly accepted that as little as 0.15% of consumed oxygen is converted to ROS [57]. While the contribution of skeletal muscle mitochondria to ROS production during exercise is somewhat equivocal, several studies, utilizing mitochondrial targeted antioxidants, have provided compelling evidence that mitochondria-derived ROS contribute to vascular endothelial dysfunction with age in murine models [58,59] and that even the thin endothelial

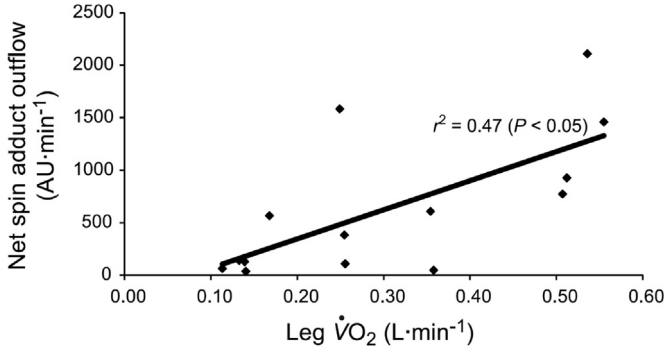

Fig. 2. The relationship between net PBN (α-phenyl-*tert*-butylnitrone) spin-adduct outflow (venous–arterial difference), a direct measure of free radical outflow, and single-leg oxygen uptake during dynamic single-leg knee extension exercise performed at 25 and 70% of work rate maximum. Data were collected in a heterogeneous group of 7 healthy men (48 ± 25 yr). Each exercise intensity was continued for 3 min to achieve steady-state pulmonary VO_2. Modified from [47].

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