Editorial Focus. Oxidative stress in carotid body contributes to enhanced chemoreflex in heart failure: focus on mitochondrial superoxide anion

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Chronic heart failure (CHF) is characterized by exaggeration of sympathetic nerve activity (SNA) that elicits dual effects. By maintaining cardiac output and preserving cardiovascular homeostasis during CHF, sympathoexcitation is initially a beneficial compensatory mechanism. Sustained activation of SNA, however, exacerbates cardiovascular deterioration, leading to cardiac decompensation and progression of CHF (11). The sympathetic hyperactivity observed in CHF is closely related to abnormalities in cardiovascular reflexes. Thus, sympathoinhibitory cardiovascular reflexes such as the arterial baroreflex are depressed, and sympathoexcitatory reflexes, including cardiac sympathetic afferent reflex and arterial chemoreflex, are significantly augmented (12,13). In addition to reports on the increase of sympathetic outflow from the central nervous system, a series of studies from Dr. Donald Schultz’s laboratory during the past few years showed that hypersensitivity of peripheral chemoreceptors is also involved in the enhancement of chemoreflex that leads to sympathetic activation in CHF (9).

Activation of chemoreceptors in the aortic body and carotid body (CB) initiates the arterial chemoreflex in response to hypoxia. Although controversy still exists on details of the chemo-neurotransduction cascade in the CB, the general consensus depicts that the glomus or type I cells, which lie in synaptic apposition with afferent axons, are the initial sites of chemotransduction in the CB. The glomus cell expresses several types of membrane ion channels that influence its excitability. Of these channels, the hypoxia-inactivated outward K⁺ channels are known to play a key role in the initial depolarization, with subsequent activation of voltage-gated Ca²⁺ channels, release of neurotransmitters, and increase of sensory discharge in the carotid sinus nerve (4). In CB glomus cells from CHF rabbits, the outward voltage-gated K⁺ current (Iₒ) is suppressed and their sensitivity to hypoxic inhibition is enhanced, resulting in discharge of chemoreceptor afferents under normoxic state and an increase in discharge responsiveness to hypoxia (9). The observations that these alterations occur in intact (blood perfused) and isolated CB cells suggest that an intrinsic alteration within the CB, rather than a circulating factor, drives the augmented chemoreceptor
afferent sensitivity in the CHF state (10).

Contemporary efforts to delineate the molecular mechanism underlying the enhancement of CB chemoreceptor sensitivity in CHF focused on the reactive oxygen species (ROS), in particular superoxide anion (O$_2^-$), and the enzymes that are involved in the generation or degradation of the ROS. In a rabbit model of left ventricular pacing-induced CHF, Li et al. (6) reported that both mRNA and protein expressions of NADPH oxidase components (gp91$^{phox}$, p40$^{phox}$ and p47$^{phox}$) are upregulated, and the NADPH oxidase-derived O$_2^-$ signaling pathway contributes to the enhanced chemoreceptor sensitivity to hypoxia by suppressing I$_k$ currents in CB glomus cells (9). The causal relationship between oxidative stress and the enhanced CB chemoreceptor activity in CHF is further confirmed by observations that adenovirus (Ad)-mediated gene transfer to the CB tissue of copper/zinc superoxide dismutase (CuZnSOD), the major cytosolic antioxidant enzyme regulating O$_2^-$ metabolism, effectively reduces the elevated O$_2^-$ levels and reverses the enhanced CB chemoreceptor hypersensitivity and reflex function during normoxia and isocapnic hypoxia (3). This is accompanied by normalization of the blunted I$_k$ currents in CB glomus cells in CHF rabbit.

In addition to the cytosol, Ding et al. reported in this issue (2) that the mitochondrion could be another cellular source of O$_2^-$ in CB chemoreceptors mediating an enhanced chemoreflex in CHF. The authors showed suppressed mitochondrial manganese SOD (MnSOD) expression and elevated mitochondrial O2- levels in CB glomus cells of CHF rabbits. Overexpression of MnSOD by Ad gene transfer selectively to the CB increases MnSOD expression and reverses the elevated mitochondrial O$_2^-$ levels in CB tissue, along with normalization of enhanced chemoreflex response to hypoxia. This is accompanied by a decrease in baseline discharge of chemoreceptor afferents, chemoreceptor hypersensitivity to hypoxia and reversal of the blunted I$_k$ in CB glomus cells. These results suggest that decreased mitochondrial MnSOD in the CB and elevated mitochondrial O$_2^-$ levels contributes to the enhanced CB chemoreceptor activity and peripheral chemoreflex function in CHF.
rabbits.

This study is a logical extension of previous work by the same group showing the importance of NADPH oxidase-derived $\text{O}_2^-$ and cytosolic SOD in the augmented chemoreflex function in CHF (1,3,5-9). Their findings highlight the significance of mitochondrial $\text{O}_2^-$ and its degradation by MnSOD in the pathophysiology of CB chemoreceptor hypersensitivity and enhanced chemoreflex in CHF. However, with observations that $\text{O}_2^-$ generated from different subcellular compartments contributes almost equally to the enhanced chemoreflex in CHF, several questions emerged that need to be answered. For example, are the downstream signaling cascades mediating the gating of the hypoxia-inactivated outward K$^+$ channels in CB by $\text{O}_2^-$ derived from NADPH oxidase and mitochondrion the same or different? Are these signaling pathways modified under CHF condition? What are the mechanisms that underlie the downregulation of CuZnSOD and MnSOD expression in CB glomus cells in CHF? Since insertion of a CuZnSOD (3) or a MnSOD (2) transgene in the CB almost completely reverses the augmented chemoreflex function in the CHF rabbit, is there any interaction between them in regulation of $\text{O}_2^-$ level in CB glomus cells under normal or CHF conditions? Obviously, answers to these questions will provide further insight into the role of oxidative stress in CB chemoreceptors in the manifestation of an enhanced chemoreflex in CHF.

In conclusion, the study by Ding et al. (2) clearly provides novel evidence to suggest that MnSOD deficiency and elevated mitochondrial $\text{O}_2^-$ level in glomus cells contributes to CB dysfunction in CHF. Nonetheless, since neither Ad CuZnSOD (3) nor MnSOD (2) gene transfer to CB improves cardiac function in this model of CHF, therapeutic strategies aiming at protection of CB from oxidative stress in the treatment of CHF still wait future validation.

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REFERENCES


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