Targeting Arterial Chemoreceptor Over-Activity in Heart Failure With a Gas

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With an aging population the prevalence of heart failure (HF) continues to rise. In the United States almost 5 million people experience HF, often with a poor prognosis resulting in 20% of patients dying within 1 year and ≈80% mortality within 8 years. Although the mechanisms underpinning cardiac failure are not firmly established, several converging events ranging from depressed contractility itself, diastolic dysfunction, failing energy stores, abnormal cell growth, and defective beta adrenergic signaling are implicated. Neurohumoral activation also appears to play a significant role in amplifying harmful substrate to trigger lethal ventricular arrhythmia which may account for ≈50% of all deaths that are sudden and unexpected. The precise role of abnormal neurohumoral signaling is still unclear but is thought to involve a synergistic activation of the sympathetic nervous system with the renin-angiotensin–aldosterone system and diminished parasympathetic activity. Emerging evidence now suggests that an aspect of impaired neurohumoral signaling in HF may arise from dysregulation of the arterial chemoreflex at the level of the carotid bodies by oxygen-free radicals.

Stimulation of the carotid body (CB) arterial chemoreceptors provides an excitatory input to activate the sympathetic nervous system. Chronic HF causes a sustained activation of the sympathetic nervous system and is also associated with enhanced chemosensitivity in both clinical and experimenter HF. The type I (glomus) cell of the CB is thought to be the primary chemoreceptor sensor. There is an extensive plexus of nitric oxide synthase (predominately nNOS) positive immunoreactivity and NADPH-diaphorase activity in the intrinsic neurons that innervate intraglomic arterioles, glomus cells, and intraglomal vascular endothelial cells, thereby providing a structure for potential autocrine and paracrine signaling by nitric oxide (NO). Physiologically, when NO is inhibited during hypoxia or when the enzyme is knocked out, chemoreceptor afferent activity and ventilation increase. Hypoxia also decreases NOS activity suggesting that endogenous NO may act to inhibit chemoreceptor output. Moreover, decreased NO production is observed in the enhanced CB chemoreceptor response seen in HF.

In this issue of Circulation Research Li and colleagues from Schultz’s group in a series of challenging experiments show that gene transfer of adenovirus encoding nNOS (Ad.nNOS) into the CBs reversed enhanced chemoreceptor activity in rabbits with HF. They reported that nNOS expression and NO production was suppressed in the CBs in HF and that these animals had higher chemoreceptor activity compared with the sham-operated group. Targeting Ad.nNOS into the chemoreceptor increased expression of nNOS and NO bioavailability resulting in a reversal of the HF chemoreceptor phenotype. The beneficial effects of nNOS gene transfer were abolished by nNOS inhibition. In addition the inhibitor also enhanced chemoreceptor activity in the sham operated group supporting the idea that nNOS-derived NO has a tonic inhibitory action under normal conditions. NOS inhibition alone in the HF group failed to increase chemoreceptor activity without the presence of Ad.nNOS, indicating the removal of the tonic inhibitory influence in HF. Interestingly, Ad.nNOS also lowered basal renal sympathetic nerve activity (RSNA), peripheral chemoreflex sensitivity, and reduced respiratory responses to hypoxia. However, these reflex responses were not normalized to levels seen in the sham animals suggesting dysregulation at other autonomic sites not targeted by Ad.nNOS, because central sympathetic outflow is increased in HF.

Adenoviruses can give rise to promiscuous transfection. This is particularly important with gene transfer studies targeting NOS given the potential paracrine action of the gaseous messenger if the gene gets placed in cell types not normally involved in physiological function. NOS is a highly-conserved enzyme in the nervous system and is known to exert its action in a very site-specific manner relative to its target. The vector used by Li et al has previously been used with good effect in targeting both central and peripheral cardiac autonomic neurons with a high degree of specificity because of its CMV promoter. Nevertheless one cannot rule out a nonspecific autocrine and paracrine action that might be set up in cell types not directly involved in chemoreception (eg, type II cells). Most evidence supports the idea that the action of NO in the CB is predominately paracrine in nature and arises from intrinsic neurons, because there is no convincing data for the primary source of NOS residing in either type I or type II chemoreceptor cells.

How does gene transfer rescue the CB phenotype in HF and what mechanisms are involved? The glomus cell as the primary chemosensor releases excitatory neurotransmitter(s) resulting in depolarization of the carotid sinus afferent nerve. NO targets cGMP and non-GMP dependent pathways to modulate ion channels that regulate calcium entry. A decrease in excitatory neurotransmitters is brought about by a
increase in calcium-dependent exocytosis that can be influenced by a number of simultaneous events. Several pathways, outlined in the Figure, may explain the beneficial action of nNOS gene transfer on the physiology of the glomus cell in HF. First, NO can activate the calcium-gated–potassium channel (K_{CaL}) because of NO-cGMP dependent stimulation of PKG.\(^\text{26,27}\) This increases potassium channel conductance, in particular I_k, that is blunted in HF rabbits.\(^\text{13,26}\) Activation of this channel leads to a more negative membrane potential and in turn results in decreased voltage activation of the L-type calcium channel (I_{CaL}). Secondly, NO can also decrease the open time of I_{CaL} via cGMP independent processes that probably act by nitrosylation of calcium channel proteins on the channel itself to inhibit the current.\(^\text{28}\) Thirdly, when these events are taken together there is a significant decrease in intracellular calcium-dependent transmitter release. Fourthly, what is the excitatory transmitter that NO modulates? The strongest candidates appear to be ATP and acetylcholine (Ach). Both are released from type I cells in response to hypoxia\(^\text{29–31}\) and excite the sinus nerve. Importantly, recent work shows Ach release can be significantly inhibited by L-arginine,\(^\text{29}\) the precursor for NOS, or NO donors over a wide range of oxygen tensions.\(^\text{32}\)

The present study is an important step in unraveling the complex link between the failing heart and nervous system. They have identified a potentially interesting target in the CB that warrants further investigation beyond the stage of physiological proof of principle. It remains to be seen how sustained nNOS gene expression (eg, lentiviral nNOS constructs) in the CB affects the progression of the HF model in the awake animal. Future studies will likely involve understanding more about the molecular and cellular basis for suppressed sinus nerve activity that is brought about by NO. How does NO interact with other gaseous messengers? For example, carbon monoxide uses heme-oxygenase-2 that is localized in the type 1 cell and causes an inhibitory action on sensory activity.\(^\text{14}\) The neural axis from the CBs to the brain may also be important because HF can modify central autonomic outflow. Is NO also a key messenger in sinus nerve efferent inhibition of the CB? Understanding the integrative response from the CB to the end organ response is clearly desirable to establish whether chemoreceptors should be viewed as a potential therapeutic target in heart failure.

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References


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