Carotid body and sympathetic activation in heart failure: a story of sensors and sensitivity

Río Aguilar Torres

Servicio de Cardiología, Hospital Universitario Vall d’Hebron, P. Vall d’Hebron 119–129, Barcelona 08035, Spain

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This editorial refers to 'Role of CuZn superoxide dismutase on carotid body function in heart failure rabbits' by Yanfeng Ding et al.,6 pp. 678–685, this issue.

The carotid body (CB) is a peripheral chemoreceptor organ that contains clusters of electrically excitable secretory cells, the glomus cells, which express several types of membrane ion channels that influence its excitability. These cells act as sensors or chemotransducers, detecting different chemical stimuli and triggering an action potential in the afferent fibres that lie in synaptic apposition. The main stimulus for glomus cells are constant falls in arterial partial pressure of oxygen (PaO₂), in opposition to the highly sensitive partial pressure of carbon dioxide (PaCO₂) chemoreceptors at the central nervous system (CNS). The afferent nerve supply of the CB, which is accompanied by the afferent fibres from carotid sinus baroreceptors, provides a highly O₂-dependent input to the CNS.1 CB exhibits great sensitivity to hypoxia (low threshold and high gain) that is accompanied by great resistance to its deleterious effects, being possible to detect nervous activity up to 30 min after an animal’s death; owing to this fact, the CB has been called ‘ultimum moriens’ (the last to die).2

In chronic heart failure (CHF) the sympathetic-humoral activation that, at the initial phases of this syndrome, is directed to attenuate systemic hypoperfusion may ultimately exacerbate the progression of cardiac dysfunction that subsequently increases the extra-cardiac abnormalities, a positive feedback cycle of progressive deterioration, or less euphemistically, a vicious cycle with ominous consequences. It was thought that much of the increase in the sympathetic nerve activity (SNA) in CHF was based on the increase of sympathetic flow at the CNS and on the depression of arterial baroreflex function. However, in the past several years, it has been demonstrated that an increase in the sensitivity of peripheral chemoreceptors activity also plays an important role in the enhanced SNA that occurs in CHF.3–6 Perhaps surprisingly, but not paradoxically, chemoreflexes that are dedicated under normal conditions to correcting hypoxia contribute to increase the sympathetic tone in CHF, even under normoxic conditions.

The understanding of how abnormally enhanced sensitivity of the CB contributes to the tonic elevation in SNA in CHF has come from several studies that in some instances have been contradictory because of the differences in the animal models employed.6 According to the more accepted scheme, the local angiotensin (Ang) II–Ang II type 1 (AT1) receptor system plays a fundamental role in the enhanced CB chemoreceptor sensitivity in CHF, as the NADPH oxidase–derived superoxide signalling pathway is the one that mediates the effects of Ang II by suppressing outward voltage-gated K⁺ currents (Iₖ) of the membrane of glomus cells from CHF rabbits.3–6,7

As reported in this issue of the journal, Ding et al.8 employed a model of pacing-induced cardiomyopathy to examine whether the decreased expression of a superoxide anion scavenger, CuZnSOD, which is an intracellular isoform of the superoxide dismutase (SOD), contributes to CB chemoreceptor hypersensitivity in CHF. In addition, the authors showed that successful adenovirus-mediated CuZnSOD gene transfer to the CB tissue enhanced the expression of the enzyme. The increase in the amount of CuZnSOD was accompanied by an effective reduction of the elevated superoxide anion levels that finally resulted in reversion of the enhanced CB chemoreceptor hypersensitivity and reflex function during normoxia and isocapnic hypoxia. This was accompanied by an increase of the previously suppressed Iₖ of the glomus cell in the CB of CHF rabbits. The present study suggests that CuZnSOD downregulation, mediated by the elevated superoxide anion levels, as well as the increased Ang II–NADPH oxidase–derived superoxide anion signalling, contribute to signalling in the enhanced chemosensor and reflex function of the CB in CHF.

In this paper, the authors offer an interesting hypothesis and a nice set of experiments in a rabbit model of CHF with very well-controlled conditions for the study of chemoreflex function. Despite the fact that the mechanisms provoking depression of myocardial function are not well known, and that cardiac dysfunction is at least partially reversible after cessation of pacing, the model of pacing-induced biventricular cardiomyopathy in the rabbit has proven to be almost ideal for these kinds of
pathophysiological studies. This model simulates, in a very reproducible and predictable fashion, many aspects of human CHF with moderate functional repercussion. Pacing-induced CHF, which minimizes uncontrolled cardiac damage owing to surgical intervention, however, shows its ability to produce intense neurohormonal stimulation, including the renin–angiotensin system, natriuretic peptides, NO, and endothelin systems, and the sympathetic nervous system at all of its levels. However, the ‘realism’ of this model regarding sympatho-humoral activation, which is very closely linked to CB function, makes it mandatory to isolate effects at the CB and to control some potential confounders at loci in the CNS and other visceral sites (e.g. heart, kidneys, etc.).

The idea that the degree of oxidative stress and the level of reactive oxygen species (ROS) are determined by the balance between ROS generation and oxidant scavenging is not new. Several studies before this have documented reductions in SOD activity in peripheral tissues in the CHF state. The hypothesis of this work—that decreased levels of CuZnSOD might contribute to the enhanced sympathetic activity within the CB in models of established CHF—is a logical conclusion based on previous work by the same group showing that the reduction of this superoxide anion scavenger also participates in the exaggerated sympathetic activity from autonomic areas of the CNS in CHF rabbits.10,11

The more important consequence of this study stems from the fact that this downregulation, which can be at least partially and transiently corrected by local CB gene transfection of CuZnSOD or by the administration of SOD mimetics like tempol, makes more plausible the causal relationship between oxidative stress and the enhanced chemoreceptor activity that is shared by both peripheral chemoreceptors and CNS loci in CHF. It is also important to remark that establishing causal relationships in such a complicated scenario, despite the evidence provided by this and previous work, does not allow one to discard the possible alteration of other simultaneous mechanisms. Although the evidence provided by this study seems quite convincing, participation of ROS other than superoxide anion cannot be completely excluded.

In the regulation of glomus cell function within the CB in CHF, or at other loci in the CNS, CuZnSOD could be considered to be a main character in this story or just one among many secondary actors. These intermediate actors, however, allow us to identify the final effectors that once again appear to be ROS—in this case, superoxide anion. Remember that important potential therapeutic tools, such as exercise and antioxidants, are still awaiting an opportunity to prove their success in CHF treatment.

References