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# The Damaging Impact of Chronic Heart Failure on A Critical Interoreceptor and the Therapy for it

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**Abstract**

Congestive Heart Failure (CHF) is among the heart diseases which accounted for > 54% of deaths world-wide in 2013 in a World Health Organizations report. CHF patients most often have a more sensitized carotid body (CB) chemoreceptor than normal. CB neural output stimulates output from the sympathetic nervous system. Increased CB output in CHF has in animal models been attributed to a loss of shear stress on the luminal surfaces of the CBs' vascular endothelial cells. This down regulates KLF2. Methods to remove or attenuate the CB's activity have been devised. These and variations of them could be therapeutic for CHF patients.

**Keywords**

Carotid body, Chronic heart failure, Kruppel-like factor 2 (KLF2), Shear stress

## Introduction

The central nervous system (CNS) needs input from the peripheral receptors to participate in maintaining appropriate homeostasis. And sometimes the most critically important receptors malfunction. All tissues, but especially neural tissue, needs oxygen and glucose in constant supply. Human subjects can go without food for a month, occasionally longer. They can survive without fluid for several days, even a week. But they cannot survive without oxygen for more than three to four minutes without initiating irreversible damage to the tissues, especially neural tissue. Therefore, the receptor primarily and uniquely responsible for detecting a want of oxygen in the circulating blood would seem to be the most important interoreceptor in the organism. In humans that receptor is the bilaterally located carotid body (CB) found at the bifurcation of the common carotid arteries into the internal and external carotid arteries.

### Carotid body and carotid sinus

Stimulation of this structure with a lowered arterial partial pressure of oxygen ($P_aO_2$), an increase in $P_aCO_2$ or $H^+$, or with hypoglycemia can generate an impressive array of respiratory, cardiovascular, endocrine, and renal reflex responses [1]. Involved in several of these systemic reflex responses is the stimulation of the sympathetic nervous system (SNS). Located at the base of the internal arteries are the carotid sinuses, only millimeters away from the CBs, housing the carotid baroreceptors, principal detectors and regulators of arterial blood pressure. Noteworthy is the fact that the CBs and the baroreceptors send their neural outputs via fibers in a branch of the same nerve, the glossopharyngeal, through the petrosal ganglion and on to the bilateral Nucleus tractus solitarii in the medulla. However, whereas stimulation of the baroreceptors (e.g., in high blood pressure) attenuates neural output from the SNS, stimulation of the CBs increases output from the SNS.

### Carotid body structure

Hypoxia depolarizes the glomus cells of the CB in most species [2]. These cells contain neurotransmitters (NTs). This is accomplished by a blocking of several types of $K^+$ channels, elevating the membrane potential and activating voltage-gated calcium channels. Calcium influx promotes the exocytosis of several NTs acutely from glomus cell vesicles into the synaptic-type space between the glomus cell and the abutting afferent chemosensitive neuron. The two essential excitatory NTs are acetylcholine (ACh) and ATP [3]. Hypoglycemia promotes the release of excitatory NTs with a different mechanism. Though the transmembrane influx of extracellular calcium into the glomus cells is an essential step for the release of the NTs. But it appears that transient receptor potential channel C is involved [4].

### Carotid body action in chronic heart failure

Recently CB behavior has become quite significant from a clinical perspective. Patients suffering chronic heart failure (CHF) have sensitized CBs which promotes bursts from the SNS. One study showed patients suffering from CHF. The group was divided into those with the sensitized CBs (Group 1; n = 27) and those with much less sensitized CBs, relatively normal responders (Group 2; n = 53). The survival rate of the Group 1 patients after three years was 41% (11 of 27). Group 2 patients had a three- year survival rate of 77% (41 of 53) [5]. A second study showed how CB removal improved the condition of a patient with chronic systolic heart failure [6].

Dr. Harold D Schultz and his collaborators at the University of Nebraska Medical Center in Omaha have conducted several seminal studies attempting to identify mechanisms involved in the role of the CBs in CHF using animal models. CHF was produced in rabbits by the placement of a pacemaker, subjecting the animals to weeks of a regimen of greatly increased heart rate, which resulted in severe reduction in resting heart rate [7]. The rats had the anterior coronary artery ligated [8].

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Well-known is the fact that CHF reduces blood flow throughout the organism including the common carotid artery. With reduction in blood flow in the common carotid artery there is reduction of blood flow in the CBs. This produces a highly sensitive CB, more easily made to increase its neural output to the CNS. In addition to the malfunctioning heart in CHF, breathing is also affected as is kidney function and the sympathetic branch of the autonomic nervous system (SNS) [9-12]. CB denervation [13] attenuates these effects.

Decreased CB blood flow reduces the shear stress on the endothelial cells in the CBs' vasculature. Shear stress under normal conditions is continually activating the transcription factor KLF2 via a cascade of intermediate steps. KLF2 has several effects among which are the endothelial nitric oxide synthase (eNOS)-generation of NO [14]. NO in the feline model reduces the hypoxia- generated increase in CB neural output [15].

This gasotransmitter balances CB neural output at least in part by reducing the exocytotic release of the excitatory transmitter ACh from the CB's glomus cells [16,17]. At reduced levels of KLF2 a combination of molecules promote the lowering of NO and activating of the angiotensin1 receptor. This produces ROS which blocks K channels in the glomus cells, depolarizing the cells, and opening Ca channels. The influx of Ca promotes the release excitatory transmitters [18].

### Elimination of CHF-generated CB hypersensitivity

Several methods have been proposed to eliminate or reduce CB input into the SNS during CHF. First, CB removal has been tried [5,6]. In the rabbit model once the CB was exposed, a metal rod, previously soaking in liquid nitrogen, was placed against the CB, freezing the structure and destroying the glomus cells [13]. This was seen to reduce the CB-mediated ventilatory response to a 10% $O_2$ stimulus in rabbits from 550 ml/min to 240 ml/min. Further, the Cheyne-Stokes breathing pattern seen in the CHF rabbits was completely abolished by the CB denervation (CBD). In the hearts of CHF rabbits CBD restored left ventricular end systolic and end diastolic volumes to the before-pacing values, and prevented the ejection fractions from further deterioration [18]. Finally CBD improved kidney function in the CHF rabbits. And, of course, CBD improved the survival rate among the CHF animals, similar to the comparison of the two groups of men mentioned above [18].

### Effect of exercise

A second method for countering the effects of CHF was exercise [19]. Since it had been shown previously that reducing blood flow in the common carotid artery and, thus, in the carotid body produced results in the CB very similar to the results seen in the CHF rabbits [18], it was hypothesized that exercise with the increased cardiac output would benefit the CHF rabbits. A group of normal rabbits was compared with a group suffering from CHF. Each group was further divided into sedentary and exercised. Neural output from the CB in response to an increasing hypoxic challenge showed exercise had no effect on the sedentary normal group, but did reduce the output in the exercised CHF group so that it almost superimposed on the normals' responses. Not surprisingly renal sympathetic nerve output was qualitatively the same as the CB neural output [20]. Exercise may have acted via KLF2 as exercise in the CHF groups increases KLF2 whereas before there is very little KLF2 in the CBs [18].

### Physical and molecular factors involved in CB activity in CHF

Other studies have shown more directly the effect of carotid blood flow on KLF2 which were corroborative of the role of vascular shear stress in the CB [21]. This physical force acts upon a mechanoreceptor in the luminal membrane of the endothelial cell which action activates mitogen-activated protein kinase 5 (MEK5), then mitogen-activated protein kinase 7 (ERK5), and finally myocyte- enhancing factor 2 (MEF2). This cascade up regulates KLF2. Shear stress and KLF2 are closely linked in blood flow problems. For the CB KLF2 stimulates an increase in eNOS and NO. Increased NO would attenuate CB neural output as we have seen above. But in CHF with lowered CB blood flow KLF2 levels drop resulting via the activity of several intermediates in the generation of ROS. Superoxide depolarizes the transmitter-containing glomus cells in the CB, generating the release of excitatory neurotransmitters [22]. Since exercise increases blood flow in the CB, the more normal shear stress would be reestablished. This would make the KLF2 levels head up towards more normal values [18].

### Statins

Since more normal levels of KLF2 operate to balance CB neural output, methods to act on KLF2 were tried. A third method to quiet the CBs in CHF via KLF2 used the administration of simvastatin. In CHF rats this compound was included in their diet. The effect was to abolish Cheyne-Stokes breathing, heart rate variability, and significantly reduce the hypoxia-generated increase in CB neural output [23]. At the molecular level in the CHF rats simvastatin normalized KLF2, eNOS, and angiotensin II type 1 receptor protein expression in both the CBs and nucleus tractus solitarii. Similar effects were found in human aorta endothelial cells [24].

## Summary and Conclusion

To maintain homeostasis the CNS needs input from peripheral mechano- and chemo- receptors for regulating such variables as blood pressure and quality of the circulating blood. Inasmuch as the organism cannot survive without oxygen for more than 4-5 minutes without doing irreversible damage to tissues, especially neural tissue, it seems that the most important receptor is that for detecting oxygen levels in the blood, the CB. Thus understanding how this structure works and what it controls would be desirable, especially since recently the CB has been found to become hypersensitive in patients with chronic heart failure (CHF). CHF is a major killer world-wide. After a review of basic CB physiology, a series of studies were presented outlining how the hypersensitive CB was responsible for cardiovascular, pulmonary, and renal malfunctioning. The absence of shear stress on the luminal surface of the vascular endothelial cells of the CB was the factor creating the problem. This absence reduced KLF2, which promotes the production of NO in the CB, balancing the CB's neural output. Hyperactive CBs give phasic input into the nucleus tractus solitarii and cause bursting of the SNS which produces ventricular arrhythmias and poor cardiac performance. CB malfunction in these CHF animals was eliminated or attenuated by ablating (by freezing) the CB, by exercise, and by statin administration.

Inasmuch as over 50% of the deaths world-wide, as reported by the World Health Organization in 2013, are due to cardiac problems, these animal studies provide some insights into therapies for CHF patients that might be considered.

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