Arterial Chemoreceptors and Sympathetic Nerve Activity
Implications for Hypertension and Heart Failure

Harold D. Schultz, Yu L. Li, Yanfeng Ding

Chronic elevation in sympathetic nerve activity (SNA) is associated with the development and maintenance of certain types of hypertension\(^1\) and contributes to the progression of chronic heart failure (CHF).\(^2\) The mechanisms involved in sympathetic dysfunction in these disorders appear to be complex and multifactorial. A unified hypothesis is likely to encompass alterations in multiple autonomic reflex pathways, central integratory sites, and chemical mediators that control sympathetic outflow. For example, tonic restraint of sympathetic outflow by arterial and cardiopulmonary baroreflexes is depressed in CHF\(^2\) and depressed or reset in hypertension.\(^3\) Moreover, maladaptive changes also occur in the central nervous system at integrative sites for autonomic control in both disease processes.\(^4,5\) It is also clear that sympathoexcitatory cardiac,\(^6\) somatic,\(^7\) and central/peripheral chemoreceptor reflexes\(^8\) are enhanced in CHF and hypertension.

Arterial chemoreceptors serve an important regulatory role in the control of alveolar ventilation, but they also exert a powerful influence on cardiovascular function.\(^9\) Activation of arterial chemoreceptors by hypoxemia increases sympathetic outflow to systemic vascular beds to compensate for the direct vasodilating effects of hypoxia on these vessels and to redistribute blood flow to essential organs. In this review, we highlight relevant information that implicates the arterial chemoreflex as a contributory mechanism for the sympathetic hyperactivity in CHF and hypertension and illustrate proposed mechanisms for this altered function.

The Sympathetic Response to Arterial Chemoreceptor Activation

Arterial chemoreceptors located in the aortic and carotid bodies (CBs) respond to hypoxemia and hypercapnia. Because central chemoreceptors also respond to hypercapnia, hypoxia is typically used as a specific stimulus to arterial chemoreceptors. In some mammals, such as rats and rabbits, reflex responses to hypoxemia arise solely from the CB, whereas in other species, the aortic chemoreceptor contribution can be significant. However, it is not possible to experimentally separate the relative contribution of the aortic and CBs to reflex responses in conscious animals or humans. For these reasons, discussions on the arterial chemoreflex generally relate functionality to that of the CB, which has been more extensively studied.

Glomus cells in the CB depolarize in response to hypoxia and release multiple putative neurotransmitters (including acetylcholine, serotonin, ATP, and substance P) that activate impulses in afferent fibers traveling to the medulla via the carotid sinus nerve.\(^10\) Arterial chemoreceptor stimulation in freely breathing humans and conscious animals increases sympathetic vasoconstrictor outflow to muscle, splanchnic, and renal beds to elevate arterial pressure, and, in humans, increases cardiac sympathetic activity to increase heart rate and contractility.\(^9\) There is preferential activation of sympathetic fibers going to the adrenal gland to increase norepinephrine but not epinephrine release.\(^11\) However, sympathetic activity to brown adipose tissue is decreased\(^12\) to facilitate a lowering of body temperature, an adaptive response to reduce oxygen consumption during hypoxia. Parasympathetic and sympathetic fibers to the heart and cerebral vessels are concomitantly activated.\(^9\) This dual response likely serves to limit sympathetic vasoconstriction of coronary and cerebral vessels during hypoxemia and to limit or modify cardiac chronotropic and inotropic responses, depending on the conditions.\(^9\)

Sympathetic efferent responses to arterial chemoreflex activation are tightly coupled to the increase in rate and magnitude of phrenic nerve activity (PNA) to increase ventilation.\(^13\) Significant interaction of central respiratory areas with presympathetic neurons in the medulla dictate that SNA is often clustered in bursts in phase with ventilation, peaking during early expiration.\(^13\) In addition, enhanced SNA during chemoreceptor activation is progressively blunted as tidal volume increases because of inhibitory feedback from pulmonary volume receptors.\(^14\) As a result, when chemoreceptor activation occurs during apnea, where pulmonary volume feedback is abrogated, sympathetic activation is maximized. The sympathetic response is also influenced by the rate of ventilation. Rapid breathing rate enhances the sympathetic response to chemoreflex activation.\(^15\) Conversely, slow breathing reduces arterial chemoreflex responsiveness.\(^16\)

The dynamics of the ventilatory and sympathetic responses to arterial chemoreceptor stimulation are complex. PNA and SNA increase within seconds of exposure of the CB to...
hypoxemia, and as hypoxia ensues, the magnitudes of SNA and PNA increase asymptotically and are maintained, whereas the ventilatory rate increases transiently and then progressively declines. When hypoxic stimulation is removed, PNA and SNA gradually return to baseline rather than decrease abruptly (short-term potentiation). In humans, a sustained period of hypoxemia for \( \approx 20 \) minutes can elevate muscle SNA for as long as 1 hour after blood gases and ventilation return to control. In rats (acute intermittent hypoxia), both PNA and SNA remain elevated for as long as \( \approx 1 \) hour, a phenomenon called long-term facilitation.

The extent to which hypertension and CHF influence this complex and highly differentiated integration of sympatho-spiro-motor responses to arterial chemoreceptor activation is far from being fully realized. However, there is good evidence to indicate that the sensitivity of the arterial chemoreflex is enhanced in certain types of neurogenic hypertension and in CHF and that the enhanced CB function contributes to tonic elevation in sympathetic outflow to resistance vessels and kidney.

### Arterial Chemoreflex in Heart Failure

The role of arterial chemoreflex mechanisms in heart failure has received considerable attention but not without controversy. An exaggerated ventilatory response to hyperoxic hypercapnia, indicative of an enhanced central chemoreflex, has been consistently observed in humans with CHF, but the ventilatory response to isocapnic hypoxemia, an index of arterial chemoreflex function, is not altered in many patients with CHF. Similarly, acute inhibition of arterial chemoreceptors with hyperoxia (Dejou’s effect) has no effect on resting muscle SNA in some studies on CHF patients. By contrast, other groups have found an enhanced ventilatory response to hypoxia in CHF patients, particularly those in more severe stages of the disease.

Although results from clinical studies have been variable, we have documented an enhanced arterial chemoreflex function in a rabbit model of pacing-induced CHF. Although the cardiac pathology of tachycardia-induced ventricular failure differs somewhat from ischemic heart disease in patients, it induces a similar systemic hemodynamic impairment, with sympathohumoral activation and altered autonomic reflexes, as observed in patients and animal models with ischemic heart failure.

With monitoring of renal SNA (RSNA) in conscious animals as an index of sympathetic outflow, we have documented that resting (normoxic) and hypoxic activation of RSNA (Figure 1) and ventilation progressively increase in rabbits as they are paced over 3 to 4 weeks. During this interval, unpaced left ventricular contractility and ejection fraction decline to levels equivalent to moderate compensated CHF in patients. Single-unit discharge activity of CB chemoreceptors, both at rest and in response to hypoxia, is similarly enhanced over the same time course (Figure 2A). This increased central input from the CB provides a tonic excitatory influence on sympathetic outflow, because hyperoxia reduces resting RSNA in CHF but not control animals (Figure 2B). Moreover, resting RSNA and plasma norepinephrine levels are attenuated in CHF rabbits with CB denervation. These studies confirm clinical evidence suggesting that arterial chemoreflex function is enhanced in CHF and further demonstrate that enhanced CB function is an important contributory mechanism for sympathetic activation in CHF.

### Mechanisms of Enhanced Arterial Chemoreflex in Heart Failure

Because sleep apnea (SA) is highly correlated with CHF, and SA enhances arterial chemoreflex function (see discussion below), it is possible that SA may contribute to arterial chemoreflex activation in patients with CHF with breathing disturbances. However, chronic recordings of breathing in CHF rabbits discount this as an essential mechanism in this animal model. Enhancement of arterial chemoreflex func-
tion begins to occur as early as the first week of pacing, with no evidence of arterial hypoxemia, hypercapnia, or altered breathing. Similarly, the incidence of SA in patients with CHF correlates with the severity of the disease and, thus, does not seem to be a predisposing factor for altered chemoreflex function in early heart failure.

Although neither chronic nor intermittent hypoxia can be implicated in the alteration in CB function in CHF animals, there are numerous neurohumoral factors that are altered in the CHF, such as angiotensin II (Ang II), NO, catecholamines, and endothelin, among others, that are known to affect CB chemoreceptor function. The role of some of these factors in altered CB function in CHF remains largely unexplored, but there is good evidence that Ang II and NO play major roles.

Systemic and tissue Ang II levels are increased in patients with CHF, and Ang II enhances chemoreceptor activity via the angiotensin II receptor subtype 1 receptor (AT1R) in the CB. Furthermore, a local Ang II system is operational in the rabbit CB. CHF upregulates the Ang II level and the expression of AT1R in the CB. The marked down regulation of endogenous nNOS in the CB activity and normalized RSNA in CHF rabbits compared with normal. Hyperoxia inhibited CB activity and normalized RSNA in CHF rabbits. *P<0.05 vs room air; #P<0.05 vs normal.

Systemic administration of Ang II in conscious rabbits (to levels equivalent to the endogenous plasma Ang II level in CHF rabbits) enhances hypoxia-induced chemoreflex activation of sympathetic outflow. Furthermore, blockade of AT1R in CHF rabbits attenuates (i.e., normalizes) the exaggerated hypoxia-induced chemoreflex responses observed in CHF rabbits. Afferent recordings from the isolated CB confirm that elevation of Ang II and AT1R in the CB enhances chemoreceptor sensitivity to hypoxemia in CHF rabbits.

The mechanism by which Ang II enhances the hypoxic sensitivity of the CB chemoreceptors involves an interaction with oxygen sensitive, voltage-gated potassium channels (Kvo2) in CB glomus cells. Hypoxic inhibition of Kvo2 channels is enhanced in isolated CB glomus cells from CHF rabbits, and blockade of AT1R alone is capable of reversing this enhanced hypoxic sensitivity. In addition, exposing normal rabbit CB glomus cells to Ang II mimics this effect of Ang II on Kvo2 channel function.

AT1R promotes activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase with superoxide anion production. In the CB, expression of NADPH oxidase subunits and superoxide anion production are enhanced in CHF rabbits. The elevated superoxide anion level can be normalized by AT1R antagonists, NADPH oxidase inhibitors, and the superoxide anion scavenger Tempol. Similarly, NADPH inhibitors and Tempol normalize the enhanced CB chemoreceptor discharge to hypoxemia and normalize the enhanced sensitivity of Kvo2 channels to hypoxia in CB glomus cells from CHF rabbits. These results suggest that the NADPH oxidase–superoxide anion pathway mediates the effects of Ang II in the CB to enhance hypoxic sensitivity in the CHF state.

Despite the potent effects of Ang II–AT1R on the sensitivity of the CB to hypoxemia, AT1R blockade does not alter chemoreceptor discharge or Kvo2 currents in glomus cells at normoxia in CHF animals. Thus, Ang II cannot account for the enhanced chemoreceptor activity under normal resting conditions observed in CHF rabbits. Other evidence suggests that downregulation of an NO mechanism is likely to participate in the enhanced basal activity in the CB in CHF.

Both neuronal NO synthase (nNOS; NOS) and endothelial NOS are present in the CB, and NO is inhibitory to CB activity. Because O2 is essential for biosynthesis of NO, during normal normoxic conditions, basal production of NO acts as an amplifier of O2 to keep CB chemoreceptor discharge suppressed. However, basal NO production and nNOS expression within the CB are depressed in CHF. Thus, the tonic inhibitory effect of NO on the activity of CB chemoreceptors, demonstrated in the CB of normal rabbits, is virtually absent in CHF rabbits.

The marked down regulation of endogenous nNOS in the CB plays a major role in the enhanced CB chemoreceptor activity in CHF rabbits. Adenoviral gene transfer of nNOS to the CB in CHF rabbits enhances protein expression and NO production in the CB and reverses the enhanced CB chemoreceptor activity seen in the CHF state. Furthermore, gene transfer of nNOS to the CB in CHF rabbits reduces resting RSNA. These results provide important evidence of a measurable contribution of enhanced CB chemoreceptor input to elevated sympathetic outflow in CHF and the contribution of nNOS downregulation in the CB to this effect.

We have shown further that NO inhibits CB chemoreceptor discharge by activation of calcium-dependent voltage-gated K ( KCa) channels via a cGMP-dependent pathway in CB glomus cells in rabbits. KCa channel current is markedly
suppressed in glomus cells from CHF rabbits under normoxic conditions because of NO depletion, and the attenuated \( \text{K}\text{Ca} \) channel current contributes to the depolarized resting membrane potential observed in the CHF glomus cells. However, an inwardly rectifying \( \text{K}^+ \) current carried by the HERG-like \( \text{K}\text{Ca} \) channel (named for the human ether-a-go-go related gene that encodes the channel protein) has been reported in rabbit glomus cells, which could also influence the resting membrane potential.

The concurrent downregulation of the nNOS/NO pathway and upregulation of the Ang II/superoxide anion pathway in the CB of CHF rabbits raises the question of whether these pathways interact to enhance CB excitability via oxidative stress. Ang II may contribute to depressed bioavailable NO in the CB by suppressing nNOS gene expression and/or increased scavenging of NO through superoxide anion production. Conversely, the downregulation of NO production in the CB in CHF is likely to enhance the effects of Ang II by reduced scavenging of superoxide anion by NO. The relationship among nNOS, NO, Ang II, and superoxide anion on CB chemoreceptor function is not yet clear and deserves further study.

Existing evidence of the role of endothelial NOS versus nNOS in the CB is somewhat controversial. Studies have shown that specific nNOS inhibitors are ineffective in altering CB ventilatory responses in rats. On the other hand, transgenic mice lacking nNOS show greater ventilatory responses to hypoxia than wild-type controls, whereas responses to hypoxia are blunted in mutant mice lacking endothelial NOS. We have observed a downregulation endothelial NOS in the CB of CHF rabbits (YL Li and HD Schultz, unpublished data) but have not yet investigated the functional consequence of this change.

**Blood Flow Effects on CB Function in Heart Failure**

The stimulus for upregulation of local Ang II/AT1R signaling and downregulation of NOS/NO in CB glomus cells during CHF is not clear. However, the changes in potassium voltage channel function described in glomus cells in CHF rabbits and in glomus cells from rabbits exposed to chronic hypoxia are similar in most respects to those described in glomus cells from CHF rabbits exposed to chronic hypoxia. Thus, a decreased cardiac output from the failing heart may decrease blood flow and \( \text{O}_2 \) delivery to the CB sufficiently to mimic effects of chronic hypoxia.

In CHF rabbits, a progressive decline in carotid flow occurs as cardiac function deteriorates over the course of 3 weeks of pacing (please see the data supplement, available online at http://hyper.ahajournals.org). A similar profile of progressive reduction in carotid artery blood flow imposed with bilateral adjustable cuff occluders enhances CB chemoreflex activation of RSNA in response to hypoxia (Figure 3A and 3B) and enhances CB chemoreceptor discharge (Figure 3C), similar to changes observed in CHF rabbits. It is unlikely that these responses are driven simply by an acute reduction in blood flow to the CB, because chemoreflex and afferent responses are still normal after only 1 day of occlusion. Immunohistochemical examination of the CB after chronic carotid occlusion revealed an increase in AT1R and decrease in nNOS expression. These results support the concept that a chronic reduction in oxygen delivery to the CB precipitates altered CB function in CHF.

The link between reduced carotid flow and altered signaling in the CB has not yet been explored. Relevant evidence indicates that angiotensin-converting enzyme in the CB is markedly increased in the CB of rats within 1 week of exposure to chronic hypoxia. A similar phenomenon may occur in response to chronically reduced blood flow to the CB. Ultimately, such changes in protein expression must be related to effects on gene transcription. Possibilities include activation of hypoxia-inducible factor-1 and/or activator protein-1, gene transcription factors that are known to be activated in the CB in response to hypoxia.

Although enhanced Ang II/AT1R and reduced NOS/NO in the CB were shown to have direct effects on \( \text{K}^+ \) channel...
function in CB glomus cells, it is not known whether these altered signaling pathways also act to further reduce blood flow to the CB and enhance CB chemoreceptor sensitivity by way of their vasoactive properties. In addition, it is known that sympathetic efferent feedback to the CB can reduce CB blood flow and activate CB chemoreceptors. The contribution of these various factors to CB vascular function in CHF need to be elucidated.

**Arterial Chemoreflex in Hypertension**

Functional studies in humans with established and borderline essential hypertension and in genetic spontaneously hypertensive rats (SHRs) have shown a hyperventilation under resting conditions and enhanced respiratory and SNA reactions to hypoxia. In addition, CB chemoreceptor neural discharge to hypoxemia is exaggerated in SHRs.

One study, however, suggests that the exaggerated CB chemoreflex in SHRs is not linked to hypertension but to differences in rat strain. In addition, not all forms of hypertension are correlated with enhanced chemoreflexive drive. In renal hypertensive rabbits, CB function appears to be unaltered. Despite these inconsistencies, studies on humans with borderline and established essential hypertension consistently show enhanced arterial chemoreflexive drive. Furthermore, acute inhibition of arterial chemoreceptors with hyperoxia evokes ventilatory and SNA depression to a much greater extent in patients with essential hypertension than in control subjects.

A link between neurogenic hypertension and enhanced arterial chemoreflex function has been more extensively studied in patients and in animal models of SA. Patients with SA are at high risk for developing sustained arterial hypertension and exhibit an elevated level of resting muscle SNA that persists throughout the day when periods of apnea are nonexistent. Patients with SA exhibit markedly enhanced chemoreflex responses to hypoxemia, whereas SNA responses to hyperoxic hypercapnia (central chemoreflex) and cold pressor tests are normal. Similar to that seen in patients with essential hypertension, hyperoxia markedly blunts muscle SNA and reduces arterial pressure in patients with SA.

A rat model of chronic intermittent hypoxia (CIH) exposure that mimics a pattern of hypoxic episodes experienced by patients with SA has been instrumental in the exploration of this issue. Rats exposed to extended periods of nighttime-only CIH develop hypertension and persistent sympathetic activation similar to that seen in patients with SA. Chronic CB denervation prevents the development of hypertension and SNA activation. Furthermore, CIH enhances CB chemoreceptor discharge to hypoxemia but not to hypercapnia. In fact, even a single bout of intermittent hypoxia evokes sustained activation of both CB chemoreceptor activity and SNA for extended periods after the hypoxic challenge is removed (sensory and functional long-term facilitation of the CB chemoreflex). These studies provide compelling evidence that intermittent periods of hypoxemia can tonically enhance arterial chemoreceptor drive to increase sympathetic outflow and precipitate hypertension.

There is a high correlation of obesity and metabolic syndrome with elevated SNA and hypertension as well. The fact that obstructive SA is often associated with these conditions may explain why arterial chemoreflex function is enhanced in these patients. Although the concept has been proposed, no one has evaluated whether chemoreflex function is enhanced in metabolic syndrome independent of SA as a risk factor or whether chemoreflex function contributes to the sympathetic hyperactivity.

**Mechanisms of Enhanced Arterial Chemoreflex in Hypertension**

To our knowledge, the mechanism by which arterial chemoreflex function is enhanced in SHRs has not been explored. Fukuda et al demonstrated that multiunit chemoreceptor activity is enhanced from the CB in SHRs in response to hypoxia but not hypercapnia, but mechanisms for the enhanced CB activity in SHRs are not known. Other studies have shown that inhibition or lesions of commissural subnuclei of the nucleus tractus solitarii in the medulla, where CB chemoreceptors project, reduce blood pressure in SHRs. Although such lesions may not be specific for the arterial chemoreflex, this evidence raises the possibility that enhanced CB chemoreceptor function contributes to elevated sympathetic activity in genetic hypertensive rats.

Essential hypertensive patients and SHRs exhibit hypertrophied CBs, resembling that which occurs in chronic exposure to high altitude or chronic hypoxia. The mechanisms responsible for this effect and its relation to enhanced CB function are still poorly understood. However, CB hypertrophy has not been consistently observed in patients or animal models of CHF and SA, despite enhanced CB function in these disease states.

Peng et al demonstrated that CIH in rats enhances normoxic and hypoxic CB chemoreceptor discharge. Chronic intermittent hypercapnia was without effect. It was proposed that the effects of CIH on the CB are comparable to that of ischemia–reperfusion in other tissue, which is known to enhance superoxide anion production and oxidative stress. Indeed, the facilitatory effect of CIH on CB afferent activity is completely abolished in rats treated with a superoxide scavenger. Congruently, superoxide anion levels are elevated in CBs from CIH-exposed animals.

The cellular mechanisms of CIH-induced superoxide anion production in the CB suggest alterations in both mitochondrial and membrane redox pathways. Downregulation of mitochondrial complex I but not complex III occurs in CBs from CIH rats. In addition, inhibition of complex I increases reactive oxygen species in mitochondria from CB of normal rats but not from that of CIH rats, whereas inhibition of complex III increases oxygen radicals in both groups. On the other hand, evidence also suggests that 5-hydroxytryptamine in the CB may be involved in the response, because 5-hydroxytryptamine can induce long-term facilitation in the CB by way of activation of NADPH oxidase and superoxide anion production. Still unresolved is the mechanism by which CIH-induced superoxide anion production increases the sensitivity of CB glomus cells and afferent chemoreceptor activity to hypoxia. Based on our work described above, an inhibitory effect of superoxide anion on KVO2 channels in glomus cells is possible.
Other investigators have demonstrated that endothelin-1 (ET-1) may also be involved in the enhanced CB function with CIH. ET-1 is expressed in the CB, induces CB chemosensory excitation, and potentiates the chemosensory response to acute hypoxia. ET-1 immunostaining in the CB vasculature and glomus cells is increased in cats exposed to CIH, whereas ET-1 plasma levels are unchanged. A nonselective ET receptor antagonist, bosentan, reduces the elevated normoxic and hypoxic CB discharge induced by CIH.

Upregulation of both ET-1 expression and enhanced superoxide anion signaling in the CB in response to CIH appears to be related to activation of hypoxia-inducible factor-1 and/or activator protein-1. These transcription factors, induced by hypoxic challenges to the CB by either periodic bouts of hypoxemia during apneas or chronically reduced blood flow, may be the common denominator for altered CB function in hypertensive and CHF states.

Vascular Effects on CB Function in Hypertension

Indirect evidence suggests that the excitatory effect of ET-1 on CB chemoreceptor activity in CIH is because of its vasoconstrictive effect to reduce CB blood flow and O₂ delivery, at least during normoxic conditions. ET-1 itself has little effect on chemoreceptor activity under normoxic conditions in the superfused CB preparation, which is devoid of vascular effects. Nevertheless, ET-1 can enhance CB responses to hypoxia in superfused CB preparations, possibly by enhancing voltage-gated (L-type) calcium current in CB glomus cells in response to hypoxia via a cAMP/nositol triphosphate pathway. However, because CB chemoreceptor activity is elevated under normoxic conditions in CIH animals, the vascular effects of the peptide are likely to play a major role in this tonic activation ofafferent input.

The sympathetic innervation of the CB and/or circulating catecholamines could conceivably play a role in enhanced CB excitability in certain hypertensive states by way of α₂ adrenergic vasoconstriction with reduction of CB blood flow. However, α₂ adrenergic receptors in the CB inhibit chemoreceptor discharge by inhibiting norepinephrine release; thus, the net effects of sympathetic feedback on the CB are difficult to predict. Although it is generally thought that sympathetic activation in response to hypoxemia has an inhibitory effect on CB responsiveness, the effects of a chronic elevation in sympathetic feedback to the CB under normoxic conditions in hypertensive states has not been addressed.

Based on evidence that Ang II and downregulation of NO are important contributory mechanisms to the development of neurogenic hypertension, these factors may exert important roles on CB function in hypertension, as well as in CHF. Alternatively, in a hypothesis article in 1981, Przybylski proposed that atherosclerosis or vascular hypertrophy may act to reduce CB blood flow and enhance chemoreceptor activity in hypertensive states. This concept also seems worthy of pursuit based on our results with chronic reduction in carotid flow.

Perspectives

To what extent does the arterial chemoreflex contribute to a chronic sympathetic activation in either CHF or hypertension? Neurohumoral control of sympathetic activity is a highly complex network of peripheral and central neural pathways, neurotransmitters, and neuromodulators. Most if not all of these integrative inputs are altered to variable degrees in these disease states and are likely to play a collective role in the sympathetic dysfunction. In this regard, there is indisputable evidence that arterial chemoreceptor activity is elevated in CHF and in essential and SA-related hypertension, and this input can contribute to sympathetic activation. Indeed, interruption of afferent input from CB chemoreceptors, by way of either hyperoxia or denervation, reduces sympathetic outflow in many patients and in animal models of these diseases. The relative importance of this chemoreflex effect, however, must be viewed in context with other changes that occur in the sympathetic system as a whole.
Summary
Chemoreceptor input is exaggerated in CHF and hypertension by chemical and hemodynamic factors in the CB. As we have summarized here, a predisposing factor involved in the enhanced chemoreceptor activity appears to be oxidative stress because of impaired oxygen delivery to the CB, either by way of intermittent hypoxic exposure from periodic apneas or reduced blood flow from impaired cardiac or vascular function (Figure 4). In CHF, upregulation of Ang II/NADPH oxidase and downregulation of NOS in the CB secondary to reduced blood flow contribute to this effect. In SA-related hypertension, upregulation of 5-hydroxytryptamine/NADPH oxidase and downregulation of mitochondrial complex I in the CB secondary to periodic bouts of hypoxemia contribute to the effect. In essential hypertension, mechanisms for enhanced CB function remain unexplored but may be related to altered vascular function in the CB. Regardless of the initial stimulus, the resultant chronic activation of sympathetic outflow is likely to amplify and perpetuate the CB disturbance, in a feed-forward manner, by exacerbating deterioration of cardiac function and cardiac output with reduced flow to the CB in CHF and by vasoconstriction with reduced flow to the CB in hypertension. Future inroads in this area will rely on further identification of chemical stimuli, signaling pathways, altered gene expression, and transcription factors responsible for this cascade of events on neural and vascular function within the CB.

Acknowledgments
We thank Lisa Rasmussen for technical assistance and Dr Irving Zucker for editorial comments.

Source of Funding
This work was supported by National Institutes of Health grant PO-1 HL62222.

Disclosures
None.

References
36. Li YL, Sun SY, Overholt JL, Prabhakar NR, Rozanski GJ, Zucker IH, Schultz HD. Attenuated outward potassium currents in carotid body


Arterial Chemoreceptors and Sympathetic Nerve Activity: Implications for Hypertension and Heart Failure

Harold D. Schultz, Yu L. Li and Yanfeng Ding

Hypertension. 2007;50:6-13; originally published online May 14, 2007;
doi: 10.1161/HYPERTENSIONAHA.106.076083

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/50/1/6

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2007/05/14/HYPERTENSIONAHA.106.076083.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/