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The Carotid Body as a Therapeutic Target for the Treatment of Sympathetically Mediated Diseases

Julian F.R. Paton, Paul A. Sobotka, Marat Fudim, Zoar J. Engelman, Emma C.J. Hart, Fiona D. McBryde, Ana P. Abdala, Nephthali Marina, Alexander V. Gourine, Mel Lobo, Nik Patel, Amy Burchell, Laura Ratcliffe and Angus Nightingale

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● Online Data Supplement

Hypertension, heart failure (HF), type II diabetes mellitus, and chronic kidney disease represent significant and growing global health issues.¹ The rates of control of blood pressure and the therapeutic efforts to prevent progression of HF, chronic kidney disease, diabetes mellitus, and their sequelae remain unsatisfactory.^{2–5} Although patient nonadherence and nonpersistence with medications participate in this failure, especially in asymptomatic disorders, the inherent complexity of drug titration, drug interactions, and both the real and perceived adverse events collectively contribute to the failure of lifelong polypharmacy. Furthermore, therapy targeting the potentially unique contribution of autonomic imbalance is limited by the poorly tolerated systemic adverse effects of adrenergic blocking agents. Recent introduction of medical procedures, such as renal denervation,^{6,7} and devices such as deep brain stimulation,⁸ baroreceptor stimulation,⁹ and direct vagus nerve stimulation¹⁰ begin to address these gaps in selective patients.

The contribution of excessive sympathetic nerve activity to the development and progression of hypertension, insulin resistance, and HF has been demonstrated in both preclinical and human experiments. Preclinical experiments in models of these diseases have successfully used sympathetic or parasympathetic modifications to alter the time course of their progression.^{11,12} Reduction of blood pressure after dorsal rhizotomy in rats with renal hypertension and reduced total body noradrenaline and muscle sympathetic nerve activity in humans after renal denervation confirm that the afferent signals from the kidney underlie some of the excessive sympathetic drive seen in these states.^{13,14} However, additional afferent signals may arise from sites elsewhere in the body and in particular the carotid body (CB). We propose targeting the CB in patients with increased chemosensitivity to address the underlying autonomic imbalance seen in hypertension, HF, insulin resistance, and chronic kidney disorders.

Rationale for the CB as a Therapeutic Target for Sympathetic Hyperactivity Syndromes

The CB: A Peripheral Chemosensor

The CB (Figure 1), the dominant peripheral chemoreceptor in humans, responds primarily to acute hypoxemia, increases in arterial carbon dioxide tension (P_{CO_2}), acidotic pH, hypoglycemia, and hypoperfusion. The CBs are 1.5- to 7.0-mm ovoid bilateral organs located at the bifurcation of each common carotid and are innervated by the nerve fibers from the glossopharyngeal (carotid sinus nerve), vagal, and the sympathetic nerve of the nearby superior cervical ganglion. The CB is the most perfused organ per gram weight in the body (2000 mL/min per 100 mg of tissue) and receives blood via an arterial branch arising from internal or external carotid artery. Proposed underlying mechanisms for hyperactivity of the chemoreceptors are local hypoperfusion, inflammation, and changes in ASIC/TASK (acid-sensing ion channel/2-pore domain acid-sensing K(+) channel) channels, as well as the balance between carbon monoxide and hydrogen sulphide and the relative activity of hypoxia-inducible transcription factor (HIF)-1 α versus HIF-2 α .^{15–18} Stimulation of the CB drives systemic sympathetic tone through direct signaling to the nucleus tractus solitarius and rostral ventrolateral medulla oblongata resulting in an increase in blood pressure and minute ventilation.¹⁹ Separately, the carotid baroreflex originates from the carotid sinus, an outpouching of the internal carotid artery, and houses mechanoreceptors, which buffer acute changes in blood pressure through modulation of both parasympathetic and sympathetic nervous systems. Additional baroreflex input to the brain comes from numerous mechanoreceptors, including those found in walls of the internal, external, and common carotid arteries; aorta; and kidney. Chemoreflex and baroreflex are linked in control of sympathetic tone; chemoreflex mediates sympathoactivation and inhibition of baroreflex function.²⁰

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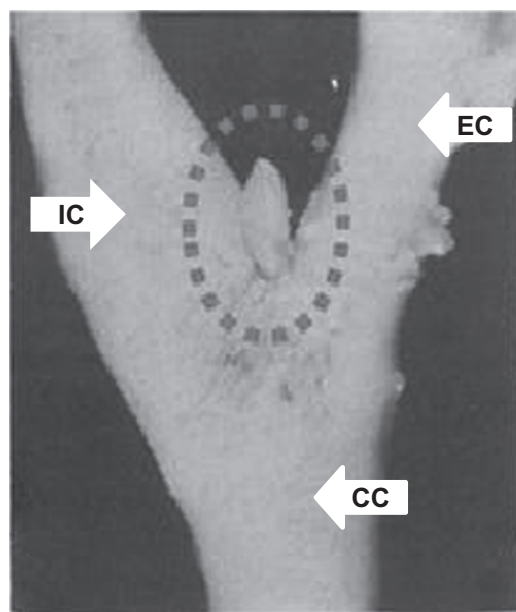


Figure 1. Gross-anatomical appearance of the human carotid body (CB). The CB is ≈ 1.5 – 7.0 mm long and equivalent to the size of a grain of rice. CC indicates common carotid artery; EC, external carotid; IC, internal carotid. Modified from Khan et al.⁶⁶

Peripheral chemosensitivity is clinically assessed by measuring the ventilatory response, changes of muscle sympathetic nerve activity, or physiological changes in heart rate or blood pressure in response to either inhibition or stimulation of the peripheral chemoreceptor by manipulating inhaled gas mixtures. Transient or progressive hypoxia stimulate, whereas brief hyperoxia or low-dose dopamine inhibits the peripheral chemoreflex.^{21–24} Whether CB hyperactivity can occur in the absence of increased chemosensitivity or whether increased chemosensitivity is always associated with CB hyperactivity remains to be fully validated.

As with many of the beneficial compensatory mechanisms activated in acute stress, we propose that chronic hyperactivity of the defensive chemoreflex is maladaptive and leads to the development and progression of diseases affected through chronic overstimulation of the sympathetic nervous system and inhibition of the protective baroreflex.

Therapeutic Reduction of Chemoreceptor Hyperactivity to Treat Syndromes of Sympathetic Hyperactivity

Therapeutic reduction of hyperactive peripheral chemoreflex activity to reduce systemic sympathetic hyperactivity could favorably impact the morbidity and mortality in diseases noted for autonomic imbalance, including HF, chronic and end-stage renal disease, insulin resistance, sleep disorders, and essential hypertension (Figure 2). Next, we review the available data in hypertension and HF, which identify the potential value of targeting the hypersensitive chemoreflex.

Hypertension

Preclinical Data

CB hyperactivity increases central sympathetic drive and thus contributes to hypertension through direct increases in renal neurogenic sodium avidity and increases in renal secretion of

renin, as well as neurogenically mediated increases in vascular resistance.²⁵ The physiological significance of this has been explored in both preclinical and human trials.

Lesske et al²⁶ induced hypertension in rats using 30 days of intermittent hypoxia. Unlike animals with intact CBs, the chemoreceptor-denervated animals lost their hypertensive response to hypoxic stimuli. In the same model of intermittent hypoxia, chemical denervation of the peripheral sympathetic synapses by 6-hydroxy dopamine or hexamethonium eliminated the expected hypoxia-induced increase in blood pressure, confirming that the CB initiated a sequence of neurally mediated events and that CB ablation is sufficient to obliterate this sequence.^{26,27}

More recently, Abdala et al²⁸ have reported that interference with CB signaling, by interrupting its afferent nerves, results in significant blood pressure reduction in both developing and adult spontaneously hypertensive rats but no changes of pressure in normotensive animals. This was reported originally in April 2011.^{29,30} Interestingly, CB denervation caused an improvement in baroreceptor function, potentially caused by a resetting of the central baroreceptor control (Figure 3).²⁸ It follows that the latter may contribute to the blood pressure-lowering effect of CB denervation. Given the increase in baroreceptor cardiac vagal gain,²⁸ it is predicted that cardiac vagal tone and heart rate variability are enhanced, but this awaits confirmation.

Whiteis et al³¹ recently showed that spontaneously hypertensive rats that underwent CB denervation demonstrated significantly lower mean blood pressure than sham-operated spontaneously hypertensive rats (202 ± 2 versus 239 ± 6 mm Hg; $P < 0.05$) and prevented the development of left ventricular hypertrophy at 5 months postsurgery.

Inhibition of CB Activity for the Treatment of Hypertension in Humans

Similar to rats, human experiments have documented the relation between hypersensitive chemoreflex and abnormalities of blood pressure. Trzebski et al³² studied 20 subjects with mild hypertension versus age- and sex-matched control subjects. Ventilatory and blood pressure responses to hypoxia were greater in the hypertensive subjects. Interestingly, there was a significant correlation between the responses to hypoxia and hypercapnia in the normotensive subjects but not the hypertensive subjects, suggesting a predominant role for peripheral but not central chemosensors in hypertension.³²

Two independent studies of acute hyperoxia in young untreated hypertensive subjects demonstrated a marked reduction in systolic and diastolic blood pressures mediated by substantial reduction in peripheral vascular resistance.³³ The results suggest that augmented tonic drive from arterial chemoreceptors is one of the mechanisms responsible for the elevated arterial blood pressure and total peripheral resistance in human early essential hypertension, which is consistent with the spontaneously hypertensive rats.²⁸ Similar results have been reported after chemoreflex inhibition with hyperoxia in young patients with borderline or mild hypertension or a family history of hypertension.³⁴ These data suggest that the CB may be an early contributor to the genesis of essential hypertension. Thus, increased chemosensitivity, identified by enhanced hypoxic ventilatory drive, is characteristic of subjects with essential hypertension, in young subjects with

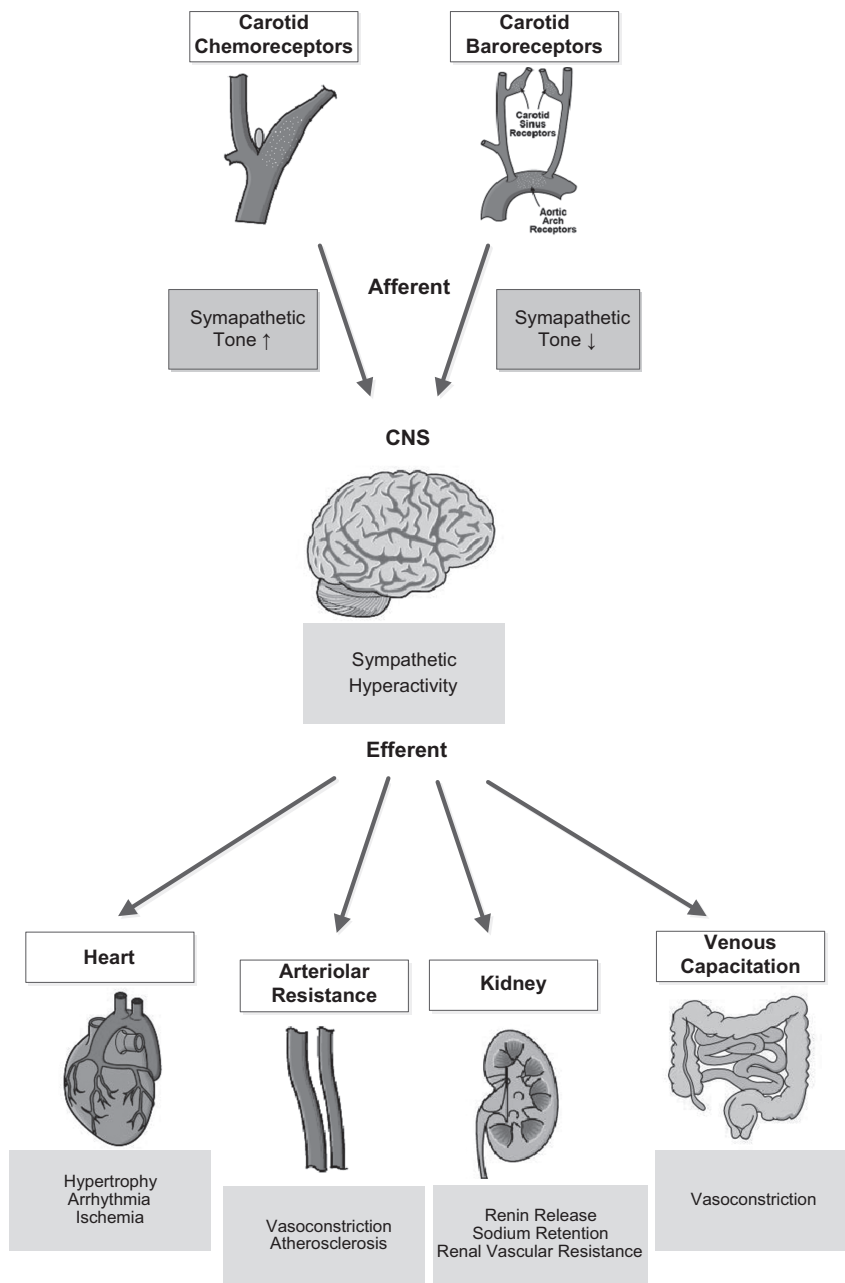


Figure 2. Schematic representation of the carotid chemoreceptor and baroreceptor reflexes. Afferents relay through the brain stem to affect sympathetic activity controlling the function of a variety of end organs. This includes both physiological responses affecting arterial pressure and pathophysiological effects, such as hypertrophy and atherosclerosis. CNS indicates central nervous system.

mild hypertension, and in subjects with normal blood pressure but with a family history of hypertension.^{26,34–36} In addition, muscle sympathetic nerve activity responses to hypoxia are potentiated in patients with borderline hypertension.³⁷ This later result confirms the contribution of the peripheral chemosensor to central sympathetic drive.

Is Surgical Removal of the CB a Treatment for Hypertension?

Nakayama³⁸ documented sustained blood pressure reductions after CB resection, while performing a clinical series from 1940s to 1960s. Although he did not show long-term benefit in ventilatory parameters in those disease states, he reported blood pressure findings in 29 patients in a single series: a reduction in systolic blood pressure from 170 mm Hg preoperative to 130 mm Hg at 5 days postoperative and this reduction

was maintained throughout the duration of the study (ie, 6 months; Figure 4).³⁸ Additionally, Winter and Whipp³⁹ noted acute blood pressure reductions (Figure 5) after CB removal.

These results are comparable with the results of selective renal nerve ablation, as demonstrated in the Symplicity hypertension 1 and hypertension 2 trials with an average reduction of $-28/-10$ mm Hg at 6 months,^{6,7} and the carotid sinus stimulator experience in hypertension with an average reduction of $-34/-20$ mm Hg.^{9,40,41}

Heart Failure

Sympathetic activation is a seminal feature of chronic HF, underlying both initiation and progression of the syndrome.^{42,43} These elevations of sympathetic tone are linked to impairment of inhibitory baroreflex control of cardiovascular function.⁴⁴

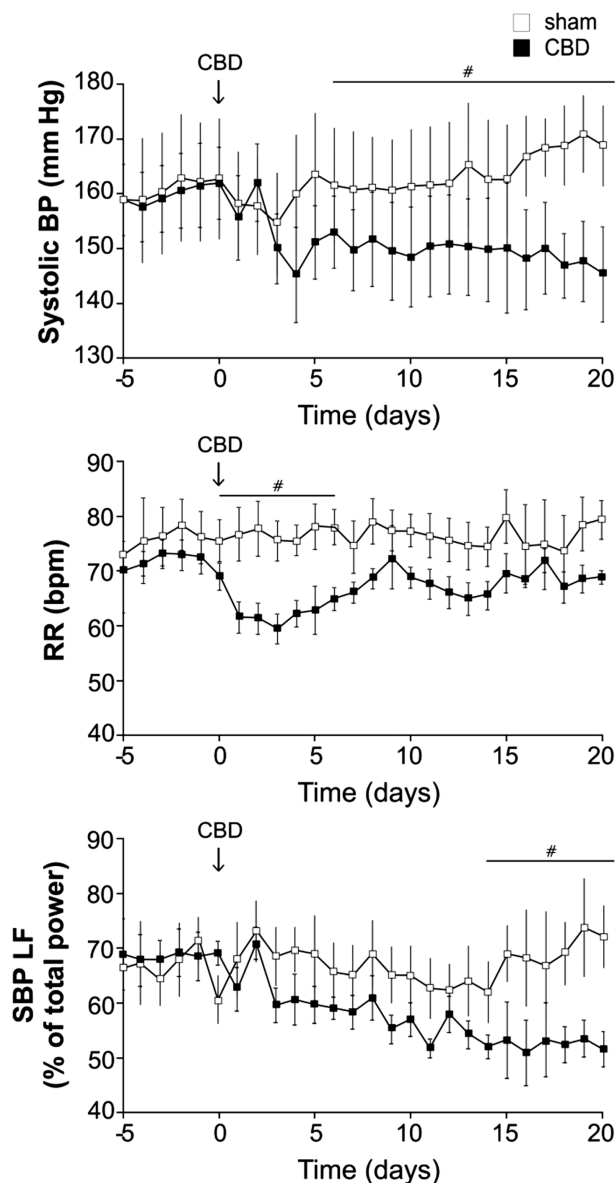


Figure 3. In established hypertension, carotid body denervation (CBD) is antihypertensive, lowers respiratory rate (transiently) and the low frequency of systolic pressure in the spontaneously hypertensive rats (SHR). Time profile of systolic blood pressure (SBP), respiratory rate (RR, breaths per minute), and low frequency (LF) of SBP (an indirect index of vasomotor tone) 5 days before and 21 days after either CBD (arrowed; $n=8$) or sham surgery ($n=7$) in adult (12 week) SHR. SBP fell by ≈ 25 mm Hg post-CBD and showed no signs of recovery. $\#P<0.05$. Data from Abdala et al.²⁸

Increased tonic excitatory input from peripheral chemoreceptors can contribute to sympathetic overactivity⁴⁵ and cardiac baroreceptor dysfunction²³ and poor outcome.^{23,24} Increases in peripheral chemoreflex sensitivity directly decrease baroreceptor function in congestive heart failure patients, possibly contributing to sympathetic overactivity.⁴⁵

Preclinical Data Linking Chemoreflex Sensitivity to Congestive Heart Failure Pathology

Chemoreflex sensitivity is enhanced in rabbits with pacing-induced HF.⁴⁶ Nerve activity of CB chemoreceptors and renal sympathetic nerve activity (RSNA), both at rest and in response

CHANGES IN BLOOD PRESSURE FOLLOWING CAROTID BODY REMOVAL

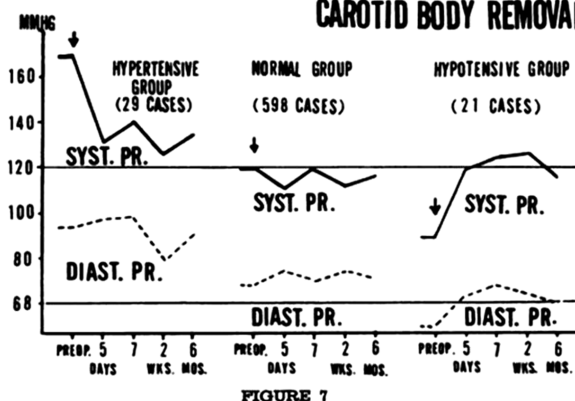


Figure 4. Blood pressure changes in patients after bilateral removal of the carotid body (CB). Follow-up until 6 months postprocedure. Arrow indicates time of CB resection. Note the persistent drop in systolic (SYST) and diastolic (DIAST) pressure (PR) in the hypertensive group. Data from Nakayama et al.³⁸

to hypoxia, is enhanced in a pacing model of HF in rabbits.⁴⁷ In this model, hyperoxic inhibition of the chemoreflex reduces resting RSNA, documenting that the chemoreceptor hyperactivity underlies the systemic and renal-specific sympathetic hyperactivity. This increased RSNA initiates the triad of renin release, sodium retention, and reduced renal blood flow, all 3 documented components of the cardiorenal syndrome. Furthermore, CB denervation in this HF model results in attenuation of both resting RSNA and plasma norepinephrine levels. These animal data demonstrate that CB chemoreflex function is hyperactive in HF and that excessive CB activity is sufficient to cause chronic increases of systemic and renal-specific sympathetic signaling, whereas CB removal attenuates both systemic sympathetic nerve activity and RSNA.

The specific mechanisms underlying the excessive chemosensory output from the CB in HF are being elucidated. Studies indicate that activation of the local angiotensin II system^{18,46} and a decreased neural nitric oxide synthase–nitric oxide pathway^{48–50} in the CB are involved in the augmentation of CB chemoreceptor activity induced by HF. Recently, Ding et al⁵¹ showed that chronically reducing blood flow to the CB, to the same degree as seen in pacing-induced HF, results in excessive CB activity. This implies that derangements of CB perfusion, secondary to HF or because of elevated sympathetic activity to CB arterioles and local inflammation, are sufficient to initiate chemoreflex hypersensitivity and subsequent further increases in systemic sympathetic and decreases in parasympathetic function.

These data provide a mechanistic basis for the hypothesis that a reduced cardiac output and attendant CB hypoperfusion in advanced HF may underlie a tonic activation of CB afferent output sufficient to cause reflex sympathetic hyperactivation. Additional intermittent hypoxia or acidosis or inflammation (all likely to occur in patients with sleep apnea) could cause further episodic activation of CB reflexes. Inactivation of CB reflexes would therefore attenuate this process.

Chemoreflex inhibition after selective CB infusion with dopamine has been used to demonstrate the physiological

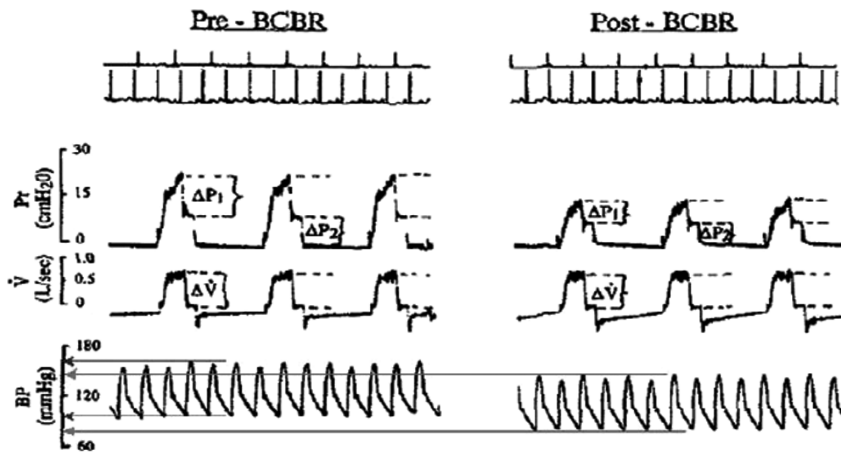


Figure 5. Cardiovascular and respiratory changes after bilateral removal of the carotid body (CB). CB removal in a cohort of 32 patients with chronic obstructive pulmonary disease and asthma.³⁹ Although not the primary purpose of surgery in these patients, arterial blood pressure reduction was noted. This figure illustrates the hemodynamic responses to prebilateral carotid body removal (pre-BCBR) data are at the end of 15 minutes of steady state and the postbilateral carotid body nonselective denervation (post-BCBR) corresponds with 5 minutes after the completion of the procedure. Importantly, there was an acute reduction in both systolic and diastolic blood pressures of ≈ 20 mm Hg.

importance of chemoreflex hypersensitivity in a pacing model of HF in dogs. In healthy dogs, CB inhibition during exercise (but not at rest) caused an immediate vasodilatory response and a decrease in blood pressure. When comparing vasodilation from CB inhibition versus α -adrenergic blockade, CB activity accounts for approximately one third of the total sympathetic activity during exercise. In contrast to healthy dogs, CB inhibition at rest in HF dogs produces vasodilation, and a similar vasodilatory response during exercise, findings that were abolished by α -adrenergic blockade. These results verify an important role for the CB in sympathetically mediated cardiovascular control in the healthy animal during exercise and in the HF animal both at rest and during exercise.⁵² This pathophysiology is consistent across multiple diseases, such as hypertension, sleep apnea, and chronic kidney diseases, all of which are characterized by enhanced chemosensitivity causing high sympathetic activity and exaggerated sympathetic restraint of blood flow to skeletal muscles. Thus, the hypersensitive chemoreflex in HF might play a critical role in the sensation of dyspnea and hence exercise intolerance in patients with these diseases.⁵²

CB Hypersensitivity Is Associated With Increased Mortality in HF

In the pre- β -blocker era, Ponikowski et al^{23,53} correlated to enhanced peripheral chemosensitivity and baroreflex sensitivity (BRS), with mortality in 80 consecutive HF patients. In these studies, chemosensitivity was defined on the basis of abnormal ventilatory responses to hypoxia and hyperoxia. The 3-year survival was 41% in patients with high chemosensitivity when compared with 77% in 53 patients without ($P < 0.0002$; Figure 6).^{23,53} In the post- β -blocker era of 110 consecutive systolic HF patients, 31 (28%) had enhanced chemosensitivity to both hypoxia and hypercapnia.²⁴ Although the high chemosensitivity patients had the same left ventricular ejection fraction as the patients with normal chemosensitivity, they were statistically more symptomatic (by New York Heart Association class), had higher plasma brain natriuretic peptide and norepinephrine levels, a steeper regression slope relating minute ventilation/carbon dioxide output (\dot{V}_E/\dot{V}_{CO_2} slope), more prevalent Cheyne-Stokes respiration, and more ventricular arrhythmias compared with the patients with normal chemosensitivity. Four-year survival was only 49%, in marked contrast to 100% for patients with normal chemosensitivity ($P < 0.001$). A multivariate analysis revealed that

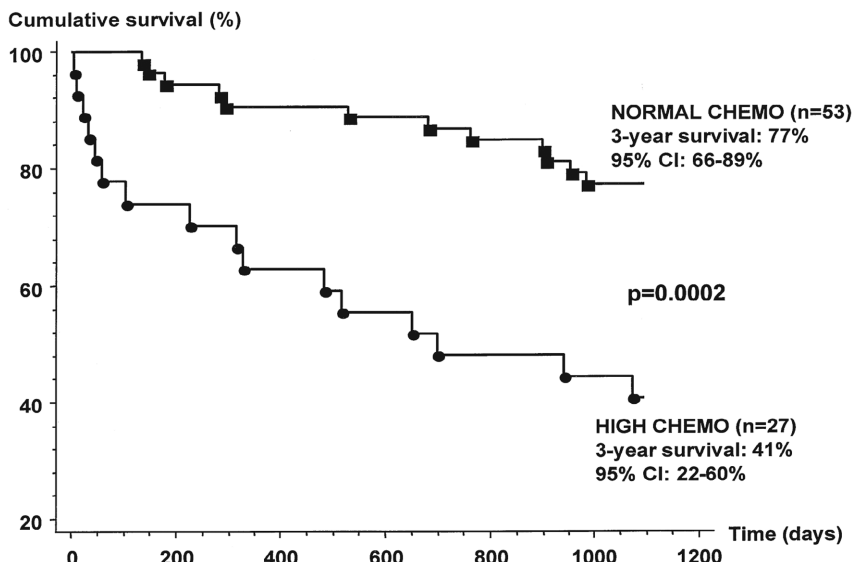


Figure 6. Kaplan-Meier plot showing survival rates of patients postmyocardial infarction. Those with high peripheral chemosensitivity, as indicated by an augmented ventilatory response to hypoxia, have a poorer prognosis than those patients with normal chemosensitivity. Data from Ponikowski et al.⁵³

elevation in chemosensitivity was the strongest independent predictor of mortality.²⁴ These data support elevated sympathetic tone from CB activation/hypersensitivity correlates, and may underlie mortality and morbidity in CHF.

CB Removal, Denervation, or Blockade Improves CHF Physiology

Transient hyperoxia to suppress CB activity has a marked beneficial effect on BRS and heart rate variability in patients with HF. In 26 stable HF patients, peripheral chemosensitivity, heart rate variability, and BRS were performed by spectral analysis of HR, and 12 patients underwent repeat testing under conditions of transient 100% O₂ hyperoxia. At baseline, peripheral chemosensitivity correlated inversely with heart rate variability ($r=-0.52$; $P=0.006$) and BRS ($r=-0.60$; $P=0.005$). Transient hyperoxia resulted in an improvement in both autonomic balance and BRS.²³

Subsequently, Moore et al⁵⁴ evaluated 12 patients with chronic HF who underwent serial submaximal and maximal exercise tests at inspired oxygen concentrations of 21% (room air), 30%, and 50%, sufficient to suppress excess chemoreflex activity. Mean (\pm SD) exercise duration during progressive testing to maximum exercise capacity was prolonged from 548 seconds (\pm 276 seconds) on room air to 632 seconds (\pm 285 seconds) on 50% oxygen ($P<0.05$). During steady-state exercise at 45 W, oxygen enrichment to 50% was associated with significantly increased arterial oxygen saturation ($94.6\pm1.9\%$ to $97.5\pm1.3\%$), and significantly reduced minute ventilation (36.1 ± 8.6 to 28.1 ± 5.9 L/min), and subjective scores for fatigue and breathlessness (13.9 ± 3.1 to 11.5 ± 3.5). Compared with room air, intermediate changes were observed with 30% inspired oxygen. Importantly, these changes occurred, despite essentially unchanged total oxygen delivery, suggesting the functional improvement was mediated by chemosensitivity modulation and not by improved peripheral oxygen delivery.⁵⁴

Beyond these hemodynamic changes, inactivation of peripheral chemoreflex hyperactivity may alter the underlying perception of dyspnea and improve respiratory dynamics. Initial experience of surgical resection of the CB for chronic lung diseases demonstrates reduced respiratory rate, which itself may contribute to reduced sympathetic tone and reductions of blood pressure, and further alters the subjective perception of dyspnea: after CB resection in 27 patients, 16 had a long-term decrease in dyspnea and 9 had increased physical activity.⁵⁵ We propose that the mechanism must be linked to removal of the peripheral chemosensitivity to CO₂.

Certainly, a hyperactive chemoreflex contributes to excessive RSNA, leading to an increase in sodium retention and volume expansion. Additionally, acute shifts of blood volume from the highly sympathetically innervated splanchnic venous storage sites to central circulation are a result of the static changes in sympathetic activity, consequent to chemosensitivity.⁵⁶ Selectively reducing splanchnic sympathetic signaling or reducing the potential for acute changes in CB contribution to systemic sympathetic drive may significantly reduce the frequency or severity of acute decompensated HF.

Similarly, the role of the peripheral chemoreceptors in modifying baroreceptor function and global sympathetic and parasympathetic activity may contribute to the propensity for HF

patients to develop tachy atrial and ventricular rhythms. Life events that are associated with excessive sympathetic drive are associated with sudden death^{57,58} and recent reports of successful treatment of catecholaminergic ventricular tachycardia with renal denervation provide a potential link between systemic adrenergic state and tachyarrhythmic potential.⁵⁹

Other Diseases of Elevated Systemic Sympathetic Activity

Similar to hypertension and HF, end-stage renal disease, chronic kidney disease, and insulin resistance are disorders associated with elevated sympathetic activity. Removal of sources of excessive sympathetic drive, such as the kidney, has been associated with improvements in blood pressure in both chronic kidney disease and reduction of insulin resistance.^{60,61} The CB may prove to be an inviting novel therapeutic target to treat chronic kidney diseases and insulin resistance. Regarding the latter, although the animal data are controversial,⁶²⁻⁶⁴ hypoglycemia has been shown to stimulate peripheral chemoreceptors with the expectation for a reflex elevation of blood glucose levels.⁶⁴ Because diabetes mellitus is often prevalent in cardiovascular disease, CB ablation could have an additional benefit in controlling plasma glucose levels.

Safety

Open surgical removal of the CB has been extensively reported between the 1940s and 1980s for the treatment of drug-resistant asthma, chronic lung diseases, emphysema, CB tumors, and carotid sinus syndrome. Details on the acute procedural and chronic outcomes of single and bilateral CB removal are available in >15 000 patients providing the basis for understanding the risks that might be associated with therapeutic CB ablation for chemoreceptor hypersensitivity syndromes.

Several different surgical techniques have been used to remove the CB and the nerves innervating this organ. Both medial and lateral surgical approaches to the CB have been used, the medial approach requiring extensive mobilization of the common carotid and its bifurcation. As a result of the small size of the CB, the procedure was typically performed without direct visualization or knowledge of its precise location.

Death From Surgical Removal of the CB Is Extremely Rare

Although initially investigators expressed concerns that CB resection might remove functions critical for survival, published mortality rates are not increased as a result of bilateral CB resection, despite the preexisting serious comorbidity.^{55,65} Among the >15 000 published cases, there are scant documentation of mortality linked to the CB removal. In the 15 000 cases, 13 cases of perioperative death were described within 48 hours after surgery. None of the deaths were related to the removal of the chemosensory function of the CB; most were related to vascular misadventure and comorbidity in a population with severe chronic lung diseases. In the online-only Data Supplement, we list the number of patients who underwent CB resection (unilateral or bilateral) for each of the reported studies we have found in the literature.

Initial anecdotal reports of mortality among deep diving, breath-holding Japanese men raised concerns about hypoxic

and hypercapnic unawareness; however, in 1991, an editorial⁶⁵ noted the complete absence of medical information on the causes of these deaths or reason to attribute the mortality to the CB resections. A reported death of a single patient with progressive and severe chronic obstructive pulmonary disease with reduced baseline PO_2 , who refused to use oxygen, suggested possible hypoxic unawareness.⁶⁶ However, and importantly, this 1 of 15 000 cases is the only known documented death that can be directly linked to CB removal. The follow-up time of the studies with >15 000 was usually >1 year, up to 20 years. Additionally, a long-term mortality study of 384 consecutive bilateral CB removal surgeries performed by the Medicare Appeals Council did not show an increased mortality.⁶⁵

Despite the theoretical concern about asymptomatic hypoxia related to the loss of peripheral chemoreceptors in patients with severe underlying lung disease, the peer-reviewed literature makes mention of only occasional episodes of asymptomatic hypoxia and identifies no patient who required medical intervention or suffered clinical consequences. This may be a consequence of the high number of redundant chemoreceptors throughout the body. Unilateral and bilateral CB removal may result in a fall in respiratory rate and minute ventilation. In hypertensive rats, bilateral CB denervation resulted in a reduction in respiratory frequency, but this was transient and recovered to baseline.²⁷ Historical surgeries for CB removal have reported a rise in CO_2 and fall in PO_2 . The changes were more pronounced in cases with structural lung disease like chronic obstructive pulmonary disease rather than in patients without structural lung like asthma.^{55,66} The rise of P_{CO_2} may provide clinical benefit to HF patients with chronic respiratory alkalosis and associated sleep disorders.

Surgical Adverse Events Related to CB Resection

The medial and lateral approaches to CB resection have associated neurological and vascular complications that might be

expected from blunt dissection of the CB and surgical denervation of surrounding periaarterial space. From the 15 000 reported CB removals and denervations, 5600 patients are reported in publications that detail surgical and perioperative complications. These complications are detailed in the table below. The most commonly reported adverse effects include transient self-limited headaches and temporary numbness of lower jaw, a probable complication of inadvertent nerve damage. The overall frequency of any adverse event during open blunt dissection is <3% (Table). Notably, these cohorts include patients with predominantly severe underlying chronic and acute pulmonary diseases and may not have had identified risk factors for advanced atherosclerosis. Thus, it is possible that open dissection with common carotid and bifurcation manipulation in atherosclerotic prone individuals could be associated with different complication rates.

Conclusions

The preclinical animal and surgical human studies have confirmed the importance of the CB in mediating sympathetic hyperactivity, heightened RSNA, and baroreflex inhibition, while demonstrating that selective CB suppression ameliorates blood pressure and left ventricular hypertrophy in animal models of hypertension and improving exercise intolerance in humans. Human epidemiologic data confirm the association of clinical chemoreflex hypersensitivity with mortality in HF. These data support the pursuit of therapeutic CB removal as a treatment strategy for human conditions where autonomic imbalance is a critical component of disease or its progression. Safety studies in humans have been initiated to examine the feasibility and describe the potential benefits of this therapeutic target. Ultimately, sufficiently powered, randomized, and controlled trials will be necessary to confirm the value of targeting the hypersensitive chemoreflex in conditions, such as essential hypertension, HF, and chronic kidney disease and insulin resistance.

Table. Sum Total of All Reported Adverse Events in 5600 Patients From 31 Publications

Adverse Event	Cases Reported	Range, %	Frequency, %
Hypertension (transient)	12	0–39	0.2
Hypertension (permanent)	22	0–33	0.4
Hypotension (transient)	4	0–3.6	0.1
Hypotension (permanent)	29	0–4.5	0.5
Headache	2	0–3.6	<0.1
Hypoglossus paresis (transient)	163	0–10	2.9
Hypoglossus paresis (permanent)	3	0–1.8	0.1
Hemiparesis (transient)	9	0–1.8	0.2
Hemiparesis (permanent)	1	0–0.08	<0.1
Vessel injury	12	0–9.5	0.2

Range is the maximum reported adverse events in individual reports. Note that the 33% only occurred in 1 article reporting a total of 3 cases in which the hypertension occurred in 1 of 3 patients and may be attributed to significant permanent damage of the baroreceptor nerves from being on the surgical learning curve with only a small number of actual CB surgeries (3) performed. Frequency = % of total reported events in all 5600 patients across 31 articles.

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Disclosures

P.A. Sobotka, M. Fudim, and Z.J. Engelman are employed by Coridea NC1, which has interests in conducting trials for carotid body resection in patients with cardiovascular disease. The other authors have no conflicts to report.

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The carotid body as a therapeutic target for treatment of sympathetically mediated diseases

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Running title: Carotid chemoreceptors and hypertension

Publication	Total n	Unilateral	Bilateral
Bencini A. Reduction of reflex bronchotropic impulses as a result of carotid body surgery. <i>International surgery</i> . 1970;54(6):415-23. Also personal communication.	2000	Non specified (according to personal communication mostly unilateral)	Non specified
Bencini C, Pulera N. The carotid bodies in bronchial asthma. <i>Histopathology</i> . 1991;18(3):195-200.	50	50	
Bernett P. [Extirpation of the glomus caroticum in bronchial asthma]. <i>Klinische Medizin; osterreichische Zeitschrift fur wissenschaftliche und praktische Medizin</i> . 1962;17:305-8.	65	59	6
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