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Carotid Body Ablation: a New Target to Address Central Autonomic Dysfunction

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Abstract

Purpose of Review An abnormal heightened carotid body (CB) chemoreflex, which produces autonomic dysfunction and sympathetic overactivation, is the common hallmark of obstructive sleep apnea (OSA), resistant hypertension, systolic heart failure (HF), and cardiometabolic diseases. Accordingly, it has been proposed that the elimination of the CB chemosensory input to the brainstem may reduce the autonomic and cardiorespiratory alterations in sympathetic-associated diseases in humans.

Recent Findings A growing body of evidence obtained in preclinical animal models support that an enhanced CB discharge produces sympathetic hyperactivity, baroreflex sensitivity and heart rate variability impairment, breathing instability, hypertension, and insulin resistance. The elimination CB chemosensory input reduces the sympathetic hyperactivity, the elevated arterial blood pressure in OSA and hypertensive models, abolishes breathing instability and improves animal survival in HF models, and restores insulin tolerance in metabolic models. These results highlight the role played by the enhanced CB drive in the progression of sympathetic-related diseases and support the proposal that the surgical ablation of the CB is useful to restore the autonomic balance and normal cardiorespiratory function in humans. Accordingly, the CB ablation has been used in pilot human studies as a therapeutic treatment for resistant hypertension and HF-induced sympathetic hyperactivity.

Summary In this review, I will discuss the supporting evidence for a crucial contribution of the CB in the central autonomic dysfunction and the pros and cons of the CB ablation as a therapy to revert autonomic overactivation. The CB ablation could be a useful method to reverse the enhanced chemoreflex in HF and severe hypertension, but caution is required before extensive use of bilateral CB ablation, which abolished ventilatory responses to hypoxia and may impair baroreceptor function.

Keywords Autonomic dysfunction · Carotid body ablation · Heart failure · Intermittent hypoxia · Metabolic disease · Neurogenic hypertension · Obstructive sleep apnea

Abbreviations

BCBA	bilateral carotid body ablation
BCSD	bilateral carotid sinus denervation
BP	arterial blood pressure
BRS	baroreceptor reflex sensitivity
CB	carotid body
CIH	chronic intermittent hypoxia
CSN	carotid sinus nerve
HF	systolic heart failure
HRV	heart rate variability
NA	nucleus ambiguous
NTS	nucleus of the tractus solitarius
OSA	obstructive sleep apnea
PVN	paraventricular nucleus
RVLM	rostral ventral lateral medulla
SHR	spontaneous hypertensive rats
TASK	Twik-related acid-sensitive K^+ channel

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Introduction

The carotid body (CB) is a polymodal chemoreceptor organ strategically located in the carotid artery bifurcations and is considered the main systemic sensor of the arterial PO_2 levels [1–3]. The natural stimuli (i.e., hypoxia, hypercapnia, acidemia,

temperature, low glucose, low flow, and high osmolarity) increase the rate of the chemosensory discharge in the carotid sinus nerve (CSN) eliciting reflex sympathetic activation, hypertension, and hyperventilation. The primary oxygen sensor in the CB is the glomus (type I) cells, which make synaptic contacts with the nerve terminals of the chemosensory petrosal neurons [1–3]. The most accepted hypothesis of oxygen sensing in the CB states that hypoxia inhibits voltage-independent TASK K+ and voltage-gated K+ channels in the glomus cells, leading to cell depolarization, increases of intracellular Ca2+, and release of one or more excitatory transmitters, which in turn increases the rate of discharge in the petrosal neurons [2, 3]. The CSN conveys chemosensory fibers that project to the caudal portion of the nucleus of the tractus solitarius (NTS), where second- and third-order sensory neurons integrates inputs from chemosensory, barosensory, and cardiopulmonary afferents. The NTS projects to other regions cardiovascular nuclei, such as the nucleus ambiguous (NA), the paraventricular nucleus of the hypothalamus (PVN), and the rostral ventrolateral medulla (RVLM), where the pre-sympathetic neurons are located [4]. The classical paradigm considers the CB as the main systemic chemoreceptor involved in the oxygen homeostasis and ventilatory acclimatization to high altitude [1]. Although the CB has been linked with human pathologies (i.e., sudden infant death and congenital central hypoventilation syndrome), the most common medical condition associated with the CB is the CB tumors [5, 6]. However, in the last decade, the idea that CB is implicated in several sympathetic-related human diseases received much attention. Indeed, a growing body of new evidences support the novel idea that an abnormal heightened CB chemosensory discharge contributes to potentiate the sympathetic output in several human diseases. Indeed, the CB is involved in sympathetic-related diseases such as neurogenic hypertension, obstructive sleep apnea (OSA), systolic heart failure (HF), and diabetes [6–11, 12••, 13, 14]. New experimental results showed that an abnormal enhanced CB chemosensory discharge produces hyperreflexia, characterized by sympathetic hyperactivity, reduced cardiac baroreflex sensitivity (BRS), alterations of heart rate variability (HRV), and breathing instability [6, 8, 9, 11, 12••, 13, 14]. Moreover, the bilateral CB ablation (BCAB) or the bilateral carotid sinus denervation (BCSN) reduces the sympathetic hyperactivity, restores BRS and the elevated BP in spontaneous hypertensive rats, abolishes the respiratory instability and improves rat survival in HF, and restores the insulin tolerance in rats exposed to rich fat and carbohydrate diets (see Table 1). These results support the idea that the elimination of the enhanced CB chemosensory drive to the brainstem is useful to restore the autonomic and cardiorespiratory dysfunction in sympathetic-associated diseases in humans [12••, 13, 23, 24, 25•]. Accordingly, the selective CBA has been recently used in pilot human studies as a treatment for resistant hypertension and to relief of the HF-induced sympathetic hyperactivity [26••, 27••, 28].

CB Ablation in Preclinical Models of Cardiorespiratory and Metabolic Diseases

Hypertension Trzebski et al. (1982) found that vasopressor and ventilatory responses to hypoxia were higher in hypertensive subjects, suggesting that an enhanced hypoxic CB-mediated chemoreflex participates in the progression of systemic hypertension [29]. In untreated hypertensive male patients, Sinski et al. (2012) found that 100% O2 breathing (Dejour's Test), which transiently silence the CB chemosensory discharge, reduces the resting muscle sympathetic neural activity (MSNA), suggesting that CB chemosensory activity is enhanced in hypertension [30]. Neural recordings of the CSN in spontaneously hypertensive rats (SHR) confirmed that CB chemosensory response to hypoxia was higher than control rats, although the amplitude of the responses to hypercapnia was the same [31]. Abdala et al. (2012) [15•] provided further evidences that the CB is involved in the progression of neurogenic hypertension in SHR. They found that BCSN performed in 4-week-old SHR delayed the onset of the hypertension, while BCSN performed in in adult SHR produced a mild reduction of BP. In addition, they reported that BCSD reduced the sympathetic hyperactivity and improved the BRS in SHR [15•]. It is worth to note that the unilateral CSN is ineffective to reduce the elevated BP, while the neurotomy of both CSN carotid is necessary to produce any hypotensor effect [15•]. More recently, the same group showed that BCSD in Goldblatt hypertensive rats reduced the elevated BP, increased the BRS, and normalized the cardiac sympatho-vagal balance [32]. These results support that an enhanced CB chemoreflex mediates central autonomic dysfunction and the progression of the systemic hypertension [15•, 23, 25•]. The CB seems to be also involved in pulmonary hypertension. In a model of pulmonary hypertension produced by monocrotaline in rats, BCSN improved the survival of the pulmonary hypertense rats (100%) compared with the rats with functional CBs (53%) at 4 weeks, reduced the 24-h urinary norepinephrine, and restored the normal HRV [33].

Obstructive Sleep Apnea OSA in humans is also associated with autonomic imbalance feature by sympathetic hyperactivity, reduction of BRS, alterations of HRV, and enhanced vasopressor and ventilatory responses to acute hypoxia [34–37]. Similarly, exposure of rodents to CIH, the gold-standard preclinical model of OSA, elicits similar autonomic and cardiorespiratory alterations, sympathetic hyperactivity, and systemic hypertension [38–41]. The first evidence that the CB plays a crucial role in the onset and maintenance of the hypertension was provided by Fletcher et al. (1992). They found that bilateral CSN prevents the systolic hypertension in rats exposed to CIH for 35 days [7]. The idea that an enhanced CB chemosensory reactivity is responsible for the central autonomic disbalance received further support when Prabhakar and Iturriaga's lab

Table 1 Effects of bilateral carotid sinus denervation or carotid body ablation on the autonomic and cardiorespiratory alterations observed in preclinical models of sympathetic-related diseases

Animal model	Effects	Reference
Hypertension in SHR rats	BCSN in young rats prevented BP to reach hypertensive levels observed in sham-SHR rats. BCSD in adult SHR reduced BP by ~ 20 mmHg. BCSN decreased sympathetic hyperactivity and improves BRS.	Abdala et al. (2012) [15•]
Chronic HF induced by coronary ligation in rats	BCBA reduced RVLM neuronal activation. Normalized sympathetic outflow and BRS and reduced incidence of apneas. Early BCBA reduced cardiac remodeling, deterioration of left ventricle ejection fraction, and cardiac arrhythmias. Early BCBA increased rat survival rate.	Del Rio et al. (2013) [16•]
Pacing-induced HF rabbits	BCBD abolished sympathetic and ventilatory augmented responses. Reduced augmented renal sympathetic activity, restored HRV, reduced respiratory instability and arrhythmia incidence.	Marcus et al. (2014) [17•]
Metabolic syndrome in rats	BCSN normalized sympathetic hyperactivity. BCSD reversed weight gain induced by high-energy diets. BCSN normalized plasma glucose and insulin levels, insulin sensitivity lipid profile, BP and endothelial function by improving glucose uptake by the liver and perienteric adipose tissue.	Ribeiro et al. (2013) [18•], Sacramento et al. (2017) [19]
OSA rat model	BCBA normalized BP after 21 days of CIH. Reduced potentiated ventilatory response to hypoxia. Restored cardiac autonomic and BRS, improves HRV and reduced the number of arrhythmias.	Del Rio et al. (2016) [20••]
OSA mice model	BCSD prevented fasting hyperglycemia and increases in baseline hepatic glucose. BCSD blunted ventilatory responses to hypoxia. BCSD abolished serum epinephrine levels and augmented liver sympathetic innervation.	Shin et al. (2014) [21]
Hypertensive- HF model in Dahl salt-sensitive rat	BCBD reduced 24-h urinary norepinephrine accumulation and attenuated BP increase BP. BCSN attenuated myocardial hypertrophy and improved rat survival.	Fuji et al. (2017) [22]

BCBA bilateral carotid body ablation, *BCSD* bilateral carotid sinus denervation, *BP* arterial blood pressure, *BRS* baroreceptor reflex sensitivity, *CIH* chronic intermittent hypoxia, *HF* systolic heart failure, *HRV* heart rate variability, *OSA* obstructive sleep apnea, *RVLM* rostral ventral lateral medulla, *SHR* spontaneous hypertensive rat

recorded CB chemosensory discharges from rodents and cats exposed to CIH. Indeed, the in vitro and in situ CSN recordings have shown that CIH selectively increases CB chemosensory discharges in normoxia and hypoxia, sensitizing the peripheral CB chemoreceptors [42–46]. Thus, CIH enhanced the reactivity of CB chemosensory discharges to oxygen—a phenomena known as hyperreflexia. At the same PO_2 levels, the CB chemosensory discharges are higher, increasing its excitatory drive to the brainstem cardiorespiratory nuclei. The CIH-enhanced chemosensory discharge in turn activates neurons in the NTS and in the RVLM leading to sympathetic hyperactivity [47–49]. The BCSD abolished the oxidative stress in the NTS and RVLM and prevents the hypertension induced by CIH, showing that the enhanced CB chemosensory drive is necessary for the autonomic alterations [50]. More recently, Del Rio et al. (2016) [20••] study the effects of BCBA in hypertense rats exposed to CIH for 21 days and maintained for 7 additional days in CIH. The BCBA promptly normalized the elevated BP, reduced the hypoxic ventilatory response, and restored HRV and BRS. These results indicate that autonomic alterations and the hypertension induced by CIH are crucially dependent on the enhanced CB chemosensory drive [50, 51].

Congestive Heart Failure Left heart failure (HF) is characterized by a progressive cardiac dysfunction that reduced cardiac output. Patients with HF and animal models show autonomic imbalance and altered respiratory patterns, associated to an enhanced CB chemoreflex and sympathetic outflow, impaired HRV and BRS [13, 24, 51]. Like what is found in preclinical models of OSA, recordings of CB chemosensory discharges in HF animal models have shown an enhanced CB chemosensory discharge in normoxia and hypoxia [52]. Moreover, BCBA in the rat myocardial-infarct model and BCSD in the pacing-induced HF in rabbit, reduce the sympathetic and the RVLM overactivation, normalizes breathing instability, reduces the ventricular fibrosis, and markedly improves survival of HF-rats [16•, 17•]. The elimination of the CB inputs markedly reduced the elevated resting ventilation and the potentiated hypoxic ventilatory responses in both animal models. More recently, Fuji et al. (2017) [22] found that BCSD in a mixed hypertensive-HF model in Dahl salt-sensitive rat reduces the 24-h urinary norepinephrine and attenuates the increase in BP. In this model, the BCSD also attenuates the myocardial hypertrophy and improves the rat survival [22]. Thus, the available evidence supports a main role for the CB in the autonomic alterations induced by HF.

Metabolic Syndrome Metabolic alterations are associated with autonomic dysfunction, characterized by sympathetic hyperactivation, impaired BRS, and mild hypertension. The CB are involved in the regulation of glucose and insulin [14, 53]. Ribeiro et al. (2013) [18•] found that BCSN prevents the insulin resistance and the hypertension in rats feeding with rich energy diets, suggesting that the CB mediates the sympathetic hyperactivity and metabolic alterations [18•]. More recently, Sacramento et al. (2017) [19] reported that BCSN reverses insulin resistance, dyslipidemia, autonomic dysfunction, and hypertension in rats fed with a high-fat diet. The BCSD normalizes plasma glucose and insulin levels, insulin sensitivity, and BP by improving glucose uptake by the liver and adipose tissue [19]. In mice exposed to CIH, BCSD blunts the enhanced ventilatory responses to hypoxia and abolishes the elevated serum epinephrine levels and augmented liver sympathetic innervation. In addition, BCSD prevents the fasting hyperglycemia and increases in baseline high glucose output from the liver [21].

In summary, the results obtained in preclinical models of human sympathetic-related diseases reveal the crucial role played by the CB in the generation and maintenance of autonomic imbalance (see Table 1) and suggest that the ablation of the CB input may be used as anti-hypertensive treatment in drug-resistant hypertensive patients, as well as to improve the life conditions in HF patients [12••, 13, 16•, 17•, 23, 24, 25•].

Pilots Studies of CB Ablation in Patients with Drug Resistant Hypertension and Heart Failure

Recently, three clinical pilot studies examined the effects of CB ablation in humans with severe resistant hypertension or HF [26••, 27••, 28]. Narkiewicz et al. (2016) studied the safety, feasibility, and effectiveness of CBA in patients with resistant severe hypertension. This was the first study in man that evaluated the effects of unilateral CB resection in seven males and eight females with systolic and diastolic pressures over 180 and 103 mmHg, respectively. Although some transient hypotensor effects were observed, in the long term (1 year), the unilateral CBA failed to produce a stable reduction of the elevated BP. Authors classified patients into two groups according to their response to the unilateral CB resection: responders, 8 patients with evidence of CB glomus cells in the resected tissue and a ≥ 10 mmHg drop in BP at 3-month follow-up visit, and non-responder: 6 patients with evidence of glomus cells in the resected tissue but did not show a ≥ 10-mmHg drop in BP after 3-month follow-up. In one patient, no evidence of glomus tissue was found. The responder group showed a reduction of MSNA that paralleled the BP fall time-course. The responder group showed a higher respiratory frequency than the non-responders, suggesting an enhanced CB basal reactivity. The unilateral CBA produced a transient reduction of the elevated BP in the eight responders. At 3 months after CBA, the responder group showed a reduced day time BP that persisted until the 6 months, but not at 12 months. The transient reduction of BP indicates that the enhanced CB chemosensory discharge in the remained CB was enough to maintain elevated BP in the long term [26••].

Niewinsky et al. (2017)[27••] performed the first-in-man of effects the CBA on sympathetic hyperactivity in 10 male patients with systolic HF (left ventricle ejection of $27 \pm 7\%$). From these ten patients, six patients underwent unilateral right-sided CB ablation and four patients BCBA ablation. They found that CBA reduced the ventilatory response to hypoxia and MSNA during 2 months after CBA. The quality of life showed an improvement at 1 month, but not at 2 months following CBA. The fatigue score showed some improvements at 1 and at 2 months. Patients with BCBA showed mild oxygen desaturations at night, while one patient required non-invasive ventilation due to the severe oxygen fall. Thus, this first study in man showed that CBA in patients with systolic HF decreased sympathetic hyperactivity, but BCBA increases the risk of worsening nocturnal oxygenation [27••].

More recently, the results of a study using endovascular venous catheters for right CBA ablation performed in patients with resistant hypertension were published in abstract form [28]. The unilateral right CB ablation was performed using an ablation catheter system (Cibiem, USA) delivering ultrasound waves through the jugular vein under intravascular

imaging guidance. The preliminary data from 15 patients showed that unilateral CBA resulted at 6 months in a modest reduction of 7 ± 19 and 5 ± 7 mmHg (systolic and diastolic arterial pressure, respectively), compared to the previous high BP baseline [28].

In summary, the available clinical evidences support a mild effect for unilateral CBA to improve quality of life in HF patients, but a fail to induce a stable reduction of BP in resistant hypertension (see Table 2).

Pros and Cons of a Wide Use of CBA in Humans with Sympathetic Hyperactivity

Results obtained in preclinical models support the idea that bilateral CBA is useful to reduce the sympathetic hyperactivity, breathing variability, arrhythmia incidence, and hypertension in patients with HF and severe hypertension [16•, 17•, 23, 25•]. Furthermore, recent pilot studies performed in patients show that unilateral CB ablation produced a modest improve on the quality of life in HF [27••] patient but failed to produce a stable reduction of BP in resistant hypertension [26••]. However, these studies show a persistent reduction of the hypoxic ventilatory responses and the enhanced sympathetic activity. Thus, results from clinical studies and preclinical animal models reveal a major contribution of the CB chemoreceptor in the progression of the autonomic dysfunction in human sympathetic-related diseases. Nevertheless, the ablation of one CB does not evoke persistent improvements of autonomic and cardiorespiratory dysfunction. Clearly, the elimination of the chemosensory inputs from one CB is not sufficient to produce permanent benefits. It is necessary to remove both CBs to produce a persistent reduction of the elevated BP in SHR [15•]. The bilateral ablation of the CBs has been subject of controversy since its massive use in Japan during the late 1940. Indeed, more than 3500 patients with bronchial asthma had therapeutic CB resections to improve the sensation of air hunger. The CB resections were performed by Dr. Nakayama, who developed a surgical procedure for removing the CBs preserving the baroreceptor function [54]. Nakayama (1961) reported that after a 6-month follow-up, BCBA performed in asthma patients resulted in reduction of BP in 29 hypertensive patients, no changes in 596 normotensive patients, while 21 hypotensive patients showed an elevation in BP. Thus, BCBA resulted in a reduction of the elevated BP, but the bilateral CB ablation completely abolished the ventilatory response to NaCN. Dr. Yoshiyuki Honda had the opportunity to study the hypoxic and hypercapnic responses in some of these

Table 2 Effects of CBA in patients with resistant hypertension and heart failure

Pathology	Effects	Reference
Resistant hypertension	First-in-man study to test the safety and feasibility of unilateral CBA carotid in 15 patients with drug-resistant hypertension.	Narkiewicz et al. (2016)[26••]
	Overall, no change in BP was found. However, 8 patients showed transient reductions in ambulatory BP coinciding with decreases in sympathetic activity.	
Congestive heart failure	First-in-man study to test the safety and feasibility of unilateral right-sided CBA in 4 patients and BCBA in 6 patients with heart failure.	Niewinski et al. (2017)[27••]
	At 1-month CBA both MSNA and hypoxic peripheral chemosensitivity were reduced.	
	The quality of life, exercise tolerance and fatigue scores showed transient improvement at 1–2 months.	
	BCBA patients showed worsening oxygen saturation at night.	
Resistant hypertension	Preliminary data from 15 patients with a mean systolic and diastolic arterial pressure of 152 ± 11 and 89 ± 12 mmHg, respectively. Transvenous catheter-based unilateral right CBA.	Schlaich et al. (2017)[28]
	At 6 months ambulatory mean systolic and diastolic BP was reduced by 10 ± 15 and 4 ± 7 mmHg compared to the initial BP.	

BCBA bilateral carotid body ablation, *CBA* unilateral carotid body ablation, *MSNA* muscle sympathetic nerve activity

patients 20 years after the surgical elimination of both CBs. He found that BCBA resulted in a persistent 90% loss of ventilatory reflex response to hypoxia and a depression of the CO_2 chemosensitivity [55]. Since the CB plays a main physiological role during sleep, exercise, and hypoxia, some concerns on the potential side effects of BCBA have been advanced [6, 56, 57]. The principal concerns are as follows: (1) selective CB ablation must be archived without affecting baroreceptor function, (2) lack of complete long-term compensation of the concomitant reduced CO_2 chemosensitivity, (3) possible appearance of apneas in older patients or patient with metabolic comorbidities (hyperglycemia, dyslipidemia, and insulin resistance), (4) persistent reduction ventilatory responses to hypoxia. Niewinsky et al. (2017) [27••] recognized that "A bilateral procedure may carry a risk of worsening oxygenation at night. CB modulation constitutes an interesting research avenue, but careful consideration of the balance between safety and efficacy is necessary before further clinical trials". Thus, the potential limitations of BCBA must to be considered before the massive use of this approach as a therapeutic treatment for diseases associated with sympathetic hyperactivity. In addition, the large number of exclusion criteria precludes a wider use of the BCBA ablation (Niewinsky et al. 2017) [27••]. An alternative approach for appeasing the enhanced CB chemosensory discharge is the use of pharmacological therapy [58]. Several common mechanisms including oxidative stress and inflammation are associated with the enhanced CB chemosensory discharge and sympathetic hyperactivity in OSA, HF, neurogenic hypertension, and metabolic diseases. Indeed, endothelin-1, angiotensin II, NO, H_2S, pro-inflammatory cytokines, and purinergic receptor P_2X_3 have been involved in the CB chemosensory potentiation in sympathetic mediated diseases [6, 11, 13, 14, 23, 24, 42, 43, 46, 59].

Conclusion

In preclinical models of sympathetic-related human diseases, an abnormal enhanced CB discharge elicits central sympathetic hyperactivity, impairs BRS and HRV, and induces breathing instability, hypertension, and insulin resistance. The bilateral elimination of the CB input to the NTS reduces the sympathetic hyperactivity, the elevated BP in OSA and genetic hypertensive models, abolishes breathing instability and improves animal survival in HF models, and restores insulin tolerance in metabolic models. Accordingly, the ablation of the CBs has been used in pilot human studies as a surgical treatment for resistant hypertension and HF-induced sympathetic hyperactivity. The results obtained from these studies showed modest and transient effects of unilateral CBA, suggesting that both CB must be eliminated to achieve persistent results. However, due to the pivotal role played by the CB in oxygen homeostasis, major concerns on the potential adverse side effects have been advanced. In conclusion, CB ablation could be a useful method to reverse enhanced CB chemosensory discharges and chemoreflexes in HF and severe hypertension, but caution is required before extensive use of BCBA, which abolished ventilatory responses to hypoxia and may impair baroreceptor function. New studies are required to assess the long-term effects of CB ablation and mortality rates in experimental models of OSA and metabolic syndrome, particularly in aging animals. New pharmacological studies are needed to target the mechanisms underlaying the enhanced CB chemosensory discharge.

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Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest relevant to this manuscript.

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