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REVIEW

Human carotid bodies as a therapeutic target: new insights from a clinician's perspective

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Abstract

From the physiological point of view, carotid bodies are mainly responsible for the ventilatory response to hypoxia; however, they also take part in the regulation of sympathetic tone. According to preclinical data, these structures likely contribute to the development and progression of sympathetically mediated diseases. Moreover, carotid body deactivation in animal models improved blood pressure control in hypertension and reduced mortality in heart failure, along with reducing sympathetic activity. On this basis, two first-in-man studies have been recently performed to investigate the safety and feasibility of such an approach in humans. In this review we summarise the current knowledge regarding the function of carotid bodies, the prevalence of their abnormalities, and the consequences of their excision in human hypertension and heart failure.

Key words: carotid body, chemoreflex, resection, deactivation, hypertension, heart failure

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INTRODUCTION

Peripheral chemoreceptors (PChs), also known as arterial chemoreceptors, are located at the bifurcation of common carotid arteries (carotid bodies [CBs]) and along the aorta and its main branches (aortic bodies [ABs]). Activation of PChs leads to both hyperventilation and sympathoexcitation via the stimulation of medullary centres [1, 2]. These structures are also believed to contribute to the sensation of dyspnoea [3]. CBs were identified as dominant structures in terms of the reflex ventilatory response to hypoxia. The magnitude of this response can be easily assessed, which, along with the easily identifiable anatomical structure and location of CBs, makes them suitable for interventional deactivation [4].

Surgical excision of CBs was performed in the mid-20th century in thousands of patients with pulmonary diseases, such as bronchial asthma or chronic obstructive pulmonary disease [5]. At that time CB deactivation (CBD) was considered a palliative procedure — it reduced the sensation of dyspnoea, but negligibly improved spirometry parameters [6]. Thus, due to the development of effective bronchodilators, this approach was abandoned.

Nowadays autonomic imbalance has been identified as an important aetiological factor contributing to the occurrence and progression of cardiovascular diseases such as hypertension (HT) and heart failure (HF) [7–13]. This finding resulted in the development of pharmacological and non-pharmacological methods for restoring the autonomic balance, including renal denervation, baroreceptor stimulation, and vagal nerve stimulation as well as the concept of CBD [5, 10, 13, 14].

The contribution of PChs to the increased sympathetic tone is well documented in humans. Stimulation of PChs with hypoxia increases sympathetic nerve traffic in the healthy, in hypertensives, and in HF patients [15, 16]. On the contrary, PChs inhibition with hyperoxia in hypertensives causes a decrease in sympathetic tone, blood pressure (BP), and systemic vascular resistance [17, 18].

Deactivation of carotid bodies, as a novel therapeutic approach, is further supported by the promising results from experiments performed in animal models [19–21]. Bilateral CBD, both in spontaneously hypertensive rats and in rats with ischaemia-induced HF, along with decreasing sympathetic traf-

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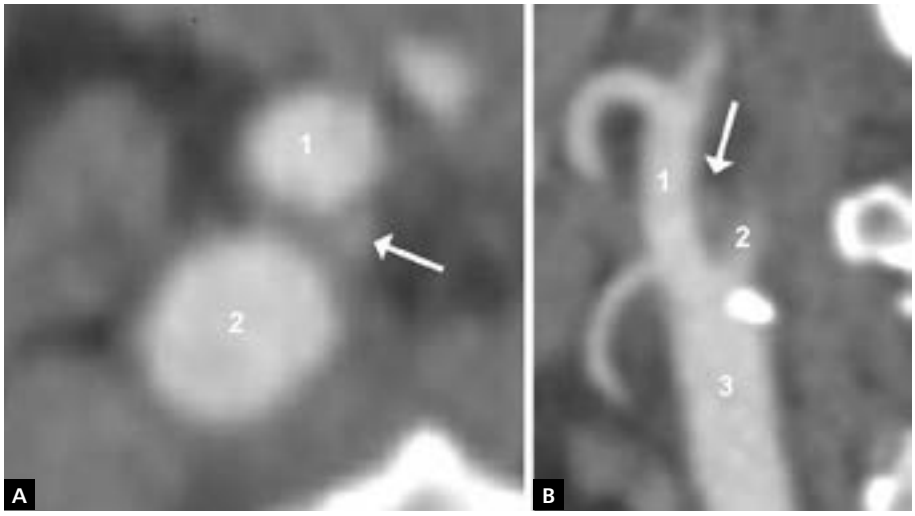

Figure 1. Visualisation of a carotid body (indicated by an arrow) in arterial phase of computed tomography angiography of the neck; **A.** Transverse axis; **B.** Longitudinal axis; 1 — external carotid artery; 2 — internal carotid artery; 3 — common carotid artery

fic, reduced BP in the former group of animals and increased the survival rate in the latter group [19, 20, 22].

The results of two first-in-human studies evaluating the feasibility and safety of surgical excision of CBs in HF and HT have recently been presented [23, 24]. The purpose of this review is to summarise the current knowledge regarding the function of human PChs, analyse the results of recent studies, and define the scientific targets for future CBD clinical trials.

ASSESSMENT OF CAROTID BODY ANATOMY AND FUNCTION

Visualisation of carotid bodies in humans

The anatomy and anatomical variations of human CBs have been precisely described in the past on the basis of cadaver studies [25]. These ovoid, 1.5 to 7-mm long structures are usually located bilaterally at the level of common carotid artery bifurcation [5]. CBs in hypertensive and HF subjects were reported to be significantly larger than in healthy people [26]. The close proximity of important vessels and nerves (e.g. vagal nerve) as well as anatomical variability regarding CB size, symmetry, and location demand careful evaluation of CB anatomy prior to their deactivation.

It was shown recently that CBs can be identified and assessed in more than 80% of cases using computed tomography angiography (CTA) of the neck region [27, 28]. During the arterial phase of CTA, CBs can be described as ovoid, avidly contrast-enhancing structures localised in the inferomedial region of the carotid bifurcation (Fig. 1). Moreover, a recent small study in patients with HT revealed that CBs can be also visualised and assessed with carotid Doppler ultrasound [29].

Assessment of peripheral chemoreceptors function

The function of PChs is usually described using a parameter called PChs sensitivity (PChsS), which illustrates the magnitude of PChs-mediated ventilatory response to the stimuli. Several well-established and validated methods for PChsS evaluation can be found in the literature, such as transient hypoxia test, steady-state hypoxic isocapnic test, progressive hypoxic isocapnic test, and single breath of CO_2 test [30, 31]. Despite the correlation that has been found between the individual results of these tests, the numerical differences related to various aspects of the testing process (e.g. type of stimulus and its kinetics) make it difficult to compare them directly [30].

Notably, none of these methods allows a selective assessment of a single CB function, which is of particular interest in the context of pre-CBD target organ evaluation. Hitherto, the only method designed for this goal is an invasive one, employing intra-carotid adenosine injections [32]. During the test adenosine is administered via an angiographic catheter directly into the common carotid artery, which leads to selective excitation of ipsilateral CB. An increase in minute ventilation following the injection reflects the sensitivity of the investigated CB. Such a test performed during CBD allows the intraoperative assessment of the procedure's efficacy. The results of adenosine test have been found to correlate with individuals' PChsS assessed using transient hypoxia test [32]. This observation confirms that ventilatory response to transient systemic hypoxia corresponds with CB sensitivity and justifies the employment of this non-selective test for the pre-CBD screening.

Table 1. Proposed molecular mechanisms for peripheral chemoreceptors oversensitivity in hypertension and heart failure

Heart failure	Hypertension
Downregulation of heme oxygenase protein (HO-2), neuronal and endothelial NO synthases (NOS) [39]	Overexpression of amiloride-sensitive acid-sensing sodium channel (ASIC3) [40]
Enhanced sensitivity of Kv channels (mediated by angiotensin type 2) to hypoxia [41]	Overexpression of 2-pore domain acid-sensing K+ channel (TASK) [40]
Reduction of blood flow in carotid arteries [42]	Upregulation of adenosine P2X3 receptors [43]

FUNCTION OF PERIPHERAL CHEMORECEPTORS IN THE HEALTHY AND THE DISEASED

The term "PChs oversensitivity" (or hypersensitivity) has been used for the first time in HF studies, in which this patient characteristic was identified as a predictor of poor prognosis [33, 34]. According to these trials, PChs oversensitivity is defined as PChsS exceeding the mean value of PChsS assessed in a healthy group plus two standard deviations. The proportion of patients with PChs oversensitivity differs between studies, due to divergent methods of PChsS testing employed and contrasting characteristics of the studied populations [33, 35].

Data regarding the level of PChsS and the prevalence of PChs oversensitivity in healthy subjects come from studies in small populations, the results of which are presented in **Supplementary Table S1** (**see journal website**). In line with this research, the mean PChsS in healthy subjects varies from 0.2 ± 0.26 L/min/SpO_2% to 0.44 ± 0.31 L/min/SpO_2% for transient hypoxia test and from 0.35 ± 0.21 L/min/SpO_2% to 0.44 ± 0.41 L/min/SpO_2% for progressive hypoxia test. Furthermore, the prevalence of PChs oversensitivity in the healthy population can be estimated at around 8%. Potential clinical consequences of PChs oversensitivity in healthy subjects have never been studied.

Otherwise, PChs oversensitivity is a frequent finding in patients with congestive HF and can be established in 34% to 44% of cases using transient hypoxia test and in 40% of cases with progressive hypoxic isocapnic test (**Suppl. Table S1 — see journal website**) [33, 34, 36]. The mean PChsS in HF patients is between 0.66 ± 0.45 L/min/SpO_2% and 0.69 ± 0.5 L/min/SpO_2% for transient hypoxia test and around 0.74 ± 0.46 L/min/SpO_2% for progressive hypoxia test [33, 34, 36].

Exaggerated ventilatory response to hypoxia, in comparison with healthy controls, was found in subjects with untreated mild essential HT [37]; however, the prevalence of PChs oversensitivity has never been assessed in this population. Recently presented early results of an ongoing study in patients with advanced HT requiring multi-drug antihypertensive therapy (receiving 4.5 ± 1.6 antihypertensive medications) revealed that PChs oversensitivity can be found in 38% of cases (**Suppl. Table S1 — see journal website**) [38].

The molecular mechanisms leading to the oversensitivity of PChs are not fully understood, and the only available data come from experiments in animal models. The proposed mechanisms of PChs oversensitivity in HT and HF are presented in Table 1 [39–43].

CAROTID BODY DEACTIVATION IN PATIENTS WITH ARTERIAL HYPERTENSION

Almost one-third of the world's adult population suffers from HT, which is one of the leading preventable risk factors for premature death [44, 45]. Only a half of these subjects receive treatment; furthermore, despite the therapy, one in 10 (10.1%) patients fulfil the definition of "true uncontrolled resistant hypertension" [46]. The aetiology of HT is heterogenous and can be clearly identified only in 5% to 10% of cases [47]. It is currently being investigated whether PChs oversensitivity can be viewed as a secondary, potentially reversible cause of HT in humans.

Encouraging data from experiments in animals, in parallel with the observation of BP reduction following CB excision in subjects with asthma or CB tumours, resulted in the first-in-human clinical trial evaluating the effects of unilateral CBD in hypertensives [22, 48, 49]. The safety and feasibility of the procedure was confirmed; however, the study failed to show a reduction in BP, sympathetic activity, respiratory parameters, or PChsS in the whole studied group of 15 patients with primary resistant HT [24]. Interestingly, an analysis of individual data revealed a reduction of ≥ 10 mmHg in systolic BP (SBP) measured with ambulatory BP monitoring (ABPM) in 57% of subjects, defined later as "responders." Separate analysis of the responders' data showed: (1) mean drop in daytime SBP with ABPM of 26 ± 4 mmHg, (2) improvement in autonomic nervous system function indices, such as decreased sympathetic nerve activity to the muscle (MSNA) and increased baroreflex sensitivity, and (3) reduction in whole-dose equivalents of antihypertensive drugs [24]. Thus, CBD seems to be an effective treatment, but only in the particular group of subjects characterised, according to the study results, by higher baseline PChsS, greater ventilatory frequency, and right- vs. left-sided procedure [24]. Established effects of CBD in human HT and potential future directions are summarised in Figure 2.

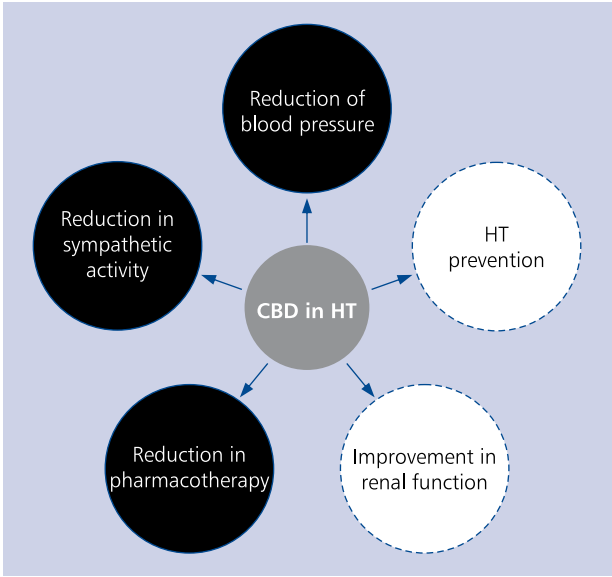

Figure 2. Established effects of carotid body deactivation (CBD) in human hypertension (HT) — black circles; potential future directions described so far only in animal models — white circles

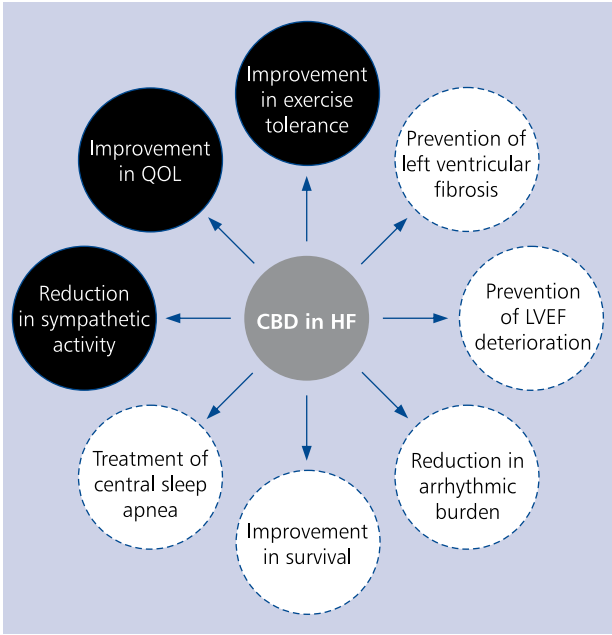

Figure 3. Established effects of carotid body deactivation (CBD) in human heart failure (HF) — black circles; potential future directions described so far only in animal models — white circles; LVEF — left ventricular ejection fraction; QOL — quality of life

Crucial for upcoming studies is the development of a screening test to preselect patients who will respond to treatment. Higher PChsS was shown to be characteristic for "responders" to CBD; however, the cut-off level of the parameter has not been established yet. Moreover, relying only on PChsS analysis might not be a sufficient screening approach because long-lasting hypertension leads to irreversible changes in artery wall structure (thickening of intima-media, increase in stiffness of elastic arteries, increase in media-to-lumen ratio in muscular arteries, acceleration of atherogenesis), which may thwart the effects of CBD [50]. Thus, an ideal screening test should incorporate an assessment of the effect of transient CBs suppression (e.g. with low-dose dopamine) on BP or at least include an analysis of arterial wall stiffness by means of pulse wave velocity.

CAROTID BODY DEACTIVATION IN PATIENTS WITH HEART FAILURE

Heart failure affects 1% to 2% of the adult population worldwide, and its prevalence is growing [51]. The aetiology of HF is heterogenous, with coronary artery disease being the most common cause. In animal models, HF induced both with coronary artery ligation (in rats) and tachypacing (in rabbits) was found to be associated with an increase in PChsS, impairment of baroreflex function, shift toward increased sympathetic tone, raised arrhythmia burden, and disordered breathing incidence [52, 53]. Bilateral CBD reversed, at least partially, these abnormalities and prevented further deterioration of left ventricular function [52, 53]. Additionally, CBD performed early (two weeks) after myocardial infarction in rats significantly reduced mortality compared to sham treatment [52].

Data regarding CBD in human HF is limited to the study in 10 subjects, which assessed the safety and feasibility of the procedure [23]. In contrast to the hypertensive subjects, all HF patients undergoing CBD had elevated PChsS (> 0.6 L/min/SpO_2%; transient hypoxia test), and in all patients at least a right-sided procedure was performed (unilateral — four cases, bilateral — six cases) [24]. CBD reduced sympathetic activity (assessed with MSNA) and prolonged exercise time in the whole studied population but did not influence peak oxygen consumption. In contrast to the study in hypertensives discussed above, CBD in HF decreased PChsS, probably due to the predominance of bilateral procedures [23]. CBD in HF patients did not change resting heart rate, office BP, or N-terminal pro–B-type natriuretic peptide levels, but decreased minute ventilation, which resulted in statistically, but not clinically, significant CO_2 retention — individual arterial blood CO_2 levels were still within the normal range. Already proven and potential future positive effects of CBD in human HF are presented in Figure 3.

Higher mortality rate in patients with PChs oversensitivity is well documented [33, 34]. Thus, excessive input from PChs needs to be reduced, but the following remain uncertain: (1) optimal level of PChsS at which CBD should be performed and (2) the phase of the disease during which it should be carried out — early, asymptomatic or end-stage. Results of the study in rats with ischaemic HF suggest that intervention performed shortly after the onset of HF, when maladaptive myocardial

remodelling is particularly prominent, is the most beneficial [20]. Such an approach has not been tested in humans. An early intervention approach is also supported by the observation that excessive reduction in general sympathetic activity, particularly in advanced HF, may even be harmful. As was shown in the MOXCON trial, which studied the influence of a central-acting sympathoinhibitor (moxonidine) on clinical endpoints in HF, reduction in sympathoexcitation increased mortality [54]. This might be a result of excessive inhibition of the sympathetic system, leading to further reduction in cardiac output and hence the progression of the disease.

POTENTIAL PITFALLS OF CAROTID BODIES DEACTIVATION

Open surgical removal of CBs in patients with respiratory disorders has been reported to be safe, with a periprocedural complication rate < 3%. Among 15,000 cases death occurred in 13 patients and was caused by vascular complications or was a consequence of an underlying lung disease. In 5600 cases precisely described in the literature the following complications were reported: hemiparesis, non-fatal vessel injury (both occurred in 0.2% of cases), and transient numbness of the jaw caused by unintended hypoglossal nerve injury [5]. These local complications should be at least partially eliminated with a less invasive percutaneous approach, which is currently being tested (ClinicalTrials.gov; NCT02099851, NCT03314012).

Apart from procedure-related complications, one can expect the consequences of chemoreflex removal. Because PChs take part in blood gas homeostasis and are responsible for the dyspnoea sensation, CBD may lead to unawareness and delayed ventilatory response to hypoxia. This concern may be supported by a case report of a patient with a severe respiratory disorder and low baseline PaO_2 levels, who underwent bilateral CBD and died after refusing oxygen supplementation [5]. However, taking into consideration the fact that more than 15,000 procedures were performed, and such a case was described only once, this death was probably caused by the progression of the underlying disease.

Delayed and blunted respiratory response to hypoxia may also exaggerate sleep-disordered breathing (SDB). Both Narkiewicz et al. [24] in unilateral CBD hypertensives and Niewinski et al. [23] in uni- and bilateral CBD HF patients described lowering of average blood saturation levels during dyspnoeic episodes at night. This deterioration was mild in most of the cases, and no intervention was required; however, one hypertensive patient and one HF subject after bilateral procedure (both with pre-existing moderate obstructive SDB) presented with disease progression to severe SDB. These patients were successfully treated with non-invasive ventilation devices. Otherwise, bilateral CBD in HF animals led to normalisation of disordered breathing [22, 52, 53]. This discrepancy may be justified by a different pathophysiology of apnoea episodes in these models. While in the human cases mentioned here, obstructive SDB was dominant (which is concomitant with findings in general HF and HT populations), this abnormality is not reported in the rat model, where breathing irregularity is usually of central origin [55–57]. Whether CBD can reduce SDB of central origin in humans remains unknown. This hypothesis may be supported by the case of an HF patient whose moderate SDB (apnoea–hypopnoea index [AHI] 19.1 events/hour) with the predominance of central episodes (84%) was reduced to mild SDB (AHI 11.4 events/hour) with a significant decrease in the occurrence of central episodes (to 20.4%) following unilateral CBD [58]. The described reduction in central episodes may be driven by an increase in arterial blood CO_2 levels following CBD because mild hypercapnia was previously found to reduce central SDB in HF patients [59]. Thus, if the results from animals were transferred to humans, CBD would become an attractive alternative to servo-ventilation, which failed to decrease mortality in an HF trial [60].

Defected responsiveness to hypoxia may also mask symptoms of HF decompensation and postpone the diagnosis and treatment of this condition. It was shown that uni- and bilateral CBD significantly reduce the sensation of dyspnoea in HF patients assessed with the Kansas City Cardiomyopathy Questionnaire scale [23]. Moreover, blunted dyspnoea sensation is probably responsible for exercise time prolongation in these subjects because peak oxygen consumption was unchanged [23]. However, the pathophysiology of exertional dyspnoea differs from the one during acute HF decompensation. The origin of exertional dyspnoea in HF is complex and consists of (1) muscle ischaemia and activation of chemo-, metabo- and ergoreceptors, (2) ventilatory and peripheral muscle dysfunction, (3) pulmonary circulation dysfunction including futile alveolar ventilation, and (4) decreased lung compliance and increased airway resistance [61]. Otherwise, dyspnoea during HF decompensation is mainly the consequence of pulmonary congestion, leading to lung compliance reduction and lung injury, which activate vagal mechanoreceptors and C-fibres [62]. Hence, while CBD at least partially alleviates exertional dyspnoea, it is less plausible that it can disguise the symptoms of HF decompensation. This may be supported by the case of a patient after bilateral CBD reported by Niewinski et al. [23], who experienced HF decompensation, and the symptoms of this condition, including typical dyspnoea sensation, were not disturbed.

Peripheral chemoreceptors are also known to be sensitive to hypoglycaemia [63]. It was recently shown that bilateral CBD significantly blunts hypoglycaemia-induced increase in heart rate and BP in humans [64]. This observation suggests that bilateral CBD may mask hypoglycaemic symptoms by reducing sympathoexcitation; however, clinical data are not yet available to confirm this hypothesis.

Despite the lack of PChsS restoration after bilateral CBD in humans in six-month follow-up (Fig. 4), there is evidence

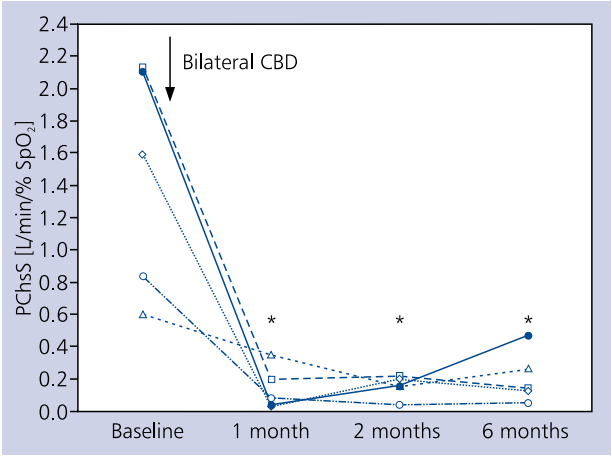

Figure 4. Peripheral chemoreceptors sensitivity (PChsS) changes following bilateral carotid body deactivation (CBD) in patients with heart failure (n = 5) [23]; *p < 0.01 vs. baseline

for the recovery of sympathetic activity following unilateral procedures. A one-year follow-up of hypertensives after unilateral CBD revealed slow restoration of BP levels in the responders group. Compared to the baseline value, BP was significantly reduced at three and six months but not at 12 months [24]. This observation could be simply explained by the reduction in whole-dose drug equivalents, which was reported in all study visits. However, the concomitant increase in sympathetic activity measured with MSNA supports the restoration of CB afferent sympathetic activity. A potential mechanism of this restoration is compensatory overactivity of contralateral CB. This problem may be hypothetically solved with subsequent ablation of contralateral CB, but such an approach has not been tested so far.

CONCLUSIONS

Unilateral CBD seems to be a promising novel approach for further reduction of sympathetic overactivity in HF and HT subjects. However, patient selection should be carried out with caution because this treatment is potentially harmful. It is also known that, due to the heterogeneity of HT and HF populations, some patients will not respond to the therapy. Nevertheless, certain characteristics may help to identify potential responders and non-responders to treatment. Thus, screening tests for preprocedural patient selection need to be developed urgently.

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