Anatomy of the carotid sinus nerve and surgical implications in carotid sinus syndrome

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Background: **The carotid sinus syndrome (CSS) is characterized by syncope and hypotension due to a hypersensitive carotid sinus located in the carotid bifurcation. Some patients ultimately require surgical sinus denervation, possibly by transection of its afferent nerve (carotid sinus nerve [CSN]). The aim of this study was to investigate the anatomy of the CSN and its branches.**

Methods: **Twelve human carotid bifurcations were microdissected. Acetylcholinesterase (ACHE) staining was used to identify location, side branches, and connections of the CSN.**

Results: **A distinct CSN originating from the glossopharyngeal (IX) nerve was identified in all specimens. A duplicate CSN was incidentally present (2/12). Mean CSN length measured from the hypoglossal (XII) nerve to the carotid sinus was 29 ± 4 mm (range, 15-50 mm). The CSN was frequently located on anterior portions of the internal carotid artery, either laterally (5/12) or medially (6/12). Separate connections to pharyngeal branches of the vagus (X) nerve (6/12), vagus nerve itself (3/12), sympathetic trunk (2/12), as well as the superior cervical ganglion (2/12) were commonly observed. The CSN always ended in a network of small separate branches innervating both carotid sinus and carotid body.**

Conclusion: **Anatomical position of the CSN and its side branches and communications is diverse. From a microanatomical standpoint, CSN transection as a single treatment option for patients with CSS is suboptimal. Surgical denervation at the carotid sinus level is probably more effective in CSS. (J Vasc Surg 2009;50:177-82.)**

Clinical Relevance: **Some patients suffering from CSS ultimately require surgical carotid sinus denervation, possibly by transection of its afferent nerve (CSN). This study was performed to investigate the anatomy of the CSN using a nerve-specific ACHE staining technique. Microdissection demonstrated a great variability of the CSN and its branches. Simple high transection of the CSN may lead to an incomplete sinus denervation in patients with CSS. Surgical denervation at the level of the carotid sinus itself may be more effective in CSS.**

Carotid sinus syndrome (CSS) is an ill-recognized condition leading to dizziness, syncope, and falls in senior people. It is caused by dysregulation of heart rhythm and/or blood pressure, probably following aging and subsequent instability of carotid sinus baroreceptors. CSS prevalence may be up to 45% in elderly populations.[1,2] A quarter of these individuals sustain serious injuries including fractures (predominantly femoral neck) during these episodes.[3] If left untreated, CSS mortality rates exceed 25% in the first 5 years.[4]

Diagnosis and treatment of CSS is challenging. Patients may be managed with medication, although clinical responses are disappointing.[5] Pacemaker implantation is considered the treatment of choice for cardioinhibitory CSS, but is not effective in vasodepressor CSS.[6,7] Especially in the latter type, one may opt for interrupting the pathological baroreceptor reflex using a variety of surgical approaches. A recent review evaluating adventitial stripping of the carotid sinus in 110 CSS patients demonstrated an excellent short- and long-term clinical response.[8] Transection of the glossopharyngeal nerve may also offer relief of symptoms in CSS patients, although this sort of surgery requires a craniotomy.[9-11] Simple carotid sinus nerve (CSN) transection is less invasive, but clinical studies are scarce.[12]

Anatomical studies performed in the beginning of the previous century suggest great anatomic CSN variability. Assuming that the CSN is an important afferent link in the pathologic baroreceptor reflex of CSS, effective surgery requires transection of its main trunk and important side branches. Moreover, interconnections must also be identified as the carotid sinus (implicated as the source of baroinstability) must ideally be completely denervated. If one considers surgery for CSS, it is imperative to recognize different patterns of carotid sinus innervation, ideally using modern techniques.

The aim of the present study is to perform mapping of nerve structures surrounding the carotid bifurcation using a unique combination of microdissection and nerve staining techniques with special emphasis on CSN and its branches in relation to the carotid sinus and carotid body.

MATERIALS AND METHODS

Twelve halves (6 left sides, 6 right) of human cadaver heads fixed by 3% formaldehyde were used. Ten specimens

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Competition of interest: none.

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0741-5214/$36.00

doi:10.1016/j.jvs.2009.03.029

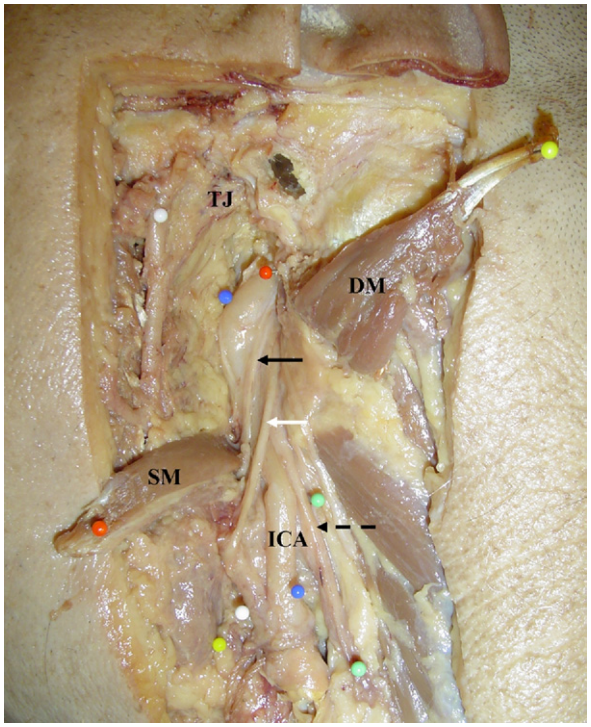

Fig 1. Overview of left carotid area. *TJ,* temporomandibular joint; *DM,* digastric muscle; *SM,* styloid muscles; *ICA,* internal carotid artery. *Black arrow* glossopharyngeal nerve; *white arrow* hypoglossal nerve; *dotted arrow* vagus nerve.

were male and the mean age was 74 ± 3 years (range, 59 to 92-years-old).

Carotid bifurcations were exposed by a standard approach routinely used for open carotid surgery. A skin incision was made along the medial border of the sternocleidomastoid muscle followed by division of the platysma and ligation of the facial vein (FV). The posterior belly of the digastric muscle was cut, and stylohyoid, styloglossus, and stylopharyngeus muscles were subsequently divided from the styloid process. The FV was used as a landmark for identifying the carotid bifurcation. Common carotid artery (CCA), external carotid artery (ECA), internal carotid artery (ICA), vagus nerve (X), hypoglossal nerve (XII), and the associated superior root of the cervical ansa were subsequently identified. In order to reach the glossopharyngeal nerve (IX) and origin of the CSN, the temporomandibular joint was exarticulated and the dorsal 2 cm of the ramus of the mandible including the condylar process was resected. The ICA was further dissected towards the carotid canal located in the base of the skull (Fig 1). Sympathetic trunk and superior cervical ganglion (SCG) were identified after lateralizing the carotid arteries and neighboring nerves. The CSN was identified using 4-10× microscopic magnification. The following distances between landmark structures were measured on a millimeter scale: FV to carotid bifurcation, mandibular angle to carotid bifurcation, and XII to carotid bifurcation. Length and diameter of the CSN were also measured, followed by 'en bloc' resection of carotid arteries and nerves.

Nerve structures including CSN, IX, X, XII, sympathetic trunk, and their respective side branches and communications were additionally studied with microdissection after staining with a nerve-specific sensitive acetylcholinesterase (ACHE) staining technique. In order to reach optimal circumferential tissue staining, specimens were fixed on a Sylgard medium (Down Corning, Wiesbaden, Germany) in a Petri dish. Consecutive steps associated with the staining procedure include incubation in a medium composed of acetylthiocholine iodide, cupric sulfate, and potassium ferrocyanide, followed by intensification of the stain using diaminobenzidine, nickel ammonium sulphate, and hydrogen peroxide. All cholinergic, adrenergic, and sensory nerves present are stained black following this procedure.[13-15] The technique has been optimized for human whole-mount specimens.[16] If nerve side branches became progressively indistinguishable during the microscopic dissection process, a second or third period of staining was performed. Data are shown as mean ± standard deviation (SD).

RESULTS

Mean distance between FV and carotid bifurcation was 5 ± 2 mm (range, −15 to +20 mm). The CSN usually became clearly visible after one staining procedure. However, optimal visualization of its branches usually required two or even three staining attempts.

Each preparation clearly demonstrated a distinct CSN, located in loose tissue close to the ICA wall. It consistently (12/12) originated from IX some millimeters after its appearance from the jugular foramen. The CSN ran parallel to or together with X, as a single branch in close proximity to the ICA and always ended at the level of the carotid bifurcation. Its position was anteromedially (6/12), anterolaterally (5/12), or anteriorly (1/12) relative to the ICA.

Fig 2 shows a schematic diagram of the anatomical variations of the CSN. A double origin from IX was found in two specimens. These two branches joined after 15-20 mm to form one single CSN (Fig 2, *b* and Fig 3). Mean diameter of CSN was 0.8 ± 0.1 mm (range, 0.5-1.5 mm), and mean length was 60 ± 15 mm (range, 40-88 mm). Mean distance from mandibular angle to carotid bifurcation was 36 ± 4 mm (range, 18-60 mm), whereas mean length from hypoglossal nerve to bifurcation was 29 ± 4 mm (range, 15-50 mm).

Location and number of CSN side branches were inconsistent. Six of 12 specimens clearly showed separate branches traveling to the carotid body and carotid sinus. Surprisingly, there were separate loops of communication with X (3/12), X's superior pharyngeal branches (6/12), sympathetic trunk (2/12), and superior cervical ganglion (2/12) (Fig 2, *c*, *d*, Fig 3, and Fig 4). In contrast, no connection was present with XII or superior root of cervical ansa. In one specimen, an overt CSN side branch traveled to the ICA and ended in its wall some 38 mm proximal to

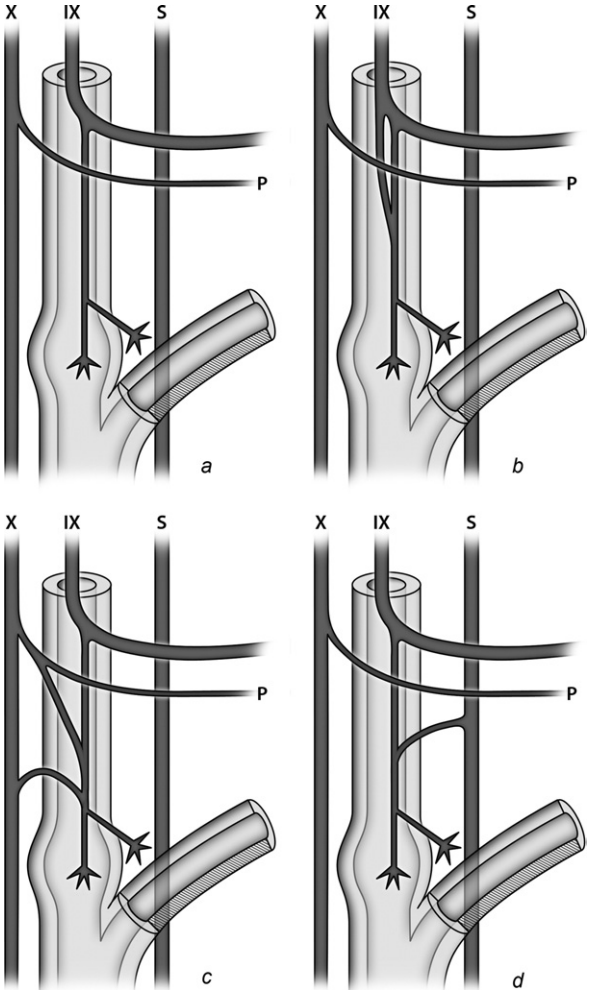

Fig 2. Schematic diagram of anatomical variations of the carotid sinus nerve (CSN). Right carotid bifurcation. The hypoglossal nerve (XII) has been omitted. **a,** CSN originating from the glossopharyngeal nerve (IX). Separate branches to carotid sinus and carotid body. **b,** Double origin from the glossopharyngeal nerve (IX). **c,** Communications with the vagus nerve (X) and its pharyngeal branches (P). **d,** Communications with sympathetic trunk (S).

Fig 3. Right carotid bifurcation and neighboring nerves after ACHE staining magnification 2×. The hypoglossal nerve (XII) is placed caudally to visualize nerves in the carotid bifurcation. *IX,* glossopharyngeal nerve; *X,* vagus nerve; *S,* sympathetic trunk; *OA,* occipital artery; *ICA,* internal carotid artery; *ECA,* external carotid artery; *black arrows* carotid sinus nerve (CSN) (double origin); *white arrow* communication between CSN and pharyngeal branches of X; *dotted white arrows* loops of communications with vagus nerve.

the carotid bifurcation. In all 12 specimens, distal portions of CSN were characterized by numerous branches ending in the carotid sinus' wall and/or carotid bifurcation (Fig 5).

DISCUSSION

Physiology. The CSN contains afferent fibers traveling from the carotid sinus' baroreceptors located in the adventitia of the ICA. It joins the glossopharyngeal nerve and ends in the nucleus tractus solitarius in the brain stem. A normal baroreflex is triggered by afferent pulses evoked by increasing ICA wall pressures. The efferent loop originating from the brain stem is conducted by the vagus nerve to the heart leading to a physiologic bradycardia, inhibited conduction, and reduced myocardial contractility. Furthermore, a blocked sympathetic nerve system may cause vasodilatation and lowered blood pressure.[17-19] Carotid sinus syndrome (CSS) is caused by a pathologic 'overshoot' of this baroreflex and is clinically characterized by syncope or dizziness due to asystole or hypotension.

Anatomic considerations. The CSN is a long descending branch of the glossopharyngeal nerve. An early detailed description was obtained in a 7-month-old fetus in the 1920s.[20] Various other names were introduced for the CSN including ramus caroticus glossopharyngei, nerve of Hering, ramus descensus glossopharyngei, intercarotid nerve, or Castro nerve.[21-23]

Anatomic description of cranial portions of the CSN nerve was debated for a number of decades. Early anatomists found nervous networks rather than a distinct CSN. For instance, Hovelacque et al[24] reported on a carotid plexus that was formed by branches from glossopharyngeal and vagus nerve and cervical sympathetic trunk innervating both carotid body and carotid sinus. Sheehan et al[25] described an intercarotid plexus that mainly consisted of

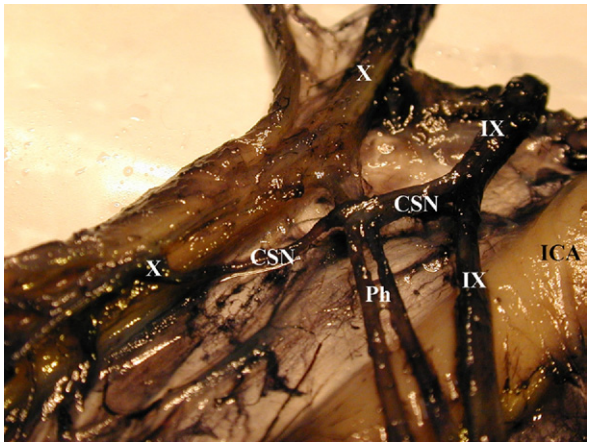

Fig 4. Detailed view of connections between vagus nerve, its pharyngeal branches and the carotid sinus nerve (CSN). Right carotid bifurcation, magnification 4×. *X,* vagus nerve; *Ph,* pharyngeal branches; *IX,* glossopharyngeal nerve; *CSN,* carotid sinus nerve; *ICA,* internal carotid artery.

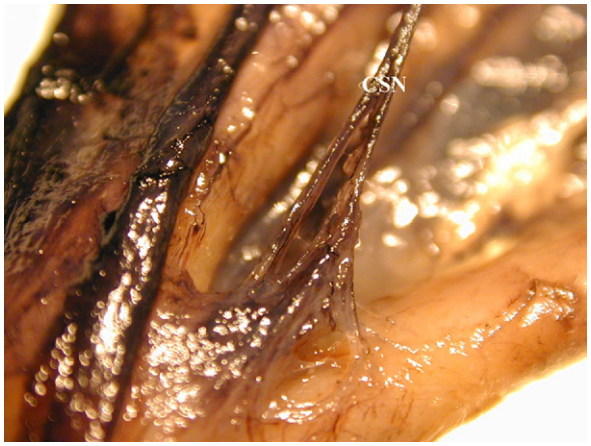

Fig 5. Detailed view of termination of the carotid sinus nerve (CSN) by little branches in the wall of the carotid sinus. Left carotid bifurcation, magnification 6×.

branches of cervical sympathetic trunk and vagus nerve and an occasional glossopharyngeal nerve. He claimed that this plexus was mostly situated posteromedially to the ICA. Many of the plexus' fibers were destined for the carotid body, whereas the minority innervated the carotid sinus. The present study found that 100% of the specimens contained a separate CSN. A single trunk phenomenon was also suggested by Boyd et al[26] describing the CSN as a single branch not only ending in the carotid sinus but also in the carotid body and in an intercarotid plexus. Observed differences in descriptive anatomy of the cranial CSN may be largely due to the advent of modern dissection and staining techniques.

Is there also a variable pattern of caudal portions of the CSN? The CSN observed in our study always terminated in numerous little branches penetrating the carotid sinus wall or carotid bifurcation. In contrast, two earlier studies demonstrated that CSN branches beyond the carotid bifurcation were invariably present.[22,26] Furthermore, Tchibukmacher[27] observed that the CSN forms small branches at the level of the carotid bifurcation participating in formation of a carotid sinus plexus. A small number of branches were found to enter the plexus enveloping the ICA from above. Some ended in the carotid body whereas others continued along the common carotid artery.

Early CSN descriptions suggest great variability in number of side branches and other communications with neighboring nerve structures. The present study also demonstrated variations including an inconstant contribution to innervation of carotid sinus by the vagus nerve (25%), superior pharyngeal branches of the vagus nerve (50%), the sympathetic trunk (17%), and superior cervical ganglion (17%). In one specimen, a little CNS branch penetrated the ICA wall approximately 38 mm above its bifurcation. Interestingly, various types of communicating loops originating from the vagus nerve running towards a distinct CSN were already documented in the 1930s.[28] Another study found CSN communications with a pharyngeal branch of the vagus nerve in almost half of the specimens.[25] CSN connections with the hypoglossal nerve were reported in just one study.[25] With respect to its position relative to the ICA, the CSN is consistently found in an anterior rather than posterior plane. Location in our study was usually anteromedially (50%) or anterolaterally (42%), and once anteriorly (8%) in accordance to an earlier study.[29]

Some of the variability in anatomic descriptions may also be explained by improved analytic methodology. In the present study, a nerve-specific whole-mount staining technique (ACHE) was used to identify small nerve branches and its communications. The technique is very useful as it allows distinction between collagen and nerve tissue.[16] However, ACHE staining procedures require fixation in formaldehyde. Time consumption is a major disadvantage of the whole-mount staining method as all the surrounding tissue has to be carefully removed without damaging nerve branches so the stain reaches the tissue of interest. Even then, multiple staining procedures may have to be applied before nerve identification is considered reliable.

Surgical considerations. Carotid denervation by transection of the CSN has been proposed as a treatment option for CSS. A recent feasibility study in formalin-fixed non stained human cadavers concluded that the CSN was surgically accessible.[29] If a standard surgical approach along the medial sternocleidomastoid muscle is used, positioning of the hypoglossal nerve (XII) limits exposure of cranial portions of the CSN. The 'working distance' for CSN access is defined as the distance between XII and the carotid bifurcation, rather than the distance from mandibular angle.[29] Although this working distance for CSN transection appears sufficient (29 ± 4 mm), the orientation of CSN relative to the ICA is frequently anteromedially (50% in this

study), which makes exposure difficult without additional surgical dissection.

In contrast to this earlier report on cadavers, the present data suggest that a CSN could not clearly be identified without en-bloc excision of carotid arteries and surrounding nerves and further staining procedures. This discrepancy could first be explained by the fact that specimens in our study were bloodless and pale as they required thorough rinsing prior to fixing, steps that are necessary for ACHE staining. Second, the finding that cadavers in our study were approximately 25 years older may also have contributed to this discrepancy. Although older age results in increased amounts of connective tissue and a more difficult dissection, we choose specimens of an age associated with CSS. A third explanation was a different study perspective. Our aim was to perform mapping of nerve structures surrounding the carotid bifurcation using microdissection and nerve staining techniques with special emphasis on CSN and its branches in relation to the carotid sinus and carotid body. A less rigorous dissection for identification of the CSN trunk was performed in order to preserve important objects of our interest, being its smallest branches and communications.

What are the surgical implications of our anatomical findings? The present data suggest that simple CSN transection for treatment of CSS may be insufficient. A great variability of CSN branches is described as well as unpredictable loops of communications. These anatomic features indicate that carotid sinus denervation using simple CSN transection may be far from complete. Others also hypothesized that simple CSN transection would leave fibers destined for the sinus using an alternative route (intercarotid plexus-carotid body), perfectly intact.[25] Moreover, high CSN transection may be associated with 'collateral damage'. In our study, we observed CSN branches traveling to both carotid sinus and carotid body. Transection would therefore not only denervate the carotid sinus but also damage innervation of the carotid body. Uncertainty exists on the clinical consequences of a carotid body denervation, especially if performed bilaterally. An abnormal hypoxic ventilatory drive was found after bilateral carotid body tumor resection and experimental carotid body resection in asthmatic patients.[30-32] These data, and common sense, indicate that carotid body denervation is to be avoided if possible.

Although not a major aim of the present study, our anatomic data may support the contention that dissection during routine carotid endarterectomy is ideally limited to the circumference of the intended clamping place of the distal ICA. By doing so, unintended damage of the CSN or carotid sinus afferents near the carotid bifurcation is avoided. As a consequence, peri- and postoperative changes in blood pressure and heart rate in endarterectomized patients may be attenuated.

CONCLUSION

In conclusion, modern staining and microdissection techniques allow for a detailed description of CSN networks innervating the carotid sinus. High transection of the CSN may lead to an incomplete sinus denervation in patients with carotid sinus syndrome. In contrast, surgical denervation at the level of the carotid sinus (as performed in adventitial stripping) may be more effective in CSS.

We thank Mr J.W. de Groot for expert assistance in the staining procedures and Mr J.J. Doorn for processing of the photographs.

AUTHOR CONTRIBUTIONS

Conception and design: RT, MS, FM, RB
Analysis and interpretation: RT, RB
Data collection: RT, RB
Writing the article: RT, MS
Critical revision of the article: RT, MS, FM, RB
Final approval of the article: RT, MS, FM, RB
Statistical analysis: RT, MS
Obtained funding: RT, MS
Overall responsibility: RT

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Submitted Jan 17, 2009; accepted Mar 14, 2009.