Surgical interventions and studies of the carotid sinus

Raechel Toorop

Surgical interventions and studies of the carotid sinus

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(met een samenvatting in het Nederlands)

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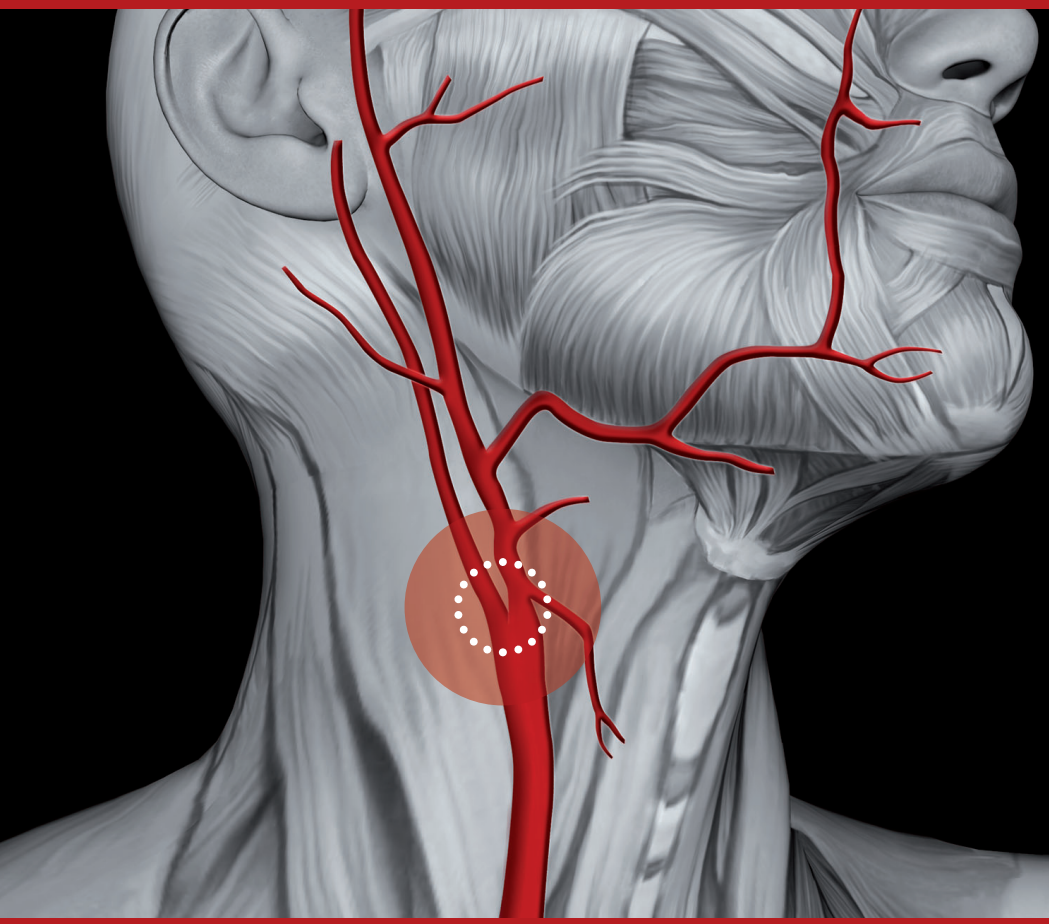

CHAPTER 1

Introduction

INTRODUCTION

The carotid sinus and its baroreflex

The word "carotis" is the Latinized form of the ancient Greek word "καρώδης" meaning "in a deep sleep". In the first century AD the physician Rufus of Ephesus wrote: "The ancients named the vessels traversing the neck 'carotids', because when you press upon them, people become sleepy and speechless". This citation was most probably the very first description of the carotid baroreflex.[1] In 1927 Hering localized the origin of this reflex.[2] He observed that changes in heart rate and blood pressure experienced during external neck pressure were caused by activation of nerve endings in the arterial wall of the carotid bifurcation. This carotid baroreflex is thought to buffer acute changes in blood pressure and is triggered by stretch receptors originating in the arterial wall of the carotid sinus.[3] Afferent fibers from these baroreceptors form the carotid sinus nerve (CSN) that subsequently joins the glossopharyngeal nerve (IX) and projects towards the nucleus tractus solitarii in the brain. Efferent portions of this reflex loop consist of parasympathetic fibers traversing towards the heart as well as sympathetic fibers innervating smooth muscles in peripheral blood vessels (figure 1). Baroreceptor firing results in an increased parasympathetic tone and a decreased sympathetic tone leading to reduced heart rate and blood pressure.[4,5]

Carotid sinus denervation for carotid sinus syndrome

Under normal conditions, sympathetic and parasympathetic action at the level of the carotid sinus is balanced. In contrast, patients suffering from a carotid sinus syndrome (CSS) may demonstrate an exaggerated carotid baroreflex response. Symptoms of dizziness and syncope may occur because of episodes of a brief asystole or a profound drop in blood pressure.[6,7] In a mostly elderly patient group these 'attaques' may be associated with frequent falls leading to serious sequelae.[8] Pacemaker implantation is nowadays considered 'gold standard' for treating patients with repetitive syncope.[9] However, recent papers question the efficacy of pacing.[10,11] Over the years, several non-surgical strategies have been explored with varying success.[12-14] Only few studies have been published on a surgical procedure called carotid sinus denervation, a technique that aims at interrupting the pathological carotid baroreflex.

Carotid sinus stimulation for hypertension

Hypertension is a major risk factor for the development of cardiovascular events.[15] An adequate treatment plan consists of adopting life style changes in combination with the use of pharmacological agents.[16] Large clinical trials indicate that up to 30% of these hypertensive patients do not reach normotension despite these measures.[17,18] The sympathetic nervous system plays a crucial role in the pathofysiology of hypertension. For instance, an association was found between systemic hypertension and the presence

of an abnormal baroreflex.[19] Novel procedure- and device based therapies targeting at modulating sympathetic nerve activity are currently being studied.[20,21] One strategy explores the concept of stimulating the carotid sinus in order to trigger baroreceptor firing, thus reducing sympathetic outflow and blood pressure.

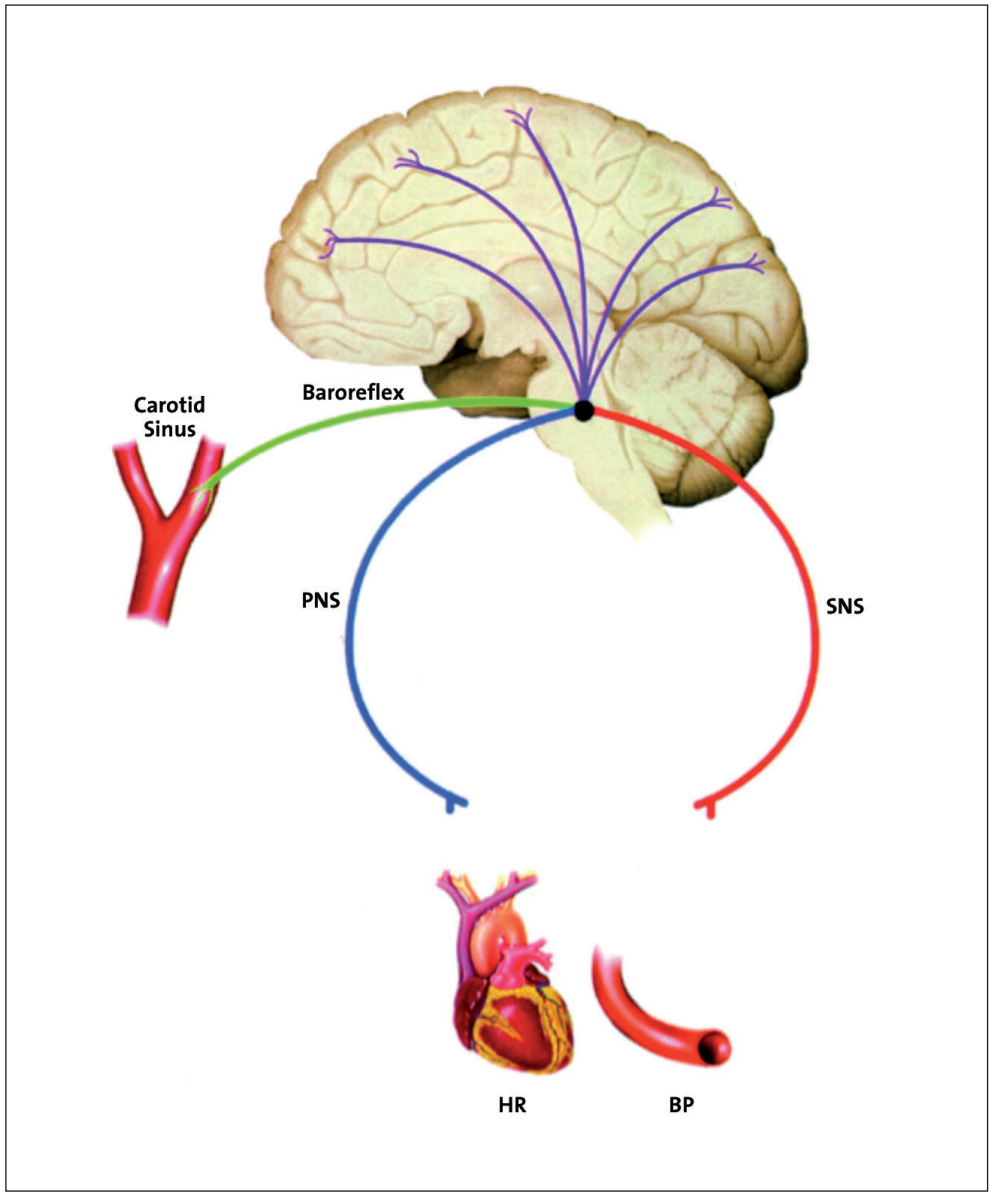

Figure 1. The carotid baroreflex.
PNS=parasympathetic nerve system, SNS=sympathetic nerve system, HR=heart rate, BP=blood pressure.

GENERAL AIMS OF THIS THESIS

To study the effects of carotid sinus denervation by means of adventitial stripping in patients suffering from carotid sinus syndrome (CSS). To explore the concept of mechanical carotid sinus stimulation in the treatment of hypertension.

SPECIFIC AIMS

1. To perform a literature study on technique, efficacy and safety of a surgical technique termed adventitial stripping of the carotid sinus as a treatment of CSS.
2. To study the anatomy of nerve structures surrounding the carotid bifurcation with special emphasis on the carotid sinus nerve (CSN) and its branches.
3. To investigate the microscopic anatomy of the carotid sinus and study the distribution of baroreceptors in the carotid bifurcation.
4. To describe the short term efficacy and safety of adventitial stripping of the carotid sinus in CSS patients.
5. To study the long term efficacy and safety of adventitial stripping of the carotid sinus in CSS patients.
6. To perform a first-in-man study of mechanical carotid sinus stimulation.

OUTLINE

Carotid sinus denervation for treatment of carotid sinus syndrome
Symptoms of dizziness and syncope are frequently encountered in an elderly patient population. However, an underlying disease may not always be identified. **Chapter 2** decribes three patients suffering from these symptoms who were eventually diagnosed with carotid sinus syndrome (CSS).

Some patients with CSS present with atypical symptoms. **Chapter 3** reports the case of a female CSS patient presenting with excessive gagging and vomiting elicited by pressure on the neck. Surgical carotid sinus denervation abolished her symptomatology.

Several treatment modalities have been proposed for CSS including 'the gold standard' being pacemaker implantation. In **chapter 4** the literature is reviewed on type of technique, efficacy and safety of a surgical procedure termed adventitial stripping of the carotid sinus.

The aim of **chapter 5** is mapping of nerve structures surrounding the carotid bifurcation

using an unique combination of microdissection and nerve staining techniques with special emphasis on the CSN and its branches.

In **chapter 6** baroreceptors in the human carotid bifurcation are visualized by immunohistochemical staining and light microscopy and the distribution of baroreceptors in the carotid bifurcation is investigated.

Short term and long term results on efficacy and safety of adventitial stripping of the proximal 3 cm portion of the proximal internal carotid artery in patients with CSS are described in **chapter 7** and **chapter 8**, respectively.

Carotid sinus stimulation for treatment of hypertension
In **chapter 9** the development of some novel non-pharmacological therapies in the treatment of hypertension is described. These device-based treatments include electrical stimulation of the carotid sinus.

A first-in-man study in a small cohort of patients undergoing carotid endarterectomy was performed to test feasibility and safety of implantation of a device that lowers blood pressure via direct mechanical carotid sinus stimulation. These data are presented in **chapter 10**.

Chapter 11 provides a summarizing discussion, conclusions and future directions.

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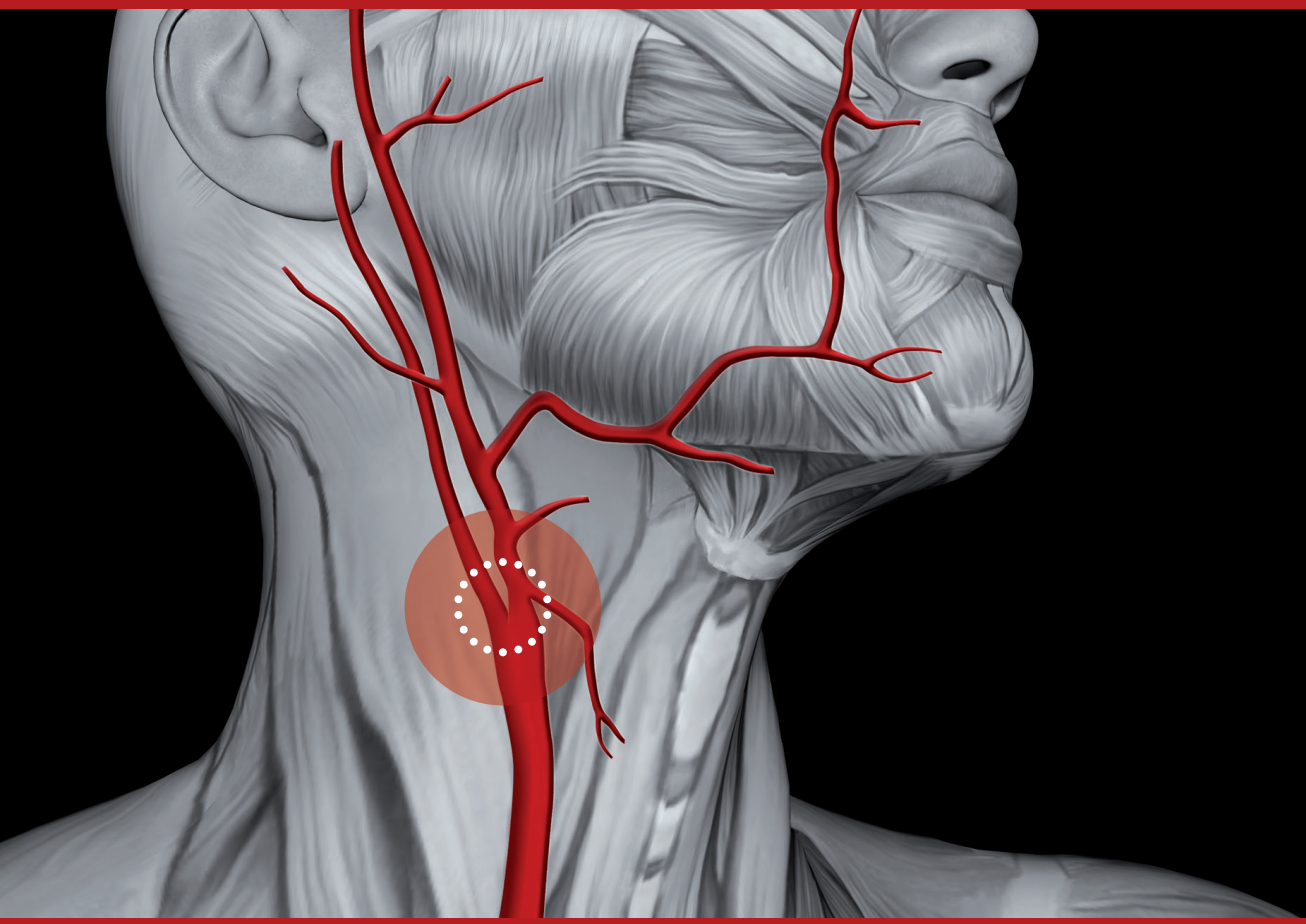

CHAPTER 2

Effective surgical treatment of the carotid sinus syndrome

Toorop RJ, Scheltinga MR, Bender MH, Charbon JA, Huige MC, Moll FL, Bruijninckx CM

Journal of Cardiovascular Surgery 2009;50(5):683-686

ABSTRACT

Elderly patients frequently suffer from dizziness and syncope; however, an underlying disease may not always be identified. Three patients aged 69, 71 and 56, respectively, experienced spells of dizziness and syncope. Massage of the carotid sinus demonstrated the presence of a carotid sinus syndrome (CSS), an abnormal baroreflex response of the carotid sinus leading to asystole and extreme hypotension. Conventional treatment is generally by insertion of a pacemaker. These patients, however, were referred to the vascular surgery department of our hospital for surgical stripping of the adventitia of proximal portions of the internal carotid artery. Recovery was uneventful, all three patients are now free of symptoms. CSS should be considered in the differential diagnosis of dizziness and syncope. Surgical denervation of the carotid artery is a valid treatment option, especially in the vasodepressor or mixed type of CSS.

INTRODUCTION

Carotid sinus hypersensitivity (CSH) is characterized by prolonged heart rate (HR) slowing or a profound drop in systolic blood pressure (BP) in response to carotid sinus massage (CSM). Carotid sinus syndrome (CSS) may be present if massage also elicits symptoms, most frequently dizziness and syncope.[1] Some patients report that external pressure on the neck region, for instance when shaving, wearing tight collars or rotating the head, provokes their symptoms.

CSS is an ill-recognized cause of syncope and consequent falls. CSH may be rare in individuals younger than 50 years, but its prevalence increases with advancing age. A recent study in 272 unselected individuals older than 65 years showed that CSH was present in 39%, and symptomatic (CSS) in 16%.[2] According to recent guidelines, the recommended treatment of syncope in CSS is cardiac pacing.[3]

We report three cases of CSS successfully treated with surgical denervation.

CLINICAL SERIES

Case 1

A 69 year-old male in otherwise good health was referred to the emergency department of our hospital because of syncope. One night, after awaking suddenly and reaching down for his leg because of a cramp, he became syncopal for several minutes, according to his wife. After regaining consciousness he felt dizzy and sick. In the months before admission he had frequently experienced similar symptoms, mostly after turning his head or looking down. He received no medication. During transfer to the hospital, he was hypotensive; the systolic BP was 70-80 mmHg. The HR was 36 beats per minute. On arrival, the systolic BP had normalised to 145 mmHg and HR to 64 beats per minute. Examination revealed no carotid bruit. Neurologic evaluation showed no abnormalities. An electrocardiogram (ECG) showed a regular sinus rhythm. Routine blood tests were normal. The patient was admitted to the cardiology department. After a carotid duplex scanning ruled out significant stenoses, a CSM was performed. Right-sided CSM evoked an asystole of 7.5 seconds along with the patient's familiar symptoms. Left-sided CSM was uneventful. Echocardiography showed normal left and right ventricle function. A tilt table test ruled out vasovagal origin of the syncope. The next day, CSM was repeated with continuous ECG and intra-arterial BP monitoring. Right-sided CSM evoked an asystole of almost 10 seconds, during which the patient was syncopal (figure 1). To block the parasympathetic nerve system, 1 mg of atropine was administered intravenously. CSM ceased to evoke an asystole but systolic BP dropped >50 mmHg and, again, the patient experienced symptoms. A right-sided carotid sinus syndrome of the mixed type was diagnosed. The case was discussed in our interdisciplinary syncope team (neurologists, cardiologists and vascular surgeons), which decided that right-sided surgical denervation of the carotid sinus was indicated. The intervention was conducted under general anesthesia and with continuous ECG and BP monitoring. A skin incision was made along the anterior border of the sternocleidomastoid muscle. After the carotid bifurcation was exposed, the proximal 3 cm of the internal carotid artery was stripped from peri-advential tissue (figure 2). The postoperative period was uneventful, except for a period of hypertension for which oral nifedipine (30 mg once a day) was given and then discontinued one month after the operation. The patient has been free of syncope and medication for more than 2 years now.

Case 2

A 71 year-old man was found lying unconscious at the curbside. In the emergency department he could not recall what had happened. He reported that in the months before admission he often found himself lying on the floor. A clear causal factor was absent. His medical history included primary hyperparathyroidy, diaphragmatic hernia and diverticulitis. The BP was 180/70 mmHg and the HR 60 beats per minute. On clinical examination there were no bruits over the carotid arteries. ECG showed a regular sinus rhythm with a left ventricle hypertrophy. Holter monitoring, table tilt testing and carotid duplex were all normal. Echocardiography showed a hypertrophic left ventricle and grade 1 aortic valve insufficience. Both right-sided and left-sided CSM evoked an asystole of 5 seconds and syncope. The next day, CSM was repeated under continuous ECG and intra-arterial BP monitoring. Right-sided CSM reduced BP from 180/70 mmHg to 70/35 mmHg; the HR dropped from 60 to 32 beats per minute. A similar reduction in

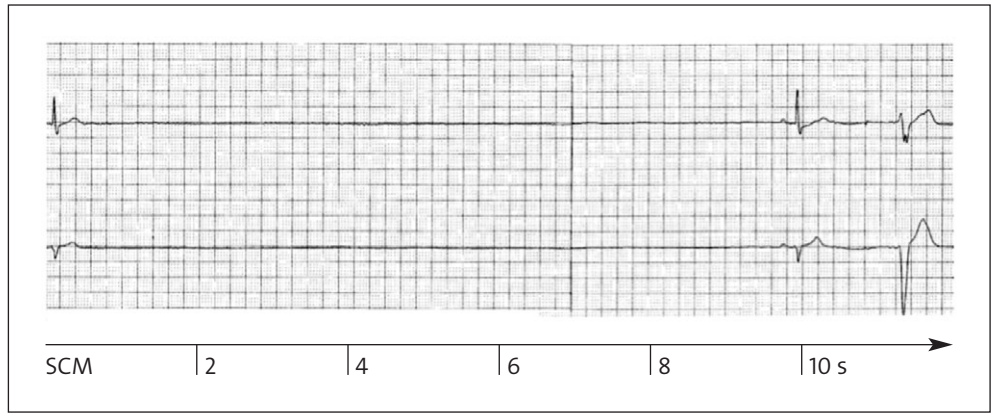

Figure 1. ECG (leadings II en V6, 25 mm/s) in patient 1.
Carotid sinus massage (CSM) evokes an asystole of almost 10 s.

BP and HR was evoked by left-sided CSM. A bilateral CSS of the mixed type was diagnosed. Following team consultation, a bilateral surgical denervation of the carotid sinus was performed. The postoperative period was complicated by a brief period of atrial fibrillation with fast response. Oral metoprolol (50 mg twice a day) was given and then discontinued a few weeks later. The patient has been free of syncope for 2 years.

Case 3

A 56 year-old man was brought to the emergency department because of syncope. He had a history of hypertension and supraventricular tachycardia. In the preceding 3 months he had experienced dizziness when turning his head. He avoided wearing tight collars and grew a beard, because he was afraid he would collapse while shaving. He received one dose of nifedipine 30 mg once a day, two doses of hydrochlorothiazide/enalapril 20/12,5 mg and atenolol 100 mg once a day. Examination revealed a healthy man with a BP of 130/75 mmHg and HR of 64 beats per minute. No carotid bruits were present. Carotid duplex scanning showed no stenoses. ECG showed a normal sinus rhythm. CSM evoked an asystole of 5 seconds on both sides, while BP remained normal. During the CSM the patient felt dizzy and reported a near-syncope. Holter monitoring and table tilt testing were normal. A cardioinhibitory type of CSS was diagnosed. Bilateral carotid denervation was performed. Postoperatively the patient was free from syncope. Medication was unchanged. During a follow-up of 30 months he could shave every day without experiencing symptoms.

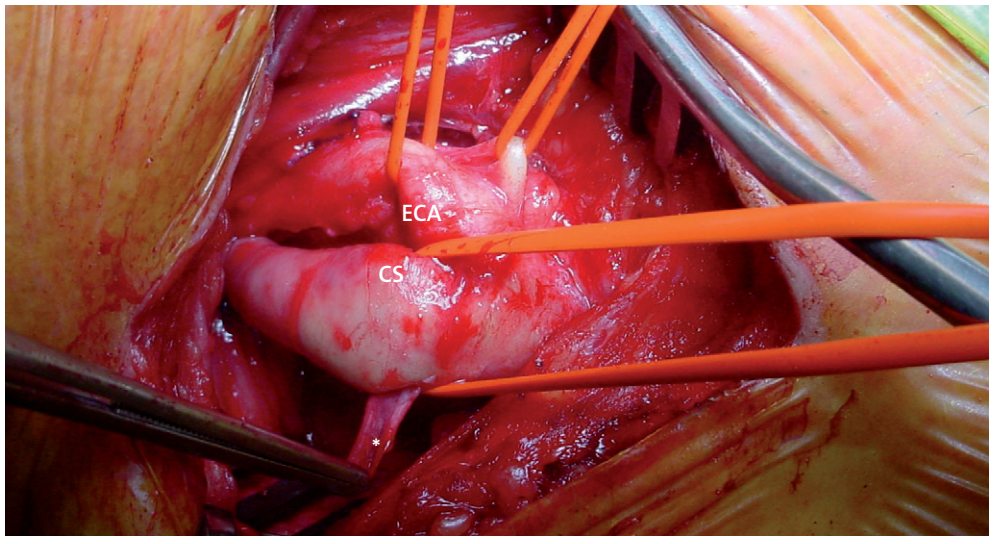

Figure 2. Surgical carotid denervation.
Adventitial stripping of the proximal 3 cm of the internal carotid artery.
ECA=external carotid artery, CS=carotid sinus, *=peri-adventitial tissue

DISCUSSION

In these three patients with a characteristic history and recurrent syncope, a CSS was diagnosed by CSM. The carotid sinus, a small organ in proximal portions of the internal carotid artery, contains baroreceptors that are stimulated by afferent pulses evoked by pressure changes in the carotid arterial wall. The afferent fibres form Hering's nerve (carotid sinus nerve), which runs along the glossopharyngeal nerve and ends in the brainstem. Impulses are conducted through the efferent pathways (the vagus nerve) to the heart and cause bradycardia, inhibit cardiac conductivity and reduce myocardial contractility. Inhibition of the sympathic nerve system may also cause vasodilatation and a reduction in BP. The carotid sinus syndrome (CSS) is characterized by an abnormal baroreflex response (overshoot) of the carotid sinus. External pressure on or stretching the neck region, as produced by certain head movements, can cause an excessive carotid sinus response, leading to asystole or extreme hypotension with associated (pre) syncope. Three types of carotid sinus syndrome have been defined: 1) cardioinhibitory (asystole for at least 3 seconds) 2) vasodepressor (decrease in systolic BP >50 mmHg) 3) mixed (combination of cardioinhibitory and vasodepressor elements).[4] Parasympathicolytic medications including atropine or cardiac pacing block the cardioinhibitory response and reveal the vasodepressor element.[5] Unfortunately, an abnormal baroreflex response is not always reproducible, but may only be transient. In our second patient, for instance, repetition of CSM did not elicit another asystole, whereas the bilateral vasodepressor element remained present. It is therefore imperative that patients presenting on the emergency department undergo a CSM as soon as possible.[6]

CSS is generally considered a rare diagnosis. However, the syndrome may be quite prevalent, especially among the elderly, according to recent reports. CSS was found in 45% of elderly people being evaluated for pre(syncope) and frequent falls and the vasodepressor type was most commonly diagnosed.[7] Investing in a cost-effective regimen of diagnostics and treatment is therefore warranted since CSS, syncope and associated falls may carry an intrinsic high morbidity (femoral neck fractures) and mortality in the elderly.

Several proposed treatment modalities for CSS (avoiding stretching of the neck region, medication, radiotherapy) have yielded inconsistent outcomes.[8,9] Cardiac pacing has become the treatment of choice in recent decades; in fact recent guidelines list cardioinhibitory CSS as a class 1 indication for pacemaker therapy in syncope.[3] In this type of CSS a 66% reduction in fall frequency was observed in patients with a pacemaker when compared to those without cardiac pacing.[10] Even so, only a limited effect of pacing can be expected in the vasodepressor or mixed type, as diagnosed in 2 of our patients. Since pacemaker action prevents bradycardia and asystole, but has no effect on vasodilatation,

alternative treatments such as surgical carotid sinus denervation should be considered, especially in the vasodepressor and mixed type of CSS.[11]

Surgical treatment for CSS is generally beneficial. In one study, denervation was performed in 6 CSS patients with mixed type, and in 2 with cardioinhibitory type. These latter 2 patients experienced severe symptoms, even after pacemaker implantation. All 8 patients were free of syncope after a follow up of 30 months.[12] In the largest series described (19 patients) so far, Trout et al. reported complete relief of symptoms after surgical denervation in 14 patients and substantial improvement in 4 patients.[13] Both studies conclude that carotid denervation is safe, simple and effective for treating all types of CSS.

Some question the safety of surgical denervation, as severe baroreflex dysfunction may result from iatrogenic denervation of the carotid sinus following bilateral carotid body tumor resection.[14] After unilateral surgical denervation, a fatal hypertensive crisis occurred in 1 patient.[15] In our patients, however, no severe complications were observed. Transient hypertension resolved with a one month course of nifedipine in 1 patient; an episode of atrial fibrillation after bilateral denervation was successfully treated with a β-blocker in another patient. Temporary hypertension and altered cardiac rhythm after manipulation of the carotid sinus are not infrequent. None of our patients experienced altered baroreflex response after surgery.

CONCLUSIONS

Carotid sinus syndrome is a relatively common cause of syncope and subsequent falls in the elderly. Immediate CSM is mandatory to avoid diagnostic delay. Surgical carotid denervation should be considered as a valid alternative to pacing, especially in the mixed or vasodepressor type. Surgical treatment of CSS appears effective, simple and safe.

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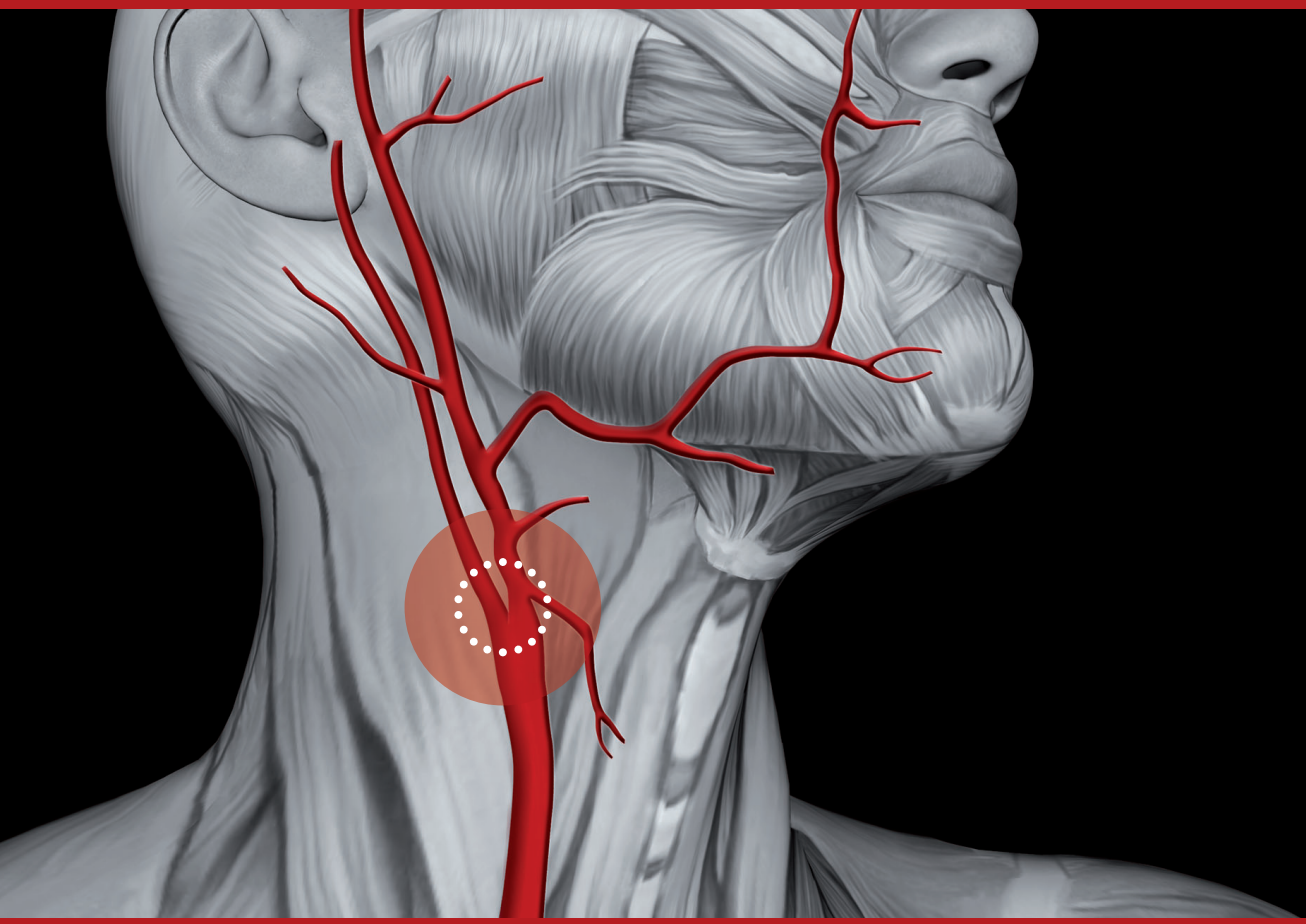

CHAPTER 3

Excessive vomiting abolished by carotid denervation

Toorop RJ, Scheltinga MR, Huige MC, Luirink MR

Autonomic Neuroscience: Basic and Clinical 2007;133(2):175-177

ABSTRACT

The carotid sinus syndrome (CSS) is characterized by repetitive syncope due to prolonged heart rate slowing or a profound drop in systolic blood pressure. CSS is due to an inappropriate response of a hypersensitive carotid sinus following pressure on or stretching of the neck. We report on a patient with excessive gagging and vomiting elicited by pressure on the right side of the neck as an aberrant presentation of the CSS. Her incapacitating symptoms were abolished by a surgical carotid denervation.

The carotid sinus syndrome (CSS) is characterized by repetitive syncope due to extreme cardioinhibition and subsequent asystole, or by intense vasodilatation with severe hypotension. CSS is due to an inappropriate response of a hypersensitive carotid sinus following stretching of the neck. Patients suffering from this syndrome loose consciousness following activities such as shaving or head rotations.[1] They usually do not remember these attacks but may experience prodromes such as dizziness or nausea. Inducing a syncope or near syncope by carotid massage or 'neck stretching' is considered diagnostic. A permanent pacemaker is traditionally inserted, although surgical denervation of the carotid bifurcation may be effective as well. [2,3]

We were recently confronted with an unusual presentation of a CSS. A 50-year-old female suffered from spells of nausea and vomiting, about 10 times daily since 6 years. She could provoke such spells by manually touching the right side of the neck. She had lost about 5 kg of body weight in previous years but was able to maintain her recent weight by frequently eating small meals. She avoided wearing tight collars, as they appeared to facilitate these bouts of vomiting. She had consulted a number of specialists including a psychiatrist who declared the patient ´realistic´ and judged the vomiting 'nonpsychogenic'. Various treatments including all sorts of anti-emetic medication had proved unsuccessful. She was progressively socially incapacitated since attacks always came unannounced. Imaging techniques of neck vessels and brain had not revealed any structural abnormalities. She was referred to our team of surgeons and cardiologists who have a longstanding interest in CSS.

On examination she looked healthy and had a blood pressure of 130/70 mmHg, and a heart rate of 90 per minute. Inspection of the neck region did not demonstrate any abnormalities. A bruit along the carotid axes was not present. Stretching of the left neck under continuous ECG monitoring and intra-arterial blood pressure measurement did not result in any symptoms or alterations in heart rate or blood pressure. In contrast, just a light manual touch of the right neck's side immediately resulted in severe gagging. We could not reliably perform a carotid sinus massage because of the instaneous onset of gagging and excessive motion of the patient. It was therefore an impossibility to reliably measure blood pressure and heart rate during these episodes.

Since an unprecedented form of CSS was suspected, the patient agreed to a strategy including general anesthesia, followed by injection of a local anesthetic around proximal portions of the internal carotid artery aimed at blocking the baroreceptor reflex. A rapid sequence intubation was performed after induction of anesthesia with etomidate and suxamethonium. Anesthesia was maintained with sevoflurane in a mixture of oxygen and nitrous oxide. Blood pressure during anesthesia was 130/70 mmHg and heart rate was 115 beats per minute. During carotid sinus massage of the right side, systemic blood pressure dropped to 90/40 mm Hg and heart rate diminished to 83 beats per minute. Massage of the left side reduced blood pressure to 100/55 mm Hg and heart rate to 90 beats per minute. Both responses were considered physiological. Under ultrasonic guidance 5 ml of lignocaine 2% was injected in close proximity to the right carotid sinus. After emerging from anesthesia, carotid stretching could not provoke any reaction such as gagging or vomiting. There was no significant drop in heart rate or blood pressure. However, after two hours of subjective happiness, the abnormal response fully returned as expected.

After the patient gave her informed consent, we performed a surgical denervation. After induction and intubation, the carotid bifurcation was dissected free from surrounding tissue and the adventitia of the proximal internal carotid artery was stripped from nervous tissue over a 3 cm distance (figures 1 and 2). Her postoperative recovery was uneventful. She was immediately free of symptoms and still is after 24 months. She even wears clothing with tight collars and she undergoes stretching of the neck without any problems.

Carotid sinus syndrome usually presents as repetitive syncopes or presyncopes. This syndrome is diagnosed by carotid sinus massage which elicits either an asystole or

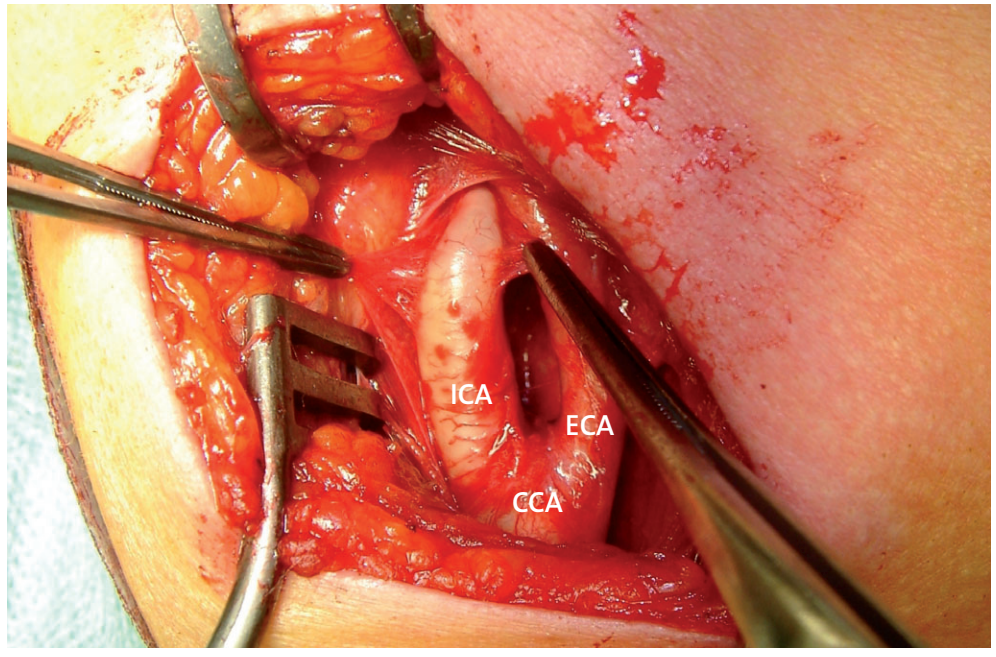

Figure 1. ***Tweezers clear nervous tissue from underlying internal carotid artery.***
CCA: common carotid artery, ICA: internal carotid artery, ECA: external carotid artery.

extreme reduction in blood pressure with associated symptoms. An unusual presentation of CSS, characterized by gagging and vomiting, was observed in our patient. Interestingly, results of a recent animal study by Uchino et al. indicate that carotid baroreceptor activation plays an important role in the development of emesis as well as in the prodromal autonomic response.[4]

It is unclear if stretching of the neck in this individual resulted in reflex bradycardia as a trigger for gagging or vomiting as an associated parasympathetic response. In our awake patient it was technically impossible to document reflex bradycardia because of the extreme movements during gagging. In an anaesthetized patient the effect of carotid sinus massage is unreliable, because anesthesia by itself decreases blood pressure and heart rate, but more importantly, can also cause a depression of baroreceptor sensitivity.[5] Therefore it is doubtful to consider a reduction in heart rate to be a reflex bradycardia. However, the fact that symptoms were abolished by both local anesthetics that were administered close to the carotid sinus and by surgical carotid denervation, forms presumptive evidence for a carotid sinus syndrome. Repetitive vomiting combined with subjective avoidance of tight collars should alert the physician on the presence of this unusual form of CSS.

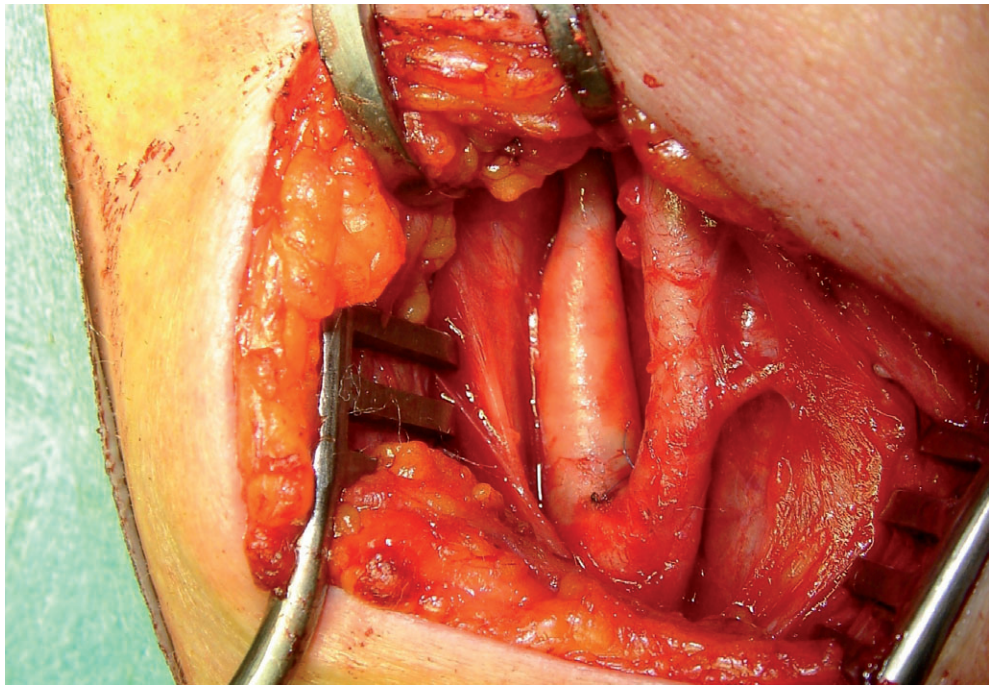

Figure 2. Proximal 3-cm portion of internal carotid artery is circumferentially 'bare'. The common and external carotid branches are purposely left alone.

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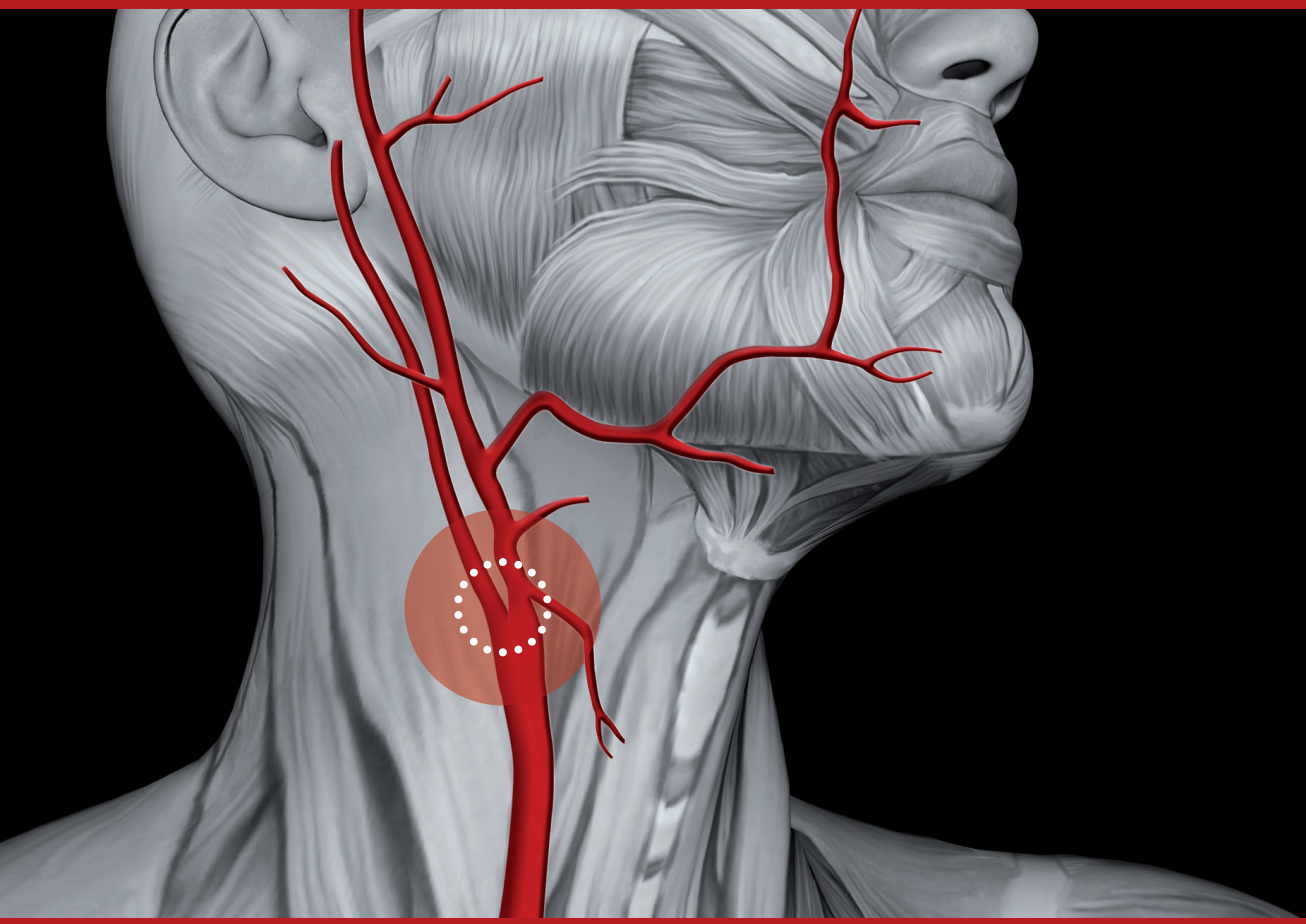

CHAPTER 4

Adventitial stripping for carotid sinus syndrome

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ABSTRACT

Patients with a carotid sinus syndrome (CSS) suffer from spells of dizziness and loss of conscience due to an exaggerated carotid baroreflex response. Three types of the syndrome are described: cardioinhibitory, vasodepressor and a mixed form. The gold standard for treatment is insertion of a pacemaker, but this therapy may only be effective in a pure cardioinhibitory type. In contrast, surgically interrupting afferent nerves at its origin may offer relief of symptoms in all three types. The present review analyzes the results of a surgical technique termed adventitial stripping of the carotid sinus. Data from 130 procedures demonstrate that carotid denervation is effective in 85% of CSS with low complication rates. Postoperative monitoring is mandatory as transient alterations in blood pressure and heart rate may occur.

INTRODUCTION

Blood pressure and heart rate are regulated by a sophisticated feedback system that is fed by information from several pathways including carotid baroreceptors. In some patients however these receptor bodies may generate disproportionate afferent input. A clinical syndrome that is associated with such a hypersensitive carotid sinus reflex is termed "carotid sinus syndrome" (CSS), characterized by sudden spells of dizziness and loss of consciousness. CSS is evoked by pressure or stretching forces on one or both carotid sinuses leading to extreme low heart frequency and/or hypotension. Three separate forms of CSS are identified: cardioinhibitory (bradycardia/asystole), vasodepressor (hypotension) and mixed (both elements).

Forty-five percent of patients with "unexplained syncope", and about 30% of patients referred to an emergency department with "non-accidental falls" are found to suffer from CSS.[2,3] Pacemaker implantation is considered the treatment of choice, but this modality may only be effective in the pure cardioinhibitory type.[4,5] In contrast, surgical denervation of the carotid sinus may be successful in all three types as the afferent limb of the pathologic baroreflex is blocked at its origin. However, operative procedures for CSS are infrequently performed.

The purpose of this review is to analyze the available literature on the efficacy of adventitial stripping of the carotid sinus as a simple surgical treatment of CSS.

METHODS

A literature search using Medline and Google was performed using the keywords "hypersensitive carotid sinus syndrome", "carotid denervation"," surgical treatment", "periarterial carotid stripping" and "adventitial carotid stripping" in combinations with the Boolean operators AND and OR. Studies were only included if they reported on CSS patients undergoing carotid denervation by adventitial stripping. Case reports were also included. Reference lists of identified articles were searched for additional reports.

RESULTS

Clinical features

A limited number of articles (n=31) on CSS patients undergoing a carotid denervation by adventitional stripping was published between 1933 and 2007. A total of 130 procedures was performed in 110 patients as twenty patients were operated bilaterally (table 1).

Mean age was 55 years (range 13-84), and the male-to-female ratio approximates 2.5:1 (data not shown). Comorbidity is listed in table 2. Interestingly, CSS was associated with significant carotid stenosis in only 8% of patients.

Table 3 displays symptomatology of CSS. Common clinical features are dizziness and syncope. However, a wide variety in symptoms including vomiting and feelings of choking is reported. Factors evoking CSS are found in only a minority of patients (35%, 39 patients) and are summarized in table 4. Turning of the head appears to be the most frequent provocative cause. Some authors have identified prodromal signs including disturbed vision, epigastric discomfort and tinnitus.[6-8]

Secundary CSS is sparsely identified in the literature. One patient developed CSS 3 weeks after an ipsilateral carotid endarterectomy (CEA).[9] The syndrome was diagnosed in a second patient 8 months after receiving radiation therapy for epipharyngeal carcinoma and cervical metastases.[10] Radical mastoidectomy for chronical mastoiditis was associated with the onset of CSS in a third patient one month postoperatively.[11]

Diagnostic evaluation

Carotid sinus massage (CSM) is used as a standard diagnostic tool in all reported studies, but its execution varies greatly. Moreover, several sets of criteria are used to classify the different forms, although most authors agree on a system that includes a cardioinhibitory, a vasodepressor and a mixed type (table 5). The latter type (bradycardia/ asystole combined with hypotension) can only be discriminated from the pure cardioinhibitory form on the basis of maintainance of an adequate heart rate. The parasympaticolytic agent atropine is used to make this distinction.[12-15] Others insert a temporary pacemaker for securing levels of heart rate in order to unveil a vasodepressor component.[9,13,15,16]

Two early studies published prior to the 1950's claimed the existence of a fourth type of CSS termed "cerebral". This variant was characterized by typical symptomatology without significant change in heart rate or blood pressure.[6,7,17] It may well be that this fourth group of patients may have demonstrated syncopal attacks due to cerebrovascular insufficiency, although significant carotid stenoses were not mentioned. This cerebral type is omitted from most modern classifications.

Table 1 also allows a classification on incidence. Almost half (46%) of all patients receiving surgical denervation are of the cardioinhibitory type, and 38% have a mixed form of CSS. The vasodepressor form is found in 8%. Unfortunately, two large studies (encompassing 25% of the operated population) do not make this distinction.[6,18]

Reference	Year	Pt	n	Type (n)	VD test	Intraoperative adjuncts	Operation technique	Follow-up (m)	PO CSM	Outcome
18	1979	19	25	n.r.	n.r.	Lidocaine	stripping 1 cm CCA, ECA, ICA CEA (n=6)	76 (10-185)	No	14 complete relief 4 improved
6	1939	13	14	n.r.	n.r.	No	stripping CCA, 4 cm ECA, ICA glomectomy (n=6)	11 (1-22)	No	4 complete relief 5 improved
19	1998	8	10	MIX 8	No	Lidocaine	stripping of CCA, 1 cm ECA, ICA CEA (n=2)	30 (6-53)	Yes	8 complete relief
29	1960	8	8	CI 2 VD 2	No	Procaine	stripping 3 cm CCA, ECA, ICA	13 (12-14)	No	3 complete relief 5 n.r.
13	1986	7	9	CI 1 VD 2 MIX 6	Atropine	No	n.r. CEA (n=2)	35 (6-89)	No	6 complete relief
7	1935	7	7	CI 1 MIX 2 CER 4	n.r.	No	stripping 2 cm CCA, ECA, ICA	6 (1-9)	Yes	7 complete relief
16	1988	6	7	CI 4 VD 2 MIX 1	Pacing	No	stripping 3 cm ICA	17(5-31)	Yes	5 complete relief 1 contralat CSS
8	1941	5	5	CI 5	No	No	n.r.	4(0-15)	Yes	5 complete relief
50	1952	4	6	CI 3 MIX 1 n.r. 2	n.r.	No	stripping 2 cm CCA, ECA, ICA	10 (3-24)	Yes	4 complete relief
24	1962	4	4	n.r.	n.r.	No	stripping 2.5 cm CCA, ICA CSN section	21 (6-36)	No	4 complete relief
14	2009	3	5	CI 2 MIX 3	Atropine	No	stripping 3 cm ICA	26 (24-30)	No	3 complete relief
25	1947	3	3	MIX 3	n.r.	No	stripping 2 cm CCA, 2 cm ECA glomectomy	39 (18-50)	Yes	2 complete relief 1 improved
27	1976	3	4	CI 4	No	Pacing	n.r.	43 (19-89)	Yes	3 complete relief

Reference	Year	Pt	n	Type (n)	VD test	Intraoperative adjuncts	Operation technique	Follow-up (m)	PO CSM	Outcome
12	1958	2	2	CI 2	Atropine	No	n.r.	4 (4)	Yes	1 complete relief 1 improved
51	1952	2	2	CI 2	No	No	n.r.	2	Yes	1 complete relief 1 n.r.
52	1948	1	2	CI 2	No	Procaine	stripping 5 cm CCA, ECA, ICA	14	Yes	complete relief
26	1987	1	2	CI 2	No	No	n.r. CSN section	6	No	complete relief
30	1967	1	2	MIX 2	n.r.	No	n.r.	1		complete relief
1	1933	1	1	MIX 1	n.r.	No	n.r. CSN section	n.r.	No	n.r.
20	1994	1	1	MIX 1	n.r.	Pacing	stripping 1cm CCA, ICA	n.r.	Yes	complete relief
21	1975	1	1	CI 1	No	No	n.r.	9	Yes	complete relief
15	1973	1	1	MIX 1	Atropine +pacing	Lidocaine	stripping 2 cm CCA, ECA, ICA glomectomy	19	Yes	complete relief
23	1980	1	1	MIX 1	n.r.	Lidocaine Pacing	stripping 2 cm CCA, ECA, ICA	24	Yes	improved
22	1987	1	1	CI 1	No	Lidocaine Atropine	stripping 2 cm ICA	30	Yes	complete relief
9	1982	1	1	MIX 1	Pacing	Pacing	n.r.	n.r.	Yes	complete relief
28	1956	1	1	CI 1	No	Procain	n.r.	-	No	†
10	1985	1	1	MIX 1	n.r.	No	n.r. glomectomy	12	No	no relief
11	1941	1	1	MIX 1	n.r.	No	stripping 1 cm CCA, 2 cm ECA, ICA	n.r.	Yes	complete relief
53	2007	1	1	n.r.		No	stripping 3 cm ICA	24	No	complete relief
17	1950	1	1	CER 1	n.r.	No	n.r. glomectomy	84	No	improved
54	1965	1	1	CI 1	No	No	n.r.	n.r.	No	no relief

Table 1. ***Outcome following carotid adventitial stripping for CSS.***
Pt: number of patients, n: number of denervations, Type: type of CSS, MIX: mixed, CI: cardioinhibitory, VD: vasodepressor, CER: cerebral, VD test: test for vasodepressor component, CCA: common carotid artery, ECA: external carotid artery, ICA: internal carotid artery, CEA: carotid endarterectomy, CSN: carotid sinus nerve, Intraop: intraoperative adjuncts preventing pathologic baroreflex, m: months, PO CSM: postoperative carotid sinus massage, n.r.: not reported, †: died.

Hypertension	30%	Carotid stenosis	8%
Arteriosclerosis*	27%	TIA/CVA	4%
IHD/ MI	23%	Heart valve	2%
Dysrhythmia	13%	Epilepsy	2%
LVH	12%	DM	2%

Table 2. Comorbidity in CSS patients.
Data are based on 110 patients who underwent carotid adventitial stripping. LVH: left ventricular hypertrophy, IHD: ischemic heart disease, MI: myocardial infarction, TIA: transient ischemic attack, CVA: cerebrovascular accident, DM: diabetes mellitus. *generalized, without discriminating organs affected.

	Incidence
Syncope	72%
Dizziness	45%
Convulsions	13%
Choking	4%
Staggering gait	4%
Nausea/retching/vomiting	3%
Suffocation	3%
Visual symptoms	2%
Urinary incontinence	2%
Retrograde amnesia	2%
Mental confusion	2%

Table 3. CSS and symptomatology.
Data are based on 110 patients who underwent carotid adventitial stripping.

	Incidence
Head turning	59%
Shaving/collars/ties	33%
Stooping	10%
Looking upward	8%
Operation/tumor/irradiation neck	8%
Exertion/excitement	8%
Arm raising	5%
Coughing	3%

Table 4. Activities that elicit symptomatology in patients with CSS.
Data are based on 39 patients who underwent carotid adventitial stripping; data on the remaining 71 patients were incomplete and were not included in the table.

Some authors visualize the carotid bifurcation using angiography or Duplex sonography prior to CSM as they fear dislodgement of atherosclerotic debris.[13, 15, 16, 18-22] Others suggest additional diagnostic screening using table tilt testing, Holter monitoring, 24-hr blood pressure measurements and echocardiography.[16, 19, 20]

Characteristics of Operative technique

Unilateral CSS was more than twice as frequently located on the right side (53%) compared to the left (23%). In the remaining group of bilateral CSS (18%), some surgeons perform a one- or a two-stage procedure, whereas others exclusively operate on the most symptomatic side. [6, 15, 23] A concomittant carotid endarterectomy (CEA) for carotid stenosis is performed in 9 patients. [13, 18, 19]

Reference	Type *Cardioinhibitory*	*Vasodepressor*	*Mixed*
18	Asystole>2 sec or bradycardia>30%	Drop SBP>30 mmHg	-
19	Asystole>3 sec	Drop SBP>50 mmHg and bradycardia<30%	Bradycardia>30% and drop SBP>30 mmHg
13,16	Asystole>3 sec or complete AV block	Drop SBP>50 mmHg	Asystole>3 sec and drop SBP>50 mmHg*

Table 5. Classification criteria for different types of CSS based on CSM.
SBP: systolic blood pressure, AV: atrioventricular. *After intravenous administration of atropine or pacing.

Side	Percentage	n
Right	53%	58
Left	23%	25
Bilateral	11%	14
Bilateral staged	4%	4
Right+CEA	4%	4
Left+CEA	3%	3
Bilateral+CEA	2%	2

Table 6. Side of adventitial stripping in various combinations with CEA.
CEA: carotid endarterectomy, n: number of patients.

Technical aspects of the operation were quite diverse with reference to extent of length and extent of circumference of adventitial stripping (table 1). Some combine adventitial stripping with carotid body removal or with transection of the carotid sinus nerve.[1, 6, 10, 15, 17, 24-26] Intraoperative adjuncts were also frequently used. For instance, one author used a nerve stimulator as a means of testing the completeness of adventitial stripping during operation.[21] Lidocaine injection into the carotid sinus during a procedure was thought to block intraoperative hypotension and bradycardia in some studies. Others promoted intraoperative pacing or administration of atropine for the prevention of extreme bradycardia or asystole.[9, 20, 22, 23, 27]

Clinical Outcome

Complete relief of symptoms (mean follow-up 2.5 years, range 1-185) was obtained in 73% of patients (80/110), whereas substantial improvement occurred in another 12% (13/110). The operation had no effect on symptoms in 7% (8/110) whereas the effect was unknown in 6% (7/110). Major complications (death, cerebrovascular accident, CVA or transient ischemic attack,TIA) were observed (3%) in early reports published prior to the 1980's. However, complications of this severity were not identified in modern series. The only fatal case, published in 1956, used intraoperative infiltration of the carotid sinus with procaine, resulting in a profound rise of blood pressure complicated by intracranial hemorrhage and death.[28] One patient displayed mild right paralysis after a rightsided carotid denervation in 1939.[6] A second patient developed hemiparesis of an unknown side 48 hours after right carotid denervation that disappeared after a fortnight.[29] Hemiparesis with a mild persistent weakness of the left hand was also present in a third patient following a combined CEA-denervation procedure in 1979.[18]

Minor complications (9%) were often related to postoperative disturbances in the autoregulation of blood pressure. One patient, developing hypertension up to 210/160 mm Hg and tachycardia of 120/min in the early postoperatively hours, responded well to intravenous drug medication and was discharged normotensive without medication.[30] A 20-30 mm Hg increase in postoperative blood pressure was documented in 7 patients, but normalization occurred spontaneously or with the help of medication in the first postoperative week.[14, 20-22, 30] Supraventricular tachycardia and atrial fibrillation were also successfully treated with the temporary administration of digitalis and metoprolol.[14, 27] One patient developed longstanding orthostatic hypotension.[18]

Flushing on the right side of the face with a temporary dilated right pupil was observed after right carotid denervation in another patient.[8] Slight transient ptosis of the left eye developed after a left carotid denervation in a second patient.[25] Temporary marginal mandibular nerve injury was observed in a third patient.[13] Surgical evacuation of a wound hematoma was performed once.[8]

A small number of patients required additional therapies on the long term. One successfully operated patient developed a CSS from a contralateral hypersensitive carotid sinus after 4 years and chose treatment with a pacemaker.[16] A second individual required a pacemaker after successful carotid denervation for associated sick sinus syndrome. A third patient received a pacemaker for residual symptoms after bilateral staged carotid denervation, but to no avail.[13] A pacemaker was successfully inserted in another patient who developed a complete atrioventricular block postoperatively.[18] Of 85 % of patients (93/110) demonstrating complete or substantial long term relief after operation, 82 % (90/110) was also free of pacemaker.

DISCUSSION

CSS is characterized by repetitive, seemingly spontaneously occurring attacks of dizziness and syncope. These and other symptoms may be evoked by pressure on the carotid sinus causing an asystole or extreme hypotension as a result of hypersensitivity of the carotid baroreceptor area.[1] Afferent fibers from the carotid sinus form Hering's nerve (carotid sinus nerve), which runs along the glossopharyngeal nerve and ends in the brainstem. Efferent pulses are conducted by the vagus nerve to the heart and by the sympathetic nerve system to systemic blood vessels. The exact pathophysiology of CSS has not been clarified in detail yet. A recent study suggests that neuromuscular structures surrounding carotid baroreceptors are also involved in CSS.[31] The syndrome is commonly associated with older age, hypertension and coronary heart disease (table 2) and the patient's profile is mainly "atherosclerotic". Medication or direct pressure by tumors, cervical adenopathy, aneurysmal dilation and scar tissue are also identified as etiologic factors, although most cases are idiopathic as confirmed by the present review.[9, 32] Only one third of the population under review recognize a clear provocative factor, usually head turning (table 4). In contrast, the majority of patients spontaneously experienced serious symptoms without prior warning by prodromal signs. Dominating symptoms were syncope and dizziness, although the present review identifies a wide variation in expression of the syndrome (table 3).

CSS substantially contributes to the expanding population of older patients with unexplained syncope, falls and femoral neck fractures.[2, 3] Mortality rates without proper treatment exceed 25% in the first 5 years.[33] Institution of an effective diagnostic and treatment regimen is therefore justified. The European Society of Cardiology guidelines recommend testing for CSS by CSM in all patients older than 40 years who have syncope that is unexplained after basic evaluation, including patient's history, physical examination, table tilt test and standard ECG.[4] Contra-indications for CSM are a carotid bruit, recent acute myocardial infarction, or recent stroke. However, neurological complications

following CSM are thought to occur in only one of 1000 patients.[34] In the present review CSM also appeared safe. Although consensus exists on the diagnostic tool, most authors do not agree on method of CSM and interpretation of ensuing alterations in systolic blood pressure (SBP) and HR (table 5). These discussions have led to a standardized method of CSM that is universally adopted. Following a 10 min supine rest, the patient's skin overlying the carotid bifurcation is stretched from clavicle to jaw for 10 seconds on the right side, followed by the left side after an 1 minute interval. CSM is then repeated in 60° tilt. Beat-to-beat or intra-arterial SBP is recorded whereas a surface electrocardiogram monitors HR. Institution of this standardized approach will facilitate future comparison of study populations.[35]

An international discussion fuelled by earlier confusion on descriptions of types of CSS has also resulted into a universally accepted definition. A cardioinhibitory CSS is characterized by an asystole of 3 sec or more. In contrast, vasodepressive CSS should entail a SBP drop of at least 50 mmHg. The mixed type harbours a combination of both cardioinhibitory and vasodepressor characteristics.[35] The "cerebral" type, merely as an expression of cerebrovascular insufficiency, has been omitted. Distinguishing different hemodynamic responses to CSM is important, because patients with a prominent vasodepressor component do not respond to pacing.[4, 36] Moreover, they have a higher rate of recurrent symptoms and a worse prognosis.[37] A detailed description of subtypes will also help investigators to report clinical results in a standardized way.

Several treatment modalities have been proposed for CSS. A conservative policy may be justified in mild or multimorbid patients. Avoiding provocative head movements and modifying medication may both ameliorate symptomatology. Unfortunately, the use of ephedrine, fludrocortisone, dihydroergotamine or midodrine often proved ineffective and poorly tolerated.[38, 39] Irradiation of the carotid sinus was successful in some patients, but considerable exposure is required and beneficial effects are generally delayed.[40] Ironically, radiotherapy can also cause CSS by itself.[10, 41]

The gold standard of treating CSS is pacemaker therapy. However, on theoretical grounds its efficacy may only be assumed if the syndrome harbours an abnormal cardioinhibitory reflex in the presence of normal vasodepression.[39] Dual chamber pacing abolishes symptoms in 80% of syncope patients with cardioinhibitory CSS[5, 42] The present review has unveiled that a vasodepressor component is present in at least 46% of the operated patients. The real vasodepressor component percentage may even be higher as pacing or intravenous administration of atropine (standard tests that allow a distinction between mixed or cardioinhibitory type) during SCM was not performed in all patients. Moreover, recent studies also determined that only a small portion of patients exhibit a pure cardioinhibitory type of response (18-24%), whereas a vasodepressor (19-29%) or mixed (52-57%) type is usually much more prevalent.[35, 39] In this review, two patients with mixed type CCS were successfully denervated after pacemaker insertion appeared ineffective.[19] These data clearly indicate that pacemaker therapy may not be first choice treatment modality in over half of the CSS population.

What is the potential role of surgery in CSS ? The surgical literature identifies several techniques of interrupting the pathological baroreflex including glossopharyngeal nerve transection, carotid sinus (Hering's) nerve transection, and carotid adventitial stripping. The former two techniques have been abandoned in recent years. Glossopharyngeal nerve transection requires a craniotomy and may result in dysphagia, hypalgesia, loss of taste and a diminished gagging reflex. It may be considered as a last resort in individuals with a 'hostile neck' following radiation or extensive inoperable neck masses who do not respond to pacemaker treatment.[43, 44] Transection of Hering's nerve is technically challenging as this nerve has a small calibre, follows an inconstant course along the internal carotid artery and harbors communicating loops to vagus nerve and cervical sympathetic chains.[24, 45, 46]

Adventitial carotid stripping is the least invasive surgical technique for the treatment of CSS. The present review identifies a great diversity in operative details. This variety of operations reflects lack of knowledge on localization, density and distribution of baroreceptors along the carotid bifurcation. Nevertheless, all of these different forms of operations are apparently effective at abolishing symptomatology as complete relief is obtained in almost three-quarters of patients (80/110), whereas substantial improvement occurs in an additional 12% (13/110). Microscopic studies may shed light on some of the uncertainties associated with distribution of the carotid pressure bodies and may lead to a standard approach of stripping and even higher success rates. Adventitial stripping appears also effective on the long term as none of the included patients had recurrence of symptoms after a mean follow-up of 2.5 years, indicating that nerve regeneration is clinically absent.

Some have raised questions on the effect of surgical stripping on blood pressure in the immediate postoperative phase and the onset of hypertension on the long term. Animal studies on bilateral carotid denervation showed postoperative enhanced variability of blood pressures, but these effects were transient.[47] Additional reports on bilateral carotid sinus surgery for human epilepsy suggested that this form of surgery may lead to instability in postoperative pressures. The situation may not be different in human surgery for CSS. Unilateral denervation for CSS usually causes a 6-12 hr mild increase in blood pressure. Moreover, bilateral denervation may lead to a marked temporary hypertension which gradually returns to normal within 1 week.[48] To attenuate these untoward blood pressure effects, some performed a staged, two-tempi bilateral

denervation in bilateral CSS whereas others limited surgery to one side exclusively. However, clinical results were suboptimal as only 4 out of 13 patients experienced complete relief.[6] Transient postoperative hypertension and cardiac dysrhytmia were also observed in 9% of the reviewed patients, but these events were amendable to conservative treatment.[14, 19-22, 27, 30]

The present review identified major complications (3%) in patients that were operated prior to the 1980's. One devastating complication occurred in a patient because of intracerebral hemorrhage after an intense hypertensive crisis.[28] The combination of concomitant cerebrovascular arteriosclerosis and altered cerebral autoregulation by CSS may have resulted in a higher cerebrovascular resistance that was not able to withstand a sudden increase in arterial pressure.[49] Such a disaster illustrates the necessity of close cardiovascular monitoring in a CCU or ICU environment in the first 24 hours postoperatively. Major complications (death, CVA or TIA) were not identified in modern series published after 1979. The present review has also not found any evidence for an association between surgical denervation and altered set points for chronic regulation of SBP or hypertension.

Although data obtained in the present review supports the notion that surgical carotid sinus denervation is effective in abolishing symptoms in CSS patients, some methodological limitations should be taken into account. First, the influence of selection bias should be considered. Surgical carotid denervation by adventitial stripping is rarely performed and results are not universally published. Therefore, single case studies (n=16) were also included in the review, some lacking details on diagnostics and operation techniques. The risk of publication bias should also be considered as surgeons may hesitate to publish negative results. Thirdly, short term follow-up times (<12 months) are also included in a mean follow-up time of 2.5 years. Lastly, there is no standardized indicator of outcome, as some authors report subjective outcomes such as "improvement" and "complete relief". Taking these limitations into account, carotid denervation by adventitial stripping is effective in the treatment of CSS with a success rate of 85% after a mean follow-up of 2.5 years. There is room for future improvement as the surgical technique requires standardization. Future studies should focus on long term safety and efficacy of carotid adventitial stripping.

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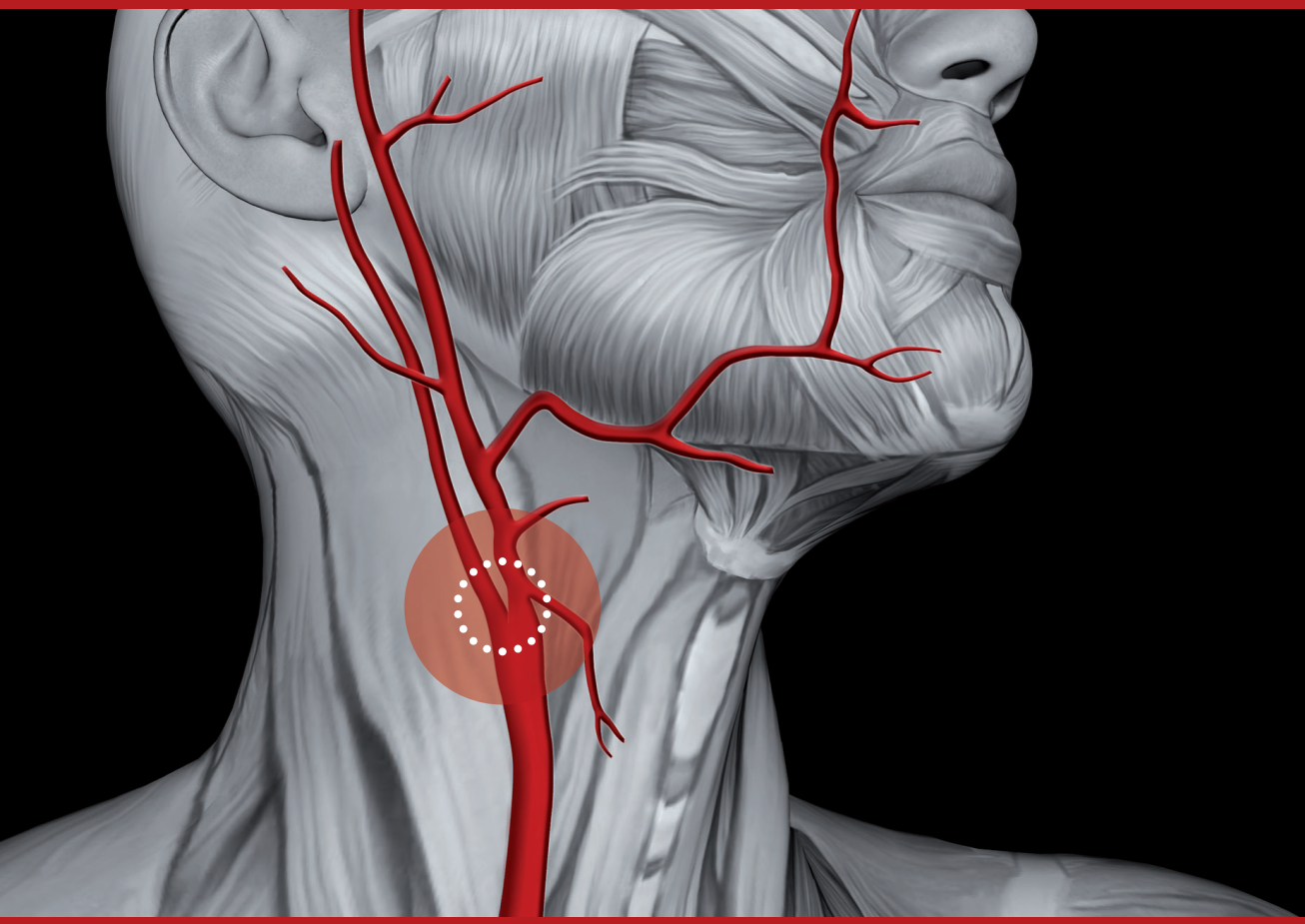

CHAPTER 5

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

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ABSTRACT

Background

The carotid sinus syndrome (CSS) is characterized by syncope and hypotension due to a hypersensitive sinus located in the carotid bifurcation. Some patients ultimately require surgical carotid 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.

Conclusions

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.

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.

INTRODUCTION

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 pathological 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 baro-instability) 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.

Aim of the present study is to perform mapping of nerve structures surrounding the carotid bifurcation using an 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 side, 6 right) of human cadaver heads fixed by 3% formaldehyde were used. Ten specimens were male and the mean age was 74±3 years (range 59- 92 years). 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 (figure 1). Sympathetic trunk and superior cervical ganglion (SCG) were identified after lateralizing the carotid arteries and neighbouring nerves. The CSN was identified using 4-10x 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 acetylthiocholineiodide, 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

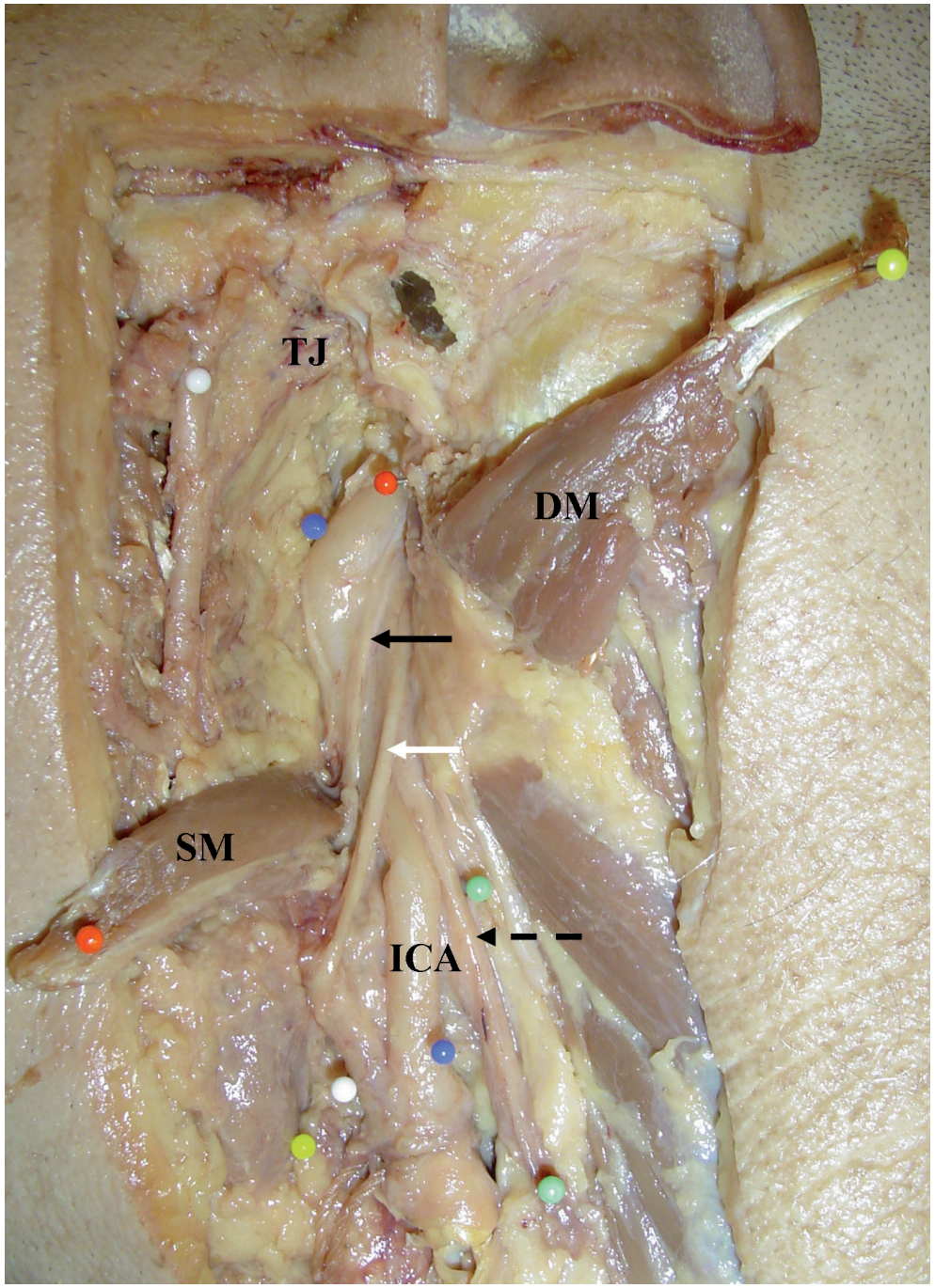

Figure 1. ***Overview of left carotid area.***
TJ: temporomandibular joint, DM: digastric muscle, SM: styloid muscles, ICA: internal carotid artery.
Black arrow: glossopharyngeal nerve, *white arrow:* hypoglossal nerve, *dotted arrow:* vagus nerve

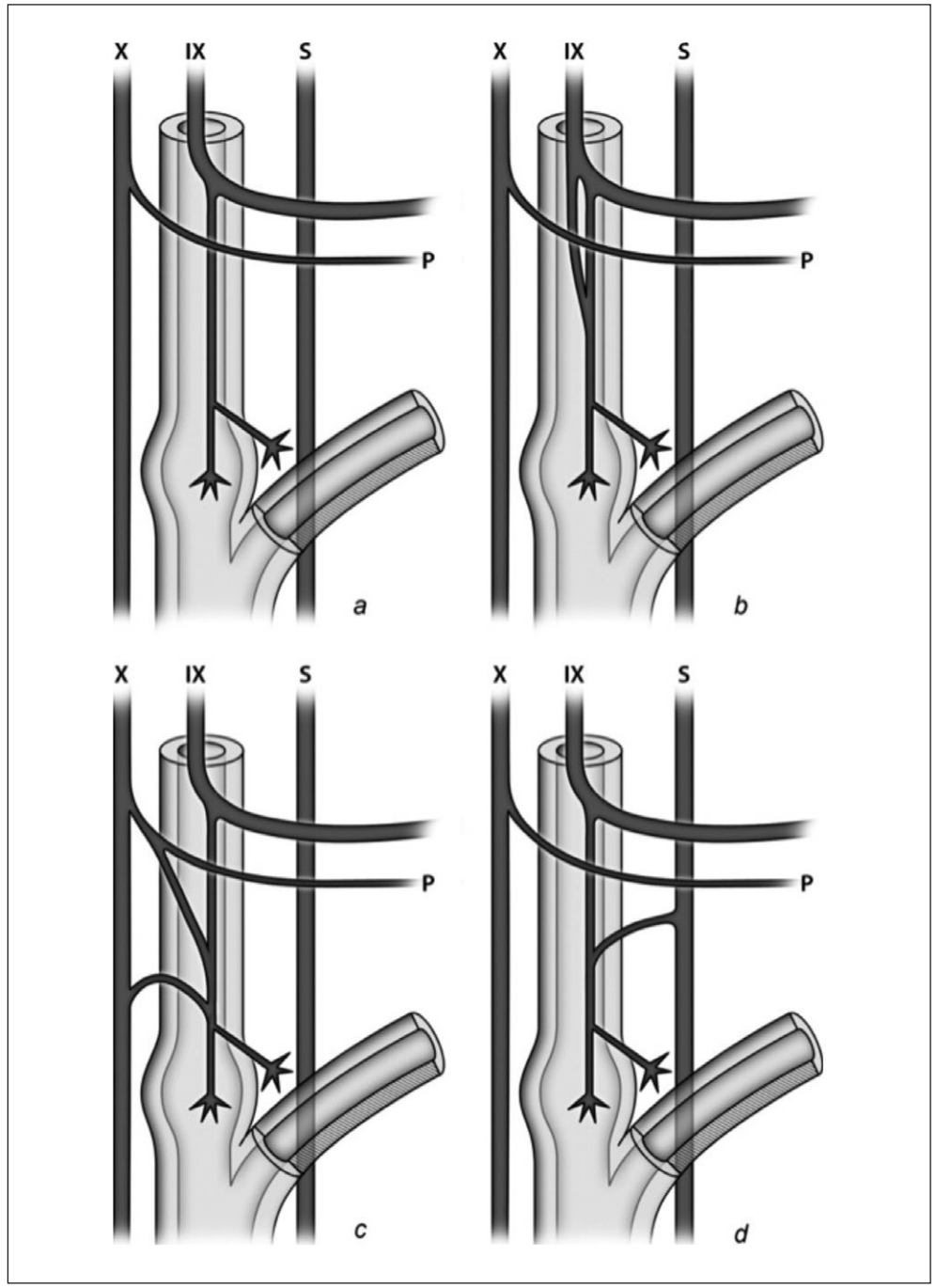

Figure 2. ***Schematic diagram of anatomical variations of the carotid sinus nerve (CSN).***
Right carotid bifurcation. The hypoglossal nerve (XII) has been omitted. **a.** CSN originating from the glossopharyngeal nerve (IX). Separate branches to carotid sinus and carotid body. **b.** Double origin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

Figure 3. ***Right carotid bifurcation and neighbouring nerves after ACHE staining.***
Magnification 2x. 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: intermal 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.

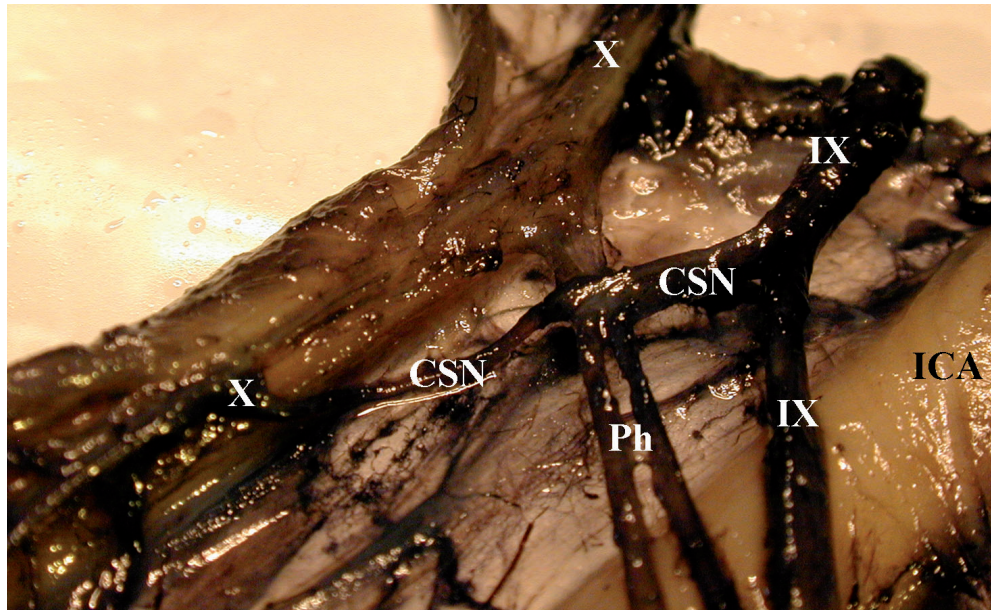

Figure 4. ***Detailed view of connections between vagus nerve, its pharyngeal branches and the carotid sinus nerve (CSN).***
Right carotid bifurcation, magnification 4x. X: vagus nerve, Ph: pharyngeal branches, IX: glossopharyngeal nerve, CSN:carotid sinus nerve, ICA: internal carotid artery

ICA wall. It consistently (12/12) originated from IX some mm's 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.

Figure 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 (figure 2b and 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 travelling 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) (figure 2c, 2d, 3 and 4). In contrast, no connection was present with XII or superior root of cervical ansa. In one specimen, an overt CSN side branch travelled to the ICA and

ended in its wall some 38 mm proximal to 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 (figure 5).

DISCUSSION

Physiology

The CSN contains afferent fibers travelling 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 physiological 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.

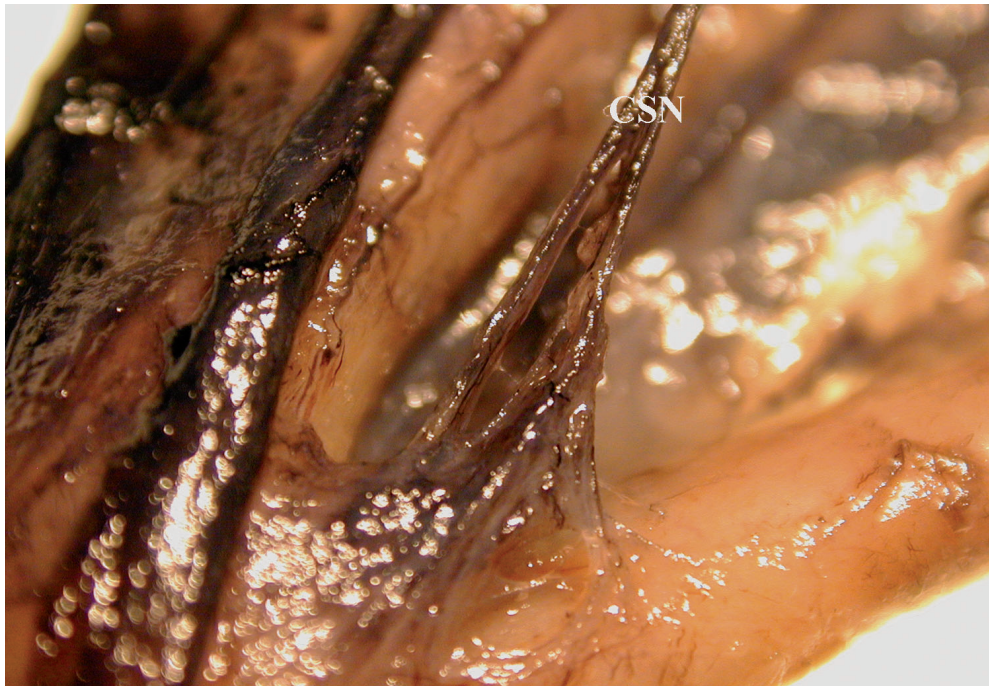

Figure 5. Detailed view of termination of the carotid sinus nerve (CSN) by little branches in the wall of the carotid sinus.
Left carotid bifurcation, magnification 6x.

Anatomic considerations

The CSN is a long descending branch of the glossopharyngeal nerve. An early detailed description was obtained in a 7 month-old foetus in the 1920's.[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 that a distinct CSN. For instance, Hovelacque et al. 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.[24] Sheehan et al. described an intercarotid plexus that mainly consisted of 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.[25] The present study found that 100% of the specimens contained a separate CSN. A single trunk phenomenon was also suggested by Boyd et al. 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.[26] 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 observed that the CSN forms small branches at the level of the carotid bifurcation participating in formation of a sinus carotid 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.[27]

Early CSN descriptions suggest great variability in number of side branches and other communications with neighbouring 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 1930's.[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 anatomical 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 transsection 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 travelling 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 anatomical 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

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.

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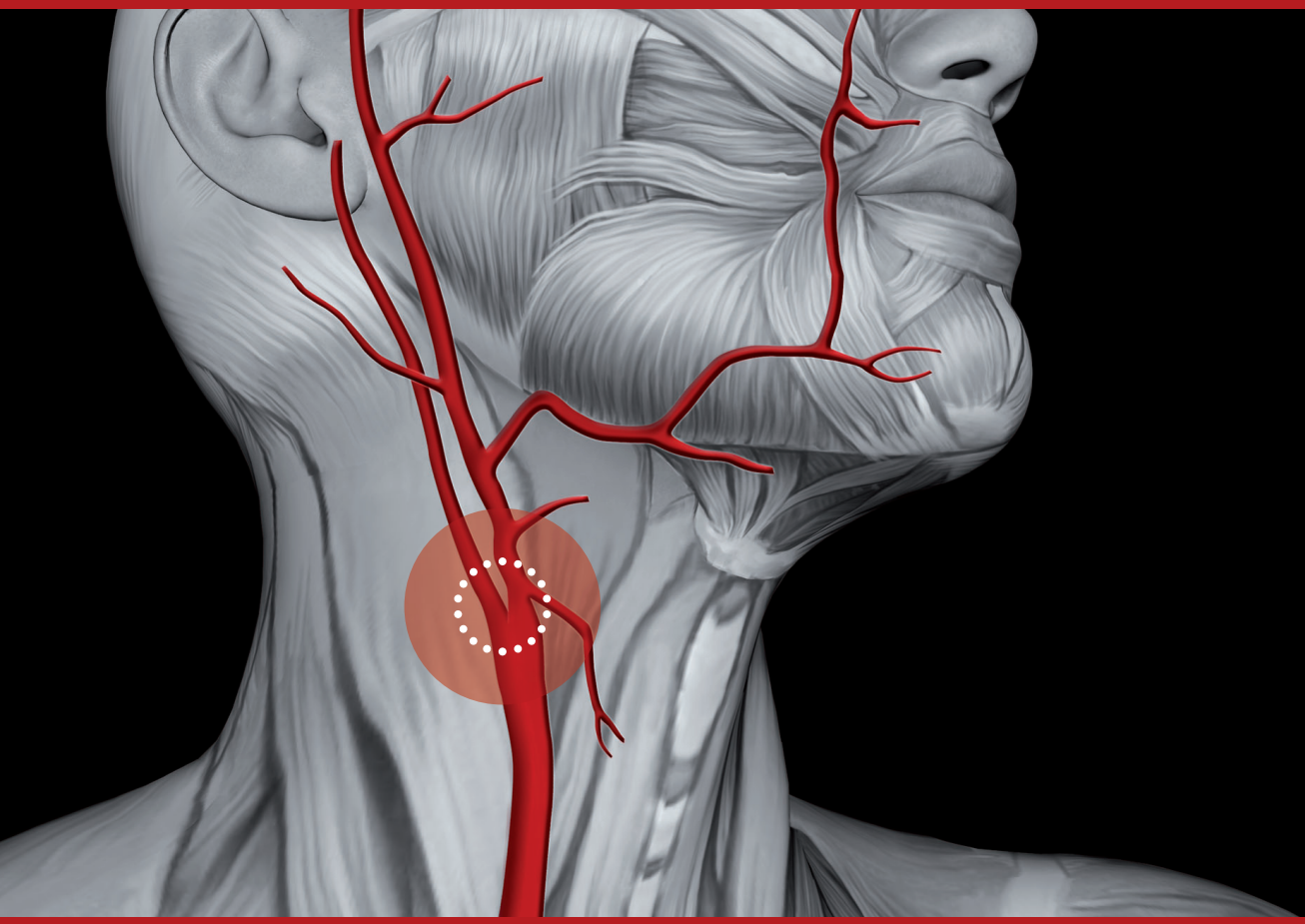

CHAPTER 6

Carotid baroreceptors are mainly localized in medial portions of the proximal internal carotid artery

Toorop RJ, Ousrout R, Scheltinga MR, Moll FL, Bleys RL

Submitted

ABSTRACT

Aim

To visualize baroreceptors in the human carotid bifurcation by light microscopy. Baroreceptor location is investigated in order to give a recommendation for extent of adventitial stripping as a treatment for carotid sinus syndrome (CSS).

Methods

Human carotid specimens were transversely cut in 20 µm sections. After immunohistochemical staining using antibodies against vesicular glutamate transporter 2 (VGLUT2) and protein gene product 9.5 (PGP 9.5), presence of baroreceptor tissue was studied using light microscopic techniques.

Results

Visual assessment indicated that VGLUT2 and PGP 9.5 immunoreactivity was present in the adventitia of the carotid arteries and that nerve density was highest in the medial wall of the proximal first cm of the internal carotid artery (ICA).

Conclusion

Human carotid baroreceptors, as reflected by immunoreactivity for VGLUT2 and PGP 9.5, are mainly localized in medial portions of the proximal ICA. If surgical carotid denervation is indicated in patients suffering from carotid sinus syndrome, adventitial stripping of the proximal portion of the ICA should be sufficient.

INTRODUCTION

Some 30% of senior populations with unexplained syncope suffers from the carotid sinus syndrome (CSS). CSS is caused by an occasionally disfunctioning carotid baroreflex system leading to extreme bradycardia and/or hypotension, diminished brain perfusion and collapse.[1-6] It is thought that the human baroreceptor system is mainly located in the proximal area of the internal carotid artery (ICA), termed the carotid sinus. Symptomatic treatment for CSS including pacemaker implantation is sometimes advised, whereas others advocate operative carotid denervation procedures such as adventitial stripping of the ICA. The latter approach is based on the premise that circular stripping of the carotid sinus disconnects most baroreceptor tissue from their afferents to the carotid sinus nerve and interrupts the malfunctioning baroreflex.[1] Indeed, short term results of adventitial stripping of the proximal 3 cm ICA in CSS patients were encouraging with a one-month 93% success rate.[6]

The exact neuroanatomy of the human carotid sinus is a matter of debate. A recent macroscopic study of adjacent nervous networks demonstrates that innervation of the sinus is variable and unpredictable.[7] Microscopic research on baroreceptor location and distribution using electron and light microscopy is scarce. Electron microscopy has revealed the ultrastructure of the carotid baroreceptor in several animal and a few human studies, but the technique is not able to unveil its exact distribution.[8-11] Alternatively, immunohistochemical staining techniques are used for the identification of neuronal tissue such as protein gene product 9.5 (PGP 9.5).[12-14] This general neural marker stains parasympathetic, sympathetic and sensory 'elements'. Ideally, a highly specific marker should be used that exclusively stains sensory neurons such as baroreceptors. Some studies have identified the role of glutamate in transmission of baroreflex signalling.[15] Vesicular glutamate transporters (VGLUTs) are specific markers for neurons that use glutamate as a neurotransmitter.[16,17]

The aim of this study is to visualize baroreceptors in the human carotid bifurcation by light microscopy, using PGP 9.5 and VGLUT2 as markers for immunohistochemical staining. Visualisation of baroreceptors is a prerequisite to determine the distribution of baroreceptors in the carotid bifurcation.

MATERIALS AND METHODS

Human tissue processing

Five carotid segments (3 males, 2 females, median age 81 years, range 61-90) including a 1 cm distal portion of the common carotid artery (CCA) and 2 cm proximal portions of internal (ICA) and external carotid arteries (ECA) were processed within 24 hours after death. The specimens were fixed by an one hour immersion of 4% paraformaldehyde and were stored overnight in 30% sucrose for cryoprotection (phosphate buffered saline, 4 °C). All specimens were subsequently divided into 1 cm pieces and were mounted in Tissue Tek (figure 1). Transverse sections of 20 µm thickness were obtained on a cryostat at -20 °C followed by one night of drying on microscopic slides at 37 °C. The sections were consecutively divided in three series: VGLUT2 staining, PGP 9.5 staining and controls in which the primary antibody was omitted.

Immunohistochemical staining

The staining protocol consisted of a fixed number of consecutive steps of washing, blocking, rinsing and incubation. All incubations were carried out at room temperature (20 °C) except for the incubation with primary antisera against VGLUT2 or PGP 9.5 (4°C).

Endogenous peroxidase activity was blocked using a 30 min incubation with Tris buffered saline (TBS) and 5% H_2O_2 (Merck Darmstadt, Germany) followed by overnight incubation with anti-VGLUT2 (Abcam, Cambridge, U.K.) or anti-PGP 9.5 (Ultra Clone, England) at 4 °C. The used concentrations for anti-VGLUT2 and anti-PGP 9.5 were 1:1000 and 1:800, respectively. Subsequently, the sections were incubated using a second antibody (Polyclonal Goat Anti-Rabbit Immunoglobulins/biotinylated, concentration 1:250; Dako Denmark A/S, Glostrup, Denmark). All primary and secondary antisera were diluted in TBS, 1% bovine serum albumin (Sigma-Aldrich, Steinheim, Germany) and 1% Triton X-100. Normal serum (1%; Dako Denmark A/S, Glostrup, Denmark) was also added to the solution of the secondary antisera. After another series of washes, sections were incubated for 30 minutes using Avidin-Biotin peroxidase Complex reagents (ABC; 1:1000; Vector laboratories Inc., Burlingame, U.S.A.). Immunoreaction was visualized with 3-3-diaminobenzidine (Sigma-Aldrich, Steinheim, Germany) enhanced by the addition of 3% ammoniumnickelsulfate which resulted in a black stain. All incubations were followed by triple rinsing at room temperature in TBS with or without 1 % Triton X-100. After the specimens were dried, they were coverslipped with Entellan.

In control slides the primary antibody was replaced with TBS, and staining proved consistently negative.

Microscopic analysis

A light microscope (Carl Zeiss, type Axiophot, Germany) was used to examine VGLUT2 and PGP 9.5 immunoreactivity (IR). Specific staining was analyzed in randomly selected fields in the medial, anterior (ventral), lateral and posterior (dorsal) wall of the ICA. The wall of the internal carotid artery adjacent to the ECA is referred to as the 'medial wall' and the opposite wall, the 'lateral wall'(figure 2). The CCA and ECA were also searched

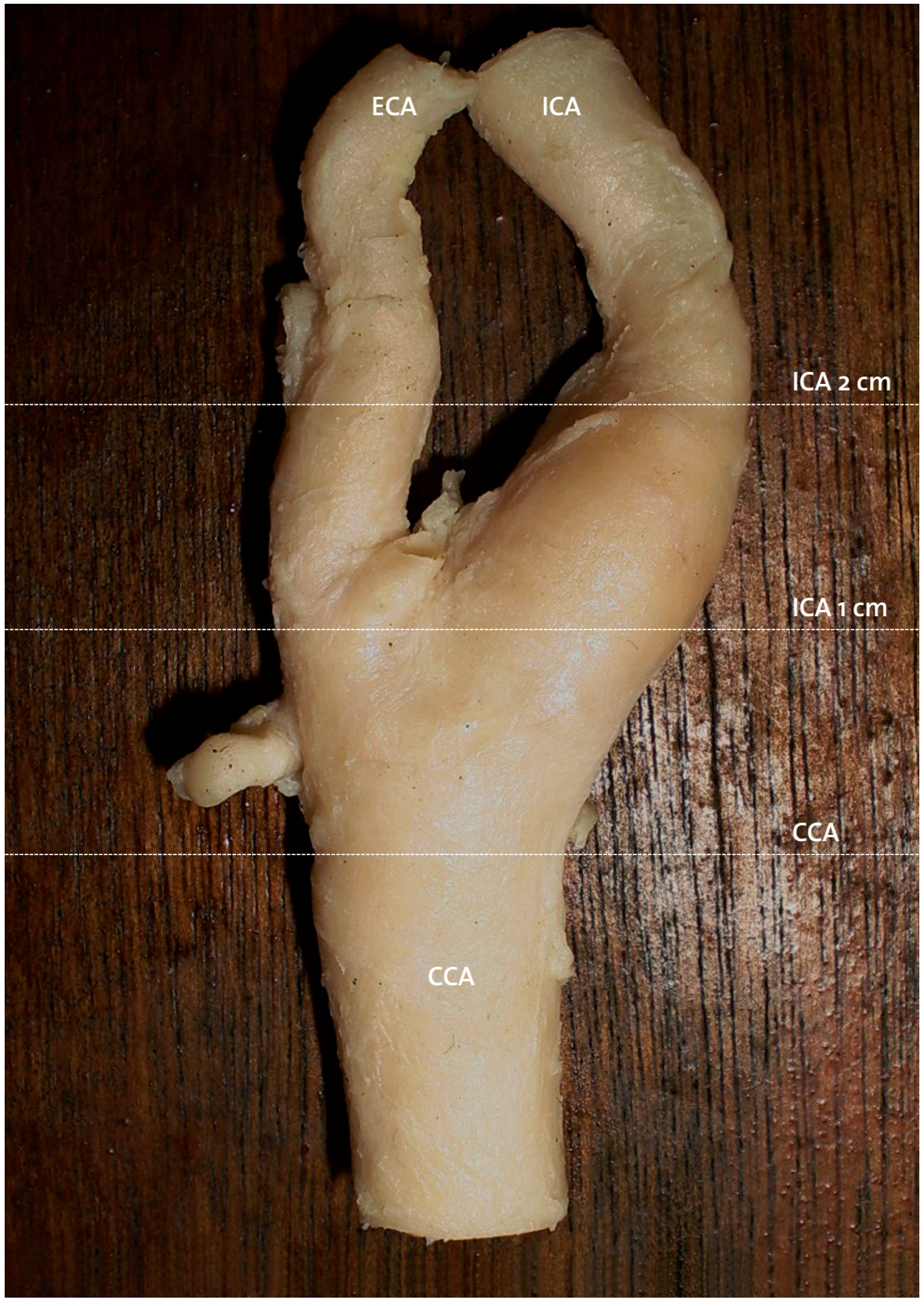

Figure 1. Left human carotid specimen consisting of the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA).
The lines refer to the divisions of the carotid segments.

for positive staining. Histological images (Leica, type DFC420 C) were made in each of these positions to build a photo-database. Occasionally, random selection of fields was judged suboptimal or just impossible because of artefacts or high background noise. VGLUT2 and PGP 9.5 IR were then surveyed in the adjacent section in clockwise direction until areas of acceptable staining contrast were identified.

RESULTS

The use of antibodies against PGP 9.5 and VGLUT2 resulted in positive labelling in all the carotid specimens. Although PGP 9.5 staining quality varied, in most sections PGP 9.5 staining was intense and showed nerves throughout the adventitia (figure 3 and 4). The staining quality of VGLUT2 was even more intense and showed nerves throughout the adventitia (figure 5-7). VGLUT2 positive staining could inconsistently be found deeper in the adventitia, including the adventitia-media border. VGLUT2 and PGP 9.5 positive staining mainly demonstrated a black striated aspect and the longitudinally and transversely orientated nerves were predominantly of a fine calibre and well defined. Control slides were consistently negative.

On visual assessment of VGLUT2 positive staining results it was demonstrated that neural elements were abundantly present in the medial wall of the proximal first cm of

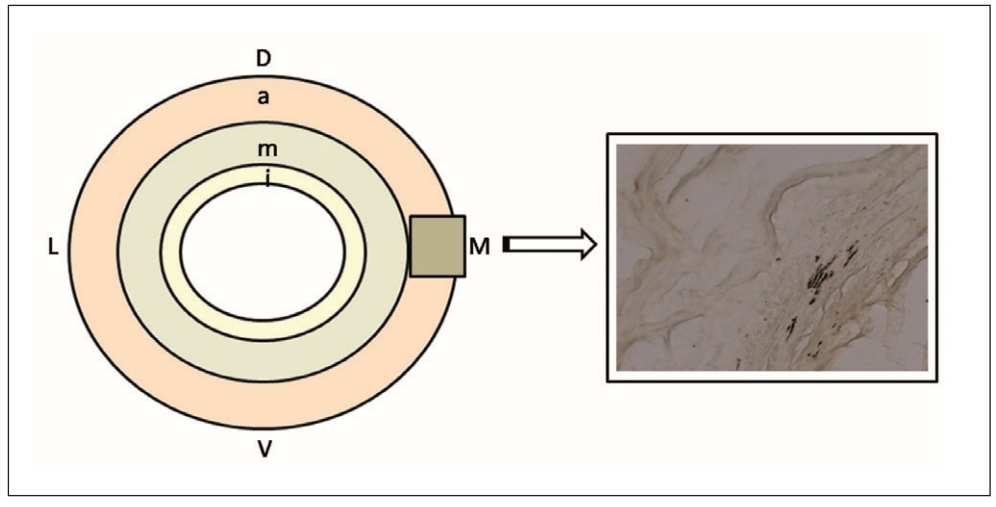

Figure 2. A schematic representation of a transverse section of the internal carotid artery (ICA).
Analysis for positive staining was performed at the medial (M), ventral (V), lateral (L) and dorsal (D) wall of the ICA. The medial wall of the ICA is orientated towards the ECA. The square indicates the location of the photomicrograph (one of the four positions). i = tunica intima, m = tunica media, a = tunica adventitia.

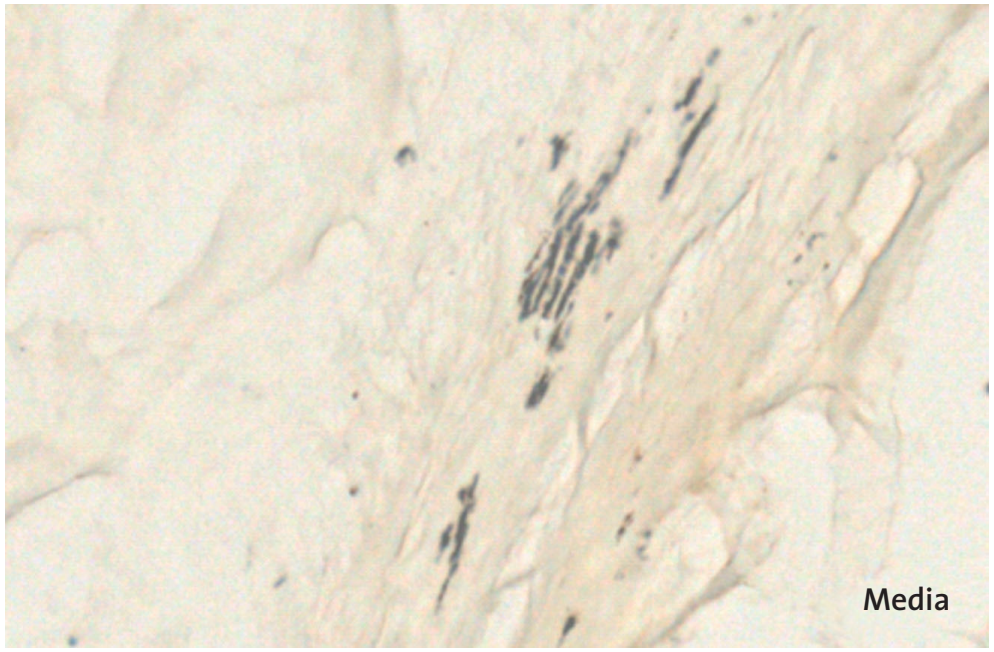

Figure 3. Transverse section ICA 1 cm stained for PGP 9.5.
Medial wall. The positive stainings have mainly a black striated aspect. Magnification 20x.

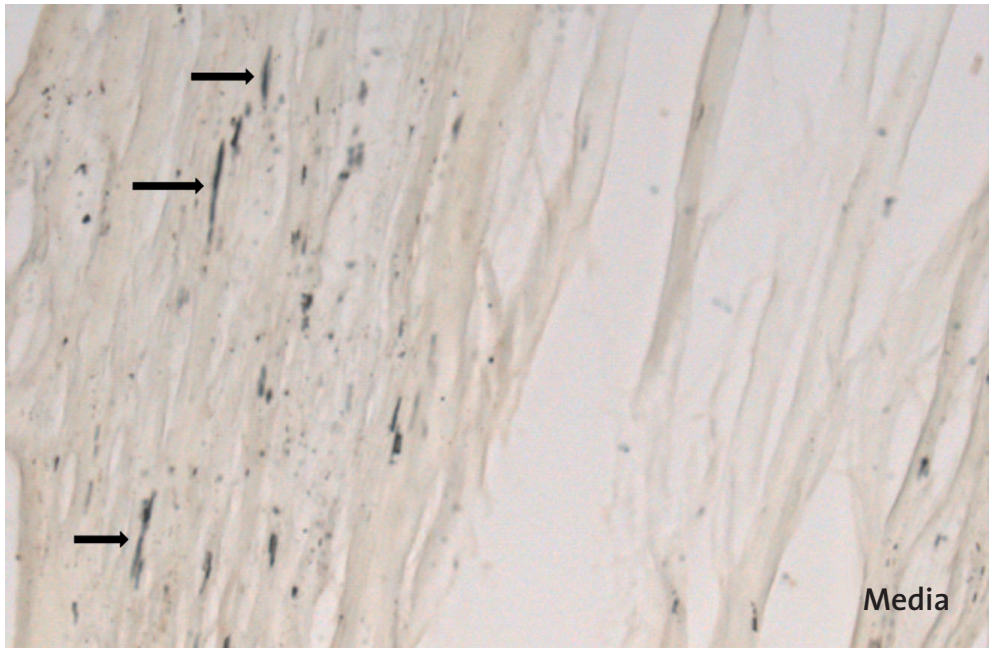

Figure 4. Transverse section ICA 1 cm (near bifurcation) stained for PGP 9.5.
Medial wall. Arrows: transversely orientated nerves. Magnification 20x.

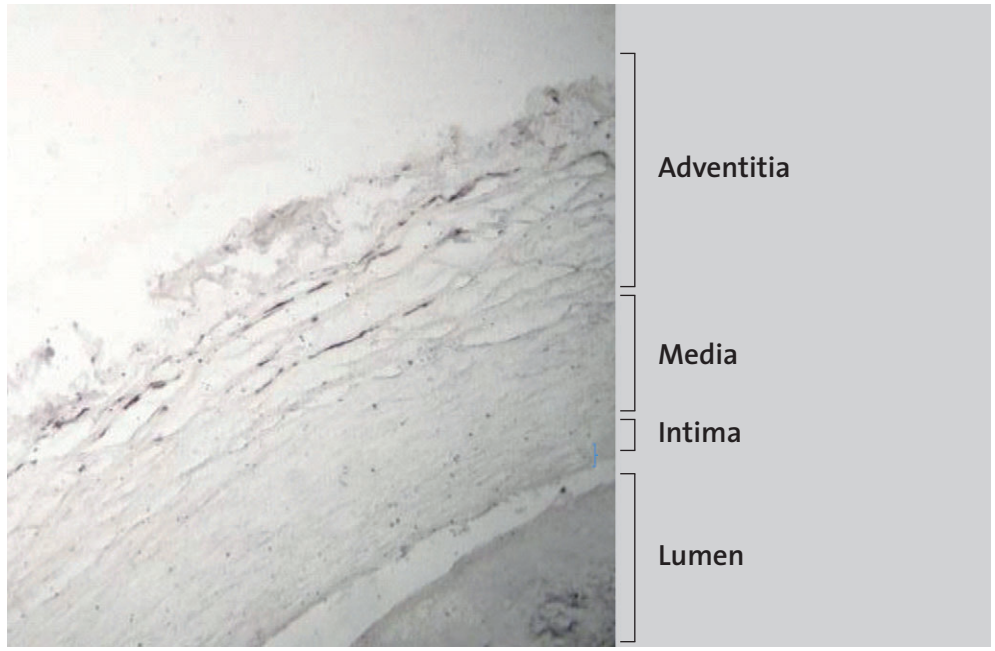

Figure 5. Transverse section ICA 1cm stained for VGLUT2
Medial wall. Transversely orientated nerves are present throughout the adventitia. Magnification 10x.

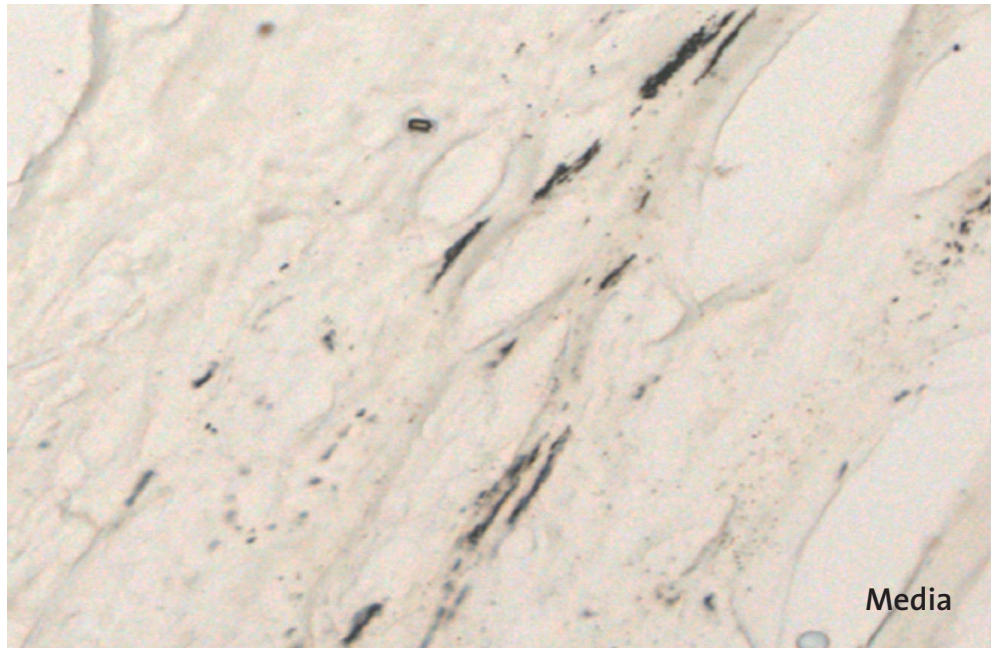

Figure 6. Transverse section ICA 1cm stained for VGLUT2.
Medial wall. The positive stainings have mainly a black striated aspect. Magnification 20x.

the ICA. VGLUT2 positive staining was remarkably less or absent in the lateral, anterior or posterior wall. VGLUT2 IR was not found in the CCA, ECA or in the ICA 2 cm distal of the bifurcation. PGP 9.5 demonstrated positive staining in the first cm segment of the ICA. In contrast to VGLUT2, PGP 9.5 positive staining could be determined, but to a lesser extent, in ICA 2 cm, CCA and ECA segments as well.

Tissue processing and immunohistochemical procedures were identical for all carotid bifurcations. However, due to the high background staining, the quality of the photo-database did not permit computerized quantification of nerve densities and statistical analysis.

DISCUSSION

Aim of this study was to visualize baroreceptors in the human carotid bifurcation by light microscopy using PGP 9.5 as a general neural marker and VGLUT2 as a specific sensory marker. VGLUT2 and PGP 9.5 appeared suitable markers for visualization of carotid baroreceptors. Visual assessment indicates that baroreceptors are abundantly present in the medial wall of proximal portions of the ICA but not in the wall of the CCA or ECA.

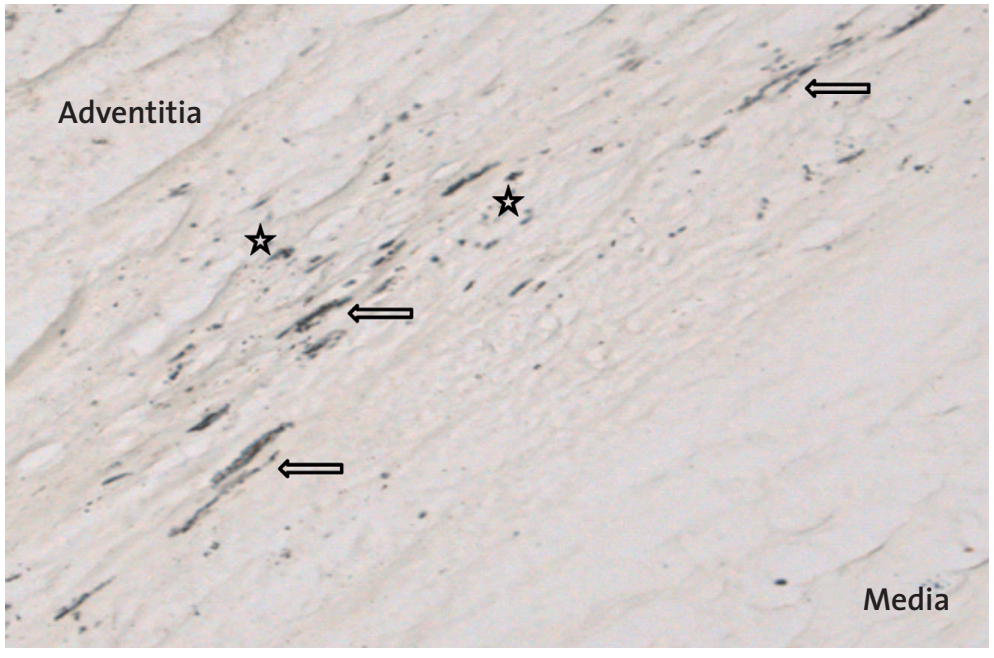

Figure 7. Transverse section ICA 1cm (near bifurcation) stained for VGLUT2.
Medial wall. Asterix: longitudinally orientated nerve bundle, arrow: transversely orientated nerve bundle. Magnification 20x.

Several studies have investigated location and distribution of animal carotid baroreceptors.[8,9] In contrast, microscopical studies on the human carotid bifurcation are relatively scarce. Electron microscopic studies by Rees et al. demonstrated the presence of myelinated and unmyelinated nerves with a varying diameter of 0.6-8µm in the adventitia of the human carotid sinus.[18] For quantification of neural structures in the human carotid bifurcation, light microscopic studies are needed. Previous histological studies used silver as a general neural marker. For instance, Muratori et al. studied longitudinal and transversal sections of the human carotid bifurcation but failed to publish images. He reported that presumptive baroreceptor nerve endings were exclusively present in the proximal portion of the ICA.[19] Meyerson et al. observed 'an impressive collection of neurons' in the medial wall of the internal carotid artery. At this location the tunica media was composed of a dense accumulation of circular elastic fibers, which was presumed to facilitate the transmission of blood pressure fluctuations to the baroreceptors.[20]

The present study used PGP 9.5 as an alternative staining method for neuronal structures in the human carotid bifurcation. Like silver staining, PGP 9.5 is a general marker for nerve fibers. PGP 9.5 was previously used in humans to study the innervation of neuroepithelial bodies and sensory neuroendocrine cells in the epithelium of the airways.[21,22] A recent rat study showed that this marker is an ideal stain for neuronal structures of the carotid artery, subclavian artery and aortic arch.[23] In our human carotid specimens we observed highest PGP 9.5 IR in the proximal ICA corroborating previous baroreceptor studies. PGP 9.5 appears a reliable immunohistochemical marker for human carotid baroreceptors. Moreover, it may also prove a valuable staining technique for examination of neuronal structures in the human extracarotid baroreceptor areas including the aortic arch and thoracic vessels.

For the purpose of our study, ideally a highly specific marker is used that exclusively stains sensory neurons such as baroreceptors. In the present study we used VGLUT2 as a specific sensory marker. To the best of our knowledge, this is the first time that VGLUT2 IR is correlated with human carotid baroreceptors. VGLUTs, vesicular glutamate transporters, are responsible for the vesicular storage of glutamate and play an essential role in glutamatergic signal transmission.[24,25] Currently, three isoforms of VGLUTs have been characterized. It has been demonstrated that glutamate signalling is also functional in peripheral neuronal tissues.[26] Tong et al. showed that neurons in the gut contain glutamate and markers of intrinsic primary afferent neurons display VGLUT2 IR in several species, including humans.[27] Raab et al. demonstrated VGLUT 2 IR of mechanosensor terminals of the mouse and rat oesophagus.[16] A rat study conducted in the 1980's already identified the role of glutamate as neurotransmitter of baroreceptor afferent nerve fibers.[15] The present study showed VGLUT2 to be a specific marker for carotid baroreceptors.

VGLUT2 IR was abundantly present in the medial wall of the first centimetre of the ICA. A major part of the total positive staining demonstrated with PGP 9.5 is also determined with VGLUT2. In contrast to PGP 9.5, no positive staining for VGLUT2 could be found in the CCA, ECA or distal to the first centimetre of the ICA. This might be explained by the fact that PGP 9.5 also stains other neuronal structures in the carotid bifurcation besides sensory nerve fibers, such as (para-)sympathetic nerve fibers. However, for both markers IR is highest in the medial wall of the proximal internal carotid artery (fork of the carotid bifurcation), reflecting the presence of the baroreceptors.

A recent anatomical study of the carotid sinus nerve (CSN) supports the finding that carotid baroreceptors are preferentially located in the medial wall of the proximal ICA. The CSN contains afferent fibers travelling away from the carotid baroreceptors and is formed by numerous little nerve branches originating from the medial ICA wall near the bifurcation.[7]

Carotid denervation by adventitial stripping of the ICA is considered a valuable alternative treatment option in patients suffering from carotid sinus syndrome (CSS). One review identified a great diversity in surgical techniques for CSS.[1] The present microscopic study showed no VGLUT IR in the CCA, ECA or distal ICA (cranial from ICA1 cm). These results suggest that stripping of CCA, ECA and distal ICA portions is not necessary. Indeed, short term clininal results of CSS patients undergoing adventitial stripping of the proximal 3 cm ICA were encouraging.[6]

The present study has several limitations. Interindividual variability of baroreceptor distribution should be taken into account as only a limited number of carotids was examined. In human carotid specimens, high quality staining of neural elements remains difficult. We succeeded to visualise baroreceptors in the human carotid bifurcation by using VGLUT2 and PGP 9.5 as markers. However, these immunohistochemical staining techniques may be further optimized to reduce background staining allowing extensive computerized density measurements and statistical analysis.

CONCLUSION

This study succeeded to visualize baroreceptors in the human carotid bifurcation by light microscopy using PGP 9.5 and VGLUT2 as markers for immunohistochemical staining. Visual assessment demonstrated that human carotid baroreceptors are mainly localized in medial portions of the proximal ICA. These results suggest that, if surgical carotid denervation is needed in patients suffering from carotid sinus syndrome, adventitial stripping of the proximal portion of the internal carotid artery is sufficient. Future studies with computerized baroreceptor density measurements may provide further support for this finding.

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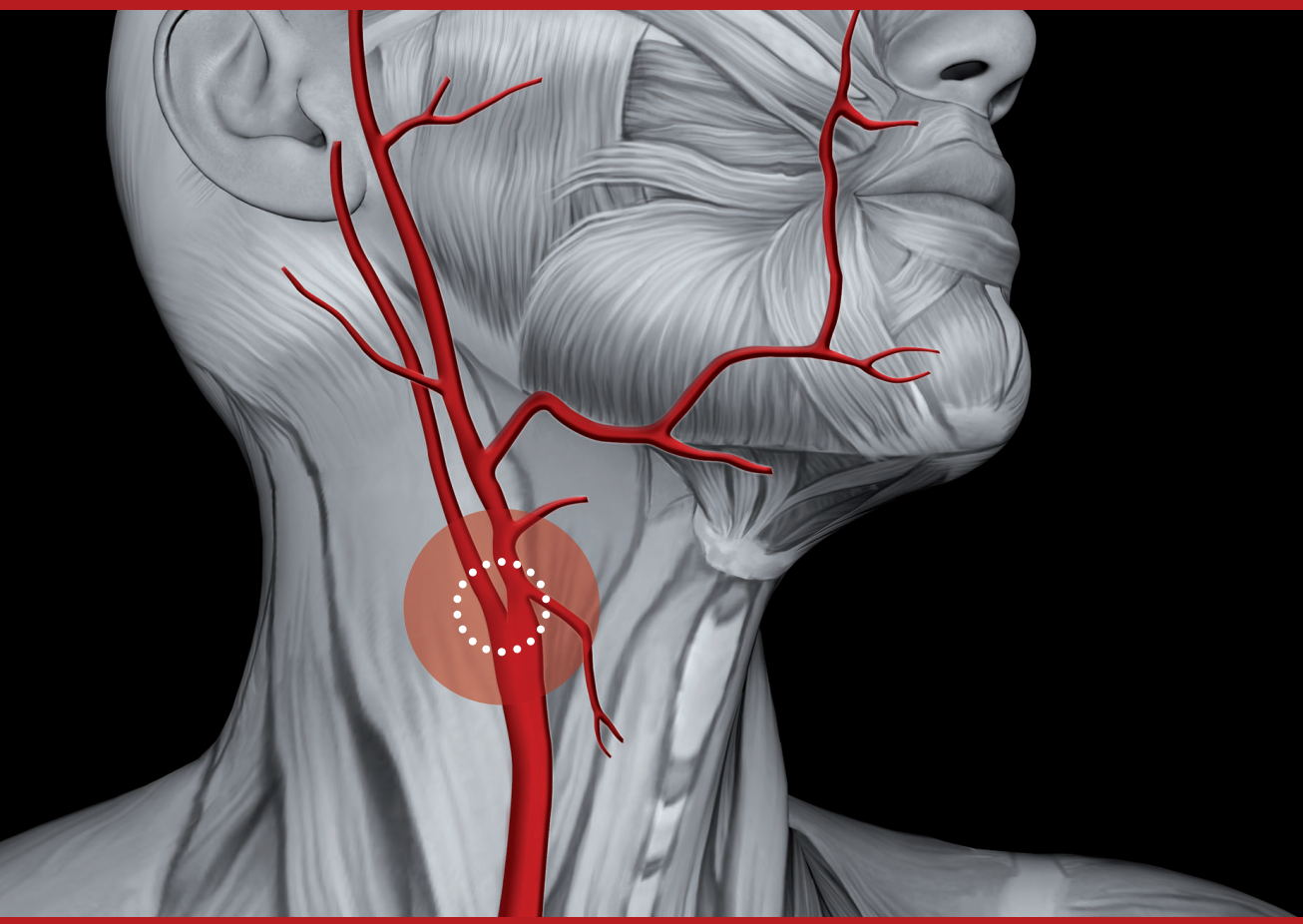

CHAPTER 7

Clinical results of carotid denervation by adventitial stripping in carotid sinus syndrome

Toorop RJ, Scheltinga MR, Huige MC, Moll FL

European Journal of Vascular and Endovascular Surgery 2010 Feb;39(2):146-152

ABSTRACT

Aim

Older patients with spells of syncope may suffer from a carotid sinus syndrome (CSS). Patients with invalidating CSS routinely receive pacemaker treatment. This study evaluated the safety and early outcome of a surgical technique termed carotid denervation by adventitial stripping for CSS treatment.

Methods

Carotid sinus massage (CSM) during cardiovascular monitoring confirmed CSS in patients with a history of repeated syncope and dizziness. The internal carotid artery was surgically denervated by adventitial stripping over a minimum distance of 3 cm via a standard open approach. Patient characteristics, perioperative complications and 30-day success rate were analyzed.

Results

A total of 39 carotid denervation procedures was performed in 27 individuals (23 males, mean age 70±3 years) between 1980-2007 in a single institution. Eleven patients had a bilateral hypersensitive carotid sinus. Procedure related complications included wound hematoma (n=4), neuropraxia of the marginal mandibular branch of the facial nerve (n=2) and dysrhythmia responding to conservative treatment (n=3). Significant alterations in systolic and diastolic blood pressure and heart rate were not observed. One patient developed a cerebral ischemic vascular accident on the 24th postoperative day. One patient with residual disease had a successful redenervation within 1 month after the initial operation. Two patients with persistent symptoms received a pacemaker but also to no avail. At 30-day follow up 25 of 27 patients (93%) were free of syncope, and 24 free of a pacemaker (89%).

Conclusion

Carotid denervation by adventitial stripping of the proximal carotid internal artery is effective and safe and may offer a valid alternative for pacemaker treatment in patients with carotid sinus syndrome.

INTRODUCTION

Some elderly patients with recurrent syncope, dizziness and falls may harbour a hypersensitive carotid sinus. The carotid sinus is a small organ located in proximal portions of the internal carotid artery and is a major contributor to regulation of cardiac frequency and blood pressure. Nerve fibers originating from this baroreceptor area transfer pulses via an afferent carotid sinus nerve (CSN) and the glossopharyngeal nerve (IX) towards the brain. Efferent portions of the reflex loop may exert differential influence on cardiac performance. A stimulated vagus nerve (X) results in a fall in heart rate (cardioinhibition) and decreased conductivity. Diminished sympathetic vasoconstrictor activity induces arterial vasodilatation and venous vasodilatation with a subsequent decrease in preload and cardiac inotropism leading to lowered blood pressure (vasodepression). In carotid sinus hypersensitivity, this loop mechanism is dysregulated leading to an exaggerated response, either spontaneously or following mechanical strain in the neck area. When hypersensitivity results in incapacitating episodes of dizziness and syncope, this symptom complex is termed carotid sinus syndrome (CSS).[1-3] The European Society of Cardiology (ESC) has defined 3 types of CSS (table 1).[4]

Patients with CSS are routinely evaluated by cardiologists who prefer to prescribe medication or insert a permanent pacemaker. However, these devices are not always effective in abolishing symptoms and have disadvantages including risk of pneumothorax, infection or lead displacement. Furthermore regular maintenance is necessary.[5-7] Some studies evaluated operative treatment regimens aimed at interrupting the pathological baroreflex by means of a nerve transection (CSN or glossopharyngeal nerve) or adventitial stripping.[8,9] It was recently shown that, from an microanatomical point of view, transection of the CSN may be difficult and may possibly lead to an incomplete carotid sinus denervation.[10] Glossopharyngeal nerve transection includes a craniotomy and may be associated with complications including loss of gag reflex and taste perception on the posterior third of the tongue.[9]

A recent review of 110 CSS patients demonstrated that clinical results of denervation of various portions of the carotid artery bifurcation by adventitial stripping were very encouraging, although most studies were small.[11]

Aim of this study is to report the safety and early postoperative results of carotid denervation by adventitial stripping of a 3-cm portion of the proximal internal carotid artery in 27 CSS patients.

MATERIALS AND METHODS

Study population

All patients receiving an operation for CSS between 1980 and 2007 were studied. The hospital (Máxima Medical Center) is a 865-bed community hospital in the southeastern part of the Netherlands and it accomodates approximately 350.000 inhibitants in a semi-rural area. Patients (>45 yr) presenting to departments of emergency medicine or cardiology with a history suggestive of CSS were offered a standard evaluation program including a physical examination, a table tilt test, electrocardiography, holter ECG and cardiac ultrasonography. The diagnosis CSS was confirmed by carotid sinus massage (CSM). Duplex scanning was used to exclude a diseased and stenotic carotid artery.

Patients were initially examined in supine position. CSM was performed during a 10 second period by digital stretching of the skin and subcutaneous tissue of the neck area overlying the carotid bifurcation. This test was also repeated on the contralateral side after an one minute interval. After 1999, intra-arterial blood pressure using standard catheter techniques and cardiac rhythm were additionally recorded (n=11). If no pathological reflex was present, the manoeuvre was repeated in 60° tilt (anti-trendelenburg position). Criteria for CSS as described by the ESC were followed (table 1).[4] An asystole >3 seconds (cardioinhibitory response) or a >50 mmHg systolic blood pressure drop (vasodepressor response) were considered pathognomonic. Temporary cardiac pacing or a 1 mg i.v. dose of atropine was used in cardioinhibitory CSS to maintain an adequate heart rate. These additional tests were helpful in identifying vasodepressive elements in the response (mixed type CSS, both cardioinhibitory and vasodepressor). Patients typically recognized symptoms during massage. Candidates were subsequently discussed in a team consisting of a cardiologist, vascular surgeon and anaesthesiologist, all having a long term interest in CSS.

Operative procedure

Location of the carotid bifurcation was preoperatively marked on the skin by duplex ultrasonography. The operation was performed under general anesthesia and continuous monitoring of intra-arterial blood pressure and heart rate. The carotid bifurcation was exposed through a 6-7 cm skin incision parallel to the anterior border of the sternocleidomastoid muscle. Nervous tissue attached to adventitial layers of the proximal internal carotid artery (ICA) was circumferentially removed over a distance of at least 3 cm, starting at the carotid bifurcation (figure 1 and 2). Surgical manipulation of the ICA frequently resulted in bradycardia or hypotension. Severe bradycardia (<30 beats/min)

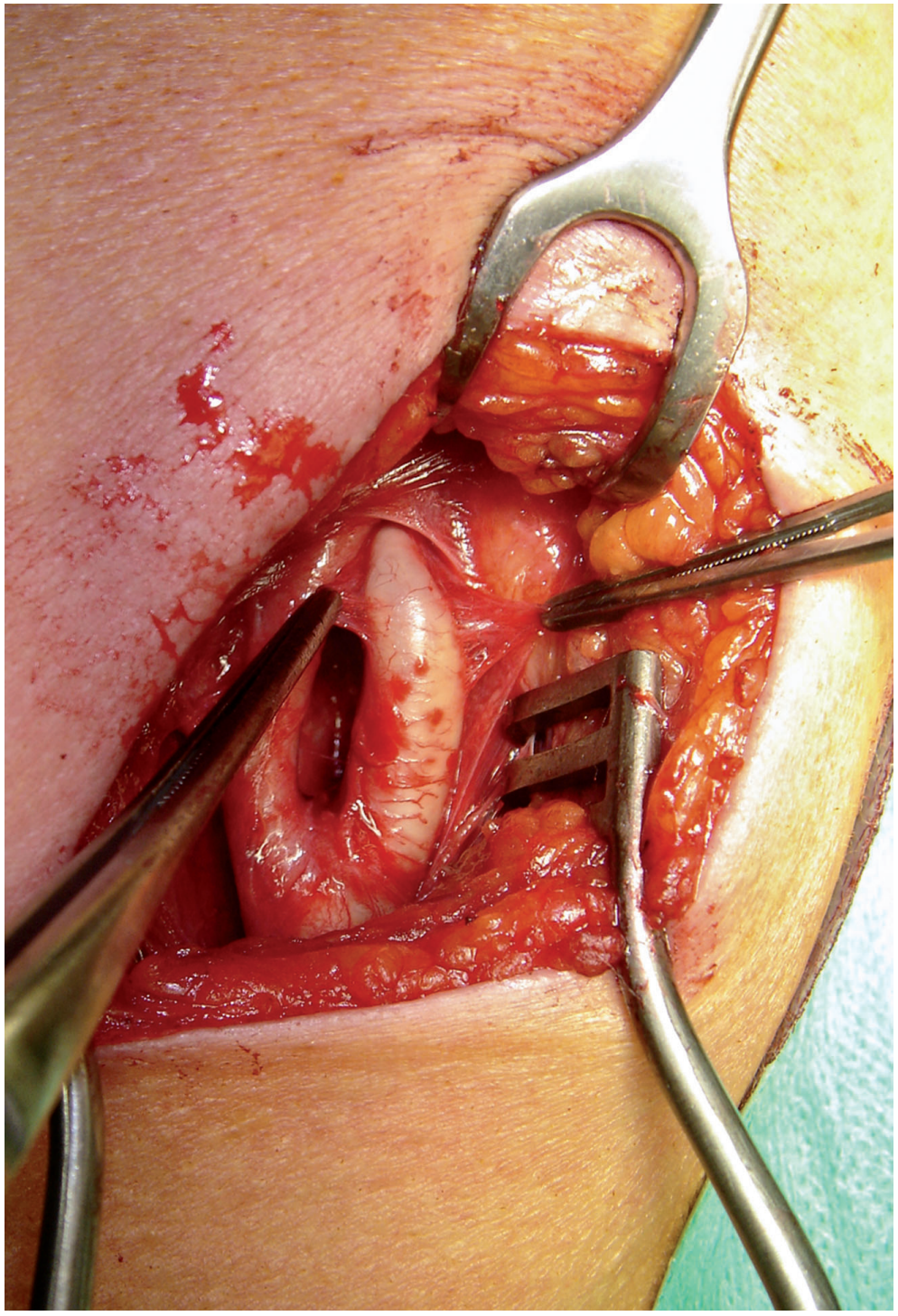

Figure 1. Adventitial stripping of the left internal carotid artery. Nervous tissue is held by tweezers.

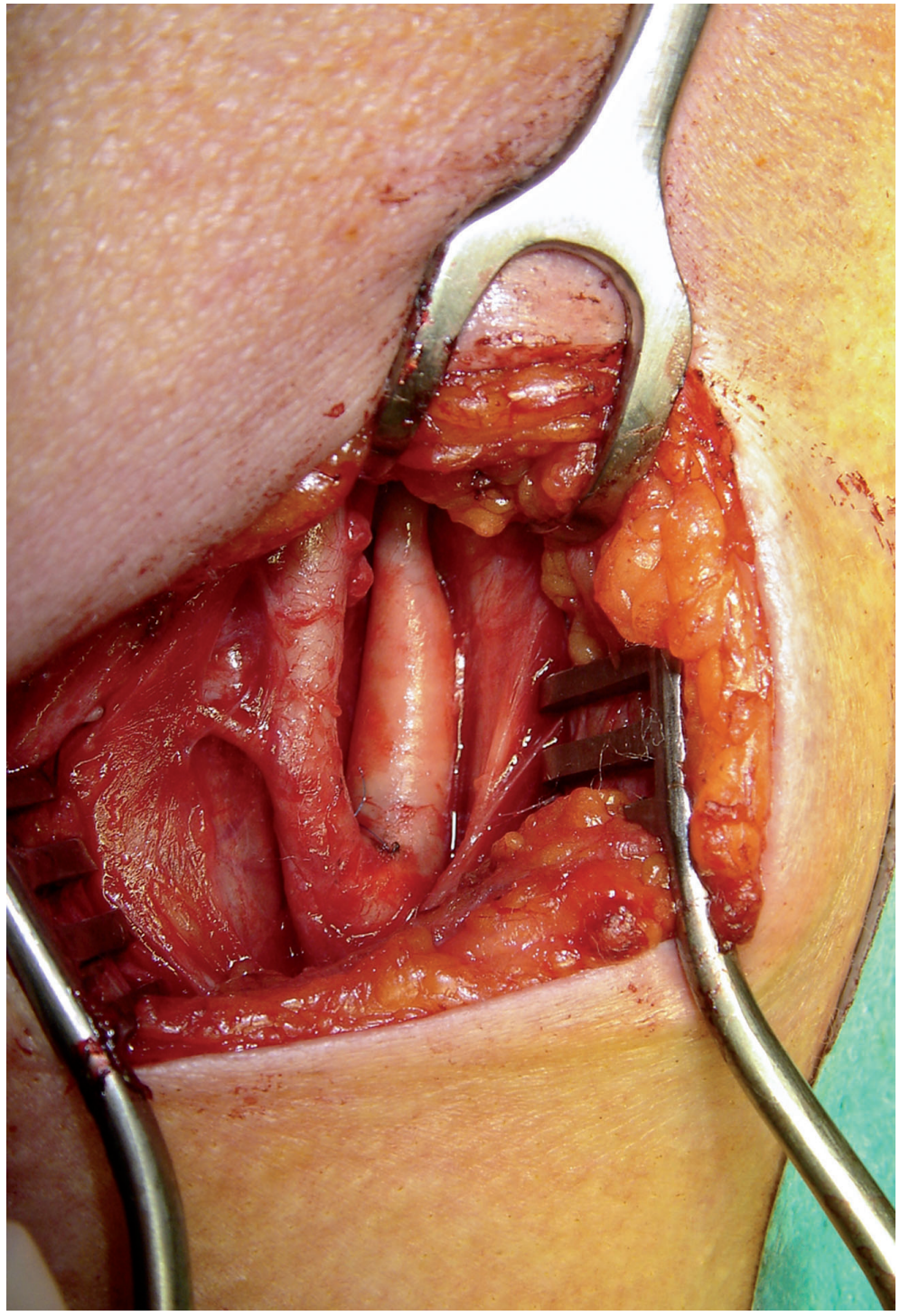

Figure 2. 'Nude' proximal 3 cm of the stripped internal carotid artery.

or hypotension (systolic blood pressure <70 mmHg) was treated by intravenous administration of atropine or norepinephrine or application of lidocaine around the ICA. Following completion of the stripping procedure, patients were monitored in a Cardiac Care Unit during the first 24 postoperative hours.

Data accrual

Data were accumulated in two different ways. From 2000 on, a prospective registry of patients served as a basis for analysis. Characteristics of earlier patients were identified by a retrospective chart review. Once patients were identified, demographics, preoperative evaluation and perioperative data were extracted from cardiological and surgical charts.

Statistical analysis was performed using standard computer software. A paired T-test was utilised to compare values of pre- and postoperative blood pressure and heart rate. The Bonferroni correction was used. Data were expressed as mean±SEM. Significance was set at the P<.05 level.

RESULTS

The patient's history combined with physical examination and diagnostic test panels identified a group of 27 patients diagnosed with CSS (23 male, mean age 70±3, range 48-83, table 2). Symptoms are listed in table 2. The majority experienced syncope (74%, n=20), and most episodes occurred spontaneously (56%, n=15). In a minority of patients

Symptoms	Recurrent syncope/dizziness		
Tests	Holter ECG Table tilt test	Cardiac ultrasonography Carotid duplex	
CSM	Cardioinhibitory	Vasodepressor	Mixed
	Asystole>3 s	Drop SBP>50 mm Hg	Asystole>3 s and drop SBP>50 mmHg *

Table 1. Criteria for diagnosis of CSS.
CSM: carotid sinus massage, SBP: systolic blood pressure. *With pacing or after intravenous administration of 1 mg atropine.

Patient	Sex	Age	Symptoms	Provocative factor	CSM	Operation
1	M	67	S	Spontaneous	MIX pacing	Staged bilateral
2	F	80	S	Spontaneous	CI*	Right
				Spontaneous	CI*	Left
3	M	79	D	Spontaneous	CI*	Left
4	F	80	S	Spontaneous	CI*	Staged bilateral
5	M	55	S	Turning head Coughing	CI*	Right
6	M	69	D	Turning head Wearing collar	CI*	Bilateral
7	M	78	D	Spontaneous	CI*	Bilateral
8	M	48	D	Spontaneous	CI*	Bilateral
9	M	82	S	Spontaneous	MIX pacing	Staged bilateral
10	M	74	S	Turning head Wearing collar	MIX pacing	Right
11	M	62	S	Turning head	CI*	Right
12	M	73	S	Spontaneous	CI*	Right
13	M	64	D	Looking upward	MIX pacing	Staged bilateral
14	M	61	S	Turning head	CI*	Right
15	M	80	S	Spontaneous	CI*	Right
16	F	81	S	Coughing	CI*	Left
17	M	83	S	Spontaneous	MIX pacing	Staged bilateral
18	M	77	S	Coughing	MIX pacing	Right
19	M	65	S	Spontaneous	MIX pacing	Left
20	M	81	S	Turning head	CI*	Right
21	M	56	D	Turning head Collar, shaving	CI*	Bilateral
22	M	50	S	Spontaneous	VD	Right
23	M	81	S	Spontaneous	MIX atropine	Bilateral
24	M	69	S	Looking downward	MIX atropine	Right
25	F	53	D, V	Wearing collar	unknown	Right
26	M	62	S	Spontaneous	CI	Right
27	M	83	S	Spontaneous	MIX atropine	Bilateral

Table 2. Demographics and symptomatology in CSS patients.
M: male, F: female, D: dizziness, S: syncope, V: vomitus, CI: cardioinhibitory, VD: vasodepressor, MIX: mixed.
*not tested with atropine or pacing for vasodepressor component.

(44%, n=12) provocative factors were reported, most frequently head movements (33%, n=9). Three patients regularly fainted following coughing. One patient consistently collapsed while knotting his tie. Symptoms resulted in serious complications including a car accident leading to loss of driver's license (n=1), or fractures of femoral neck (n=1) or humeral bone (n=1). Additional comorbidity is shown in table 3.

Carotid bruits were absent in all patients. Subsequently, CSM identified eleven patients (41%) with a bilateral CSS. In the remaining 16 patients (59%) symptoms were only evoked following unilateral neck stimulation, usually on the right side (80%). CSM elicited a cardioinhibitory response in most patients (59%, n=16) and a pure vasodepressor type in just one. A mixed response was observed in the remaining 10 individuals (37%). This latter subgroup was unveiled after atropine (n=3) or by temporary cardiac pacing (n=7).

Hypertension	33%	PAOD	15%
IHD/ MI	30%	Malignancy	15%
COPD	26%	TIA/CVA	11%
Hyperchol	19%	Dysrhythmia	11%
DM	15%	LVH	3%

*Table 3. **Comorbidity in CSS patients.***
LVH: left ventricular hypertrophy, IHD: ischaemic heart disease, MI: myocardial infarction, TIA: transient ischaemic attack, CVA: cerebrovascular accident, PAOD: peripheral arterial occlusive disease, hyperchol: hypercholesterolaemia, DM: diabetes mellitus, COPD:chronic obstructive pulmonary disease.

Complication	Management
Hematoma (n=4)	Surgical evacuation (n=2) Spontaneous resolution (n=2)
Dysrhythmia (n=3)	Medication (n=2) Cardioversion (n=1)
Neuropraxia (n=2)	Spontaneous resolution (n=2)
Hypertension (n=2)	Medication (n=2)
CVA (n=1)	Full recovery

*Table 4. **30- Day complication rate.***

Mean duration of asystole was 7±2 seconds (3-13 seconds), and mean drop in systolic blood pressure 66±3 mmHg (50-120 mmHg).

A total of 39 carotid denervations by adventitial stripping was performed in 27 patients. Staged bilateral surgery was done in 5 patients (1980-1995), whereas from 1995 onwards 6 patients received surgery in just one operation. The remaining 16 patients underwent unilateral carotid denervation (table 2). Patient 2 developed a CSS on the contralateral side 2 years after carotid denervation and was again operated with a satisfying result. Complications associated with surgery (table 4) included wound hematoma and neuropraxia of the marginal mandibular branch of the facial nerve. Dysrhythmias (atrial fibrillation n=2, sinus tachycardia n=1) within 48 hours following surgery mandated temporary medication (n=2) or cardioversion (n=1). An elevated blood pressure (195/115 mmHg, preoperative 145/85 mmHg) some hours postoperatively in one patient undergoing an unilateral denervation was treated with a calcium antagonist for four weeks. However, normotension without antihypertensive medication was observed at the 30-day control period.

Figure 3 demonstrates that systolic blood pressure (SBP) on the 1st postoperative day was not different compared to preoperative values (145 ± 4 vs 141 ± 5 mmHg, P=.41).

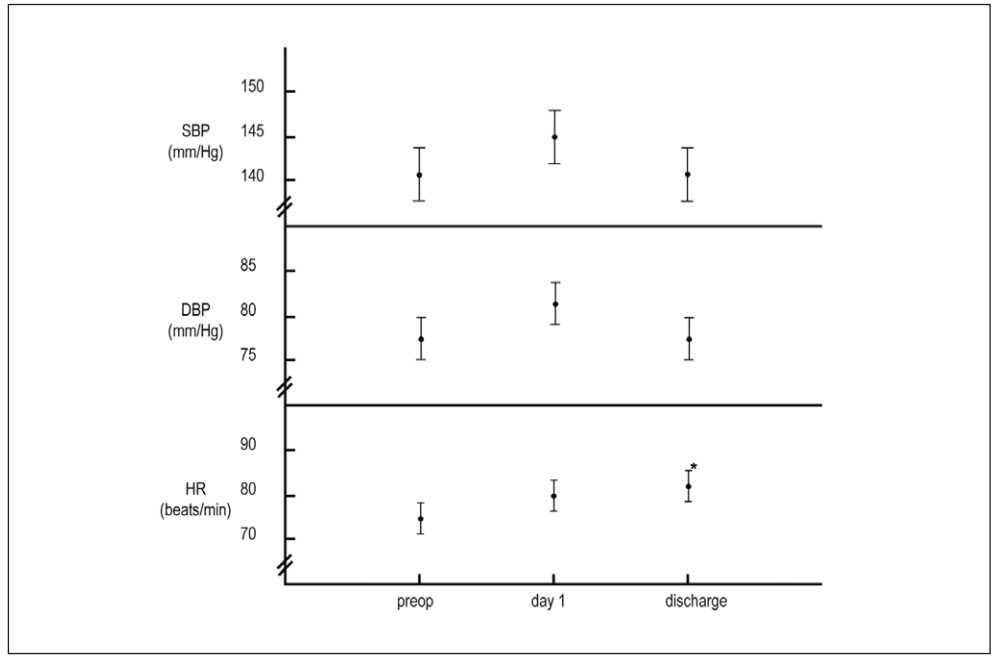

*Figure 3. **Effect of adventitial stripping on systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) over time.***
Preoperative (n=27), 1st day postoperative (n=27), prior to discharge (n=9). Values are shown as mean ± SEM.

There was also no difference in diastolic blood pressure (DBP, 81 ± 2 vs 77 ± 3 mmHg, P=.09) or heart rate (HR, 80 ± 2 vs 75 ± 3 beats/min, P=.17). SBP, DBP and HR were also determined in a portion of patients (n=9) just prior to discharge (day 4±1). No significant differences existed compared to preoperative values.

One patient experienced a CVA with left sided paralysis 24 days after a bilateral carotid denervation. He had an occlusion of the left ICA and 50% stenosis of the right ICA and may have suffered a CVA on the basis of a low flow state. Fortunately, recovery was uneventful and syncope free. One patient had residual disease within one month after the initial procedure. Repeat CSM could still evoke symptoms and an asystole. A redenervation 1 month after the initial operation resulted in abolishment of all symptoms. Two additional patients also did not respond to carotid denervation while still demonstrating a positive CSM. On their request, both received a permanent pacemaker instead of a reoperation. However, even with this device, they were still not free of symptoms. One patient experienced renewed CSS symptoms after pacemaker implantation for cardioinhibitory CSS 5 years earlier. CSM under pacing showed a significant drop in blood pressure. He underwent a successful bilateral carotid denervation. On the advice of the cardiologist his pacemaker was not removed.

After 30 days of follow up, 25 of 27 patients (93%) were free of syncope and 24 of them free of a pacemaker (89%).

DISCUSSION

The incidence of CSS in elderly people is probably underreported.[12] A 50% incidence was present in patients evaluated for unexplained dizziness and syncope.[13] CSS was found associated with atherosclerosis, diabetes and hypertension as also observed in the present study.[14,15] Controversy exists on its natural history. One randomized study demonstrated that symptoms of severe CSS recurred within 3 years in more than half of individuals that were only observed.[16] A decision for a 'wait-and-see' policy must be dictated by severity of the symptom complex. It should be appreciated that CSS patients with a vasodepressor component have a threefold increased incidence of recurrent symptoms compared to patients with a cardioinhibitory form.[17] It must also be realized that a substantial portion of CSS patients is subject to additional morbidity associated with frequent falls including fractures.[13,18,19] A 7% fracture rate was also observed in the present population.

Typology of CSS is diverse but largely dictates management. A pure cardioinhibitory form of CSS is thought to respond successfully to either pacemaker therapy or surgery.[20]

On the other hand, mixed or vasodepressor forms of CSS are not effectively treated by pacing but may exclusively benefit from surgery.[15] For instance, successful carotid denervation was reported in 2 mixed CSS patients that were still experiencing syncope after earlier pacemaker treatment.[21] Moreover, recent ESC guidelines also state that only cardioinhibitory CSS is a strict indication for pacemaker treatment.[22] In the 1999-2007 period of our study (n=11), only one patient exhibited a pure vasodepressor form, whereas the minority of patients evaluated between 1980-1999 were additionally tested for a vasodepressor component. One may therefore assume that the vast majority of CSS patients is of a mixed type, whereas pure cardioinhibitory or pure vasodepressor forms are less common as also suggested by others.[23,24]

Various treatment regimens for CSS have been explored including instructions avoiding stimulation of the neck area (head turning), medication[3] and even carotid sinus irradiation.[25,26] Others have suggested pacemaker implantation[27] or surgery including nerve transection or carotid denervation by means of adventitial stripping.[28] This plethora of strategies illustrates that a tailored management in patients with CSS is not attained. Medication may be prescribed in mild disease but is ineffective in moderate and severe CSS.[3, 24] Carotid irradiation is potentially hazardous, whereas glossopharyngeal transection requires a craniotomy and may be reserved for incurable patients not responding to any other regimen. Therefore, the treatment of choice in severe CSS is either pacemaker implantation or (limited) surgery.

Some vascular surgeons do not advise surgery for CSS but recommend pacemaker implantation.[29] However, a claim that an electrical device is superior was based on a study just comparing populations with and without pacemaker.[16] Patients without pacemaker showed a 62% recurrence of symptoms after a mean follow-up of 4 years. In contrast, a 16 % recurrence rate was observed in patients that were paced. This study merely illustrated that CSS requires an effective treatment rather than a wait-and-see policy but did not allow for a comparison of different treatment regimens. To date, no randomized trial comparing the efficacy of pacemaker versus surgical treatment has been completed yet.

A rather slim body of literature seems to indicate that many patients may benefit from surgery. However, which method is most effective ? If one accepts the assumption that a hypersensitive carotid sinus plays a pivotal role in the pathophysiology of CSS, surgery that is based on removal of all nervous tissue that is in close contact to the carotid sinus ('adventitial stripping') may be effective. Several techniques have been reported in the literature, some in more detail than others.[10] In the present study, an adventitial stripping of a minimal 3-cm portion of proximal internal carotid artery was performed since this section is hypothesized to contain the majority of afferent nerve

fibers. The finding that 93% of patients were free of symptoms after this procedure confirms this hypothesis. Modern microanatomical studies may further identify distribution of nerve fibres in the carotid area.

Some have questioned the safety of a carotid denervation. However, their fear is fuelled by case studies reporting on severe baroreflex dysfunction due to iatrogenic denervation of the carotid sinus following bilateral carotid body tumor resection.[30] For instance, a fatal hypertensive crisis was reported in the 1950's after an unilateral surgical carotid denervation.[31] Because of these findings, bilateral disease in our patient population prior to 1995 was treated using a two stage procedure. As no baroreflex dysfunction was observed, we operated bilateral disease in just one operation after 1995. Patients demonstrated stable postoperative heart rate and blood pressure. The present study shows that, in experienced hands, carotid denervation by adventitial stripping has few complications.

The clinical results of carotid denervation by adventitial stripping, at least at short term follow up, are very satisfactory. Naturally, the limitations of a retrospective study and all its disadvantages should be taken into account. Although out of the scope of this paper, long term follow up is needed to evaluate the durability and definitive efficacy of carotid denervation, as possible reinnervation of the carotid baroreflex has been described.[32] However, at long term follow up other factors and events may play a role in the clinical outcome of these elderly patients, which will ask for a renewed set of diagnostic tests.

CONCLUSION

Carotid denervation by adventitial stripping of a 3 cm portion of the proximal internal carotid artery is simple, safe and effective at short term follow up. This operation may offer a valid alternative for pacemaker treatment in patients with carotid sinus syndrome. A randomized trial is needed to compare these two treatment options.

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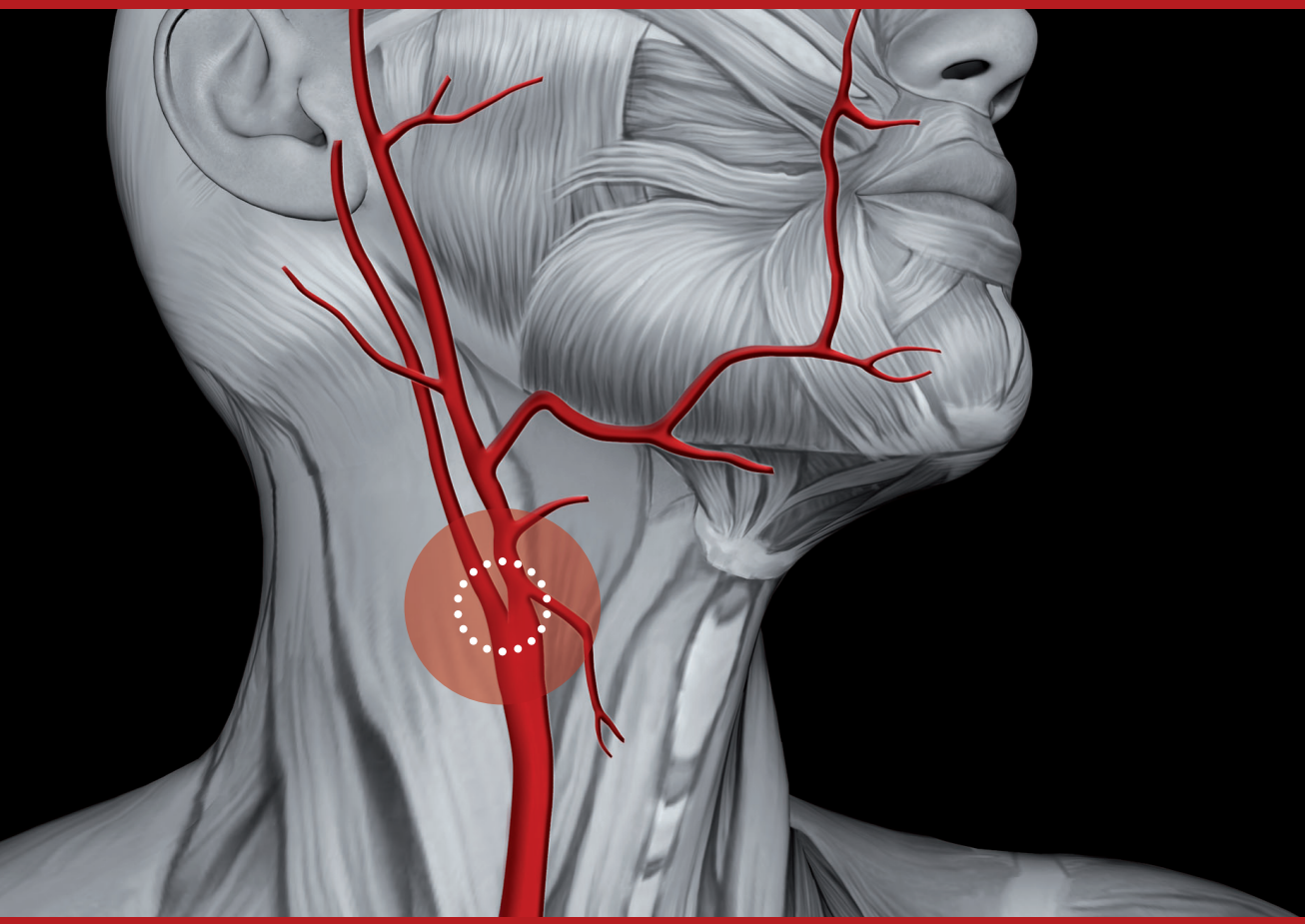

CHAPTER 8

Long term safety and efficacy of internal carotid artery adventitial stripping in carotid sinus syndrome

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Submitted

ABSTRACT

Background

To investigate the long term efficacy of carotid denervation by adventitial stripping of the internal carotid artery (ICA) for carotid sinus syndrome (CSS). Secondly, the long term safety of this technique is investigated with emphasis on the effects on blood pressure (BP), heart rate (HR) and carotid artery diameter.

Methods

Characteristics of patients that were operated for CSS in a single institute between 1980-2007 were studied by a retrospective chart review. Alive and fit patients additionally received a standardized interview investigating symptoms of residual CSS or baroreflex failure. They underwent a test panel consisting of office BP measurement, carotid sinus massage (CSM), table tilt testing, 24-hour ECG and ambulatory BP measurement (ABPM) and carotid duplex imaging. Unoperated, age- and sex- matched individuals without CSS served as controls.

Results

After a total follow up of 91±34 months, 22 of 26 patients (85%) were asymptomatic and 21 of them (81%) without a pacemaker. Of the 7 surviving and fit patients, six were free of CSS symptoms (follow up 114 ± 81 months). Recurrence of CSS after an initial successful carotid denervation was not observed. BP level, BP variability and carotid diameters were not different compared to controls.

Conclusion

Carotid denervation by adventitial stripping of the ICA for CSS is effective and safe on the long term. A randomised controlled trial comparing the efficacy and safety of carotid denervation, pacing and medical treatment is needed for optimal future treatment of patients suffering from CSS.

INTRODUCTION

Carotid sinus syndrome (CSS) is caused by a dysfunctioning carotid baroreflex. The syndrome leads to symptoms of dizziness and syncope because of an asystole (cardioinhibition), extreme hypotension (vasodepression) or by a combination of both.[1,2] Adventitial stripping of the internal carotid artery (ICA) interrupts the afferent arch of the carotid baroreflex.[3-5] Studies in the early 1930's suggested that this technique may offer a valid treatment option in CSS.[6-8] In a previous study of 27 patients, adventitial stripping of a 3 cm portion of the ICA appeared safe with a 93% short term success rate.[9] However, no literature is available on the long term efficacy of this technique, whereas the effects on blood pressure (BP), heart rate (HR) and carotid artery diameter are largely unknown.

After surgical denervation, autonomic reinnervation of the carotid baroreflex has been described in several animal studies.[10,11] Regeneration of carotid sinus afferent innervation may potentially account for recurrent CSS and may limit long term efficacy following adventitial stripping. This hypothesis is somewhat challenged by a recent review demonstrating complete relief of symptoms in 73% of CSS patients, although the mean follow up in this heterogeneous group of patients was just 2.5 years.[5] Therefore, the issue of prolonged freedom from syncope after carotid denervation is unsolved.

Similarly, the long term effects of carotid denervation on BP are virtually unknown. Some well controlled denervation experiments in animals suggested substantial loss of BP stability.[12-15] Moreover, data obtained from a small number of patients suffering from inadvertent iatrogenic baroreflex damage caused by carotid body tumor resection also suggest an increased incidence of orthostatic hypotension and substantial increase in BP fluctuations.[16] Some reports even describe a baroreflex failure syndrome.[17,18] To our knowledge, follow up studies on BP characteristics in patients who were intentionally denervated for treatment of a CSS are not available.

The aim of the present study was to investigate the long term efficacy of carotid denervation by adventitial stripping of the ICA as a treatment of carotid sinus syndrome in terms of freedom from syncope and pacemaker implantation. Secondly, the long term safety of adventitial stripping is investigated with emphasis on the effects on BP, HR and carotid artery diameter.

METHODS

Patients

The study was performed between January 2010 and June 2010 in the Máxima Medical Center (MMC) in Veldhoven, the Netherlands. The MMC is a 865-bed hospital serving some 400.000 individuals in a semirural environment. Patients with CSS who underwent a carotid denervation in the MMC between 1980 and 2007 were eligible for study. These patients all had a history of recurrent dizziness and syncope whereas CSS was subsequently diagnosed by performing a carotid sinus massage (CSM). Carotid denervation was performed under general anesthesia and continuous monitoring of intra-arterial blood pressure and heart rate. The carotid bifurcation was exposed through a 6-7 cm skin incision parallel to the anterior border of the sternocleidomastoid muscle. Nervous tissue attached to adventitial layers of the proximal internal carotid artery (ICA) was circumferentially removed over a distance of 3 cm, starting at the carotid bifurcation. Further details and short term results of carotid denervation in this CSS population were described in detail elsewhere.[19] Characteristics in the follow up as documented in surgical and cardiological charts as well as additional entries in the electronic patient files of all of these operated patients were studied in detail. If a patient had died, relatives and/or general practitioners were contacted for further pertinent information. Living patients were contacted by telephone and invited for the present follow up study. The study protocol was approved by the hospital's ethics committee and all patients gave their informed consent.

Study protocol

Patients eligible for the long term follow up study underwent a standardized history taking investigating residual CSS. Furthermore, they were also asked if they suffered from symptoms of baroreflex failure such as flushes, headaches, palpitations and emotional instability. Office BP was measured on both arms using standard noninvasive techniques, and the highest of 3 consecutive measurements was tabulated.

Following the standard interview, physical examination and carotid duplex imaging, they underwent a CSM on the Coronary Care Unit. Cardiac rhythm and BP were continuously recorded by means of a 12-lead electrocardiogram and an intra-arterial line that was positioned in the radial artery. CSM was initially performed in a supine position by digital stretching of the skin and subcutaneous tissue of the neck area overlying the carotid bifurcation during a 10 second period. This test was also repeated on the contralateral side after an 1 minute interval. If no pathological reflex was present, this manoever was repeated in 60° head up tilt (anti-trendelenburg position). A normal physiologic response to CSM is defined as 'no or moderate' heart rate slowing (≤ 50%) and BP drop (≤ 30 mmHg).[19] Criteria for CSS as described by the European Society of Cardiology (ESC) were

followed. An asystole >3 sec (cardioinhibitory respons) and/or a >50 mmHg systolic BP drop (vasodepressor response) were considered pathognomic of (residual or recurrent) CSS.[20]

Tilt table testing is able to identify a neurally-mediated reflex.[21] A standard table with footboard support was used. Patients were monitored by a 12-lead electrocardiogram and continuous intra-arterial blood pressure monitoring. After 20 minutes of passive 60° head up tilt testing, 5 mg of nitroglycerine was given sublingually and the test was continued for a maximum of 20 minutes. The procedure was immediately terminated when symptoms of a (pre)syncope were reported. Orthostatic hypotension was defined as a drop in systolic BP (SBP) of more than 20 mmHg or a drop in diastolic BP (DBP) of more than 10 mmHg within 3 min of adopting the upright position.[22]

Twenty-four hour ambulatory BP measurements (ABPM) were performed on the day after the study during normal activities at home in order to determine BP fluctuations. During daytime (8 am-23 pm), the reading interval was 30 minutes whereas the interval was 60 minutes during night time (23 pm-8 am). Hypertension was defined as a mean ABPM during daytime of ≥ 135 mm Hg/85 mm Hg and ≥ 120 mm Hg /70 mm Hg during nighttime, respectively. BP fluctuations are expressed by BP variability, which is assessed by calculation of the standard deviation of 24 hour systolic and diastolic BP. ABPM readings obtained from 10 subjects, with a similar cardiovascular risk profile as the patient group, were used as control values. This age and sex-matched control group was not suffering from CSS and never underwent a carotid denervation previously. Twenty-four hour ECG's were recorded with two bipolar electrodes in V2 and V5 positions. Data were labeled for normal QRS complexes, AV block and asystole.

Carotid duplex

Duplex imaging of the carotid arteries (ATL HDI 5000 sono CT, Philips, Eindhoven, The Netherlands) was performed prior to CSM as a means to exclude significant carotid stenosis, as this condition is considered a contraindication for performing CSM. Diameters of the carotid vessels were determined at standard levels: common carotid artery (CCA) 1 cm proximal to the bifurcation, internal carotid artery (ICA) 1 cm distal to the bifurcation, and ICA 4 cm distal to the bifurcation. Data obtained from age- and sex-matched individuals undergoing Duplex measurements because of ocular symptomatology (n=22) served as control values. Carotid stenoses were not present in these controls.

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS for windows). Results are given as mean±sd. Differences between patients and controls were compared using the Student t-test. A two-sided $p<0.05$ was taken as the level of significance.

RESULTS

Study population

Twenty-seven patients suffering from CSS underwent a carotid denervation in the MMC between 1980 and 2007. Sixteen of these initial 27 patients had already died at time of initiation of this follow up study (January 2010). Cause of death were malignancies (n=6) or cardiovascular events (n=10). Elapsed mean number of months from carotid denervation until death was 67±10 mo (range, 3-156 mo). Thirteen of these 16 succumbed patients were free of any symptom possibly associated with CSS during this period. One patient experienced new-onset symptoms of the vasodepressor type CSS after pacemaker implantation for cardioinhibitory CSS 5 years earlier. Subsequently, he underwent a bilateral carotid denervation and became long term symptom free. In patient no 14 further information on CSS associated symptoms was not obtained. Patient no 15 and 16 were documented as still symptomatic until death. These failures continued to suffer from syncopes, even though they had received a pacemaker after an unsuccesful carotid denervation.

Therefore, at the inception of the long term follow up investigation, 11 of 27 patients were alive and eligible for the long term study. Of these 11 surviving patients, 2 considered themselves unfit for an outpatient examination because of high age of 87 and 95, respectively. The 87 year-old male was free of symptoms. A 95-year-old female had received a pacemaker for an AV- block 6 years after an initially successful surgical denervation. CSM prior to pacemaker insertion did not demonstrate a hypersensitive carotid sinus. However, after pacing she still experienced symptoms of syncope. Two additional patients aged 75 and 82 refused to participate for personal reasons. The interview by telephone revealed that they were both free of CSS associated symptoms some 63 and 230 months postoperatively.

The study protocol was completed by 7 patients. Demographic and clinical data are presented in table 1. Age was 65±11 years and follow up was almost 10 years (114±81 mo). Six of seven patients were free of symptoms. However, patient number 3 still reported episodes of dizziness although two-three times less frequent compared to preoperatively. Previous cardiovascular evaluation using ergometry, echocardiography and coronary arteriography showed no abnormalities in this patient. Palpitations, sweating, flushing, headache or emotional instability were not reported by any of the 7 patients.

Blood pressure level, blood pressure variability and heart rate

Prior to the denervation, mean systolic and diastolic BP were 141±16 mmHg and 76±13mmHg, respectively. These values remained stable at the various postoperative time points as demonstrated in figure 1. Before surgery, 4 patients used a total of 7

different antihypertensive medication. Patient no 1 was diagnosed with hypertension 14 years after carotid denervation and amlodipine was started. At follow up he was normotensive. Patient no 3 showed hypertensive values both on pre- and postoperative blood pressure measurements and ABPM. For personal reasons he did not use anti-hypertensive drugs. Blood pressures during daytime ABPM were substantially lower

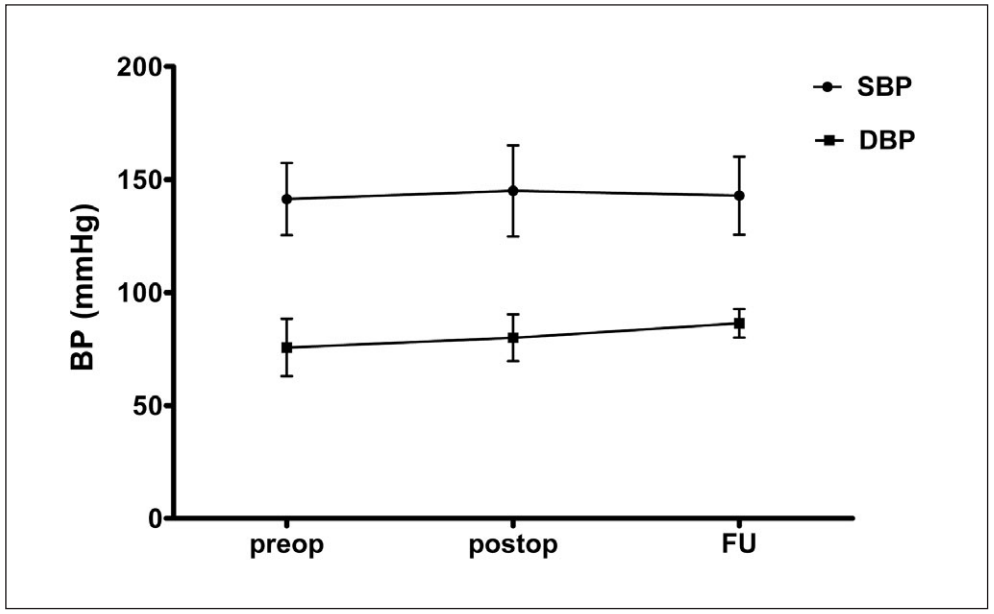

Figure 1. Blood pressure in CSS patients (n=7) before and after carotid denervation.
BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, preop: preoperative, postop: postoperative, FU: at follow up (mean 114±81 months).

Patient	Sex	Age	Type CSS	Operation side	FU time (mo)	Free of symptoms	Antihypertensive medication
1	m	70	CI	R	179	yes	amlodipine
2	m	63	CI	bilateral	73	yes	metropolol, adalat
3	m	55	VD	R	55	no	no
4	m	66	CI	R	56	yes	no
5	f	59	CI	R	59	yes	bisoprolol, furosemide
6	m	58	CI	bilateral	110	yes	metoprolol
7	m	87	MIX	bilateral	267	yes	no

Table 1. Patient characteristics of CSS patients (n=7) during long term follow up.
CSS: carotid sinus syndrome, m: male, f: female, VD: vasodepressor, CI: cardioinhibitory, MIX: mixed, HR: heart rate, R: right, L: left, FU: follow up, mo: months.

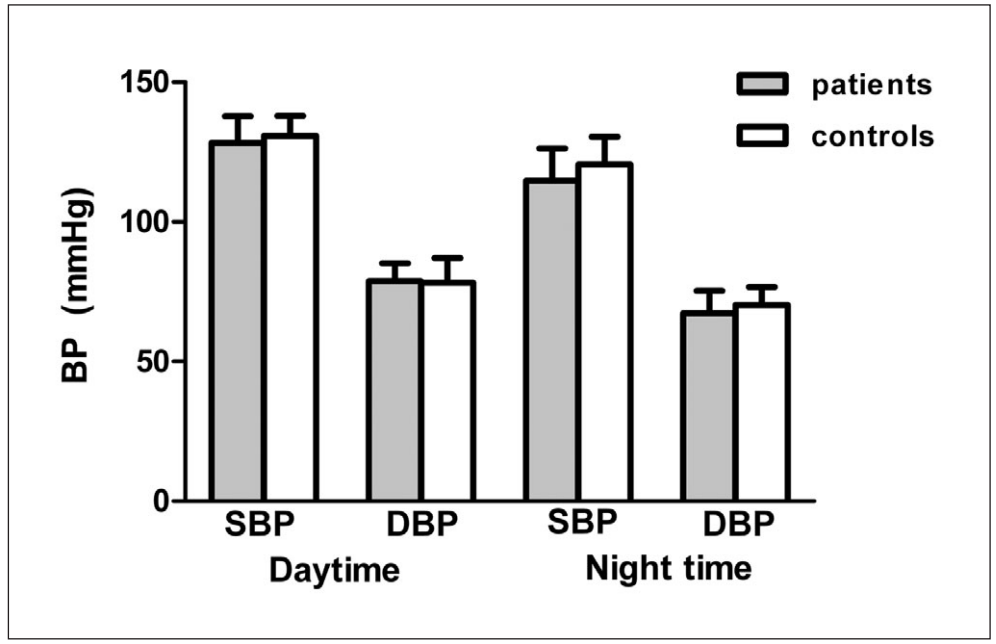

Figure 2. Ambulatory blood pressure in patients (after carotid denervation, n=7) and controls (no carotid denervation, n=10).
BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, daytime: 8 am-23 pm, nighttime: 23 pm-8 am.

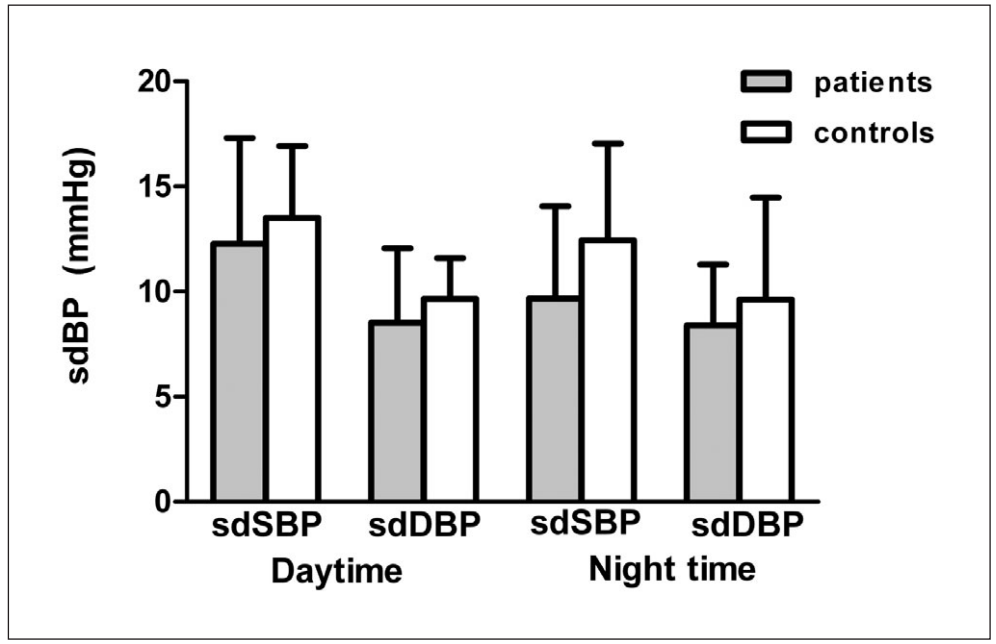

Figure 3. Blood pressure variability in patients (after carotid denervation, n=7) and controls (no carotid denervation, n=10).
Sd: standard deviation, BP: blood pressure, SBP: systolic blood pressure (mmHg), DBP: diastolic blood pressure (mmHg), daytime: 8 am-23 pm, nighttime: 23 pm-8 am.

compared to office blood pressure readings at follow up (SBP: 128±10 mmHg vs 143 ±17mmHg, n.s., DBP: 79±6 mmHg vs 86±6 mmHg, p<0.05).

Mean daytime ABPM values were similar between patients (after carotid denervation) and controls (no carotid denervation) (figure 2). BP variability (standard deviations) of daytime and night time ABPM was not significantly different between controls and patients (figure 3).

All patients demonstrated a normal sinus rhythm during 24-hour ECG recording without signs of AV block or asystoles.

Carotid sinus massage (CSM) and table tilt test
During CSM in supine or upright position, no patient reported symptoms associated with CSS, although an average 13±9 mmHg SBP decrease was observed. A >50 mmHg SBP drop was not recorded in any of the patients during CSM of the operated side. In patient no 1 massage of the unoperated carotid region in 60 °head up tilt elicited an asymptomatic 60 mmHg SBP drop (carotid sinus hypersensitivity rather than CSS). However, patient no 3 reporting residual symptoms did not demonstrate an abnormal baroreflex after CSM. Heart rates drops (HR) during CSM were 3±1 bpm on either side. No asystole was reported.

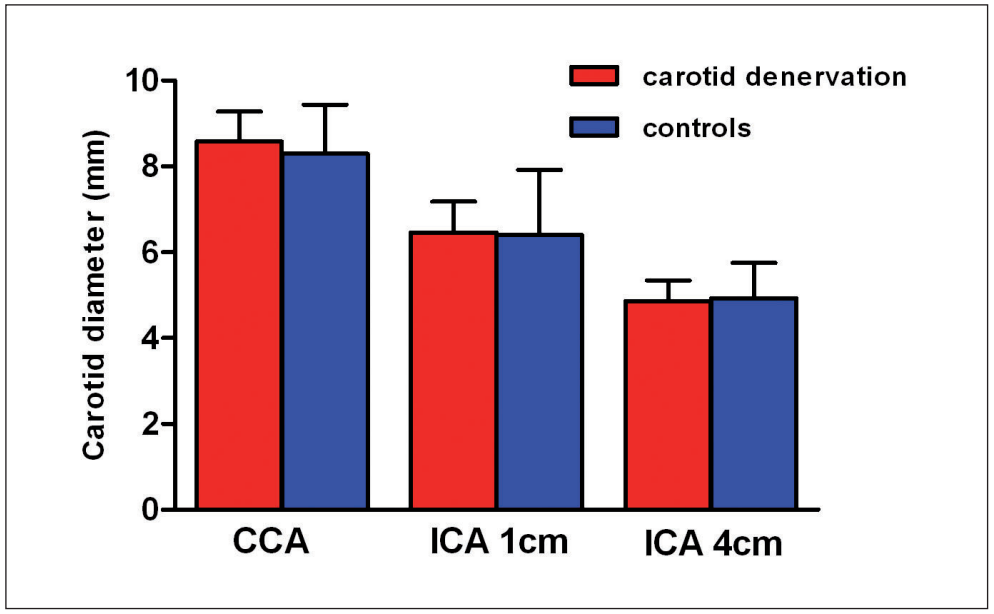

Figure 4. Carotid diameters after carotid denervation (n=7) and controls (n=22).
CCA: common carotid artery, ICA: internal carotid artery

Table tilting resulted in a 5 mm Hg drop in SBP (143±30 vs 138±28 mmHg, n.s.). DBP remained stable during tilting (87±12 vs 86 ±12 mmHg, n.s.). No patient met criteria for orthostatic hypotension.

Carotid duplex
A significant carotid stenosis was not observed in either patients or controls. Moreover, diameters of operated and control internal carotid arteries were identical (6.5±0.2 mm vs 6.4±0.3 mm, n.s.) (figure 4).

DISCUSSION

In the 1930's Weiss and Baker were the first to document carotid denervation by adventitial stripping in a patient with CSS.[6] Since then this operative procedure has rarely been performed. Instead pacemaker implantation is recommended in patients with pure or predominantly cardioinhibitory types of CSS.[20,23-27] However, recent randomised controlled trials found little benefit of pacing in decreasing the number of syncopes and falls in older patients with CSS.[28,29] Medical therapy has been suggested for CSS patients with a predominantly vasodepressor type or ongoing symptoms despite pacing, but again with little compelling evidence for its effectiveness.[25] Carotid denervation could be a valid alternative treatment option for all types of CSS as it interrupts the afferent arch of the pathologic carotid baroreflex. However, this operation has never gained much popularity as safety and long term efficacy were doubted.[25] In a previous study we showed the short term safety and efficacy of carotid denervation.[9] The present study is the first to investigate long term effects of carotid denervation by adventitial stripping of the ICA for CSS. History taking and available data from charts indicate that 85% (22/26) of the patients was asymptomatic over a more than seven year time period, and 81% (21/26) free of a pacemaker. Patients that were still alive (n=7) demonstrated stable blood pressures and heart rates almost one decade after the denervation. These data strongly suggest that adventitial stripping of the internal carotid artery for CSS is safe and effective on the long term.

It was unclear if recurrent disease possibly develops following an initially successful denervation in CSS. Hypothetically, regeneration of carotid sinus afferents may result in recurrent CSS and adversely affect success rates on the long term.[30] The phenomenon of 'autonomic reinnervation' has been described in several animal studies. An increase in sensory baroreceptor afferents of the aortic arch and carotid sinus was documented 3 months postoperatively in sino-aortic denervated rats.[10] Moreover, recovery of chemoreceptor function after carotid sinus nerve section appeared to be associated with reinnervation of glomus tissue in another rabbit model.[11] Human data suggestive

of sympathetic and parasympathetic reinnervation are documented after heart transplantation although these signs of reinnervation generally occurred after more than 5 years.[31,32] A review covering the world literature on internal carotid adventitial stripping for CSS between 1933-2007 just identified 110 cases. Complete symptom relief was obtained in three-quarters of the denervated patients.[5] If a patient was asymptomatic after denervation, recurrent disease was not observed although the follow up was short (2.5 years). The present study also demonstrated an absence of recurrent disease. Two patients still demonstrated residual disease but they never became asymptomatic even after pacemaker placement, as also previously reported.[9] On the other hand, no patient became symptomatic after an initially successful denervation. CSM of the operated neck region could not evoke a pathologic baroreflex anymore. One may conclude that there is no evidence for the existence of recurrent disease after successful carotid denervation in CSS.

Surgical therapy of CSS has been regarded with scepticism because of the assumed long-term alterations of BP after uni- and bilateral denervation of the carotid sinus. The contribution of carotid baroreceptors to baroreflex function and compensation after functional loss of these receptors has been investigated intensively in denervation studies. In animals, extra-carotid baroreceptors have a large ability to compensate for the loss of carotid baroreceptor tissue. In denervated dogs and baboons, BP level and variability increased but returned to normal levels after 14 days.[12,33] However, chronic hypertension did not occur by selective carotid denervation in these animal models.[14,15] Information on impact of carotid sinus denervation in humans is limited and is obtained from investigations following iatrogenic damage to the carotid sinus. For instance, unilateral carotid endarterectomy did not lead to higher ambulatory BP level or variability.[34] Moreover, bilateral carotid denervation following bilateral carotid body tumor also did not elicit chronic hypertension but caused a long term increase of BP variability. These patients also showed pronounced elevations of BP on mental stress.[16] Real labile hypertension due to baroreflex failure syndrome may arise from both uni- or bilateral carotid denervation.[17,18] This syndrome is accompanied by palpitations, sweating, flushing, headache and emotional instability. In the present study data are reported from patients who underwent an unilateral or bilateral carotid denervation as treatment for carotid sinus syndrome. In contrast to abovementioned studies, this unique study population received an intentional denervation of a 3 cm portion of the internal carotid artery exclusively. In line with iatrogenically denervated patients, no increase in BP was documented after a mean follow up period of almost 10 years. Antihypertensive medication was unaltered in previously hypertensive patients. Mental stress in the present study group had a clear influence on BP readings as office BP at follow up was significant higher than ambulatory BP. In contrast to prior human denervation studies, daytime BP variability was similar to, and nighttime BP variability even higher (although non-significant) compared to the control group. None of the patients demonstrated orthostatic hypotension or symptoms of baroreflex failure. These data support the view that cardiopulmonary baroreceptors can compensate for the loss in baroreceptor function after bilateral denervation. After unilateral denervation, the contralateral carotid baroreceptor probably also plays a prominent role in this compensatory mechanism.

Disruption of the continuity of the arterial wall may lead to aneurysm formation on the long term. For instance, blunt injury to the extracranial carotid artery has been found to cause intimal and medial tears and dissection, leading to arterial dilatation.[35] Little is known on the effect of adventitial stripping on dimensions of the target artery. In 1913 Leriche suggested periarterial sympathectomy by adventitial stripping of the femoral artery for lower extremity wounds.[36] His successor Black did not observe a femoral aneurysm in 10 clinical cases in 1924.[37] He stated that 'aneurysm formation is unlikely provided the operator has been careful not to damage the muscular coats of the vessel wall'. More recently, digital sympathectomy by adventitial stripping of the radial and ulnar arteries for patients suffering from Raynaud's disease also did not result in aneurysm formation.[38,39] Our study also found stable diameters of denervated internal carotid arteries which were not different compared to carotid arteries of age- and sex matched control patients. One may safely conclude that adventitial stripping of the internal carotid artery for CSS does not lead to aneurysm formation.

The present study is suffering from limitations associated with the retrospective retrieval of data. The absence of preoperative data on ABPM and baroreflex function did not allow for a statement on the effects of denervation. To partly overcome some of the limitations, a for sex, age and cardiovascular risk profile matched control group not suffering from CSS was used as a comparison. As denervation is not often performed and mostly in elderly patients with a limited life expectancy, only a small number of alive and fit patients were eligible. Data of a limited size sample study in surviving individuals may thus be biased as relatively young patients were studied (65±11 yr). The number of patients also does not allow for a discrimination between results obtained from unilateral and bilateral denervation.

CONCLUSION

Data from the present study suggest that carotid denervation by adventitial stripping of the ICA for CSS is effective and safe on the long term as blood pressure, heart rate and carotid diameters were stable over time. A randomised controlled trial comparing the efficacy and safety of carotid denervation, pacing and medical treatment is needed for optimal future treatment of patients suffering from CSS.

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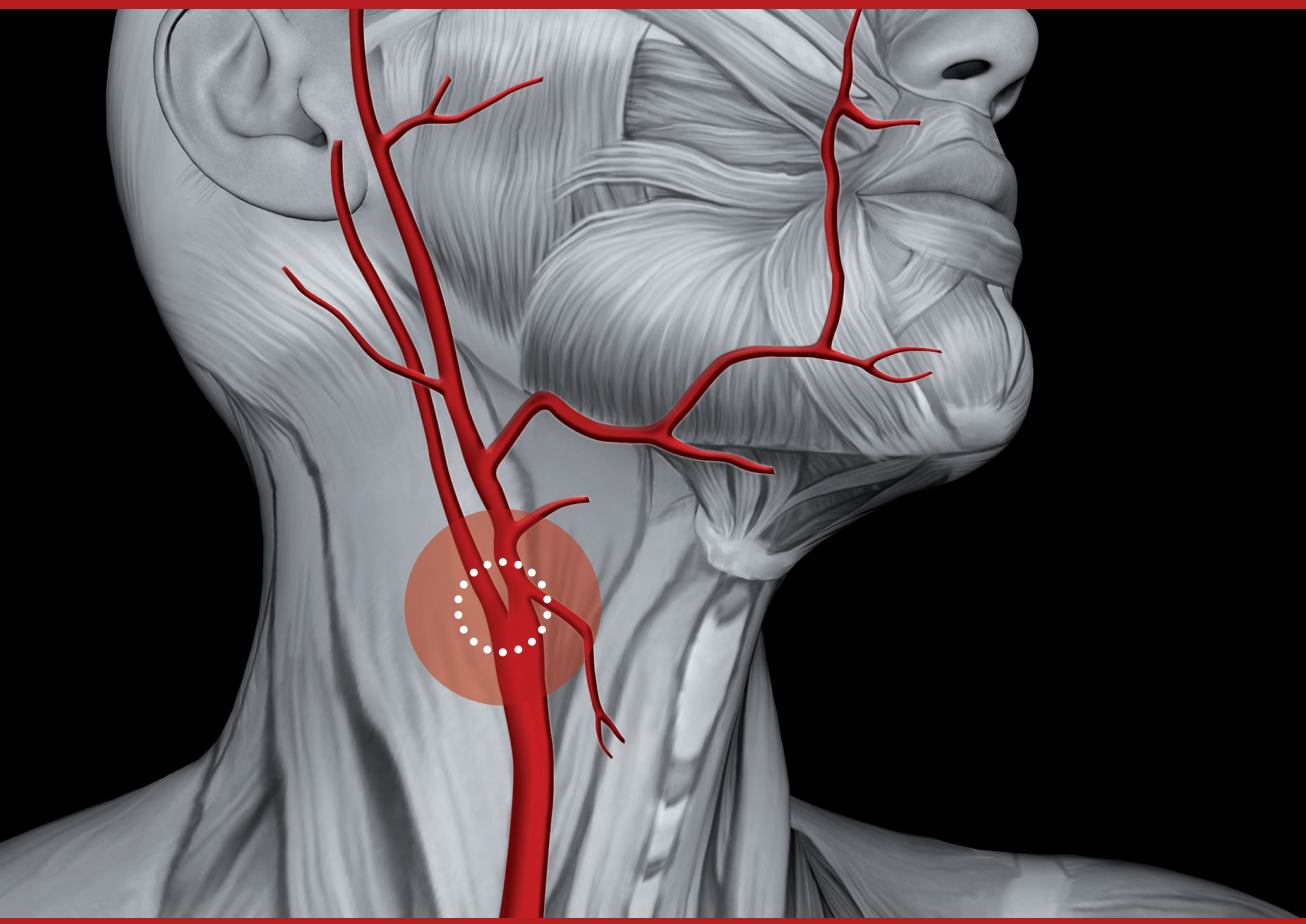

CHAPTER 9

Rationale of novel interventions for resistant hypertension

Toorop RJ, Scheltinga MR, Ricco J-B, Moll FL

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Hypertension treatment is challenging. As effective therapeutic measures were lacking, severe hypertension in the first half of the 20th century was successfully treated by performing an open surgical thoracolumbar sympathectomy.[1] With the advent of medical therapy, such extensive operative procedures lost popularity, particularly because of severe adverse events. However, despite current optimal pharmacological treatment including the combination of three anti-hypertensive medications of which one is a diuretic, blood pressure control remains disappointingly unsatisfactory in many patients.[2] As resistant hypertension is accompanied by severe cardiovascular morbidity and mortality, it is crucial to re-explore non-pharmacological blood pressure lowering strategies. The past few years have witnessed the development of novel minimally invasive interventions modulating various levels of the autonomic nervous system. Aim of the present paper is to discuss some relevant developments of non-pharmacological antihypertensive treatment modalities.

Renal sympathetic denervation

In 2009 a 59-year old male was successfully treated for resistant hypertension by renal sympathetic nerve ablation. During this intervention, a catheter is advanced into the renal arteries and four to six discrete low-power radiofrequency treatments are applied along the length of both renal arteries.[3] The rationale for this treatment is the denervation of sympathetic efferent nerve fibers responsible for increasing blood pressure by renal vasoconstriction, enhanced sodium/water reabsorption and renin secretion. Denervation of renal afferents results in reduced central sympathetic outflow and lower blood pressure. The efficacy of this new technique was confirmed in the Simplicity HTN-2 trial including 106 patients, randomly allocated to renal denervation or control groups. After 6 months, office-based blood pressure measurements in the renal denervation group was reduced by 32/12 mmHg (SD 23/11, baseline of 178/96 mm Hg, p<0.0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg (21/10), baseline of 178/97 mm Hg, p=0.77 systolic and p=0.83 diastolic). Twenty-four hour ambulatory blood pressure (evaluated in only half of the patients) decreased by 11/7 mm Hg in the renal denervation group (SD 15/11, p=0.006 systolic and p=0.014 diastolic), whereas there was no change in the control group. Reason for this discrepancy in blood pressure reduction may be caused by the 'white coat effect', which can lead to an overestimation of the blood lowering effect, when office-based blood pressure is measured. It may therefore seem more appropriate to use ambulatory blood pressure for determining the treatment effect.[4] The investigators tried to address the question of possible reinnervation of renal nerves by reporting the durability of denervation after 2 years. Although it is unclear why just 18 patients reached the 24-month end point, clinical evidence of reinnervation was not observed. Renal denervation appeared safe as cholesterol embolic events, de novo renal artery stenosis or renal artery aneurysm were not

reported. A limitation of this technique is an unsuitable renal artery anatomy precluding catheterization in almost 20% of patients.[5]

Electrical carotid baroreceptor stimulation

The first successful experience of human blood pressure reduction by continuous electrical stimulation of the carotid baroreceptors was reported in 2004.[6] During this procedure carotid arteries are surgically exposed and electrodes are placed around the carotid sinuses. Electrode leads are connected to a subcutaneously implanted pulse generator responsible for continuous electrical baroreflex stimulation. In hypertensive patients the baroreceptor reflex is thought to have adjusted to a higher operating pressure by a shift in pressure threshold.[7] Electrical stimulation may lower the baroreceptor set point with consequent lowered blood pressures due to a reduced central sympathetic outflow. Data from the DEBUT trial using the Rheos implantable carotid stimulator (CRVx, Minneapolis, USA) suggest a substantial reduction of blood pressure over 3 years after device implantation. A large randomized controlled study (n=265) investigating efficacy and safety of electrical carotid baroreceptor stimulation is currently being conducted. For obvious reasons, patients with a carotid stenosis >50% are excluded from treatment.[8] A clear disadvantage of this procedure is its invasiveness with possible adverse events such as infection, cranial nerve injury or long term arterial complications. However, no de novo carotid artery stenosis was documented after one year of follow up.[9]

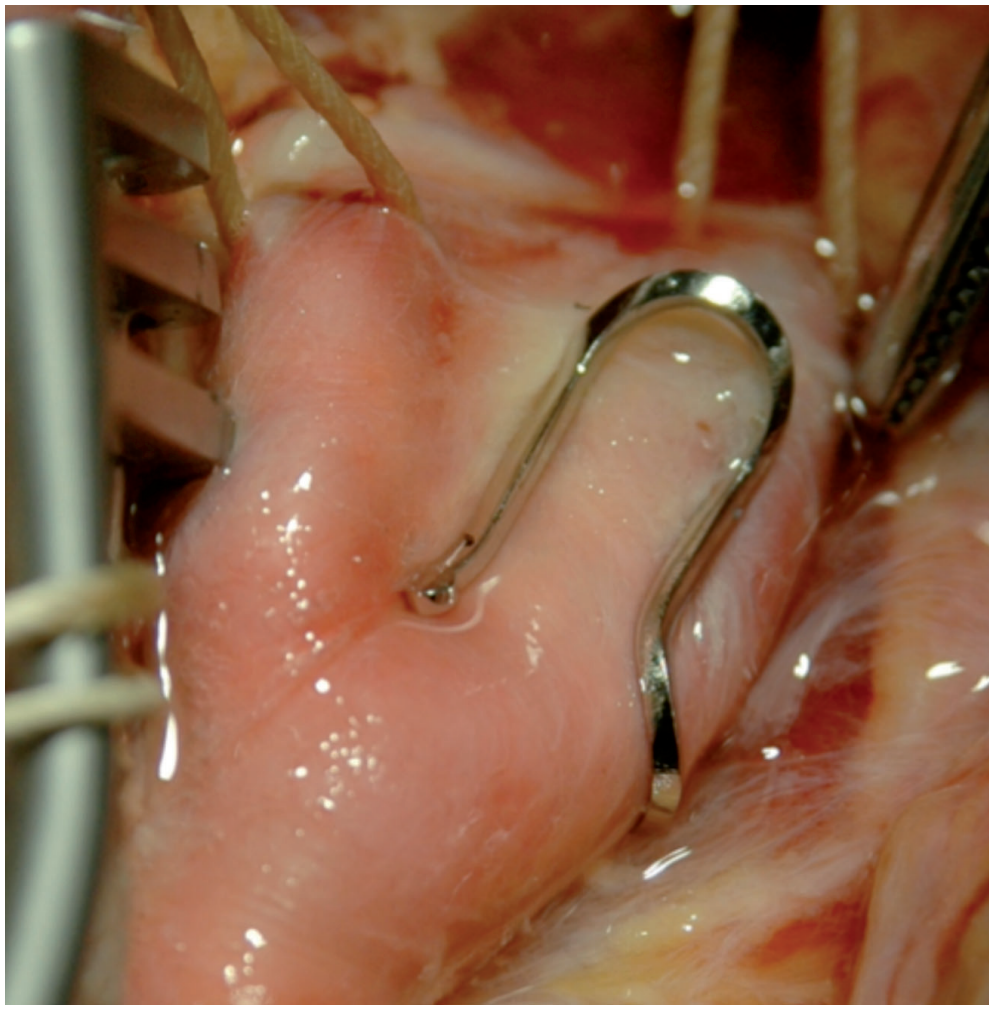

Figure 1. Extravascular device (Starfix) placed on a left carotid sinus of a human cadaver.

Future concepts in blood pressure control

Triggered by the physiological blood lowering effect of carotid sinus massage, a simple passive extravascular device positioned around the carotid sinus (Starfix, Vascular Dynamics, Israel) has been developed (figure 1). This device continuously increases mechanical strain at the carotid sinus by changing the geometric shape of the arterial wall while preserving arterial pulsatility (figure 2). Augmentation of baroreceptor firing and, as in electrical baroreceptor stimulation, inhibition of central sympathetic outflow

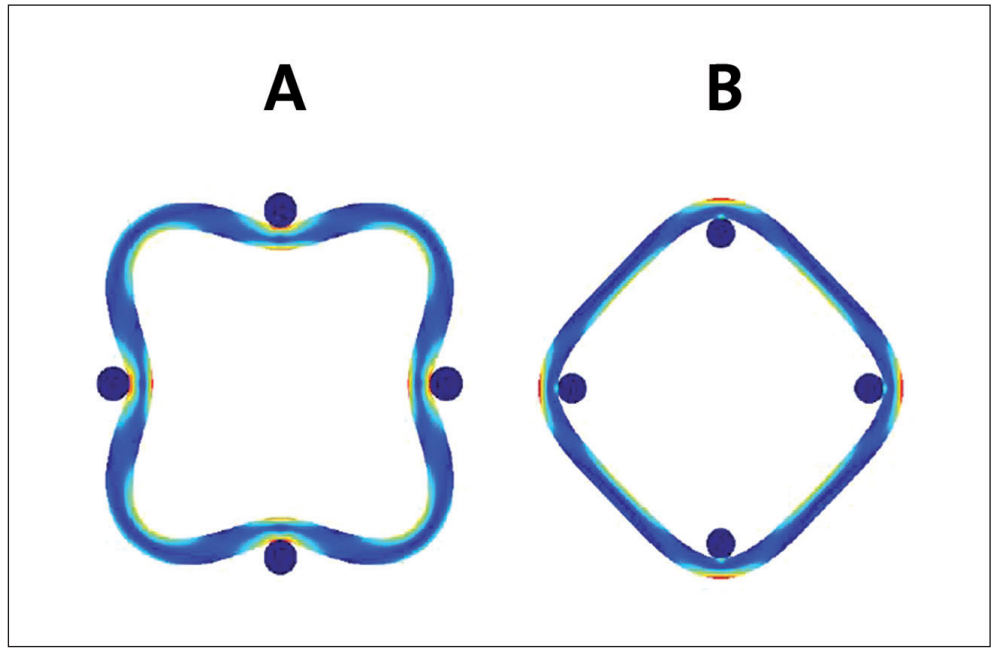

Figure 2. Schematic drawing showing the working mechanism of mechanical carotid baroreceptor stimulation.
Strain in the arterial wall of the carotid sinus is increased by changing its geometrical shape by a) an extravascular device or b) an intratravascular device.

causes subsequent blood pressure reduction. In view of minimally invasive endovascular procedures, an intravascular stent-like nitinol device (Mobius, Vascular Dynamics, Israel) has been developed which meets the requirements to reduce blood pressure by means of mechanical carotid baroreceptor stimulation. Proof of concept and safety studies are underway for both devices.

Resistant hypertension treatment may be boosted by the recent advent of these exciting new invasive and minimally invasive procedures modulating the autonomic nervous system. These novel interventions may prove a valuable adjunct to medication in lowering blood pressure and may result in a substantial reduction of life-long antihypertensive drugs. As carotid baroreceptor stimulation and renal sympathetic denervation act on different levels of the autonomic nervous system, a combination of these approaches may hypothetically act synergistically. However, long term studies with sufficient power are required to evaluate efficacy, durability and safety of these interventional techniques in the treatment of resistant hypertension and its cardiovascular adverse sequels.

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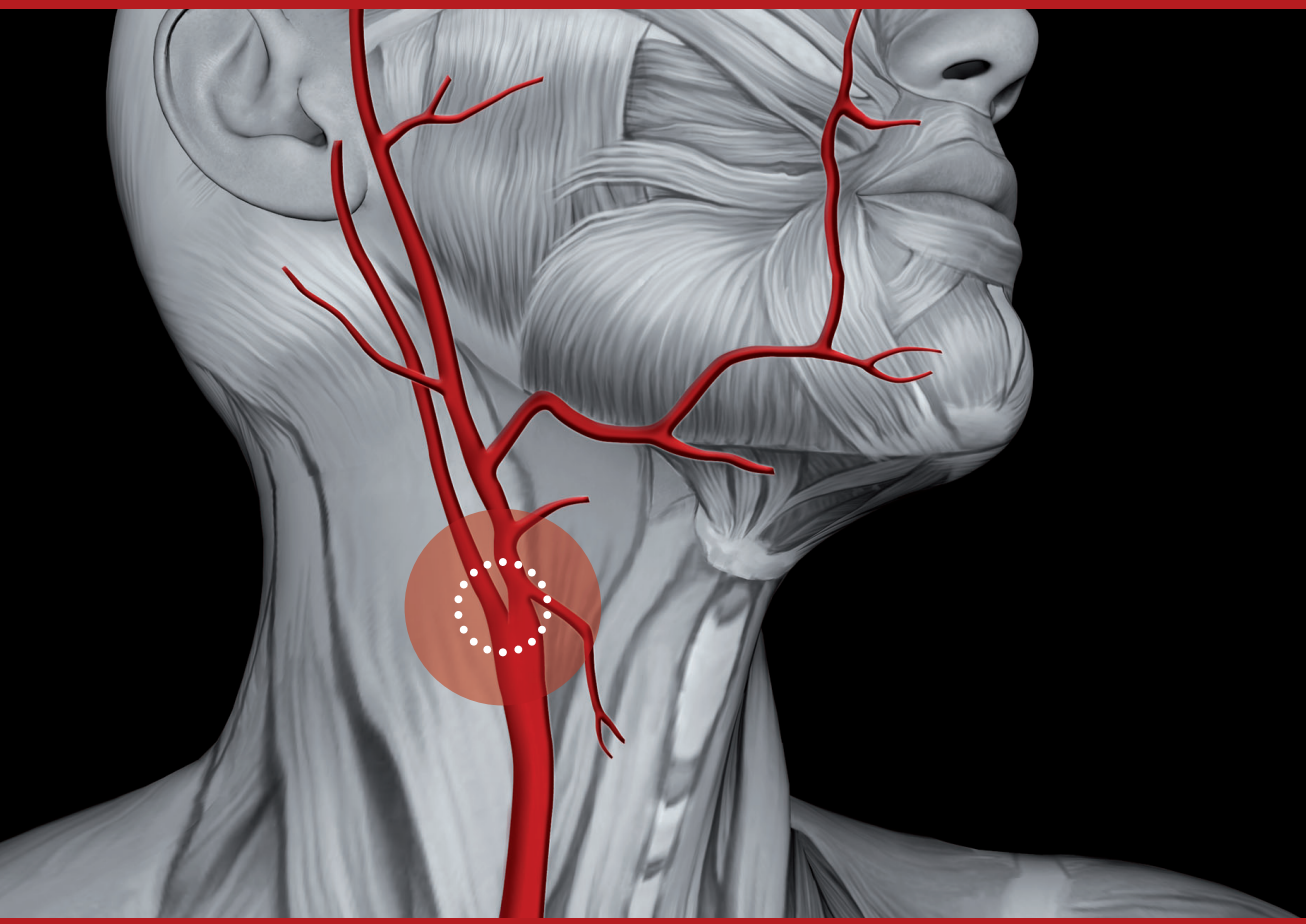

CHAPTER 10

Mechanical stimulation of the carotid sinus baroreflex by an implantable device: first experience in man

Toorop RJ, Krievins DK, de Borst GJ, Moll FL

Submitted

ABSTRACT

Aim

The carotid baroreflex plays a dominant role in blood pressure control by altering the sympathetic nervous system activity. This study investigates the acute effect of mechanical stimulation of the human carotid sinus by a novel implantable device.

Methods

Device placement was tested on 4 carotids in 2 freshly frozen human cadaveric heads. Both common carotid arteries were connected to a pump (Watson Marlow 313S) in order to create pulsatile arterial pressure. Next, 5 patients undergoing elective carotid surgery were studied. After carotid endarterectomy the device was placed on the carotid sinus for 15 minutes.

Results

Visible compression of the carotid sinus was obtained by using a device diameter that was 2 mm smaller than the proximal internal carotid artery diameter. The device could easily be placed without causing evident damage to the arterial wall. A good anchoring of the device was observed without any slippage. Baseline BP of studied patients was 134/57±14/10 mmHg. Reduction in SBP after device placement in patients who did not receive atropine was 22±14mmHg, and on DBP 8±5mmHg. No visible damage to local tissue, arterial wall or carotid patch was observed after device removal. Device placement was not associated with intraoperative or postoperative complications.

Conclusion

This study may present proof of concept for mechanical activation of the human carotid baroreflex using a passive implantable device that is placed on the carotid sinus. The clinical development of such a system, if proven safe and effective on the long term, could be a viable approach to the management of hypertension.

INTRODUCTION

The pivotal role of the autonomic nervous system in the pathogenesis of hypertension is well established. However, pharmacological therapies that block sympathetic activity have not achieved the desired outcomes.[1,2] The past few years witnessed various attempts to modulate the sympathetic nervous system activity. These included catheter based renal sympathetic denervation and continuous electrical baroreceptor pacing.[3,4]

Recently a canine study was performed to test the feasibility of a novel concept in modulation of sympathetic nervous system activity. By applying mechanical forces to the arterial wall at the proximal internal carotid artery, the geometrical shape of the carotid sinus wall is changed, resulting in a greater strain at the baroreceptor area. This strain triggers baroreceptor firing and reduces sympathetic nervous system activity. Mechanical forces that were applied to both carotid sinuses by bilateral placement of an implantable device in an acute setting, elicited an impressive acute blood pressure reduction in dogs of 26.8±7.6 mmHg (unpublished data).

The aim of the present study is to prove the feasibility of this concept of mechanical stimulation of the carotid baroreflex by an implantable device in humans. For this purpose, first we performed an experimental study in a human cadaveric test model a) to determine the extent of carotid dissection needed for device placement, b) to test the technique of device placement and c) to test adequacy of device design to the human carotid sinus. Secondly, we performed an acute first in man study in patients undergoing carotid endarterectomy (CEA) to test the effect of device placement on blood pressure and heart rate.

METHODS

1. Human cadaver study

Setting

The human cadaver study was performed at the department of Anatomy of the University Medical Center, Utrecht, the Netherlands in June 2010.

Cadavers

Two thawed freshly frozen cadaveric heads of 72 year old males were used. Each head was separately secured on a stand placed in a basin. Both common carotid arteries were connected to a pump (Watson Marlow 313S) in order to create pulsatile arterial pressure.

Dissection

The dissection of the carotid bifurcation was performed in the usual manner as for carotid endarterectomy using a 6-7 cm skin incision parallel to the anterior border of the sternocleidomastoid muscle and then continued as necessary for device placement.

Device placement

The main feature of the stainless steel device is a design based on 4 rods, parallel to the artery. The rods are connected, forming an open C shaped cylinder which encircles the artery, while leaving one side open (figure 1). The 4 rods apply mechanical forces to the arterial wall at the carotid sinus, thus changing its geometric shape, while preserving the arterial pulsatility (figure 2).

Before placement of the device, arterial dimensions of the common carotid (CCA), external carotid (ECA) and internal carotid arteries (ICA) were measured using a caliper. The device, which is made of stainless steel, is available in 3 diameters: 6 mm, 8 mm and 10 mm. The devices were consecutively, and in order of decreasing diameter, placed on each of the four proximal internal carotid arteries. Devices were left in place for 10 minutes.

2. Clinical study

Setting

The study was performed in the Paul Stradins Clinical University Hospital, Riga, Latvia

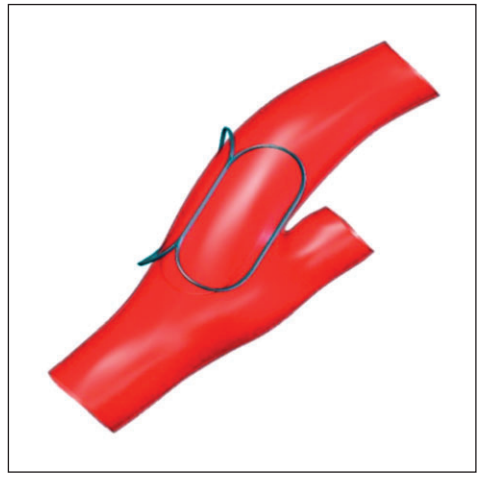

Figure 1. The implantable device.

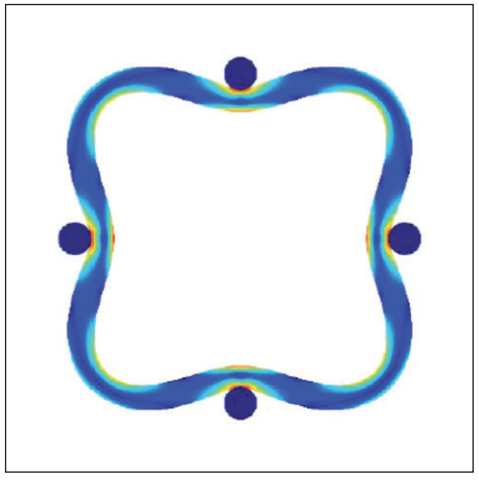

Figure 2. Schematic drawing showing the working mechanism of mechanical baroreceptor stimulation by the implantable device.

in September 2010. The study was approved by the ethical review committee of the Pauls Stradins Clinical University Hospital, Riga, Latvia and by the Latvian state agency of medicines. Written informed consent was obtained from all patients.

Patients

Patients were eligible if they were scheduled for an elective CEA operation. Exclusion criteria were: requirement of an eversion endarterectomy, prior carotid surgery, neck irradiation or endovascular stent placement in either carotid sinus, known or suspected baroreceptor failure, contralateral carotid disease with stenosis >70%, AV block and severe chronic kidney disease.

Operative procedure

Patients were intubated and maintained on total intravenous anesthesia using Remifentanil and Propofol. Blood pressure (BP) was measured via an intra-arterial catheter placed in the radial artery. Heart rate (HR) was measured continuously using a surface ECG. Recording of patients' BP and HR was performed using a VitaLogic 4500 patient monitoring system (Mennen Medical, Yavne, Israel) at a sampling rate of 640Hz. The carotid bifurcation was exposed through a 6-7 cm skin incision parallel to the anterior border of the sternocleidomastoid muscle. The carotid artery bifurcation was then dissected free of surrounding tissues. However dissection within the bifurcation was avoided to minimize risk of injury to the carotid sinus nerve. The clamping place on the internal carotid artery (ICA) was circumferentially dissected. After administration of systemic heparin (110 IU/kg body weight) a standard CEA was performed. A Gore Acuseal Cardiovascular Patch (W.L. Gore & Associates, Inc., Arizona, USA) was used for closure, if deemed necessary by the surgeon. Following this procedure, patients underwent placement of the implantable device on the carotid sinus after intraoperative measurement of the diameter of the endarterectomized ICA. The device was kept in place for a time period of approximately 15 minutes, while BP and HR were recorded.

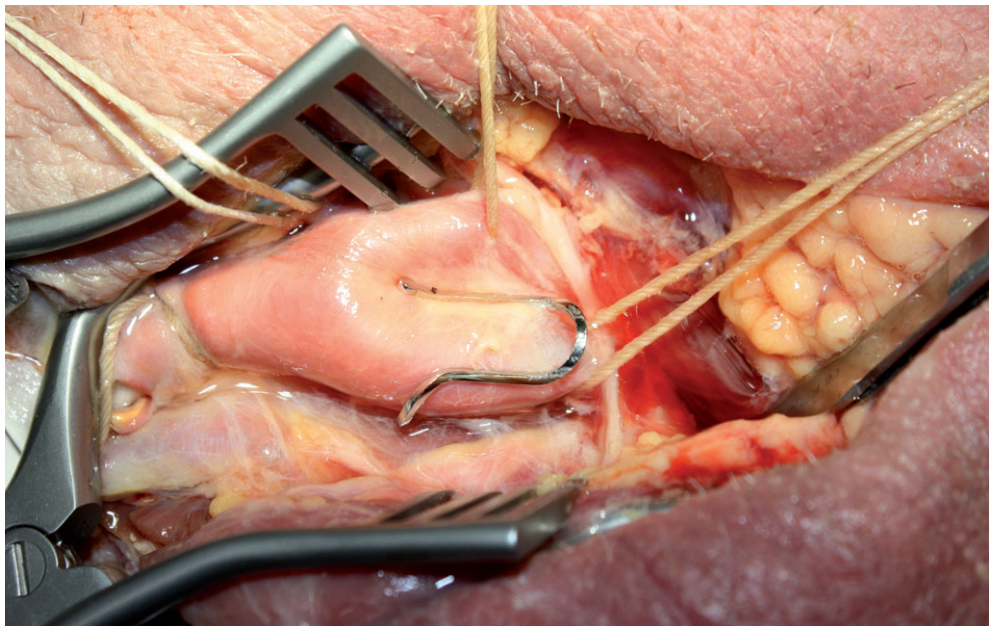

Figure 3. Overview of device placement in a left cadaver carotid bifurcation.
Adquate device placement is allowed by dissecting the internal carotid artery 270 degrees around its circumference, leaving the side opposite to the external carotid artery intact.

Postoperative follow up

No additional postoperative care was required as a result of this protocol, beyond that routinely provided for patients undergoing elective carotid artery surgery.

Data analysis

Baseline values of SBP, DBP and HR were calculated as the mean of values during the two minutes prior to device placement. Post placement values were calculated as the mean of values starting one minute after device placement until one minute after device removal. The effect was calculated as the difference between baseline and post placement values.

RESULTS

1. Human cadaver study

The internal carotid artery was dissected free from its surroundings over 270 degrees around its circumference, leaving the side opposite to the external carotid artery (bifurcation) intact to spare the carotid sinus nerve and its afferents.[5] In all dissections this provided enough room to place the device and no further dissection was necessary.

The technique most suitable for device placement was found to slide the device from the bifurcation upwards while holding the device at its upper arch with a Mosquito clamp. In this way the device could easily be placed without causing evident damage to the arterial wall.

The diameter of the ICA was 10 mm in the first cadaver and 8 mm in the second cadaver. It was experienced that placing a device which was 2 mm smaller in diameter, 8 mm and 6 mm respectively in our cadaver models, provided a macroscopic visible compression to the arterial wall. During 10 minutes of placement, a good anchoring of the device on the pulsating proximal ICA (carotid sinus) was observed without any slippage (figure 3).

The abovementioned findings for dissection and placement techniques as well as the choice of device diameter were implemented during placement of the device in the clinical study.

2. Clinical study
Five patients undergoing elective carotid surgery for obstructive carotid artery disease were enrolled in this feasibility study. Patient characteristics are summarized in table 1. All patients were hypertensive and were receiving pharmacological treatment (table 2).

During CEA a shunt was used in one patient. Clamping time was 27±15 minutes. In patients no. 1 and 2 atropine was administered because of bradycardia during endarterectomy. As atropine is known to attenuate the baroreflex, the next three patients received a continuous drip of low dose ephedrine which prevented bradycardia, so that atropine was not required.

Mean preoperative BP was 145/82±18/5 mmHg and mean baseline BP at the time of device placement was 134/57±14/10 mmHg. The effect of device placement in each patient is shown in table 3. The SBP lowering effect ranged from -35 mmHg to almost no effect in one patient who received atropine. The mean effect on SBP among patients who did not receive atropine was -22±14mmHg, and on DBP -8±5mmHg. The effect on HR was negligible (figure 6). Figure 7 shows an example of the effect of device placement (patient 4).

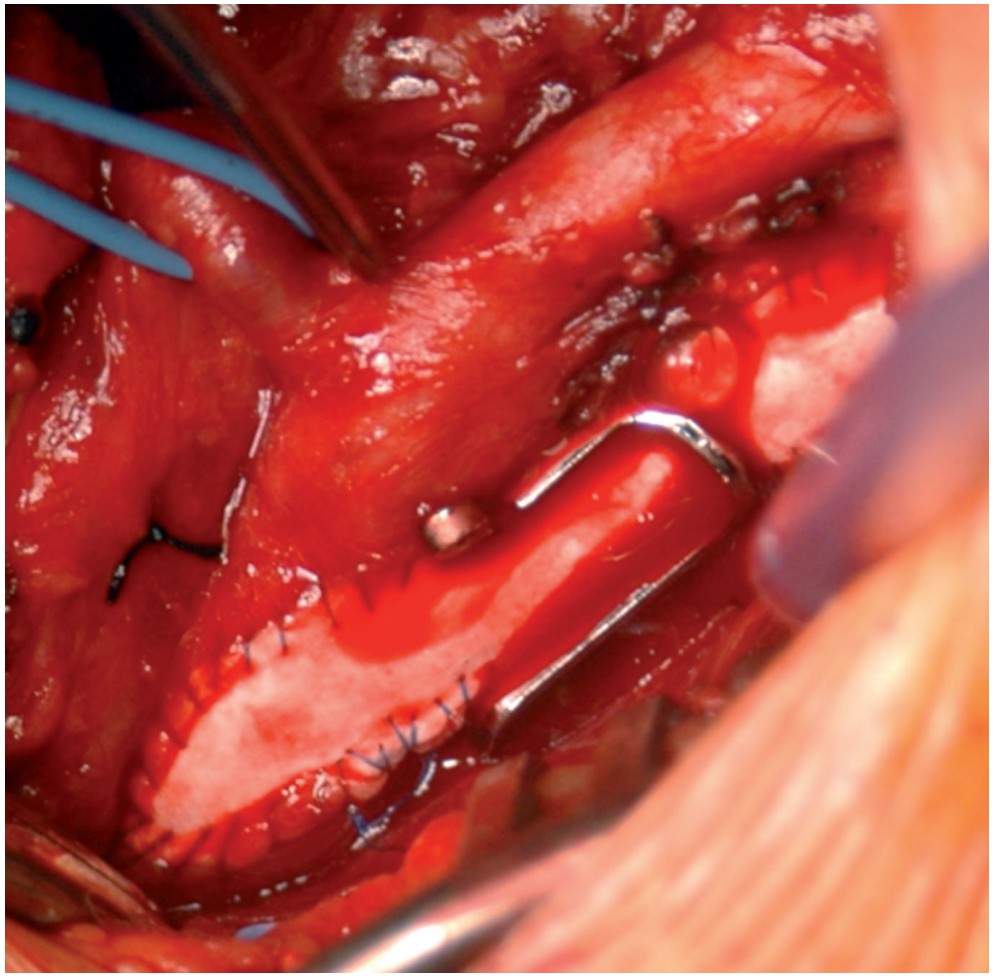

Figure 4. Implantable device placed on a right internal carotid artery after CEA and patch closure.

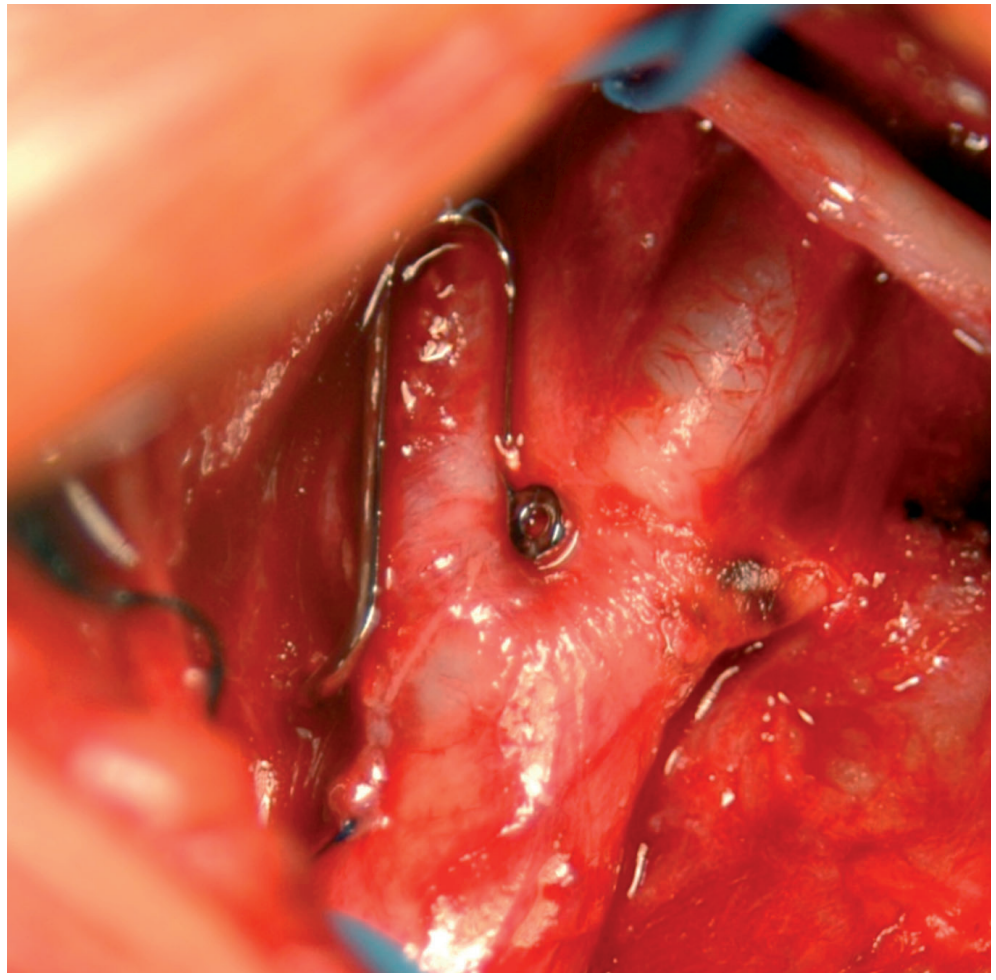

Figure 5. Implantable device placed on a left internal carotid artery after CEA and primary closure.

Age (years)	72±4
Gender (female)	3 (60%)
Hypertension	5 (100%)
DM type II	1 (20%)
Preoperative BP (mmHg)	145/82±18/5
Preoperative HR (bpm)	66±13
Baseline BP (mmHg)	134/57±14/10
Baseline HR (bpm)	66±10

Table 1. ***Patient characteristics.***
Data are mean±SD and number (%). DM=diabetes mellitus, BP=blood pressure, HR=heart rate.

Patient 1	Amlodipine 5 mg	1dd1
	Quinapril HCl/ hydrochlorothiazide 20/12.5 mg	1dd1
Patient 2	Lercanidipine HCl 10 mg	1dd1
	Perindopril 10 mg	1dd1
	Clonidine HCl 0.15 mg	1dd1
Patient 3	Perindopril 10 mg	1dd1
	Amlodipine 5 mg	1dd1
Patient 4	Ramipril/ hydrochlorothiazide 5 mg	1dd1
Patient 5	Enalapril 20 mg	1dd1

Table 2. ***Antihypertensive medication in studied patients.***

Patient	ΔSBP	ΔDBP	ΔHR
1*	-11	-4	-1
2*	-1	0	-4
3	-35	-13	-2
4	-23	-6	-2
5	-8	-3	-1

Table 3. ***Effect of device placement on blood pressure and heart rate.***
Δ=baseline value minus value after placement, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, *received atropine.

Device placement was not associated with intraoperative complications in any of the patients. There were no cranial nerve injuries, perioperative stroke or myocardial infarctions, wound healing complications or deaths.

The device's technical performance characteristics were excellent, placement and removal were easy and the device was well anchored to the ICA with a good anatomical fit. Additionally, no visible damage to local tissue, arterial wall or carotid patch was observed.

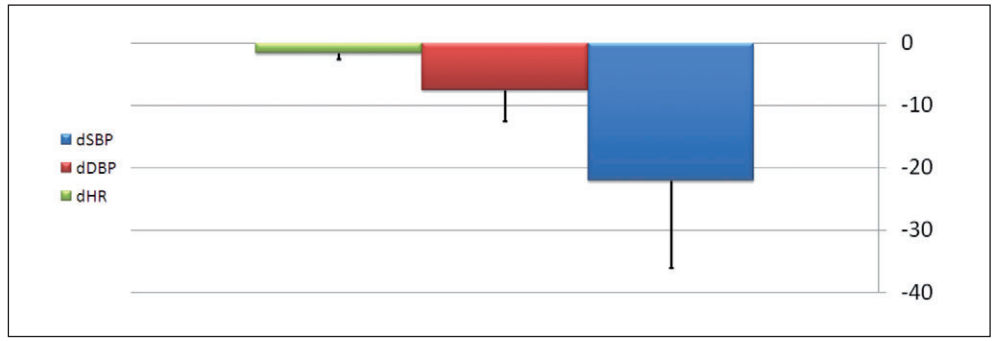

Figure 6. ***Mean effects on blood pressure and heart rate in patients who were not given atropine.***
SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate

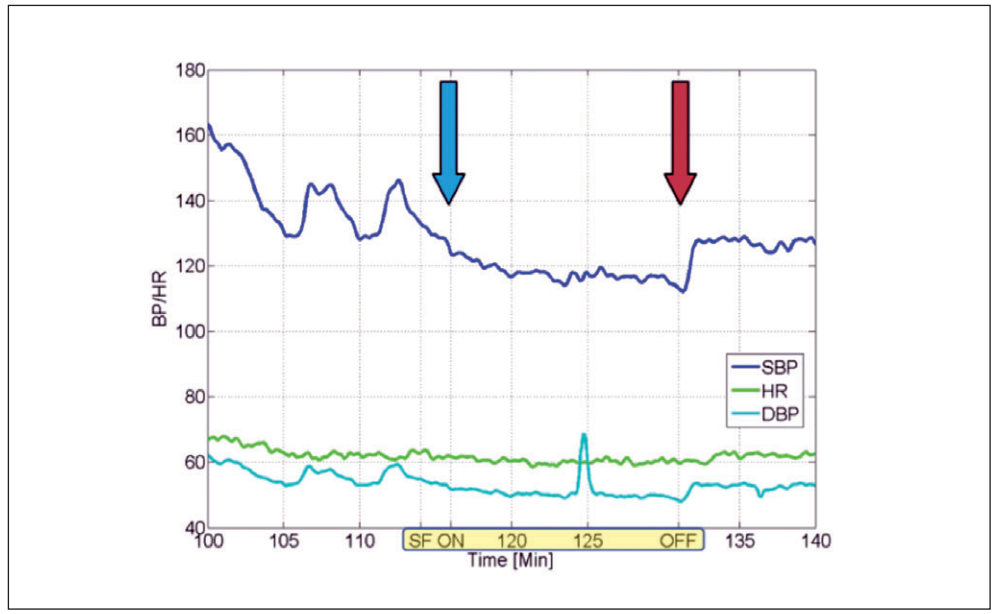

Figure 7. ***Effect of device placement on blood pressure and heart rate in patient 4.***
SF=beginning of device placement, ON=device in place, OFF=device removed, BP=blood pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate.

DISCUSSION

Our study results represent the first acute assessment of this new concept of mechanical baroreflex stimulation in humans. By testing placement of the device in a human cadaver model first, we optimized the surgical technique and safety before starting the clinical study. Visible compression of the carotid sinus was obtained by using a device diameter that was 2 mm smaller than the proximal internal carotid artery diameter. The fact that we observed reductions in blood pressure indicates that by this passive mechanical stimulation we have activated the baroreflex in a manner that simulates the response to an increase in BP. The safety of device placement was demonstrated as no immediate or late complications resulted from the procedure.

Device placement caused significant BP reduction in four out of five patients. In the first two patients the BP changes were less pronounced, probably because they received atropine due to a bradycardia resulting from manipulation of the carotid sinus during carotid endarterectomy. Unfortunately, atropine is known to attenuate the baroreceptor reflex.[6,7] We consequently began using an ephedrine drip in an attempt to maintain a heart rate that will not require atropine administration.[8] This approach proved useful and allowed a stable cardiovascular state in patient no 3 and 4 without change of medications. Despite this, patient no 5 was very unstable, precluding a clear determination of a net effect.

The reduction in BP of 35/13 mmHg in patient 3 is impressive especially when considering a few important factors. First the device was placed unilaterally. It is well known that bilateral activation is much more effective than a unilateral stimulation. This has been demonstrated by electrical carotid stimulation studies[9] as well as in preclinical mechanical stimulation studies in dogs (unpublished data). The non activated contralateral carotid sinus may counteract the effect of the stimulated side, so that a bilateral response is often much greater than a unilateral response.

Second, the device was tested after endarterectomy which is known to reduce the responsiveness of baroreceptors. Schmidli and colleagues tested electrical stimulation of the carotid sinus in patients undergoing elective carotid surgery before the endarterectomy by placing electrodes on the carotid.[10] We chose to alter this sequence in order to minimize the risk of cerebral thrombo-embolism during the procedure. However, during endarterectomy the clamping place on the internal carotid artery is circumferentially freed from surrounding tissue, and although a strong effort is made to avoid this, damage can occur to baro-afferents and the carotid sinus nerve, resulting in an impairment of baroreflex function.[11] Moreover, declamping the carotid after a long period of clamping probably oversaturates the baroreceptors leaving very little range for an increase in their activity.[12,13] We believe therefore, that the same device placed on an unstenosed artery that was not endarterectomized would yield a much greater response.

Third, the study was performed under general anesthesia. Inhaled anesthetics are well known to attenuate the baroreflex and were therefore avoided in our study.[14,15] It has been demonstrated both in CEA studies and in electrical baroreflex stimulation studies that local anesthesia is better than general anesthesia for demonstrating effects on the baroreflex.[10,14] However, local anesthesia was not an option for this type of operation according to the policy of the center where the study was conducted. Instead, total intravenous anesthesia based on Remifentanil and Propofol was used. These drugs have also been shown to attenuate the baroreflex, but to a lesser extent.[15] Thus, we expect the device to be more effective when placed in a conscious, non sedated patient.

Finally, another factor that probably interfered with the BP lowering effect was a low mean baseline blood pressure of 134/57± 14/10 mmHg, leaving little room for large blood pressure effects.

In the present study the effect on HR was negligible. This may be the result of atropine and ephedrine administration during the procedure. This is in accordance with a previous study demonstrating the effects of electrical baroreceptor stimulation in humans. In this study unilateral carotid sinus stimulation elicited a smaller maximal reduction in HR using general anesthesia versus local anesthesia (3.75±3.4 bpm vs 20.9±15.6 bpm).[10]

This study suffers from several limitations. The small sample size did not allow to test the variability in response of individual patients. Second, the study setting and strict time frames in the protocol did not easily allow for a stable cardiovascular system during device placement. Therefore, future study designs should address these drawbacks and allow for an optimal anesthetic protocol, device testing in an unoperated carotid sinus and bilateral placement of the device. Furthermore, long term data on safety and efficacy are necessary.

In summary, our results indicate that mechanical forces applied to the carotid sinus in patients undergoing carotid endarterectomy activate the carotid baroreflex and reduces blood pressure in an acute setting. This response may be considered proof of concept for mechanical activation of the human baroreflex using a passive implantable devices that is placed on the carotid sinus. The clinical development of such a system, if proven safe and chronically effective, could be a viable approach to the management of hypertension.

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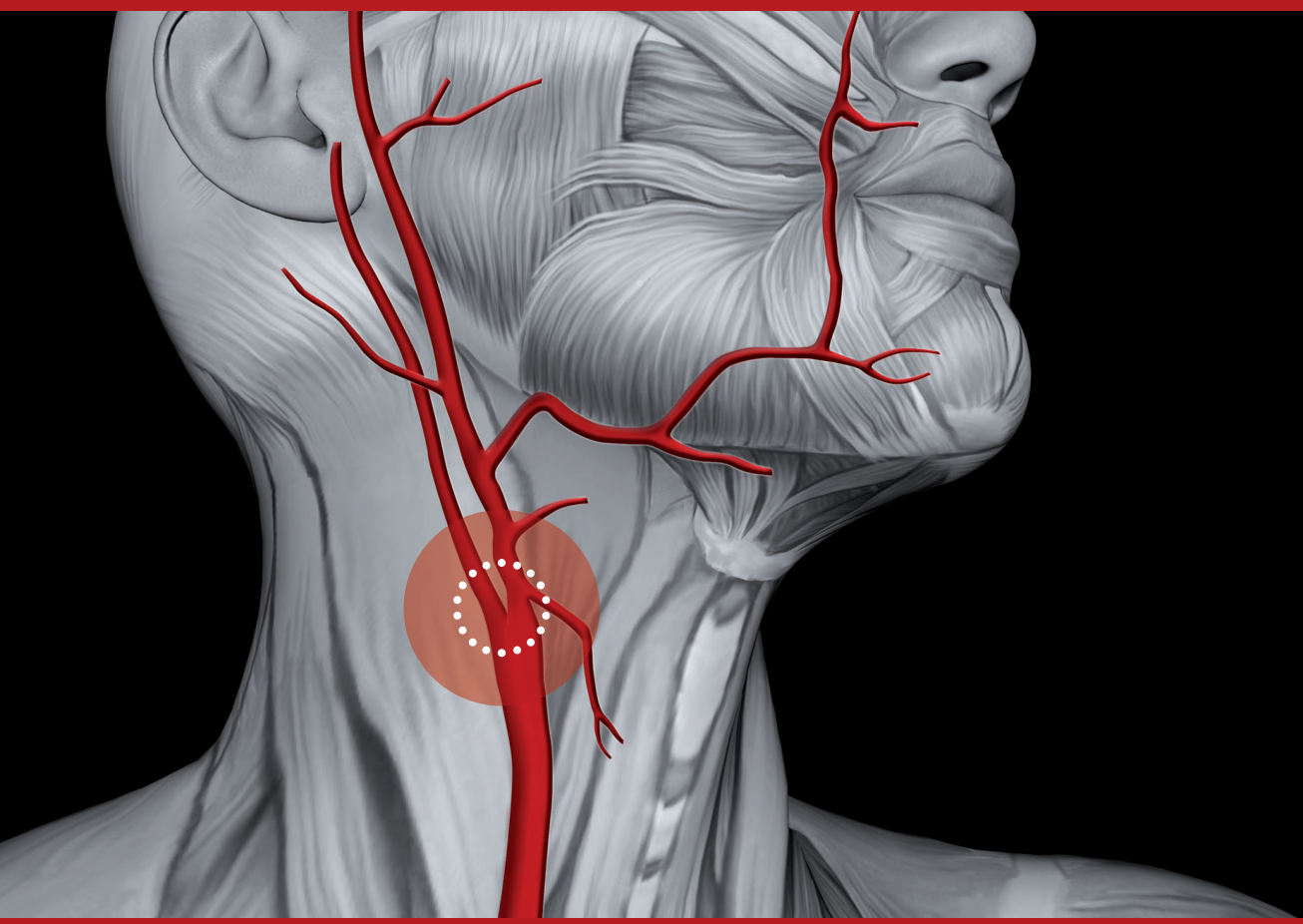

CHAPTER 11

Summarizing discussion, conclusions and future perspectives

SUMMARIZING DISCUSSION

1. Carotid sinus syndrome (CSS)

a. Some general issues

Carotid sinus syndrome (CSS) is an ill recognized cause of recurrent unexplained dizziness and syncope in older persons. The diagnosis is therefore challenging and a high dose of clinical suspicion is usually required to determine the diagnosis with certainty.[1] Its clinical presentation is sometimes typical characterized by a clear association between mechanical manipulation of the carotid sinus (mostly head movements or extrinsic compression) and the onset of syncope. On the other hand, recurrent unexplained syncope lacking a specific trigger may be the only manifestation of CSS **(chapter 2)**. Occasionally an aberrant clinical presentation including intermittent gagging and vomiting is present **(chapter 3)**.

As CSS is thought to be due to an inappropriate 'overshoot' of the carotid baroreflex, carotid sinus hypersensitivity (CSH) documented by carotid sinus massage (CSM) may be the only finding indicating the possibility of CSS as the cause of syncope. Therefore, CSM in both supine and 60 degrees head up tilt position is recommended in older patients with recurrent unexplained syncope and a negative diagnostic work-up.[2] CSH is defined by the European Society of Cardiology (ESC) as either an asystole >3 sec (cardioinhibitory type) or a reduction in blood pressure greater than 50 mmHg (vasodepressor type) in response to 5-10 seconds of CSM. The mixed type of CSH is characterized by both aspects.[3] **Chapter 4** reports on a review including a diagnostic evaluation of CSS patients reported in the literature. CSS originates twice as often from the right carotid system. This finding is in line with previous studies which demonstrated a more prevalent cardioinhibitory response on the right carotid sinus.[4,5] A predominantly right-sided vagal input to the SA node may be an explanation for this phenomenon.[6] Studying characteristics of patients that were reported in the (somewhat dated) literature demonstrated that almost half had cardioinhibitory CSS. However, this may be an overestimation as the vasodepressor portion of the response was not always tested, for instance by intravenous administration of atropine or temporary cardiac pacing.[7,8] More recent studies suggest the following relative prevalences: cardioinhibitory 18-24%, vasodepressor 19-29% and mixed 52-57%.[9] These data indicate that any diagnostic protocol should be standardized and should include the administration of atropine or pacing during CSM to identify patients who have a significant vasodepressor response.

Carotid sinus syndrome was previously assumed to be rare. The average age of patients was thought to range from 61 to 74 years.[5,10] Risk factors include male gender, diabetes and coronary/carotid atherosclerosis.[11,12] The incidence has been estimated anywhere

between 35-40 patients/million persons/year.[13,14] Probably in concert with the introduction of specialized syncope units, this condition is now being diagnosed with increasing frequency. Recent reports demonstrate a pathological response after CSM in 14%-54% of individuals investigated for syncope.[15-17] Elderly individuals diagnosed with CSS sustain high injury and fracture rates of 25% and 47%, respectively.[5,18] In our patient series this rate was 11%, a relatively low percentage that is most probably due to the retrospective character of the analysis **(chapter 7)**. The prognosis of CSS is determined by the onset of recurrent symptoms. As patients with vasodepressor CCS have a threefold increased incidence of recurrence compared to other CSS forms, this subtype requires a more agressive treatment regimen aimed at avoiding syncope and associated injury.[19]

Several treatment modalities have been proposed for CSS including avoidance of head movements and tight neckwear.[20] Irradiation was also suggested but ironically appeared to elicit CSS by itself.[21] There is no compelling evidence for the effectiveness of medical therapy such as anticholinergics (maintains heart rate), fludrocortisone, ergotamine or ephedrine (increases blood pressure).[22-25] These studies are limited because of their small size, non-randomized character as well as diverse and subjective outcomes. Permanent pacemaker implantation is recommended for pure or predominant cardioinhibitory types of CSS.[3] A 2011 retrospective analysis of 138 patients with pacemakers showed a 38% recurrence rate in patients with a mixed type CSS compared to 13% in the cardioinhibitory group. It was concluded that symptom recurrence was two to threefold more frequent in patients with mixed CSS as their vasodepressor component was left 'untreated'.[26] In 2009 and 2010 the first two randomized, double-blind controlled trials were published showing the results of pacing in a CSS patient group. Surprisingly, even in cardioinhibitory CSS patients, no benefit of pacing on number of syncope and falls was demonstrated.[27,28] The available literature thus clearly questions the effectiveness of pacing in a CSS patient, especially when a vasodepressor component is present. These dismal efficacy data illustrate the need of a search for alternative treatment options.

b. Aspects of surgical management of CSS

Several operation techniques for carotid sinus syndrome have been proposed. The rationale behind these procedures is an interruption of the afferent portion of the pathological carotid baroreflex at various anatomical levels. Transection of the glossopharyngeal nerve was first described in 1933.[29] This procedure requires a suboccipital craniotomy to interrupt all of the glossopharyngeal afferent fibers running towards the brain stem. Complications such as dysphagia, hypalgesia, loss of taste sensation and diminished gagging reflex have been described.[30,31] Glossopharyngeal nerve transection has largely been abandoned because of its invasiveness and morbidity. However, this procedure can be considered as an 'ultimate refugium' in patients with a hostile neck following irradiation and inoperable neck masses who do not respond to pacemaker therapy.[32]

Transection of the carotid sinus nerve (CSN, Hering's nerve) has also been proposed as a treatment option. This appoach is less invasive compared to glossopharyngeal nerve transection as the CSN can be localized via a neck incision.[33-35] Effective surgery requires transection of its main trunk and important side branches. Moreover, interconnections should also be identified as the carotid sinus must ideally be completely denervated. **Chapter 5** describes an anatomical study of the CSN in human cadaver heads. Using a unique combination of nerve staining techniques and microdissection, a great variability in CSN position, side branches and interconnections to the vagus nerve and cervical sympathetic chain were demonstrated. It may be concluded from this micro-anatomical standpoint that CSN transection as a single treatment option for patients with CSS may be insufficient in most patients. An addional disadvantage of this procedure is the collateral damage to the innervation of the carotid body with unstudied consequences.

The surgical technique most frequently used in CSS patients probably is carotid denervation by adventitial stripping of the carotid sinus.[36] This procedure is based on removal of all nervous tissue that is in close contact to the carotid sinus. By doing so, carotid baroreceptor afferents are most likely removed. In **chapter 4** a review of the literature on this operation identified a great diversity in techniques with reference to extent of length and circumference of adventitial stripping. Some authors limited stripping to the internal carotid artery (ICA) [37,38] whereas others also treated the common carotid artery (CCA) and external carotid artery (ECA).[36,39] In some patients stripping was combined with a glomectomy[40] or CSN transection[41]. This diversity in operation technique merely reflects a lack of knowledge on location and distribution of baroreceptors in the carotid bifurcation.

In **chapter 6** immunohistochemical staining techniques are used to microscopically visualize baroreceptors and to investigate baroreceptor distribution. Results of visual assessment indicate that carotid baroreceptors were mainly localized in the proximal portion of the medial ICA. No staining of baroreceptors was observed in the CCA and ECA. These data strongly suggest that adventitial stripping of the proximal portion of the ICA may suffice in patients with CSS.

c. Efficacy of carotid sinus denervation

A review covering the literature on carotid denervation for CSS demonstrated complete symptom relief in 73% and a substantial improvement in an additional 12% of operated patients (n=110), respectively **(chapter 4)**. Between 1980 and 2007, 27 patients suffering from CSS underwent adventitial stripping of a 3 cm proximal portion of the ICA in a single center (Maxima Medical Center, Veldhoven, the Netherlands). **Chapter 7** reports on the short term clinical results of this patient cohort. At the 30-day follow up point, 25 of 27 patients (93%) were free of syncope, and 24 free of a pacemaker (89%). Two

patients did not respond to surgery whereas CSM still elicited syncopal symptoms. These two subsequently received a pacemaker but also did not attain freedom of symptoms. A third patient had residual disease immediately after the operation whereas repeat CSM still evoked an asystole and symptoms. A re-denervation rendered him free of syncope. Although these short term results may seem excellent, some suggest that symptoms recur as carotid sinus afferents may potentially regenerate.[42] Autonomic reinnervation of the carotid baroreflex after denervation has been found in several animal studies.[43,44] A long term follow up study was therefore initiated aimed at studying the onset of recurrent disease. **Chapter 8** focuses on the long term follow up in our 27 CSS patients. After a more than 7 year time period after the operation, 85% (22/26) of patients was still asymptomatic and 81% (21/26) free of a pacemaker. One patient was lost to follow up. Two patients still demonstrated residual disease even after successful pacemaker implantation. A third female patient had received a pacemaker for an AV-block 6 years after an initially successful surgical denervation but still experienced symptoms of syncope. CSM prior to pacing did not demonstrate a hypersensitive carotid sinus. A fourth patient still reported symptoms of dizziness although three times less frequent compared to preoperatively. Repeat CSM could neither elicit symptoms nor demonstrate CSH. In summary, not a single patient became symptomatic due to recurrent CSS after an initially successful denervation. It is concluded that there is no clinical or physiological evidence for the phenomenon of autonomic reinnervation after successful carotid denervation in humans.

d. Safety of carotid sinus denervation

Beneficial effects of surgery must be balanced against its side effects. Immediate complications after carotid denervation in our study population included wound hematoma (15%) and transient cranial nerve injury (7%). Eleven percent of our patients developed atrial fibrillation or sinus tachycardia within 48 hours of surgery mandating medication or cardioversion with good results **(chapter 7)**. Severe adverse events after adventitial stripping such as CVA, TIA and death have been reported in case reports published between 1939-1979.[36,40,45] In our series one patient developed a CVA 24 days after a bilateral carotid denervation, probably on the basis of a low flow state in the presence of bilateral diseased carotid arteries. Carotid ultrasonography in our 7 patients undergoing a set of follow up studies almost 10 years after operation demonstrated no carotid stenosis or carotid aneurysm **(chapter 8)**. These data demonstrate that surgical denervation by adventitial stripping is not a risk factor for the onset of stenotic or aneurysmatic carotid disease on the long term.

Surgical therapy of CSS is generally regarded with caution as alterations of blood pressure (BP) after uni- and bilateral denervation of the carotid sinus are feared. In animals, extra-carotid baroreceptors have a large ability to compensate for the loss of carotid baroreceptors. After carotid denervation, BP level and variability in animal models

increased but returned to normal levels after 14 days.[46,47] A transient increase in BP after carotid denervation was also observed in 2 of our 27 patients, but levels returned to normal after one month **(chapter 7)**. Chronic hypertension did not occur in animal models.[48,49] Information on impact of carotid sinus denervation on long term BP regulation in humans is limited and is based on investigations following iatrogenic damage to the carotid sinus. One human study showed that bilateral carotid denervation following bilateral carotid body tumor resection did not elicit chronic hypertension but did cause a long term increase of BP variability. These patients also responded with pronounced elevations of BP after mental stress.[50] Other studies found that true labile hypertension due to baroreflex failure syndrome may arise from both uni- or bilateral carotid denervation.[51,52] In contrast to data obtained after iatrogenic damage of the carotid sinus, the present thesis reports on data obtained from patients who underwent an intentional unilateral or bilateral carotid denervation. In line with iatrogenically denervated patients, no increase in BP was documented after a mean follow up period of almost 10 years. Antihypertensive medication was unaltered in previously hypertensive patients. Mental stress in the present study group had a clear influence on BP readings as office BP at follow up was substantially higher than ambulatory BP (SBP: 143±17mmHg vs 128±10 mmHg, n.s., DBP: 86±6 mmHg vs 79±6 mmHg, $p<0.05$). In contrast to prior human denervation studies, BP variability in our patient population was similar compared to a control group whereas none of the patients demonstrated symptoms of baroreflex failure **(chapter 8)**. These data support the view that human cardiopulmonary baroreceptors can compensate for the loss in baroreceptor function after bilateral denervation without clinically significant side-effects. After unilateral denervation, the contralateral carotid baroreceptors probably play a prominent role in this compensatory mechanism.

2. Carotid sinus stimulation for treatment of hypertension

As carotid denervation can be used as a treatment option for profound hypotension associated with CSS, stimulation of the carotid sinus may also offer a new therapeutic strategy in patients suffering from drug resistant hypertension. In **Chapter 9** the rationale of novel interventions in hypertension treatment is discussed, including renal sympathetic denervation and electrical carotid baroreceptor stimulation. The latter invasive procedure has the disadvantage of subcutaneously implanting a pulse generator that is susceptible to infection and maintenance.[53] In **chapter 10** the first assessment of mechanical baroreflex stimulation by a simple implantable device is described in humans undergoing carotid endarterectomy. Surgical technique and safety of device placement were optimized prior to the clinical study by first testing the device in a human cadaver model. It was demonstrated that placement and removal of the device were easy, whereas the anatomical fit to the carotid sinus was good. Moreover, no

damage to local tissue or arterial wall was observed. The mean reduction in human systolic and diastolic blood pressure was 22±14 mmHg and 8±5 mmHg, respectively. Although only acute effects on blood pressure were tested, we postulate that mechanical stimulation may also prove useful as a treatment strategy for long term hypertension.

CONCLUSIONS

1. Several adventitial stripping techniques are used for treatment of carotid sinus syndrome (CSS). Substantial or complete relief of symptoms was achieved in 85% of the patients reported in the literature.
2. Carotid sinus nerve (CSN) anatomy is characterized by a great variability in position, side branches, interconnections to the vagus nerve and cervical sympathetic chain. Therefore, CSN transection as a single treatment for patients with CSS may be insufficient.
3. Baroreceptor density is highest in the first cm portion of the medial internal carotid artery (ICA). Therefore, adventitial stripping of the proximal ICA is sufficient for CSS.
4. Adventitial stripping of the proximal 3 cm of the ICA appears effective in 93% of our CSS population (n=27), whereas clinical and physiologic evidence of autonomic reinnervation was absent on the long term.
5. Carotid denervation by adventitial stripping is safe and does not result in hypertension.
6. Mechanical carotid stimulation lowers blood pressure in an acute human model and may be useful in the treatment of hypertension.

FUTURE PERSPECTIVES

Carotid sinus denervation for carotid sinus syndrome

Literature on diagnosis and treatment of CSS is hampered by the absence of high-quality, clinical trials. Most data are derived from case reports, small series and unblinded, underpowered trials. This thesis is also limited by its small sample size, although our cohort of 27 patients represents the largest published population treated by adventitial stripping. Because of a general lack of adequate numbers of CSS patients, no comparison has hitherto been made between medical, surgical or pacemaker therapy. However, the prevalence is likely to increase with advancing age and increasing life expectancy of populations at risk for CSS. If general awareness on emergency wards is stimulated and CSM is implemented as a standard diagnostic test for unexplained syncope, future patients will be diagnosed with increasing frequency. These developments will facilitate design of adequately powered randomized trials comparing efficacy and safety of different treatment options for CSS.

How can the periprocedural aspects of adventitial stripping be optimized? Preoperative imaging could play a role in planning the surgical procedure. Carotid ultrasound may be standardly performed as a means to localize the carotid bifurcation in order to minimize length of the neck incision. Preoperative imaging of the CSN and baroreceptor afferents using novel powerful MRI techniques may also facilitate adventitial stripping. Although not reported in this thesis, we attempted to visualize the CSN and baro- afferents using a 3 Tesla MRI, unfortunately without results. Neighboring vagus nerves however were clearly visible using this approach. With the advent of a 7 Tesla MRI, preoperative nerve mapping may seem within reach. The efficacy of carotid denervation in our patient series was tested by clinical assessment after the operation combined with a repeat CSM. However, it is advisible to test completeness of adventitial stripping intraoperatively using a nerve stimulator on the denervated carotid sinus in order to test for a pathological HR and BP response. Residual disease may thus be avoided.

Is there possibly room for less/minimal invasive techniques? Some surgeons block fluctuations induced by the carotid baroreflex during carotid endarterectomy by locally injecting a short acting anesthetic agent such as lidocaine. The baroreflex in CSS patients can also be blocked percutaneously using an ultrasound guided carotid sinus injection. However, only a transient therapeutic effect is to be expected whereas surrounding intracranial nerves may possibly be damaged. Theoretically, percutaneous catheter-based techniques using radiofrequency energy (as used to disrupt renal sympathetic nerves in the treatment of hypertension) could also be applied to treat the carotid baroreceptor afferents in CSS patients. Moreover, alternative energy sources such as ultrasound, laser and cryotherapy could be administered by this endovascular approach. Safety of such procedures in the carotid artery, with regard to complications as TIA and CVA, cranial nerve injury and development of carotid stenosis, should be studied first.

Carotid sinus stimulation in hypertension

Baroreceptor resetting could be responsible for a progressive decay in baroreceptor firing. This phenomenon may subsequently result in a gradual rise in blood pressure. Therefore, studies are needed to examine efficacy and safety of mechanical carotid sinus stimulation on the long term. Future human study designs should allow for bilateral device testing on unoperated carotid arteries. An intravascular stent-like device mechanically stimulating the carotid baroreceptor has been developed meeting the same requirements as the extravascular device that is proposed in this thesis. In view of minimally invasive procedures these devices may offer an innovative future endovascular treatment strategy in patients with hypertension.

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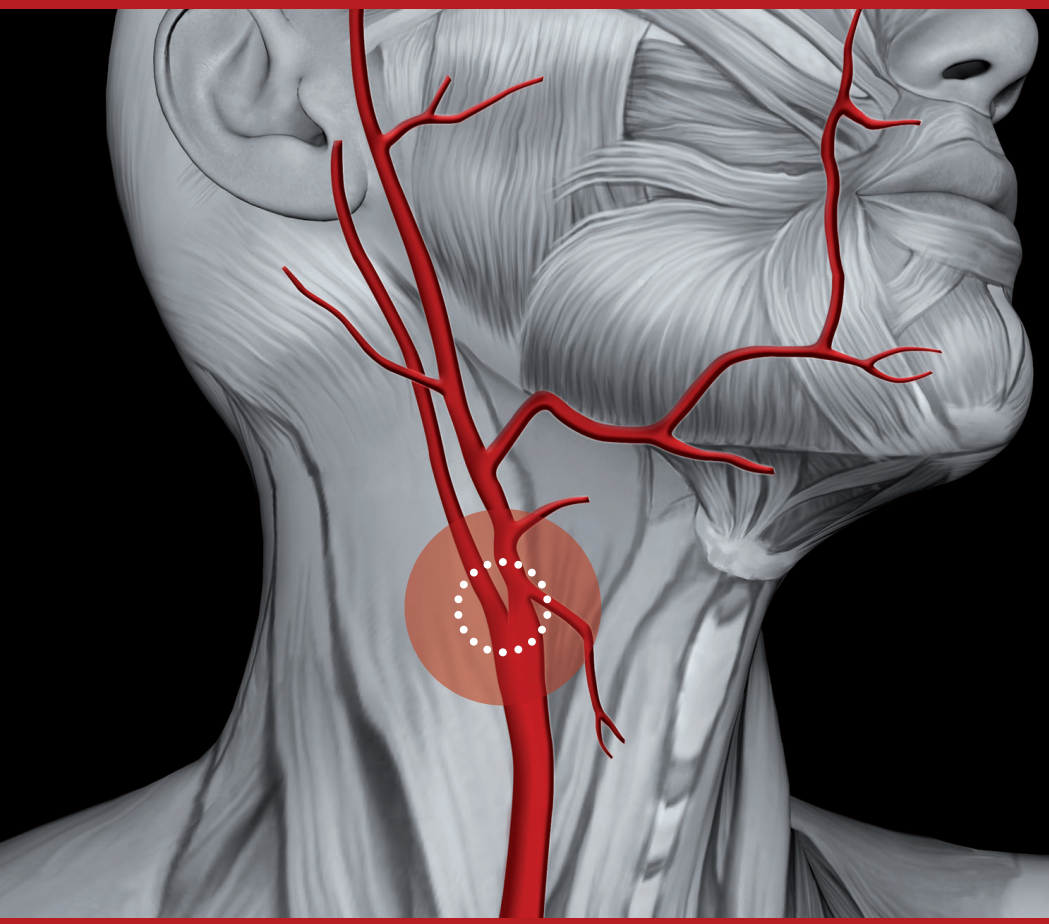


CHAPTER 12

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

1. Hypersensitief sinus carotis syndroom

a. Algemene aspecten

Het hypersensitief sinus carotis syndroom (HSCS) is een weinig bekende oorzaak van herhaaldelijk bewustzijnsverlies (syncope) en duizeligheid in de oudere populatie. De diagnosestelling is uitdagend, maar kan vermoed worden door een specifieke klinische presentatie. Hoofdbewegingen of uitwendige druk op de hals kunnen in sommige patiënten leiden tot stimulatie van de sinus carotis met symptomen tot gevolg. In andere patiënten echter is er geen duidelijke uitlokkende factor aan te wijzen **(hoofdstuk 2).** Een bijzondere klinische presentatie kan aanwezig zijn, zoals intermitterend kokhalzen en braken **(hoofdstuk 3)**.

Het HSCS wordt veroorzaakt door een hyperactiviteit van de carotis baroreflex. Sinus carotismassage (SCM) in liggende houding en 60° anti-Trendelenburg positie kan een hypersensitiviteit van de sinus carotis aantonen. Deze test wordt door de European Society of Cardiology (ESC) geadviseerd bij oudere patiënten met herhaaldelijke syncopes en een verder negatieve diagnostische evaluatie. Sinus carotis hypersensitiviteit wordt hierbij gedefinieerd als een asystolie> 3 s (cardioinhibitoir type), een afname in systolische bloeddruk > 50 mmHg (vasodepressor type) of beide (gemengd type). **Hoofdstuk 4** toont een overzicht van de diagnostische evaluatie van 110 HSCS patiënten zoals gerapporteerd in de literatuur tot 2006 aan toe. Hypersensitiviteit van de sinus carotis kon tweemaal vaker aan de rechter zijde aangetoond worden. Deze bevinding is in overeenkomst met eerdere studies die een frequentere cardioinhibitoire respons aantoonden ter hoogte van de rechter sinus carotis, waarschijnlijk door een predominante rechtszijdige vagale bijdrage aan de sino-atriale nodus. In hoofdstuk 4 werd in bijna 50% van de patiënten de diagnose cardioinhibitoire HSCS gesteld. Recente studies daarentegen toonden de volgende verdeling: cardioinhibitoir 18-24%, vasodepressor 19-29% en gemengd 52-57%. Dit verschil in voorkomen kan berusten op een overschatting van de pure cardioinhibitoire respons in het overzicht aangezien niet altijd getest werd op een vasodepressor respons. Deze gegevens laten zien dat een gestandaardiseerd protocol voor SCM noodzakelijk is. De toediening van atropine of (tijdelijke) pacemakertherapie tijdens SCM is nodig om patiënten te identificeren met een significante vasodepressor respons.

In het algemeen wordt het hypersensitief sinus carotis syndroom beschouwd als een zeldzaam fenomeen. Risicofactoren voor het ontwikkelen van het syndroom zijn mannelijk geslacht, diabetes mellitus en atherosclerose van de krans- en halsslagaders. HSCS incidentie werd geschat op 35-40 patiënten/miljoen personen/jaar. Met de komst van

gespecialiseerde syncopecentra wordt HSCS meer en meer gediagnosticeerd. Recent onderzoek in patiënten met recidiverende syncopes toont een hypersensitiviteit van de sinus carotis aan in 14-54%. Bij bejaarde HSCS patiënten is een hoog risico op fracturen (47%) aanwezig door herhaaldelijk vallen. In onze patiëntenserie (n=27) is dit risico relatief laag, namelijk 11%, wat verklaard kan worden door het retrospectieve karakter van de analyse **(hoofdstuk 7)**.

De prognose van het HSCS wordt bepaald door het al dan niet recidiverende karakter van de symptomen. In vergelijking met de pure cardioinhibitoire HSCS, hebben patiënten met een vasodepressor HSCS een driemaal hoger risico op een recidief van de klachten, wat een agressieve therapie rechtvaardigt.

Verschillende behandelingsmogelijkheden voor het HSCS worden in de literatuur genoemd, inclusief het vermijden van halsbewegingen en druk op de carotisregio. Sinus carotisbestraling als behandeling voor het HSCS is paradoxaal, aangezien radiotherapie in de halsregio ook een HSCS kan veroorzaken. Er bestaan geen gerandomiseerde vergelijkende studies naar de effectiviteit van farmaceutische therapie, zoals anticholinergica (toename hartritme), fludrocortisone, ergotamine of ephedrine (toename bloeddruk). De ESC adviseert pacemakertherapie als behandeling voor een pure of predominante cardioinhibitoire HSCS. Een retrospectieve analyse uit 2011 van 138 patiënten behandeld met een pacemaker toonde een twee- tot driemaal hogere symptoomrecidief in gemengd type HSCS patiënten vergeleken met cardioinhibitoir type HSCS. Twee recente vergelijkende studies toonden echter geen reductie van het aantal syncopes of de valfrequentie aan in de pacemakergroep in vergelijking met de niet-pacemakergroep, zelfs niet in een cardioinhibitoire HSCS patiëntengroep. De matige resultaten van bovenstaande studies laten de noodzaak zien van alternatieve behandelingen.

b. Aspecten van chirurgisch behandeling
In de behandeling van het HSCS worden verschillende operatietechnieken beschreven die tot doel hebben de pathologische carotis baroreflex te onderbreken. Transectie van de negende hersenzenuw (nervus glossopharyngeus) via een schedeloperatie werd voor het eerst beschreven in 1933. Deze operatie is grotendeels verlaten omdat zij zeer invasief is en gepaard kan gaan met ernstige complicaties. Echter zij kan uitkomst bieden voor patiënten met een ontoegankelijke nek (bijvoorbeeld na bestraling) die niet reageren op pacemakertherapie.

Transectie van de sinus carotis zenuw is minder invasief, maar slechts effectief als een volledige denervatie uitgevoerd wordt door zowel de hoofdtak alsook de belangrijke zijtakken door te nemen. **Hoofdstuk 5** beschrijft een anatomische studie van de sinus carotis zenuw in humane cadaver hoofden. Door gebruik te maken van een combinatie van zenuwkleuringstechnieken en microdissectie, kon een grote variabiliteit in zenuwpositie, zijtakken en connecties met de nervus vagus en de cervicale sympatische grensstreng aangetoond worden. Wij concludeerden dat, vanuit een micro-anatomisch oogpunt, alleen de transectie van de nervus sinus carotis, niet voldoende voor een adequate behandeling van het HSCS. Een bijkomend nadeel van deze techniek is de beschadiging van de bezenuwing van het glomus caroticum.

De meest beschreven chirurgische techniek voor de behandeling van HSCS patiënten is adventitiële stripping van de arteria carotis, waarbij het peri-adventitiële zenuwweefsel ter hoogte van de sinus carotis verwijderd wordt. De review in **hoofdstuk 4** laat zien dat deze operatie tot op heden op verschillende manieren werd uitgevoerd. Sommige auteurs beperken zich tot het strippen van de arteria carotis interna (ACI), anderen breiden de operatie uit naar de arteria carotis communis (ACC) en/of de arteria carotis externa (ACE), al dan niet in combinatie met een resectie van het glomus caroticum of transectie van de sinus carotis zenuw. Deze verscheidenheid aan operatietechnieken toont aan dat er onduidelijkheid bestaat over de exacte lokalisatie van baroreceptoren in de carotisbifurcatie.

In **hoofdstuk 6** maken we gebruik van speciale zenuwkleuringstechnieken (PGP 9.5, VGLUT2) om humane carotis baroreceptoren aan te kleuren en te lokaliseren. Uit onze studie blijkt dat baroreceptoren voornamelijk aanwezig zijn in het proximale gedeelte van de mediale ACI. Daarentegen werd geen baroreceptoraankleuring gevonden in de ACC of ACE. Op grond van deze resultaten concluderen we dat adventitiële stripping van de proximale ACI voldoende is in de behandeling van het HSCS.

c. Effectiviteit van sinus carotisdenervatie
In **hoofdstuk 4** worden de resultaten van de in de literatuur gepubliceerde adventitiële stripping procedures in HSCS patiënten (n=110) beschreven. Na de operatie was 73% van de patiënten volledig symptoomvrij terwijl 12% een duidelijke verbetering van hun symptomen rapporteerde.

Tussen 1980 en 2007 werden 27 HSCS patiënten geopereerd in het Máxima Medisch Centrum te Veldhoven. Zij ondergingen een adventitiële stripping van de proximale 3 cm van de ACI. **Hoofdstuk 7** rapporteert de korte termijnsresultaten van dit patiëntencohort. Op de 30e postoperatieve dag was 93% (25/27) van de patiënten symptoomvrij, en 89% (24/27) symptoomvrij zonder pacemaker. De 2 patiënten met aanhoudende symptomen ontvingen een pacemaker, echter zonder resultaat. Een derde patiënt met aanhoudende symptomen onderging een succesvolle redenervatie kort na de eerste operatie.

In verschillende dierstudies werd een autonome reïnnervatie van de carotis baroreflex

na denervatie aangetoond. Autonome reïnnervatie zou de oorzaak kunnen zijn van het recidiveren van klachten na een carotisdenervatie. **Hoofdstuk 8** beschrijft de lange termijnsresultaten van ons patiëntencohort. Na een follow-up periode van 7 jaar, was 85% (22/26) van de patiënten asymptomatisch en 81% (21/26) zonder pacemaker. Van 1 patiënt ontbraken controlegegevens. Eén patient ontving een pacemaker voor een AV block 6 jaar na een succesvolle carotisdenervatie. Desondanks bleef zij symptomen houden. Sinus carotis massage vóór pacemaker implantatie toonde geen sinus carotis hypersensitiviteit. Een vierde patiënt vertoonde een verbetering van de klachten na denervatie, maar was niet symptoomvrij. Herhaaldelijke SCM kon geen sinus carotis hypersensitiviteit aantonen.

Samenvattend vertoonde geen enkele patiënt recidiverende klachten na een initieel succesvolle denervatie. Wij concluderen dat er geen klinische of physiologische argumenten zijn voor autonome reïnnervatie in onze patiëntengroep.

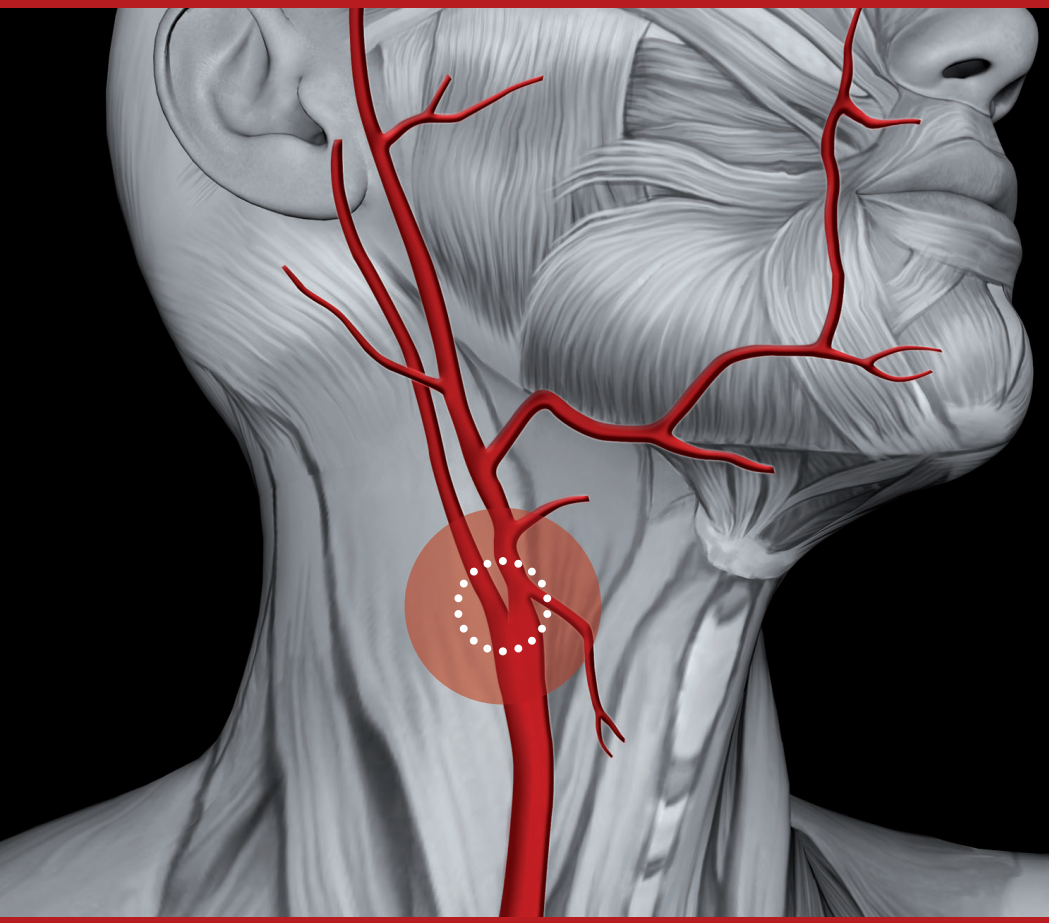
d.Veiligheid van sinus carotisdenervatie

Carotisdenervatie in onze patiëntengroep werd gecompliceerd door een wondhematoom (15%), neuropraxie van de nervus facialis (7%) en atriumfibrilleren/sinustachycardie binnen 48 uur na de operatie (11%) **(hoofdstuk 7)**. Eén patient ontwikkelde een CVA 24 dagen na een bilaterale carotis denervatie, waarschijnlijk tengevolge van een 'low flow state'. Duplexonderzoek van de carotiden in 7 patiënten toonde geen carotisaneurysma of carotisstenose na een gemiddelde follow up van bijna 10 jaar (n=7) **(hoofdstuk 8)**.

Wegens gevreesde postoperatieve bloeddrukveranderingen staat men in het algemeen sceptisch tegenover een carotis denervatie als behandeling voor het HSCS. In 2 van onze 27 patiënten werd een postoperatieve toename van de bloeddruk waargenomen, echter deze normaliseerde binnen 1 maand. Informatie over de impact van carotisdenervatie op de lange termijns bloeddrukregulatie in de mens is gebaseerd op studies na iatrogene beschadiging van de sinus carotis. Zo werd een toename van de bloeddrukvariabiliteit en bloeddrukstijging na mentale stress aangetoond bij patiënten die een bilaterale glomusresectie ondergingen. In deze thesis worden data gerapporteerd van patiënten die een intentionele uni- of bilaterale carotisdenervatie ondergingen. Geen bloeddruktoename werd gezien na een follow up van bijna 10 jaar. De bloeddrukverlagende medicatie die hypertensieve patiënten reeds preoperatief ontvingen, bleef ongewijzigd. Mentale stress door het zogenaamde "witte jassen effect" had, in overeenkomst met iatrogene denervatie, een duidelijke invloed op de bloeddruk (bloeddruk gemeten in spreekkamer vs ambulante bloeddruk: systolisch: 143±17mmHg vs 128±10 mmHg, n.s., diastolisch: 86±6 mmHg vs 79±6 mmHg, $p<0.05$). Een verhoogde bloeddrukvariabiliteit of baroreflexfalen werden daarentegen niet aangetoond. Bovenstaande data ondersteunen ons idee dat humane cardiopulmonale baroreceptoren een sinus carotisdenervatie kunnen compenseren. Waarschijnlijk speelt na unilaterale denervatie de contralaterale carotisbaroreflex een prominent rol in dit compensatiemechanisme.

2.Sinus carotis stimulatie voor hypertensiebehandeling

Zoals carotis denervatie als behandeling toegepast kan worden voor uitgesproken hypotensie geassocieerd met het HSCS, kan stimulatie van de sinus carotis een rol spelen in de behandeling van patiënten met hypertensie. In **hoofdstuk 9** wordt het werkingsmechanisme van verschillende nieuwe interventies voor de behandeling van hypertensie besproken. Electrische carotis baroreceptorstimulatie heeft als nadeel dat een subcutane impulsgenerator geplaatst dient te worden. Deze kan gaan infecteren en moet frequent onderhouden worden. **Hoofdstuk 10** beschrijft de eerste humane studie waarbij in 5 patiënten, voorafgaand aan een carotis desobstructie, een 'exostent' rondom de sinus carotis wordt geplaatst, resulterend in mechanische baroreceptor stimulatie. De chirurgische techniek werd voorafgaand aan de klinische studie getest in een humaan cadavermodel. Plaatsing en verwijdering van de stent is eenvoudig zonder zichtbare schade aan het lokale weefsel of arteriewand. De gemiddelde reductie in systolische en diastolische bloeddruk was respectievelijk 22±14 mmHg en 8±5 mmHg. Alleen een acuut effect op de bloeddruk werd gemeten. Toekomstige studies zullen moeten uitwijzen of mechanische sinus carotis stimulatie toegepast kan worden in de behandeling van hypertensie.



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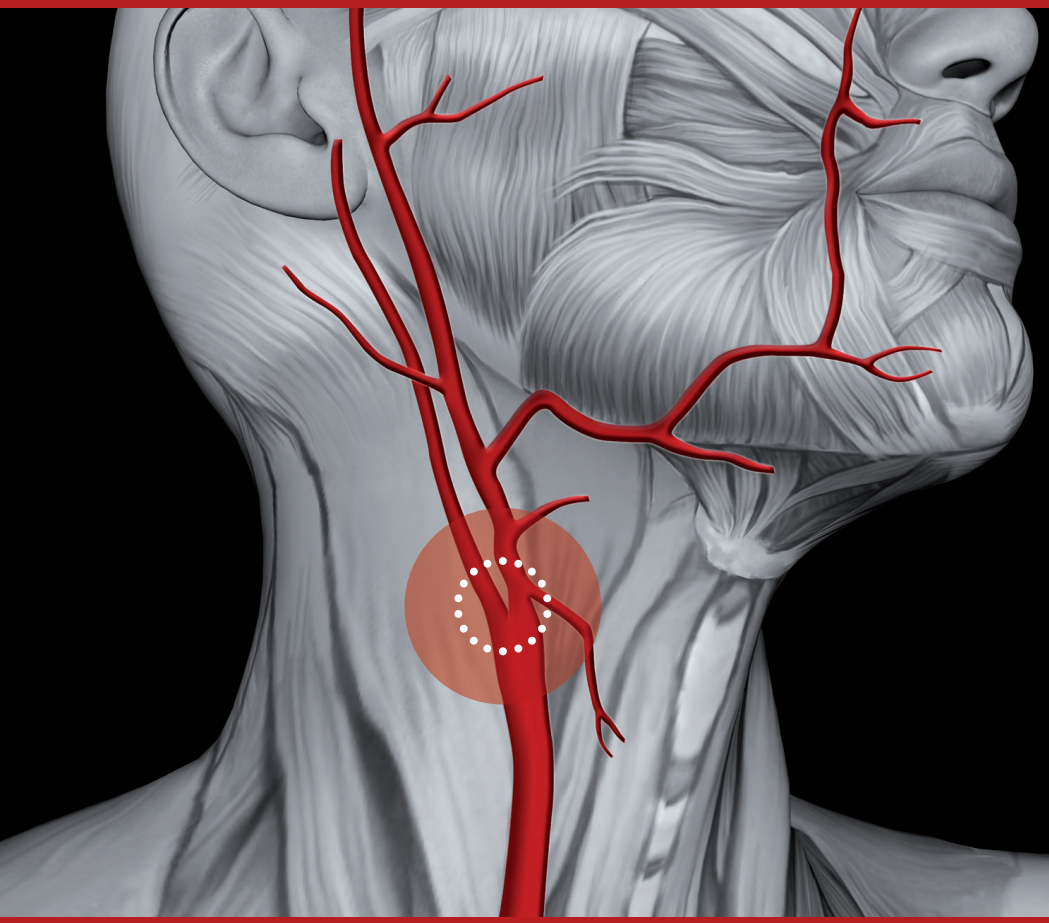

Curriculum Vitae

Raechel Toorop was born on January 26, 1973 in Waalwijk. After graduating from secondary school (Dr. Mollercollege, Waalwijk) in 1991, she completed the first year of Biomedical Health Science in Leiden.

In 1992 she started Medical school at the University of Antwerp, Belgium. During this period she performed a foreign clinical elective at the Department of Gynaecology and Obstetrics in Bandung, Indonesia. In 1999 she obtained her Medical Degree from the University of Antwerp. In the same year surgical residency was started in the University Hospital of Antwerp (UZA, prof.dr. W. Vaneerdeweg) and continued in the St-Vincentiusziekenhuis, Antwerp (dr. Y. Vanderstighelen). The final 2 years of surgical residency was completed in the Máxima Medical Center in Veldhoven (dr. F.A.A.M. Croiset van Uchelen en dr. R.M.H. Roumen). At this time she started scientific research in the field of the carotid sinus and the carotid sinus syndrome.

After she registered as a general surgeon in November 2005, she continued her training as a fellow and a CHIVO (Chirurg In Vervolg Opleiding) in Vascular Surgery at the Máxima Medical Center in Veldhoven (dr. M.R.M. Scheltinga). In 2008 she worked as a vascular surgeon in the Elkerliek Hospital In Helmond. From 2009 onwards she is a staff member of the Vascular Surgery department of the University Medical Center in Utrecht.