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Carotid baroreceptor stimulation blood pressure response mapped in patients undergoing carotid endarterectomy (C-Map study)☆

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ABSTRACT

Objective: Continuous stimulation of the carotid baroreceptors has been shown to evoke a sustained systolic blood pressure (SBP) reduction in hypertensive subjects. This study conducted a detailed mapping of the SBP and heart rate response to electrical stimulus at different locations in the carotid sinus region in patients undergoing a carotid endarterectomy (CEA).
Methods: The Carotid Sinus Autonomic Response Mapping (C-Map) Study is a multicenter, prospective, non-randomized, acute feasibility study conducted in 10 hypertensive subjects undergoing CEA. Electrode pairs were placed in multiple locations in the region of the carotid sinus for acute stimulation, and the tests were repeated after plaque removal and vessel repair.
Results: The configuration that elicited the largest pressure reduction in 8 of 10 patients was with the electrodes arranged longitudinally along the medial (in relation to the bifurcation) wall of the internal carotid artery (ICA) near the bifurcation (11.2 ± 8.1 mm Hg, $p < 0.05$). There was no difference in average maximum response pre vs. post plaque removal. Spontaneous baroreflex sensitivity increased from 6.0 ± 3.2 ms/mm Hg pre-CEA to 8.2 ± 5.4 ms/mm Hg post-CEA ($p = 0.040$).
Conclusions: Endarterectomy surgery did not affect maximal acute stimulation response but improved baroreflex sensitivity acutely. Acute extravascular baroreceptor stimulation (BRS) mapping demonstrated that blood pressure reductions are dependent on electrode location and orientation. In most subjects, the largest SBP reductions were elicited in the region of the medial wall of the ICA. This area can be targeted for future BRS lead design and implant.

1. Introduction

Hypertension (HTN) is a growing health problem estimated to affect 67 million (31%) adults in the U.S. (CDC, 2011). Of those with HTN, it is estimated 10%–15% have resistant hypertension and do not respond to medication (Egan et al., 2011; Persell, 2011; Roberie and Elliott, 2012). A non-pharmacological method of HTN treatment involving electrical stimulation of the carotid has been under investigation (Bakris et al., 2012; Kroon et al., 2010; Scheffers et al., 2010).

Baroreceptors in the carotid sinuses are central in blood pressure (BP) regulation. They are located in the carotid sinus wall at the bifurcation of the common carotid artery (Muratori, 1964) and are highly sensitive to vascular stretch and distortion. Activation of the baroreceptors causes an increase in the frequency and amplitude of carotid sinus afferent nerve impulses which are integrated with input from other sensors in the medulla and modulate neurohumoral and autonomic nervous system activity (Hering, 1923; Smit et al., 2002). Output from the central nervous system affects the function of the heart, kidneys, and peripheral vasculature to maintain appropriate BP. Originally believed to be only involved in short-term regulation, more recent preclinical studies suggest they are also integral to long-term BP control (Thrasher, 2004).

Activation of the carotid sinus afferent nerves can be achieved artificially by electrical stimulation. Studies as far back as the 1950s and 1960s demonstrated that both acute (Carlsten et al., 1958) and chronic (Bilgutay and Lillehei, 1965; Braunwald et al., 1967) stimulation of the carotid sinus nerve in humans can reduce BP and heart rate (HR). Chronically implanted devices using this technique have been utilized for the clinical treatment of angina (Braunwald et al., 1967), and clinical studies are being conducted to investigate the use of chronic carotid sinus stimulation in treating hypertension (CVRx, 2011b - [cited 2016 Jul. 7]) and heart failure (CVRx, 2011a - [cited 2016 Jul. 7]). Studies have shown chronic reductions in office systolic blood pressure (SBP)

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of 30–35 mm Hg after one year of carotid sinus stimulation (Bisognano et al., 2011; Scheffers et al., 2010). A critical component of these implanted systems is the electrodes that are placed at the tissue interface in the region of the carotid sinus. Optimal design of the electrodes is dependent on the anatomy of the carotid sinus and surrounding tissue and knowledge of the exact location to target the electrical field. Anatomical studies of the carotid sinus and associated nerves are well documented (Fig. 1) (Muratori, 1964), with recent research showing that the anatomy can be variable. Although many studies have documented the efficacy of carotid sinus stimulation to affect the autonomic nervous system and BP, no studies have published a detailed mapping of the region of stimulation at the CS. This information is critical in refining electrode designs to be less invasive to reduce patient risk, minimize the energy output needed for stimulation to maximize device longevity, and reduce side effects from current spread to unwanted areas.

Previous work studying the acute change in mechanical response of carotid baroreceptors after carotid endarterectomy (CEA) surgery suggests that they can be affected by associated trauma and manipulation (Sigaudo-Roussel et al., 2002). Because implantation of electrodes on the carotid sinus also can produce acute trauma, although to a lesser extent than CEA, it is important to understand the potential magnitude of the effect on acute electrode response.

This study conducted a detailed mapping of the BP and HR response of different locations in the area of the carotid sinus in patients undergoing a carotid endarterectomy. In addition, the stimulus response of the carotid sinus was compared before and after the surgery.

2. Methods

The C-Map study was a prospective, acute study conducted at San Diego Veteran's Administration Hospital and Cleveland Clinic Foundation. The protocol was approved by local institutional review boards, and written consent was obtained from all patients.

Ten patients undergoing a clinically indicated CEA who had a history of hypertension, as determined by being on at least one antihypertensive medication, were enrolled in the study. Exclusion criteria included the following: ASA (American Society of Anesthesiologists) score >4, ejection fraction <25%, hypotension on the day of the study prior to administration of anesthesia, history of atrial fibrillation and/or ventricular arrhythmia that poses a risk to the subject during the procedure, moderate or severe aortic valve stenosis, or implantation of an active cardiac device.

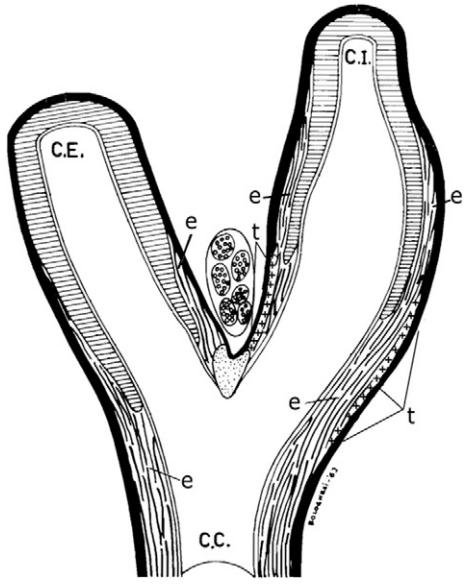

Fig. 1. Detailed longitudinal section of the carotid bifurcation in man. The internal and external carotid arteries are a mixture of elastic (e) and muscular membranes. The proximal elastic portion of the C.I. is abundantly supplied with baroreceptors, represented by small crosses (t). C.I. = internal carotid artery, C.E. = external carotid artery, C.C. = common carotid artery.
(Modified from Muratori, 1964.)

2.1. Anesthesia

All procedures were performed under general anesthesia with mechanical ventilation. The study goals related to anesthesia were to avoid the following: blunting of the baroreflex response, severe hypotension, and medication adjustments and blood draws during data collection. The appropriate anesthetic regimen was determined by the site's clinical staff assigned to each procedure. Seven subjects received a combination of propofol (50–150 mcg/kg/min) with nitrous oxide (50–70%), while three subjects received sevoflurane (0.8–1.5%). Phenylephrine infusion (20–100 mcg/kg/min) was provided for blood pressure support throughout the procedure in 9 of 10 subjects. No medication adjustments or blood draws occurred during baroreceptor stimulation.

2.2. Procedure and instrumentation

Electrocardiograms and arterial blood pressure measured from a fluid-filled pressure transducer in the brachial, radial, or femoral artery were continuously monitored, and analog signals were obtained via a data logger (Model DI-718B, Dataq Instruments) recorded continuously on a notebook computer.

After surgical exposure of the carotid bifurcation, the electrodes were placed in the region of the carotid sinus and held in place against the vessel wall. A test neural stimulator (Medtronic, Model 37022) and programmer (Medtronic, Model 8840) were used to deliver bipolar stimulation pulses up to 510 μs, 100 Hz and 8 V. Because of the limited number of subjects in the study, in order to limit the number of variables tested, variation in output amplitude was only evaluated in three subjects and variation in frequency and pulse width in one subject. After determining that maximum output levels would be unlikely to produce a response that had to be halted for safety reasons of low BP or HR, all other tests were conducted with output parameters of 510 μs, 100 Hz and 8 V.

Upon completion of the stimulation protocol, an arteriotomy was performed for removal of the atheromatous plaque. After vessel repair via patch angioplasty, blood pressure was allowed to stabilize and the stimulation protocol was repeated.

2.3. Stimulation protocol

Fig. 2 illustrates the 11 stimulation sites on the ICA, ECA and the CCA evaluated in this study. These sites were chosen because anatomical studies (Muratori, 1963; Muratori, 1965) indicated the vascular walls in these regions are rich with baroreceptors or close to the carotid sinus nerve. The medial and lateral ICA (sites H and K) were evaluated in all subjects; however, the remaining sites were not tested in all subjects due to time considerations.

Stimulation order was varied from patient to patient to minimize order biasing effects. Each stimulation test at a given site lasted approximately 45 s, and blood pressure was allowed to stabilize approximately 90 s before the next stimulation test. Although BP may not have returned to baseline values, stimulation was only continued if BP appeared to be stable. The total stimulation time before and after the endarterectomy lasted about 20 min. To facilitate a more granular evaluation of each site, site sweeps lateral to medial and superior to inferior along the ICA were performed in some subjects prior to testing of individual sites. During the sweeps, each site was evaluated approximately 20 s before quickly moving the lead to the next site. Stimulation sites appearing to elicit notable decreases in systolic blood pressure were repeated as individual tests with appropriate baseline and recovery periods. Every effort was made to repeat the tests in the same