Long-Term Effects of Carotid Sinus Denervation on Arterial Blood Pressure in Humans

Arthur A.J. Smit, MD, PhD; Henri J.L.M. Timmers, MD; Wouter Wieling, MD, PhD; Mariette Wagenaar, MD; Henri A.M. Marres, MD, PhD; Jacques W.M. Lenders, MD, PhD; Gert A. van Montfrans, MD, PhD; John M. Karemaker, PhD

Background—After experimental carotid sinus denervation in animals, blood pressure (BP) level and variability increase markedly but normalize to preoperative levels within 10 to 14 days. We investigated the course of arterial BP level and variability after bilateral denervation of the carotid sinus baroreceptors in humans.

Methods and Results—We studied 4 women (age 41 to 63 years) who were referred for evaluation of arterial baroreflex function because of clinical suspicion of carotid sinus denervation attributable to bilateral carotid body tumor resection. The course of BP level and variability was assessed from repeated office and 24-hour ambulatory measurements (Spacelabs/Portapres) during 1 to 10 years of (retrospective) follow-up. Rapid cardiovascular reflex adjustments to active standing and Valsalva’s maneuver were assessed. Office BP level increased from 132/86 mm Hg (range, 118 to 148/80 to 92 mm Hg) before bilateral surgery to 160/105 mm Hg (range, 143 to 194/90 to 116 mm Hg) 1 to 10 years after surgery. During continuous 24-hour noninvasive BP recording (Portapres), a marked BP variability was apparent in all 4 patients. Initial symptomatic hypotension on change to the upright posture and abnormal responses to Valsalva’s maneuver were observed.

Conclusions—Acute carotid sinus denervation, as a result of bilateral carotid body tumor resection, has a long-term effect on the level, variability, and rapid reflex control of arterial BP. Therefore, in contrast to earlier experimental observations, the compensatory ability of the baroreceptor areas outside the carotid sinus seems to be of limited importance in the regulation of BP in humans. (Circulation. 2002;105:1329-1335.)

Key Words: baroreceptors • carotid sinus • denervation • blood pressure • hypertension

Bilateral carotid sinus denervation in dogs and baboons increases blood pressure (BP) and BP variability with severe hypertensive surges during agitation.1–3 Normalization of averaged daily BP and variability (10-minute averages) was observed within 2 weeks after surgery.3 The aortic and cardiopulmonary baroreceptors were stated to compensate for the lack of carotid baroreceptor function in those experimental animals.3–5

In humans, bilateral carotid sinus denervation may result in acute baroreflex failure, producing severe, labile hypertension, headache, diaphoresis, and emotional instability.6 Baroreflex failure may result from bilateral carotid body tumor resection (bCBTR) attributable to damage of the adjacent carotid sinus or glossopharyngeal nerves.7 Data on the long-term effect of bilateral carotid sinus denervation on arterial BP are limited and controversial. Reports vary from normalization of BP8,9 to increased BP variability6,5 and sustained hypertension in individual patients.10

The aim of this study was to assess the long-term effects of carotid sinus baroreceptor denervation in humans on the level and variability of BP. Repeated office BP readings during follow-up were documented and ambulatory (beat-to-beat) BP measurements were carried out in 4 patients with acute baroreflex failure after bilateral carotid body tumor resection. Functional baroreflex integrity was assessed by means of standard cardiovascular reflex testing.

Methods

Patients

Four patients were referred to the department of internal medicine for the evaluation and management of symptoms and signs suggestive of baroreflex failure after bCBTR. All results presented in this study were obtained when the patients were not taking medication. The study protocol was approved by the ethics committee of the Academic Medical Center, Amsterdam, the Netherlands, and all patients gave their informed consent. Followed procedures were in accordance with institutional guidelines.

Patient A, a 45-year-old, normotensive woman with a positive history for familial paragangliomas, underwent bCBTR at age 35 years with an interval of 2 months between the first (left-sided) and second (right-sided) operation. Pathological examination revealed
complete excision and no signs of malignancy. Immediately after the second operation, the patient had an unreadable headache with a diastolic BP up to 140 mm Hg. Despite antihypertensive treatment during the following 2 years, she was referred to our institution for labile hypertension and orthostatic lightheadedness. Physical examination and routine laboratory examination were unremarkable except for BP values as described below.

Patient B, a 63-year-old woman, had undergone radical excision of a right-sided carotid body tumor at the age of 23 years. Forty years later, a contralateral left-sided carotid body tumor was resected. Surgery was radical, and no malignancy was found. The second (left-sided) operation was followed by attacks of severe headache evoked by mental stress and physical exercise and of postural lightheadedness. In addition, she had developed dysphagia and voice changes attributable to surgical damage to the superior laryngeal nerve.11

Patient C, a 63-year-old normotensive woman, underwent left- and right-sided bCBTR, respectively, within 3 months. Pathological examination revealed nonradical excision of the right-sided tumor. During the first postoperative day after bCBTR, a BP up to 140/100 mm Hg was measured. During a 5-year follow-up period without medication, episodic lightheadedness on standing in the morning persisted. Chronic attacks of headache with a red face and perspiration in the neck during mental or physical exercise were present.

Patient D, a 41-year-old normotensive woman, underwent right- and left-sided bCBTR within 1 year because of a globus feeling in the neck and difficulty swallowing. Immediately after the second operation, she developed a severe headache accompanied by flushedness of the head and upper trunk, nervousness, and tremulousness. During these episodes, BP reached 210/120 mm Hg. These attacks occurred during emotional events, and a marked emotional lability was present. Occasionally the patient experienced lightheadedness on standing. She was treated with moxonidine, atenolol, and clonidine.

Effect of Carotid Sinus Denervation on BP Level
The course of arterial BP level was evaluated by means of retrospective analysis of office BP readings obtained from the medical records on presurgery and postsurgery follow-up. Sphygmomanometric measurements were performed in sitting position. BP level was also assessed by means of a 24-hour intermittent ambulatory BP recording (SpaceLabs) after the second resection. Values were obtained every 15 and 30 minutes during the daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM), respectively. The first 3 automatic BP readings in the doctor’s office were taken as a second measure of casual BP. Normotension was defined as a mean BP <135/85 mm Hg during daytime and <120/70 mm Hg during nighttime, and a day-night difference ≥10% was considered normal.13,15 SpaceLabs recordings were performed 2 years (patients A and C) and 3 months (patient D) after the second operation, respectively. In patient B, it was performed shortly before as well as 1 year after removal of the second tumor.

Effect of Carotid Sinus Denervation on 24-Hour BP Variability
Arterial BP variability was assessed by means of a 24-hour beat-to-beat registration of finger arterial pressure using the Portapres device (model 1, TNO-BioMedical Instrumentation). This device is suitable for analysis of BP variability during daily activities.14–16 Readings were taken from the third and second finger alternating every half hour. The continuous ambulatory recording was stored on a built-in cassette recorder along with a marker signal superimposed on a hydrostatic height-correcting signal for offline AD conversion. A 24-hour Portapres recording started at 12 AM and comprised strictly scheduled standardized activities, as follows: supine rest without sleep for 1.5 hours (siesta, starting at 2 PM), cycling at 50 W/50 to 60 rpm on a bicycle ergometer for 20 minutes (starting at 4:30 PM), and 2 periods of walking for 30 minutes (patient A, starting at 10 AM and 11 AM; patients B, C, and D, starting at 4 PM and 10 AM). When no standardizations were performed, patients were left free to perform nonfatiguing daily activities. They stayed in bed between 11 PM and 6:30 AM and kept a diary to report the time of nonstandardized activities. Five-minute averages were calculated and used for presentation of 24-hour BP profiles and BP frequency distributions. Portarres recordings were performed 2 years (patients A and C) and 3 months (patient D) after the second operation, respectively. In patient B, it was performed shortly before as well as 1 year after removal of the second tumor.

Effect of Carotid Sinus Denervation on Rapid Cardiovascular Reflex Adjustments
Functional baroreflex integrity was assessed by measuring the beat-to-beat BP and heart rate responses to active standing. Valsalva’s maneuver, and forced breathing. Patients were nonsmokers and abstained from caffeine and food 2 to 4 hours before reflex testing. Investigations were performed in a room with an ambient temperature of 22°C to 24°C. Continuous finger arterial BP was measured by the Finapres device (model 5, TNO-BioMedical Instrumentation).17 BP was obtained from the mid-phalanx of the third finger of the left hand, which was held at heart level.

The BP and heart rate responses to active standing and Valsalva’s maneuver were used to assess overall baroreflex-mediated heart rate and vasomotor control.18 Normal baroreflex-mediated vasomotor control was defined as an initial BP decrease ≥40/25 mm Hg with return of BP to prestanding levels and by the presence of a late phase II recovery and phase IV overshoot during the Valsalva’s maneuver.18 The initial maximal heart rate increase on standing (dHRmax) and the highest heart rate in phase II divided by the lowest heart rate in phase IV of the Valsalva’s maneuver (Valsalva ratio) was calculated to assess baroreflex-mediated heart rate control.19 The inspiratory-expiratory difference in heart rate during forced breathing was used as a selective test for efferent cardiovascular innervation. The dHRmax, Valsalva ratio, and inspiratory-expiratory difference were compared with age-matched normotensive data.19 Cardiovascular reflex testing was carried out after removal of the second tumor at intervals of 2 years (patient A), 3 days and 2 years (patient C), and 3 months (patient D), respectively. In patient B, it was performed shortly before as well as 1 month and 1 year after the second operation.

Results

Effect of Carotid Sinus Denervation on BP Level
Before any surgery was carried out, averaged office BP obtained by sphygmomanometry was normal in patients A, B, and D (Table 1). In patient C, BP was slightly increased (148/92 mm Hg, normal <140/90). After the first carotid body tumor resection, BP level increased to 177/98 mm Hg in patient B and 152/99 mm Hg in patient D (Table 1). Compared with preoperative values, BP levels were elevated immediately after the second operation as well as on the long term after bCBTR in patients A, B, and D (Table 1).

The first 3 office BP readings by the ambulatory monitor were in agreement with those obtained by sphygmomanometry (Table 1). Compared with office BP readings, averaged ambulatory daytime values were lower in all patients but still above the proposed values for normotension in patients A, B, and D. In patient B, mean daytime ambulatory values had increased from 131/87 mm Hg before bCBTR to 156/100 mm Hg after bCBTR.

Effect of Carotid Sinus Denervation on 24-Hour BP Variability
Prospective evaluation of BP variability by means of repeated Portapres recordings was assessed in patient B only. One
month after the operation, the variability of BP had increased compared with before the operation (Figure 1). As can be observed in the BP distribution curves, the increase in BP variability was attributable to the occurrence of more high BP values. For example, after the operation, 75% of mean arterial BP values were found between 66 to 110 mm Hg, whereas 75% of BP values occurred between 69 to 97 mm Hg before the operation. The marked BP increments were observed during scheduled activities like walking (from 111/66 to 160/79 mm Hg) and cycling (from 139/68 to 160/80 mm Hg). However, nonscheduled activities like undressing before going to bed and dressing the next morning were also associated with marked increases in BP (212/99 and 180/100 mm Hg, respectively). During mental activity, such as watching television or having a telephone conversation, BP rose to values between 192/96 and 232/123 mm Hg. During supine rest, mean arterial BP was significantly lower than the remaining daytime (siesta 115/56 mm Hg versus ambulation 134/72 mm Hg, \( P<0.001 \), Students \( t \) test). In Figure 2, the 24-hour BP recordings of all patients after BCCTR are shown. It is apparent that BP during the day and night is markedly variable in these patients, especially when compared with healthy normotensive subjects (Figure 1, left).

**Effect of Carotid Sinus Denervation on Rapid Cardiovascular Reflex Adjustment**

In response to standing up, patient A showed a large initial decrease in BP from 142/92 to 77/55 mm Hg with a slow and incomplete recovery to 108/79 mm Hg after 1 minute at 2 years after BCCTR. The maximal initial increase in heart rate (dHRmax) was abnormally low (10 beats/min; normal, \( >15 \)).\textsuperscript{19} Valsalva’s maneuver provoked a progressive decrease in BP during strain without overshoot after release of strain. The heart rate response during Valsalva’s maneuver was abnormal. These findings were indicative of impaired baroreflex-mediated vasomotor and heart rate control.\textsuperscript{18–20} During forced

---

**TABLE 1.** Averaged Casual and Ambulatory BP Before and After Uni- and Bilateral CBTR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Casual BP, mm Hg (No. of Visits)</th>
<th>ABPM* After Bilateral CBTR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before CBTR</td>
<td>After Unilateral CBTR</td>
</tr>
<tr>
<td></td>
<td>No. of Recordings</td>
<td>BP of First 3 Measurements</td>
</tr>
<tr>
<td>A</td>
<td>130/85 (2)</td>
<td>143/104 (10)</td>
</tr>
<tr>
<td>B</td>
<td>Normal 177/98 (6)</td>
<td>194/116 (11)</td>
</tr>
<tr>
<td>C</td>
<td>148/92 (2)</td>
<td>130/83 (2)</td>
</tr>
<tr>
<td>D</td>
<td>118/80 (2)</td>
<td>152/99 (3)</td>
</tr>
</tbody>
</table>

*Ambulatory blood pressure measurements (ABPMs) obtained by Oxford or SpaceLabs. Normotension is defined as averaged daytime BP ≤135/85 mm Hg and at night ≤120/70 mm Hg.\textsuperscript{12}

---

**Figure 1.** Effect of carotid sinus denervation on 24-hour BP. Profiles in a healthy subject (top left) and a patient with carotid body tumors before (top middle) and after (top right) the second resection. BP variability for mean BP, as shown in the histograms (bottom), had increased in the patient after the second carotid body tumor resection. MAP indicates mean arterial pressure.
breathing, a normal inspiratory-expiratory difference in heart rate was observed, indicative of normal efferent vagal heart rate control (Table 2). Presently (10 years after operation), no improvement in the BP response on standing or Valsalva’s maneuver is present.

Patient B was evaluated shortly before the second operation. On standing, BP decreased from 150/80 mm Hg to 100/43 mm Hg within 12 seconds. At 1 minute of standing, BP had returned to 135/65 mm Hg. The maximal initial heart rate increase was abnormally low (5 beats/min; normal, 13). The inspiratory-expiratory difference in heart rate at forced breathing was just above the lower limit of normal (10 beats/min; normal, 9) at a basal heart rate of 70 beats/min. One month after the second operation, the initial decrease in BP was more pronounced (170/110 to 90/75 mm Hg) with a sluggish recovery (Figure 3, top left). At 1-year follow-up, the BP response to standing had improved, but the initial BP decrease was still marked (55/35 mm Hg; normal, <40/25) (Figure 3, top right, and Table 2). At that time, Valsalva’s maneuver showed a progressive decrease in BP during straining without a BP overshoot after release of the strain. Heart rate did not change during this procedure (Table 2). The heart rate response to forced breathing was abnormally low (5 beats/min; normal, >9). These findings indicated the persistence of impaired baroreflex-mediated vasomotor and heart rate control.

Patient C was evaluated within 3 days after the second operation. On standing, BP showed a marked initial decrease in BP (170/110 to 90/75 mm Hg) with a sluggish recovery (Figure 3, top left). At 1-year follow-up, the BP response to standing had improved, but the initial BP decrease was still marked (55/35 mm Hg; normal, <40/25) (Figure 3, top right, and Table 2). At that time, Valsalva’s maneuver showed a progressive decrease in BP during straining without a BP overshoot after release of the strain. Heart rate did not change during this procedure (Table 2). The heart rate response to forced breathing was abnormally low (5 beats/min; normal, >9). These findings indicated the persistence of impaired baroreflex-mediated vasomotor and heart rate control.

TABLE 2. Long-Term Effects of bCBTR on Cardiovascular Reflex Responses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Postoperative Period</th>
<th>Active Standing BP</th>
<th>FRSA: I-E Diff, bpm</th>
<th>Valsalva Maneuver</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2 y</td>
<td>10 (&gt;15)</td>
<td>17 (&gt;10)</td>
<td>a 1.19 (±1.20)</td>
</tr>
<tr>
<td>B</td>
<td>1 y</td>
<td>5 (&gt;12)</td>
<td>5 (&gt;8)</td>
<td>a 1.07 (±1.08)</td>
</tr>
<tr>
<td>C</td>
<td>2 y</td>
<td>23 (&gt;12)</td>
<td>16 (&gt;8)</td>
<td>n 1.66 (±1.08)</td>
</tr>
<tr>
<td>D</td>
<td>3 mo</td>
<td>34 (&gt;15)</td>
<td>12 (&gt;10)</td>
<td>n 1.24 (±1.20)</td>
</tr>
</tbody>
</table>

n denotes a normal BP response and a, an abnormal response. Age-matched reference values are given in parentheses. FRSA indicates forced respiratory sinus arrhythmia; I-E diff, inspiratory-expiratory heart rate difference in beats per minute; and dHRmax, maximal initial heart rate increment in beats per minute.
decrease from 122/61 to 78/48 mm Hg with a low increment in heart rate (dHRmax 16 beats/min) with respect to the fall in BP (Figure 3, bottom left). After 2 years of follow-up, normal cardiovascular responses to standing (Figure 3, bottom right), Valsalva’s maneuver, and forced breathing (Table 2) were found, indicating a normal baroreflex functioning.

Three months after bCBTR, patient D showed a large asymptomatic initial decrease in BP from 153/90 to 94/64 mm Hg (59/26 mm Hg; normal, <40/25), with a normal heart rate response. The cardiovascular responses to Valsalva’s maneuver and forced breathing were normal.

Discussion
The results of the present study document the long-term effects of carotid sinus denervation in humans. It seems to have a definite influence on the level of BP, BP variability, and rapid reflex adjustments.

Effect of Carotid Sinus Denervation on the Level of Arterial BP
Shortly after the second operation, an increase in BP was observed (Table 1) in all patients. This is consistent with the short-term effect of carotid sinus denervation both in experimental animals1–3 and in humans.6,8,9,21 In animal studies,
arterial BP has been shown to return to preoperative levels within 14 days postoperatively. In humans, knowledge relies on office BP measurements, where both normalization of BP and sustained hypertension have been observed.

Our study suggests that these different observations on the long-term effects of bCBTR on BP in humans can be explained by differences in completeness of denervation. In patient C, histological evaluation revealed incomplete resection of the glomus body tumor, which may imply that baroreceptor afferents from the carotid sinus on one side were left intact as well. Normal BP and heart rate responses during cardiovascular reflex testing support this view. In this patient, almost normal averaged daytime and nighttime BP were observed after 1 year. In patient B, dysphagia, impaired rima glottidis closure, and decrease in inspiratory-expiratory heart rate difference during forced breathing were indicative of iatrogenic vagus nerve impairment. In addition to efferent cardiac vagal fibers, afferent baroreceptor fibers from the aorta, afferent low pressure baroreceptor fibers, and afferent lung fibers could have been affected by the operative procedure as well, giving rise to a more extensive baroreceptor denervation than a selective carotid sinus denervation. Baroreflex-mediated vasomotor control was still abnormal after 1-year follow-up. The highest outpatient BP values were measured in this case.

Effect of Carotid Sinus Denervation on the Variability of Arterial BP
Arterial baroreceptors provide the central nervous system with a continuous stream of information on changes in BP, on the basis of which efferent autonomic neural activity is dynamically modulated. Arterial baroreceptors are especially sensitive to abrupt transients in BP, whereas they adapt within 10 to 15 minutes to a persisting change in BP. Their main role seems to be the limitation of excursions in heart rate and BP in response to short challenges like orthostatic challenge, mental stress, and exercise during daily life. Disruption of this dynamic reflex control of blood pressure explains our observation of an increased BP variability after bCBTR during these challenges. The BP level in patients after bCBTR seems to depend largely on the use of either office or ambulatory measurements. Casual BP measurements in the office on long-term follow-up after bCBTR suggest overt hypertension in the patients presented here (Table 1). This finding is in line with the observations of Holton and Wood in 2 patients, Palatini and Pessina in 1 patient, and Sleight in 1 patient. In these reports, it was concluded that carotid baroreceptors are of great importance to provide rapid adjustment of BP and heart rate to standing. In the 3 patients with intact cardiac vagal control (patients A, C, and D), the reciprocal relationship between heart rate and BP on standing provides circumstantial evidence for mediation of the heart rate by the aortic baroreceptors. But the abnormally small heart rate peak in relation to the pronounced decrease in BP, despite a normal cardiovagal innervation, suggests a low sensitivity of these receptors compared with the carotid baroreceptors.

Limitations of the Study
Because bilateral carotid body paraganglioma is a rare disorder, we studied the effects of carotid sinus baroreceptor denervation in only 4 patients. Except for 1 prospectively studied patient, BP data were obtained retrospectively from the individual clinical follow-up, which ranged from 1 to 10 years. In addition, there were considerable differences in the intervals between bCBTR and additional investigations of the baroreflex. Systematic prospective evaluation of baroreflex function in these patients is needed.

Conclusion
Our data provide support for the view that after carotid sinus denervation in humans, BP remains slightly elevated over normotensive values. In addition, BP variability remains markedly increased. Apparently, in contrast to some experimental observations in animals, the lack of carotid baroreceptors cannot be compensated for by other reflex mechanisms on the long term. This leads to elevated BP during mental stress and might explain the isolated office hypertension that can be observed in these patients. Initial orthostatic lightheadedness can be observed and results from a large initial orthostatic fall in BP, insufficiently buffered by the aortic baroreceptors. The hydrostatic position of the carotid sinuses in the upright posture in humans gives these baroreflex afferent areas a major role in defense of upright BP and, thereby, brain perfusion. In addition, it seems that the sensitivity of this part of the baroreflex cannot be compensated for by other (aortic) baroreceptor areas. This is different from observations in experimental animals.

References


Long-Term Effects of Carotid Sinus Denervation on Arterial Blood Pressure in Humans


_Circulation_. 2002;105:1329-1335; originally published online February 25, 2002;
do: 10.1161/hc1102.105744

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/105/11/1329

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/