The trigeminal nerve is the largest of the cranial nerves, and it provides primarily sensory supply to the face, scalp, and mucosa of the nose and mouth. Stimulation of the trigeminal receptors that innervate the nose and nasal passages is thought to provide the most important afferent input for initiation of the oculocardiac reflex (OCR) and the trigeminorespiratory reflex, which were first described in the cat and rabbit. These reflexes are well-recognized phenomena consisting of bradycardia, arterial hypotension, apnea, and gastric hypermotility. It occurs during ocular surgery and during other manipulations in and around the orbit. Thus far, it has not been shown that central stimulation of the trigeminal nerve can also cause this reflex.

Methods. The TCR was defined as clinical hypotension with a drop in mean arterial blood pressure (MABP) of more than 20% and bradycardia lower than 60 beats/minute. Pre-, intra-, and postoperative heart rate (HR) and MABP were reviewed retrospectively in 125 patients who underwent surgery for tumors of the cerebellopontine angle (CPA), and they were divided into two groups on the basis of the occurrence of the TCR during surgery. Of the 125 patients, 14 (11%) showed evidence of the TCR during dissection of the tumor near the trigeminal nerve at the brainstem. Their HRs fell 38% and their MABPs fell 48% during operative procedures as compared with preoperative levels. After cessation of manipulation, the HRs and the MABPs returned to preoperative levels. Risk factors for the occurrence of the TCR were compared with results from the literature.

Conclusions. The authors’ results show the possibility of occurrence of a TCR during manipulation of the central part of the trigeminal nerve when performing surgery in the CPA.

KEY WORDS • cerebellopontine angle • trigeminocardiac reflex • trigeminal nerve • bradycardia • hypotension

Trigeminocardiac reflex during surgery in the cerebellopontine angle

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Object. In different experimental studies authors have analyzed the autonomic responses elicited by the electrical, mechanical, or chemical stimulation of the trigeminal nerve system. The trigeminocardiac reflex (TCR) is a well-recognized phenomenon that consists of bradycardia, arterial hypotension, apnea, and gastric hypermotility. It occurs during ocular surgery and during other manipulations in and around the orbit. Thus far, it has not been shown that central stimulation of the trigeminal nerve can also cause this reflex.

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Conclusions. The authors’ results show the possibility of occurrence of a TCR during manipulation of the central part of the trigeminal nerve when performing surgery in the CPA.

KEY WORDS • cerebellopontine angle • trigeminocardiac reflex • trigeminal nerve • bradycardia • hypotension

To the best of our knowledge, we present the first systematic study that provides evidence of the TCR during manipulation of the central part of the trigeminal nerve during surgery.

Clinical Material and Methods

We defined the occurrence of the TCR as clinical hypotension with a drop in mean arterial blood pressure (MABP) of 20% and bradycardia lower than 60 beats/minute, cessation of traction must have resulted in a
spontaneous increase in the heart rate (HR) and the MABP to normal levels. The phenomenon had to recur when traction was repeated.

Patient Population

We retrospectively reviewed the case histories of 125 patients who underwent surgery for tumors of the cerebellopontine angle (CPA) performed by an otoneurosurgical team from January 1988 to February 1998 at the University Hospital, Basel, Switzerland. Of these 125 patients, 14 (11%) showed evidence of TCR during tumor dissection near the trigeminal nerve at the brainstem. The TCR group included nine women and five men, and their average age was 44 years (standard deviation [SD] 11 years, range 14–72 years). The non-TCR group included 58 women and 53 men, and their average age was 51 years (SD 14 years, range 34–75 years). Preoperatively, all 125 patients underwent vestibular testing (eye-tracking test, optokinetic reflex, and vestibuloocular reflex), audiological testing (pure tone audiogram, speech discrimination testing, and brainstem auditory evoked potentials), and neuroradiological examinations (cerebral computerized tomodgraphy scanning, cerebral magnetic resonance imaging, or digital subtraction arteriography of cerebral blood vessels).

In the 14 patients showing evidence of the TCR, tumor size was measured as the largest tumor diameter and categorized as medium (20–30 mm; six patients [43%]) or large (> 30 mm; eight patients [57%]). The average tumor size was 35 mm (SD 10 mm, range 22–50 mm). Tumors were classified according to the World Health Organization histological typing of central nervous system tumors. There were 10 vestibular schwannomas (six Antoni Type A and four Antoni Type B) and four meningiomas (two psammomatous, one meningothelial, and one fibroplastic).

Surgical Technique and Intra- and Perioperative Management

A retrosigmoid approach with the patient in the supine position was used in all surgical procedures. The surgical technique has been described previously. Intraoperative nerve-integrity monitoring of the cochlear nerve (Nicolet Compact Four; Nicolet Instruments, Madison, WI) and the facial nerve (Neurosign 100; Maxtim, Germany) was conducted routinely. Intracranial dissection was performed using a surgical microscope (Zeiss/Contraves; Carl Zeiss, Inc., Wetzikon, Switzerland). After surgery, patients were monitored in the intensive care unit for the next 24 hours and in the neurosurgical recovery room for the next 24 to 72 hours.

Anesthetic Technique

Patients fasted for at least 6 hours and were premedicated orally with midazolam prior to surgery. Routine monitoring during surgery included electrocardiography, HR (in beats per minute: 72, SD 10, range 58–89); end-tidal (ET) concentration of CO₂ (PₐCO₂; range 3.8–4.1 kPa) and isoflurane (P₂ISO); pulse oximetry (O₂ saturation > 96%); and esophageal temperature (Spacelabs, Redmond, WA). An indwelling radial artery catheter was inserted to allow continuous invasive MABP (83 mm Hg, SD 13, range 72–142) measurements and intermittent blood gas level samples. All hemodynamic parameters were monitored continuously and recorded throughout the surgical procedure.

Anesthesia was induced with thiopental (3–4 mg/kg⁻¹) followed by fentanyl (3 mg/kg⁻¹) and atracurium (0.5 mg/kg⁻¹). After the trachea was intubated, the lungs were mechanically ventilated (Sulla 808V; Lübeck, Germany) with a mixture of air and O₂ (F₂O₂ = 0.5). Anesthesia was maintained with isoflurane 1.2% and, when it seemed clinically necessary, an additional bolus of fentanyl and atracurium was administered.

Statistical Analysis

All statistical analyses were performed using statistical software (STATView II 1.01; Abacus Concepts, Inc., Berkeley, CA) on a commercially available computer. Data are presented as the mean ± SD unless otherwise indicated. To compare two independent proportions, Fisher’s exact test was used. The level of significance was set at a probability value of less than 0.05.

Results

Fourteen patients met the inclusion criteria. There were no significant differences in the patient age or sex, histological composition of the tumor, or duration and distribution of symptoms between the TCR and the non-TCR groups. Possible risk factors for the 14 patients compared to non-TCR patients are summarized in Table 1. During dissection of the tumor near the trigeminal nerve at the brainstem, the patient’s HR and MABP decreased significantly, as defined in the inclusion criteria. The mean HR fell 38% from a mean of 76 beats/minute (SD 11 beats/minute, range 62–91) before manipulation to a mean of 47 beats/minute (SD 12 beats/minute, range 20–59) during the procedure and returned to a mean of 77 beats/minute (SD 9 beats/minute, range 65–93) after manipulation (Fig. 1 upper). The MABP fell 48% from a mean of 84 mm Hg (SD 7 mm Hg, range 71–93) before manipulation to 44 mm Hg (SD 12 mm Hg, range 10–56) during the procedure, and returned to 82 mm Hg (SD 8 mm Hg, range 69–95) after manipulation (Fig. 1 lower). The HR and MABP after manipulation were not significantly different from before. In three cases, there was an asystole, with a duration of 30 to 70 seconds and a return to a normal cardiac rhythm within 90 to 180 seconds after the end of surgical manipulation. In these three patients, the postoperative courses were uneventful.

Intravenous administration of atropine (0.9 mg; SD 2 mg, range 0.6–1.2 mg) led to a cessation of the TCR during the remainder of the surgical procedure in all 14 cases. Routine electrocardiographic monitoring during follow-up examination in the intensive care unit after surgery showed a new intermittent nodal rhythm (sinus arrhythmia) in one patient. There was no history of previous arrhythmia. The later follow-up period in this case was uneventful. Further complications that could be attributed to the occurrence of the TCR were not detected.
Discussion

In various experimental studies, authors have analyzed the autonomic responses elicited by the electrical, mechanical, or chemical stimulation of the trigeminal nerve system.4,5,20,45 One variant of the different trigeminal reflexes, the TCR, is a well-recognized phenomenon that consists classically of bradycardia, arterial hypotension, apnea, and gastric hypermotility.21 Different variants of the TCR exhibit their own characteristics. The OCR is associated with bradycardia but not arterial hypotension.10,12 The diving reflex (elicited by facial immersion) and the nasopharyngeal reflex (caused by noxious stimulation of the nasal mucosa) are associated with an increase in peripheral vascular resistance resulting in hypertension.21

A uniform definition of the TCR does not exist thus far; however, Bosomworth, et al.,13 assumed a positive OCR response to be any reduction in HR of 10% or more. In the present series, we have defined the TCR as the occurrence of bradycardia (HR ≤ 60 beats/minute) and a 20% or more decrease in MABP.

Afferent Pathway Most Frequently Involved in the TCR

Case reports are, in general, too imprecise to allow identification of the sensory nerve involved in the afferent conduction of the TCR. Laboratory investigations, clinical experience with the TCR other than the OCR,6,8,17,22,25,33,35,39,40,43 and knowledge of the anatomical distribution of the trigeminal nerve25,33 support the assumption that stimulation of any sensory branch of the fifth cranial nerve may lead to severe bradycardia and/or arterial hypotension11 (Table 2). However, all previously described afferent pathways of the trigeminal nerve represent the peripheral part of the nerve. Until now, nothing has been known about the stimulation of the central part of the fifth cranial nerve.

In our cases in which the TCR occurred during tumor resection in the CPA, manipulation of the trigeminal nerve at the brainstem was found to trigger the reflex. According to Lang, et al.,22 the afferent pathway continues to the main sensory nucleus of the trigeminal nerve under the floor of the fourth ventricle. Short internuclear nerve fibers connect with the efferent pathway in the reticular formation, which originates in the motor nucleus of the vagus nerve.22 Depressor fibers of the vagus nerve end in the myocardium (Fig. 2),22 leading to autonomic changes.

A question arises in this context: is the so-called “TCR” simply a “pain response” and not a real reflex? Facial receptors may be linked to the spinal autonomic system.14 Ruggiero, et al.,36 have demonstrated projections from the spinal trigeminal nucleus to the entire length of the spinal cord in the rat. Menetrey and Basbaum26 have shown in the rat extensive projection of spinal and trigeminal neurons, especially from the paratrigeminal nucleus, to the nucleus solitarii. Afferent input from the face may be transmitted to the nucleus tractus solitarii by a trigeminospinal solitary tract.14 Part of this input may be nociceptive and generate pain-related somatovisceral and viscerovisceral reflexes.14 To distinguish between the hypothesis of a real reflex or a pain response, we have to establish a cause–effect relationship.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>W/ TCR (14 patients)</th>
<th>W/O TCR (111 patients)</th>
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<tr>
<td>age (yrs)</td>
<td>44</td>
<td>51</td>
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<tr>
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<td>14</td>
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<td>1 (1)</td>
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<td>53</td>
<td>NS</td>
</tr>
<tr>
<td>female</td>
<td>9</td>
<td>58</td>
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</tr>
<tr>
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<td>SD</td>
<td>17</td>
<td>12</td>
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<tr>
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<td>3 (21)</td>
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<td>83</td>
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<tr>
<td>SD</td>
<td>11</td>
<td>12</td>
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<td>84</td>
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<td>SD</td>
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<td>11 (9)</td>
<td>p &lt; 0.04</td>
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<td>calcium channel blockers</td>
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<td>11 (9)</td>
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<tr>
<td>range</td>
<td>10–65</td>
<td>5–70</td>
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</table>

* NS = not significant.
Evidence of a Cause–Effect Relationship

The retrospective nature of this study limits the certainty of establishing the cause–effect relationship. As described by Blanc,11 the criteria necessary to establish a cause–effect relationship include the consistency and strength of the association, the presence of a type of stimulus–incidence relationship, and biological plausibility. In each of the 14 cases presented in this series, the surgical manipulation of the trigeminal nerve near the brainstem elicited a specific and unequivocal effect (sudden bradycardia and arterial hypotension). Elimination of the inducing stimulus, such as manipulations near or at the trigeminal nerve, resolved the effect, and repetition of the stimulus lead each time to the same effect.

The cause–effect association can be evaluated further by examining the effectiveness of measures used to prevent the response.11 The reflex can be prevented by avoiding stimulation of the afferent pathway, as described above, or by blocking the nerves that conduct the afferent impulses. In each of our patients, anticholinergic medication to block muscarinic receptors of the heart was an effective prophylactic measure and no further episodes of dysrhythmia were detected. The surgical procedures were completed uneventfully. In addition, administration of fentanyl to block possible pain response showed no effect on further episodes of the TCR.

Variability of the TCR

In addition to the variety of factors that trigger the TCR, its responses vary widely as well. These responses include the common sinus bradycardia with or without junctional escape, junctional rhythm, as well as other cardiac arrhythmias such as atrioventricular block, bigeminy, and nodal beats.45 The bradycardia can progress to include sinus arrest or even asystole or ventricular fibrillation.45 Precious and Skulsky52 have reported an incidence of 1.6% (eight of 502 cases) of either asystole or bradycardia in patients undergoing maxillofacial orthognathic or temporomandibular surgery leading back to the TCR. The TCR persists for as long as the stimulus is present, but it weakens with repeated stimulation at short intervals.52

The critical period occurs during the first few seconds after stimulation, when cardiac depression is maximal. Initial baseline HR has no influence on the incidence of TCR.22 For this reason, tachycardia is not protective.12

The type of stimulus may modify the TCR response.11 For example, as electrical stimulation of the vagus nerve is increased up to frequencies of 20 to 30 Hz, the sinoatrial node becomes progressively more inhibited.11 At higher frequencies, the vagal response may again decrease.11 When the stimulation stops, the HR rapidly returns to its previous level, reflecting the rapid hydrolysis of the acetylcholine that was liberated during stimulation.11,22 It has been shown that abrupt and sustained traction is more likely to elicit the TCR than smooth and gentle traction.12,23

The OCR, a variant of the TCR, in infants younger than 3 months of age.16 This classification was based on the

& TABLE 2

Afferent pathways involved in TCRs*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Sensory Nerve &amp;/or Branches</th>
<th>Trigeminal Division</th>
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</thead>
<tbody>
<tr>
<td>Bainton &amp; Lizi, 1987</td>
<td>zygomaticotemporal branches</td>
<td>V2</td>
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<tr>
<td>Loevinger, et al., 1987</td>
<td>auriculotemporal nerve</td>
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</tr>
<tr>
<td>Shearer &amp; Wenstone, 1987</td>
<td>zygomaticotemporal branches</td>
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<tr>
<td>Hopkins, 1988</td>
<td>recurrent tentorial branches</td>
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<td>Shelly &amp; Church, 1988</td>
<td>maxillary nerve branches</td>
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<tr>
<td>Ragno, et al., 1989</td>
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<tr>
<td>Stott, 1989</td>
<td>frontal/supratrochlear nerves</td>
<td>V2</td>
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<tr>
<td>Barnard &amp; Bainton, 1990</td>
<td>maxillary nerve branches</td>
<td>V2</td>
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<tr>
<td>Lang, et al., 1991</td>
<td>maxillary nerve branches</td>
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</table>

* Adapted from Blanc, 1991.
Trigeminocardiac reflex

amount of cardiac change and the time course until a return to normal. However, this classification proved to be of little clinical value because no relation to risk factors could be detected.

Prophylaxis and Treatment of the TCR

Because both bradycardia and hypotension may lead to hypoperfusion and cerebral or myocardial infarction, there is potential benefit from blocking the depressor response. Based on results from ocular surgery, the following factors are known to increase the risk of the TCR: hypercapnia, hypoxemia, light general anesthesia, age (more pronounced in children, perhaps due to a higher resting vagothal tone), the nature of the provoking stimulus (stimulus strength, duration, and waveform), and drugs. Hypercapnia increases the incidence of the TCR in spontaneously breathing infants and children, and hypoxemia must be prevented due to the possibility of cardiac arrhythmias. These ventilatory abnormalities may be due to, or aggravated by, a trigeminorespiratory reflex, which is commonly associated with the TCR. They can be elicited in animals and in humans. The diving reflex in seals and other diving vertebrates results from trigeminal afferent activity. Potent narcotic agents such as sufentanil or alfentanil, beta-blockers, and calcium channel blockers may produce predisposition to this reflex. Narcotic agents may augment vagothal tone through their inhibitory action on the sympathetic nervous system.

Recognized therapeutic maneuvers include avoidance of factors known to cause predisposition for the reflex, cessation or modulation of the surgical stimulus, intravenously administered anticholinergic medication (atropine or glycopyrrolate), and local anesthetic blockade of the afferent nerves. Once the HR has returned to normal, neural blockade and/or the administration of intravenous anticholinergics are indicated for prevention of additional TCR episodes. However, cholinergic blockade reduces but does not totally prevent either bradycardia or hypotension in animals, because the response includes both activation of vagal cardioinhibitory fibers and inhibition of adrenergic vasoconstriction.

Conclusions

In this retrospective study, we have shown that significant decrease in HR and MABP occurred during tumor dissection near the trigeminal nerve at the brainstem. This decrease led to TCR in up to 11% of our surgical procedures near or at the trigeminal nerve. These findings demonstrate the presence of a central induction of the TCR in humans, which can be a potentially dangerous complication during surgery performed in the CPA.

We recommend that all patients in whom tumor is removed in the CPA undergo continuous monitoring of MABP and HR both during surgery and for at least 24 hours after the procedure. Prophylaxis of the TCR includes the use of intravenous anticholinergic agents such as atropine. In addition, it could be shown that abrupt and sustained traction on the trigeminal nerve is more prone to elicit the TCR than smooth and gentle traction. A noninvasive, temporary pacemaker that can respond rapidly to abrupt changes in HR should be considered for patients with known cardiac risk factors to prevent the occurrence of the TCR.

Acknowledgment

We thank Frances P. Harris, Ph.D., for editing the manuscript.

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