A New Neuropathologic Mechanism of Blood pH Irregularities After Neck Trauma: Importance of Carotid Body–Glossopharyngeal Nerve Network Degeneration

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■ OBJECTIVE: **We created a neck trauma model by injecting blood into the sheath of rabbits' carotid bodies (CBs). Then we determined the relationship between neuronal degeneration of the CB due to hemorrhage of this organ and its clinical effects such as blood pH and heart rhythm.**

■ METHODS: **The present study included 24 adult male New Zealand rabbits. The animals were divided into 3 groups: control ($n = 5$); sham (0.5 mL saline injected into CBs; $n = 5$); and study (CB trauma model; $n = 14$). pH values and heart rhythms were recorded before the experiment to determine the values under normal conditions, and measurements were repeated thrice in the days following the experiment. The number of normal and degenerated neuron density of CBs was counted. The relationship between the blood pH values, heart rhythms, and degenerated neuron densities was analyzed.**

■ RESULTS: **Heart rhythms were 218 ± 20 in the control group, 197 ± 16 in the sham group ($P = 0.09$), and 167 ± 13 in the study group ($P < 0.0005$). pH values were 7.40 ± 0.041 in the control group, 7.321 ± 0.062 in the sham group ($P = 0.203$), and 7.23 ± 0.02 in study group ($P < 0.0005$). Degenerated neuron densities were 12 ± 4/mm^3 in the control group, 430 ± 74/mm^3 in the sham group ($P < 0.005$), and 7434 ± 810/mm^3 in the study group ($P < 0.0001$).**

■ CONCLUSIONS: **A high degenerate neuron density in the CB can decrease blood pH and hearth rhythm after neck trauma, and there might be a close relationship between the number of degenerated neurons and clinical findings (such as heart rhythm and blood pH). This relationship suggests that injury to the glossopharyngeal nerve–CB network can cause acidosis by disturbing the breathing-circulating reflex and results in respiratory acidosis.**

INTRODUCTION

Carotid bodies (CBs) are chemosensitive structures in the human body that are localized at the carotid bifurcation.[1] They are supplied mainly by the external carotid artery or its branches and rarely by the internal carotid artery. CBs are considered as the most vascularized tissues in the human body.[1,2] In CBs, glossopharyngeal nerve (GPN) endings are the chemosensory afferents of neurons. Action potentials are triggered in those terminals and relayed to the nucleus of the tractus solitarius to evoke chemoreceptor reflexes. Thus CBs play important roles in the chemotransduction of chemical changes in arterial blood, which is essential for respiratory and cardiovascular activities.[3,4] Glomus cells are known to be the major chemosensitive cells in CBs.[5] These cells form lobular clusters and are opposed to afferent nerve endings, which are essential for sensory chemotransduction.[3]

In this study, we hypothesized that CB dysfunction may occur due to hemorrhage in this organ following neck trauma, tumor resection at this region, carotid artery surgery, or neck irradiation. It is known that neck traumas are sometimes associated with the risk of life-threating complications.[6] Although neck traumas might be minor, the complex and vulnerable anatomy of the neck can increase the risk of major life-threatening complications. The management of neck traumas can be challenging and sometimes overwhelming, as this anatomic region contains many vital structures[7,8] that might pose diagnostic and therapeutic dilemmas in the emergency department. According to a previous report, the mortality rate in penetrating neck injury cases is as high as 10%.[9] In addition, most cases of mortality after neck

Key words
- Blood pH
- Carotid body
- Glossopharyngeal nerve
- Neck trauma

Abbreviations and Acronyms
CB: Carotid body
GPN: Glossopharyngeal nerve
TUNEL: Terminal deoxynucleotidyl transferase dUTP nick-end labeling

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trauma are considered to be associated with vascular injuries and esophageal injuries.[9,10] However, to date, CB damage associated with neck trauma and its possible effects have not been reported. In addition, to our knowledge, the relationship between histopathologic changes in CB due to hemorrhage in this organ and blood pH has not been investigated. Recent studies have suggested that acidosis is associated with poor prognosis in patients with neck trauma.[11,12] Thus knowledge of this complication and the potential risk factors for CB neuronal degeneration might be essential for improving the condition of these patients and preventing further complications. In this study, we created a trauma model by injecting blood into the CB sheath and then investigated the relationship between CB neuronal degeneration and its clinical effects on parameters like blood pH and heart rate. To our knowledge, this is the first such study in the literature.

MATERIALS AND METHODS

Animals

The present study included 24 adult male New Zealand rabbits (weight, 3.8 ± 0.35 kg). The animals were kept in polypropylene cages under a 12/12 hour light/dark cycle and controlled temperature (22°C ± 2°C) until and during the experiment. All surgical protocols were approved by the Institutional Animal Care and Use Committee of Atatürk University (07/191/25.10.2017). The animals were divided into the following 3 groups: control (no intervention to determine the normal structure of the CB-GPN network; $n = 5$); sham (0.5 mL saline injected into CBs; $n = 5$) and study (CB trauma model; 0.5 mL autologous arterial blood injected into CBs; $n = 14$).

Study Design

Blood samples of all animals ($n = 24$)were collected in heparinized syringes, and the pH values were measured using a pH meter (MP 220 pH meter, Mettler Toledo, Columbus, Ohio, USA). The blood pH values and heart rhythms of all animals were recorded before the experiment to determine values under normal conditions. Animals were anaesthetized by subcutaneous injections of ketamine hydrochloride, lidocaine hydrochloride, and acepromazine. An appropriate laboratory environment was prepared for the experiment. Animals were fixed to the operating table in the supine position after shaving the neck region, and povidone-iodine solution was used for sterilization. In the study group, an anterior midcervical incision was made at the level of the common carotid artery bifurcation (C4-5) and 0.5 mL blood obtained from the auricular arteries was injected into the sheaths of both CBs using a BD Micro-Fine Plus 0.23-mm (32G) × 4 mm (Pentapoint; Becton Dickinson, Franklin Lakes, New Jersey, USA) sterile needle tip after gently dissecting the CB, CB bifurcations, and vagal and glossopharyngeal nerves. In the sham group, 0.5 mL saline were injected into the sheaths of both CBs with the same method described earlier. Measurements of blood pH and heart rhythms were repeated thrice in the days following these experimental procedures. All animals were followed up for 2 weeks under normal laboratory standards without treatment and were sacrificed under general anesthesia at the end of the experiment. The bifurcations of both common carotid arteries were resected. The specimen usually included 2 cm of the common carotid artery, the bifurcation, and 3 cm of both internal carotid and external carotid arteries. The CB was dissected out, and using pointed scissors and fine forceps, surrounding connective tissues were dissected away.

Histopathologic Examination

The fibrous adventitial sheath was gently teased, and the CB tissues were preserved in a 10% formaldehyde solution for 7 days. The specimens were embedded in paraffin blocks, and 20 consecutive 5-μm sections of all preparations were used for stereologic examinations. CB sections were stained with hematoxylin-eosin, and the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay was performed. Sections were observed under a light microscope, and a physical dissector method was used to evaluate the number of neurons.

Data were obtained from dissector pairs consisting of parallel sections taken at known intervals. Two labeled consecutive sections obtained from tissue samples (dissector pairs) were mounted on each slide. Twenty dissector pairs were taken from each block for the analysis of neurons. A counting frame was placed on consecutive section photographs on the screen of a personal computer to count the neurons. The bottom and left edges of the frame were excluded from counting (exclusion lines) together with the extensions. The other edges of the frame and the top right corner were considered as inclusion areas, and any particles that touched these areas or were located inside the frame were counted as dissector particles. CB neurons were counted when they were visible in the reference section. The reference and look-up sections were reversed to double the number of dissector pairs without including new sections. The average numeric density of ganglial neurons (NvGN) per mm^3 was estimated using the following formula:

$$NvGN = \sum QN/txA$$

In this formula, ΣQN is the total number of counted neurons appearing only in the reference sections, t is the section thickness, and A is the area of the counting frame. The Cavalieri volume estimation method was used to obtain the total number of neurons in each specimen. The total number of neurons was calculated by multiplying the volume (mm^3) and numeric density of neurons in each CB.

The numbers of normal and degenerated neurons in the CBs were counted by stereologic methods.

Statistical Methods

Data are presented as mean ± standard error of the mean. The degenerated neuron density, blood pH, and heart rhythm were analyzed statistically. The Mann-Whitney U test was used to analyze the results. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0 (SPSS Inc., Chicago, Illinois, USA). A P value < 0.05 was considered statistically significant.

RESULTS

Losses and Exclusions

In the study group, 2 rabbits died during the experiment, likely from cardiorespiratory irregularities, and new animals were reassessed in this group.

Table 1. Heart Rhythm, Number of Neurons and pH Values in Control, Sham, and Study Groups

	Control Group	Sham Group	Study Group
Heart rhythm/minute	218 ± 20	197 ± 16 ($P = 0.09$)	167 ± 13 ($P < 0.0005$)
Blood pH	7.40 ± 0.41	7.321 ± 0.062 ($P = 0.203$)	7.23 ± 0.02 ($P < 0.005$)
Degenerated neurons (/mm^3)	12 ± 4	430 ± 74 ($P < 0.005$)	7434 ± 810 ($P < 0.0001$)

Clinical Outcomes

The heart rhythms and pH values of all animals were normal before the start of the experimental procedures. The values obtained after the experimental procedures were close to each other in each group; thus the mean values were determined. After the experimental procedures, the mean heart rhythms were 218 ± 20 beats/minute in the control group, 197 ± 16 beats/minute in the sham group ($P = 0.09$), and 167 ± 13 beats/minute in the study group ($P < 0.0005$). In addition, the mean blood pH values were 7.40 ± 0.041 in the control group, 7.321 ± 0.062 ($P = 0.203$) in the sham group, and 7.23 ± 0.002 in the study group ($P < 0.005$).

Histopathologic Findings

Histopathologically, cytoplasmic condensation, nuclear shrinkage, cellular angulations, and pericytoplasmic halo formation secondary to cytoplasmic regression and TUNEL-staining positivity were considered as the criteria of neuronal degeneration.

Histopathologic analysis showed that neuronal degeneration of CB-GPN tissues was statistically more prominent in the study group than in the control and sham groups. The degenerated neuron densities in the CBs were 12 ± 4/mm^3 in the control group, 430 ± 74/mm^3 in the sham group ($P < 0.005$), and 7434 ± 810/mm^3 in the study group ($P < 0.0001$) (Table 1). Interestingly, among the dead rabbits, the degenerated neuron density in the CBs was 4417 ± 310/mm^3.

Figure 1 shows the histologic appearance of the carotid bifurcation. Figure 2 shows the histomorphologic appearance of hemorrhagic areas around the CB and GPN (CN-IX) in a neck trauma model animal. Figure 3 shows the stereologic cell counting of the CB in a neck trauma model animal.

DISCUSSION

Historical Perspective

The first detailed study of the carotid region was published by De Castro in 1926, using tissues from both adults and embryos of mammalian species. De Castro described the complicated structure of the CB in detail and mentioned that it has a real tangle of small blood vessels, sympathetic axons, and glandular cells, which may form small glomeruli.[13] In addition, electron microscopic studies in the 1960s showed that glomus cells were abundantly supplied with nerve endings containing synaptic-like vesicles, suggesting morphologically that the glomus cell is some sort of

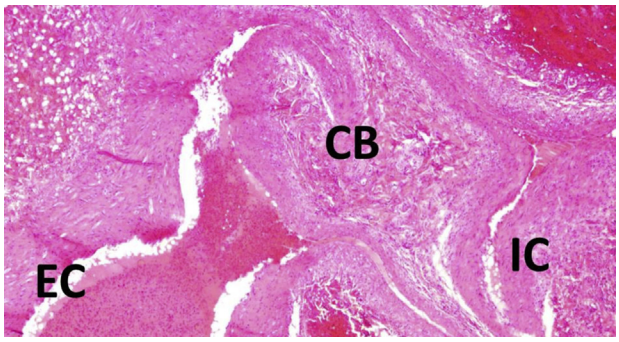

Figure 1. Microanatomic appearance of the carotid bifurcation. The carotid body is present between the internal and external carotid arteries (light microscopy; hematoxylin-eosin staining; magnification, ×10) (CB, carotid body; EC, external carotid artery; IC, internal carotid artery).

endocrine cell controlled by efferent nerve fibers.[14] Ortiz et al[15] mentioned that sustained hypoxia enhances TASKlike current inhibition in glomus cells, and Conde et al[16] showed that released neurotransmitters set the action potential frequency in carotid sinus nerves. Moreover, Gonzalez et al[17] stated that the type I cells (glomus cells) of CBs contain high levels of dopamine and have an embryologic origin and ultrastructural appearance similar to those of chromaffin cells from the intact adrenal medulla. Physical changes (temperature, flow, and osmolarity) can also be detected by CBs. Electrical coupling between glomus cells themselves appears extensive. Sustentacular cells, which were classically considered as ensheathing glia for glomus cells and nerve endings, appear to

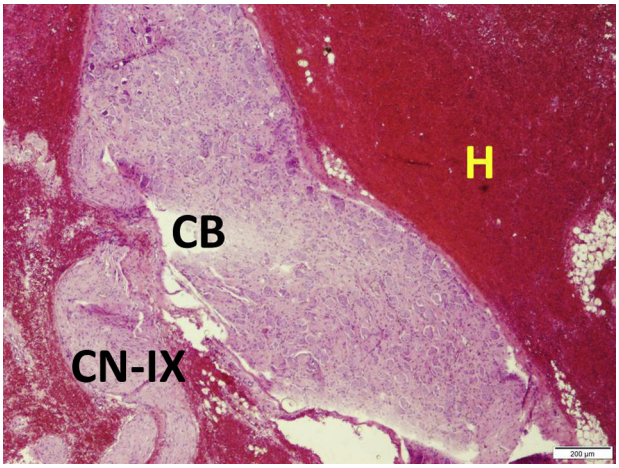

Figure 2. Histomorphologic appearance of the carotid body (CB) located between the internal and external carotid arteries, glossopharyngeal nerve (GPN; CN-IX), and hemorrhagic areas (H) around the CB-GPN in a neck trauma model animal (light microscopy; hematoxylin-eosin staining; magnification ×10/base).

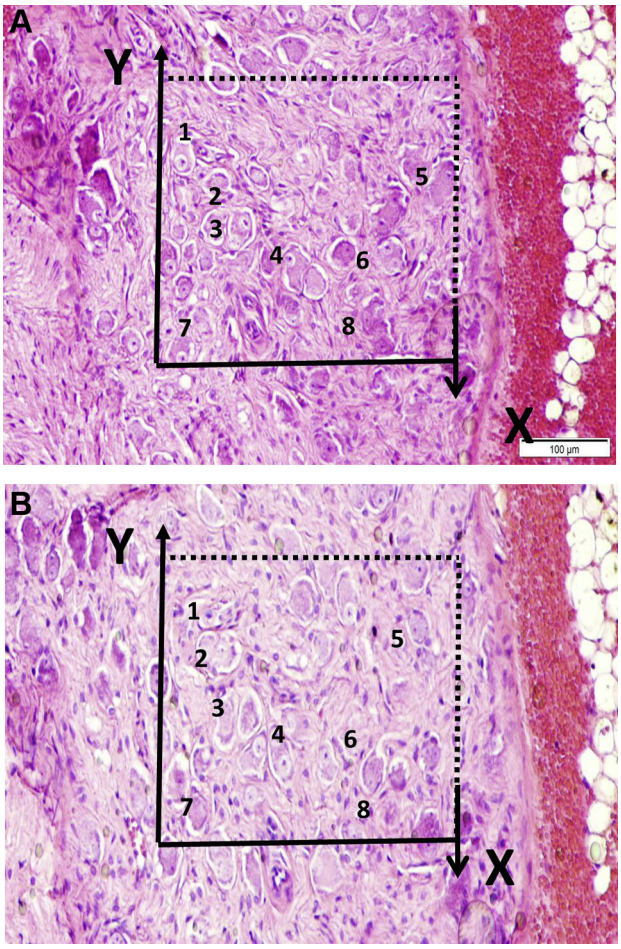

Figure 3. (**A** and **B**) Stereologic cell counting of the carotid body in a rabbit. The physical dissector method is applied, and micrographs in the same fields of view (**A** and **B**) are obtained from 2 parallel, adjacent thin sections separated by a distance of 5 µm. The upper and right lines in the unbiased counting frames represent inclusion lines, and lower and left lines, including extensions, represent exclusion lines. Neuronal nucleoli touching the inclusion lines are excluded, and nucleoli profiles touching the inclusion lines and located inside the frame are counted as dissector particles, unless their profiles extend up to the reference section. The nucleoli marked with 1, 3, 5, 6, and 7 are dissector particles in **A**. **B** shows them as they disappear. The nucleoli marked with 2, 4, and 8 are not dissector particles in **A. B** shows that they have disappeared (light microscopy; hematoxylin-eosin staining; magnification, ×20).

behave as stem cell precursors for glomus cells under chronic hypoxic conditions.[14]

Carotid Body–Glossopharyngeal Nerve Anatomy and Physiology

Human CBs are located bilaterally in the adventitia of the posteromedial aspect of the carotid bifurcation and are usually connected to the bifurcation by a Mayer ligament.[18-20] CBs are small structures measuring 3–7 mm (maximal diameter), 2–4 mm (minimal diameter), and 1.7–2 mm (depth) and weighing only about 13 mg.[2,19,21] In addition, according to the study by Heath et al,[20] their weight can range from 1.9–47.4 mg. CBs are usually reddish brown, but in cases of diseases, such as cor pulmonale, chronic bronchitis, and emphysema, they may appear mauve.[20] They have a rich vascular supply and afferent and efferent innervations. There is a close association between CBs and tissues, such as sympathetic neurons and cranial nerves (GPN [IX] and vagus [X]). An important branch of the GPN is the carotid sinus nerve; therefore the GPN supplies the CB and carotid sinus.[18,22]

CBs are chemosensory organs that monitor blood chemicals and initiate compensatory reflex adjustments to maintain homeostasis. A previous study stated that prolonged hypoxia from birth delays the onset of a mature chemoreflex response to hypoxia by CBs and that chronic hyperoxia severely depresses the responses from the carotid sinus nerve in kittens and rats.[23] When the arterial blood oxygen level drops in hypoxia, glomus cells are activated and the CB responds to a decrease in the partial pressure of oxygen (PaO_2) in arterial blood and triggers hyperventilation within seconds.[24] Chang et al[24] mentioned that a decrease in the PaO_2 increases the CB sensory discharge at the onset of hypoxia (PaO_2 = 60–80 mm Hg), with the peak at a PaO_2 value of 20–30 mm Hg. In addition, according to Chang et al,[24] the CB is stimulated by hypercapnia and low pH, in addition to hypoxia. Doux et al[25] reported that CBs have vital functions in cerebrovascular and cardiorespiratory autoregulation and that CB dysfunction can result in cerebrovascular and cardiorespiratory autoregulation disorders.

CB and Blood pH Regulation

The CB initiates compensatory reflex adjustments to maintain homeostasis by monitoring blood characteristics (e.g., low PaO_2) in the body. Changes in pH associated with CB neuronal degeneration have not been well studied until now. Kanat et al[22] found a relationship between acidosis and CB degeneration in rabbits after subarachnoid hemorrhage. In addition, Erickson et al[23] stated that chemoafferent degeneration following chronic hyperoxia causes the loss of target tissues in the CB and a decrease in CB volume. In the present study, 2 of the 24 rabbits died during the second week, probably from cardiorespiratory irregularities. The most likely mechanism leading to severe clinical conditions, such as cardiorespiratory irregularities following CB trauma (injection of blood into the CB sheaths), in these animals is neuronal degeneration involving the CB and GPN. Therefore there was a decrease in the blood pH.

Neuropathologic and Pathophysiologic Changes in Carotid Body

In this study, we found that injection of blood into the CB sheaths caused CB neuronal degeneration. In addition, we noted significantly lower blood pH values and heart rhythms in the rabbits with degenerated neurons in their CBs than in those without degenerated neurons. Thus we determined that traumatic injury-related CB degeneration might be responsible for decreased blood pH and heart rhythm. The blood injected into the CB sheaths probably disrupted the blood circulation and caused edema and ischemia, resulting in neuronal degeneration. We used the TUNEL assay to detect pathophysiologic changes. We considered cytoplasmic condensation, nuclear shrinkage, cellular angulations, and pericytoplasmic halo formation secondary to cytoplasmic regression as the criteria of neuronal degeneration. The mean degenerated

neuron density in the CB was much higher among dead rabbits than living rabbits. In this study, we used stereologic methods to estimate the number of neurons. Stereologic methods, which can calculate the 3-dimensional parameters of a structure from 2-dimensional measurements, are being frequently and safely used in most studies.[26,27] In addition, the dissector method, which was described by Sterio[28] and Cavalieri,[29] can easily estimate the particle number; can be readily performed; is intuitively simple; is free from assumptions about particle shape, size, and orientation; and is unaffected by overprotection and truncation.

Importance of This Study

Trauma is responsible for 10% of the deaths worldwide and is the leading cause of death in young people (age range 5–44 years) in developed countries.[30] Injuries to the cervical spine have been reported in 19%–51% of cases of spinal trauma.[31] Patients with cervical spine injuries are a high-risk group, and they have the highest reported early mortality rate among spinal trauma patients.[32,33] This is because there are extensive vascular and neural structures with vital functions in this region, and CB is one of these structures. The identification and assessment of cervical spine injuries during the initial trauma evaluation are challenging, as patients often present with a reduced level of consciousness because of concurrent head injury, sedative and analgesic medication, or endotracheal intubation.[32]

The incidences of various injuries after neck trauma have been reported as follows: vertebral artery injury, 0.5%[34]; carotid artery injury, 3%–10%[35]; esophageal injury, 0.10%–0.19%[36]; and traumatic airway injury (blunt and penetrating traumas), 0.4% and 4.5%, respectively.[37] However, there is no information about the incidence of CB injury after neck trauma, as this injury is difficult to determine. On the other hand, blood pH changes and cardiovascular disorders might occur after neck trauma, and they can be life-threatening. This is a serious problem, especially in unconscious and multitrauma patients. The present study had the following 2 major outcome findings after neck trauma: 1) severe degenerative cell changes occurred in the CB owing to CB injury among dead rabbits and 2) CB degeneration resulted in decreased pH, acidosis, and decreased heart rhythm. These findings might be important with regard to morbidity and mortality after neck trauma.

Limitations of Study

The present study has some limitations. Firstly, our experimental rabbit model cannot represent a human CB injury model. This is the most important limitation of this study. Secondly, in the sham group, trauma might have occurred with the injection of saline into the CB sheaths. However, we used a fine-tip needle to minimize trauma. Histopathologic findings and other findings (pH values and heart rhythms) indicated that CB degeneration was more prominent in the sham group than the control group. However, the difference was statistically more significant in the study group than the control group. Further experimental and clinical studies are necessary to overcome these limitations and confirm our findings.

CONCLUSIONS

A high degenerate neuron density in the CB can decrease blood pH and hearth rhythm after neck trauma, and there might be a close relationship between the number of degenerated neurons and clinical findings (such as heart rhythm and blood pH). Although the marked difference between the neuron density in the CB and decrease in pH is unexplained, this difference might have important implications. Our findings suggest that injury to the CB-GPN network can cause acidosis by disturbing the breathing-circulation reflex and can result in respiratory acidosis following neck trauma. Thus attention should be paid to metabolic disorders after neck trauma.

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