Full Length Research Paper

Sinus bradycardia could be caused by right ventrolateral medulla oblongata compression

[1]Zhang Guangming, [1]Chen Guoqiang, [*1]Zuo Huancong

[1]Neurosurgery Department of Yuquan, Hospital Tsinghua, University China

*Corresponding author email: zuohc@mail.tsinghua.edu.cn

Abstract

We found a new clinic phenomenon that some hemifacial spasm patients were accompanied by sinus bradycardia. We noticed that in most of these patients, ventrolateral medulla oblongata was compressed by artery loop and decompression at ventrolateral medulla oblongata was effective for their sinus bradycardia. Most of these patients were right hemifacial spasm patients (14/18). We firstly clinically studied and described this phenomenon in *Surgical Neurology* and proposed the hypotheses that compression at ventrolateral medulla oblongata can lead to heart rate decrease and decompression at ventrolateral medulla oblongata can result in heart rate increase. We designed animal experiments to verify our hypotheses and to explore the likely mechanism. We made the elastic sacculus compression system to compress in different diameter (4mm; 5.5mm; 7mm), the ventrolateral medulla oblongata of New Zealand rabbits which were randomly divided into group A (left) and group B (right). Rabbits underwent posterior medial craniotomy. We recorded and statistically analyzed the heart rates before and after ventrolateral medulla oblongata compression in different pressure on both sides. The average heart rates of pre-compression, 4mm, 5.5mm, and 7mm elastic sacculus compression system compression were respectively 132.6±5.83，114.74±9.27，110.93±10.59，105.84±5.87 beat per minute in group B. The heart rates had significant statistic difference (P＜0.01) when right ventrolateral medulla oblongata is compressed by elastic sacculus compression system in different diameter. The post-compression heart rates were lower than that of pre-compression. The average heart rates of pre-compression, 4mm, 5.5mm, and 7mm elastic sacculus compression system compression were respectively 131.85±7.8，129.49±6.4，130.2±3.9，128.58±5.43 beat per minute in group A. The heart rates had no statistic difference when left ventrolateral medulla oblongata is compressed by elastic sacculus compression system in different diameter. Compression at right ventrolateral medulla oblongata can lead to heart rate decrease. Compression at left ventrolateral medulla oblongata can't lead to heart rate decrease. Animal experiments results supported our hypotheses. Compression at right ventrolateral medulla oblongata might be one of the reasons of sinus bradycardia in human being.

Keywords: Sinus bradycardia; Heart rate; Decompression; Ventrolateral medulla oblongata.

INTRODUCTION

As we know that microvascular decompression is radical for most hemifacial spasm patients (Hyun SJ et al., 2010; Jannetta PJ et al., 2005; Funaki T et al., 2010). We found an interesting phenomenon that some hemifacial spasm patients were accompanied by sinus bradycardia. In microvascular decompression for these patients, we found that vagus and/or ventrolateral medulla oblongata was compressed by intracranial artery loop. We noticed in these patients that decompression at vagus and/or ventrolateral medulla oblongata could result in heart rate

increase and that these patients had right predominance (14/18 patients were right hemifacial spasm), which was firstly described in detail by us in *Surgical Neurology* (Guangming Zhang et al., 2009). This phenomenon has potentially important clinical significance to sinus bradycardia patients.

Cardiovascular regulator center as we know, is located at medulla oblongata. We considered ventrolateral medulla oblongata was closely related to the heart rate regulation. We found in some microvascular decompression operations for hemifacial spasm patients without sinus bradycardia that intraoperative traction stimulation to ventrolateral medulla oblongata by brain depressor could immediately lead to sinus bradycardia, which sometimes made the surgeons to suspend operation. Heart rate rebounded a few seconds after removing the traction. This phenomenon, I think is also observed by other neurosurgeons executing microvascular decompression for hemifacial spasm or trigeminal neuralgia patients. Based on this observation that stimulation to ventrolateral medulla oblongata could immediately lead to sinus bradycardia, and the knowledge that (Hyun et al., 2010) the cell bodies of preganglionic fibers of cardiac vagus locate at dorsal nucleus of vagus and ambiguous nucleus in medulla oblongata, (Jannetta PJ., 2005)sinus node is innervated predominantly by postganglionic fibers of right cardiac vagus, and (Funaki T., et al 2010) cardiac vagus has negative chronotropic and dromotropic action on heart which decreases the heart rate, we proposed that artery loop compression stimulation to dorsal nucleus of vagus and ambiguous nucleus in medulla oblongata lead to heart rate decrease (Guangming Zhang et al., 2009). For the treatment effect on sinus bradycardia observed within microvascular decompression operation, it appears that decompression at ventrolateral medulla oblongata removes the stimulation to dorsal nucleus of vagus and ambiguous nucleus, which increases heart rate. In our description most patients were right hemifacial spasm patient. This right side predominance might be explained by the fact that sinus node is innervated mainly by right cardiac vagus (Guangming Zhang et al., 2009). So we proposed the following hypotheses: Compression at ventrolateral medulla oblongata can lead to sinus bradycardia and decompression at ventrolateral medulla oblongata can increase heart rate; right predominance of this phenomenon might be related to the fact that heart rate is mainly regulated by right cardiac heart vagal nerve. To verify our hypotheses and to explore the likely mechanism we designed the following animal experiments.

MATERIAL AND METHODS

Animal and anesthesia

Experiment animal were healthy male New Zealand rabbit,3-4 month old, 2.5-3 Kg. 16 rabbits were randomly divided into two groups: group A and group B. In group A, left ventrolateral medulla oblongata is compressed by elastic sacculus compression system and right ventrolateral medulla oblongata is compressed by elastic sacculus compression system in group B. Anesthesia: 2% amobarbital, dosage: 30 mg/Kg, abdominal cavity injection.

All the animal studies were performed in line with the US National Institute of Health Guide for the Care and Use of Laboratory Animals and approved by the Beijing Administration Committee of Experimental Animals.

Preparation of elastic sacculus compression system (Figure-1, A)

Elastic sacculus compression system was designed by ourselves to compress ventrolateral medulla oblongata of New Zealand rabbits. Elastic sacculus compression system was composed of an elastic sacculus and a rigid plastic tube and a three-way connection. The elastic sacculus was tightly connected to the rigid plastic tube (1mm in diameter, 0.3 meter in length). Diameter of the elastic sacculus will increase when its inner pressure increases. We found that when the terminal pressure of the rigid plastic tub is 41cm, 76cm, and 127cm H_2O column respectively, the diameter of the elastic sacculus is accordingly 4mm, 5.5mm, and 7mm. Elastic sacculus compression system could be used repeatedly in different rabbits. When the sacculus diameter is less than 4mm, ventrolateral medulla oblongata is hard to compress efficiently. When the sacculus diameter is more than 8mm, ventrolateral medulla oblongata might be mechanically damaged by the sacculus. So we chose 4mm, 5.5mm, and 7mm as diameter of the sacculus compressing ventrolateral medulla oblongata.

Posterior medial craniotomy for rabbits

Posterior medial craniotomy procedures are similar to that in human being operation. We explored the anatomy of posterior cranial fossa, foramen magnum, and upper spinal cord of rabbits under microscopy and found that the anatomy of these areas in rabbit is similar to that in human being (Figure-1, B). In posterior medial incision, from inion to C3 spinous process muscles were stretched by opener and part of occipital squamosal and atlas was removed. In longitudinal dura incision, lower medulla oblongata and upper spinal cord were exposed clearly and elastic sacculus compression system was inserted under ventrolateral medulla oblongata (Figure-1, C).

Data collecting of heart rates

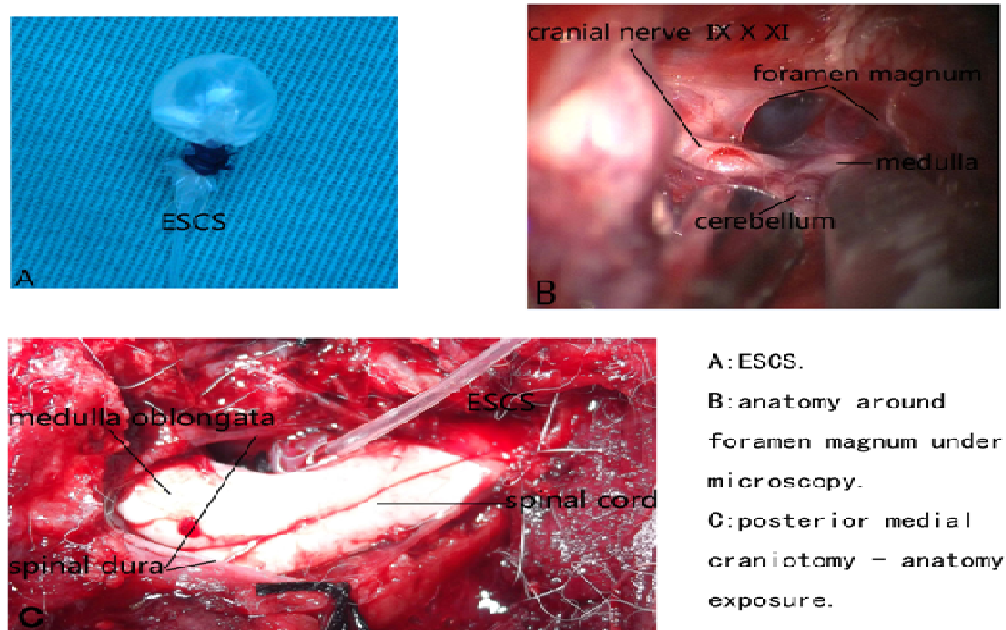When elastic sacculus compression system and posterior

A:ESCS.

B:anatomy around foramen magnum under microscopy.

C:posterior medial craniotomy – anatomy exposure.

Figure 1. ESCS and intraoperative findings under microscopy

Talbe1.heart rate（beat/minute） after left ventrolateral medulla oblongata compression in different pressure

Animal number	Pre-compression	4mm elastic sacculus compression system compression	5.5mm elastic sacculus compression system compression	7mm elastic sacculus compression system compression
1	135.2	140.3	138.2	127.4
3	134.5	130.7	130.7	133.6
5	131.6	134.8	130.4	132.9
7	137.3	132.5	127.8	129.5
9	125.1	124.3	128.3	133.2
11	117.4	120.7	124.8	117.7
13	130.8	124.5	129.5	124.3
15	142.9	128.1	131.9	130
Average	131.85±7.8	129.49±6.4	130.2±3.9	128.58±5.43

medial craniotomy are ready, we record heart rate for 5-minute before implanting elastic sacculus compression system, then implant elastic sacculus compression system under right or left ventrolateral medulla oblongata alternately, water pressure in elastic sacculus compression system was adjusted to 41cm water column (sacculus 4mm in diameter). 3 minutes later, we recorded the heart rate for the second 5-minute. Evacuate elastic sacculus compression system, 3 minutes later, water pressure in SCS was adjusted to 76cm water column (sacculus 5.5 mm in diameter). 3 minutes later, we recorded the heart rate for the third 5-minute. Evacuate elastic sacculus compression system, 3 minutes later, water pressure in SCS was adjusted to 127cm water column (sacculus 7 mm in diameter). 3 minutes later, we record heart rate for the forth 5-minute. Average heart rate of every 5-minute ECG is calculated. Detailed information is shown in table-1and table-2. These four times 5-minute

Table 2. heart rate（beat/minute）after right ventrolateral medulla oblongata compression in different pressure

Animal number	Pre-compression	4mm elastic sacculus compression system compression	5.5mm elastic sacculus compression system compression	7mm elastic sacculus compression system compression
2	140.4	127.5	103.3	107.2
4	125.3	97.6	110.8	98.5
6	138.6	119.9	106.5	104.3
8	129	116.4	112.7	104.4
10	132.5	120.3	110.3	108.3
12	126.2	113.7	96.6	98
14	138.1	116.7	133	115.3
16	130.7	105.8	114.2	110.7
Average	132.6±5.83	114.74±9.27	110.93±10.59	105.84±5.87

Table 3. One-Way ANOVA-Post Hoc Tests

	(I) VAR002	(J) VAR002	Mean Difference	Std. Error	Sig.
		2	2.36	3.02	.441
	1	3	1.65	3.02	.590
		4	3.27	3.02	.288
		1	-2.36	3.02	.441
	2	3	-.71	3.02	.815
		4	.91	3.02	.765
LSD		1	-1.65	3.02	.590
	3	2	.71	3.02	.815
		4	1.62	3.02	.595
		1	-3.27	3.02	.288
	4	2	-.91	3.02	.765
		3	-1.62	3.02	.595

Variable 1、2、3、4 respectively represent the heart rate after left ventrolateral medulla oblongata compression in different pressure (pre-compression,4mm elastic sacculus compression system,5.5 mm elastic sacculus compression system, and 7mm elastic sacculus compression system compression).

heart rates are statistically analyzed.

Statistical analysis

Heart rate data before and after compression were analyzed by One-Way ANOVA-Post Hoc Experiments (Multiple Comparisons).

RESULTS

Detailed information of heart rates pre-compression and post-compression in different diameter elastic sacculus compression system was shown in table-1 and table-2. The average heart rates of pre-compression, 4mm, 5.5mm, and 7mm elastic sacculus compression system

Table 4. One-Way ANOVA-Post Hoc Tests

	(I) VAR002	(J) VAR002	Mean Difference	Std. Error	Sig.
	1	2	17.86 *	4.08	.000
		3	21.67 *	4.08	.000
		4	26.76 *	4.08	.000
	2	1	-17.86 *	4.08	.000
		3	3.81	4.08	.358
LSD		4	8.90 *	4.08	.038
	3	1	-21.67 *	4.08	.000
		2	-3.81	4.08	.358
		4	5.08	4.08	.223
	4	1	-26.76 *	4.08	.000
		2	-8.90 *	4.08	.038
		3	-5.08	4.08	.223

Variable 1、2、3、4 respectively represent the heart rate after right ventrolateral medulla oblongata compression in different pressure(pre-compression,4mm elastic sacculus compression system,5.5 mm elastic sacculus compression system, and 7mm elastic sacculus compression system compression). * statistical significance.

compression were respectively 132.6±5.83，114.74±9.27，110.93±10.59，105.84±5.87 beat per minute in group B. The average heart rates of pre-compression, 4mm, 5.5mm, and 7mm elastic sacculus compression system compression were respectively 131.85±7.8，129.49±6.4，130.2±3.9，128.58±5.43 beat per minute in group A.

Statistical analysis results were shown in table-3 and table-4. From table-3, we found that the heart rates had no statistic difference when left ventrolateral medulla oblongata is compressed by elastic sacculus compression system at different pressure. Compression at left ventrolateral medulla oblongata can't lead to heart rate decrease. Compression at left ventrolateral medulla oblongata had no change on heart rate. From table 4, we found that the heart rates had significant statistic difference (P＜0.01) when right ventrolateral medulla oblongata is compressed at different pressure (between pre-compression and 4mm elastic sacculus compression system compression; between pre-compression and 5.5mm elastic sacculus compression system compression; between pre-compression and 7mm elastic sacculus compression system compression; between 4mm and 7mm elastic sacculus compression system compression). It seems that the higher the pressure, the lower the heart rate. But the heart rates have no significant statistic difference between 4mm and 5.5mm elastic sacculus compression system compression. The heart rates also have no significant statistic difference between 5.5mm

and 7mm elastic sacculus compression system compression. Compression at right ventrolateral medulla oblongata can effectively decrease heart rate.

DISCUSSION

Different diameters of elastic sacculus compression system represent different pressure on ventrolateral medulla oblongata. The average heart rates after 4mm compression, 5.5mm compression and 7mm compression at ventrolateral medulla oblongata are respectively 114.74±9.27, 110.93±10.59, and 105.84±5.87 beat per minute. The average heart rates showed that the greater the pressure, the lower the heart rate. Neurosurgeons who have microvascular decompression experience knows that trigeminal nerve or facial nerve is actually compressed by intracranial artery loop in most cases. Elastic sacculus compression system is similar to intracranial artery loop compression. Although, our elastic sacculus compression system might not be very perfect to mimic intracranial artery compression, we believe that the result of compression at right ventrolateral medulla oblongata can effectively decrease heart rate.

Although, the result came from rabbit, we think that this should be the same situation in human beings. For example, we found in VMD operation for hemifacial spasm patients that compression or traction to MVO could

lead to sinus bradycardia immediately and that heat rate rebound in few seconds after removing the compression or traction to ventrolateral medulla oblongata. We also found that compression at right ventrolateral medulla oblongata leads to heart rate decrease immediately and that heart rate increase to normal level (heart rate of pre-compression) few seconds after elastic sacculus compression system evacuation in animal experiment.

Animal experiment results that compression at left ventrolateral medulla oblongata can't decrease heart rate and that compression at right ventrolateral medulla oblongata can decrease heart rate supported our hypotheses. From our clinical study, 14/18 was right hemifacial spasm patients. The phenomenon of hemifacial spasm companied by sinus bradycardia had right predominance. Right cardiac vagal nerve is closely related to heart rate regulation (Prasad R et al., 2012). Compression at right ventrolateral medulla oblongata could stimulate the dorsal nucleus of vagus and ambiguous nucleus in medulla oblongata. The stimulation increases the frequency of efferent impulse of right vagal nerve, which decreases the heart rate. In human being, (Hyun et al., 2010)

Right ventrolateral medulla oblongata is compressed by intracranial artery loop; (Jannetta PJ., 2005)Dorsal nucleus of vagus and ambiguous nucleus are stimulated by this compression; (Funaki T., et al   2010)This stimulation leads to vagal nerve efferent impulse increase, which have the negative chronotropic and dromotropic effect on atrionector of right atrium. (Guangming Zhang ., et al   2009).Negative chronotropic and dromotropic effect on atrionector of right atrium leads to heart rate decrease. Decompression at ventrolateral medulla oblongata has the inverse effect: (Hyun et al., 2010) Decompression at ventrolateral medulla oblongata relieves the stimulation on dorsal nucleus of vagus and ambiguous nucleus; (Jannetta   PJ., 2005)Vagal nerve efferent impulse decrease; (Funaki T., et al   2010) Weaken the negative chronotropic and dromotropic effect on atrionector of right atrium, which leads to heart rate increase. These deduce needed to be verified in the future.

Sinus bradycardia is common in athletes and heavy manual laborers and patients with sinus bradycardia usually don't have serious clinic symptoms (MacKenzie R et al., 2012). Most of them don't need treatment. Only those with serious clinical manifestation due to insufficient heart output may need heart pacemaker implantation (Bouraoui H et al., 2011). We believe that part sinus bradycardia (provided   that there is no mass in CPA and ventral brain stem area) is caused by   vascular compression at right ventrolateral medulla oblongata. According to our clinical observation and animal experiment, decompression at right ventrolateral medulla oblongata might be, in the future, an effective method for those sinus bradycardia patients with serious clinical manifestation. Microvascular decompression might theoretically serve as an alternative method to heart pacemaker implantation for part sinus bradycardia patients with insufficient heart output.

Conflict of interest

There was no actual or potential financial and other conflict of interest related to the manuscript.

REFERENCES

Bouraoui H, Trimech B, Chouchene S, Mahdhaoui A, Ernez Hajri S, Jeridi G, Ammar H (2011). Permanent cardiac pacing: about 234 patients. Tunis Med. 2011 Jul;89(7):604-9.

Funaki T, Matsushima T, Masuoka J, Nakahara Y, Takase Y, Kawashima M (2010). Adhesion of rhomboid lip to lower cranial nerves as special consideration in microvascular decompression for hemifacial spasm: Report of two cases. Surg Neurol Int. Nov 18;1:71.

Guangming Zhang, Guoqiang Chen, Huancong Zuo (2009). First Description of Neurogenic Sinus Bradycardia in Idiopathic Hemifacial Spasm. Surigcal NeurologyJan;71(1):70-3.

Hyun SJ, Kong DS, Park K (2010). Microvascular decompression for treating hemifacial spasm: lessons learned from a prospective study of 1,174 operations. Neurosurg Rev. Jul;33(3):325-34; discussion 334.

Jannetta PJ, McLaughlin MR, Casey KF (2005). Technique of microvascular decompression. Technical note. Neurosurg Focus. May 15;18(5):E5.

MacKenzie R (2012). Bradycardia in a former professional athlete.J Insur Med. 2012;43(1):36-40.

Prasad R, Pugh PJ (2012). Drug and device therapy for patients with chronic heart failure. Expert Rev Cardiovasc Ther. Mar;10(3):313-5.