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Investigation of the relationship between laterality and vertebral arteries in rabbits

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Abstract

Cerebral dominance is well known on laterality; however, histological analysis of vertebral artery dominance has not been adequately studied. It was aimed to investigate the relationship between the dominant vertebral artery and hand preference. In this study, which fifteen male rabbits were examined, paw preference was evaluated with a food-reaching test. Vertebral artery samples just entering to the cranium were obtained from right- and left-pawed rabbits to evaluate luminal surface values histologically. Handedness preferences and vertebral arteries lumen surface values were compared statistically using the Mann-Whitney U test. As a result of the measurements made, the vertebral artery on the side with a larger diameter was accepted as dominant. The larger lumen surface values were found in the left vertebral artery than in the right vertebral artery in right-handed rabbits and vice versa. The mean lumen surface values of the left/right vertebral arteries were 0.395 ± 0.068 / 0.305 ± 0.034 mm² in the right-pawed animals ($p < 0.0001$); 0.298 ± 0.032 / 0.364 ± 0.049 mm² in the left-pawed animals ($p < 0.001$) and 0.389 ± 0.061 / 0.354 ± 0.054 mm² both pawed animals ($p < 0.001$). The vertebral artery was accepted to be dominant when there were different arterial lumen diameters from side to side. Arterial luminal diameter was dominant in 53% of the cases on the left and in 33% on the right. Left and right arterial lumen diameters were equal in 13% of cases. As a conclusion, it was found that, vertebral artery dominance may have predictive roles in the determination of handedness.

Keywords: Handedness, vertebral artery dominance, experimental animal study

Introduction

Cerebral hemispheric asymmetric architecture is the most accepted mechanism for the explanation of laterality or handedness preferences. It is not clear the reason for the existing asymmetry. The left vertebral artery is usually larger than the right vertebral artery. In one hypothesis, the reason why the two vertebral arteries were unequal in size was claimed to be related to the vascular perfusion requirements of the brain.

The association of the vertebral artery dominance and handedness has not been confirmed yet [1]. Vertebral artery dominance is

defined when there is a significant difference between the diameters of the vertebral arteries [2]. A dominant vertebral artery has larger diameters than the nondominant one [3]. Dominant vertebral artery occlusion causes important visual and motor deficits of cranial nerves [4]. Regional cerebral blood flow in the posterior parietal, occipital cortices and brainstem is supplied by the vertebrobasilar system [5]. Vertebral artery hypoplasia may have a determinative role of laterality [6]. Vertebral artery hypoplasia is supposed to be a risk factor for posterior circulation ischemia [7], and could determine contra-side laterality development. Vertebral artery lesions cause somatosensitive, motor and autonomous, auditory, visual and laterality problems [8].

In this study, to support the claim that the vertebral artery diameter is greater on the dominant side than on the non-dominant side, it was investigated the relationship between a dominant vertebral artery and hand preference.

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Materials and Methods

The necessary local experimental animal ethics committee approval (Approval date: 26.02.2021/2-55) was obtained. During the study, animal rights were protected and followed in line with the Guidelines for the Care and Use of Laboratory Animals.

Fifteen male rabbits with a bodyweight of 4.32 ± 0.45 kg were used in this study. Animals were fed with standard laboratory chow and water. The food reaching test was applied to determine paw preference [9]. Each rabbit was placed in a stainless-steel cage and followed two weeks to apply food reaching tests every day. There is a ceiling hole 40 cm above the floor where the rabbit can reach the food with both front paws. Four times a day, the carrot-containing pellet was placed in the hole. Scores for reaching food using the right or left paw of each rabbit were noted. This observation was repeated 100 times for each rabbit. Paw preference for each rabbit was determined by statistically calculating the difference between right and left paw usage numbers.

At the end of the experiment, all animals were sacrificed under ketamine/xylazine anesthesia and decapitated after intracardiac formalin injection. Brain samples were extracted with all vessels and cranial nerves and fixed in 10% formalin solution for seven days. Later, tissue sections of 5 μ m thickness were taken from vertebral arteries that had just entered the skull. All specimens were stained with hematoxylin & eosin (H&E). In the calculation of the luminal surface area of the vertebral arteries assuming as an ellipse surface, simple geometric formulas were used in line with their morphological features. The modified ellipse surface calculation formula was preferred to a single measurement of the lumen radius. This method is practical, more reliable, and unaffected by radius overestimation error, and free from assuming different vessel diameters in various segments.

Vertebral arteries of all rabbits were cut out at 20 segments, from a distance at the point which the internal carotid arteries arise to the entrance of the posterior cerebral arteries. Later, these 20 histopathological sections at 5 μ m intervals were obtained by microtome and were represented by lines 1 through 21. The mean values of three radial values were accepted as median radius and all luminal areas were accepted as a circle [10]. Lumen surface values of all vertebral arteries were calculated with the following formula:

$$S = \pi[(R1 + R2 + R3)/3]^2$$

Statistical analysis

The results were evaluated with the IBM SPSS Statistics 20.0 (NY, USA) statistical program. The categorical variables were expressed as frequencies and percentages, whereas, the numerical variables were given as means and standard deviations. Mann-Whitney U test was used to compare the two groups. For statistical significance, $p < 0.05$ was accepted in the whole study.

Results

The majority of animals ($n=8$) were found to be as the right-pawed and the fewer ones ($n=5$) used their left paws, and just two animals were both right and left-pawed.

Histopathological images of our study are presented in figures. All vertebral arteries' luminal surface values were accepted as the formula located in the left bottom corner. Radiological appearances of carotico-vertebrobasilar tree anatomical appearances of basal surface and magnified appearances of the right and left vertebral arteries on the base are shown in Figure 1. Figure 2 shows the mean three radial values accepted as median radius and all luminal areas accepted as the circle. Histological appearances of vertebral arteries and magnified appearances of a double pawed rabbit are showed in Figure 3, whereas, histological appearances of vertebral arteries of the right-pawed rabbit and left-pawed rabbit are shown in Figure 4 and Figure 5, respectively. An extremely dilated left vertebral artery is seen in the last figure.

Larger luminal surface values were found in the left vertebral artery than the right vertebral artery in the right pawed rabbits, and vice versa. The mean lumen surface values of the left/right vertebral arteries were $0.395 \pm 0.068 / 0.305 \pm 0.034$ mm² in the right-pawed animals ($p < 0.0001$); $0.298 \pm 0.032 / 0.364 \pm 0.049$ mm² in the left-pawed animals ($p < 0.001$) and $0.389 \pm 0.061 / 0.354 \pm 0.054$ mm² both pawed animals ($p < 0.001$) (Table1).

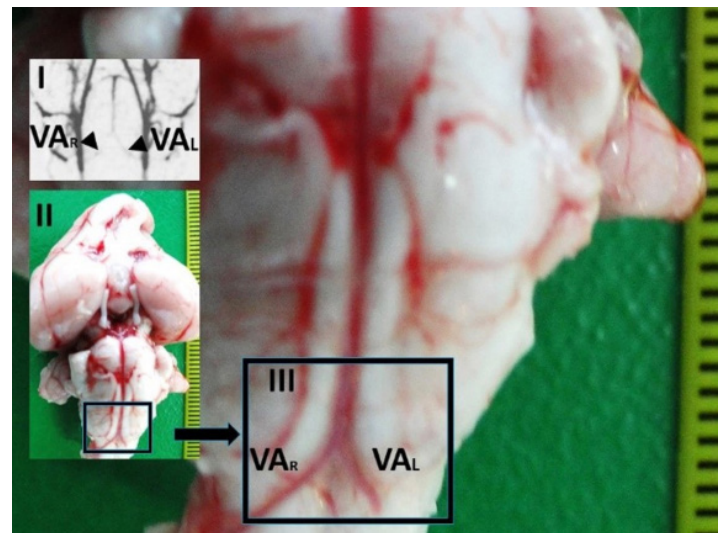


Figure 1. Radiological appearances of carotico-vertebrobasilar tree (I) (taken from M.D.A. archives) anatomical appearances of basal surface (II) and magnified appearances of the right (VAR) and left vertebral arteries (VAL) on the base (III)

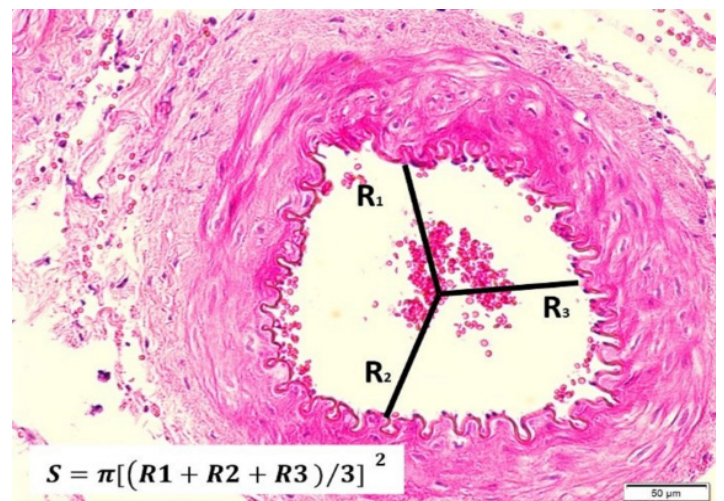


Figure 2. The mean values of three radial values were accepted as median radius and all luminal areas accepted as the circle. And all vertebral arteries' luminal surface values were accepted as the formula located in the left bottom corner

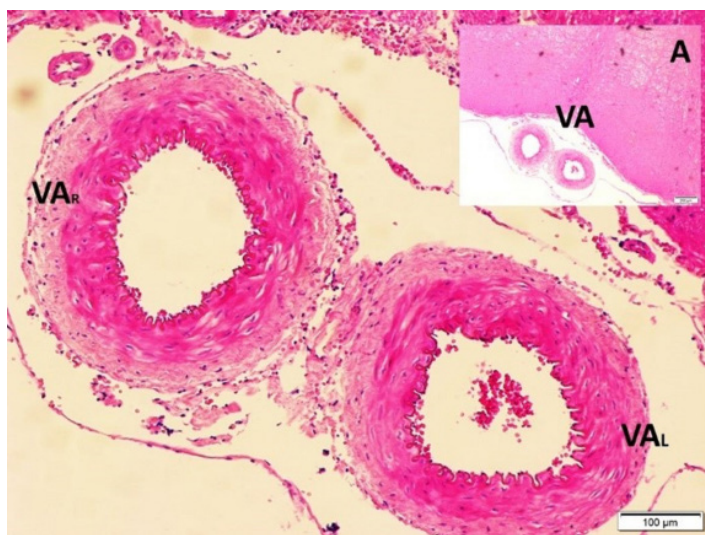


Figure 3. Cross sectional appearances of vertebral arteries (VA) of a double pawed rabbit. (Light Microscope, H&E x4/A; 10/Base)

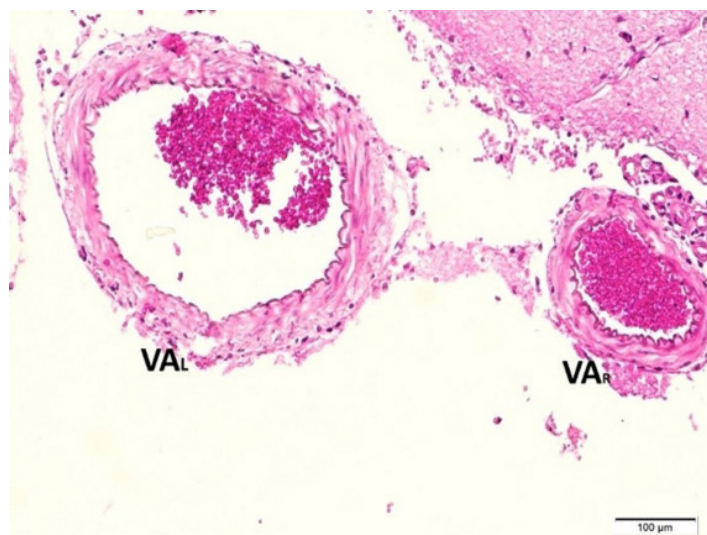


Figure 4: Histological appearances of vertebral arteries (VA) (LM, H&E x10) of a right-pawed rabbit. An extremely dilated left vertebral artery is seen



Figure 5. Histological appearances of vertebral arteries (VA) (LM, H&E x4/A) of the left-pawed rabbit.

Table 1. Left and right vertebral artery lumen width values (mean±SD)

Left/Right	(n=15)	Left	Right	p
Right-Pawed	(n=5)	0.395±0.068	0.305±0.034	p<0.0001
Left-Pawed	(n=8)	0.298±0.032	0.364±0.049	p<0.001
Both Pawed	(n=2)	0.389±0.061	0.354±0.054	p<0.001

A vertebral artery was considered to be dominant if the difference in diameter size from side to side was greater than the other. The left diameter was dominant in 53% (n=8) of the cases, while the right diameter was dominant in 33% (n=5). In 13% (n=2) of cases, the left artery diameter was equal to the diameter on the right. The larger surface values were found in the left vertebral arteries than in the right vertebral arteries in right-handed rabbits. The vertebral arteries' luminal surface values were nearly equal in both pawed rabbits.

Discussion

It is known that the left and right human hemispheres differ from each other in anatomy and function. It is assumed that hand preference and footedness can be used to predict cerebral dominance in the normal population. It has been shown that right-handed individuals have strong left hemispheric dominance, and left-handed individuals have right hemispheric dominance [11].

In our study, when vertebral artery diameters on both sides were compared, a statistically significant difference was found between right and left diameters in all rabbit groups. However, when compared between groups, even the diameter of the left vertebral artery was found to be greater in left-handed as well as in right-pawed rabbits, but the difference was not statistically significant. This result is in accordance with the literature stating that the average vertebral artery diameter is greater on the left side than the right side [12]. In the literature, separate theories have been suggested to elucidate the asymmetry in vertebral artery diameters. It has been hypothesized that the cause may be related to the vascular requirements of the brain, but has never been investigated.

A study found that the arteries on the left side of the circle of Willis are larger than those on the right and that this mechanism may entail left cerebral hemisphere dominance [13]. Although there are not enough studies in the literature, according to the embryonic theory, it is said that this asymmetry is due to a different embryological development of the left and right vertebral artery. Vertebral arteries differences can be result of their origin differences because the right vertebral artery is a branch of subclavian artery on the right side, whereas the left vertebral arteries arising directly from aorta on the left side. This fact explains the embryological differentiation theory for luminal diameter sizes of vertebral arteries.

In addition, when vascular physiological mechanisms are considered, the blood flow velocity as well as the arterial diameter determines cerebral blood flow. For this reason, physiological measurements of blood flow volume and velocity are required to fully understand the dominance of the vertebral artery. Hence, hypotheses claiming that a dominant left vertebral artery is associated with right-handed use are not finalized. Vascular

physiological measurements and comparisons of multiple electrophysiological signal recordings are required to clarify the mechanism underlying asymmetry in vertebral artery diameter [1].

Cognitive dysfunctions are also showed some cognitive differences from person to person [14]. Bilateral variability in the origin of the vertebral artery [15] could cause laterality determination. The blood flow velocity in the left internal carotid and vertebral arteries is higher in right-handed people than in left-handed people [16]. Rotational vertebral artery syndrome presented with vertigo attacks, nystagmus and some cognitive impairments result of dominant vertebral artery dysfunction [17].

Paradoxical Relations of Study

The relationship between the vertebral arteries and laterality also includes a paradoxical relationship, vertebral arteries, and cervicocranial communication ipsilateral neural structures; as neural bundles innervating the contralateral side of the upper bulbar, pontine and mesencephalic sections are also fed

Limitations

Since the data are obtained only from histopathological analysis, further studies with larger sample sizes and studies investigating the cerebral blood flow rate measurements are needed.

Conclusion

Vertebral artery dominance may have predictive roles in the determination of handedness. More research is needed to investigate the mechanism underlying asymmetry in vertebral artery diameter. Interestingly, in this experiment, it was observed that the vertebral and basilar arteries of bi-pawed rabbits were better in anatomical, histological and configurational aspects than the others.

Future Insight

We believe that evolution mechanisms would be obliged to all animals in both handed in the future to prevent cerebral asymmetry which carries a big danger for them. Unfortunately, increased blood flow and high-pressure lead to elongation, convolution, and dilatation of the dominant vertebral artery and pushes the basilar artery across in its direction. Consequently, it may cause basilar artery doligoectasis and aneurysms.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

Local experimental animal ethics committee approval (Approval date: 26.02.2021/2-55) was obtained.

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