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Opinion Article

High brain natriuretic peptide levels are associated with vulnerable plaque in cervical carotid artery

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1. Introduction

Brain Natriuretic Peptides (BNP) are commonly used in a clinical field as a serological biomarker for acute and chronic heart failure. In the cardiovascular field, the relationship between BNP and not only heart failure but also atherosclerosis is often discussed. In patients with unstable angina, elevated BNP level is said to be associated with plaque characteristic of coronary arteries, particularly vulnerable plaque, and serve as an indicator of the risk of coronary artery occlusion.[1] Also, elevated BNP level is associated with ischemic cardiovascular events.[2] Both coronary artery disease and carotid artery disease are atherosclerotic diseases, and it is known that they often occur together and have similar properties. Similar to coronary artery plaque, the plaque characteristic of carotid artery is important. It is well known that vulnerable plaque of carotid artery is associated with more cerebral ischemic events than stable plaque. Although plaque instability is associated with atherosclerosis, the relationship between plaque instability in cervical internal carotid artery (ICA) and BNP has not been investigated. Among imaging modalities, carotid ultrasonography and Black Blood Magnetic Resonance Imaging (BB-MRI) are often used to assess carotid plaque instability. High intensity plaque of both T1 and T2 weighted images of BB-MRI is associated with vulnerable plaque. Therefore, we examined the hypothesis that elevated BNP level is associated with vulnerable plaque in cervical ICA by using BB-MRI.

2. Materials and methods

In 161 patients who underwent carotid artery stenting or carotid endarterectomy at our hospital from January 2017 to March 2021, preoperative BNP levels and carotid plaque assessment in cervical ICA on BB-MRI were retrospectively evaluated. When the contralateral cervical ICA had 50% or more stenosis, measurements were taken on both sides, and a total of 206 lesions were enrolled. The MRI equipment used is a GE 1.5T, and 2D spin-echo black blood (BB) method T1 and T2 weighted images were taken. Various parameters are TR/TE:700–1000 (IR-R interval)/10.7msec, FOV:180 mm, FA:90°, matrix size:288 × 192, thickness:3.0 mm for T1-weighted image, and TR/TE:1400–1700/86msec, FOV:180 mm, FA:90°, matrix size:256 × 192, thickness:3.0 mm for T2-weighted image. The signal intensity ratio of the carotid artery plaque (Sp) to the sternocleidomastoid muscle (Sm) was calculated as the Sp/Sm ratio (Fig. 1), and Sp/Sm ≧ 2 was defined as the cutoff value for high intensity indicating the vulnerable plaque. In order to minimize the calculation error, region of interest (ROI) was set to the thickest part of the plaque. In addition to age and sex, hypertension, diabetes, hyperlipidemia, and renal function were extracted as arteriosclerotic factors.

In both T1 and T2 weighted image of BB-MRI, we divided into a high intensity group with Sp/Sm ≧ 2 and a low intensity group with Sp/Sm < 2, and investigated whether the number of patients with BNP≧100, which is often used clinically as a marker for determining heart failure, is larger in the Sp/Sm ≧ 2 group. Furthermore, multivariate analysis was performed about the relationship between vulnerable plaque with Sp/Sm ≧ 2 and preoperative BNP levels.

2.1. Statistical analysis

The cases which were outlier value of BNP were excluded using Smirnov–Grubbs test. The clinical data of patient characteristics were

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categorized, and the median values of the categorized data were compared between the Sp/Sm ≧ 2 and Sp/Sm < 2 groups in both T1 and T2 weighted image of BB-MRI, respectively, using the Wilcox test. As a univariate analysis, the X^2 test was used to examine whether there were more patients with BNP≧100 in the Sp/Sm ≧ 2 group compared to the Sp/Sm < 2 group. As multivariate analysis investigating the association between Sp/Sm ≧ 2 in BB-MRI and preoperative BNP levels, logistic regression analysis was used to calculate odds ratio (OR), 95% confidence interval (CI), and *P* value. *P*-value<0.05 was considered statistically significant.

3. Results

11 lesions were excluded as outlier value of BNP, and a total of 195 lesions were enrolled. In T1 weighted image of BB-MRI, the proportion of male was higher in the Sp/Sm ≧ 2 group than in the Sp/Sm < 2 group (*P* value = 0.049), and there was no significant difference in other background factors. In T2 weighted image of BB-MRI, the Sp/Sm ≧ 2 group had significantly higher BNP values than the Sp/Sm < 2 group (*P* value = 0.002) (Table 1).

In a univariate analysis, the ratio of patients with BNP≧100 was significantly higher in the Sp/Sm ≧ 2 group in T2 weighted image of BB-MRI (*P* value = 0.015), and no significant difference was observed in T1 weighted image of BB-MRI (Table 2).

Furthermore, in a multivariate analysis about the relationship between Sp/Sm ≧ 2 in T2 weighted image of BB-MRI and preoperative BNP levels, BNP was significantly higher in the high intensity group with Sp/Sm ≧ 2 (*P* value = 0.004, OR:1.01, 95%CI:1.0–1.02) (Table 3).

Table 1
Comparison of each parameter between Sp/Sm ≧ 2 group and Sp/Sm < 2 group.

	T1 weighted image			T2 weighted image		
	Sp/Sm ≧ 2 (*n* = 48)	Sp/Sm < 2 (*n* = 147)	*P* value	Sp/Sm ≧ 2 (*n* = 115)	Sp/Sm < 2 (*n* = 80)	*P* value
Age(median,yr)	73	73	0.382	74	72	0.679
Sex male (%)	46 (95.8)	125 (85)	0.049*	98 (85.2)	73 (91.3)	0.207
Hypertension (%)	38 (79.2)	106 (72.1)	0.336	87 (75.7)	57 (71.3)	0.494
Diabetes (%)	18 (37.5)	67 (45.6)	0.329	51 (44.3)	34 (42.5)	0.78
Hyperlipidemia (%)	22 (45.8)	82 (55.8)	0.232	62 (53.9)	42 (52.5)	0.847
BNP (pg/mL)	45.0	45.2	0.642	57.0	31.5	0.002*
eGFR (mL/min/1.73m^2)	61.8	64.0	0.964	63.3	62.6	0.627

eGFR indicates estimated Glomerular Filtration Rate.

Table 2
In a univariate analysis about the ratio of patients with BNP≧100.

	T1 weighted image			T2 weighted image		
	Sp/Sm ≧ 2 (*n* = 48)	Sp/Sm < 2 (*n* = 147)	*P* value	Sp/Sm ≧ 2 (*n* = 115)	Sp/Sm < 2 (*n* = 80)	*P* value
BNP≧100 (*n* = 38)	11	27	0.49	29	9	0.015*
BNP<100 (*n* = 157)	37	120		86	71	

4. Discussion

BNP is produced by myocardial cell of ventricle in response to ventricular wall tension due to increasing of circulating blood volume and cardiac preload. BNP is a hormone that has cardioprotective effect by promoting vasodilation and diuresis.[3] The significance of measurement of BNP has been established in the field of cardiovascular disease, and BNP is not only a useful biomarker for acute and chronic heart failure, but also a highly sensitive predictor of cardiac function prognosis. Easily measurement by hematologic test can be one of the reasons why it is often used in a clinical field.

The development of acute coronary syndrome is associated with rupture and erosion of vulnerable plaques, these so-called unstable plaques are said to be associated with elevated BNP or co-produced NT-pro BNP level.[4] It is clear that coronary artery and cervical ICA have much in common in atherosclerotic change. Similar to the importance of plaque characteristics in coronary artery, plaque characteristics in cervical ICA are important risk factor for acute cerebral embolism. Understanding exacerbation of vulnerable plaque characterized by inflammatory cell infiltration, large necrotic core, and thin fibrous cap is necessary for treating carotid artery stenosis. In general, lipid rich plaques and intraplaque hemorrhage are called unstable plaques, and the former shows high intensity in T2 and the latter in T1 weighted image of BB-MRI. In this study, we found an association between high intensity in T2 weighted image of BB-MRI and high BNP levels.

An understanding of the pathological mechanism of vulnerable

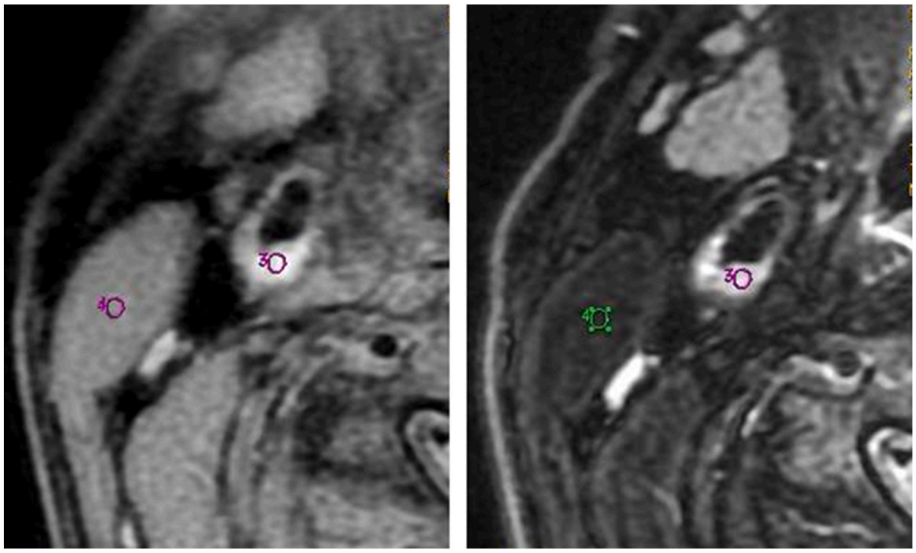

Fig. 1. The region of interest is set to the plaque in cervical carotid artery and sternocleidomastoid muscle in both T1 (left) and T2 (right) weighted image of BB-MRI.

Table 3
In a multivariate analysis about the relationship between Sp/Sm ≧ 2 in T2 weighted image and BNP.

	OR	95% CI	*P* value
Age	0.98	0.95–1.02	0.442
Sex male	0.67	0.26–1.71	0.402
Hypertension	1.0	0.51–1.95	0.996
Diabetes	1.0	0.55–1.82	0.999
Hyperlipidemia	0.97	0.53–1.76	0.919
BNP	1.01	1.0–1.02	0.004*
eGFR	1.0	0.99–1.02	0.607

OR indicates odds ratio.
CI indicates confidence interval.

plaque is important for the interpretation of the results of this study, in which the relationship between lipid rich plaque and BNP was recognized. Accumulation of lipoprotein particles in the intima of cervical ICA under hemodynamic stress recruit leukocytes to the arterial endothelium. Leukocytes attached to the endothelium remove lipid particles and become foam cells. Foam cells not only serve as reservoirs for lipids, but also release inflammatory cytokines and trigger the progression of lesion inflammation. Amplification of atherosclerotic stimulation cause foam cells to collapse and release lipids into the intercellular space. As a result, the plaque thickens and becomes lipid rich plaque. In addition, deep hypoxia due to plaque thickening causes the development of new blood vessels as vasa vasorum. This new blood vessels are immature and easily ruptured, leading to intraplaque hemorrhage. Cellular necrosis and apoptosis by inflammatory cytokines accelerate these processes of plaque destabilization.[5] BNP is associated with atherosclerotic stimulation and inflammatory cytokines in these processes.

Although not well known, BNP is said to have anti-inflammatory effect. BNP inhibits neutrophil activation and reduces oxidative stress. In addition, when BNP receptors present in macrophages, dendritic cells, and T cells are stimulated, cytokine activation is inhibited.[6] Thus, BNP is a hormone that exerts an anti-inflammatory effect through a feedback function, and is closely related to inflammation. In particular, inflammatory cytokines such as IL1β (interleukin-1β), IL6 (interleukin-6) and TNFα (tumor necrosis factor-α) are said to promote production and release of BNP by stimulating the NPPB (Natriuretic Peptide B) gene promotor via p38 MAP kinase.[7] In patients with vulnerable plaque in cervical ICA, it can be interpreted that the release of inflammatory cytokines by foam cells in the plaque indirectly causes the elevation of BNP. We considered this fact to be one of the important grounds for explaining the association between lipid rich vulnerable plaque and BNP.

However, in our study, we did not find association between high intensity in T1 weighted image of BB-MRI and BNP. It is difficult to interpret this result. We considered the effects of statistical bias. Although Sp/Sm ≧ 2 was defined as high intensity in both T1 and T2 weighted image of BB-MRI, there is previous reports that define vulnerable plaque as 1.5 or more, and the values are not constant. Also, the signal ratio may change depending on the accuracy of the MRI equipment and imaging conditions. As a result, the number of lesions with high intensity in T1 weighted image was clearly lower than that in T2, and it may not have had sufficient power. Pathologically, lipid rich plaque and intraplaque hemorrhage have similar properties, so if the number of lesions increases, there is a possibility that a statistically significant difference will be obtained even in T1 weighted image.

In recent, carotid artery stenosis has attracted attention not only for the stenosis rate but also plaque characteristics. Vulnerable plaques have a worse natural history and a higher risk of invasive treatment than stable plaques. In endovascular treatment, treatment methods are sometimes selected according to plaque characteristics, such as changing protection methods depending on plaque vulnerability. While research on diagnostic imaging of plaques is progressing, research on serological biomarkers is lacking. Based on the results of this study, it may be possible to apply the measurement of BNP to treatment content in addition to imaging studies.

Our research has several limitations. First, our study is retrospectively done in a single center. Although the number of cases is not small, it is not sufficient. Secondly, statistical bias in setting of Sp/Sm and measurement of plaque intensity can occur. Only two observers independently measured Sp/Sm ratio. If there was a difference in opinion on Sp/Sm ≧ 2 or Sp/Sm < 2, a consensus reading was performed. Thirdly, we used BB-MRI to assess plaque instability. However, other imaging modalities, such as carotid ultrasonography, are also often used. In our study, other imaging modalities are not investigated. Additionally, the most important point to diagnose plaque characteristic is pathological diagnosis. Although we perform pathological diagnosis of carotid plaque that obtained during carotid endarterectomy, plaque samples are not available when carotid artery stenting is performed. Therefore, we did not include pathological diagnosis in this study. Fourthly, our study insufficiently considered hypertension bias. Hypertension has an established link with both BNP levels and atherosclerosis. It is important that whether hypertensive disease altered the association between BNP levels and vulnerable plaque in cervical ICA. Finally, although the signal value was measured at the thickest part of the plaque, it may have to be accurately evaluated at the place in which both lipid rich plaque and intraplaque hemorrhage coexist.

5. Conclusions

We found an association between high intensity in T2 weighted image of BB-MRI and preoperative BNP levels. We speculated that atherosclerotic changes and releasing of inflammatory cytokines which are characterized by lipid rich vulnerable plaques are associated with BNP production. Further studies with large patient numbers are needed for an accurate interpretation.

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CRediT authorship contribution statement

Nozomi Sasaki: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Taku Hiramatsu:** Data curation. **Yoshihito Hasegawa:** Formal analysis, Data curation. **Motoshi Sawada:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

BNP: Brain Natriuretic Peptide
ICA: internal carotid artery
BB-MRI: Black Blood Magnetic Resonance Imaging
Sp/Sm ratio: the ratio of the plaque (Sp) to the sternocleidomastoid muscle (Sm)
ROI: region of interest
OR: odds ratio
CI: confidence interval