• Clinical Research •

Imageology of internal carotid artery siphon in non-arteritic anterior ischaemic optic neuropathy

Zhi-Yong Fu, Hong-Yang Li, Yan-Ling Wang

Department of Ophthalmology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China
Correspondence to: Yan-Ling Wang. Department of Ophthalmology, Beijing Friendship Hospital, Capital Medical University, 95 Yong-an Rd, Beijing 100050, China. b502367790@126.com
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Abstract

● **AIM:** To evaluate whether narrowing of internal carotid artery siphon (ICAS) may increase the risk of developing non-arteritic anterior ischaemic optic neuropathy (NAION).

● **METHODS:** Totally 30 consecutive patients who had unilateral NAION and 30 gender-matched control subjects were recruited in the present study. The diameter of ICAS of all the participants were measured using head-and-neck computed tomographic angiography (CTA). Color doppler flow imaging (CDI) was used to measure the haemodynamics parameters of ICAS and short posterior ciliary arteries (SPCAs) in all subjects. Comparison of parameters between the NAION patients and controls as well as between the two sides within the patients were performed. The correlation between the diameter of ICAS and NAION was analyzed.

● **RESULTS:** A comparison of parameters between the affected side of the NAION patients and the controls, including the diameter of ICAS, the resistance index (RI) of ICAS, the blood flow velocities of SPCAs and RI of SPCAs, showed significantly difference (P<0.01), while there was no significant difference in terms of the mean blood flow velocity (Vm) of ICAS; Similar results were found while comparing all the measurements of the affected and unaffected side of patients (P for RI of SPCAs <0.05). No marked difference was detected in nearly all parameters except for RI of ICAS and SPCAs between the unaffected side of the NAION patients and the controls (P<0.05). The diameter of ICAS were significantly positive correlated with both peak systolic velocity (PSV) of SPCAs and end diastolic velocity (EDV) of SPCAs in patients with NAION (r=0.514, P<0.01 and r=0.418, P<0.05, respectively).

● **CONCLUSION:** Narrowing of ICAS may increase the risk of developing NAION.

● **KEYWORDS:** internal carotid artery siphon; imageology; haemodynamics parameter; non-arteritic anterior ischaemic optic neuropathy

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INTRODUCTION

Non-arteritic anterior ischaemic optic neuropathy (NAION) is a common clinical entity characterized by sudden, painless loss of vision accompanied with optic disc oedema. Patients with NAION often develop bilateral disease several months or years later[1-4]. It's difficult for researchers to perform precise assessment without influenced by doping factors in study of NAION, because the genesis of NAION is by multiple factors[5-6]. Hypertension, diabetes mellitus, and hyperlipidemia are believed to be systemic risk factors result in NAION[7-14]. Furthermore, many vascular risk factors are associated with NAION in similar aged patients and often coexist. Efforts to clarify one single risk factor for NAION needs to exclude these potentially confusing factors by precisely designed case-control study.

Although the exact pathogenic mechanisms of NAION remain elusive, low blood perfusion caused by ischemia is generally considered to be one of the aetiologies. Internal carotid artery siphon (ICAS) is a segment with tortuous configuration always involved in cephalic and ocular ischemic diseases, many researches have studied it from the anatomical point of view[15-16]. However, there were few studies on ICAS in patients with NAION so far, and it remains uncertain whether there is any correlation between ICAS diameter stenosis and NAION. The question of the extent to which stenosis of ICAS increases the risk of NAION development is still haunting us.

SUBJECTS AND METHODS

Ethical Approval This study was approved by Ethics committee of Beijing Friendship Hospital and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patients.

Subjects Totally 30 patients (18 males and 12 females) with unilateral NAION were divided into two groups: NAION group (affected eyes) and normal group (contralateral healthy eyes). The mean age at diagnosis of NAION was 63.5±6.8y (49-77y). The average onset time was 4.8±2.5d.

Inclusion criteria included: 1) conformed to the diagnosis of NAION[11,17-18]; 2) unilateral ocular involvement; 3) first time and acute onset.

Exclusion criteria included: 1) any history of other diseases that may affect the optic nerve; 2) any history of corticosteroids, phosphodiesterase-5 (PDE5), aspirin or related drugs use.

The control group included 30 gender-matched subjects (18 males and 12 females). The mean age of the controls was 64.6±7.1y (50-78y). No control subject had any ophthalmic disease during the period of recruiting.

Methods After taking heart rate, blood pressure (BP) and intraocular pressure (IOP), all participants underwent color fundus photography, optical coherence tomography scans (OCT, Heidelberg, Germany), and fundus fluorescein angiography (FFA, Heidelberg, Germany).

The diameter of ICAS was measured by head-and-neck computed tomographic angiography (CTA; GE revolution CT, USA). With the help of software (GE post processing workstation AW4.6), we measured the chosen ICAS segment and defined the narrowest part of vessel as the diameter of ICAS (Figure 1).

The hemodynamic parameters of ICAS [mean blood flow velocity (Vm) and resistance index (RI)] were employed by color doppler flow imaging (CDI; HITCHI ALOKA, Japan) using a linear 5-10 MHz transducer (Figure 2). Esaote Mylab ClassC LA332 instrument (Esaote, Italy) was performed to detect the hemodynamic parameters of short posterior ciliary artery [SPCA; peak systolic velocity (PSV), end diastolic velocity (EDV) and RI] using a linear 3-11 MHz transducer (Figure 2).

Ocular perfusion pressure (OPP)= 2/3[diastolic BP+1/3 (systolic BP–diastolic BP)]–IOP.

Only the measurements of the right eyes were enrolled for analyses in control group.

Statistical Analysis The Kolmogorov-Smirnov test was used to check normality of distribution. The *t*-test was used to compare the mean measurements between groups. Categorical variables were compared using the Chi-square test. The correlation between the diameter of ICAS and haemodynamics parameters of SPCAs was evaluated by Pearson correlation coefficient analysis. The accuracy of the CDI for NAION were evaluated using the receiver operating characteristic curve (ROC). Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA), a *P* value of less than 0.05 was considered as statistically significant.

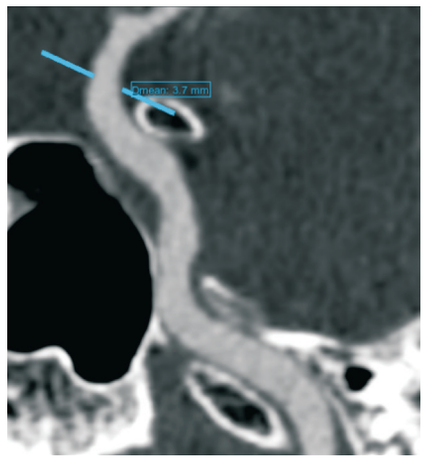

Figure 1 Head-and-neck CTA inspection showed the diameter of ICAS.

Table 1 Participants demographics at baseline

Parameters	NAION	Controls	*P*
Age (y)	63.5±6.8	64.6±7.1	0.554
IOP (mm Hg)	14.9±2.9	13.7±2.8	0.108
Systolic BP (mm Hg)	140.3±26.3	132.3±19.6	0.188
Diastolic BP (mm Hg)	78.2±12.5	74.2±10.5	0.185
Mean arterial pressure (mm Hg)	99.1±16.4	93.8±12.8	0.168
Heart rate (per min)	74.9±8.2	72.0±9.4	0.203
OPP (mm Hg)	51.1±10.0	48.8±7.9	0.319
Hypertension, *n* (%)	12 (40.0)	8 (26.7)	0.412
DM, *n* (%)	7 (23.3)	4 (13.3)	0.506
Hyperlipidemia, *n* (%)	7 (23.3)	5 (16.7)	0.748

Data are mean±SEM. NAION: Non-arteritic anterior ischaemic optic neuropathy; IOP: Intraocular pressure; BP: Blood pressure; OPP: Ocular perfusion pressure; DM: Diabetes mellitus.

RESULTS

No significant difference was found in terms of all the baseline data between NAION patients and the controls (Table 1 all $P>0.05$). Patients with NAION had a greater prevalence of hypertension (40.0% *vs* 26.7%; $P=0.412$), diabetes mellitus (23.3% *vs* 13.3%; $P=0.506$) and hyperlipidemia (23.3% *vs* 16.7%; $P=0.748$), but there was not significant difference between the two groups.

CDI had the following accuracy parameters for detection of SPCAs (PSV and EDV): sensitivity, 86.7% and 73.3%; specificity, 60% and 63.3% (95% confidence interval, 68%-92% and 63%-88%), respectively (Figure 3).

Table 2 showed the comparison of parameters in ICAS and SPCAs between the affected side of NAION patients and the controls. We found the diameter of ICAS, RI of ICAS, PSV, EDV and RI of SPCAs were significantly different between two groups ($P<0.01$). Vm of ICAS was not significantly different between two groups ($P=0.839$).

Table 3 showed the comparison of parameters in ICAS and SPCAs between the affected and unaffected side of NAION patients. We found the diameter of ICAS, RI of ICAS, PSV,

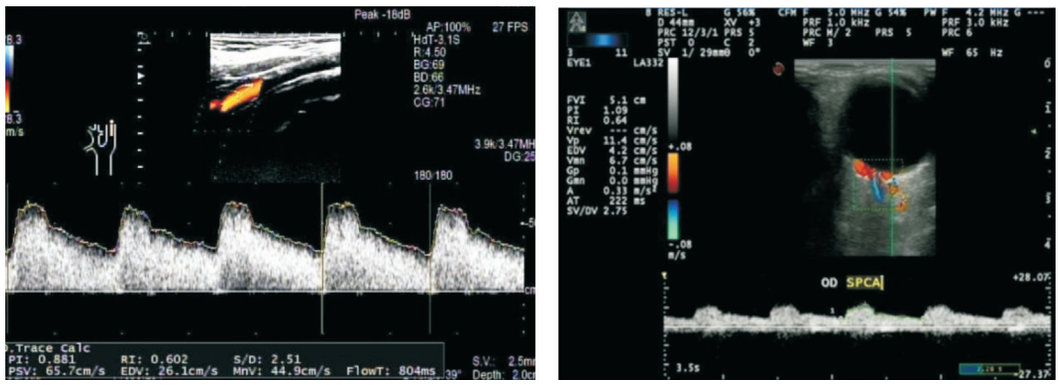

Figure 2 CDI examinations of ICAS and SPCAs showed the haemodynamics of ICAS and SPCAs.

Table 2 Comparison of parameters in ICAS and SPCAs between the affected side of NAION patients and the controls

Parameters	Diameter of ICAS (mm)	Vm of ICAS (cm/s)	RI of ICAS	PSV of SPCAs (cm/s)	EDV of SPCAs (cm/s)	RI of SPCAs
NAION eye	2.95±0.75	45.93±6.35	0.72±0.06	10.51±2.73	3.38±0.98	0.69±0.06
Controls	3.45±0.57	46.22±4.80	0.67±0.06	14.11±3.81	4.74±1.65	0.62±0.06
t	2.901	0.204	-3.264	4.209	3.867	4.298
P	<0.01	0.839	<0.01	<0.01	<0.01	<0.01

Data are mean±SEM. NAION: Non-arteritic anterior ischaemic optic neuropathy; ICAS: Internal carotid artery siphon; SPCAs: Short posterior ciliary arteries; Vm: Mean blood flow velocity; RI: Resistance index; PSV: Peak systolic velocity; EDV: End diastolic velocity.

Table 3 Comparison of parameters in ICAS and SPCAs between the affected and unaffected side of NAION patients

Parameters	Diameter of ICAS (mm)	Vm of ICAS (cm/s)	RI of ICAS	PSV of SPCAs (cm/s)	EDV of SPCAs (cm/s)	RI of SPCAs
NAION eye	2.95±0.75	45.93±6.35	0.72±0.06	10.51±2.73	3.38±0.98	0.69±0.06
Normal eye	3.30±0.50	44.80±5.57	0.70±0.05	13.63±3.89	4.56±1.67	0.65±0.07
t	-3.909	0.853	3.313	-4.222	-4.159	2.109
P	<0.01	0.401	<0.01	<0.01	<0.01	<0.05

Data are mean±SEM. NAION: Non-arteritic anterior ischaemic optic neuropathy; ICAS: Internal carotid artery siphon; SPCAs: Short posterior ciliary arteries; Vm: Mean blood flow velocity; RI: Resistance index; PSV: Peak systolic velocity; EDV: End diastolic velocity.

EDV and RI of SPCAs were significantly different between two groups (P<0.05). Vm of ICAS was not significantly different between two groups (P=0.401).

Table 4 showed the comparison of parameters in ICAS and SPCAs between the unaffected side of NAION patients and the controls. We found nearly all the parameters between two groups were not significantly different, including the diameter of ICAS, Vm of ICAS, PSV and EDV of SPCAs (P=0.285, 0.294, 0.633, 0.682, respectively), except for RI of ICAS and SPCAs (P<0.05).

Table 5 showed correlation analyses between the diameter of ICAS and the Vm of SPCAs on the affected side of NAION patients. We found both PSV and EDV of SPCAs were significantly positive correlated with the diameter of ICAS (r=0.514, P<0.01 and r=0.418, P<0.05, respectively; Figure 4).

Table 6 showed linear regression analyses between the diameter of ICAS and the Vm of SPCAs on the affected side of NAION patients (R^2=0.265, P<0.01, the diameter of ICAS and the PSV of SPCAs; R^2=0.175, P<0.05, the diameter of ICAS and the EDV of SPCAs).

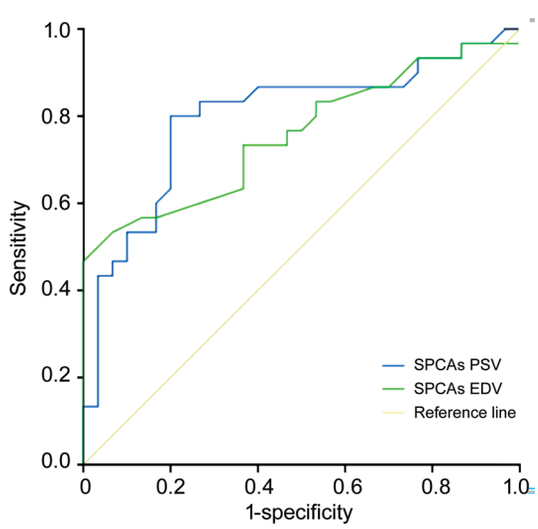

Figure 3 ROC curve analysis of PSV and EDV of SPCAs in NAION.

DISCUSSION

NAION is a common cause of acute visual loss in the middle-aged and elderly population[11]. It's well known that there are a wide variety of risk factors for NAION[19]. If researchers want to ensure the role of one factor in triggering the onset

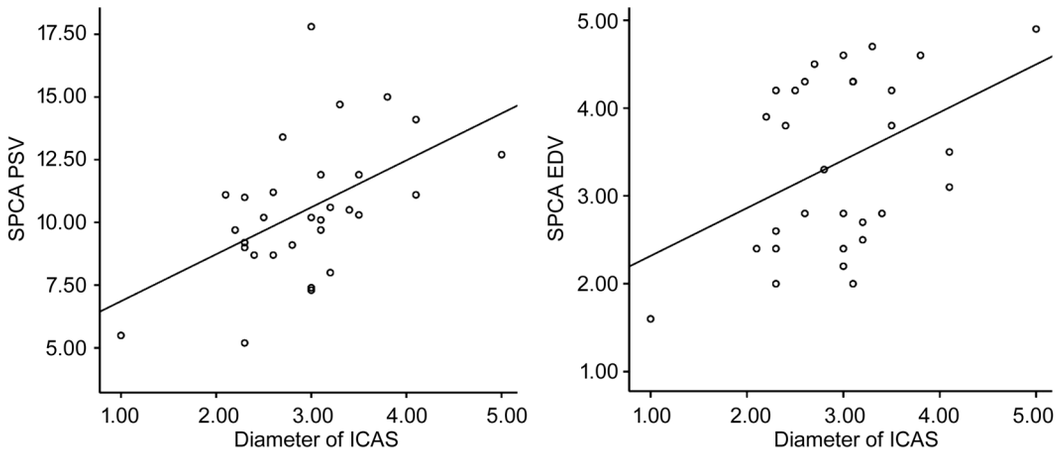

Figure 4 Correlation analyses between the diameter of ICAS and the blood flow velocities of SPCAs (affected side of NAION patients) A: Peak systolic velocity (PSV) of SPCAs significantly positive correlated with the diameter of ICAS; B: End diastolic velocity (EDV) of SPCAs significantly positive correlated with the diameter of ICAS.

Table 4 Comparison of parameters in ICAS and SPCAs between the unaffected side of NAION patients and the controls

Parameters	Diameter of ICAS (mm)	Vm of ICAS (cm/s)	RI of ICAS	PSV of SPCAs (cm/s)	EDV of SPCAs (cm/s)	RI of SPCAs
Normal eye	3.30±0.50	44.80±5.57	0.70±0.05	13.63±3.89	4.56±1.67	0.65±0.07
Controls	3.45±0.57	46.22±4.80	0.67±0.06	14.11±3.81	4.74±1.65	0.62±0.06
t	1.079	1.060	-2.095	0.480	0.412	-2.000
P	0.285	0.294	<0.05	0.633	0.682	<0.05

Data are mean±SEM. NAION: Non-arteritic anterior ischaemic optic neuropathy; ICAS: Internal carotid artery siphon; SPCAs: Short posterior ciliary arteries; Vm: Mean blood flow velocity; RI: Resistance index; PSV: Peak systolic velocity; EDV: End diastolic velocity.

Table 5 Correlation analyses between the diameter of ICAS and haemodynamics parameters of SPCAs (affected side of NAION patients)

Parameters	Diameter of ICAS (pearson correlation)	
	r	*P*
SPCAs PSV (*n*=30)	0.514	<0.01
SPCAs EDV (*n*=30)	0.418	<0.05

ICAS: Internal carotid artery siphon; SPCAs: Short posterior ciliary arteries; PSV: Peak systolic velocity; EDV: End diastolic velocity.

Table 6 Regression analyses between the diameter of ICAS and haemodynamics parameters of SPCAs (affected side of NAION patients)

Parameters	Diameter of ICAS regression analyses	
	R^2	*P*
SPCAs PSV (*n*=30)	0.265	<0.01
SPCAs EDV (*n*=30)	0.175	<0.05

ICAS: Internal carotid artery siphon; SPCAs: Short posterior ciliary arteries; PSV: Peak systolic velocity; EDV: End diastolic velocity.

of NAION, the first thing they should do is to eliminate any confusing factor that might influence the conclusion of study. Therefore, we designed a case-control study, in which there was no significant difference in the participants demographics at baseline, including mean age, sex, IOP, OPP and some common systemic diseases which could result in circulation disorders (all *P*>0.05). Among various local risk factors, changes in IOP are assumed to affect blood flow of optic nerve head (ONH) in patients who have systemic and local disorders that disrupt ONH autoregulation[2-3,20]. While ONH blood flow autoregulation has been impaired, OPP fluctuations become a very important factor in NAION pathogenesis[11,21]. Concerning IOP and OPP in our study, the differences obtained by comparing the NAION eye group and the controls were not statistically significant (*P*=0.108 and 0.319, respectively). Systemic hypertension, diabetes mellitus, and hyperlipidemia are three very common systemic risk factors for NAION. In the present study, compared to the controls, patients with NAION had a greater prevalence of hypertension (40.0% *vs* 26.7%; *P*=0.412), diabetes mellitus (23.3% *vs* 13.3%; *P*=0.506) and hyperlipidemia (23.3% *vs* 16.7%; *P*=0.748), but the differences were not statistically significant between two groups. In this respect, we were able to compare every pair of relative parameters between patients with NAION and the controls without need of concerning bias originating in these confusing factors.

Previous comparative studies of the retrobulbar haemodynamics parameters measurements in NAION were usually performed between the affected sides of patients and the healthy subjects[22] or between two sides within same patients with NAION[23-24]. In order to make the comparison more

comprehensive, we divided our clinical data into three groups, which were NAION eye group, normal eye group, and controls. Data of NAION eye group and normal eye group were obtained from different sides of same NAION patients, and data of controls were obtained from 30 gender-matched subjects with an intention to minimize the influence of mixed factors. Then we compared the haemodynamics parameters of ICAS and SPCAs between every two groups. As we expected, we found that PSV and EDV of SPCAs significantly decreased in NAION eye group compared with the controls and the normal eye group. However, PSV and EDV of SPCAs between the controls and the normal eye group showed not significantly different. PSV and EDV are both important hemodynamic parameters, PSV is the index of blood vessel filling and blood supply strength, while EDV reflects the blood perfusion situation of the distal tissue[16], the decreasing of PSV and EDV reflects the extent of hypoperfusion and ischemia. It was thought that NAION is caused by an acute ischaemia of the laminar or retro-laminar portions of the ONH, which is supplied by the paraoptic tributaries of SPCAs[6,25]. Several studies demonstrated that there was reduced blood flow in SPCAs in NAION patients[22-23], the result of our study was consistent with that.

RI is also an important hemodynamic parameter, it reflects the resistance of blood flow in the distal vascular bed. In this study, we found that both RI of ICAS and RI of SPCAs showed significantly different between every two groups. Furthermore, it's noteworthy that even RI of ICAS and SPCAs in normal eye group increased significantly compared with the controls, though Vm of ICAS showed no significantly different between any two groups. ICAS includes both cavernous segment and clinoidal segment of ICA, and it looks like a S shape from the side[26]. Previous study found that the tortuous configuration of ICAS was responsible for the change of blood flow parameters, which could impact on circulatory dynamics of blood supply[16,27]. Considering the special structure of ICAS, Vm of ICAS might be influenced by turbulence, vessel caliber, atherosclerosis plaque or tissue stiffness. In this sense, the statistical insignificant differences for RI between different groups seemed unexpected, but reasonable. The patients included in this study were all within acute phase, and the follow-up was not long enough to observe the lapsing of their fellow eyes. However, it was thought that risk of NAION development in the fellow eye of unilateral NAION patients increased in the following years. Since RI of ICAS and SPCAs in normal eye group increased significantly compared with the controls, it is crucial to recognize that the fellow "normal" eyes in NAION patients in this study should not necessarily be considered as healthy. Actually, Newman *et al*[28] found that patients with unilateral NAION have a 15%-24% chance of developing NAION in the contralateral eye within 5y following their initial presentation. The promising direction in the future should be to focus on the unaffected eyes in patients with unilateral NAION in case the healthy eyes go on to develop NAION.

In our daily work, we noticed that abnormalities in ICAS occurred frequently in patients with ischaemic neuropathy, especially the narrowing of ICAS was common. In our previous study[16], through comparing the diameter of ICAS, we found the difference between the affected and unaffected sides within the same NAION patients was significant, the diameter of ICAS distinctly decreased in NAION group (affected sides). Similarly, in this study, we compared the diameter of ICAS between the patients with NAION and gender-matched healthy subjects, we found that the diameter of ICAS significantly decreased in NAION eye group compared with the controls and the normal eye group. However, the diameter of ICAS between the controls and the normal eye group showed not significantly different. Is the narrowing of ICAS a risk factor contributing to the development of NAION? By Pearson correlation coefficient analysis, we found that the diameter of ICAS was significantly associated with PSV and EDV in SPCAs of the affected sides in NAION patients (r=0.514, P<0.01 and r=0.418, P<0.05, respectively), the decreasing of PSV and EDV in SPCAs demonstrated an excellent agreement with the narrowing of ICAS, indicating that these haemodynamics parameters of SPCAs decrease as the narrowing of ICAS. This result is similar to that of our previous study[16]. As we have mentioned above, NAION is a multi-factorial disease, different risk factors play a large or small role in the onset of NAION. By linear regression analysis, we got the R square (R^2=0.265, P<0.01, the diameter of ICAS and the PSV of SPCAs; R^2=0.175, P<0.05, the diameter of ICAS and the EDV of SPCAs), indicating that the decreased PSV and EDV of SPCAs in patients with NAION can be partly attribute to the narrowed diameter of ICAS (26.5% and 17.5%, respectively). As another risk factor for NAION, the assessment of diameter of ICAS might be an important step in the monitoring of NAION development.

There are some limitations in the present study. First, the absence of information about obstructive sleep apnea in participants and small sample size might affect our results and therefore weaken the credibility of conclusion, because obstructive sleep apnea was believed to be associated with NAION[29-32]. Second, although we controlled some systemic risk factors in this study, we couldn't exclude interference of most cardiac vascular diseases or vascular anomalies among all the patients. It is reasonable to have the patients to be evaluated beforehand by cardiologists in the future investigation. Third, with high reliability and accuracy, CDI is reliable in

the measurements of hemodynamic parameters in NAION patients. However, many factors, including experience of the sonographer, patient's coordination, blood vascular diameter, and the site of detection, can influence the results. To reduce errors, we had good communications with all the participants and all the tests were repeated by experienced operators, but we believed that there would still be measurements bias caused by unpredictable factors. Finally, since small optic disc cup is believed to be an anatomic risk factor for NAION[33-34], our control group couldn't be considered as an ideal matching one, which might potentially influence the results. Larger cohorts and adequate case-control matching studies are needed to confirm our findings.

In conclusion, narrowing of ICAS showed increased risk for NAION.

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