



Research article

Association between morphologic subtypes of vertebral artery dissection and vertebral artery hypoplastic appearance



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ABSTRACT

Objectives: The purpose of this study was to evaluate the associations between vertebral artery hypoplasia (VAH) and the morphologic types of spontaneous vertebral artery dissection (sVAD) and to assess the chronological changes of VAH after sVAD.

Methods and materials: In this retrospective study, we included 208 patients with 216 sVADs which were diagnosed between January 2003 and June 2017 at two tertiary hospitals. Morphologic types of sVAD were classified into aneurysmal dilatation without stenosis, pearl-and-string appearance, and steno-occlusion without aneurysmal dilatation. Baseline clinical characteristics and sVAD types were compared according to the presence of VAH on initial imaging. For 143 sVAD patients with follow-up imaging available, chronological changes of VAH and their associations with sVAD types were also evaluated.

Result: VAH was detected in 29 (13.9%) subjects: 18 (8.7%) with ipsilateral VAH and 11 (5.3%) with contralateral VAH to the sVAD site. Primary lesion shape was statistically associated with the presence of VAH ($P = 0.001$); steno-occlusion without dilatation was more frequently observed in the ipsilateral VAH group (44.4%) than the no-VAH group (20.9%) or contralateral VAH group (0%). Of a total 143 sVAD patients with follow-up imaging available, VAH-like diffuse VA narrowing was newly observed in seven patients and four patients who were initially classified into the VAH group showed their VAH-like appearances resolved.

Conclusions: The presence of VAH may be associated with the morphologic subtype of sVAD and the VA diameter can dynamically change, making it possible for the VAH-like appearance to be induced after a sVAD event.

1. Introduction

Vertebral artery hypoplasia (VAH) is a common congenital variation of the vertebral artery (VA) that can occur without symptoms of vertebrobasilar insufficiency [1,2]. In the past, VAH was regarded as a harmless anatomic variant because it was asymptomatic [3,4]. However, accumulating evidence has suggested VAH as an emerging risk factor for posterior circulation ischemia [1,2,5]. Moreover, recent research shows an association between spontaneous VA dissection (sVAD) and VAH as the hypoplastic VA is more frequently involved with sVAD than its normal counterparts [6].

Previous studies have established that arteries can narrow adaptively with markedly decreased proximal blood flow and that it is possible to restore the arterial diameter by restoring blood flow [7–9]. Given that arteries can change adaptively, the small diameter of ipsilateral VAs observed in sVAD patients can also be a consequence of blood flow decreasing due to sVAD, especially in the stenotic type of sVAD. Therefore, we hypothesized that VAH or the small diameter of VA in sVAD patients was associated with the stenotic type of sVAD and that a normal diameter could be regained if the stenosis improved. To prove this, we investigated the presence of VAH and VA dominance in patients with sVAD and their association with the primary morphologic

Abbreviations: VAH, vertebral artery hypoplasia; VA, vertebral artery; sVAD, spontaneous vertebral artery dissection; MRA, magnetic resonance angiography

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types of sVAD. Furthermore, we evaluated the chronological changes of both sVAD and VAH during follow-up.

2. Materials and methods

2.1. Patients

This study was a retrospective multi-center study and patient data were collected from two tertiary hospitals. From Institution A, 101 consecutive patients who were diagnosed with VAD from January 2003 to June 2014, and from Institution B, 183 consecutive patients who were diagnosed with VAD from March 2009 to June 2017 were enrolled. Patients had to have clinical and supportive radiologic evidence of sVAD and imaging studies including the proximal VA and brain had to be available before they could be included for analysis. For patients with no clinical symptoms or non-specific symptoms, diagnosis was made only by typical imaging findings which will be described later on.

Seventy-six patients were excluded because of non-visible proximal VA on imaging ($n = 56$), unavailable brain imaging ($n = 11$), traumatic dissection ($n = 6$), and basilar artery extension of the sVAD ($n = 3$). Accordingly, 208 patients (M:F = 124:84, mean age, 48.9 ± 11.2 years) with 216 sVADs were included in the final study population (Fig. 1). Among the 208 patients, there were 143 patients with follow-up imaging available. The institutional review board of each institution approved the study and waived the requirement for informed consent.

2.2. Imaging acquisition

Computed tomography angiography (CTA) examinations were

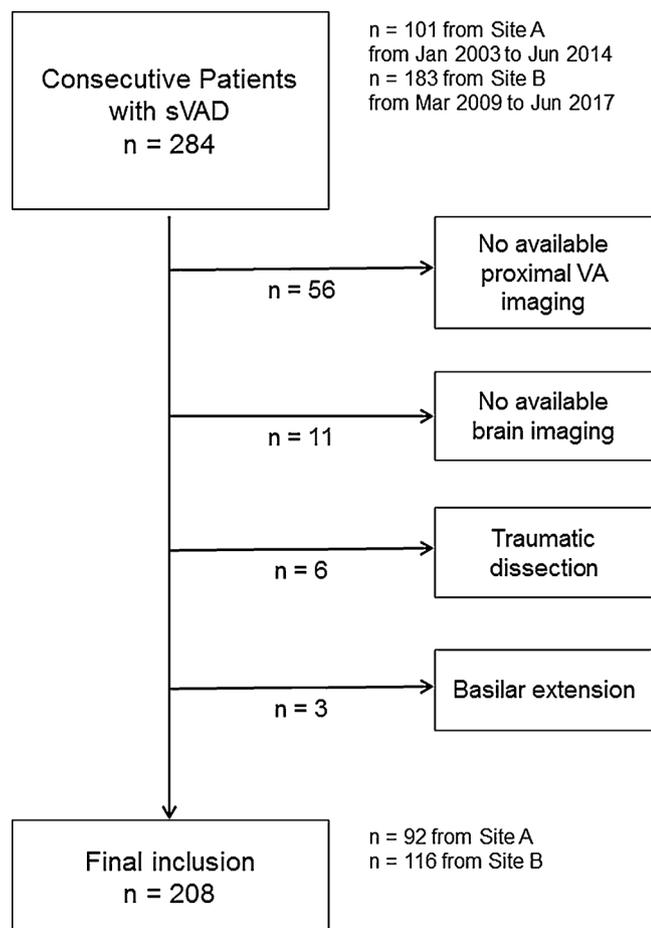


Fig. 1. Flowchart of inclusion and exclusion criteria. sVAD = spontaneous vertebral artery dissection.

performed with various multidetector CT scanners (LightSpeed Plus, GE Healthcare, Milwaukee, WI, USA or SOMATOM Sensation 64, Definition, Definition AS, Siemens Healthcare, Erlangen, Germany), with the following parameters: collimation: $16-128 \times 0.6-0.75$ mm, beam pitch: $0.3-0.75$, tube rotation time: $0.5-0.75$ s, tube voltage: $100-120$ kVp, tube current: $150-300$ mA, and slice thickness: $0.6-1.25$ mm. Brain CTA images were obtained after intravenous injection of the iodinated contrast material. All scans were performed using a bolus-tracking technique, with the region of interest placed in the ascending aorta or internal carotid artery at C1 level. Each CT image encompassed the supra-aortic arteries to the level of the vertex.

Magnetic resonance angiography (MRA) examinations were performed with either a 1.5 T (Achieva; Philips Healthcare, Best, the Netherlands) or 3 T (Achieva; Philips Healthcare, Best, the Netherlands and Verio, Siemens AG, Erlangen, Germany) scanner. For 3D-TOF-MRA, the parameters were TE, $2.4-3.7$ ms; TR, $17-23$ ms; flip angle, $18-20^\circ$; section thickness, $0.5-1.2$ mm; FOV, $180-250 \times 180-250$ mm; and matrix, $384-880 \times 269-449$. For the CE-MRA, the parameters were TE, $1.2-1.6$ ms; TR, $3.2-4.8$ ms; flip angle, $21-40^\circ$; section thickness, $0.6-3$ mm; FOV, $300-350 \times 218-350$ mm; and matrix, $288-512$. CE-MRA was obtained using a standard automated bolus injection after venous injection of a gadolinium-based contrast agent at a flow rate of $1.5-2.0$ cc/s, followed by 20 mL of saline.

2.3. Imaging analysis

Images were obtained with any of three diagnostic methods, digital subtraction angiography, MRA, or CTA, and diagnoses were made by one experienced neuroradiologist with 7 years of experience (N.Y.S.).

2.3.1. Diagnosis of sVAD

sVAD was diagnosed when any of the following findings were observed: (a) string sign or pearl-and-string sign without atherosclerotic change of the involved artery, (b) intimal flap, (c) double lumen sign, (d) aneurysmal dilatation of the arterial trunk not located at a branching point, but associated with sudden onset of a severe pulsatile posterior headache or posterior ischemic symptoms, and (e) changes in arterial shape during follow-up [10]. Occlusive forms of sVAD were confirmed by the presence of a mural hematoma on MRI or CT. Iatrogenic and traumatic VADs were excluded from the analysis.

sVADs were subdivided into three groups according to lesion morphologic type: (a) aneurysmal dilatation without stenosis, (b) pearl-and-string appearance, and (c) steno-occlusion without aneurysmal dilatation [11]. The evolution of the sVAD was evaluated for each morphologic type with the following criteria: (a) For the dilatation-without-stenosis group, improvement was determined with a decrease in aneurysm size and progression was determined with aneurysmal enlargement. (b) For the pearl-and-string group, improvement was determined with a decrease in aneurysm size and an increase in the lumen size of the stenotic portion; progression was determined with any aneurysmal enlargement or decrease in the lumen size of the stenotic occlusion. (c) For the steno-occlusion-without-dilatation group, improvement was determined with any increase in lumen size and progression was determined with the presence of any stenosis or occlusion progression [11].

2.3.2. Diagnosis of VAH

VA appearance on initial imaging was evaluated and patients were classified into the VAH or no-VAH group. VAH was presumed when VA met the following morphologic criteria on any of the vascular imagings: VA diameter ≤ 2.5 mm in the V1 and V2 segments and a concomitant diameter asymmetry ratio of $\leq 1:1.7$ throughout the whole VA [6]. A diameter of VA was measured on the largest diameter of the V1 and V2 segments on either CTA or MRA and if not available, 3D volume rendering images were used. VAH was further analyzed as ipsilateral VAH or

contralateral VAH based on the sVAD lesion site.

In the no-VAH group, VA dominancy was evaluated on the ipsilateral VA to lesion site and determined as nondominant VA when the VA did not meet the VAH criteria but was smaller by more than 0.3 mm than the contralateral VA (i.e., dominant VA). If there was no more than 0.3 mm differences in diameter between bilateral VAs, those were classified as co-dominant VAs [3].

2.4. Statistical analysis

Normal distribution was tested with the Kolmogorov–Smirnov test. Accordingly, the student *t*-test was applied to test difference in age and body mass index. Pearson’s χ^2 test or Fisher’s exact test was applied to compare categorical variables of the general characteristics between patients with VAH and those without VAH. Fisher’s exact test was applied to compare prevalence of vascular risk factors, dissection site, symptoms and diagnostic method between the VAH group and the no-VAH group and was also used to compare primary lesion shapes according to VAH classification or VA dominancy. Same statistical analyses were also performed for the subgroup analysis with patients diagnosed using CTA to reduce any possible bias from the different imaging modalities. Two-sided *P* values of < 0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS (version 24; SPSS Inc, Chicago, IL).

3. Results

3.1. Demographic comparison

Of the 208 patients with sVAD, 76 presented with left sVAD, 124 with right sVAD, and 8 with bilateral sVAD. Presumed VAH was detected in 29 (13.9%) subjects: 18 (8.7%) with ipsilateral VAH and 11 (5.3%) with contralateral VAH to the sVAD site. There were no statistical differences for the conventional vascular risk factors (Supplementary Table). The groups were comparable for demographic characteristics and for most clinical characteristics including the dissection site, brain lesion, symptoms and diagnostic methods.

3.2. Primary lesion shape and VAH classification

Among the 216 dissections, the frequency of primary lesion shapes at initial diagnosis differed according to VAH classification (*P* = 0.001; Table 1). In the no-VAH group, primary lesion shapes were similarly distributed from steno-occlusion without aneurysmal dilatation (20.9%, 39/187), pearl and string appearance (47.6%, 89/187), to aneurysmal dilatation without stenosis (31.6%, 59/187). In the ipsilateral VAH group, steno-occlusion without aneurysmal dilatation was more frequently observed (44.4%, 8/18), whereas none of the contralateral VAH group and only 20.9% (39/187) of the no-VAH group showed steno-occlusion without aneurysmal dilatation. Conversely, aneurysmal dilatation without stenosis was most frequently seen in the contralateral VAH group (54.5%, 6/11), while none of the ipsilateral VAH group and 31.6% (59/187) of the no-VAH group exhibited aneurysmal dilatation without stenosis.

Among the sVAD occurring in no-VAH VA (*n* = 187), 46 (24.6%) dissections occurred at the non-dominant VA, 19 (10.2%) at the dominant VA and 122 (65.2%) at the co-dominant VA. Among the non-

dominant VA group, steno-occlusion without aneurysmal dilatation was observed in 37.0% (17/46) of the lesions, while 5.3% (1/19) of the dominant VA group showed stenosis without aneurysmal dilatation (Table 2). On the other hand, aneurysmal dilatation without stenosis was seen in the 57.9% (11/19) of the dominant VA group and only 2.2% (1/46) of non-dominant VA had aneurysmal dilatation without stenosis. Thus, the percentage of each morphologic type in the non-dominant and dominant VA group was similar to the percentage of each morphologic type in the ipsilateral and contralateral VAH groups, respectively.

3.3. Chronological changes and VAH classification

Chronological changes were evaluated for the 151 lesions of the 143 patients with follow-up vascular imaging available during the clinical follow-up period (mean, 506.0 ± 564.6 days). Of the 151 lesions, 79 (52.3%) lesions showed improvement, 46 (30.5%) lesions showed no change and 26 (17.2%) lesions showed the sVAD progress. Among 79 lesions with improvement, 36 (23.8%) lesions exhibited complete normalization.

Among 143 sVAD patients with follow-up imaging available, seven (5.7%) patients of the 122 patients without initial VAH developed VAH-like appearance during follow-up. Among them, four had ipsilateral VAH-like appearance with a clinical follow-up period of 233.8 ± 213.3 days (Fig. 2) and three had contralateral VAH-like appearance with 637.7 ± 351.0 days. All of the 4 patients with newly appearing ipsilateral VAH-like appearance exhibited progression of steno-occlusive sVAD. Only one out of the three patients with contralateral VAH-like appearance exhibited progression of sVAD with dilatation without stenosis and the other two showed improvements of sVAD of the steno-occlusive and pearl-and-string type, respectively. On the other hand, among 21 sVAD patients with initially presumed VAH, four (19.0%) patients who were initially classified into the ipsilateral VAH group showed interval resolution of the presumed VAH within a clinical follow-up period of 650.5 ± 645.9 days (Fig. 3) and three of them showed improvement of sVAD with the stenotic component (two were the steno-occlusive type and one was the pearl-and-string type) and one showed stable steno-occlusive sVAD (Table 3).

3.4. Subgroup analysis diagnosed with CTA

89 VAD patients with 91 dissections were identified whose diagnostic methods included CTA and there were 9 (10.1%) patients with VAH and 80 (89.9%) patients with no VAH.

Among with 91 dissections, the frequency of primary lesion shapes at initial diagnosis were compared according to VAH classification and did not show statistical significance (*P* = 0.092). However, the same trends observed in the whole population were found as none of the contralateral VAH group (0%, 0/2) showed steno-occlusion without aneurysmal dilatation while 57.1% (4/7) of the ipsilateral VAH group showed steno-occlusion without aneurysmal dilatation. In terms of aneurysmal dilatation without stenosis, it was observed in half (1/2) of the contralateral VAH group but none (0/7) in the ipsilateral VAH group.

Among the dissections with no-VAH VA (*n* = 82), steno-occlusion without aneurysmal dilatation was observed in 22.7% (5/22) of the lesions, while 0% (0/8) of the dominant VA group showed stenosis

Table 1
Primary lesion shape according to the VAH classification (per lesion analysis).

	No VAH (n = 187)	Ipsilateral VAH (n = 18)	Contralateral VAH (n = 11)	<i>P</i> value
Steno-occlusion only	39 (20.9%)	8 (44.4%)	0 (0.0%)	0.001
Pearl-and-string appearance	89 (47.6%)	10 (55.6%)	5 (45.5%)	
Aneurysmal dilatation only	59 (31.6%)	0 (0.0%)	6 (54.5%)	

Table 2
Primary lesion shape according to the VA dominance (per lesion analysis).

	VA co-dominancy (n = 122)	VA non-dominancy (n = 46)	VA dominance (n = 19)	P value
Steno-occlusion only	21 (17.2%)	187 (37.0%)	1 (5.3%)	< 0.001*
Pearl-and-string appearance	54 (44.3%)	28 (60.9%)	7 (36.8%)	
Aneurysmal dilatation only	47 (38.5%)	1 (2.2%)	11 (57.9%)	

without aneurysmal dilatation. On the other hand, aneurysmal dilatation without stenosis was seen in the 62.5% (5/8) of the dominant VA group and none of non-dominant VA had aneurysmal dilatation without stenosis ($P < 0.001$).

Chronological changes were also evaluated in 52 sVAD patients with follow-up imaging available and four (8.7%) patients of the 46 patients without initial VAH developed VAH-like appearance during follow-up.

4. Discussion

This retrospective observational study resulted in two main findings. First, the presence of presumed VAH as well as VA dominance was associated with the morphologic type of dissection and the stenosis-without-dilatation type was associated with narrow VA (VAH or non-dominant VA) ipsilateral to the dissection side. Second, VAH-like appearance could either develop and presumed VAH could even be resolved during follow-up.

The VAs, which originate from the bilateral subclavian arteries and fuse into the basilar artery, are the main blood supply for the posterior fossa and similar in size in only 25% of healthy individuals with left dominance observed in 50% [12,13]. The prevalence of VAH widely ranges from 1.9–26.5% in literature and this wide range might be related to how differently VAH is defined because no consensus has been reached on the definition of VAH. In this study, we observed that 13.9% of our sVAD population had presumed VAH, which is lower than a previously reported incidence of 30.4%, although the percentage is rather similar to a previously reported VAH incidence for a normal population [14]. This may be explained by the associations we observed

between VAH and the steno-occlusive morphologic types of sVAD. In this study, sVADs with stenosis without aneurysmal dilatation were frequently found on the side of VAH while none of the sVADs with aneurysmal dilatation were found on the side of VAH. Even in the patients without VAH, sVADs with steno-occlusion without dilatation were more frequently found in non-dominant VAs with smaller diameters than the contralateral side with the same trend. In a study by M. Zhu et al., most sVAD patients exhibited either arterial occlusion or stenosis and there was only a small population (14.3%) with aneurysmal dilatation. On the other hand, 30.8% of our sVAD population presented with aneurysmal dilatation only. When considering the high incidence of ipsilateral VAH in the steno-occlusive type of sVAD, this difference in VAH prevalence may originate from differences in the percentages of subtypes included in each study's population.

Previous animal model studies have suggested that arteries can adapt to changes in blood flow by undergoing compensatory diameter adjustments [7,8,15]. Stenosis or occlusion of cervical arteries may cause insufficient blood flow and low shear stress in arteries, which may in turn, lead to reduction of the arterial diameter or even its collapse, a phenomenon called 'adaptive narrowing' [16]. Thus, the high incidence of ipsilateral presumed VAH in steno-occlusive sVAD may come from a decrease in blood flow and shear stress from stenosis induced by the sVAD and finally, this may result in adaptive narrowing in the proximal part of the affected VA. This adaptive narrowing can range from mild narrowing presenting as non-dominant VA to VAH-like appearance which meets the diagnostic criteria for presumed VAH. Therefore, we suggest that the presumed VAH observed in initial sVAD patients may not be all congenital VAH and may be a partial consequence of sVAD, which indicates that caution is needed when

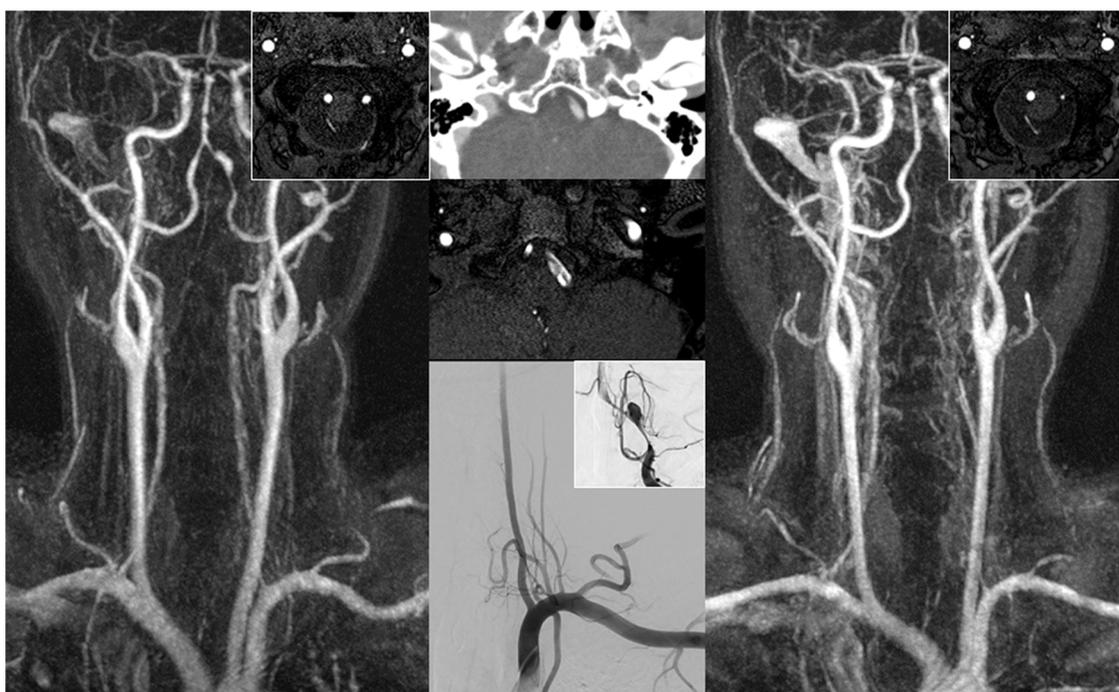


Fig. 2. A representative case showing the development of VA hypoplasia (VAH)-like appearance on follow-up MRA as the stenotic component of the VA dissection progressed.

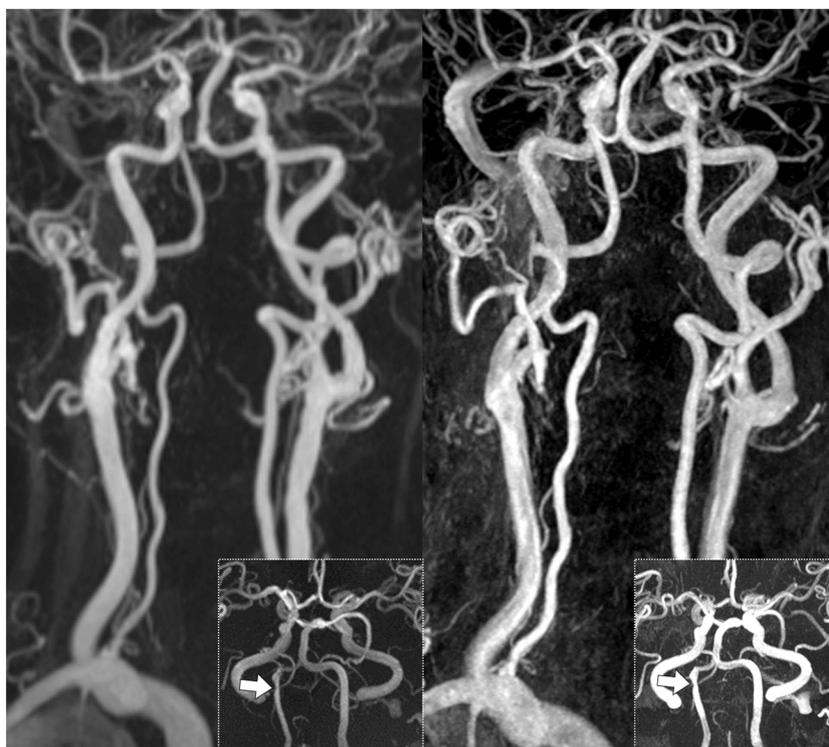


Fig. 3. A representative case showing the restoration of the VA diameter on follow-up MRA as the stenotic component of the VA dissection improved.

interpreting the association between VAH and sVAD at a single time point.

Furthermore, we found that 5.8% of the sVAD patients with initial no-VAH had newly developed diffuse narrowing in the VA on follow-up and these cases were in accordance with the definition of VAH when taking into account only the diameter or caliber discrepancy. The number of such cases was small but their presence may have clinical importance because they can be regarded as evidence that initially presumed VAH on sVAD may not be all congenital VAH and a cause of sVAD; instead, VAH-like appearance can be a result of sVAD. As four lesions with newly appearing ipsilateral VAH-like appearance had the stenotic component (i.e., pearl-and-string appearance or steno-occlusion without aneurysmal dilatation) on initial imaging and they all showed progression of steno-occlusive sVAD during the follow-up period, we speculate that VAH-like appearance can develop from decreased distal VA flow and that VAH-appearance may be derived from adaptive narrowing due to the stenotic component of sVAD. Moreover, there were also patients who were initially classified as the VAH group based on the morphologic criteria for VAH but who had no-VAH on follow-up imaging, which again suggests that initial VAH on sVAD may

not be all congenital VAH.

Our study has several limitations. First, even though we included consecutive patients with suspected sVAD, an inherent selection bias was inevitable due the retrospective study design. Moreover, a substantial number of patients were excluded due to a lack of proximal VA and brain imaging. To evaluate chronological changes in the proximal VA diameter, we only included patients with follow-up imaging available. This may have increased the selection bias. Second, we could not assess the presence of VAH before sVAD occurrence in our study population, which may lead to a misestimation of the true incidence of VAH. However, we believe this effect is negligible as the incidence of VAH in our population was comparable to that in the normal population. Third, although all of the imaging methods used in this study could diagnose VAD accurately [17], the heterogeneity of the diagnostic methods may affect the measurement of the proximal VA diameter, which can be another limitation of our study. However, we performed subgroup analyses according to diagnostic methods to overcome this limitation and the same trends were observed regardless of diagnostic methods. Moreover, previous studies have shown that the evaluation of arteries is not affected by either contrast material or

Table 3
VAH and morphologic subtypes of 143 VAD patients with follow-up imaging.

	no VAH	ipsilateral VAH	contralateral VAH	f/u period (days)
VA appearance, no change (n = 132)	115	10	7	499.0 ± 566.3
Steno-occlusion only	29 (25.2%)	5 (50.0%)	0 (0%)	
Pearl-and-string appearance	55 (47.8%)	5 (50.0%)	2 (28.6%)	
Aneurysmal dilatation only	31 (27.0%)	0 (0%)	5 (71.4%)	
Development of VAH-like appearance (n = 7)		4	3	406.9 ± 332.3
Steno-occlusion only		2 (50.0%)	1 (33.3%)	
Pearl-and-string appearance		2 (50.0%)	1 (33.3%)	
Aneurysmal dilatation only		0 (0%)	1 (33.3%)	
Resolution of VAH (n = 4)		3	1	650.5 ± 645.9
Steno-occlusion only		1 (33.3%)	0 (0%)	
Pearl-and-string appearance		2 (66.7%)	1 (100%)	
Aneurysmal dilatation only		0 (0%)	0 (0%)	

imaging methods [18,19].

5. Conclusion

We found that the incidence of presumed VAH which co-occurred in sVAD may differ according to the subtype of sVAD. VAs can dynamically change their diameters and such change can mimic VAH after a sVAD event. Therefore, the association between sVAD and VAH should be cautiously evaluated with both the sVAD subtype and time point being taken into consideration.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejrad.2019.04.021>.

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