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ORIGINAL RESEARCH

Behavior of Extracranial-to-Intracranial Extended Arterial Dissections of the Vertebral Artery

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BACKGROUND: Vertebral artery dissections (VADs) may extend from the extracranial to the intracranial vasculature (e+iVAD). We evaluated how the characteristics of e+iVAD differed from those of intracranial VAD (iVAD).

METHODS AND RESULTS: From 2002 to 2019, among consecutive patients with cervicocephalic dissection, those with iVAD and e+iVAD were included, and their clinical characteristics were compared. In patients with unruptured dissections, a composite clinical outcome of subsequent ischemic events, subsequent hemorrhagic stroke, or mortality was evaluated. High-resolution magnetic resonance images were analyzed to evaluate intracranial remodeling index. Among 347 patients, 51 (14.7%) had e+iVAD and 296 (85.3%) had iVAD. The hemorrhagic presentation occurred solely in iVAD (0.0% versus 19.3%), whereas e+iVAD exhibited higher ischemic presentation (84.3% versus 27.4%; $P<0.001$). e+iVAD predominantly presented steno-occlusive morphology (88.2% versus 27.7%) compared with dilatation patterns (11.8% versus 72.3%; $P<0.001$) of iVAD. The ischemic presentation was significantly associated with e+iVAD (iVAD as a reference; adjusted odds ratio, 3.97 [95% CI, 1.67–9.45]; $P=0.002$]). Patients with unruptured VAD showed no differences in the rate of composite clinical outcome between the groups (log-rank, $P=0.996$). e+iVAD had a lower intracranial remodeling index (1.4±0.3 versus 1.6±0.4; $P<0.032$) and a shorter distance from dural entry to the maximal dissecting segment (6.9±8.4 versus 15.7±7.4; $P<0.001$).

CONCLUSIONS: e+iVAD is associated with lower rates of hemorrhages and higher rates of ischemia than iVAD at the time of admission. This may be explained by a lower intracranial remodeling index and less deep intrusion of the dissecting segment into the intracranial space.

Key Words: extracranial-to-intracranial extended vertebral artery dissection ■ high-resolution magnetic resonance images ■ intracranial remodeling index ■ luminal morphology

Cervicocephalic artery dissection (CCAD) is an important cause of stroke in children and young or middle-aged adults.[1] It can be generally differentiated into extracranial and intracranial arterial dissections, depending on its location.[2] The incidence of intracranial artery dissections appears to be lower than that of extracranial artery dissections in populations of European ethnic origin, whereas in reports from populations of Asian ethnicity, intracranial artery dissections account for approximately two-thirds of CCAD.[3]

The differences in the clinical behavior of extracranial and intracranial arterial dissections are partly attributable to differences in arterial wall physiology. Compared with extracranial arteries, intracranial artery walls lack external elastic lamina and have a thinner media thickness. The extracranial arteries are thus more resistant to dissecting tears, resulting in dissections localized to the intima or media.[3] These patients would usually present with neck pain, headaches, or ischemia. Intracranial artery dissection is more

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CLINICAL PERSPECTIVE

What Is New?

- This study provides novel insights into extracranial-to-intracranial extended vertebral artery dissections (VADs) by comparing them with intracranial VADs based on high-resolution magnetic resonance imaging.
- Patients with extracranial-to-intracranial extended VADs tend to exhibit a higher propensity of ischemic presentations and lower hemorrhagic presentations than those with intracranial VADs, associated with lower rate of intracranial remodeling and less deep intrusion of the dissecting segment into the intracranial space.

What Are the Clinical Implications?

- This study suggests that clinicians may anticipate disparate presentations between extracranial-to-intracranial extended VADs and intracranial VADs, thus guiding tailored management strategies and indicating the potential utility of the intracranial remodeling index as a tool for risk assessment.

Nonstandard Abbreviations and Acronyms

CCAD	cervicocephalic artery dissection
e+iVAD	extracranial-to-intracranial extended vertebral artery dissection
eVAD	extracranial vertebral artery dissection
HR-MRI	high-resolution magnetic resonance imaging
IRI	intracranial remodeling index
iVAD	intracranial vertebral artery dissection
VAD	vertebral artery dissection

susceptible to subadventitial involvement and complete arterial rupture, resulting in subarachnoid hemorrhage (SAH) as well as headache or ischemia.[4]

In some patients, dissection originating from the extracranial portion of the cervicocephalic arteries may extend into the intracranial segment. Intracranial extension of extracranial dissection is known to be more frequent in vertebral artery dissections (VADs).[5] However, the clinical behavior of extracranial-to-intracranial extended VAD (e+iVAD) has not been elucidated. The rates of ischemic or hemorrhagic presentations and the subsequent risks of ischemic or hemorrhagic complications have not been extensively studied.

Accordingly, we aimed to understand the clinical and prognostic features of e+iVAD. In this single-center CCAD registry, we compared the clinical and prognostic features of e+iVAD with intracranial VAD (iVAD). We further analyzed high-resolution magnetic resonance imaging (HR-MRI) of the intracranial portion of the VAD to elucidate the cause of the differences in clinical presentation.

METHODS

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Study Population and Management

Our hospital has been appointed as a Regional Emergency Medical Center, which covers South Gyeonggi Province (population: 13 070 000, as of 2018), by the Ministry of Health and Welfare. Accordingly, we hypothesized that the analysis of our hospital database may represent the general features of VAD. Data were collected by a retrospective medical record search, as previously reported.[6] In a hospital registry of CCAD, we included patients presenting with symptomatic VAD (headache or posterior circulation neurologic symptoms within 31 days) admitted to our hospital between 2002 and 2019. Patients presenting with the below imaging findings involving the intracranial vertebral artery or both the intracranial and extracranial vertebral arteries were included: (1) luminal pearl and string sign (stenosis and dilatation), (2) luminal stenosis with intimal flap/double lumen, or intramural hematoma (fat-suppression T1-weighted magnetic resonance or magnetic resonance angiogram source images), (3) luminal fusiform aneurysmal dilatation of the vertebral arterial trunk not located at an arterial branching point, and (4) luminal occlusion with visible intimal flap/double lumen, or associated with a pearl-and-string sign.[3,7,8] The exclusion criteria were as follows: (1) pure extracranial vertebral artery dissection (eVAD) and (2) isolated basilar artery, posterior cerebral artery, and posterior inferior cerebellar artery dissections[9] (Figure 1). Basilar extension of VAD was not an exclusion criterion. Intracranial extended dissections were classified as follows: presence of a flap, intramural hematoma, or tapered stenosis extending from the extracranial vertebral artery to the intracranial portion. Ethics approval was obtained from the Ajou University Hospital Institutional Review Board (AJOUIRB-MDB-2021-674), and the study was performed following the ethical standards in the 1964 Declaration of Helsinki and its later amendments. The Ajou University Hospital Institutional Review Board waived the need for obtaining patient consent. In patients with VAD presenting with SAH, intra-arterial embolization via endovascular coiling was mostly performed. In patients with unruptured

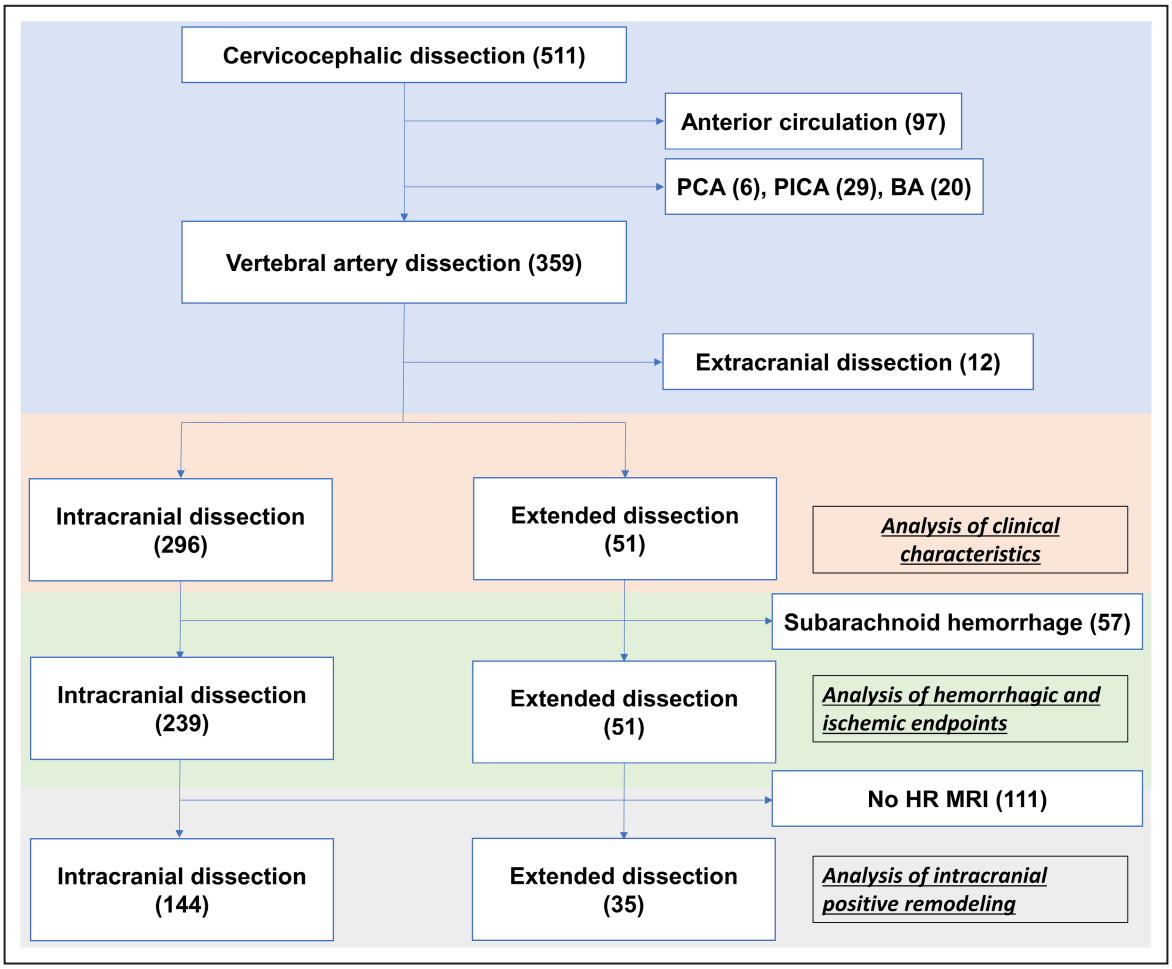

Figure 1. Flowchart of patient selection.
BA indicates basilar artery; HR-MRI, high-resolution magnetic resonance imaging; PCA, posterior cerebral artery; and PICA, posterior inferior cerebellar artery.

VAD, flow diversion via stent within stent technique[10] or intra-arterial embolization via endovascular coiling/stent-assisted coiling was selectively performed at the discretion of the attending physician in patients with fusiform/aneurysmal dilatation of the VAD with a diameter ratio between the dissecting and normal segments of the vertebral artery of ≥1.5 or progression of the dissection on follow-up images.[11]

Variables and Image Analysis

Clinical presentation was classified as ischemic, hemorrhagic, or headache and others. Baseline demographics were collected. The primary arterial luminal morphology was described as steno-occlusion and dilatation (including stenosis and dilatation) patterns.[12] The location of the dissection was categorized as intracranial (iVAD), extended (e+iVAD), or purely eVAD (excluded from study). Basilar artery involvement was documented. The primary treatment modality of the patient was classified as intra-arterial intervention (primary intra-arterial embolization, delayed intra-arterial embolization, or intra-arterial reperfusion) or medical management. In patients with ischemic presentation, the initial clinical severity was graded using the National Institutes of Health Stroke Scale, which was measured 3 times daily during acute stroke unit care and then daily until discharge. Ischemic early neurologic deterioration was classified as an increase of ≥2 points in the National Institutes of Health Stroke Scale score within 7 days postadmission in patients presenting with cerebral ischemia.[13] Subsequent ischemic stroke or hemorrhagic stroke was identified. Serial angiographic images were analyzed to evaluate arterial healing in patients who were not treated with primary intra-arterial embolization.

Definition of Clinical Outcome

In patients presenting with unruptured VAD, the rates of clinical outcomes, including subsequent ischemic events (new ischemic stroke or ischemic early

neurologic deterioration), subsequent hemorrhagic stroke, and mortality, were assessed up to the most recent follow-up. Because of the heterogeneous outcome parameters in patients with unruptured iVAD, these parameters were combined to form a composite clinical outcome (subsequent ischemic event, hemorrhagic stroke, or mortality).[14,15] Kaplan-Meier survival analysis was performed to assess the comparative outcomes across groups concerning composite clinical outcomes, instances of subsequent ischemic events, subsequent hemorrhagic stroke, and mortality. Vascular outcomes, such as aneurysmal changes or arterial healing, were also evaluated. Aneurysmal change was characterized as an increase in the luminal diameter of the dissecting segment beyond the expected original diameter in any follow-up angiography. Arterial healing was defined as any improvement observed in follow-up luminal angiography after the diagnosis of prior stenosis or dilation. Arterial healing was evaluated in patients who did not receive interventional treatment during admission.

HR-MRI Protocols

Patients underwent HR-MRI if the clinician thought it was feasible and necessary. All MRI was performed using either 2 3-T MRI scanners (Achieva, Philips Healthcare, Best, the Netherlands) with 16-channel neurovascular head coil or Discovery 750W (GE Healthcare, Milwaukee, WI) with 24-channel coil.[9] Because of the length of the study period, there were some minor changes for the HR-MRI protocol; however, it basically included 2-dimensional protocols consisting of 4 axial HR sequences (proton density-weighted imaging, T2-weighted imaging, T1-weighted imaging, and contrast-enhanced T1-weighted imaging)[16] and a time-of-flight magnetic resonance angiography.[17] After July 2014, 3-dimensional contrast enhanced motion-sensitized driven-equilibrium-T1 sequences were included in the HR-MRI protocol.[9] The detailed parameters for each MRI sequence have been reported previously.[9,16,17]

Measurement of the Intracranial Remodeling Index

Intracranial remodeling index (IRI) analysis was performed in the subgroup of patients who underwent HR-MRI. The neuroimaging indexes for IRI were measured by 2 stroke neurologists (S.Y.P. and S.-J.L.) on 2-dimensional images with time-of-flight and multiplanar reconstruction images as a reference using commercial image-viewing software (Picture Archiving and Communication System; Maroview 5.3 Infinitt Co, Seoul, Republic of Korea) without access to clinical information. The variables, including distal normal arterial diameter, maximal diameter of the dissecting segment, proximal dural arterial diameter, and the distance from the dural entry point to the maximal diameter point, were measured. The IRI was calculated as follows: maximal outer wall diameter of the intracranial dissecting segment/distal normal arterial wall diameter, modifying a previously reported method.[11] The inter-rater agreement for each variable was verified through intraclass correlation coefficient analysis. Reliability assessments yielding values <0.5 are suggestive of inadequate reliability, whereas values falling within the range of 0.5 to 0.75 suggest a moderate level of reliability. Values ranging from 0.75 to 0.90 are indicative of a substantial degree of reliability, and values >0.90 signify an exceptionally high level of reliability.[18] The values measured by 1 researcher are presented in the Results (S.-J.L.).

Statistical Analysis

The presenting symptoms, clinical characteristics, and prognoses were compared between the e+iVAD and iVAD groups. Continuous variables were compared using Student *t* test and Mann-Whitney *U* test, and categorical variables were analyzed using the χ^2 test and Fisher exact test. On the basis of this analysis, multivariable logistic regression analysis was performed to validate the differences in clinical presentation and outcomes between the groups. Variables demonstrating correlations with ischemic events in the univariate examination, and those identified as clinically significant by clinicians, were taken into account and subsequently integrated into the ultimate analysis. Second, the unruptured VAD subgroup underwent a comparison of composite primary outcome and other clinical outcomes between the e+iVAD and iVAD groups through Kaplan-Meier survival analysis. The log-rank test was used to compare rate estimates. Third, in patients with HR-MRI, the degree of IRI was analyzed to elucidate the differences between the 2 groups. Data are presented as mean±SD, number (percentage), or median (interquartile range), as appropriate for data type and distribution. Statistical analyses were performed using the IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY) and Rex Excel-based statistical analysis software, version 3.6.0 (RexSoft; http://rexsoft.org/) based on R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$.

RESULTS

Clinical Characteristics of the e+iVAD and iVAD Groups

In total, 347 patients were included in the analysis. Among them, 51 (14.7%) were in the e+iVAD group, and

Table 1. Comparison of Clinical and Anatomic Characteristics Between the e+iVAD and iVAD Groups

Variable	e+iVAD group (n=51)	iVAD group (n=296)	*P* value
Age, y	47±13	49±10	0.278
Sex, male	38 (74.5)	190 (64.2)	0.203
Hypertension	18 (35.3)	100 (33.8)	0.960
Diabetes	6 (11.8)	25 (8.5)	0.429
Dyslipidemia	12 (23.5)	33 (11.2)	0.028
Smoking	20 (39.2)	97 (32.8)	0.570
Presentation			<0.001
Hemorrhage	0 (0.0)	57 (19.3)	
Ischemia	43 (84.3)	81 (27.4)	
Headache and others	8 (15.7)	158 (53.4)	
Luminal lesion morphology			<0.001
Steno-occlusion	45 (88.2)	82 (27.7)	
Dilatation	6 (11.8)	214 (72.3)	
BA extension	0 (0.0)	30 (10.1)	0.013
Diagnostic criteria			
Pearl-and-string sign	8 (15.7)	133 (44.9)	<0.001
Flap/double lumen/ hematoma	48 (94.1)	185 (62.5)	<0.001
Fusiform dilatation on nonbranching site	2 (3.9)	106 (35.8)	<0.001
Occlusion with flap/double lumen/hematoma	36 (70.6)	28 (9.5)	<0.001
Treatment			
Intra-arterial intervention	3 (5.9)	90 (30.4)	<0.001
Acute embolization/flow diversion	3 (5.9)	78 (26.4)	
Delayed embolization/flow diversion	0 (0.0)	9 (3.0)	
Intra-arterial reperfusion	0 (0.0)	3 (1.0)	
Medical treatment	48 (94.1)	206 (69.6)	<0.001

Data are given as mean±SD or number (percentage). Baseline characteristics between groups were compared using χ^2 test or Fisher exact test. BA indicates basilar artery; e+iVAD, extracranial-to-intracranial extended vertebral artery dissection; and iVAD, intracranial vertebral artery dissection.

296 (85.3%) were in the iVAD group (Table 1). Among the vascular risk factors, only dyslipidemia was more common in the e+iVAD group than in the iVAD group (23.5% versus 11.2%; *P*=0.028). There were significant differences in the clinical presentation. The most common presentation pattern for the e+iVAD group was ischemia (84.3%), followed by headache and others (15.7%), whereas none of the patients presented with SAH. In contrast, the iVAD group most commonly presented with headache and other symptoms (53.4%), followed by ischemia (27.4%), and hemorrhage (19.3%) (*P*<0.001). Other symptoms, excluding headache (44.4% versus 72.0%), comprised dizziness (44.4% versus 11.5%) and ataxia (0% versus 7.6%), among others. There were also differences in luminal morphology; the e+iVAD group most frequently showed a steno-occlusion pattern (88.2%), whereas the iVAD group most commonly showed a dilatation pattern (72.3%) (*P*<0.001). Basilar extension was only seen in the iVAD group (0.0% versus 10.1%; *P*=0.035). Intra-arterial intervention was more frequently performed in the iVAD group (5.9% versus 30.4%; *P*<0.001). In total, among the 347 patients, 21 expired at the time of discharge, and 17 experienced follow-up loss.

Multivariable analysis was performed to confirm the association between dissection location and ischemic presentation (Table 2). In this analysis, e+iVAD was associated with ischemic presentation (iVAD as a reference; odds ratio, 3.97 [95% CI, 1.67–9.45]; *P*=0.002), along with age, sex, dyslipidemia, and steno-occlusive lesion morphology as covariables. Multivariable analysis to confirm the association between dissection extension and hemorrhagic presentation was not performed because SAH occurred only in the iVAD group.

Clinical Outcomes in Unruptured e+iVAD and iVAD

A total of 290 patients presented with unruptured VAD, 51 in the e+iVAD group and 239 in the iVAD group. The e+iVAD group showed a steno-occlusive morphology (88.2%), whereas the iVAD group showed a dilatation morphology (66.1%) (*P*<0.001). The basilar extension was only seen in the iVAD group (0.0% versus 11.7%; *P*=0.007). The rate of intra-arterial intervention was higher in the iVAD group compared with the e+iVAD group (5.9% versus 18.4%; *P*=0.046). The iVAD group exhibited a higher rate of antiplatelet use (27.5% versus 38.5%), whereas the e+iVAD group demonstrated a higher rate of warfarin use (54.9% versus 36.8%), although without statistical significance (*P*=0.074). The follow-up duration extended for a median of ≈5.6 (5.62 [2.13–8.26]) years postdischarge, with the e+iVAD group exhibiting a comparatively longer follow-up period (7.1 [5.0–10.1] versus 5.4 [1.8–8.0] years; *P*=0.005).

Table 2. Factors Associated With Ischemic Presentation

Factor	Adjusted OR (95% CI)	*P* value
Lesion location		0.002
iVAD	Reference	
e+iVAD	3.97 (1.67–9.45)	
Age (per year)	0.98 (0.95–1.00)	0.099
Sex, male	2.70 (1.37–5.31)	0.004
Dyslipidemia	2.41 (1.07–5.45)	0.035
Steno-occlusion	4.42 (2.38–8.21)	<0.001

We conducted a multivariable analysis to substantiate the relationship between the location of dissection and the occurrence of ischemic presentations. e+iVAD indicates extracranial-to-intracranial extended vertebral artery dissection; iVAD, intracranial vertebral artery dissection; and OR, odds ratio.

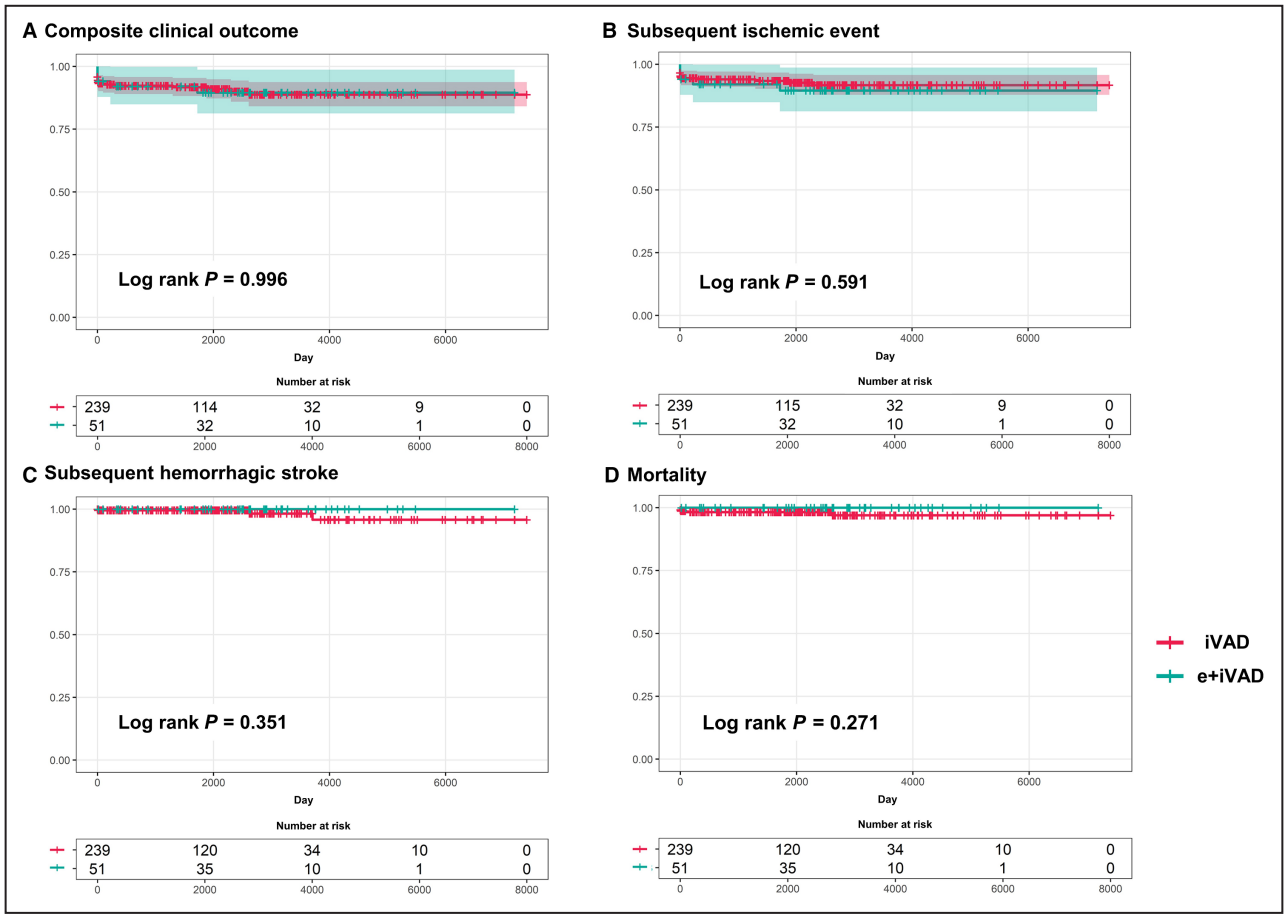

Figure 2. Comparison of clinical outcomes between patients with extracranial-to-intracranial extended vertebral artery dissection (e+iVAD) and intracranial vertebral artery dissection (iVAD) in the unruptured vertebral artery dissection subgroup. Kaplan-Meier survival analysis was conducted to compare groups in terms of composite clinical outcome (**A**), subsequent ischemic events (**B**), subsequent hemorrhagic stroke (**C**), and mortality rates (**D**). The log-rank test was used to compare rate estimates.

Kaplan-Meier survival analysis was used to evaluate the rate of subsequent ischemic events (early neurologic deterioration and new ischemic stroke) (log-rank *P*=0.591), hemorrhagic stroke (log-rank *P*=0.351), mortality (log-rank *P*=0.271), and composite clinical outcome (log-rank *P*=0.996) during the follow-up period. No statistically significant difference was observed between the groups (Figure 2). A total of 289 patients underwent angiography imaging for vascular follow-up, wherein 258 underwent angiography imaging during hospitalization, whereas 242 underwent imaging after discharge. The iVAD group showed a tendency for a higher rate of aneurysmal change (4/51 [7.8%] versus 48/238 [20.2%]; *P*=0.06), although without statistical significance. There was no statistically significant difference in arterial healing (24/48 [50.0%] versus 97/194 [50.0%]; *P*>0.999) (Table 3).

HR-MRI Analysis of IRI

Further analysis of HR-MRI imaging was performed in 35 patients in the e+iVAD group and 144 in the iVAD group, of which 174 of 179 (97.2%) had predominantly unruptured VAD. When the patients in the e+iVAD and iVAD groups were compared for remodeling of intracranial vessels (Table 4), the IRI (1.4±0.3 versus 1.6±0.4; *P*=0.032) as well as the absolute maximal diameter of the dissecting segment (5.2±1.1 versus 5.9±1.4 mm; *P*=0.003) were significantly higher in the iVAD group. The distance from the dural entry to the point of maximal diameter was significantly greater in the iVAD group (6.9±8.4 versus 15.7±7.4; *P*<0.001). Moreover, a lower rate of intramural hematoma was noted at the dissection site in the e+iVAD group compared with the iVAD group (85.7% versus 66.0%; *P*=0.038). The intraclass correlation coefficient for IRI, maximal diameter of the dissecting segment, distal normal arterial diameter, and the distance from dural entry to maximal diameter point were 0.87 (95% CI, 0.81–0.91), 0.93 (95% CI, 0.91–0.95), 0.73 (95% CI, 0.61–0.82), and 0.93 (95% CI, 0.91–0.95), respectively. The maximal diameter of the dissecting segment and the distance from the dural entry to the maximal diameter point demonstrated excellent reliability, whereas the IRI exhibited a

Table 3. Clinical and Anatomic Characteristics in the Unruptured VAD Subgroup

Characteristic	e+iVAD group (n=51)	iVAD group (n=239)	*P* value
Age, y	47±13	49±9	0.272
Sex, male	38 (74.5)	154 (64.4)	0.223
Hypertension	18 (35.3)	79 (33.1)	0.885
Diabetes	6 (11.8)	17 (7.1)	0.260
Dyslipidemia	12 (23.5)	32 (13.4)	0.106
Smoking	20 (39.2)	83 (34.7)	0.704
Luminal lesion morphology			<0.001
Steno-occlusion	45 (88.2)	81 (33.9)	
Dilatation	6 (11.8)	158 (66.1)	
BA extension	0 (0.0)	28 (11.7)	0.007
Treatment			
Intra-arterial intervention	3 (5.9)	44 (18.4)	0.046
Acute embolization/ flow diversion	3 (5.9)	32 (13.4)	
Delayed embolization/ flow diversion	0 (0.0)	9 (3.0)	
Intra-arterial reperfusion	0 (0.0)	3 (1.0)	
Medical treatment	48 (94.1)	195 (81.6)	0.046
Antithrombotic drug			0.074
Antiplatelet only	14 (27.5)	92 (38.5)	
Anticoagulation only	28 (54.9)	88 (36.8)	
Both used	2 (3.9)	6 (2.5)	
No medication	7 (13.7)	53 (22.2)	
Follow-up duration	7.1 (5.0–10.1)	5.4 (1.8–8.0)	0.005
Vascular outcome			
Aneurysmal change	4/51 (7.8)	48/238 (20.2)	0.060
Arterial healing	24/48 (50.0)	97/194 (50.0)	>0.999

Data are given as mean±SD, number (percentage), number/total (percentage), or median (interquartile range). Baseline characteristics between groups were compared using χ^2 test or Fisher exact test. BA indicates basilar artery; e+iVAD, extracranial-to-intracranial extended VAD; iVAD, intracranial VAD; and VAD, vertebral artery dissection.

substantial degree of reliability. Schematic diagrams illustrating arterial remodeling in the e+iVAD and iVAD groups are shown in Figure 3. There was a higher rate of intramural hematoma in the e+iVAD group (85.7% versus 66.9%; *P*=0.048), whereas presence of intimal flap/double lumen did not differ (71.4% versus 76.5%; *P*=0.567).

DISCUSSION

The results indicate that in contrast to iVAD, when dissection of the vertebral artery initiates from the extracranial segment and extends to the intracranial portion, it seldom results in arterial rupture and hemorrhage. In contrast, ischemic presentations were more dominant in the e+iVAD group. In unruptured VAD, there was a higher rate of neurointerventional treatment in the iVAD group. Afterwards, there were no differences in clinical outcomes, both hemorrhagic and ischemic. In addition to the clinical presentation, we conducted a comparison of the intracranial remodeling index to verify morphologic distinctions. This analysis affirmed that patients with iVAD exhibited a larger maximal diameter of the dissecting segment located more deeply into the intracranial space and displayed a propensity toward positive remodeling.

To the best of our knowledge, ours is the first study to compare the clinical characteristics of e+iVAD with iVAD. Only 1 previous study has evaluated the behavior of e+iVAD; however, that study compared it with eVAD in a predominantly European population.[19] It was reported that e+iVAD was associated with a higher risk for ischemic stroke at presentation compared with eVAD, whereas the rates of SAH were low (6% and 3%, respectively). The risk of ischemic stroke in e+iVAD is comparable between the previous study and ours, and our study results also show a low risk for hemorrhagic presentation or subsequent hemorrhagic stroke. Considering the low reported risk of SAH in extracranial VAD,[20] the current results show that e+iVAD behaves similarly to eVAD even when the dissecting flap invades the intracranial segment.

In contrast to iVAD, no hemorrhagic presentations were observed for e+iVAD, along with no subsequent hemorrhagic stroke (which, however, failed to reach statistical significance). This difference may be partly explained by the higher degree of IRI, and more deeply located maximal dissecting segment into the intracranial space in iVAD, which the current study reports for the first time. The clinical significance of IRI of the outer

Table 4. Differences in Intracranial Remodeling in the Subgroups With HR-MRI

Variable	e+iVAD group (n=35)	iVAD group (n=144)	*P* value
Intracranial remodeling index*	1.4±0.3	1.6±0.4	0.032
Dural entry point diameter	4.7±0.8	4.7±0.8	0.866
Maximal diameter of dissecting segment	5.2±1.1	5.9±1.4	0.003
Distal normal diameter	3.7±0.8	3.9±0.9	0.329
Distance from dural entry point to maximal diameter of dissecting segment point	6.9±8.4	15.7±7.4	<0.001
Findings in dissecting segment			
Intramural hematoma	30 (85.7)	95 (66.0)	0.038
Intimal flap/double lumen	25 (71.4)	112 (77.8)	0.567

Data are given as mean±SD or number (percentage). Image variables from HR-MRI were compared between the groups using Student *t* test or χ^2 test. e+iVAD indicates extracranial-to-intracranial extended vertebral artery dissection; HR-MRI, high-resolution magnetic resonance imaging; and iVAD, intracranial vertebral artery dissection.

*Intracranial remodeling index=maximal diameter of dissecting segment/distal normal diameter.

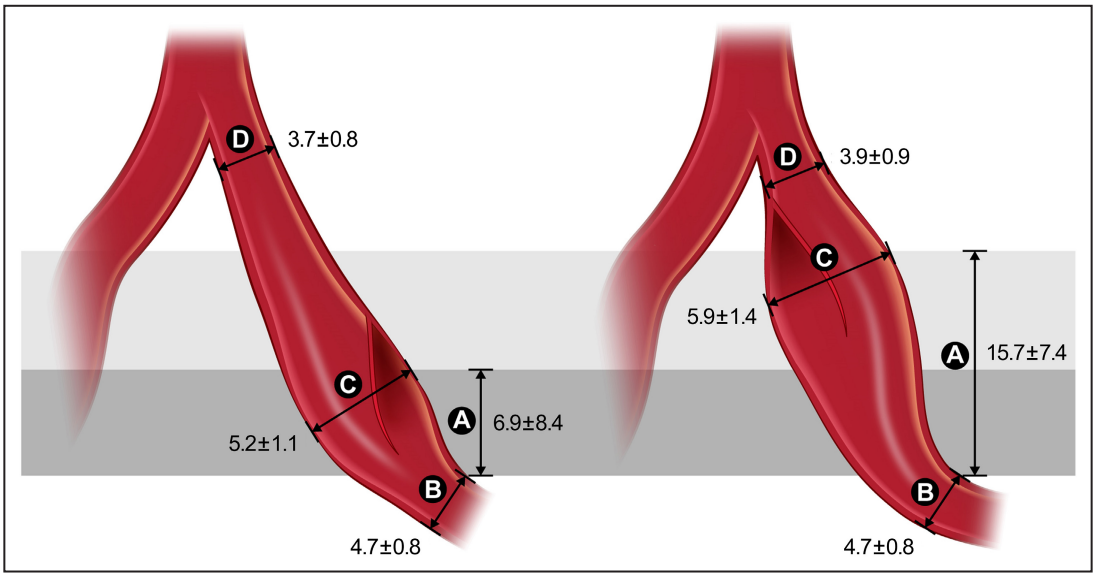

Figure 3. Intracranial remodeling of the outer arterial wall in the extracranial-to-intracranial extended vertebral artery dissection (e+iVAD) and intracranial vertebral artery dissection (iVAD) groups.
The figure illustrates intracranial remodeling of the outer arterial wall in the e+iVAD (left) and iVAD (right) groups. **A**, Distance from dural entry point to maximal diameter of dissecting segment point. **B**, Dural entry point diameter. **C**, Maximal diameter of dissecting segment, **D**, Distal normal diameter. The numbers indicate mean value of each parameter in each group from this study.

arterial wall has not been extensively studied, but it may be intuitively associated with hemodynamic stress and risk of arterial rupture. It is also known to enlarge in the acute phase and decreases significantly in the chronic stage,[21] which resembles the bleeding risk of dissecting aneurysms. The cause of the lower degree of remodeling in e+iVAD is unclear; however, it may be associated with the location of the intimal tear, wherein the hemodynamic stress causing arterial remodeling[22] is maximal. In e+iVAD, the location of the intimal tear is proximal; therefore, hemodynamic stress to the intracranial segment may be lower. Another possibility is that different pathophysiological mechanisms[3,4,19] may take a role in iVAD and eVAD, and that the pathophysiology of e+iVAD resembles that of eVAD. For example, there is evidence that direct bleeding of vasa vasorum is associated with cervical arterial dissections.[23] However, vasa vasorum is not always seen in intracranial arteries.[24] Thus, such differences in mechanisms would result in different rates of SAH.

A relatively higher rate of ischemic presentation was observed in the e+iVAD group. This was also observed in another study,[19] which reported even higher rates of ischemic presentation compared with eVAD. The relative frequency of ischemic presentations compared with eVAD could be attributable to higher rates of luminal steno-occlusions or involvement of branching arteries.[19] The relative frequency of ischemic presentations compared with iVAD could partly be secondary to the heterogeneous presentations of iVAD; however, whether e+iVAD would be more thrombogenic than iVAD requires future research. There is a chance that a longer length of the dissecting segment in e+iVAD would result in more frequent thromboembolic stroke,[25] whereas dissection attributable to perforator occlusion may vary according to the dissection location and perforator initiating sites, such as the origin of the posterior inferior cerebellar artery.[9] It may also be partly associated with higher rates of intramural hematoma observed in e+iVAD. Previous literature reports the comparatively lower rate of intramural hematoma associated with iVAD compared with eVAD,[2] also supporting our view that the behavior of e+iVAD resembles that of eVAD. The rate of intramural hematoma observed in HR-MRI is prone to change with chronological age of arterial dissection.[26] We suggest that there may not have been a higher rate of chronic lesions in the iVAD group. This proposition is based on the observation of more frequent headache presentations in the iVAD group, which is a recognized acute phase biomarker of cervicocephalic arterial dissections.[27,28]

The current study has some limitations. First, although there were differences in ischemic and hemorrhagic presentations between groups, differences in subsequent ischemic events or hemorrhagic stroke failed to reach significance. This may be attributable to the fact that patients were treated to reduce hemorrhagic or ischemic complications in an individual basis, as represented by a higher rate of interventional

treatment in the unruptured iVAD group. Furthermore, the rate of subsequent ischemic events or hemorrhagic stroke was too low to achieve statistical significance. A prospective cohort with a larger number of patients may be needed to confirm that the pathophysiological tendencies observed in the early period of VAD extends to the later periods. Second, the current study was retrospective, and HR-MRI was not performed in all patients. The design included all consecutive patients with VAD presenting to a Regional Emergency Medical Center, regardless of HR-MRI status, focusing on patient demographics. Although this is a limitation, we believe that the HR-MRI findings of higher rates of IRI in iVAD are further generalizable to excluded patients usually presenting with SAH and angiographically visible dissecting aneurysms (high IRI). Third, pure eVAD was excluded from the analysis. This was inevitable because of the limited number of patients (N=12), which would hinder statistical analysis. In the study, most patients with extracranial VAD (7 of 12) experienced symptoms associated with ischemic presentations. A single-center cervicoencephalic artery dissection registry that recruited patients of European ethnicity reported only 19 patients with purely intracranial dissections among 328 patients, showing striking differences according to ethnicity.[19] A previous literature of CCAD in Korean patients reported a predominance of 66% intracranial dissections when combining both the anterior and posterior circulation.[29] This study focused on the posterior circulation, resulting in a lower rate of eVAD. Furthermore, our hospital operates a regional trauma center, and trauma patients are admitted by the trauma team. As this study included patients only admitted to the department of neurology or neurosurgery, minor trauma patients presenting with eVAD may have been excluded. Fourth, as mentioned above, the proportion of intracranial artery dissections in all cervicocephalic dissections exhibits substantial variability across different ethnic origins and age groups. Accordingly, the current study findings may not be fully generalizable to White[19] or Hispanic patients.[30] Fifth, for the measurement of IRI, only the distal normal arterial diameter was used rather than the mean of proximal and distal arterial diameters. This was attributable to the difficulty in measuring the outer arterial wall diameter in the V3 segment adjacent to the subcutaneous tissue. However, we believe that the current methods still represent a lower degree of acute hemodynamic stress applied to the intracranial VAD for e+iVAD and differences in the subsequent risk for rupture.

In conclusion, in terms of acute presentation, e+iVAD presents with higher ischemic and lower hemorrhagic presentations than iVAD. This may be partly explained by the lower degree of IRI of the outer arterial wall in e+iVAD and less deep intrusion of the dissecting segment into the intracranial space. In patients with VAD who did not present initially with hemorrhage, a higher rate of intra-arterial intervention was performed in the iVAD group. Afterwards, there were no discernible differences in clinical outcomes between the groups. Such findings may be integrated into the management of patients with VADs.

ARTICLE INFORMATION

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Disclosures

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