Prevalence and Outcomes of Bicuspid Aortic Valve in Patients With Aneurysmal Sub-Arachnoid Hemorrhage: A Prospective Neurology Registry Report

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BACKGROUND: Intracranial aneurysms are reported in 6%–10% of patients with bicuspid aortic valve (BAV), and routine intracranial aneurysm surveillance has been advocated by some. We assessed the prevalence and features of the most important patient-outcome: aneurysmal sub-arachnoid hemorrhage (aSAH), as compared with controls without aSAH, and tricuspid aortic valve (TAV) with aSAH.

METHODS AND RESULTS: Adult patients with accurate diagnosis of aSAH and at least one echocardiogram between 2000 and 2019 were identified from a consecutive prospectively maintained registry of aSAH admissions. Controls without a diagnosis of SAH were age- and sex-matched. BAV prevalence was confirmed echocardiographically. Severity of aSAH was categorized using modified Fisher and World Federation of Neurological Scale. Neurologic outcome was assessed using modified Rankin score. A total 488 aSAH cases and 990 controls were identified and BAV status was confirmed. Prevalence of BAV in patients with aSAH was 1.2% (6/488) versus 3.5% (35/990) in controls, $P=0.01$. BAV+aSAH were noted to be younger than TAV+aSAH (56±11 versus 68±14; $P=0.03$) with smaller aneurysms (5±2 versus 7±4; $P=0.31$). The severity of aSAH was lesser in BAV+aSAH than TAV (modified Fisher grade>2 50% versus 74%; $P=0.19$, World Federation of Neurological Scale grade>3 17% versus 36%; $P=0.43$). BAV+aSAH had less severe neurologic disability (modified Rankin score 3%–6 33% versus 49% in TAV; $P=0.44$) and comparable in-hospital mortality rates ($P=0.93$). BAV had lower odds for aSAH on multivariate analysis (odds ratio 0.23[CI 0.08–0.65]; $P=0.01$).

CONCLUSIONS: Prevalence of BAV was 3 times lower in the aSAH registry than in controls without aSAH. BAV+aSAH had clinically smaller aneurysms, clinically smaller bleeds, and better neurologic outcome as compared with TAV+aSAH, which needs to be confirmed in larger studies. These findings argue against routine surveillance for intracranial aneurysms in patients with BAV without aortic coarctation.

Key Words: bicuspid aortic valve ■ intracranial aneurysms ■ sub-arachnoid hemorrhage

Intracranial aneurysms (IAs) have been associated with bicuspid aortic valve (BAV) in prior studies. The prevalence of IAs is purported to range between 6% to 10% in BAV, possibly suggesting the need for routine IA screening in patients with BAV. Patients with BAV are at a higher risk of thoracic aortopathy, including dilatation and dissection. A higher incidence of IAs in BAV could signal towards systemic arteriopathy beyond the thoracic aorta. However, it is important to recognize that in addition to valvulopathy and thoracic aortopathy, BAV is also associated with coarctation of aorta (CoA). Up to 60% of patients with CoA have concomitant BAV.
whereas only 5%–7% of BAV have CoA.8,9 With CoA as an independent risk factor for IA formation, it is currently uncertain if the association between IA and BAV is a reflection of the association of BAV and CoA, or the result of systemic arterial changes.10

Current American Heart Association/American Stroke Association guidelines recommend screening for IA in both BAV and CoA,11 while the American Heart Association/American College of Cardiology guidelines recommend screening only patients with CoA (evidence level class IIB).12 In addition, the American Association for Thoracic Surgery does not recommend screening patients with BAV without CoA.13 The purpose of routine screening for IA is the prevention of the potentially fatal and most important patient-outcome: aneurysmal sub-arachnoid hemorrhage (aSAH). Despite the association between IA and BAV, there are 2 independent studies2,14 suggesting no increased risk of aSAH in patients with BAV. Given that the outcome of interest is aSAH, shedding further light into this conundrum could be achieved by identifying patients with an accurate diagnosis of exclusive aSAH and comparing them to patients without aSAH to assess the prevalence of BAV. We hypothesize that, although there may be an association between BAV and IA, there is no significantly increased prevalence of BAV in patients with aSAH. Therefore, our primary aim was to identify the prevalence of BAV in consecutive admissions with aSAH and compare it to that of a control group without aSAH. Secondary aims included neurologic outcomes of patients with BAV with aSAH, anatomical characteristics of IA in BAV, and final disposition and outcome of BAV with aSAH.

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| aSAH         | aneurysmal sub-arachnoid hemorrhage |
| AVR          | aortic valve replacement |
| BAV          | bicuspid aortic valve |
| CoA          | coarctation of aorta |
| IA           | intracranial aneurysm |
| mid-Ao       | mid-ascending aorta |
| SoV          | sinus of Valsalva |
| STJ          | sino-tubular junction |
| TAV          | tricuspid aortic valve |
| TTE          | transthoracic echocardiography |

CLINICAL PERSPECTIVE

What Is New?

- This study assessed for the first time the prevalence of echocardiographically confirmed bicuspid aortic valve (BAV) in patients with aneurysmal sub-arachnoid hemorrhage (aSAH), within a prospectively maintained consecutive registry, versus controls without aSAH.
- We observed 3 times lower prevalence of BAV in patients with aSAH clinically, BAV-aSAH than among controls without aSAH.
- Clinically, patients with BAV-aSAH were younger, with smaller aneurysms, less severity of bleed, lower severity of neurologic disability at discharge, and similar mortality as compared with tricuspid aortic valve patients with aSAH.

What Are the Clinical Implications?

- Our study adds evidence to the developing notion of recommending against routine surveillance for intracranial aneurysm in patients with BAV without aortic coarctation.
- Although patients with BAV may have a higher incidence of intracranial aneurysms, the most important patient-outcome (ie, aSAH) does not exhibit an association with BAV.
- These clinical differences must be confirmed in a larger prospective BAV cohort, preferably population-based.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to H.I Michelena at michelena.hector@mayo.edu.

Study Population

Study flowsheet is shown in Figure 1. Patients were identified between January 2000 and December 2019, from a prospectively maintained registry of consecutive patients admitted with non-traumatic SAH to our center within 48 hours of symptom onset. We identified 497 unique adult patients who met the following inclusion criteria: (1) aSAH as identified by computed tomography or magnetic resonance brain imaging, plus angiographic finding of IA; and (2) at least one echocardiography study performed at our center. We excluded patients ≤18 years of age, denied research authorization (per Minnesota law) or non-aneurysmal causes of non-traumatic SAH like peri-mesencephalic SAH, aneurysmal pattern, or unidentified IA.15,16 Age- and sex-matched controls (cases:controls 1:2) were identified based on the following criteria: (1) no diagnosis of SAH ever (identified using Hospital International Classification of Diseases Adapted/International Classification of Diseases, Ninth and Tenth Revisions - Clinical Modification [ICD-9-CM;
ICD-10-CM], (2) from 2006 to 2019, and (3) at least one echocardiography study available in the system.

Demographic and Clinical Data
Demographic and clinical data were extracted from electronic medical records, including comorbidities, neurologic, operative, and procedural data. Severity of aSAH was categorized using the modified Fisher and the World Federation of Neurological Scale. Neurologic outcome was assessed using modified Rankin score. A score of 3–6 at end of hospital stay represented the spectrum between moderate-severe neurologic disability requiring assistance to death. This study was approved by the Mayo Clinic Institutional Review Board at Rochester, Minnesota, and patient consent was waived.

Echocardiographic Evaluation
Comprehensive transthoracic echocardiography (TTE) following standard imaging protocols was performed by experienced sonographer using standardized guidelines, supervised by a level III certified echocardiographer-physician. TTE was performed using commercially available echocardiographic systems. For patients with aSAH, echocardiography performed during the same admission was used for analysis. In controls, the first available TTE was selected for analysis and further echos were reviewed if needed to establish BAV anatomy. Review of all TTEs performed on cases and controls was carried out using the digital image repository. Direct review of videotapes was performed for patients in the earlier years (2000–2005, n=5). Diagnosis of BAV was based on short-axis imaging of the aortic valve demonstrating the existence of only 2 commissures delimiting only 2 aortic valve leaflets. In patients identified with BAV or indeterminate number of valve cusps, AV was visualized in the parasternal-long and short-axis views, and infrequently in subcostal view, by 2 experienced echocardiographers (H.I.M. and L.T.Y.), independently. In cases of conflict, final review and decision on digitally stored images without prior knowledge of case characterization and clinical data was made by a BAV specialist (H.I.M.). Patients with indeterminate valve status or poor imaging windows were excluded from the final analysis (Figure 1).

Patient and Public Involvement
Patients and/or public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
Outcomes
Our primary end point was prevalence of BAV in the aSAH registry, compared to that of a control group without aSAH. Secondary end points included (1) neurologic outcome of patients with BAV with aSAH, (2) anatomical characteristics of IA in BAV, and (3) disposition of patients with BAV with aSAH. As exploratory analysis, we carefully examined the institutional medical examiner’s autopsy registry from September 9, 2017 through August 25, 2021 and identified patients with incidental ICAs found at autopsy, as well as deaths related to aSAH, including their autopsy-derived BAV status. Clinical information was abstracted from the medical record and autopsy report, including age, sex, cause of death, and manner of death.

Statistical Analysis
Continuous variables, expressed as mean±SD or median (interquartile range) according to data distribution, were compared using the Student’s t test or Wilcoxon rank sum test, as appropriate based on distributional assumptions. Categorical data, presented as count and percentages, were compared using the Chi-Square/Fisher’s exact test. For comparison of aortic diameters in cases and controls, unindexed and indexed (aortic diameter/body surface area and aortic diameter/height) measurements were reported. Indexed diameters are a patient-specific predictor of aortopathy.22,23 Association between outcome and potential risk factors were evaluated using univariable and multivariable logistic regression with odds ratios (OR) reported. Predictors of aSAH formation (age, sex, body mass index, BAV status, right- left cusp fusion, sinus of Valsalva [SoV], sino- tubular junction [STJ], and mid-ascending aorta [mid-Ao]) were analyzed through regression modeling in the entire cohort of cases and controls. Three models were constructed for regression modeling: model 1 was a univariate model analyzing each variable independently; model 2 was performed adjusting for age and sex; and finally, model 3 was constructed adjusting for age, sex, and body mass index. Odds ratios with a 95% CI were plotted in a Forest plot for each independent determinant on its own and when adjusted. Continuous variables were depicted in estimates of 10 units allowing for better visual representation. All statistical analyses were performed using commercially available software (JMP version 14.1.0 and SAS version 9.4, SAS Institute Inc., Cary, North Carolina) with 2-sided P value ≤0.05 statistically significant.

RESULTS
A total of 488 aSAH cases and 990 controls were included in final analysis (Figure 1). The prevalence of BAV in patients with aSAH was 1.2% (6/488) versus 3.5% (35/990) in controls, P=0.01.

Baseline Demographics
The demographics and echocardiogram characteristics of patients with and without aSAH are provided in Table 1. Patients with aSAH had higher systolic pressures (135±24 versus 126±20; P<0.001) than the controls, and ejection fraction was clinically comparable to the controls (60±12 and 59±12, P=0.02). BAV was noted in 6 patients with aSAH (1.2%) with 3-times higher prevalence (n=35, 3.5%) in the controls, P=0.01. A right-left cusp fusion pattern was noted in 67% (n=4/6) and 89% (n=31/35) of patients with aSAH and controls, respectively, P=0.05. No patients with aSAH had CoA, whereas 3(0.3%; P=0.12) controls had CoA. All 3 were confirmed to have concomitant BAV as well. Aortic valve replacement (AVR) had been previously performed in 2% of patients with aSAH versus 4% controls (P=0.15). Aortic valve regurgitant/stenotic lesions (≥ moderate) were more frequent in the control group (P≤0.002) (Table 1). Of the 35 BAVs in the control group, 12 had ≥moderate combined regurgitation/stenosis, 4 had ≥moderate regurgitation, and 3 had ≥moderate stenosis. Of the 6 BAVs in the aSAH group, only 1 had moderate regurgitation, the rest had <moderate lesions or were normally functioning. Aortic diameters were compared at the levels of SoV, STJ, and mid-Ao; absolute and indexed STJ dimensions were consistently larger in patients with aSAH (Table 1).

Neurologic Outcomes in Patients With BAV and aSAH
Neurologic outcomes were compared between BAV+aSAH (n=6) and tricuspid aortic valve (TAV)+aSAH (n=482) (Table 2). BAV+aSAH were noted to be younger than TAV+aSAH (56±11 versus 68±14; P=0.06). Among risk factors for IA formation, BAV+aSAH had a higher incidence of tobacco and alcohol use than the TAV+aSAH group (33% and 33% versus 6% and 8%; P=0.01 and 0.02, respectively) (Table 1). Aneurysmal size was clinically smaller in the BAV+aSAH group (5±2 versus 7±4 in TAV+aSAH; P=0.31) (Table 2). 67% of patients with BAV+aSAH developed IA in anterior circulation, but did not reach significance on comparison with TAV+aSAH (51%, P=0.68). Patients with BAV+aSAH did not present with fusiform or dissecting IA, blister IA or recurrent aSAH in comparison to TAV+aSAH (Table 2). Similarly, the severity of the bleed was clinically lesser in BAV+aSAH than TAV+aSAH (modified Fisher scale grade>2, 50% versus 74%, P=0.19; World Federation of Neurological Scale grade ≥3, 17% versus 36%, P=0.43). Intraventricular and intracerebral hemorrhage was clinically higher in patients with TAV than BAV.
though it did not reach statistical significance (33% and 0% versus 61% and 11%; \( P=0.21 \) and 0.71; respectively). On chart review, none of the 6 patients with BAV were known to have IA prior to index aSAH admission or present with new IA formation on brain imaging follow-up. Both groups were comparable for stress cardiomyopathy, angiographic and symptomatic vasospasm, hydrocephalus, and extra-ventricular drain placement, Table 2. The BAV+aSAH group had higher disposition rate to home (67% versus 39% in TAV+aSAH, \( P=0.21 \)) with little difference in in-hospital mortality rates (17% versus 18%; \( P=0.93 \)). At the time of discharge, a modified Rankin score of 3–6 was seen in 33% of BAV+aSAH in comparison to TAV+aSAH (49%; \( P=0.44 \)).

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### Table 1. Baseline Characteristics and Echocardiographic Data of Cases and Controls

| Variable | aSAH n=488 | Controls n=990 | \( P \) value |
|----------|------------|---------------|---------------|
| Age, y   | 68±14      | 68±14         | 0.99          |
| Sex (male) | 169 (34) | 339 (34) | 0.90          |
| BMI, kg/m² | 29±7      | 30±8          | 0.03          |
| **Echocardiographic data** | | | |
| SBP, mm Hg | 135±24 | 126±20 | <0.001 |
| DBP, mm Hg | 71±15 | 70±12 | 0.26 |
| Bicuspid aortic valve | 6 (1.2) | 35 (3.5) | 0.01 |
| Coarctation of aorta | 0 (0) | 3 (0.3) | 0.22 |
| Aortic valve replacement | 11 (2) | 36 (4) | 0.15 |
| EF, % | 60±12 | 59±12 | 0.002 |
| LVEDD, mm | 50±14 | 51±14 | 0.07 |
| LVESD, mm | 33±11 | 33±11 | 0.04 |
| LAVI, g/m² | 99±37 | 99±31 | 0.84 |
| LAVI, cc/m² | 33±12 | 39±18 | <0.001 |
| Aortic regurgitation* | 1 (0.2) | 21 (2) | 0.002 |
| Aortic stenosis* | 2 (0.4) | 65 (7) | <0.001 |
| Mitral regurgitation* | 11 (2) | 80 (8) | <0.001 |
| Tricuspid regurgitation* | 13 (3) | 104 (11) | <0.001 |
| AV velocity, m/s | 2±0.5 | 2±0.8 | 0.24 |
| LVOT diameter, cm | 2±0.2 | 2±0.2 | <0.001 |
| AV mean gradient, mm Hg | 7±6 | 12±15 | 0.004 |
| Valve area (velocity), cm² | 4±16 | 3±0.8 | 0.009 |
| Valve area (TVI), cm² | 3±0.8 | 3±0.8 | 0.009 |
| **Aortic dimensions, mm (unindexed aortic diameter)** | | | |
| Sinus of Valsalva | 33±4 (n=398) | 34±5 (n=949) | 0.09 |
| Sino-tubular junction | 29±4 (n=308) | 28±5 (n=424) | 0.003 |
| Mid-ascending aorta | 34±5 (n=299) | 35±5 (n=803) | 0.03 |
| **Aortic size indices, cm/m² (aortic diameter/body surface area)** | | | |
| Sinus of Valsalva | 1.8±0.2 | 1.8±0.3 | 0.28 |
| Sino-tubular junction | 2.0±0.1 | 1.5±0.3 | <0.001 |
| Mid-ascending aorta | 1.8±0.3 | 1.8±0.3 | 0.35 |
| **Aortic height indices, cm/m (aortic diameter/height)** | | | |
| Sinus of Valsalva | 1.6±0.2 | 2.0±0.3 | 0.25 |
| Sino-tubular junction | 1.8±0.1 | 1.7±0.3 | <0.001 |
| Mid-ascending aorta | 2.1±1.5 | 2.1±0.3 | 0.01 |

Represented as mean±SD, and number (percentage). Continuous variables, expressed as mean±SD or median (interquartile range) according to data distribution, were compared using the Student’s t test or Wilcoxon rank sum test, as appropriate based on distributional assumptions. Categorical data, presented as count and percentages, were compared using the Chi-Square/Fisher’s exact test. AV indicates aortic valve; BAV, bicuspid aortic valve; BMI, body mass index; DBP, diastolic blood pressure; EF, ejection fraction; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVIDd, left ventricular mass index; LVOT, left ventricular outflow tract; SBP, systolic blood pressure; TAV, tricuspid aortic valve; and TVI, time-velocity integral.

*Regurgitant/stenotic lesion graded ≥ moderate in severity on Doppler echocardiography.
| Variable                                      | BAV+aSAH (n=6) | TAV+aSAH (n=482) | P value |
|-----------------------------------------------|----------------|------------------|---------|
| **Neurologic risk factors**                   |                |                  |         |
| Familial history of IA                       | 0 (0)          | 14 (3)           | 0.99    |
| Autosomal-dominant polycystic kidney disease | 0 (0)          | 4 (0.8)          | 0.99    |
| Estrogen replacement therapy                 | 0 (0)          | 5 (1)            | 0.99    |
| Tobacco use, prior                           | 2 (33)         | 29 (6)           | 0.05    |
| Tobacco use, current                         | 2 (33)         | 129 (27)         | 0.66    |
| Alcohol abuse                                 | 2 (33)         | 38 (8)           | 0.08    |
| Illicit drug abuse                            | 0 (0)          | 13 (3)           | 0.99    |
| Hypertension                                 | 5 (83)         | 228 (48)         | 0.11    |
| Hyperlipidemia                                | 2 (33)         | 109 (23)         | 0.62    |
| Coronary artery disease                      | 0 (0)          | 48 (10)          | 0.99    |
| Congestive heart failure                     | 0 (0)          | 14 (3)           | 0.99    |
| Atrial fibrillation                          | 0 (0)          | 30 (6)           | 0.99    |
| Diabetes mellitus                            | 2 (33)         | 51 (11)          | 0.13    |
| Chronic kidney disease*                      | 0 (0)          | 23 (5)           | 0.99    |
| **Aneurysm characteristics**                 |                |                  |         |
| Size of IA, mm                                | 5±2            | 7±4              | 0.31    |
| Multiple IA                                  | 1 (17)         | 86 (19)          | 0.98    |
| Fusiform/dissecting IA                       | 0 (0)          | 30 (7)           | 0.99    |
| Blister IA                                   | 0 (0)          | 7 (2)            | 0.99    |
| Recurrent IA/aSAH                            | 0 (0)          | 30 (7)           | 0.99    |
| Anterior circulation                         | 4 (67)         | 228 (51)         | 0.68    |
| ICA territory circulation                    | 3 (50)         | 98 (22)          | 0.12    |
| Posterior circulation                        | 1 (17)         | 191 (42)         | 0.41    |
| **Clinical variables**                       |                |                  |         |
| Age, y                                       | 56±11          | 68±14            | 0.06    |
| Sex, male                                    | 2 (33)         | 167 (35)         | 0.99    |
| mFisher grade >2                             | 3 (50)         | 326 (74)         | 0.19    |
| WFNS grade >3                                | 1 (17)         | 158 (36)         | 0.43    |
| Cardiac arrest                               | 0 (0)          | 19 (4)           | 0.99    |
| Stress-induced cardiomyopathy                | 0 (0)          | 32 (7)           | 0.99    |
| Cerebral edema                               | 1 (17)         | 109 (24)         | 0.99    |
| Angiographic vasospasm, at admission         | 2 (33)         | 163 (37)         | 0.99    |
| Symptomatic vasospasm                        | 2 (33)         | 112 (25)         | 0.65    |
| Intraventricular hemorrhage                  | 2 (33)         | 269 (61)         | 0.21    |
| Intracerebral hemorrhage                     | 0 (0)          | 51 (11)          | 0.71    |
| Stroke, post-admission                       | 0 (0)          | 17 (4)           | 0.99    |
| Obstructive hydrocephalus                    | 4 (67)         | 252 (57)         | 0.63    |
| Medical treatment only                       | 1 (17)         | 62 (13)          | 0.74    |
| Microsurgical clipping                       | 5 (83)         | 107 (23)         |         |
| Endovascular coil embolization               | 0 (0)          | 301 (64)         |         |
| Therapeutic lumbar puncture                  | 0 (0)          | 25 (5)           | 0.99    |
| Lumbar drain placement                       | 0 (0)          | 69 (15)          | 0.60    |
| Extra-ventricular drain placement            | 4 (67)         | 235 (51)         | 0.68    |
| Ventriculoperitoneal shunt placement         | 0 (0)          | 69 (15)          | 0.59    |

(Continued)
Echocardiographic Features in Patients With BAV and aSAH

In all patients with aSAH (n=488), the most common indication for TTE was suspected stress cardiomyopathy and evaluation of cardiac function (n=286, 58%); other indications were suspected or known ischemic and non-ischemic cardiomyopathy (8%), rhythm disturbances (7%), and miscellaneous causes (suspected pulmonary embolism, angina, organ donor evaluation, etc). BAV+aSAH had lower ejection fraction than TAV+aSAH (55±18 versus 60±12, \(P=0.36\)) (Table 2). Patients with BAV+aSAH demonstrated higher AV mean gradients and smaller valve orifice areas on echocardiogram on comparison with TAV+aSAH (17±13 versus 7±6; \(P=0.16\), and 2±0.8 versus 4±16; \(P=0.17\), respectively). BAV+aSAH had smaller aortic diameters than TAV+aSAH. One of the 6 patients with BAV+aSAH (76 years old, male, status-post AVR) had established thoracic aortic disease, operated a decade prior to his aSAH admission.

Predictors of aSAH Among Patients With aSAH Plus Controls

Three models were constructed for analysis using logistic regression (Table 3) for 1478 patients (488+990). Age, male sex, body mass index, presence of BAV, right-left fusion pattern, SoV, STJ, and mid-Ao were chosen. A Forest plot was plotted for the 3 models (Figure 2). In univariate analysis, body mass index per 10 units, presence of BAV, right-left cusp fusion, STJ, and mid-Ao dimensions were independently associated with aSAH formation (OR 0.86 [CI 0.74–0.99], \(P=0.04\); OR 0.34 [CI 0.14–0.81], \(P=0.02\); OR 0.26 [CI 0.09–0.72], \(P=0.01\); OR 1.03 [CI 1.01–1.07], \(P=0.02\);
and OR 0.96 [CI 0.93–0.99], P=0.007; respectively). In model 2 when adjusted for age and sex, SoV additionally achieved significance (OR 0.85 [CI 0.73–0.98], P=0.03). On further adjusting for body mass index in model 3, all variables achieved higher statistical significance and BAV continued to have lower odds (OR 0.23 [CI 0.08–0.65]; P=0.006) for aSAH (Table 3).

### Exploratory Assessment of Institutional Medical Examiner’s Autopsy Registry

A proportion of patients with ICA with aSAH die before medical care can be given. Therefore, we carefully examined the institutional medical examiner’s autopsy registry which serves the entire county of Olmsted in Minnesota, from 2017 to 2021; ≈4 years. Of a total of 3949 autopsies, 45 (1.1%) had ICAs described in the autopsy report. Ages ranged between 11 and 93 years old. A count of 26 cases were male. Of the 45 cases, 22 had incidentally discovered, intact cerebral aneurysms noted at autopsy, 1 of which was a 57-year-old man with a BAV who’s death was certified as natural due to underlying cardiovascular disease (represents 2.2% of autopsies with ICA).

Of the 45 cases, 23 cases had fatal aSAH due to ruptured cerebral aneurysms, 1 of which was a 62-year-old man with a BAV and concomitant methamphetamine detected on postmortem toxicologic blood testing; the manner of death was deemed accidental in the setting of stimulant drug use. This patient also had a history of pervasive cigarette smoking, chronic hypertension and mixed connective tissue disease, all factors associated with ICAs. Therefore, it is difficult to clinically categorize this patient as a typical BAV patient with low comorbidity index coming with aSAH due to a primary ICA.

### DISCUSSION

Within a systematic, prospectively maintained consecutive registry of accurately-diagnosed patients with aSAH with available echocardiogram, we assessed for the prevalence and neurological outcomes of patients with BAV with aSAH and compared them to a control group without aSAH. Our principal findings were: (1) BAV prevalence was 3 times lower in patients with aSAH in comparison to controls without aSAH; (2) Compared with TAV+aSAH, BAV+aSAH were younger and exhibited clinically important features; smaller aneurysms of lower severity and less neurologic disability; (3) Presence of BAV status was not predictive of aSAH in the entire cohort. Instead, BAV was associated with lower odds of aSAH across all models; (4) STJ was the only ascending thoracic aorta segment measurement that independently predicted aSAH. Additional evidence in support of our findings on BAV prevalence is the presence of less prior AVR and less significant aortic valve disease (≥moderate grade) in patients with aSAH as compared with controls. This argues that, if BAV was significantly more prevalent in the patients with aSAH due to systemic arteriopathy, more prior AVR and more aortic valve disease would have been observed in the aSAH group. On review of Olmsted county medical examiner’s autopsy registry, 2.2% (1 BAV patient) had an incidentally found ICA at autopsy, and 1 BAV patient with multiple ICA risk factors including ongoing use of methamphetamine, died due to aSAH, a death ruled accidental. This could suggest a higher prevalence of asymptomatic ICAs in patients with BAV but does not suggest a higher prevalence of aSAH in these patients, given the extenuating circumstances and comorbidities of the patient.

### BAV in Patients With IA and aSAH

Unruptured IAs are relatively common (3.2%) in the general population but, only <1% will rupture and cause aSAH. Additionally, small aneurysms (<7 mm in diameter) in the anterior circulation are the most common and have a very low risk of causing aSAH. BAV has been associated with IA with a higher prevalence than

### Table 3. Predictors for Aneurysmal Sub-Arachnoid Hemorrhage Formation in the Entire Cohort

| Variable | Model 1 OR (95% CI) | P value | Model 2 OR (95% CI) | P value | Model 3 OR (95% CI) | P value |
|----------|---------------------|---------|---------------------|---------|---------------------|---------|
| Age per 10 y | 1.00 (0.93–1.08) | 0.99     |                     |         |                     |         |
| Sex, male | 1.02 (0.81–1.28)  | 0.88     |                     |         |                     |         |
| BMI per 10 units | 0.86 (0.74–0.99) | 0.04     | 0.86 (0.74–0.99) | 0.04    |                     |         |
| Presence of BAV | 0.34 (0.14–0.81) | 0.02     | 0.33 (0.13–0.80) | 0.01    | 0.23 (0.08–0.65) | 0.006   |
| Right-left cusp fusion | 0.26 (0.09–0.72) | 0.01     | 0.25 (0.08–0.72) | 0.01    | 0.19 (0.06–0.63) | 0.007   |
| Sinus of Valsalva per 5 units | 0.89 (0.78–1.02) | 0.09     | 0.85 (0.73–0.98) | 0.03    | 0.86 (0.74–1.01) | 0.07    |
| Sino-tubular junction per 5 units | 1.21 (1.03–1.43) | 0.02     | 1.33 (1.11–1.60) | 0.002   | 1.38 (1.14–1.66) | <0.001  |
| Mid-ascending aorta per 5 units | 0.82 (0.72–0.95) | 0.007    | 0.77 (0.66–0.90) | <0.001  | 0.78 (0.67–0.92) | 0.002   |

Model 1: Univariate analysis. Model 2: Multivariate analysis adjusted for age and sex. Model 3: Multivariate analysis adjusted for age, sex, and BMI. BAV indicates bicuspid aortic valve; BMI, body mass index; and OR, odds ratio.
the general population, however, these studies lacked an appropriate control of patients without BAV.\textsuperscript{1,3} None of the 6 patients with BAV (1.2\%) with aSAH in our study had known IAs and no new IAs were observed on further imaging follow-up. One would assume that the hypothesis of systemic arteriopathy in BAV would likely present with increased de-novo aneurysm formation and/or high-risk aneurysmal features, similar to CoA.\textsuperscript{1,24} In the studies by Schievink et al\textsuperscript{1} and Shaulov et al\textsuperscript{1},\textsuperscript{2} no de-novo IA formation was detected during follow-up in patients with BAV with IA/aSAH. In the study by Egbe et al\textsuperscript{3}, 52/678 patients with BAV (7.7\%) were noted to have IAs, with 20/52 patients (38.5\%) having concomitant CoA. Of these 52 patients, IA enlargement occurred in 3 patients (5.8\%) and new aneurysm was detected in 1 patient (1.9\%), with a median follow-up duration of 9±4 years; however, it is unclear if these 4 patients with BAV had CoA or not. Importantly, in the 626 patients with BAV that did not have IA at baseline,\textsuperscript{3} no de-novo aneurysms were detected (median follow-up duration 7±2 years).

In our study, looking at all aSAH admissions with an echocardiogram over the past 2 decades, BAV was confirmed in 1.2\% of patients with aSAH, a frequency 3-times lower than controls without aSAH (Figure 2 and Table 3). This 1.2\% (n=6/488) was comparable to the previously described 1.8\% (n=1/56)\textsuperscript{2} and 0.6\% (n=2/371)\textsuperscript{25} of patients with aSAH who also had BAV, likely representative of the 0.5\%–2\% incidence in the general population.\textsuperscript{26} The presence of less prior AVR and less aortic valve disease (≥moderate grade) in patients with aSAH as compared with controls further supports the notion that BAV is not more prevalent among patients with aSAH. Finally, in the 5 studies that describe BAV and IA/aSAH,\textsuperscript{1–3,14,25} 3 independent studies\textsuperscript{2,14,25} suggest no increased prevalence of BAV in IA/aSAH, and IAs in patients with BAV did not behave differently from those in the general population. Indeed, compared with a control group of patients with TAV, our patients with BAV did not exhibit a higher clinical severity of aSAH, Table 2. This is consistent with findings from our prior study using a nationally representative population to describe the outcomes.\textsuperscript{14} We note no differences in size of ruptured IA or in-hospital mortality of BAV+aSAH in comparison to TAV+aSAH. Clinically, BAV+aSAH had lower rates of moderate-severe neurologic disability measured using modified Rankin score, Table 2. This further supports the idea that indeed BAV is not dissimilar to the general population (ie, TAV) with respect to IAs and aSAH, as described in earlier studies.\textsuperscript{2,14,25}
BAV Status and Aortic Dimensions in Relation to aSAH

In a recent meta-analysis and systemic review including 13 studies, prevalence of IA was explored among patients with aortopathy in 10 studies, with BAV in 2 studies,\(^1,3\) and CoA in 1 study.\(^27\) Pooled analysis revealed IA prevalence of 12% in all patients, with sub-group analysis revealing 8% in BAV and 10% in patients with CoA.\(^27\) However, this meta-analysis included patients with aortopathy only, and hence did not account for the heterogeneity of the BAV condition. BAV-aortopathy independent of CoA status has been described in 2 prior studies,\(^1,25\) but lacked a comparative group to draw meaningful conclusions. Among the 6 BAV+aSAH in our study, only 1 (16.7%) had thoracic aortic disease in the setting of other risk-factors for aSAH without CoA (advanced age >75 years at time of incident, hypertensive, and ex-smoker). In our study assessing for differences in aortic sizes between patients with aSAH and controls, no differences were found in the unindexed and indexed measurements at the levels of SoV and mid-Ao (Table 1). It was interesting to note that STJ (unindexed and indexed) was larger in patients with aSAH when compared with controls (Table 1). In univariate analysis, larger STJ dimensions were associated with higher odds of aSAH which continued to remain predictive on multivariate modeling (Table 3 and Figure 2). With the available literature and relatively small numbers, it is impossible to draw any significant conclusion regarding the relationship (if any) of thoracic aortic disease and IA/aSAH.

Limitations

Although our patients with aSAH were identified from a systematic prospective registry spanning 2 decades (2000–2019) and our study is one of the largest describing patients with aSAH with echocardiograms available for review, there are important limitations: (1) The identification and assessment for prevalence of BAV was performed retrospectively, which may have led to bias. However, all echocardiograms were reviewed de-novo and difficult aortic valve anatomy status was evaluated by 2 experienced echocardiographers; (2) Our BAV prevalence assessment was not population-based but rather derived from a single tertiary-referral center. Nonetheless, the compilation of a large accurate database of an infrequent condition, such as ruptured IA and aSAH, necessitates a tertiary-referral center; (3) 45% of patients within the prospective aSAH registry did not have echocardiograms available, and although we reported the indications for echocardiography, this could be a source of selection bias, such that our reported BAV-SAH prevalence may not represent the prevalence observed if all patients with SAH had undergone echocardiograms and should not be interpreted as the “real” BAV prevalence in patients with SAH, which remains unknown; (4) The comparison of 6 BAV+aSAH to 482 TAV-aSAH was statistically limited. Even so, we found striking clinical differences in age, size of aneurysm, severity of bleed, and neurologic outcomes between both groups. These clinical differences remain hypothetical and must be confirmed in a large, prospective BAV+aSAH cohort with long-term follow-up, preferably population-based. Finally, our study comprised adult patients who were predominantly White, which limits generalizability of findings.

CONCLUSIONS

This study assessed for the first time the prevalence of echocardiographically confirmed BAV in patients with aSAH, within a prospectively maintained consecutive registry, versus controls without aSAH. We observed 3 times lower prevalence of BAV in patients with aSAH than among controls without aSAH. Clinically, patients with BAV were younger with smaller aneurysms, less severity of bleed, and with lower severity of neurologic disability at discharge. Patients with BAV had comparable in-hospital mortality rates to TAV. Our study adds evidence to the developing notion of recommending against routine surveillance for IA in patients with BAV without CoA. Although patients with BAV may have a higher incidence of intracranial aneurysms, the most important patient-outcome (ie, aSAH) does not seem to exhibit an association with BAV.

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