Diagnostic Accuracy of Echocardiography and Intraoperative Surgical Inspection of the Unicuspid Aortic Valve

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Unicuspid aortic valve (UAV) is a rare malformation that is often difficult to distinguish from a bicuspid aortic valve (BAV) with commissural fusion by echocardiography or intraoperative surgical inspection. This study assessed the accuracy of intraoperative surgical inspection and two-dimensional echocardiography in diagnosing UAV compared to a gold standard of pathological diagnosis. The Mayo Clinic echocardiographic database, tissue registry database and electronic medical record were searched for all patients assigned a diagnosis of UAV by any technique. Transthoracic (TTE), transesophageal (TEE) echocardiographic, and surgical diagnoses were compared to pathological diagnosis as the standard. A clinical diagnosis of UAV was applied to 380 patients by 1 or more method and in 196 (52%) a pathologic evaluation was available to compare to the clinical description given by TTE, TEE, or surgical inspection. Of these 196 patients, only 58 (30%) had a pathological diagnosis of UAV; the majority were found to be BAVs by pathologic evaluation (n = 132, 67%). For diagnosing UAV, the sensitivity and specificity were 15% and 87% for TTE, 28%, and 82% for TEE, and 52% and 51% for surgical inspection, respectively. Valves with bicuspid morphology and extensive commissural fusion were frequently misclassified as UAV by all methods. In conclusion, intraoperative surgical inspection and echocardiography have limitations for diagnosing UAV due to difficulties in accurately assigning a correct morphological diagnosis, which suggests that the current understanding of the natural history of UAV may be inaccurate. **(Am J Cardiol 2019;123:967−971)**

Unicuspid or unicommissural aortic valve (UAV) is a rare form of aortic valvular stenosis with an estimated incidence of 0.02%.[1,2] Given the rare nature of the malformation, much is unknown regarding the optimal diagnostic method. In fact, diagnosis of UAV is often extremely challenging without careful pathological inspection due to the difficulty in distinguishing a true congenital UAV from a bicuspid aortic valve (BAV) with acquired extensive commissural fusion.[3−5] No study has ever been performed to determine the concordance of intraoperative surgical inspection or echocardiography in diagnosis of UAV based on the accepted pathological criteria that define a UAV. Despite this, nearly all studies evaluating the natural history, echocardiographic features, treatment, and prognosis of UAV have utilized intraoperative surgical inspection as their gold standard UAV definition.[2,6−8] The aim of this study was to determine the concordance of intraoperative surgical inspection, transesophageal (TEE), and transthoracic (TTE) echocardiography in diagnosing UAV when compared to pathologically confirmed UAV.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. The echocardiography and tissue registry databases at Mayo Clinic were queried for all patients seen in June 29, 1978 to July 6, 2016 with a diagnosis of UAV given by any of the following methods; gross pathologic examination, intraoperative surgical inspection, TTE or, TEE. A free-text search of the entire Mayo Clinic electronic medical record for UAV was also performed. Echocardiographic images were attained in June 1996 to July 2016. If UAV was diagnosed by 1 modality, all other diagnostic modalities were evaluated and included regardless of whether UAV was present. All patients with indeterminate diagnostic studies or patients without at least 1 TTE, TEE, or, intraoperative surgical inspection diagnosis that could be compared to a pathological diagnosis were excluded. TTE, TEE, and intraoperative surgical diagnosis were compared to pathological diagnosis as the gold standard.

From echocardiographic short-axis images (interpreted by an experienced staff cardiologist at the time of the

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Funding: Department of Cardiovascular Medicine, Mayo Clinic.

See page 970 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2018.12.010

www.ajconline.org

study), a UAV was diagnosed if it had an eccentric valvular orifice, a single commissure, or the absence of a commissural attachment to the lateral aortic wall (Figure 1).[1,3] As no uniform surgical UAV diagnostic criteria exist, surgical UAV diagnosis was based on the opinion of the individual surgeon during the procedure.

Pathology diagnosis (rendered by a cardiovascular pathologist) of UAV at time of aortic valve replacement was defined as the presence of congenital (not acquired) fusion of at least 2 commissures if 2 of the following criteria were met: (1) an obtuse angle between the fused cusps at the commissure; (2) absent cleavage plane between cusps at the point of fusion; and (3) presence of a raphe at the fused commissures (Figures 1 and 2).[9−12]

Data are summarized using diagnostic statistics with their corresponding 95% confidence limits calculated based on the binomial distribution. Analyses were done using SAS Version 9.4 (Cary, NC).

Results

Diagnosis of UAV was given on at least one occasion in 380 patients by 1 or more diagnostic methods; including TTE, TEE, intraoperative surgical inspection, and pathological inspection. Of those 380, 196 (52%) patients had a pathological diagnosis that could be compared to 1 or more of these clinical diagnostic modalities. In these 196 patients, only 58 (30%) had a pathological diagnosis of UAV. By pathology, BAV was present in 132 (67%), TAV in 5 (3%), and QAV in 1 (0.005%).

Echocardiographic and surgical inspection diagnostic statistics (as compared to pathological examination as the gold standard) are summarized in Tables 1 and 2. Surgical inspection most frequently correctly assigned a UAV diagnosis to pathologically confirmed UAVs (52%) compared to TTE (15%) and TEE (28%). Similarly, surgical inspection most frequently incorrectly assigned a UAV diagnosis to pathologically confirmed non-UAVs (i.e., bi-, tri-, or quadricuspid

Figure 2. Gross photograph of a surgically resected UAV (aortic surface) demonstrating distinguishing features of a true congenital UAV. A single definitive raphe is evident (white arrow) among the nodular calcification and fibrotic thickening of the valve.
UAV = unicuspid aortic valve.

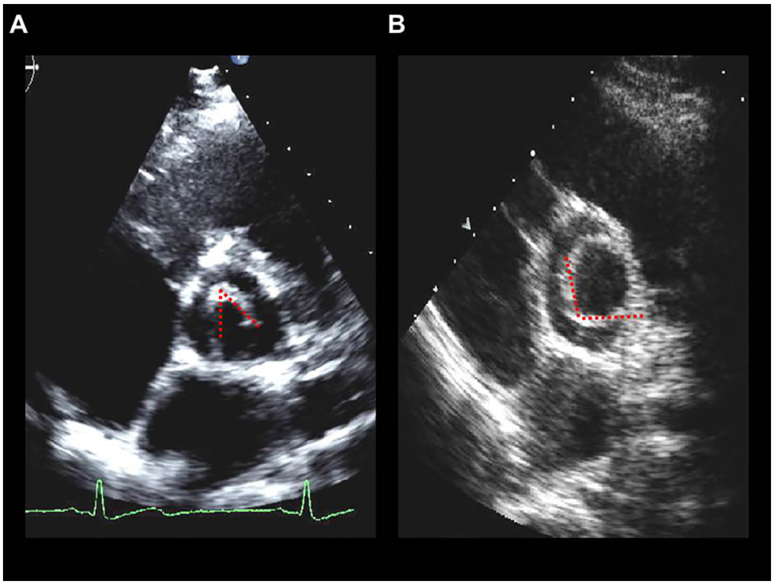

Figure 1. TTE parasternal short-axis views demonstrate the differences between a BAV with acquired commissural fusion (A) and a true congenital UAV (B). BAV with acquired commissural fusion tend to have an ovoid effective orifice and form an acute angle at the point of commissural fusion when open during systolic ejection *(A, dotted line)*. True congenital UAVs will typically have an eccentric and somewhat rounded valvular orifice with a single commissural zone of attachment to the aortic wall. These combine to form a broad, obtuse angle at the site of congenital commissural fusion *(B, dotted line)*.
BAV = bicuspid aortic valve; TTE = transthoracic echocardiography; UAV = unicuspid aortic valve.

Table 1.
Results of each method compared to pathology for detecting unicuspid aortic valve*

	Surgery (n = 172)	Age, mean (years)	Transesophageal echo (n = 129)	Age, mean (years)	Transthoracic echo (n = 81)	Age, mean (years)
True Positive	25	39	10	38	4	33
True Negative	63	40	76	40	47	43
False Positive	61	44	17	42	7	37
False Negative	23	37	26	39	23	34
	Surgery (n = 172)	95% confidence interval	Transesophageal echo (n = 129)	95% confidence interval	Transthoracic echo (n = 81)	95% confidence interval
Sensitivity	52%	37%−66%	28%	15%−45%	15%	4%−34%
Specificity	51%	42%−60%	82%	72%−89%	87%	75%−95%
Positive Predictive Value	29%	20%−40%	37%	20%−58%	36%	11%−69%
Negative Predictive Value	73%	62%−82%	75%	65%−82%	67%	55%−78%

* All descriptive statistics compared with gross pathological diagnosis

valves; 49%) compared to TTE (13%) and TEE (18%). Across all modalities, 99% of incorrectly assigned UAV diagnoses were pathologically confirmed BAVs with acquired commissural fusion, and 1 (1%) was a pathologically confirmed TAV.

Similarly, 23/23 (100%), 25/26 (96%), and 22/23 (96%) patients were incorrectly assigned a BAV diagnoses by TTE, TEE, and intraoperative surgical, respectively, but in fact had a pathologically confirmed UAV. Additionally, 1/26 (4%) and 1/23 (4%) of TEE and surgical cases, respectively, incorrectly assigned a TAV diagnosis to pathologically confirmed UAVs. Ages for all correctly and incorrectly assigned UAV and non-UAV diagnoses across all modalities are summarized in Tables 1 and 2.

Discussion

UAV is a rare malformation that presents diagnostic difficulties. The poor diagnostic accuracy of echocardiography and intraoperative surgical diagnosis demonstrated in our study highlights the challenges involved in distinguishing true congenital UAVs from BAVs with acquired commissural fusion. Moreover, our study suggests that much of the literature regarding the natural history, complications, treatments, and prognosis of UAV is likely flawed owing to the inherent limitations of previous studie's definition of UAV.

We found that both TTE and TEE had poor sensitivity (15% and 28%, respectively), but better specificity (87% and 82%, respectively) for recognizing the presence of UAV. Our results differ from a previous smaller study by Chu et al[13] which reported poor diagnostic accuracy for TTE in diagnosing UAV (27% and 50% sensitivity and specificity, respectively) and a better diagnostic accuracy for TEE (75% and 86% sensitivity and specificity, respectively). Similarly, Noly et al[6] reported a 14% accuracy rate for preoperative aortic valve determination with TTE and 69% with TEE. Our results may differ from previous literature because we included both older echocardiographic images and older patients with inferior acoustic windows. However, the limitations of surgical identification of UAV seen in our study likely apply to previous studies (most of which defined UAV surgically) and as a result, may account for some of the differences seen in our results when compared to previous literature.[2,6−8]

Our study also showed surgical inspection more frequently correctly identified a UAV (higher sensitivity), but also had a higher rate of incorrect UAV diagnoses (lower specificity) relative to echocardiography. The fewer incorrect UAV diagnoses by echocardiography may be because echocardiography allows identification of UAV features "in motion" (i.e., the angle of commissural fusion in systole and whether the commissure opens past the midpoint of coaptation [Figure 1]). In addition, echocardiographic

Table 2.
Diagnostic accuracy of surgery, transthoracic echocardiography, and transesophageal echocardiography for unicuspid aortic valve

Pathologically diagnosed unicuspid aortic valve	Total (n = 58)	Pathologically diagnosed nonunicupsid aortic valve*	Total (n = 138)
Surgical inspection		Surgical inspection	
Correct unicuspid aortic valve diagnosis†	25/48 (52%)	Incorrect unicuspid aortic valve diagnosis†	61/124 (49%)
Age, mean (years)	39	Age, mean (years)	44
Transthoracic echo		Transthoracic echo	
Correct unicuspid aortic valve diagnosis‡	4/27 (15%)	Incorrect unicuspid aortic valve diagnosis‡	7/54 (13%)
Age, mean (years)	33	Age, mean (years)	37
Transesophageal echo		Transesophageal echo	
Correct unicuspid aortic valve diagnosis§	10/36 (28%)	Incorrect unicuspid aortic valve diagnosis§	17/93 (18%)
Age, mean (years)	38	Age, mean (years)	42

* Nonunicuspid aortic valve refers to 132 bicuspid aortic valves, 5 tricuspid aortic valves, and 1 quadricuspid aortic valve pathological diagnoses
† Surgical diagnosis available for 48/58 pathologically diagnosed s and 124/138 nonunicuspid aortic valves
‡ Transthoracic echocardiography diagnosis was available for 27/58 pathologically diagnosed unicuspid aortic valves and 54/138 non-UAVs
§ Transesophageal echocardiography diagnosis was available for 36/58 pathologically diagnosed unicuspid aortic valves and 93/138 nonunicuspid aortic valves

analysis does not face the time constraints inherent to surgical replacement of a valve.

The lack of diagnostic accuracy demonstrated in this study is most likely due to the difficulty in distinguishing a true congenital UAV from an acquired, calcified commissural fusion of a BAV (i.e., a "functional" UAV) both surgically and echocardiographically.[1,3−5,9−10] Indeed, patients with incorrectly assigned UAV diagnoses by surgery, TTE and TEE in our study were older than those patients with correctly assigned UAV diagnoses (Tables 1 and 2). The older age in our patients with incorrect UAV diagnoses likely allowed for acquired, calcified fusion of their true congenital BAVs making them more difficult to distinguish from true congenital UAVs. Given this diagnostic difficulty, it also seems likely that accidental inclusion of BAVs, misclassified as UAVs, in prior studies has contributed at least some inaccuracy to our understanding of UAV. Others have similarly shown that UAVs are often mistaken as BAVs intraoperatively.[14−15]

Previously, the only feasible management of UAV was aortic valve replacement. However, UAV-specific transcatheter and surgical repair methods that are distinct from those used in BAVs are now established and require preoperative echocardiographic UAV diagnosis and anatomic evaluation.[16−18,19−21] UAV also tends to present earlier and with more frequent aortopathy than BAV.[2,7,22] Thus, earlier and more accurate echocardiographic UAV diagnosis may improve survival and decrease need for future aortic valve and ascending aorta replacement by allowing further development and earlier implementation of these repair techniques.

Future studies should be aimed at developing accurate echocardiographic and surgical diagnostic criteria for UAV with a pathological gold standard diagnosis given the important role of echocardiography and surgery in management. Previously tested echocardiographic UAV features have included a single commissural zone of attachment, a rounded leaflet-free edge on opposite side of the commissural attachment zone, and eccentric valvular orifice during systole.[8] Although these echocardiographic features correlated with surgically diagnosed UAV[8] (which we have shown may itself be an inaccurate diagnostic method), a reasonable approach may be to evaluate if these features identified by echocardiography or surgery correlate with pathologically diagnosed UAV. Other reasonable echocardiographic and surgical features for future investigations include an obtuse angle between fused commissures, presence of cleavage plane on the ventricular aspect of the fusion, presence of a raphe, and calcification pattern.

Our study was limited by a small study population owing to the relative rarity of UAV. Additionally, because of the requirement for pathologic diagnosis, our study only included patients with relatively isolated valvular disease which was severe enough to be referred for surgical valve replacement. This unavoidably led to a selection bias which may make these results less generalizable. Last, our study included older echocardiographic images (starting from 1996), which may have reduced the diagnostic accuracy of echocardiography for UAV.

In conclusion, the limited surgical and echocardiographic diagnostic accuracy demonstrated in this study suggests that the current understanding of the natural history of UAV may be inaccurate due to difficulties in distinguishing UAV from BAV. Accordingly, future studies should be aimed at assessing the natural history of pathologically diagnosed UAVs to improve our understanding of the disease.

Disclosures

The authors have no relevant disclosures or conflict of interest.

1. Novaro GM, Mishra M, Griffin BP. Incidence and echocardiographic features of congenital unicuspid aortic valve in an adult population. *J Heart Valve Dis* 2003;12:674–678.
2. Mookadam F, Thota VR, Garcia-Lopez AM, Emani UR, Alharthi MS, Zamorano J, Khandheria BK. Unicuspid aortic valve in adults: a systematic review. *J Heart Valve Dis* 2010;19:79–85.
3. Anderson RH. Understanding the structure of the unicuspid and unicommissural aortic valve. *J Heart Valve Dis* 2003;12:670–673.
4. Falcone MW, Roberts WC, Morrow AG, Perloff JK. Congenital aortic stenosis resulting from a unicommissural valve. Clinical and anatomic features in twenty-one adult patients. *Circulation* 1971;44:272–280.
5. Stephan PJ, Henry AC, Hebeler RF, Whiddon L, Roberts WC. Comparison of age, gender, number of aortic valve cusps, concomitant coronary artery bypass grafting, and magnitude of left ventricular-systemic arterial peak systolic gradient in adults having aortic valve replacement for isolated aortic valve stenosis. *Am J Cardiol* 1997;79:166–172.
6. Noly PE, Basmadjian L, Bouhout I, Viet Le VH, Poirier N, El-Hamamsy I. New insights into unicuspid aortic valve disease in adults: not just a subtype of bicuspid aortic valves. *Can J Cardiol* 2016;32:110–116.
7. Zhu Y, Roselli EE, Idrees JJ, Wojnarski CM, Griffin B, Kalahasti V, Pettersson G, Svensson LG. Outcomes after operations for unicuspid aortic valve with or without ascending repair in adults. *Ann Thorac Surg* 2016;101:613–619.
8. Ewen S, Karliova I, Weber P, Schirmer SH, Abdul-Khaliq H, Schöpe J, Mahfoud F, Schäfers HJ. Echocardiographic criteria to detect unicuspid aortic valve morphology. *Eur Heart J Cardiovasc Imaging* 2018;0:1–5.
9. Edwards JE. Pathologic aspects of cardiac valvular insufficiencies. *Arch Surg* 1958;77:634–649.
10. Mckay R, Smith A, Leung MP, Arnold R, Anderson RH. Morphology of the ventriculoaortic junction in critical aortic stenosis. *J Thorac Cardiovasc Surg* 1992;104:434–442.
11. Fealey ME, Edwards WD, Miller DV, Maleszewski JJ. Unicommissural aortic valves: gross, histological, and immunohistochemical analysis of 52 cases (1978−2008). *Cardiovasc Pathol* 2012;21:324–333.
12. Davies MJ, Treasure T, Parker DJ. Demographic characteristics of patients undergoing aortic valve replacement for stenosis: relation to valve morphology. *Heart* 1996;75:174–178.
13. Chu JW, Picard MH, Agnihotri AK, Fitzsimons MG. Diagnosis of congenital unicuspid aortic valve in adult population: the value and limitation of transesophageal echocardiography. *Echocardiography* 2010;27:1107–1112.
14. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. *Am J Cardiol* 1970;26:72–83.
15. Roberts WC, Vowels TJ, Ko JM. Comparison of interpretations of valve structure between cardiac surgeon and cardiac pathologist among adults having isolated aortic valve replacement for aortic valve stenosis (± aortic regurgitation). *Am J Cardiol* 2009;103:1139–1145.
16. Kolesar A, Toporcer T, Bajmoczi M, Luczy J, Candik P, Sabol F. Aortic valve repair of a stenotic unicuspid aortic valve in young patients. *Ann Thorac Surg* 2018;105:1351–1356.
17. Aicher D, Bewarder M, Kindermann M, Abdul-Khalique H, Schäfers HJ. Aortic valve function after bicuspidization of the unicuspid aortic valve. *Ann Thorac Surg* 2013;95:1545–1550.
18. Schäfers HJ, Aicher D, Riodionycheva S, Lindinger A, Radle-Hurst T, Langer F, Abdul-Khaliq H. Bicuspidization of the unicuspid

aortic valve: a new reconstructive approach. *Ann Thorac Surg* 2008;85:2012–2018.

19. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Scientific Document Group ESC. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.
20. Schäfers HJ, Aicher D, Langer F, Lausberg HF. Preservation of the bicuspid aortic valve. *Ann Thorac Surg* 2007;83:S740–S745.
21. Hakeem A, Cilingiroglu M. Outcomes of TAVR in bicuspid aortic valve stenosis. *J Am Coll Cardiol* 2017;70:1684–1685.
22. Mookadam F, Thota VR, Lopez AM, Emani UR, Tajik AJ. Unicuspid aortic valve in children: a systematic review spanning four decades. *J Heart Valve Dis* 2010;19:678–683.