Echocardiographic versus Histologic Findings in Marfan Syndrome

Xiaoyan Gu, MD
Yihua He, MD
Zhian Li, MD
Jiancheng Han, MD
Jian Chen, MD
J.V. (Ian) Nixon, MD, FACC

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From: Department of Ultrasound, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, People's Republic of China

Dr. Nixon is now at the Pauley Heart Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia.

Address for reprints: Yihua He, MD, Department of Ultrasound, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, PRC

E-mail: heyihuaecho@hotmail.com

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This retrospective study attempted to establish the prevalence of multiple-valve involvement in Marfan syndrome and to compare echocardiographic with histopathologic findings in Marfan patients undergoing valvular or aortic surgery.

We reviewed echocardiograms of 73 Marfan patients who underwent cardiovascular surgery from January 2004 through October 2009. Tissue histology was available for comparison in 29 patients.

Among the 73 patients, 66 underwent aortic valve replacement or the Bentall procedure. Histologic findings were available in 29 patients, all of whom had myxomatous degeneration. Of 63 patients with moderate or severe aortic regurgitation as determined by echocardiography, 4 had thickened aortic valves. The echocardiographic findings in 18 patients with mitral involvement included mitral prolapse in 15. Of 11 patients with moderate or severe mitral regurgitation as determined by echocardiography, 4 underwent mitral valve repair and 7 mitral valve replacement. Histologic findings among mitral valve replacement patients showed thickened valve tissue and myxomatous degeneration. Tricuspid involvement was seen echocardiographically in 8 patients, all of whom had tricuspid prolapse. Two patients had severe tricuspid regurgitation, and both underwent repair. Both mitral and tricuspid involvement were seen echocardiographically in 7 patients.

Among the 73 patients undergoing cardiac surgery for Marfan syndrome, 66 had moderate or severe aortic regurgitation, although their valves manifested few histologic changes. Eighteen patients had mitral involvement (moderate or severe mitral regurgitation, prolapse, or both), and 8 had tricuspid involvement. Mitral valves were most frequently found to have histologic changes, but the tricuspid valve was invariably involved. (***Tex Heart Inst J* 2015;42(1):30-4**)

The principal cardiovascular manifestations of Marfan syndrome are well known: mitral valve prolapse and dilation of the proximal ascending aorta involving the sinuses of Valsalva.¹⁻⁴ Also well established are the natural history of the syndrome and the morbidity and mortality rates of patients who exhibit these manifestations.⁵⁻¹¹ However, the involvement of other cardiac valves in Marfan patients continues to be of interest.^{3,8-11}

The purpose of this study was to retrospectively evaluate the echocardiograms of patients undergoing cardiac surgery for Marfan syndrome to determine the prevalence of overall valvular involvement and, when histopathologic tissue was available, to compare the histologic findings with the echocardiographic characteristics.

Patients and Methods

From January 2004 through October 2009, 73 patients with Marfan syndrome underwent a cardiovascular surgical procedure at Beijing Anzhen Hospital. For the purposes of our study, patients under 13 years of age already had been excluded. The study protocol was approved by the review board of the hospital. All 73 patients had criteria of Marfan syndrome as established by consensus at the 1986 Berlin conference and by subsequent revision,¹² and all 73 underwent one or more of the following cardiovascular surgical procedures: the Bentall procedure (replacement of the aortic valve, aortic root, and ascending aorta, with reimplantation of the coronary arteries), the David procedure (replacement of the aortic root and sinuses of Valsalva, with preservation of the aortic valve and reimplantation of the coronary arteries), the Wheat procedure (replacement of the aortic valve and entire ascending aorta, with reimplantation of the coronary arteries), aortic valve replacement, ascending aortic replacement, mitral valve

replacement or repair, or tricuspid valve repair. The minimum criteria for application of these procedures were aortic dissection, an aortic root diameter of ≥ 5 cm, symptomatic aneurysms, and moderate-to-severe or severe aortic regurgitation.¹³ The mitral valve was replaced or repaired in patients who had moderate-to-severe or severe regurgitation. The indication for tricuspid repair was the same as the indication for mitral repair. Whenever possible, the valvular and aortic tissue specimens were preserved and underwent histologic examination.

Echocardiograms were obtained on all the patients preoperatively with use of the Vivid 7[®] cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway), the iE33 xMATRIX Echocardiography System (Koninklijke Philips N.V.; Best, The Netherlands), or the ACUSON Sequoia[™] C512 ultrasound system (Siemens Medical Solutions USA, Inc.; Mountain View, Calif). The severity of aortic regurgitation was graded by using 2 quantitative values, the vena contracta width of the regurgitant jet and the flow convergence method of estimating the maximal effective regurgitant orifice area, in accordance with the recommendations of the American Society of Echocardiography¹⁴ and the European Association of Echocardiography.¹⁵ The severity of mitral and tricuspid regurgitation was graded by using quantitative values similar to those for aortic regurgitation and also in accordance with the recommendations of the American Society of Echocardiography¹⁴ and the European Association of Echocardiography.¹⁶ The gross morphologic features (and consequently the surgically observed findings) of myxomatous degeneration of the cardiac valves are thickened and voluminous leaflets (increased in tissue volume), and thickened, elongated, and sometimes ruptured chordae tendineae of the atrioventricular valves.^{17,18} The echocardiographic features of myxomatous degeneration of the cardiac valves include thickening of the valve leaflets, prolapse of the mitral, tricuspid, and aortic valve leaflets, or billowing during systole of the mitral or tricuspid leaflets, or billowing during diastole of the aortic leaflets.¹⁹ Mitral or tricuspid prolapse was defined as the displacement—by more than 2 mm above the high points of the mitral or tricuspid annulus—of the abnormal echocardiographic billowing of one or more mitral or tricuspid leaflets, as recorded in either the parasternal or apical long-axis views.^{19–21} This might or might not be accompanied by coaptation of the leaflets at the level of, or on the atrial side of, the mitral or tricuspid annulus during mid-to-late systole or throughout systole.

We retrospectively reviewed the echocardiograms in order to identify the abnormal echocardiographic features of the mitral, aortic, and tricuspid valves of all 73 study patients to determine the prevalence of valvular lesions and, where possible, to compare these patients' echocardiographic and available histologic findings. All

echocardiograms were reviewed by 2 experienced readers who were blinded to the individual patient's diagnosis. Unfortunately, tissue specimens were available for histologic analysis in only 29 patients who had undergone cardiovascular surgical procedures.

Results

Seventy-three patients who had met our age and Marfan syndrome criteria and had undergone cardiovascular surgery for Marfan syndrome were retrospectively analyzed. There were 52 male and 21 female patients ranging in age from 14 to 64 years (mean age, 32 ± 12 yr). All patients underwent one of the following surgical procedures: the Bentall procedure (65 patients), the David procedure (2), the Wheat procedure (3), ascending aortic replacement (2), aortic valve replacement alone (1), mitral valve repair or replacement (11), or tricuspid valve repair (2). Aortic valve replacement or the Bentall procedure was carried out in 66 patients. Of these 66 patients, 9 had moderate-to-severe aortic regurgitation and 54 had severe aortic regurgitation on preoperative echocardiograms (Table I). Aortic valve specimens were available postoperatively in 29 patients (1 patient with aortic valve replacement and 28 with the Bentall procedure) for histologic examination; all of those specimens showed myxomatous degeneration. Whereas all 29 patients with available histologic findings had moderate-to-severe or severe aortic regurgitation as reported by means of echocardiography, only 4 of those patients had been reported preoperatively—by means of echocardiography—to have abnormal aortic morphology (Table II). Two of the 4 patients had been reported to have thickened, floppy aortic valves, and 2 patients had been reported to have aortic prolapse.

Preoperative echocardiograms were available in all 73 patients. Mitral valve involvement was reported by means of echocardiography in 18 patients (Table I). The echocardiograms also revealed valvular thickening, floppy and redundant valves, chordal elongation, excess valvular motion, valvular bulging, and valvular prolapse (Figs. 1 and 2). Mitral valve prolapse was reported in 15 of the 73 patients (21%), including 13 patients with bileaflet mitral prolapse. Of the 18 patients with mitral involvement, 11 had moderate-to-severe mitral regurgitation on preoperative echocardiograms. Six of the 11 patients with moderate-to-severe mitral regurgitation also had moderate or severe aortic regurgitation. Mitral valve surgery was performed in the 11 patients: 4 underwent repair and 7 underwent replacement. Tissue specimens for histologic examination were available from the 7 patients who underwent mitral valve replacement; all 7 specimens showed valvular thickening and myxomatous degeneration.

Tricuspid valve involvement was reported preoperatively in 8 patients (Table I). Echocardiographic reports

TABLE I. Cardiac Valvular Lesions in the Patients with Marfan Syndrome

Condition	Pathologic Valvular Disease		
	Mitral (n=18)	Aortic (n=66)	Tricuspid (n=8)
Prolapse	15	2	8
No prolapse	3	64	0
Mild regurgitation	4	0	5
Moderate-to-severe regurgitation	11	63	2

TABLE II. Isolated or Multiple Valve Lesions in the Patients with Marfan Syndrome

Valve	Isolated Lesions	Multiple Lesions
Aortic	4	0
Mitral	11	7*
Tricuspid	1	7*

*Involving the mitral and tricuspid valves

included tricuspid prolapse in all 8 patients, with valvular thickening, floppy and redundant valves, chordal elongation, and excess valvular motion (Fig. 3). Each tricuspid valve patient had prolapse of all 3 leaflets. Of the 8 patients with tricuspid involvement, 2 had severe tricuspid regurgitation (Table I). These 2 patients underwent tricuspid repair, and both had tricuspid valve specimens available postoperatively; histologic examination of those specimens showed valvular thickening and myxomatous degeneration.

Mitral valve lesions (followed by tricuspid valve lesions) were most often associated with Marfan syndrome. Among the Marfan patients with mitral prolapse, 87% had bileaflet involvement, and among the Marfan patients with tricuspid prolapse, 100% had trileaflet involvement. The incidence rate of abnormal aortic morphology detected by echocardiography was low—seen as an isolated lesion in 4 patients (5.5%) (Tables I and II). Tricuspid valve involvement was always seen in association with mitral involvement. Both mitral and tricuspid involvement were seen in 7 patients (9.6%) (Table II).

Discussion

This study gave us the opportunity to survey the prevalence of cardiac valvular involvement in Marfan syndrome in a patient population that had been referred for cardiovascular surgery to a large cardiovascular hospital in a major city.

Fig. 1 Transthoracic echocardiogram (parasternal long-axis view) of the mitral valve in a patient with Marfan syndrome shows leaflet thickening, redundant prolapsed anterior and posterior leaflets (arrowheads) and chordal elongation.

Ao = aorta; LA = left atrium; LV = left ventricle

Fig. 2 In the same patient with Marfan syndrome, a transthoracic echocardiogram (parasternal short-axis view) shows leaflet thickening of both the mitral (MV) and tricuspid (TV) valves, and leaflet prolapse of the tricuspid valve.

Fig. 3 Transthoracic echocardiogram (nonstandard off-axis apical view) of the tricuspid valve in a patient with Marfan syndrome shows 2 of the 3 redundant prolapsed leaflets (arrowheads).

LV = left ventricle; RA = right atrium; RV = right ventricle

The prevalence of mitral valve prolapse in Marfan patients as seen upon echocardiography has been variably reported from 28% to 80%.^{1,9-11} The prevalence of mitral prolapse is reported to be even higher among children with Marfan syndrome than among adults.²² In this study, we found that the prevalence of mitral prolapse in patients with Marfan syndrome as detected echocardiographically and then confirmed by surgical observation was 23%—a significantly lower prevalence than some have reported, but closer to the 28% prevalence reported by Taub and colleagues.¹¹ Possible explanations for this reported disparity in the prevalence of mitral prolapse among Marfan patients are several. One is that more rigid echocardiographic criteria now exist for the diagnosis of mitral prolapse.^{16,19,21} Previously, mitral prolapse was reported as “mitral valve bulging,” a relatively loose criterion for diagnosis.²⁰ The more precise diagnostic criterion is systolic atrial displacement of the valve leaflets by ≥ 2 mm beyond the annular plane in the echocardiographic long-axis view,^{19,21} which leads inevitably to a lower prevalence. Another possible explanation for the disparity between our study and previous ones is our lack of attention to other possible cardiac manifestations of Marfan syndrome, particularly in the absence of valvular regurgitation. Furthermore, the introduction of readily available genetic testing and earlier diagnosis of Marfan syndrome might have resulted in comprehensive echocardiographic evaluation before detectable valvular involvement.

The aortic valve findings in our study were of substantial interest. In the preoperative echocardiograms of the 66 Marfan patients who underwent either the Bentall procedure or aortic valve replacement, 63 patients had moderate-to-severe or severe aortic regurgitation. Furthermore, only 4 preoperative echocardiograms showed aortic valve morphology: 2 patients had thickened, floppy aortic valve cusps and 2 patients had aortic valve prolapse. Surgical histologic data were available for 29 of the 66 patients: the single patient with aortic valve replacement and 28 of the patients who underwent a Bentall procedure. All 29 histologic specimens showed myxomatous degeneration.

The reasons for the disparity between the histologic findings and the reported echocardiographic findings are several. Marfan syndrome is a diffuse disease process that can affect any or all cardiac valve tissues.²² Furthermore, dilation of the aortic root and the ascending aorta can alter aortic leaflet stress and thereby affect coaptation of an otherwise normal aortic valve,²³ resulting in significant aortic regurgitation as revealed by echocardiography. This is consistent with the observations of Roberts and colleagues,^{24,25} who reported, in the histologic specimens of patients with Marfan syndrome, severe loss of medial elastic fibers in the sinuses of Valsalva and in the ascending aorta. In addition, the findings of myxomatous involvement of the aortic valve suggest that

surgical decisions regarding the aortic valve in patients with Marfan syndrome should not arise only from the echocardiographic appearance of the valve. The absence of morphologic thickening or variable degrees of aortic regurgitation seen on the echocardiogram might not indicate the extent of aortic valve tissue involvement in patients with Marfan syndrome.²³

Studies of patients with Marfan syndrome have generally excluded descriptions of the tricuspid valve. Although tricuspid involvement was not often detected in our study (12%), diffuse valvular disease was prevalent. In the 8 patients with tricuspid involvement, each had abnormal echocardiograms showing valvular thickening and prolapse with chordal elongation involving all 3 leaflets, accompanied by histologic findings consistent with valvular thickening and myxomatous degeneration. Furthermore, in each case the mitral and the tricuspid valves were concurrently involved. These findings suggest that the surgical evaluation of Marfan patients should include detailed evaluation of the tricuspid valve.

Limitations. An acknowledged limitation of our study is that all surgical specimens were not available for histologic analysis. Nevertheless, a sufficient number of specimens was available to enable conclusions regarding the necessity for a comprehensive preoperative evaluation of all the cardiac valves in Marfan patients who are to undergo corrective surgery. Another limitation of our study is its confinement to the retrospective evaluation of Marfan patients undergoing such surgery. Although we were able to study the involvement of all cardiac valves, further studies are necessary to determine whether histologic involvement of the cardiac valves—in the absence of significant echocardiographic findings—is associated with deterioration in valvular function that needs surgical correction.

Conclusion. In summary, this study has been able to confirm that a comprehensive echocardiographic evaluation of all valves is recommended in the overall evaluation of Marfan patients and, in particular, in the evaluation of patients under consideration for surgery. Such an appraisal enables the surgeon to determine the extent of the surgical procedure. In particular, the study has shown that the aortic and tricuspid valves should be evaluated to determine the extent of their involvement, although the mitral valve is most frequently involved in Marfan syndrome.

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