

Appendix 1. Valvular Regurgitation Grading Scale

Valve	Grade	Description
Aortic*	Not evaluable	Inadequate image quality to assess grade.
	None	No regurgitation color flow in any view.
	Trace	Regurgitant jet diameter in the parasternal (or apical long-axis view) <5% of the left ventricular outflow tract diameter.
	Mild	Regurgitant jet diameter >5% and <25% of the left ventricular outflow tract diameter.
	Moderate	Regurgitant jet diameter <25% and <47% of the left ventricular outflow tract diameter.
	Moderately severe	Regurgitant jet diameter <47% and <65% of the left ventricular outflow tract diameter.
	Severe	Regurgitant jet diameter <65% of the left ventricular outflow tract diameter and usually associated with diastolic flow reversal in the abdominal aorta.
Mitral and Tricuspid†‡	Not evaluable	Inadequate image quality to assess grade.
	None	No regurgitant color flow in any view.
	Trace	Non-sustained jet within 1 cm behind the annular plane with a maximal jet area <5% of atrial area.
	Mild	Sustained color flow jet with a maximal jet area >5% and <20% of atrial area.
	Moderate	Maximal jet area >20% and <40% of atrial area.
	Severe	Maximal jet area >40% or a color flow jet reaching the back of the atrium with associated systolic flow reversal in the pulmonary area.
Pulmonic	Not evaluable	Inadequate image quality to assess grade.
	None	No regurgitant color flow in any view.
	Trace	Trivial jet extending <1.0 cm into the right ventricular outflow tract.
	Mild	Minimal jet extending 1.0 to 2.0 cm into the right ventricular outflow tract.
	Moderate	Jet extending more than 2.0 cm that does not reach the body of the right ventricular cavity.
	Severe	Jet extending more than 2.0 cm that reached the body of the right ventricular cavity.

*Aortic regurgitation was visually graded based on modified Perry criteria.¹⁵

†Eccentric jets of the mitral and tricuspid valves were upgraded one grade if jet impingement on a chamber wall precluded development of the full jet area.

‡Mitral and tricuspid regurgitation were graded based on modified Helmcke criteria.¹⁶

Echocardiographic Assessment

Two-dimensional, M-mode, color-flow, pulsed and continuous wave Doppler echocardiograms were performed within one month of study enrollment by trained sonographers who were blinded to all aspects of subject history. The echocardiograms were obtained according to a specified imaging protocol using standardized echocardiographic equipment (Sonos 2000 or 2500 Imaging Systems; Hewlett-Packard, Andover, MA) and were recorded on videotape. The tapes were forwarded to an established central core laboratory staffed by board-certified cardiologists specializing in echocardiography who were blinded to subject group and medical history.

The standardized echocardiographic imaging protocol included a parasternal long-axis view; parasternal short-axis views at the aortic valve, mitral valve, and left ventricular levels; and apical 4-chamber, 2-chamber, and long-axis views. Mitral, aortic, pulmonic and tricuspid valves were imaged by color Doppler in multiple views to determine the degree of regurgitation. The aortic and mitral valves were assessed by 2-dimensional echocardiography in both the parasternal long- and short-axis views to evaluate valve thickness and mobility. Two-dimensionally directed M-mode echocardiography was performed at the level of the aortic and mitral valves and left ventricle, and measurements of left ventricular (LV) and left atrial (LA) dimensions were performed according to American Society of Echocardiography convention.¹⁷ If the images were not optimally aligned for M-mode measurement, chamber dimensions were acquired from the 2-dimensional images. Technical inability to evaluate one valve parameter did not preclude evaluation of other parameters.

Parameters of valvular function and morphology were evaluated, including 1) aortic, mitral and tricuspid regurgitation as well as pulmonic regurgitation, and 2) aortic and mitral

valve leaflet thickness and mobility. For all valves, regurgitation was graded *not evaluable* if assignment of a grade was considered impossible because of technical difficulty. Aortic and mitral valvular regurgitation were considered present in accordance with FDA criteria, that is, subjects were aortic regurgitation positive when mild or greater aortic regurgitation was present and mitral regurgitation positive when moderate or greater mitral regurgitation was present.³

Valve leaflets were considered abnormally thickened if mitral valve leaflets appeared >4 mm during diastole, or if echo-densities were detected involving the tip, body and/or base of aortic valve leaflets. Valve leaflet mobility was considered abnormal if there was restriction of motion due to morphologic changes according to the following grades: aortic (mild - minimal restriction at the base, commissure, or leaflet tips with maximal cusp separation > 1.5 cm; moderate – restriction with cusp separation of 1.0-1.5 cm; severe - restriction of all 3 leaflets with cusp separation less than 1.0 cm), anterior mitral leaflet (mild - mildly diastolic doming or decreased mobility that does not impair excursion into the left ventricular outflow tract by more than 50%; moderate – impaired motion by > 50% but mobility of part of the leaflet body maintained; severe - complete immobility of the anterior leaflet), posterior mitral leaflet (mild - slightly decreased mobility that does not impair excursion to the posterior wall by more than 50%; moderate – impaired motion by > 50% but mobility of part of the leaflet body maintained; severe - complete immobility of the posterior leaflet). Pulmonary artery systolic pressure was calculated utilizing the modified Bernoulli equation, $PAP=4v^2+RAP$, where v= peak systolic velocity or tricuspid regurgitation jet recorded by continuous wave Doppler and RAP (right atrial pressure) was assumed to be 10 mmHg. Visual estimates of left ventricular ejection fraction were made by integrating information from all views and left ventricular ejection fraction was considered normal if above 0.50.

The number of echocardiographic readings performed were equally distributed among three cardiologists at the core echocardiography laboratory. A second, independent, blinded reading of an echocardiogram was performed when abnormal aortic or mitral regurgitation (FDA criteria), leaflet thickening, or restricted leaflet mobility was detected on the initial reading. Disagreements between readers were resolved by consensus readings.