

Right Ventricular Remodeling and Dysfunction With Subsequent Annular Dilatation and Tethering as a Mechanism of Isolated Tricuspid Regurgitation

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Background Secondary tricuspid regurgitation (TR) as a result of pulmonary hypertension and/or left-sided heart disease is caused by tricuspid valve (TV) annular dilatation and tethering of the tricuspid leaflet after right ventricular (RV) dilatation. However, the mechanism of isolated TR without significant pulmonary hypertension remains unknown. The present study investigated the RV function and TV deformations in patients with isolated TR to find out the mechanism and etiology of the disease.

Methods and Results Twelve patients with isolated, severe TR were included. RV area, volume, ejection fraction (EF), tenting distance and tenting area were measured. These parameters were compared with 12 age- and gender-matched controls and 12 patients with secondary TR. The cause of isolated TR was incomplete coaptation associated with annular dilatation without other problems. Compared with the controls, RV end-diastolic volumes and annular diameters were significantly larger and RVEF was significantly lower in patients with isolated TR. Tenting area and tenting distance were also significantly higher. However, there were no significant differences in these parameters between patients with isolated and secondary TR.

Conclusions Isolated TR was associated with RV remodeling, systolic dysfunction and resultant annular dilatation and tethering of tricuspid leaflets. (Circ J 2008; 72: 1645–1649)

Key Words: Cardiomyopathy; Isolated tricuspid regurgitation; Right ventricle

In adults, tricuspid regurgitation (TR) usually occurs secondary to left-sided valvular lesions or chronic pulmonary disease. Secondary TR, in conjunction with left-sided valve disease and left ventricular (LV) dysfunction, even with a structurally normal tricuspid valve (TV), is thought to be caused by tricuspid annular dilatation¹ and tethering of the TV leaflet after right ventricular (RV) dilatation. In contrast to secondary TR, acquired isolated TR can be defined when TR is present without other valvular lesions, pulmonary disease or pulmonary hypertension.^{2,3} Because of the paucity of data, management and clinical decision-making regarding patients with isolated TR is difficult. Furthermore, the mechanism of isolated TR remains unknown. We hypothesize that RV remodeling and dysfunction would be the most important mechanism for isolated TR. Therefore, we evaluated RV function and TV deformities (TV annular dilatation and tethering) in patients with isolated TR and compared these parameters with age- and gender-matched patients with secondary TR, as well as

age- and gender-matched controls.

Methods

We reviewed approximately 20,000 patients who had echocardiograms in our laboratory over a 5-year period retrospectively. Patients with secondary TR associated with significant other valvular disease, LV systolic dysfunction, coronary artery disease and a RV systolic pressure greater than 50 mmHg were excluded. We also excluded the patients with Ebstein's anomaly and thyroid dysfunction.

TR was graded qualitatively by Framingham Heart Study criteria:⁴ mild if the regurgitant jet area/right atrial area was 19% or less; moderate if 20% to 40%; or severe if $\geq 41\%$. Enlargement of the RV was considered mild if the RV was greater than two-thirds of the LV but less than the LV size; moderate if the RV equaled the LV; and severe if the RV was greater than the LV at apical 4-chamber view.⁵ The peak TR velocity was measured by continuous-wave Doppler, and pulmonary arterial systolic pressure was estimated by measurement of the systolic regurgitant tricuspid flow velocity and an estimate of right atrial pressure (RAP) applied in the modified Bernoulli method: $RVSF = 4V^2 + RAP$.^{6,7} RAP is estimated value from characteristics of the inferior vena cava with respiratory variation.⁸

Twelve patients were diagnosed as isolated severe TR. We also selected the age- and gender-matched patients with secondary TR associated with pulmonary hypertension and control participants for comparison of echocardiographic parameters with isolated TR patients. Among patients with

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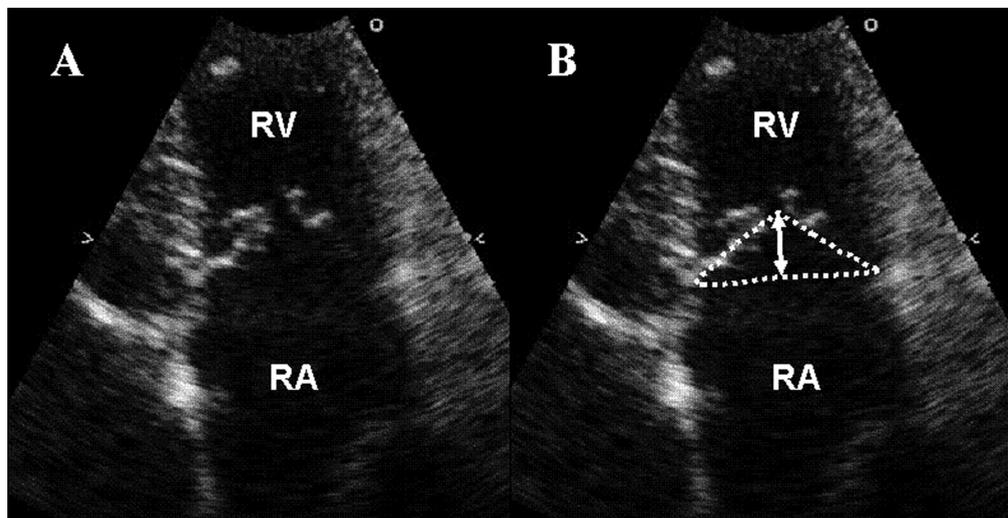


Fig 1. Dilated tricuspid valve annulus, tenting distance and tenting area in an isolated tricuspid regurgitation patient. (A) Tricuspid valve at midsystolic phase. (B) Traced tenting distance (solid line) and tenting area (dotted line). RA, right atrium; RV, right ventricle.

Table 1 Clinical Characteristics of Patients With Isolated TR

Sex/Age	Rhythm	LVEF (%)	Peak velocity of TR jet (m/s)	Annular diameter of TV (mm)	Etiology of TR
M/39	AF	73	2.1	57	Incomplete coaptation
F/56	AF	50	1.6	62	Incomplete coaptation
M/76	AF	66	2.7	36	Incomplete coaptation
F/46	Pacing	65	2.59	52	Incomplete coaptation
F/63	NSR	60	2.4	42	Incomplete coaptation
M/83	AF	69	2.13	38	Incomplete coaptation
F/80	NSR	69	2.35	42	Incomplete coaptation
F/68	AF	67	2.6	45	Incomplete coaptation
M/68	AF	56	2.8	46	Incomplete coaptation
F/63	NSR	68	2.3	41	Incomplete coaptation
F/66	AF	62	2.45	45	Incomplete coaptation
F/60	NSR	58	2.7	42	Incomplete coaptation

TR, tricuspid regurgitation; LVEF, left ventricular ejection fraction; TV, tricuspid valve (annular diameter is measured in the apical 4-chamber view); AF, atrial fibrillation; NSR, normal sinus rhythm.

severe TR, those with RV systolic pressure more than 50mmHg associated with mitral valve disease were considered as secondary TR group.

Routine transthoracic echocardiography examination, including 2-dimensional (D) and Doppler echocardiography with color flow mapping, were done in all patients using a standard scanner. After recording TR velocity with continuous-wave Doppler, RV systolic pressure was calculated by the simplified Bernoulli equation.⁵ TR severity was assessed by color Doppler flow mapping of the spatial distribution of the regurgitant jet within the right atrium (RA). The TR jet area on color flow mapping and RA in the same frame was measured by planimetry, and the ratio of the maximal regurgitant area to RA area was obtained. The diastolic tricuspid annular diameter (TAD) was measured as previously described on a still image of the apical 4-chamber view as the maximal distance between the insertion hinge points of the septal and anterior tricuspid leaflets at the time of maximal leaflet excursion in diastole.⁹ Systolic diameter was the minimal distance in systole. Annular fractional shortening was calculated by the measured dimension as the [(maximal diastolic diameter – minimal systolic diameter)/maximal diastolic diameter] × 100. Tenting distance was measured

from the annular plane to the coaptation point and the tenting area calculated by tracing the leaflets from the annular plane at mid-systolic phase (Fig 1).¹⁰

The RV end-systolic and end-diastolic cavity areas were traced in the apical 4-chamber view and RV end-diastolic volume, RV end-systolic volume, and RV ejection fraction (EF) were calculated using the single-plane subtraction method.^{11–13} LV end-diastolic and end-systolic dimensions, as well as ventricular septum and posterior wall thickness were measured by M-mode tracing, and LVEF was calculated by the modified method of Quinones et al.¹⁴ In patients with atrial fibrillation, we measured these parameters during relatively regular rhythm and calculated the mean value over 5 consecutive beats. Measurements were carried out off-line by a single investigator who was unaware of the status of the study patients and reviewed by 2 other investigators. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written. The present study was approved by the institutional review board of Yonsei University College of Medicine.

Table 2 Echocardiographic Parameters in the Isolated TR Group Compared With Age- and Gender-Matched Controls and Functional TR

	Control (n=12)	Isolated TR (n=12)	Secondary TR (n=12)
Age (years)	62.3±11.7	64.0±12.9	60.4±9.6
M/F	4/8	4/8	4/8
LVEDD (mm)	49.0±3.9	45.8±4.6	52.3±11.7**
LVESD (mm)	31.7±5.6	31.5±4.9	37.0±8.4**
LVEF (%)	69.5±6.5	63.6±6.6	56.9±12.3*
TR velocity (m/s)	2.4±0.4	2.4±0.3	3.1±0.9***
RV systolic pressure (mmHg)	27.4±7.6	35.9±5.2	49.8±19.6***
Tricuspid annular EDD (mm)	32.5±3.9	45.7±7.7*	41.8±8.1*
Tricuspid annular ESD (mm)	24.3±2.9	37.3±8.8*	35.9±7.3*
Annular fractional shortening (%)	24.9±5.8	18.7±8.4*	13.7±7.9*
Tenting area (mm ²)	60.8±18.6	213±103.3*	176±75.7*
Tenting distance (mm)	3.9±0.8	10.3±2.3*	10.6±3.0*
RVED volume (mm ³)	162.4±26.8	227.9±65.5*	249.5±47.0*
RVES volume (mm ³)	73.8±24.3	158.7±57.9*	150.6±48.9*
RVEF by volume (%)	54.5±13.8	30.7±15.1*	40.0±12.8*

*Different from normal with p-value <0.05; **different from isolated TR with p-value <0.05.

LV, left ventricular; EDD, end diastolic dimension; ESD, end systolic dimension; EF, ejection fraction; RV, right ventricular. Other abbreviations see in Table 1.

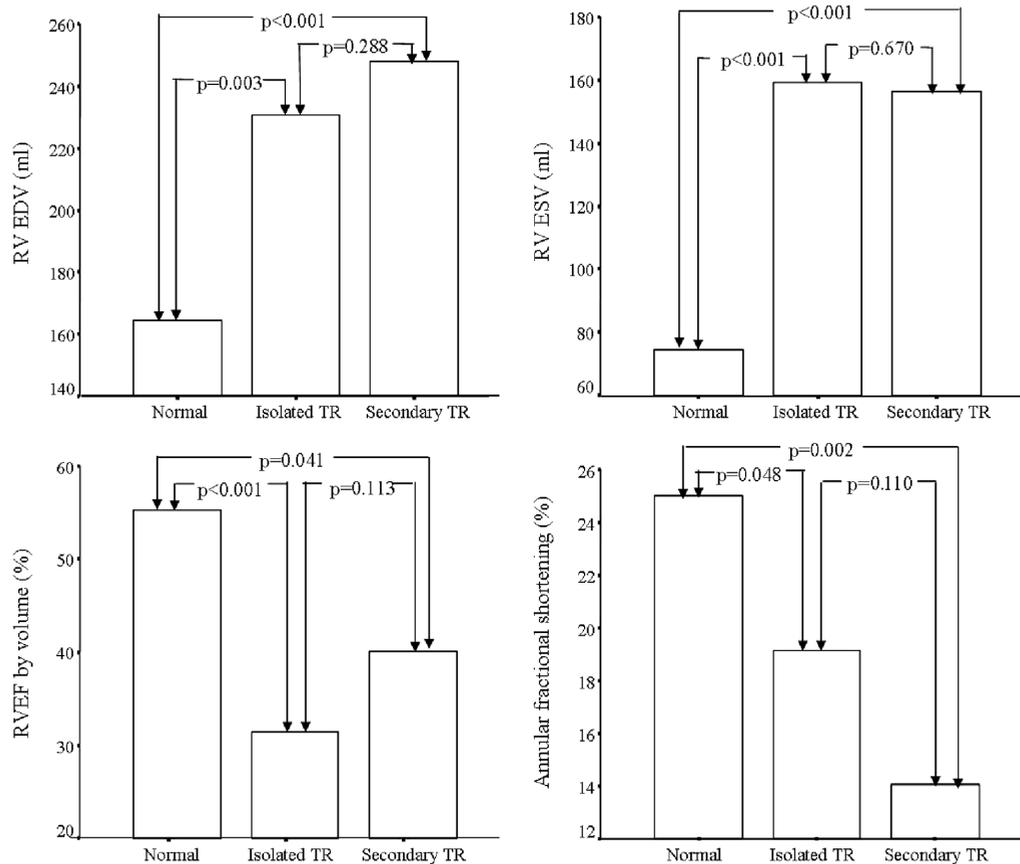


Fig 2. Right ventricle (RV) volume and RV systolic function between normal, isolated tricuspid regurgitation (TR) and secondary TR groups. EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction.

Statistical Analysis

Values were expressed as mean±SD. Differences between proportions were assessed by chi-squared analysis. To compare the 3 groups of patients, the 1-way ANOVA test was used. P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of the patients are shown in Table 1. Seven of the 12 patients had atrial fibrillation and 1 patient (the fourth patient in Table 1) had a pacemaker as a result of atrial fibrillation with symptomatic bradycardia.

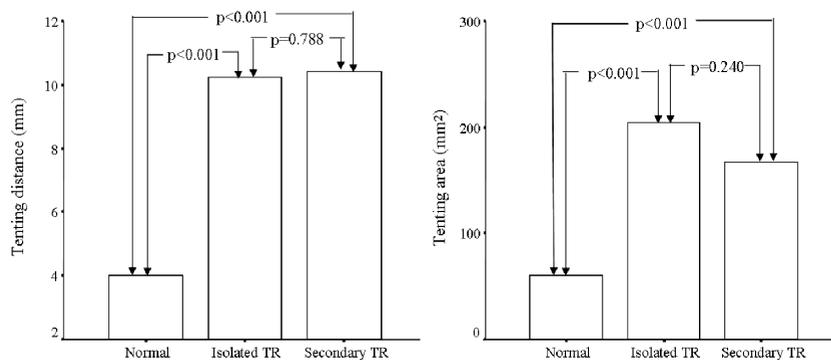


Fig 3. Tenting distance and tenting area between normal, isolated tricuspid regurgitation (TR) and secondary TR groups.

LV size and systolic function were normal and other abnormalities in LV were not found. The mean diameter of the tricuspid annulus was 45.7 ± 7.7 mm and TR velocity was 2.4 ± 0.3 m/s, which was consistent with the normal RV systolic pressure when calculated with the simplified Bernoulli equation. The cause of TR was incomplete coaptation as a result of idiopathic annular dilatation and leaflet tethering in the absence of valve problems, such as prolapse or chordae rupture (Fig 1).

Differences in Echocardiographic Parameters Between the 3 Groups

There were no significant differences in age and gender between the isolated TR group and the age- and gender-matched controls (Table 2). LV size and EF were normal in patients with isolated TR, and were not significantly different from that of the controls. However, LV end-diastolic dimension was significantly larger and the LVEF was lower in the secondary TR group compared with those of the control group and isolated TR. TR velocity (3.1 ± 0.9 m/s vs 2.4 ± 0.4 m/s vs 2.4 ± 0.3 m/s, respectively) and RV systolic pressure (49.8 ± 19.6 mmHg vs 27.4 ± 7.6 mmHg vs 35.9 ± 5.2 mmHg, respectively) were higher in the secondary TR group compared with the other 2 groups. RV end-diastolic volume, annular diameter, tenting distance and tenting area were higher in the isolated and secondary TR groups compared to the control group, but did not differ significantly between the isolated and secondary TR groups (Figs 2,3). Isolated and secondary TR groups also exhibited lower RVEF compared to the control group ($30.7 \pm 15.1\%$ and $40.0 \pm 12.8\%$ vs $54.5 \pm 13.8\%$), but the RVEF was the lowest in the isolated TR group. Tricuspid annular fractional shortening also decreased in patients with isolated and secondary TR compared with the control group, although no difference was found between patients with isolated and secondary TR.

Discussion

Isolated TR is uncommon, although the incidence is increasing, and the prognosis of patients with isolated severe TR is poor. In contrast to mitral regurgitation, for which medical and surgical approaches have been developed concomitant with elucidation of the underlying mechanism, examination of the RV and its pathophysiologic processes in TR has not progressed very far. As such, the strategies for medical management and optimal timing for surgical treatment of TR are not well established.

The results of the present study provide several new findings. First, patients with isolated TR had dilated RV

with depressed RV systolic function, independent of LV. Secondly, enlarged TAD, tenting distance and tenting area were noted in patients with isolated TR, suggesting that tethering of the TV, associated with remodeling of the RV, might be a predominant mechanism for isolated TR. These findings are consistent with those of Tei and colleagues.⁹ The present study offers a new concept that can potentially be applied to improve therapeutic approach for isolated TR, especially emphasizing medical treatment for RV remodeling and function.

Suggested Mechanisms of the New Disease Entity

In our study, in patients with isolated TR, the RV was dilated and RV systolic function and TV annular fractional shortening were decreased compared with the controls. These findings are quite similar to functional mitral regurgitation in dilated cardiomyopathy, which augments the tethering force and restricts leaflet closure.¹⁵ When considering these findings, isolated TR might be viewed as functional regurgitation associated with dilated cardiomyopathy, exclusively involving the RV. Because dilated cardiomyopathy is characterized by cardiac enlargement and impaired systolic function of one or both ventricles, we would like to propose the new disease entity of isolated RV dilated cardiomyopathy and isolated TR as a functional TR associated with this pathologic condition. Although this entity has not been well recognized in the literature as LV dilated cardiomyopathy, its concept has already been described.¹⁶ In patients with isolated TR, pulmonary arterial hypertension is not present. Pulmonary hypertension usually results from hypoxic vasoconstriction, a decrease in pulmonary vascular bed area, and chronically increased pulmonary blood flow. Patients with isolated TR exhibited depressed RV systolic function in the presence of severe TR, which results in low forward stroke volume to the pulmonary artery.¹⁷ Therefore, pulmonary arterial pressure is not usually elevated in patients with isolated TR. These findings further support our hypothesis of isolated TR as functional regurgitation associated with dilated cardiomyopathy. We would like to suggest that 'isolated' TR is not truly isolated, but rather is the result of RV dilatation and RV systolic dysfunction. In the setting of dilated cardiomyopathy, differences in the degree of RV dilatation can be seen in clinical practice.¹⁸ Whether this represents different pathological entities or different stages in the disease process is unclear.

Previous Studies

Previous studies showed that chest trauma,^{19,20} endocarditis,¹³ carcinoid syndrome,²¹ malformation of the TV apparatus,²² and severe annular dilatation²³⁻²⁵ were associated

with isolated severe TR. Girard et al showed the normal morphology of TV on operative inspection and clinical improvement after valve surgery in patients with isolated TR. Given the advanced age of these patients, Girard et al speculated that annular dilatation was degenerative.²⁵ Recently, 3-D geometry of TV annulus was evaluated with 3-D echocardiography in patients with functional TR and revealed the bimodal shape of TV annulus remained present in reference patients with similar RV pressure and LV dysfunction.²⁶ Thus, it has been speculated that it is not RV pressure load or left-sided heart disease that influence the annular remodeling changes in functional TR. These findings are consistent with the results of our study showing that the TV annulus dilatation and leaflet tethering were important mechanisms for the development of isolated TR, in which RV pressure load or left-sided heart disease are not present. Changes in RV geometry presumably caused displacement of the papillary muscles, resulting in tethering of the TV leaflet, which could not be evaluated in this study.

Study Limitation

The sample size is relatively small. However, the patients with isolated TR without left heart disease are not common, and the statistical analysis showed significant difference in RV volume and RV systolic function between these patients and the normal control group. Therefore, we believe that the results found in this study are meaningful despite the small sample size. Because this is a retrospective study, the sequential changes of chamber size, the severity of regurgitation and ventricular function could not be evaluated. Therefore the question of which comes first, TR or the enlarged RV still remains. However, we found the enlarged RV chamber with dysfunction in patients with isolated TR in the absence of significant pulmonary hypertension or other TV problem, which can cause secondary TR. A further prospective study would be needed to clarify these issues.

Conclusions

Isolated TR was associated with RV remodeling and systolic dysfunction with annular dilatation, decreased annular fractional shortening, and tethering of tricuspid leaflets, suggesting remodeling of RV with subsequent tethering of TV as the predominant mechanism for isolated TR.

Disclosure

No financial or other potential conflicts of interest exist.

References

- Sagie A, Schwammenthal E, Padiyal LR, Vazquez de Prada JA, Weyman AE, Levine RA. Determinants of functional tricuspid regurgitation in incomplete tricuspid valve closure: Doppler color flow study of 109 patients. *J Am Coll Cardiol* 1994; **24**: 446–453.
- Aaron BL, Mills M, Lower RR. Congenital tricuspid insufficiency: Definition and review. *Chest* 1976; **69**: 637–641.
- Pernot C, Hoeffel JC, Henry M, Pivnicka A. Congenital tricuspid insufficiency. *Cardiovasc Radiol* 1978; **1**: 37–44.
- Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham heart Study). *Am J Cardiol* 1999; **83**: 897–902.
- Otto C. Textbook of clinical echocardiography. 2nd edn. Philadelphia: W.B. Saunders; 2000; 120–121.
- Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984; **70**: 657–662.
- Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, et al. Continuous wave Doppler determination of right ventricular pressure: A simultaneous Doppler-catheterization study in 127 patients. *J Am Coll Cardiol* 1985; **6**: 750–756.
- Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: A simultaneous catheterization and echocardiographic study. *Mayo Clin Proc* 2000; **75**: 24–29.
- Tei C, Pilgrim JP, Shah PM, Ormiston JA, Wong M. The tricuspid valve annulus: Study of size and motion in normal subjects and in patients with tricuspid regurgitation. *Circulation* 1982; **66**: 665–671.
- Fukuda S, Song JM, Gillinov AM, McCarthy PM, Daimon M, Kongsarepong V, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation* 2005; **111**: 975–979.
- Matsunaga A, Duran CM. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. *Circulation* 2005; **112**(Suppl 9): I-453–I-457.
- Mongkolmai D, Williams GA, Goodgold H, Labovitz AJ. Determination of right ventricular ejection fraction by two-dimensional echocardiographic single plane subtraction method. *J Am Soc Echocardiogr* 1989; **2**: 119–124.
- Mukherjee D, Nader S, Olano A, Garcia MJ, Griffin BP. Improvement in right ventricular systolic function after surgical correction of isolated tricuspid regurgitation. *J Am Soc Echocardiogr* 2000; **13**: 650–654.
- Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL Jr, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981; **64**: 744–753.
- Otsuji Y, Kumanoohoso T, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, et al. Isolated annular dilation does not usually cause important functional mitral regurgitation: Comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. *J Am Coll Cardiol* 2002; **39**: 1651–1656.
- Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980; **44**: 672–673.
- Sugimoto T, Okada M, Ozaki N, Kawahira T, Fukuoaka M. Influence of functional tricuspid regurgitation on right ventricular function. *Ann Thorac Surg* 1998; **66**: 2044–2050.
- Brieke A, DeNofrio D. Right ventricular dysfunction in chronic dilated cardiomyopathy and heart failure. *Coron Artery Dis* 2005; **16**: 5–11.
- Sakuragawa H, Koyama N, Watanabe Y, Yoshihara K, Kawamura K, Yamazaki S. A successful valve repair case of isolated tricuspid regurgitation due to traumatic lacerated papillary muscle of the tricuspid valve. *Jpn J Thorac Cardiovasc Surg* 1998; **46**: 91–95.
- dos Santos J Jr, de Marchi CH, Bestetti RB, Corbucci HA, Pavarino PR. Ruptured chordae tendineae of the posterior leaflet of the tricuspid valve as a cause of tricuspid regurgitation following blunt chest trauma. *Cardiovasc Pathol* 2001; **10**: 97–98.
- Sirois I, Pothier J, Couture C, Bolduc P. Atypical presentation of a carcinoid syndrome. *Can J Cardiol* 1999; **15**: 469–471.
- Shibata Y, Sato M, Chanda J, Sato S, Fujiwara R. Isolated tricuspid regurgitation due to atypical morphology of anterior-posterior leaflets in an adult: A case report and review of the literature. *J Cardiovasc Surg* 1999; **40**: 527–530.
- Marui A, Mochizuki T, Mitsui N, Koyama T, Horibe M. Isolated tricuspid regurgitation caused by a dilated tricuspid annulus. *Ann Thorac Surg* 1998; **66**: 560–562.
- Aoyagi S, Maruyama H, Akasu K, Kawara T. Isolated tricuspid valve regurgitation resulting from severe annular dilatation: Case report. *J Heart Valve Dis* 1999; **8**: 457–459.
- Girard SE, Nishimura RA, Warnes CA, Dearani JA, Puga FJ. Idiopathic annular dilation: A rare cause of isolated severe tricuspid regurgitation. *J Heart Valve Dis* 2000; **9**: 283–287.
- Ton-Nu TT, Levine RA, Handschumacher MD, Dorer DJ, Yosefy C, Fan D, et al. Geometric determinants of functional tricuspid regurgitation: Insights from 3-dimensional echocardiography. *Circulation* 2006; **114**: 143–149.