J Cardiol 2006 Dec; 48(6): 315−323

Severe Tricuspid Regurgitation in the Aged: Atrial Remodeling Associated With Long-Standing Atrial Fibrillation

Naohito YAMASAKI, MD
Fumiaki KONDO, MD*
Toru KUBO, MD
Makoto OKAWA, MD
Yoshihisa MATSUMURA, MD, FJCC
Hiroaki KITAOKA, MD, FJCC
Toshikazu YABE, MD
Takashi FURUNO, MD*
Yoshinori DOI, MD, FJCC

Abstract

Objectives. Severe idiopathic tricuspid regurgitation（TR）occurs in the aged, but the mechanism of TR is unclear and there is little information on atrial abnormalities associated with this condition. This study retrospectively analyzed patients with severe functional TR presenting with common clinical features suggesting a distinct syndrome.

Methods. Eleven patients with severe functional TR were identified by reviewing the records of 16,235 consecutive patients. All patients had undergone clinical evaluation including echocardiography, electrocardiography and laboratory data.

Results. The median age of patients with severe functional TR was 78 years. All had a long-standing history of atrial fibrillation（median duration, 23 years）. Clinical features are characterized by severe functional TR due to annular dilation, markedly dilated right atrium, episodes of right-sided heart failure, absent or diminished fibrillation waves on electrocardiogram, bradycardia probably due to partial atrial standstill, and decreased atrial natriuretic peptide secretion. During long-term follow up, right atrial size progressively increased in association with worsening TR.

Conclusions. Severe functional TR occurs with long-standing atrial fibrillation and causes right-sided heart failure. The TR is caused by tricuspid valve systolic coaptation loss due to tricuspid annular dilation associated with atrial dilation. This condition is associated with atrial abnormalities, such as atrial standstill and impaired atrial natriuretic peptide secretion. We propose that atrial remodeling associated with atrial fibrillation is central to the occurrence of the syndrome.

J Cardiol 2006 Dec; 48(6): 315−323

Key Words

■**Tricuspid regurgitation** ■**Atrial fibrillation** ■**Elderly**
■**Atrial function（remodeling）**

INTRODUCTION

Tricuspid regurgitation（TR）mainly occurs secondary to left-sided heart disease and secondary pulmonary hypertension in adults, but can also occur as a primary valvular lesion. For example,

高知大学医学部 老年病科・循環器科：〒783−8505 高知県南国市岡豊町小蓮；*幡多けんみん病院 循環器科，高知
Department of Medicine and Geriatrics, Kochi Medical School, Kochi；*Section of Cardiology, Hata Prefectural Hospital, Kochi
Address for correspondence：DOI Y, MD, FJCC, Department of Medicine and Geriatrics, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783−8505；E-mail：ydoi@med.kochi-u.ac.jp
Manuscript received June 23, 2006；revised September 3, 2006；accepted September 22, 2006

elderly patients with severe idiopathic TR have been reported with structurally normal tricuspid valves and severe TR caused by annular dilation.[1−3] However, the mechanism of annular dilation is unclear and there is little information on atrial abnormalities in these patients. In this report, we retrospectively investigated elderly patients with common clinical features suggesting a distinct syndrome of severe functional TR. We suggest that this syndrome is caused by atrial remodeling associated with long-standing atrial fibrillation (AF).

SUBJECTS AND METHODS

Patients

Eleven patients with severe idiopathic TR were identified by reviewing reports of 16,235 consecutive patients who had undergone echocardiography at Kochi Medical School and Hata Prefectural Hospital during a 5-year period between January 2000 and December 2005. Exclusion criteria were as follows: Anatomically abnormal tricuspid valves (rheumatic, infective endocarditis, Ebstein anomaly, carcinoid heart disease, history of trauma); presence of significant pulmonary hypertension (TR pressure gradient $>$ 40 mmHg by cardiac echo); severe organic left-sided valvular heart disease or congenital heart disease; left ventricular systolic dysfunction; previous history of cardiac surgery; and TR due to previously implanted permanent pacemaker or implantable cardioverter-defibrillator leads. All patients had undergone clinical evaluation including physical examination, chest radiography, electrocardiography, laboratory data and echocardiography.

The control group consisted of 10 subjects (5 males and 5 females; mean age: 78 $\pm$ 6 years) without cardiovascular disease who had no abnormalities on echocardiography.

Echocardiography

Two-dimensional and Doppler echocardiograms were obtained from all patients according to a standard protocol using a commercially available imaging system (Sequoia 512, Mountain View). All recordings were performed on S-VHS videotape for analysis. Mitral regurgitation (MR) and TR were identified as a color mosaic systolic jet. The maximum regurgitant jet area was planimetered in an apical four-chamber view. The right atrial area and left atrial area were measured on a still-frame image at the same time. The severity of TR or MR was determined by the ratio of the color Doppler jet area to the right or left atrial area in mid-systole. The degree of TR or MR was estimated as trace, mild, moderate or severe defined as ratios of $>$ 0−10%, $>$ 10−20%, $>$ 20−40% and $>$ 40%, respectively.[4] The right ventricular (RV) area was manually traced in the apical four-chamber view at end-diastole and end-systole. Right ventricular ejection fraction was calculated as (RV end-diastolic area-RV end-systolic area)/RV end-diastolic area (%).[5] The tricuspid and mitral annuli were identified as the hinge points of the leaflets defined by their insertion on the right or left ventricular wall. The tricuspid annular diameter and mitral annular diameter were measured on a still image of the apical four-chamber view at the time of mid-systole. The peak TR velocity was measured by continuous-wave Doppler, and pulmonary artery systolic pressure was estimated by the modified Bernoulli method in all patients.[6]

Atrial and brain natriuretic peptides measurements

Blood was withdrawn from a forearm vein in each patient after the patient had remained in the supine position for at least 15 min. Immunoradiometric assay was performed to measure plasma human atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels (ShionoRIA kit; Shionogi Co., Ltd).

Data analysis

Data are expressed as the mean $\pm$ SD. The unpaired Student's *t*-test was used to assess differences between the patient and control groups. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Clinical characteristics

Table 1 summarizes the clinical characteristics of the 11 patients. All patients were elderly (age range: 65−86 years; median age: 78 years) and had a long-standing history of AF (10−30 years; median duration: 23 years). Edema was the first manifestation in all patients. Auscultation detected pansystolic murmur with tricuspid mid-diastolic rumble. Hepatomegaly was observed in all patients. Four patients (patients 1, 3, 4 and 8) presented with anasarca and required multiple hospitalizations for decompensated right-sided heart failure. All

Table 1 Clinical characteristics of 11 patients with idiopathic severe tricuspid regurgitation

Patient No.	Age (yr)	Sex	History of AF (yr)	Pacemaker implantation	Chest radiography CTR (%)	Pancytopenia
1	79	Male	30	−	75	+
2	80	Female	20	+	82	+
3	79	Male	20	+	73	+
4	83	Female	30	+	67	+
5	68	Male	26	−	63	−
6	65	Male	10	−	58	−
7	81	Male	20	−	60	−
8	86	Male	20	−	67	+
9	81	Male	25	+	68	+
10	74	Female	20	−	51	−
11	81	Female	30	−	69	+

AF = atrial fibrillation; CTR = cardiothoracic ratio.

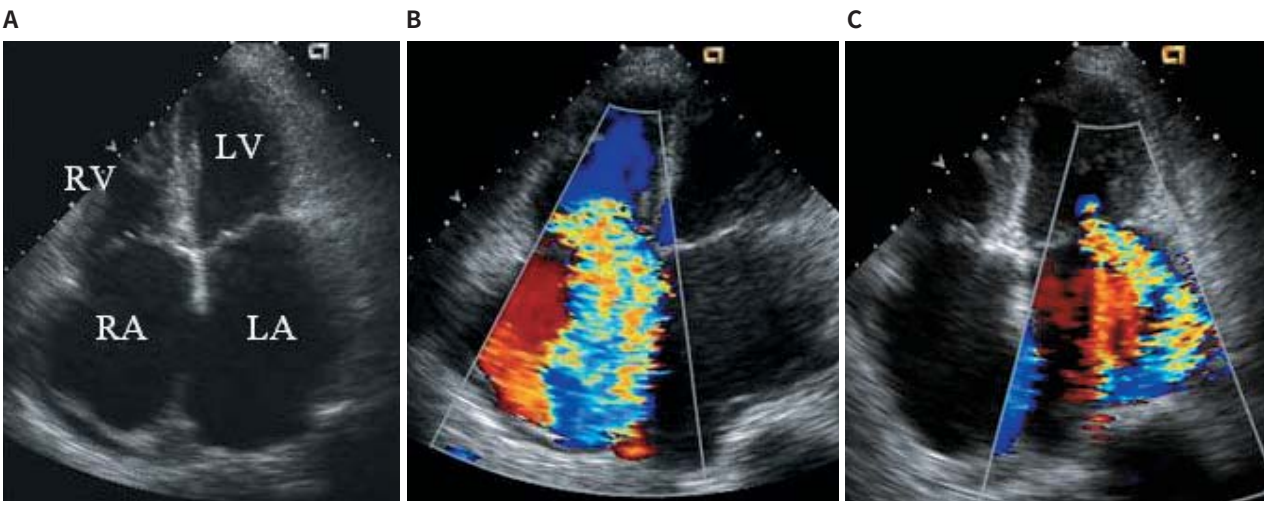

Fig. 1 Echocardiograms
Apical four-chamber view of the heart in a representative patient (patient 1) revealing markedly dilated right atrium and left atrium (*A*). Color flow imaging shows severe tricuspid regurgitation (*B*) and moderate mitral regurgitation (*C*).
RV = right ventricle; RA = right atrium; LV = left ventricle; LA = left atrium.

patients needed diuretic therapy to relieve symptoms of edema. Heart failure symptoms were always right-side dominant, and no patient presented with pulmonary edema. Four patients required permanent pacemaker implantation because of symptomatic bradycardia. Chest radiography showed marked cardiomegaly in all patients (**Table 1**). Seven patients had pancytopenia, and splenomegaly secondary to congestive liver was thought to be responsible for this pancytopenia.

Echocardiography

All patients had markedly dilated right atrium and severe TR (**Fig. 1**). Although functional MR was present in all patients, TR was always the predominant valvular lesion compared with MR. The tricuspid valve and supporting structures were normal without prolapse, ruptured chord, flail segment, or any other disruption of the tricuspid apparatus. However, the tricuspid annulus was markedly dilated, and associated with systolic coaptation loss between septal and anterior tricuspid valve leaflet

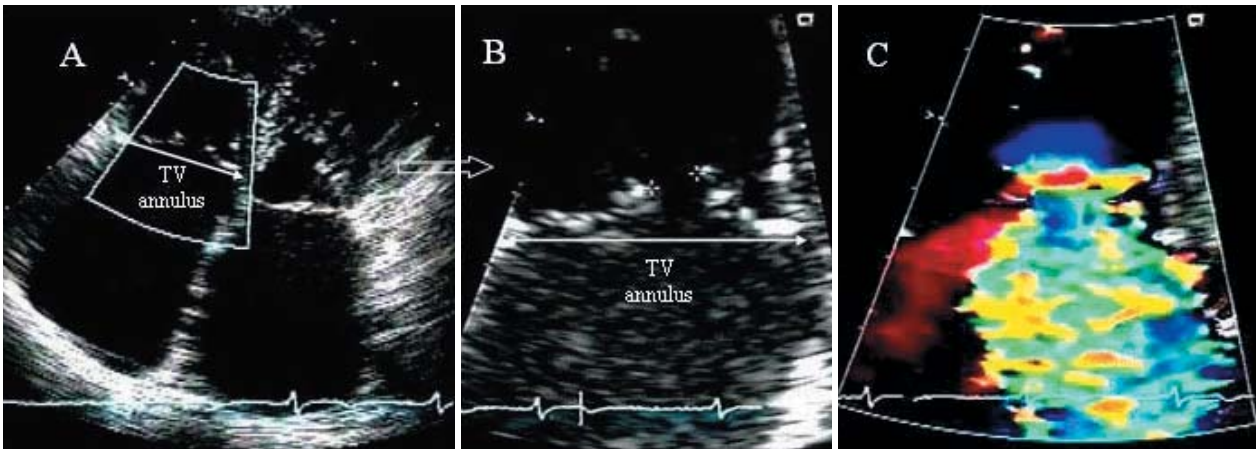

Fig. 2 Mechanism of severe tricuspid regurgitation
Apical four-chamber echocardiographic images in patient 2. *A* shows a markedly dilated tricuspid valve annulus. In the magnified view(*B*), coaptation loss is evident and a systolic gap is present between the septal and anterior tricuspid valve leaflet tips. The color Doppler image(*C*)shows severe tricuspid regurgitation jet with prominent flow convergence.
TV = tricuspid valve.

Table 2 Echocardiographic data

Patient No.	RA area (cm^2)	TAD (mm)	LA area (cm^2)	MAD (mm)	MR grade	RV area (cm^2)	RVEF (%)	LVDd (mm)	LVEF (%)	TR ΔP (mmHg)	IVC size (mm)
1	54	54	66	56	Severe	21	73	57	53	31	38
2	42	45	38	37	Moderate	24	63	48	68	38	37
3	64	50	60	48	Moderate	22	41	55	71	24	38
4	53	46	51	53	Severe	11	31	58	62	32	36
5	46	44	40	40	Moderate	19	29	58	60	34	25
6	37	40	26	35	Trace	17	40	51	58	26	17
7	43	44	37	41	Mild	24	36	48	60	16	26
8	52	46	31	33	Mild	20	39	48	61	29	34
9	39	42	26	41	Mild	27	55	50	64	31	13
10	36	41	31	35	Trace	19	29	41	67	29	21
11	37	42	33	32	Mild	16	44	48	79	24	28
Control	14	28	15	31	Trace	10	43	48	63	19	10

RA=right atrial; TAD=tricuspid annular diameter; LA=left atrial; MAD=mitral annular diameter; MR=mitral regurgitation; RV=right ventricular; LVDd=left ventricular diastolic diameter; R(L)VEF=right (left)ventricular ejection fraction; TR ΔP=tricuspid regurgitation pressure gradient; IVC=inferior vena cava.

tips as shown in **Fig. 2**. A large systolic jet of TR originated from the gap that was caused by the annular dilation.

Echocardiographic data are presented in **Table 2**. Both atria were markedly dilated(right atrial area: 45.7 ± 9.0 vs $14.2 \pm 3.6\,cm^2$, left atrial area: 39.9 ± 14.0 vs $15.3 \pm 5.8\,cm^2$, patients vs controls, both $p < 0.0001$)with severe annular dilation(tricuspid annular diameter: 44.9 ± 4.1 vs 27.7 ± 3.1 mm, mitral annular diameter: 41.0 ± 8.1 vs 31.2 ± 3.4 mm, patients vs controls, both $p < 0.0001$). The right ventricle was significantly dilated(RV end-diastolic area: 20.0 ± 4.4 vs $9.9 \pm 2.7\,cm^2$, patients vs controls, $p < 0.0001$). RV systolic function assessed by right ventricular ejection fraction was relatively preserved(right ventricular ejection fraction: $43.6 \pm 14.3\%$). Regional RV hypokinesia and segmental dilation of the RV suggesting arrhythmogenic right ventricular cardiomyopathy were not detected in any patient. The left

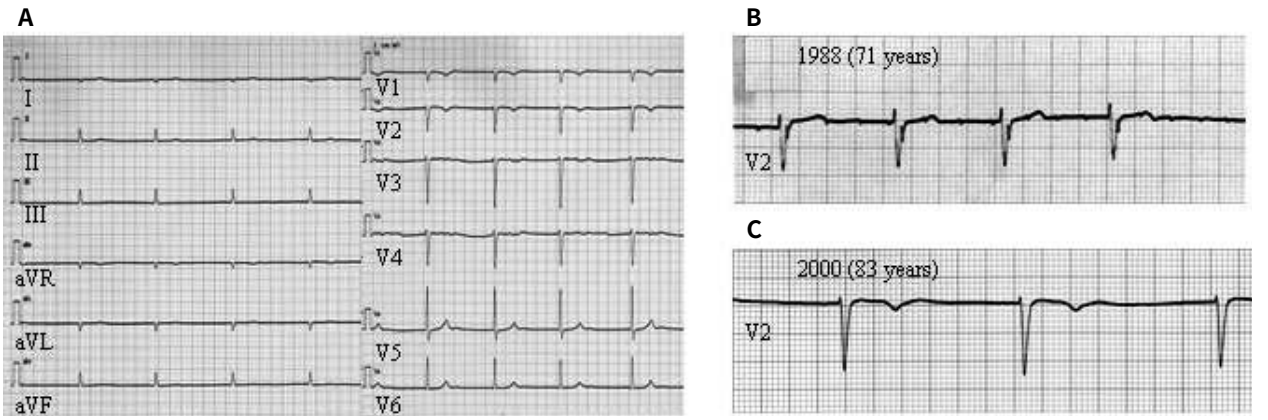

Fig. 3 Electrocardiograms

Electrocardiogram of a representative patient (patient 4) with severe functional tricuspid regurgitation (*A*). Note the absence of fibrillation waves and junctional escape rhythm of 44 per minute. The previous electrocardiogram recorded in 1988 showed atrial fibrillation with fine fibrillation waves in lead V_2 (*B*). The height of the fibrillation waves progressively diminished and the waves were no longer visible in 2000 (*C*).

Table 3 Plasma atrial and brain natriuretic peptide concentration

Patient No.	ANP (pg/m*l*)	BNP (pg/m*l*)
2	57.6	190
3	11.4	103
4	6.3	45
5	17.1	120
7	67.2	341
11	74.6	217
(Reference value)	<43.0	<18.4

ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide.

ventricle was mildly dilated with preserved systolic function (ejection fraction: 63.9 ± 7.1 %). Significant pulmonary hypertension (TR pressure gradient > 40 mmHg) was not present in any patient. All patients had markedly dilated inferior vena cava (median: 28.5 ± 8.9 mm in diameter) with loss of respiratory diameter change.

Electrocardiography

All patients had AF. Seven patients had slow AF (heart rate < 60 beats/min). Three patients were initially treated with digitalis, which was later discontinued due to bradycardia. Six patients showed flattened baseline without fibrillation waves. In these patients, RR intervals were mostly regular, suggesting partial atrial standstill with junctional escape rhythm. Four patients had AF with diminished fibrillation wave height (less than 1 mm). A representative electrocardiography is shown in **Fig. 3−A**. In all patients, the height of atrial fibrillation waves progressively diminished during follow up (**Figs. 3−B**, **C**).

Plasma atrial natriuretic peptide concentration

In six patients, both ANP and BNP plasma concentrations were measured at the same time. The plasma ANP concentration was normal to slightly elevated in the patients despite marked elevation of plasma BNP concentration (**Table 3**).

Long-term echocardiographic data

The progressive nature of TR severity was documented by serial echocardiograms (≥ 10 years) in two patients (patients 1 and 4). When first evaluated, both patients had AF rhythm and dilated right atrium (right atrial areas of 25 and 36 cm^2, respectively). The severity of TR was moderate at most (TR jet areas of 6 and 8 cm^2, respectively). During long-term follow-up (≥ 10 years), right atrial size progressively increased in association with tricuspid valve annular dilation. As the tricuspid annular diameter increased, regurgitation severity worsened, and TR finally became severe (TR jet areas of 54 and 42 cm^2, respectively).

DISCUSSION

Severe functional TR was identified in 11 elderly patients with common clinical features suggesting a distinct syndrome characterized by occurrence in

the elderly with long-standing AF, severe functional TR due to annular dilation, giant right atrium, signs of right-sided heart failure, absent or diminished fibrillation waves on electrocardiography, bradycardia probably due to partial atrial standstill, and decreased ANP secretion.

Several previous reports of elderly patients with severe functional TR[1–3] have not identified the mechanism of such TR or explained the atrial abnormalities associated with this syndrome. The present study suggests that atrial remodeling associated with AF is central to the cause of this syndrome.

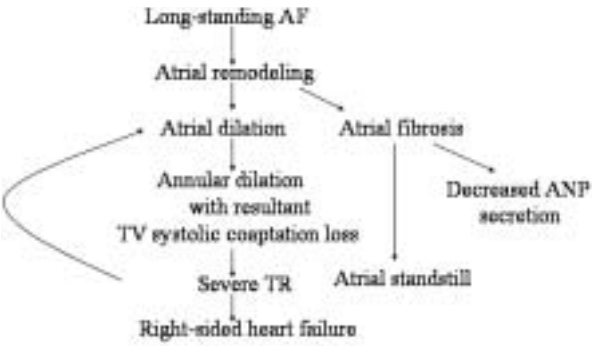

Fig. 4 Proposed pathophysiological mechanism of severe tricuspid regurgitation development in patients with long-standing atrial fibrillation
Long-standing atrial fibrillation causes chronic atrial remodeling and leads to atrial dilation. The dilated atrium enlarges the tricuspid annulus and causes tricuspid regurgitation due to coaptation loss. The resultant tricuspid regurgitation further dilates the atrium, resulting in progressive annular dilation. Therefore, a vicious circle in which "tricuspid regurgitation begets tricuspid regurgitation" is established. Marked stretching of the atria associated with increased pressure causes atrial fibrosis.
TR = tricuspid regurgitation. Other abbreviations as in Tables 1, 3, Fig. 2.

Mechanism of tricuspid regurgitation

The mechanism of severe TR in this syndrome is thought to be tricuspid valve systolic coaptation loss due to tricuspid annular dilation associated with long-standing AF. The tricuspid annulus was markedly dilated and the tricuspid valve leaflets and their supporting structures were normal. Although four of our patients had permanent pacemaker implantation due to bradycardia, severe TR was present prior to the pacemaker implantation, indicating that damage to the tricuspid valve by pacemaker leads was not the main cause of TR.[7] Other causes of TR, such as rheumatic heart disease, infective endocarditis, Ebstein anomaly, carcinoid heart disease, traumatic chordal rupture, and presence of significant pulmonary hypertension, were excluded by echocardiography and careful chart reviews.

We consider that atrial remodeling is central to the progression of TR, based on the longitudinal follow up data in two of our patients. In these patients, right atrial size progressively increased over a period of 10 years in association with tricuspid annular dilation. As the tricuspid annular diameter increased, TR severity worsened due to progressive systolic coaptation loss. This observation supports the causative relationship between atrial remodeling and severe TR. The proposed pathophysiological mechanism is summarized in **Fig. 4**. Long-standing AF causes progressive atrial remodeling and leads to atrial dilation. The dilated atrium makes the tricuspid annulus larger and causes TR due to systolic coaptation loss. The resulting TR further dilates the atrium, resulting in progressive annular dilation. Therefore, a vicious circle in which " TR begets TR " is established.

All of our patients had functional MR, but TR was always the more predominant valvular lesion. The cause of severe TR was not thought to be secondary to MR because no significant pulmonary hypertension (TR pressure gradient $>$ 40 mmHg) was present in any patient and no patient presented with pulmonary congestion. The reason why TR was more predominant can be explained by the recent examinations of the impact of AF on the tricuspid and mitral valves which showed that annular dilation and valvular regurgitation associated with AF are significantly greater in the tricuspid valve than in the mitral valve[4] and that isolated annular dilation caused by AF does not usually cause significant MR.[8]

Atrial remodeling associated with atrial fibrillation

AF is characterized by structural and functional remodeling in the atrial myocardium.[9] Atrial enlargement occurs as a consequence of AF.[10] Our patients had a long-standing history of AF, and atrial size progressively increased during follow up. In addition, we found two atrial abnormalities in our patients that reflect the remodeling process, namely, decreased ANP secretion and partial atrial standstill.

Atrial natriuretic peptide

Our patients had impaired ANP secretion. ANP is secreted mainly from the atria, whereas BNP is secreted mainly from the ventricles.[11] The plasma concentrations of ANP and BNP are elevated in proportion to the severity of congestive heart failure. In our patients, the plasma ANP concentration was normal to slightly elevated despite marked elevation of the plasma BNP concentration. Considering the presence of moderate to severe heart failure and significantly increased BNP, ANP secretion was thought to be impaired in our patients. In patients with heart failure, ANP is secreted from the ventricles in addition to the atria.[12] This suggests that ANP production by the atria is more impaired than that predicted from the measured ANP value in our patients.

Long-standing AF leads to reduced ANP production by the atria resulting from atrial structural remodeling and eventually irreversible damage.[13] Plasma ANP concentration inversely correlates with left atrial collagen volume fraction in patients with AF.[14] Therefore, the low ANP secretion in our patients suggests high atrial collagen content and significant atrial structural remodeling.

Atrial standstill

Atrial standstill is a rare disorder caused by injury to the atrium. The diagnosis is established by confirming both electrical silence and mechanical silence of the atria. The following criteria have been proposed for the diagnosis of atrial standstill: [15] Absence of P wave on surface and intracardiac electrocardiograms; absence of *a* wave in the intracardiac pressure record; regular rhythm; and angiographic evidence of immobile atrium. A partial form of atrial standstill has also been reported, which is defined as the absence of electrical activity in a discrete area of the atrium.[16]

In six of our patients, electrocardiography showed bradycardia probably due to partial atrial standstill. In these patients, the AF waves progressively diminished and finally became flattened in all leads, suggesting electrical silence. Our echocardiographic investigation revealed absence of atrial contraction (mechanical silence) in the patients. Furthermore, the RR intervals were mostly regular with junctional escape rhythm. Taken together, the results suggest that the bradycardia in our patients was caused by partial atrial standstill.

Moreover, a low plasma concentration of ANP has been demonstrated in patients with atrial standstill.[17] Attenuated increase in plasma ANP concentration to the increase in BNP concentration has been suggested as a useful marker of atrial standstill.[18] Our patients' plasma ANP data are in agreement with this proposal.

Limitations

Our study has several limitations. First, the number of the patients was small and cases were collected retrospectively. Therefore, it is difficult to estimate the frequency of this clinical entity in the elderly with AF. Also, a moderate degree of functional TR is frequently observed in patients with lone AF and may be an early stage of this syndrome. A longitudinal follow up of a large group of patients with AF is necessary to characterize the patients who present with and without this syndrome. Longer duration of AF, older age, and genetic factors might be related to the occurrence of this syndrome. Second, the echocardiograms were reviewed retrospectively. Therefore, we could not evaluate the severity of TR by quantitative methods such as the PISA method[19] or vena contracta width.[20] In addition, only two-dimensional echocardiography was available which has limitations in characterizing the complex three-dimensional structure of the tricuspid valve. Three-dimensional imaging techniques may provide more accurate information for tricuspid valve geometry such as tethering. Third, none of our patients underwent cardiac surgery to correct TR, so we could not obtain any tissue samples. Histological data to show the presence of atrial cardiomyopathy await further study, although the low serum ANP level in our patients suggests fibrotic change of the atrium.

CONCLUSIONS

Severe functional TR occurs in the elderly with long-standing AF and causes right-sided heart failure. This TR is caused by tricuspid valve systolic coaptation loss due to tricuspid annular dilation. This condition is associated with atrial abnormalities, such as atrial standstill and impaired ANP secretion. We propose that atrial remodeling associated with AF is central to the occurrence of this syndrome. This syndrome warrants further recognition.

要　約

高齢者における重症三尖弁閉鎖不全症: 長期持続する心房細動による心房リモデリングとの関連

山崎　直仁　近藤　史明　久保　亨　大川　真理　松村　敬久
北岡　裕章　矢部　敏和　古野　貴志　土居　義典

目　的: 高齢者において明らかな基礎疾患を有しない特発性の重症三尖弁閉鎖不全症が存在することが報告されている．しかし，三尖弁閉鎖不全を生じる機序は明らかではなく，また本症での心房の異常について検討した報告は少ない．本研究では，特発性重症三尖弁閉鎖不全症患者の臨床的特徴を明らかにすることを目的とする．

方　法: 心エコー図検査を施行した連続16,235例のうち，基礎疾患を有しない重症三尖弁閉鎖不全症の患者は11例存在した．これらの患者において，心エコー図，心電図，採血データなどの臨床データの検討を行った．

結　果: 患者の平均年齢は78歳で，11例全例が長期(平均23年)持続する心房細動を有していた．これらの患者は，1）弁輪拡大のため重症の三尖弁閉鎖不全症を有する，2）著明な右心房の拡大が認められる，3）右心不全を繰り返し生じる，4）心電図において心房細動波(f波)が減高し消失している，5）部分的心房停止による徐脈が認められ，一部の患者では恒久的ペースメーカー植え込みを必要とする，6）心房性ナトリウム利尿ペプチドの分泌低下が認められる，といった共通の臨床的特徴を有しており，一つの症候群と考えられた．三尖弁閉鎖不全が重症化していく過程を長期間にわたり観察しえた症例では，心房細動に伴う三尖弁輪径の経時的な拡大に伴い，初期には軽度であった三尖弁逆流が重症化した．

結　論: 長期間持続する心房細動のために重症の三尖弁閉鎖不全を生じ，右心不全症状を呈する高齢者の一群が存在する．三尖弁閉鎖不全の原因は，心房細動により三尖弁輪が拡大する結果生じる三尖弁の接合不全である．本症では心房の機能異常を伴っており，部分心房停止，心房性ナトリウム利尿ペプチドの分泌不全が認められる． 長期間持続する心房細動に伴う心房のリモデリングが本症候群の発生に深く関係していると考えられる．

J Cardiol 2006 Dec; 48(6): 315−323

References

1）Kasai A, Nishikawa H, Ono N, Unno M, Kakuta Y, Hamada M, Nakano T: Clinical evaluation of severe idiopathic tricuspid regurgitation. J Cardiol 1990; **20**: 937−944(in Jpn with Eng abstr)

2）Iga K, Konishi T, Matsumura T, Miyamoto T, Kijima K, Gen H: Markedly enlarged right atrium associated with physical signs of tricuspid regurgitation: A cause of congestive heart failure in the elderly. Jpn Circ J 1994; **58**: 683−688

3）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

4）Zhou X, Otsuji Y, Yoshifuku S, Yuasa T, Zhang H, Takasaki K, Matsukida K, Kisanuki A, Minagoe S, Tei C: Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. Circ J 2002; **66**: 913−916

5）Kaul S, Tei C, Hopkins JM, Shah PM: Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984; **107**: 526−531

6）Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, Reeder GS, Nishimura RA, Tajik AJ: Continuous wave Doppler determination of right ventricular pressure: A simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985; **6**: 750−756

7）Lin G, Nishimura RA, Connolly HM, Dearani JA, Sundt TM Ⅲ, Hayes DL: Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. J Am Coll Cardiol 2005; **45**: 1672−1675

8）Otsuji Y, Kumanohoso T, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, Minagoe S, Levine RA, Tei C: 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

9）Allessie M, Ausma J, Schotten U: Electrical, contractile and structural remodeling during atrial fibrillation.

Cardiovasc Res 2002; **54**: 230−246
10) Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, Weyman AE: Atrial enlargement as a consequence of atrial fibrillation: A prospective echocardiographic study. Circulation 1990; **82**: 792−797
11) Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K: Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994; **90**: 195−203
12) Tsuchimochi H, Yazaki Y, Ohno H, Takanashi R, Takaku F: Ventricular expression of atrial natriuretic peptide. Lancet 1987; Ⅱ: 336−337
13) van den Berg MP, van Gelder IC, van Veldhuisen DJ: Depletion of atrial natriuretic peptide during longstanding atrial fibrillation. Europace 2004; **6**: 433−437
14) Yoshihara F, Nishikimi T, Sasako Y, Hino J, Kobayashi J, Minatoya K, Bando K, Kosakai Y, Horio T, Suga S, Kawano Y, Matsuoka H, Yutani C, Matsuo H, Kitamura S, Ohe T, Kangawa K: Plasma atrial natriuretic peptide concentration inversely correlates with left atrial collagen volume fraction in patients with atrial fibrillation: Plasma ANP as a possible biochemical marker to predict the outcome of the maze procedure. J Am Coll Cardiol 2002; **39**: 288−294
15) Bloomfield DA, Sinclair-Smith BC: Persistent atrial standstill. Am J Med 1965; **39**: 335−340
16) Levy S, Pouget B, Bemurat M, Lacaze JC, Clementy J, Bricaud H: Partial atrial electrical standstill: Report of three cases and review of clinical and electrophysiological features. Eur Heart J 1980; **1**: 107−116
17) Seino Y, Shimai S, Ibuki C, Itoh K, Takano T, Hayakawa H: Disturbed secretion of atrial natriuretic peptide in patients with persistent atrial standstill: Endocrinologic silence. J Am Coll Cardiol 1991; **18**: 459−463
18) Suguta M, Hara K, Nakano A, Amano A, Hasegawa A, Kurabayashi M: Serum atrial natriuretic peptide concentration is a useful predictor of atrial standstill in patients with heart failure. Jpn Circ J 2000; **64**: 537−540
19) Grossmann G, Stein M, Kochs M, Hoher M, Koenig W, Hombach V, Giesler M: Comparison of the proximal flow convergence method and the jet area method for the assessment of the severity of tricuspid regurgitation. Eur Heart J 1998; **19**: 652−659
20) Tribouilloy CM, Enriquez-Sarano M, Bailey KR, Tajik AJ, Seward JB: Quantification of tricuspid regurgitation by measuring the width of the vena contracta with Doppler color flow imaging: A clinical study. J Am Coll Cardiol 2000; **36**: 472−478