Ventricular Tachyarrhythmia Associated with Cardiac Sarcoidosis: Its Mechanisms and Outcome

HIROSHI FURUSHIMA, M.D., MASAOMI CHINUSHI, M.D., HIROTAKA SUGIURA, M.D., HIDEHIRO KASAI, M.D., TAKASHI WASHIZUKA, M.D., YOSHIFUSA AIZAWA, M.D.

The First Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan

Summary

Background: Cardiac sarcoidosis is increasingly recognized and is associated with poor prognosis. Ventricular tachycardia (VT) associated with cardiac sarcoidosis is the most likely cause of sudden death in most patients, but the mechanism has not been well established.

Hypothesis: This study investigated the mechanisms and outcome of VT associated with cardiac sarcoidosis.

Methods: The study included eight consecutive patients (five men, three women, aged 54 ± 19 years) who had sustained monomorphic VT associated with cardiac sarcoidosis in our hospital.

Results: The average ejection fraction was $43 \pm 11\%$. Twenty-two VTs were observed in these patients, and mean heart rate during VT was 192 ± 29 beats/min (range 144–259). The phenomenon of transient entrainment was documented in 10 of 22 (45%) VTs by ventricular pacing (eight in the active phase). Another five (23%) VTs could not be entrained, but could be initiated by programmed stimulation and terminated by rapid pacing, reproducibly. In 3 of the 22 (14%) VTs, cardioversion was required urgently because of the fast rate, while the remaining 4 (18%) could be induced during electrophysiologic study.

Conclusions: In this study, there was a high possibility that the mechanism of 15 (68%) VTs was reentry. Reentrant substrate is formed not only in association with the healing of cardiac granulomas in the inactive phase of cardiac sarcoidosis but also in the active phase. Ventricular tachycardia with car-

diac sarcoidosis, even if this mechanism is reentry, has different inducibility between the active and inactive phases in an electrophysiologic study. This makes the therapy for cardiac sarcoidosis (e.g., corticosteroids, antiarrhythmic agents, and catheter ablation) difficult. The implantable cardioverter-defibrillator is an effective treatment for ventricular tachyarrhythmia with cardiac sarcoidosis.

Key words: cardiac sarcoidosis, ventricular tachycardia, electrophysiologic test, reentry

Introduction

Cardiac sarcoidosis has been recognized increasingly and is associated with poor prognosis.^{1–6} In the series by Roberts *et al.*, sudden death was the most common manifestation of cardiac sarcoidosis, involving more than 60% of patients.⁷ Sudden death was associated with a complete heart block in 40% of patients and ventricular tachyarrhythmias were noted in the rest. However, the mechanism by which ventricular tachyarrhythmias develop in patients with cardiac sarcoidosis has not been well clarified. We recently demonstrated the phenomenon of transient entrainment in monomorphic sustained ventricular tachycardia (VT) associated with cardiac sarcoidosis,⁸ which implies reentry as the mechanism. Corticosteroids have been used extensively in patients with cardiac sarcoidosis^{9–11} and are thought to heal cardiac granulomas.¹² However, in most patients, ventricular arrhythmias remain even if cardiac functions are ameliorated by treatment with corticosteroids. On the other hand, it has not been well established whether VT in the active phase of cardiac sarcoidosis is due to reentry. This study investigated the mechanisms of VT and the outcome of eight patients who had cardiac sarcoidosis.

Methods

Patients and Clinical Characteristics (Table I)

This study included eight consecutive patients (five men, three women, aged 54 ± 19 years) with VT associated with car-

Address for reprints:

Hiroshi Furushima, M.D.
First Department of Internal Medicine
Niigata University School of Medicine
1-754 Asahi-machi-dori
Niigata, 951-8510 Japan
e-mail: chimiri@med.niigata-u.ac.jp

Received: February 3, 2003

Accepted with revision: April 24, 2003

TABLE I Characteristics of eight patients with cardiac sarcoidosis

Patient No.	Age (years)	Sex	ACE	Lys	BHL	Biopsy	Uptake on ⁶⁷ Ga citrate	Conduction block	Echocardiogram	LVEF (%)
1	57	F	20.1	11.2	(-)	Lung (TBLB)	Lung, heart	cAVB	Thinning of IVS	36
2	23	M	42.1	15.5	(-)	Cervical lymph	BH	RBBB	Diffuse hypokinesis	50
3	71	M	28.1	12.3	(+)	Lung (TBLB)	BH, heart	RBBB	Increased thickness of IVS	50
4	29	M	19.8	9.7	(-)	Myocardium	BH, heart	RBBB+RAD	Thinning of IVS	20
5	50	M	28.9	14.7	(+)	Lung (TBLB)	BH, mediastinal lymph	RBBB	Thinning of IVS	48
6	65	M	24.0	6.0	(+)	Lung (TBLB)	(-)	LBBB	Multiple aneurysm	51
7	72	F	22.6	17.8	(-)	Skin	Lung, heart	cAVB	Diffuse hypokinesis	49
8	64	F	17.7	13.9	(-)	Inguinal lymph	Lung, heart	RBBB	Regional hypokinesis	40

Abbreviations: (-) = negative, (+) = positive, ACE = angiotensin-converting enzyme (7.0 to 25.0 U/l), Lys = lysozyme (5.0 to 10.0 µg/ml), BHL = bilateral, lymph = lymphadenopathy, BH = bilateral hilum, TBLB = transbronchial lung biopsy, LVEF = left ventricular ejection fraction, RBBB = right bundle-branch block, RAD = right axis deviation, LBBB = left bundle-branch block, cAVB = complete atrioventricular block, IVS = intraventricular septum.

diac sarcoidosis. All patients had conduction abnormalities: right bundle-branch block in four, bifascicular block in one, left bundle-branch block in one, and complete atrioventricular block in two. Bilateral hilar and mediastinal lymphadenopathy were found on chest roentgenograms or chest computed tomography in five patients. Serum angiotensin-converting enzyme (ACE) and lysozyme values were 25.4 ± 7.8 IU/l and 12.6 ± 3.7 µg/ml, respectively (normal ranges are shown in Table I). Three patients had elevated levels of both ACE and lysozyme, three had elevated lysozyme, and the remaining two had normal values. All patients had echocardiographic abnormalities: a thinning of the interventricular septum in three, increased thickness of the interventricular septum in one, multiple ventricular aneurysms in one, diffuse hypokinesis of the left ventricle in two, and regional hypokinesis of the left ventricle in one; ejection fraction of the left ventricle was reduced to $43 \pm 11\%$. All patients but one had abnormal accumulations of gallium-67 citrate in the heart and/or lung. Histopathologic findings specific for sarcoidosis (i.e., noncaseating granulomas composed of epithelioid and giant cells) were noted in all patients; they were evident in the biopsy specimens from the lung in four patients, and from the myocardium, the cervical or inguinal lymph nodes, or the skin, in one patient each. The criteria for the diagnosis of cardiac sarcoidosis was based on the *Handbook of the Diagnosis of Cardiac Sarcoidosis*, prepared by the Specific Diffuse Pulmonary Disease Research Group, Sarcoidosis Division, organized by the Japanese Ministry of Health and Welfare.¹³ Activity of cardiac sarcoidosis was evaluated by gallium scanning: abnormal accumulation of gallium in the heart indicates the active phase, and no accumulation of gallium in the heart indicates the inactive phase.¹⁴

Electrophysiologic Study

After obtaining informed consent, a standard electrophysiologic study (EPS) was performed. For the control study, all antiarrhythmic drugs were discontinued for at least five half-lives prior to the study. The induction protocol for VT consisted

of one to three extrastimuli and rapid ventricular pacing up to the rate of 210 beats/min delivered at two right ventricular and one left ventricular site. When ventricular tachyarrhythmia could not be induced, isoproterenol was infused to increase heart rate by 20% and the protocol was repeated. When sustained monomorphic VT was induced, rapid ventricular pacing at a cycle length 10–20 ms shorter than the cycle length of the VT was applied in an attempt to entrain it. Pacing was repeated after decrementing the paced cycle length by steps of 10 ms until VT was interrupted or VT acceleration occurred.¹⁵ Criteria of transient entrainment in earlier studies included constant fusion, progressive fusion, and localized block.^{16,17}

Definitions

We classified monomorphic sustained VT into three types, as follows:

Type A: Ventricular tachycardia in which transient entrainment was demonstrated during EPS

Type B: Ventricular tachycardia in which transient entrainment was not demonstrated during EPS but could be initiated by programmed stimulation and could be terminated by rapid pacing, reproducibly

Type C: Ventricular tachycardia in which rapid pacing during VT could not be performed or induced during EPS, reproducibly.

Endocardial Mapping and Radiofrequency Catheter Ablation

The site of VT origin was determined as the critical slow conduction site during VT using a steerable 7 French quadripolar electrode catheter with a 4 mm tip electrode (Marina, Medtronic, Inc., Minneapolis, Minn., USA).¹⁸ If an abnormal local electrogram, such as mid-diastolic potential or continuous activity, was recorded during VT, rapid pacing was performed and the central common slow pathway of the reentry

TABLE II Inducibility in the active and inactive phases with cardiac sarcoidosis

Patient No.	EPS in active phase			EPS in inactive phase		
	Inducible VT	No inducible VT	Reentry	Inducible VT	No inducible VT	Reentry
1	1	1	1	2	—	2
2	—	—	—	0	1	—
3	1	1	1	0	—	—
4	0	1	—	0 (poly VT)	—	—
5	0	1	—	3	—	1
6	—	—	—	2	1	2
7	3	0	3	2	—	2
8	3	1	3	—	—	—

Abbreviations: EPS = electrophysiologic study, VT = ventricular tachycardia.

circuit was determined.^{19, 20} Radiofrequency currents were produced using a temperature-controlled radiofrequency ablation unit (Medtronic, Inc).

Data Analysis

Values are expressed as mean $\pm$ standard deviation (SD).

Results

Electrophysiologic Findings and Ventricular Tachycardia

Twenty-two sustained monomorphic VTs were obtained in eight patients, and mean heart rate during VT was $192 \pm$

29 beats/min (range 144–259). There were 13 right bundle-branch block patterns and 9 left bundle-branch block patterns. Of 22 VTs, 12 were detected clinically, whereas the remaining 10 VTs induced by extrastimulation were nonclinical. In the active phase, eight sustained monomorphic VTs were induced in four patients under EPS (Table II), while five spontaneous VTs were not induced (Table II). Of eight VTs, six were classified as Type A (Fig. 1) and two were classified as Type B. In the inactive phase, nine sustained monomorphic VTs were induced in four patients and polymorphic VT was induced in one patient; there were two spontaneous (i.e., not induced) VTs (Table II). Ventricular tachyarrhythmia was not induced in two patients. Of nine VTs, four were of Type A, three were of Type B, and two were of Type C. The two VTs (one in each of two patients) not induced in EPS emerged clinically during tapered prednisolone (Type C).

FIG. 1 Entrainment of ventricular tachycardia (VT) from the apex of the right ventricle (RVA). Ventricular tachycardia with a cycle length of 400 ms was entrained with rapid ventricular pacing at cycle lengths of 380 and 350 ms, and terminated by ventricular pacing at a cycle length of 330 ms. Constant fusion and progressive fusion are evident. The return cycle in the local electrogram at the site of the earliest activation in the outflow of the right ventricle (MAP) is identical to each paced cycle length, and its morphology during pacing is identical to that during VT. VTCL = ventricular tachycardia cycle length, PCL = pacing cycle length, HBE = His bundle site.

TABLE III Treatment, efficacy, and outcome of cardiac sarcoidosis and ventricular tachycardia

Patient No.	Prednisolone initial dose (mg)	Improvement in ⁶⁷ Ga citrate	AA	RF therapy	Efficacy of EPS	ICD therapy	ICD delivery	Outcome
1	40	(+)	Mexiletine	(-)	NE	(+)	(+)	12 m alive
2	40	(+)	—	(-)	NE	(+)	(-)	18 m alive
3	60	(+)	Pilsicainide	(-)	E	(-)	—	85 m alive
4	50	(+)	—	(-)	E	(-)	—	12 m after SD
5	60	(+)	DL-sotalol	(-)	NE	(+)	(+)	49 m alive
6	—	—	DL-sotalol	(-)	NE	(+)	(+)	17 m alive
7	40	(+)	Mexiletine	(+)	NE	(+)	(+)	16 m alive
8	40	(+)	DL-sotalol	(+)	—	(+)	(-)	12 m alive

Abbreviations: RF = radiofrequency, EPS = electrophysiologic study, ICD = implantable cardioverter defibrillator, AA = antiarrhythmic agent, E = effective, NE = not effective, m = months, SD = sudden death.

Treatment and Outcome for Cardiac Sarcoidosis and Ventricular Tachycardia and Outcome (Table III)

In seven of eight patients, prednisolone at dosages of 40–60 mg/day were started and tapered gradually (by 5–10 mg every 2–4 weeks) to maintenance dosages of 10–15 mg/day. All seven patients who underwent treatment with prednisolone showed disappearance of abnormal accumulation of gallium 67 citrate. Two patients received only prednisolone administration. The other patients were prescribed antiarrhythmic agents (mexiletine in two, dl-sotalol in three, and pilsicainide in one) in addition to concomitant prednisolone because of incessant VT or rapid nonclinical VT during EPS.

Two patients who had no inducibility of ventricular tachyarrhythmia at EPS during the low active phase of sarcoidosis during prednisolone administration continued to be treated with prednisolone only or prednisolone and an antiarrhythmic agent. While all patients who had inducibility of ventricular tachyarrhythmia in the inactive phase were implanted with a defibrillator (ICD), Case No. 8, who did not have EPS in the inactive phase, also underwent ICD implantation. In two patients, however, catheter ablation was effective on some induced VTs of Type A (Fig. 2); other different VTs were induced in the inactive phase. Ventricular tachycardias on which catheter ablation was performed did not recur. The average period of observation was 23 ± 27 months (3–72). One patient who could not be induced died suddenly. The other patients survived, with four receiving repeat ICD treatment.

Discussion

Ventricular tachycardia is one of the most frequently reported major cardiac arrhythmias^{4,6,7,21} and is presumed to be the cause of sudden death in most patients with cardiac sarcoidosis. Sarcoid granulomas might become the foci for abnormal automaticity or may serve to disperse both ventricular activation and recovery processes that can cause reentrant arrhythmias. In addition, it is possible that the healing of the granulomas caused by corticosteroid treatment provides the substrate

for the development of reentrant arrhythmias. In the present study, there was a high possibility that the mechanism of 15 of 22 VTs (68%) was reentry (Type A + Type B), and most reentrant VTs were induced in the active phase of cardiac sarcoidosis. This suggests that the slow conduction zone might be growing not only during the healing stage in the inactive phase but also in active granulomatous inflammation. In previous studies, the mechanisms of VT with cardiac sarcoidosis were seldom referred to because VT inducibility was unstable.²² In the present study, spontaneous VT in the active phase, confirmed to be a reentrant mechanism in EPS during the healing stage, was not induced in EPS in the active phase (Case No. 5). In previous studies and the present one, we investigated the reproducibility of transient entrainment as well as inducibility and termination of VT with cardiac sarcoidosis by ventricular rapid pacing in EPS,^{8,23} and suggested that most VTs were reentrant, except for incessant VT (especially that occurring immediately after the start of prednisolone administration). Two VTs (11%) were suggested to be due to abnormal automaticity because of incessantly unstable R-R interval, noninducibility in EPS, and emergence at the beginning of prednisolone treatment. This suggests that attention should be paid to ventricular tachyarrhythmia at the beginning of prednisolone therapy.

Reentrant VTs with cardiac sarcoidosis were variable after becoming inactive due to corticosteroids; however, cardiac function and conduction disturbance improved.^{22,24} This variable effect of corticosteroids on reentrant VT often makes its treatment difficult. In the present study, one patient died suddenly in spite of experiencing no induction of ventricular tachyarrhythmia in the inactive phase under EPS.

Recently, it was reported that in high-risk patients with coronary artery disease, electrophysiologically guided antiarrhythmic therapy without ICD implantation did not reduce the risk of sudden death.²⁵ According to our study, ventricular tachyarrhythmia with cardiac sarcoidosis may also make the predictive value of programmed electrical stimulation-guided pharmacologic therapy less accurate. In addition, ventricular fibrillation has been reported in several cases of cardiac sarcoidosis during an inactive phase.^{1,26,27} In the present study,

FIG. 2 A–C show tracings of ventricular tachycardia (VT). The findings in (A) are consistent with pacing at a site in the reentry circuit. From the top of each tracing, the surface electrocardiographic leads I, II, V₁, and His bundle site (HBE) are shown; intracardiac recording was from the apex of the right ventricle (RVA), the distal site of the ablation catheter electrode (ABLd), and the proximal site of the ablation catheter electrode (ABLp). Sustained monomorphic VT exhibits a cycle length of 420 ms. A vertical line indicates the QRS onset in (A) and (B). In (A), the last four beats of a train of stimuli at a cycle length of 350 ms are shown. The VT is continually reset without an alteration in the QRS morphology consistent with entrainment with concealed fusion. The S-QRS interval is 110 ms. An electrogram could not be recorded from the distal catheter ablation electrode during pacing, and the postpacing interval therefore could not be obtained. In (B), diastolic potential (DP, arrow) is recorded from the ABLd 110 ms preceding the QRS onset. In (C), catheter ablation is applied to VT after three beats (an arrow indicates the start of the radiofrequency current [RF]), with restoration of sinus rhythm.

one patient had polymorphic VT at EPS in the inactive phase. Ventricular fibrillation is probably the final event in many of the cases that present with sudden death and, as such, is clinically underdiagnosed. It is suggested that the ICD is an effective alternative in the face of a changing myocardial substrate and provides a more reliable therapeutic option for patients with cardiac sarcoidosis.

Conclusions

In the present study, we demonstrated that 68% of VT associated with cardiac sarcoidosis could be due to reentry. However, the reproducibility of most of these cases of reentrant VT was unstable. This makes the treatment for VT in cardiac sarcoidosis difficult. Nevertheless, the ICD is an effective treatment for ventricular tachyarrhythmia with cardiac sarcoidosis.

References

1. Matsui Y, Iwai K, Tachibana T, Shigematsu N, Izumi T, Homma AH, Mikami R, Hongo O, Hiraga Y, Yamamoto M: Clinicopathological study on fatal myocardial sarcoidosis. *Ann NY Acad Sci* 1975;278:455–469
2. Porter GH: Sarcoid heart disease. *N Engl J Med* 1960;263:1350–1357
3. Gozo EJ Jr, Cosnow I, Cohen HC, Okun L: The heart in sarcoidosis. *Chest* 1971;60:379–388
4. Fleming HA: Sarcoid heart disease. *Br Heart J* 1974;36:54–58
5. Phinney AU Jr: Sarcoid of the myocardial septum with complete heart block: Report of two cases. *Am Heart J* 1961;62:270–276
6. Bashour FA, McConnell J, Skinner W, Hanson M: Myocardial sarcoidosis. *Dis Chest* 1968;53:413–420
7. Roberts WC, McAllister HA, Ferrans VJ: Sarcoidosis of the heart: A clinicopathologic study of 35 necropsy patients (group I) and review of 78 previously described necropsy patients (group II). *Am J Med* 1977;63:86–105
8. Chinushi M, Mezaki T, Aoki Y, Nakagawa I, Washizuka T, Aizawa Y: Demonstration of transient entrainment in monomorphic sustained ventricular tachycardia associated with cardiac sarcoidosis. *Jpn Circ J* 2000;64:635–637
9. Ishikawa T, Kondoh H, Nakagawa S, Koiwaya Y, Tanaka K: Steroid therapy in cardiac sarcoidosis: Increased left ventricular contractility concomitant with electrocardiographic improvement after prednisolone. *Chest* 1984;85:445–447
10. Shammas RL, Movahed A: Sarcoidosis of the heart. *Clin Cardiol* 1993;16:462–472
11. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M: Cardiac sarcoidosis: Diagnostic, prognostic, and therapeutic considerations. *Cardiovasc Drugs Ther* 1996;10:495–510
12. James TN: Sarcoid heart disease: Clinicopathologic correlations. *Circulation* 1977;56:320–326
13. Disease Control Division, Health Service Bureau, Ministry of Health and Welfare. A manual of diagnosis and therapy for the intractable diseases for general practitioner, p. 77 (in Japanese). Tokyo: Roppoh, 1990
14. Palevsky HI, Alavi A: Gallium-67-citrate scanning in the assessment of disease activity in sarcoidosis. *J Nucl Med* 1992;33:751–755

15. Aizawa Y, Niwano S, Chinushi M, Tamura M, Kusano Y, Miyajima T, Kitazawa H, Shibata A: Incidence and mechanism of interruption of reentrant ventricular tachycardia with rapid pacing. *Circulation* 1992;85:589–595
16. Waldo AL, Henthorn RW, Plumb VJ, MacLean WA: Demonstration of the mechanism of transient entrainment and interruption of ventricular tachycardia with rapid atrial pacing. *J Am Coll Cardiol* 1984;3:422–430
17. Okumura K, Olshansky B, Henthorn RW, Epstein AE, Plumb VJ, Waldo AL: Demonstration of the presence of slow conduction during sustained ventricular tachycardia in man: Use of entrainment of the tachycardia. *Circulation* 1987;75:369–378
18. Chinushi M, Aizawa Y, Kusano Y, Washizuka T, Miyajima T, Naitho N, Takahashi K, Shibata A: Radiofrequency current catheter ablation for ventricular tachycardia. *Jpn Circ J* 1994;58:315–325
19. Morady F, Kadish A, Rosenheck S, Calkins H, Kou WH, deBuitler M, Sousa J: Concealed entrainment as a guide for catheter ablation of ventricular tachycardia in patients with prior myocardial infarction. *J Am Coll Cardiol* 1991;49:207–220
20. Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, Wiener I: Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993; 88(part 1):1647–1670
21. Fleming HA: Sarcoid heart disease: A review and an appeal. *Thorax* 1980; 35:641–643
22. Paz HL, McCormick DJ, Kutalek SP, Patchefsky A: The automated implantable cardiac defibrillator. *Chest* 1994;106:1603–1607
23. Mezaki T, Chinushi M, Washizuka T, Furushima H, Chinushi Y, Ebe Katuya, Okumura H, Aizawa Y: Discrepancy between inducibility of ventricular tachycardia and activity of cardiac sarcoidosis—requirement of defibrillator implantation for the inactive stage of cardiac sarcoidosis. *Intern Med* 2001;40:731–735
24. Lorell B, Alderman EL, Mason JW: Cardiac sarcoidosis: Diagnosis with endomyocardial biopsy and treatment with corticosteroids. *Am J Cardiol* 1978;42:143–146
25. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G: A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–1890
26. Stein E, Stimmel B, Siltzbach LE: Clinical course of cardiac sarcoidosis. *Ann NY Acad Sci* 1976;278:470–474
27. Tornling G, Olsson G, von Unge H: Ventricular fibrillation in myocardial sarcoidosis. *Eur J Respir Dis* 1985;66:347–349

Clin. Cardiol. 27, 222 (2004)

Images edited by Richard A. Kerensky, M.D.

Images in Cardiology: Accidental Perforation of the Left Ventricle during Angiography

MARTIN BRUECK, M.D., WILFRIED KRAMER, M.D., JOSEF LUDWIG, M.D.

Department of Cardiology, Clinic of Wetzlar-Braunfels, Wetzlar, Germany

FIGS. 1 and 2 Perforation of the left ventricle during angiography. See text for explanation.

A 67-year-old woman underwent left heart catheterization due to dyspnea. A multipurpose catheter was used for ventriculography due to calcification of the aortic valve. During injection, the multipurpose catheter penetrated the myocardium and contrast dye was injected into the myocardium and pericardium. The mechanical pressure pushed the contrast dye through the myocardium, filling the middle cardiac vein and opacifying the coronary sinus. A small amount of contrast entered the pericardium (Fig. 1). The patient was asymptomatic.

Aortography performed 30 min later revealed persistent intramyocardial retention of injected contrast dye (Fig. 2).

Reference

- Metz V, Farres MT, Grabenwoger F: Perforation of the right ventricle during pulmonary angiography: Possible causes and their prevention. *Rontgenblätter* 1989;42:92–94