creased as the stage of AKI advanced, and overall mortality in patients with AKI was 15%, which was 7.5-fold higher as compared to those without AKI (2%).[19]

Comorbid factors and the severely ill condition of patients with AKI are at least in part responsible for the higher mortality of these patients. Even after adjusting these factors, however, AKI remains as an independent predictor of mortality in AMI patients. Previous studies have suggested that AKI can affect the heart through several pathways.[24–26]

Predictors of AKI in AMI

Worsening of renal function may have negative effects on heart and circulation, resulting in higher mortality after AMI in patients with AKI.[27] In turn, a rapid worsening of cardiac function may lead to AKI. The concept of cardiorenal syndrome (CRS) has become widely accepted in recent years.[17,28] The latter condition, characterized by initiation and/or progression of renal insufficiency secondary to heart failure, is the most common type of CRS, but its mechanisms are multiple and complex.

Acute decline in renal function is not simply due to decreased renal blood flow; acceleration in cardiovascular pathobiology through activation of inflammatory pathways is considerably responsible for the development of AKI. In patients with AMI, neurohormonal, immunological and inflammatory pathways are activated, resulting in kidney injury.[28] Inflammatory biomarkers, including pentraxin 3, interleukin-1 and -6, tumor necrotic factor-α and so on, have been shown to be associated with AKI.[29–31]

Recently, several studies have focused on the importance of acute hyperglycemia as a determinant of outcome in patients with AMI. Elevation of PG on admission, acute hyperglycemia, is a common feature early after AMI, even in the absence of diabetes mellitus.[7,8,11,12] Numerous studies have described the association between acute hyperglycemia and adverse outcome in patients with AMI. Multiple physiological studies have shown that hyperglycemia has a direct detrimental effect on ischemic myocardium through several mechanisms, including oxidative stress, inflammation, apoptosis, endothelial dysfunction, hypercoagulation, and platelet aggregation.[14–16]

Brief episodes of antecedent myocardial ischemia have protective effects against subsequent prolonged ischemia, termed 'ischemic preconditioning'. Such effects are also generated by brief intermittent ischemia after the ischemic event (post-conditioning) and observed even in remote organs (remote conditioning). A recent study has reported that remote post-conditioning prevents the development of AKI after PCI.[32] We have previously reported that admission hyperglycemia abolishes ischemic preconditioning.[33,34] It may also attenuate renoprotective effects of ischemic preconditioning in patients with AMI.

Previous clinical studies have reported that elevated PG is associated with worsening of renal function after cardiac surgery or coronary angiography.[21,35] In the current study, patients with elevated glucose on admission were at higher risk of death during hospitalization for AMI, regardless of the use of coronary angiography or primary PCI. Although it remains unknown whether hyperglycemia is causally related to deterioration of kidney function, the positive relationship between admission glucose and the development of AKI remained significant even after adjusting potential confounding factors, suggesting that hyperglycemia is not a simple surrogate marker of AKI.

Study Limitations

The present results should be interpreted in the context of several potential limitations. First, the present study was a single-center and retrospective study. We did not obtain sufficient data on contrast medium volume to analyze the relationship between volume of contrast medium and AKI. Second, the mechanisms by which acute hyperglycemia is correlated with AKI in AMI patients remained unclear. The relationship between acute hyperglycemia and systemic inflammatory responses, and the mechanisms of kidney injury following AMI should be analyzed in basic and clinical studies in the future.

Conclusions

Admission hyperglycemia could be an independent predictor for AKI in AMI patients. Careful monitoring of renal function should be done for patients with AMI and admission hyperglycemia.

Disclosures

There is no financial support for this study.

References

1. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: A cohort study. *Lancet* 2010; **376:** 2096–2103.
2. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 2009; **53:** 961–973.
3. Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M, et al; Osaka Acute Coronary Insufficiency Study (OACIS) Investigators. Incidence, predictors, and subsequent mortality risk of recurrent myocardial infarction in patients following discharge for acute myocardial infarction. *Circ J* 2013; **77:** 439–446.
4. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol* 2006; **17:** 2886–2891.
5. Stolker JM, McCullough PA, Rao S, Inzucchi SE, Spertus JA, Maddox TM, et al. Pre-procedural glucose levels and the risk for contrast-induced acute kidney injury in patients undergoing coronary angiography. *J Am Coll Cardiol* 2010; **55:** 1433–1440.
6. Amin AP, Salisbury AC, McCullough PA, Gosch K, Spertus JA, Venkitachalam L, et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch Intern Med* 2012; **172:** 246–253.
7. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol* 2002; **40:** 1748–1754.
8. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet* 2000; **355:** 773–778.
9. Teraguchi I, Imanishi T, Ozaki Y, Tanimoto T, Kitabata H, Ino Y, et al. Impact of stress hyperglycemia on myocardial salvage following successfully recanalized primary acute myocardial infarction. *Circ J* 2013; **76:** 2690–2696.
10. Ishihara M. Acute hyperglycemia in patients with acute myocardial infarction. *Circ J* 2012; **76:** 563–571.
11. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Nishioka K, Uemura T, et al. Impact of acute hyperglycemia on left ventricular function after reperfusion therapy in patients with a first anterior wall acute myocardial infarction. *Am Heart J* 2003; **146:** 674–678.
12. Ishihara M, Kojima S, Sakamoto T, Kimura K, Kosuge M, Asada Y, et al. Comparison of blood glucose values on admission for acute myocardial infarction in patients with versus without diabetes mellitus. *Am J Cardiol* 2009; **104:** 769–774.
13. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: Role of oxidative stress. *Circulation* 2002; **106:** 2067–2072.
14. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation* 1998; **97:** 1695–1701.

15. Stegenga ME, van der Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP, et al. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes* 2006; **55:** 1807–1812.
16. Sakamoto T, Ogawa H, Kawano H, Hirai N, Miyamoto S, Takazoe K, et al. Rapid change of platelet aggregability in acute hyperglycemia. Detection by a novel laser-light scattering method. *Thromb Haemost* 2000; **83:** 475–479.
17. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52:** 1527–1539.
18. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11:** R31.
19. Goldberg A, Hammerman H, Petcherski S, Zdorovyak S, Yalonetsky S, Kapeliovich M, et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J* 2005; **150:** 330–337.
20. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Wiviott SD. Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: A report from the national cardiovascular data registry. *Circulation* 2012; **125:** 497–504.
21. Naruse H, Ishii J, Hashimoto T, Kawai T, Hattori K, Okumura M, et al. Pre-procedural glucose levels and the risk for contrast-induced acute kidney injury in patients undergoing emergency coronary intervention. *Circ J* 2012; **76:** 1848–1855.
22. Tehrani S, Laing C, Yellon DM, Hausenloy DJ. Contrast-induced acute kidney injury following PCI. *Eur J Clin Invest* 2013; **43:** 483–490.
23. Abe D, Sato A, Hoshi T, Kakefuda Y, Watabe H, Ojima E, et al. Clinical predictors of contrast-induced acute kidney injury in patients undergoing emergency versus elective percutaneous coronary intervention. *Circ J* 2013; **78:** 85–91.
24. Krishnagopalan S, Kumar A, Parrillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. *Curr Opin Crit Care* 2002; **8:** 376–388.
25. Chen D, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med* 2008; **36:** S9–S16.
26. Selby NM, McIntyre CW. The acute cardiac effects of dialysis. *Semin Dial* 2007; **20:** 220–228.
27. Hsieh MJ, Chen YC, Chen CC, Wang CL, Wu LS, Wang CC. Renal dysfunction on admission, worsening renal function, and severity of acute kidney injury predict 2-year mortality in patients with acute myocardial infarction. *Circ J* 2013; **77:** 217–223.
28. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: Pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012; **60:** 1031–1042.
29. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; **109:** 1594–1602.
30. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol* 2002; **86:** 123–130.
31. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000; **102:** 3060–3067.
32. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, et al. Effect of acute hyperglycemia on the ischemic preconditioning effect of prodromal angina pectoris in patients with a first anterior wall acute myocardial infarction. *Am J Cardiol* 2003; **92:** 288–291.
33. Deftereos S, Glannopoulos G, Tzalamouras V, Raisakis K, Kossyvakis C, Kaoukis A, et al. Renoprotective effect of remote ischemic postconditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013; **61:** 1949–1955.
34. Kersten JR, Schmeling TJ, Orth KG, Pagel PS, Warltier DC. Acute hyperglycemia abolishes ischemic preconditioning in vivo. *Am J Physiol* 1998; **275:** H721–725.
35. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, William BA, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc* 2005; **80:** 862–866.

Catheter closure of patent foramen ovale in patients with cryptogenic cerebrovascular accidents: initial experiences in Japan

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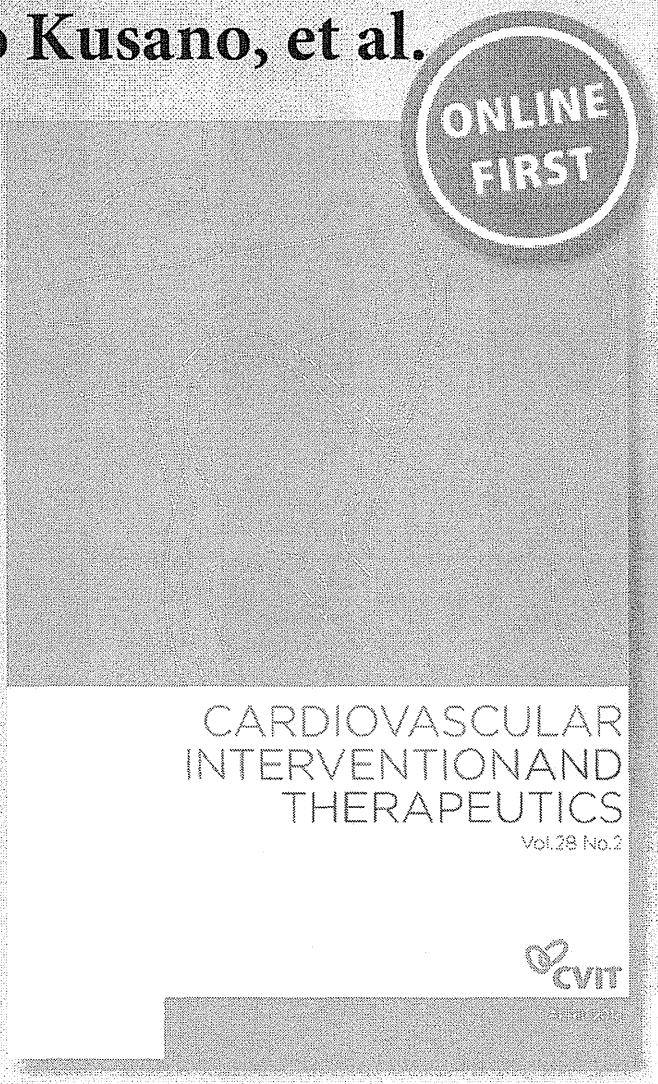
Cardiovascular Intervention and Therapeutics

ISSN 1868-4300

Cardiovasc Interv and Ther
DOI 10.1007/s12928-013-0193-9



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Cardiovasc Interv and Ther
DOI 10.1007/s12928-013-0193-9

ORIGINAL ARTICLE

Catheter closure of patent foramen ovale in patients with cryptogenic cerebrovascular accidents: initial experiences in Japan

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Received: 17 January 2013 / Accepted: 14 June 2013

Abstract Although numerous studies have shown an association between a patent foramen ovale (PFO) and cryptogenic cerebrovascular accidents (CVA), there has been no definitive control study that demonstrated the benefit of percutaneous device closure of a PFO compared to medical therapy in patients with CVA. Additionally, few clinical data exist for Japanese patients in this field. We demonstrate the initial experiences in catheter closure of a PFO as secondary prevention of CVA in Japan. Catheter closure of a PFO was attempted in 7 patients who were diagnosed with cryptogenic CVA. Mean age at the procedure was 54 ± 19 years. The presence of spontaneous interatrial right-to-left shunts was demonstrated by transesophageal contrast echocardiography without Valsalva maneuver in all of the patients. Amplatzer Cribriform device ($n = 4$) or Amplatzer PFO Occluder ($n = 3$) was used for the procedure and was successfully deployed. Device-related complications were not observed at the time of the procedure or during the follow-up period (mean period of 16 ± 9 months). Catheter closure of a PFO could be safely performed with Amplatzer Cribriform or Amplatzer PFO Occluder. This procedure may contribute to prevention of recurrent cryptogenic CVA in Japanese patients.

Keywords Patent foramen ovale · Catheter intervention · Cryptogenic stroke · Prevention

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Introduction

In Japan, catheter closure of an atrial septal defect (ASD) using Amplazter Septal Occluder (St. Jude Medical, St. Paul, MN) was clinically approved in 2005 [1]. This procedure has since spread from the pediatric population to the adult population. However, reports on this procedure in adult patients, especially in patients with complication of stroke, have been limited in Japan [2, 3].

Approximately, 20 % of adults have a patent foramen ovale (PFO) [4]. A PFO is highly associated with cryptogenic cerebrovascular accidents (CVA) [5, 6], especially when combined with atrial septal aneurysm (ASA) [7, 8]. Although a randomized trial using STARFlex device (NMT Medical, Boston, MA) failed to demonstrate a benefit of catheter closure of a PFO compared to medical therapy for preventing recurrent cryptogenic CVA [9], results of several observational studies in which the effect of PFO closure for secondary prevention of cryptogenic CVA was investigated have been positive [10–12]. However, this procedure is not clinically approved in Japan as

Published online: 04 July 2013

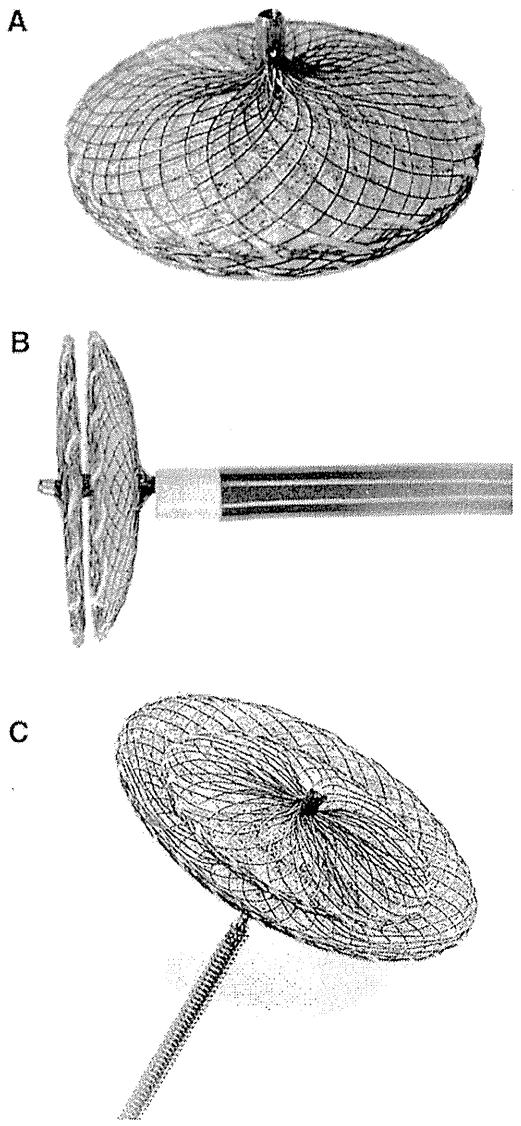

Fig. 1 **a**, **b** Photograph of Amplatzer Cribriform device. **c** Photograph of Amplatzer PFO Occluder

well as in the USA. Hence, there is no published report on clinical experiences of catheter closure of a PFO in Japanese patients with cryptogenic CVA.

Amplatzer Cribriform device (St. Jude Medical, St. Paul, MN) and Amplatzer PFO Occluder (St. Jude Medical, St. Paul, MN) have been reported as feasible devices for catheter closure of a PFO (Fig. 1a, b) [10, 12, 13]. Amplatzer PFO device has been approved in European countries, and results of large-scale clinical studies, including results for procedural efficacy and safety, have been published. In this study we demonstrate the initial experiences in catheter closure of a PFO as secondary prevention of cryptogenic CVA in Japan.

Methods

Patients

Between January 2011 and August 2012, 7 patients diagnosed with cryptogenic CVA were referred to our institution for catheter closure of a PFO as secondary prevention. All patients had a previous history of CVA as a result of cryptogenic embolism. The diagnosis of CVA was based on symptoms and signs of neurologic deficit and corresponding findings by computed tomography and magnetic resonance imaging (MRI) scans. All neurological findings were independently evaluated by a neurological specialist. Magnetic resonance angiography was performed and intracranial artery stenosis corresponding to the patient's symptoms and/or stenosis in the carotid or vertebral artery was not demonstrated in any of the patients. In all of the 7 patients, spontaneous interatrial right-to-left shunts were demonstrated by contrast transesophageal echocardiography (TEE) without Valsalva maneuver. Existence of cardiac embolic sources and aortic plaque was also excluded by TEE. For all the patients, 24-h ECG monitoring, which demonstrated that none of the patients had complication with atrial arrhythmias including atrial fibrillation, was performed. The diagnostic decision of "cryptogenic CVA" was made with the agreement of the neurologists and the cardiologists in our hospital.

Criteria for diagnosis of "cryptogenic CVA" were established as: (1) MRI images of brain suggesting embolic event; (2) absence of embolic sources such as atrial fibrillation, intracardiac thrombus or vegetation, plaques in the aortic arch, and atrial stenotic lesion in the corresponding artery; (3) existence of right-to-left shunt which was visualized with contrast agents crossing the PFO by TEE; (4) diagnostic agreement of the neurologists and the cardiologists. The option of catheter closure of PFO was offered to the patient if the criteria of "cryptogenic CVA" were fulfilled with confirmation of interatrial right-to-left shunt.

This procedural protocol complied with the Declaration of Helsinki regarding investigations in humans and approved by the Institutional Ethics Committee at Okayama University Hospital (Approval numbers #890 and #1323). Written informed consent was obtained from all patients.

Patients' characteristics are shown in Table 1. Mean age at the procedure was 54 ± 19 years. At least one CVA was documented in all of the 7 patients. Six patients had complication with cerebral infarction and 1 patient with cerebral abscess.

Transesophageal echocardiography

For pre-interventional diagnosis and interventional guidance, a Philips IE 33 echocardiography system (Philips

Table 1 Patients' characteristics

Case no.	1	2	3	4	5	6	7
Gender	Male	Male	Male	Female	Female	Male	Male
Age	62	81	53	69	43	37	32
Cerebrovascular accident	CA	CI	CI	CI	CI	CI	CI
Number of events	1	1	1	2	1	2	1
DVT	−	−	−	+	−	+	−
HT	−	+	+	+	−	−	−
DM	−	−	−	+	−	−	−
DL	−	−	−	+	−	−	−
Smoking	−	−	−	−	−	+	−
Migraine (headache)	−	−	+	−	+	+	−
Atrial arrythmia	−	−	−	−	−	−	−

CA cerebral abscess, *CI* cerebral infarction, *DVT* deep vein thrombosis, *HT* hypertension, *DM* diabetes mellitus, *DL* dyslipidemia

Medical Systems, Andover, MA) with a multiplane probe and a fully sampled matrix array transducer probe was used. TEE was performed to visualize the interatrial septum and exclude the possibility of thrombi or other structural abnormalities. The diagnosis of a PFO, an ASA and a Eustachian valve were based on TEE findings. To distinguish PFO from ASD, PFO parameters, including PFO height, PFO length and septal excursion distance, were measured with a two-dimensional TEE image on the vertical plane (Fig. 2a) [14]. An ASA was diagnosed when the atrial septum extended >10 mm into the left or right atrium or if the sum of excursion into the left and right atria was >15 mm with a basal diameter ≥15 mm. A Eustachian valve was a clearly defined laminar, echo-dense, ridge-like structure at the junction of the inferior vena cava and right atrium. Interatrial right-to-left shunt was defined as the appearance of contrast agents across the interatrial septum (Fig. 2b). Hand-agitated air bubbles were used for the contrast agent.

Procedure

The procedure was performed under general anesthesia with the assistance of TEE and fluoroscopy. Balloon sizing by an AGA sizing balloon (St. Jude Medical, St. Paul, MN) was used for device selection. Due to the institutional ethical committee approval, Amplatzer Cribriform device was the device used for catheter closure of a PFO in the former 4 patients and Amplatzer PFO Occluder was the device in the latter 3 patients.

After the diagnostic procedure had been completed, a size 8 French long sheath was placed in the atrial septum. The device size was selected from the balloon sizing diameter. 25-mm Amplatzer Cribriform or 25-mm Amplatzer PFO Occluder, in which the size of the right-sided disc corresponds to 15-mm Amplatzer Septal Occluder,

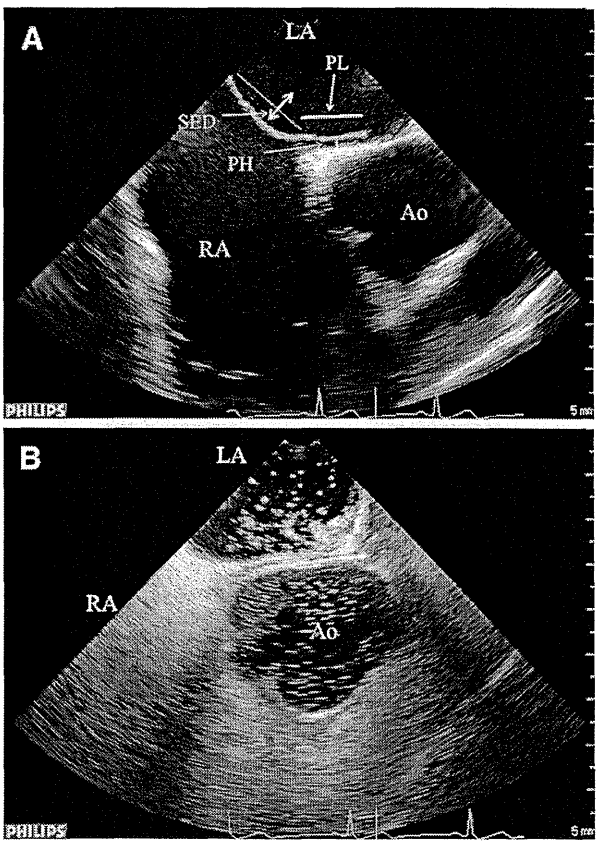

Fig. 2 **a** Measurements of PFO parameters on a transesophageal echocardiogram. Transesophageal echocardiogram in the vertical plane demonstrates how the PFO was measured and evaluated. PH was measured as height of the PFO tunnel. Maximal and minimum PL was measured as overlap of the septum primum and septum secundum. SED was measured as excursion distance of the septum into the right and the left atrium. **b** Bubble contrast image at rest on a transesophageal echocardiogram. Contrast agent demonstrates a shunt from the right atrium to the left atrium. *Ao* indicates aorta, *LA* left atrium, *RA* right atrium, *PL* PFO length, *PH* PFO height, *SED* septal excursion distance

was selected if the balloon sizing diameter was equal to or <15 mm. If the balloon sizing diameter was more than 15 mm, 30-mm Amplatzer Cribriform was selected. The selected device was mounted on the delivery system and loaded into the transseptal sheath. Then the device was delivered through the sheath into the left atrium until the left atrial part of the device was unfolded. The whole unit was then withdrawn under fluoroscopic and transesophageal echocardiographic monitoring against the interatrial septum. After confirmation of stable device deployment, the device was unscrewed and released (Fig. 3a, b).

To prevent infectious complications, all patients received antibiotic prophylaxis. Cefazolin at 1 g was intravenously administered 30 min before the procedure and 6 h later. All patients were discharged from the hospital 1 day after the procedure.

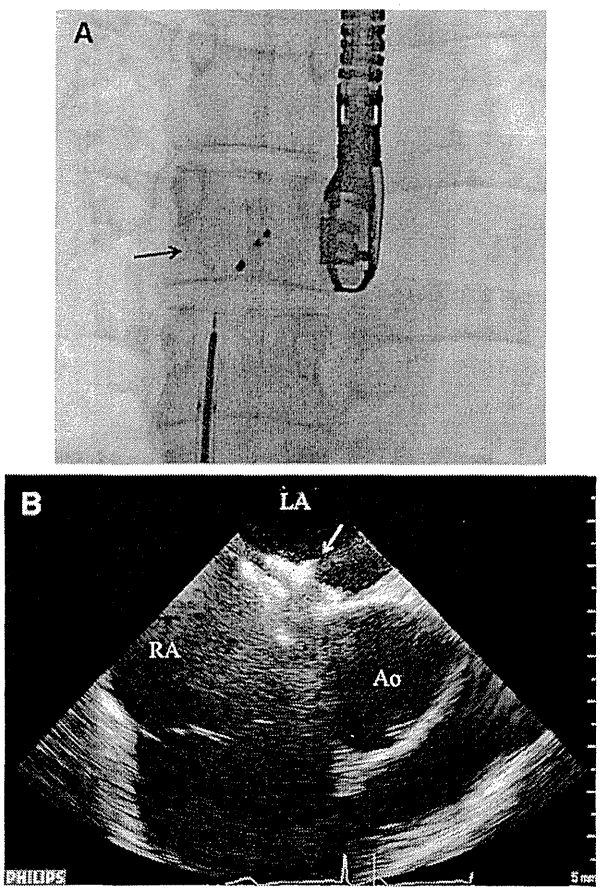

Fig. 3 **a** Fluoroscopic image showing an Amplatzer PFO Occluder deployed against the interatrial septum (*black arrow*). After the appropriate position of the device had been confirmed, the device was detached from the delivery cable. **b** Transecocardiogram image showing an Amplatzer PFO Occluder deployed in a patent foramen ovale (*white arrow*)

Postinterventional treatment and follow-up evaluation

Vitamin K antagonist with adjustment to a target international normalized ratio of 2.0 to 3.0 was the preferred first-line medical treatment for patients with previous cerebral infarction. Four patients received acetylsalicylic acid at 100 mg daily for 6 months in addition to vitamin K antagonist. One patient (case no. 4) received clopidogrel at 75 mg daily in addition to vitamin K antagonist. One patient (case no. 3) who could not receive vitamin K antagonist received acetylsalicylic acid at 100 mg daily for 6 months and clopidogrel 75 mg a day for 1 month. One patient (case no. 1) who had complication with cerebral abscess received acetylsalicylic acid at 100 mg daily for 6 months and clopidogrel 75 mg a day for 1 month.

Transthoracic echocardiography (TTE) study was performed 1 day after catheter closure. After discharge from the hospital, clinical examinations, including neurological and medical examinations and TTE, were carried out at 1, 3, 6 and 12 months after the procedure.

Statistical analysis

Data are presented as mean ± SD (Microsoft Excel, Redmond, WA, USA).

Results

PFO morphology

The morphological characteristics of PFO are shown in Table 2. In all the patients, TEE images demonstrated PFO distinguished from ASD, which allowed the measurement of PFO tunnel length. An ASA existed in 3 patients and a Eustachian valve existed in 3 patients. One patient had complication with both ASA and Eustachian valve.

Procedural results and follow-up results

Procedures were performed successfully in all 7 patients without any related complications. No patient developed atrial arrhythmias during or after the procedure. At the 1-, 3-, 6- and 12-month follow-up, procedure-related complications were not confirmed by medical interview and examinations in all the patients. During the follow-up period, no recurrent CVA was observed and no procedure-related complication was observed (mean period of 16 ± 9 months).

Discussion

We described our initial case series of 7 patients who underwent catheter closure of a PFO with Amplatzer

Table 2 Characteristics of patent foramen ovale and procedural results

Case no.	1	2	3	4	5	6	7
Spontaneous R → L shunt	+	+	+	+	+	+	+
ASA	+	−	+	+	−	−	−
Eustachian valve	+	−	−	+	−	+	−
PFO height, mm	3	2	5	7	3	2	2
Maximum PFO length, mm	12	3	13	16	10	18	13
Minimum PFO length, mm	6	1	7	8	3	14	7
Septal excursion distance, mm	12	6	14	17	8	4	4
BSD, mm	10	7	9	16	6	9	7
Devcie size†	CB25	CB25	CB25	CB30	PFO25	PFO25	PFO25

PFO patent foramen ovale, *ASA* atrial septal aneurysm, *BSD* balloon sizing diameter

† A size 25-mm Amplatzer Cribriform is expressed as CB25, and a size 30-mm Amplatzer Cribriform is expressed as CB30. A size 25-mm Amplatzer PFO Occluder is expressed as PFO25

Cribriform device or Amplatzer PFO Occluder. Our experience indicates that catheter closure of a PFO can be safely performed without serious procedural complications.

Cerebrovascular events are the fourth leading cause of death among the Japanese population and more than half of them are events of ischemic stroke. A previous report demonstrated that at least 5 % of acute ischemic stroke in patients in Japan was caused by definite paradoxical brain embolism [15]. As there are more than 200,000 ischemic stroke patients annually in Japan, at least 10,000 Japanese ischemic stroke patients will be estimated to be caused by cryptogenic embolism. Cryptogenic embolism was reported to be associated with a PFO, which is a major right-to-left shunt in adults. The association was confirmed in a recent meta-analysis of case control studies and in a prospective PFO study [8, 16]. Clinical evidence suggested a correlation of a PFO with stroke not only in young adults, but also in older patients [17, 18].

In Japan, Amplatzer Septal Occluder and Amplatzer Cribriform device are the only devices approved for clinical use in catheter closure of interatrial communications. Amplatzer Cribriform device is similar to Amplatzer PFO Occluder, which is only available outside Japan. There are other types of device occluder systems for which periprocedural and mid-term safety and efficacy have been reported [19, 20]. Since previous reports suggested that Amplatzer Cribriform device and Amplatzer PFO Occluder are both feasible devices for catheter closure of a PFO [10, 12, 13], we selected these devices for our initial treatment in catheter closure of a PFO for secondary prevention of CVA. Amplatzer PFO Occluder was introduced to the patients after the safety of catheter closure of a PFO with Amplatzer Cribriform device had been demonstrated in the first 4 patients. A PFO with right-to-left interatrial shunt, which was morphologically different from ASD, was demonstrated by TEE images in all our patients. Previous report, which demonstrated the actual morphologies of PFO in human hearts, suggested PFO tunnel length as an important morphological characteristic to evaluate PFO [21]. The mean minimal length of PFO in our patients was demonstrated to be 6.6 ± 4.1 mm, which was not substantially different from the previously reported actual measurements. Although several devices designed for usage in catheter closure of a PFO had already been reported as safe and effective for Asian patients [22], these morphological characteristics should be important to provide appropriately designed device to close PFO for Japanese patients.

It is important to understand the potential risks associated with catheter closure of a PFO [23]. Catheter closure of a PFO is quite effective, with nearly 90 % of patients displaying complete closure of their PFO after 1 year [24]. Various PFO devices can be inserted percutaneously with a high degree of success and low complication rate. Besides, multiple observational studies have shown the apparent safety of PFO closure with percutaneous devices [10–12]. However, a randomized trial did not provide evidence of clinical superiority of catheter closure of a PFO over medical management in patients with cryptogenic CVA [9]. The results of a few non-randomized trials have suggested that the risk of recurrent stroke is the same or lower after catheter closure of an interatrial communication compared to medical therapy [25–28]. A recent meta-analysis showed a benefit of catheter PFO closure compared with medical management [29]. All of these reports indicated and emphasized that patient selection for catheter closure of a PFO was crucial for providing benefits of the catheter procedure beyond complications.

Pathophysiology and proper management of a PFO remain far from being fully clarified. It is intuitively acceptable that patients with spontaneous right-to-left interatrial shunt are at high risk for cryptogenic embolism

[30]. Thus, such patients might have obvious benefits from catheter closure of a PFO as secondary prevention for cryptogenic CVA. As spontaneous interatrial right-to-left shunt without particular technique had been documented in our cohort, our patients seemed to be a high-risk population.

Limitations of the study

The major limitation of this study is that only a small number of patients were included. As catheter closure of a PFO is not clinically approved in Japan, difficulties existed in including a large number of patients in this study. Besides, the follow-up period may not be adequate to conclude the future safety of this procedure. Another limitation is our selection of patients. Lower extremities ultrasound and carotid artery ultrasound were not performed in some patients. The absence of these examinations might be insufficient to diagnose "definite" PFO-related cryptogenic CVA. Moreover, all the patients were previously diagnosed with cryptogenic CVA at the referring hospital. Although we added necessary examinations to fulfill the criteria of "cryptogenic CVA", our patients' profile might have some bias.

Conclusion

Our experiences demonstrate the safety of catheter closure for a PFO using Amplatzer Cribriform device or Amplatzer PFO Occluder in Japanese patients with complication of cryptogenic CVA. This procedure has the possibility of eliminating the risk of recurrent cryptogenic embolism by diminishing or decreasing right-to-left shunt of a PFO.

Acknowledgments The authors thank Yasuharu Tanabe, Nobuhisa Watanabe, Rika Takemoto and Madoka Ikeda for supporting this study and correcting the clinical data. This study was not supported by any funding. The authors have no conflict of interest to declare.

References

1. Oho S, Ishizawa A, Akagi T, Dodo H, Kato H. Transcatheter closure of atrial septal defects with the Amplatzer septal occluder—a Japanese clinical trial. Circ J. 2002;66:791–4.
2. Kijima Y, Akagi T, Taniguchi M, Nakagawa K, Deguchi K, Tomii T, et al. Catheter closure of atrial septal defect in patients with cryptogenic stroke: initial experience in Japan. Cardiovasc Interv Ther. 2012;27:8–13.
3. Hara H, Nakayama T, Matsuura H, Sato K, Hashimoto G, Yoshikawa H, et al. Transcatheter atrial septal defect closure in a patient with paradoxical brain emboli: who should treat it and who should be treated? Cardiovasc Interv Ther. 2012;27:8–13.
4. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59:17–20.
5. Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, et al. Patent foramen ovale in young stroke patients. Lancet. 1988;2:11–2.
6. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med. 1988;318:1148–52.
7. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med. 2001;345:1740–6.
8. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case–control studies. Neurology. 2000;55:1172–9.
9. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012;366:991–9.
10. Bruch L, Parsi A, Grad MO, Rux S, Burmeister T, Krebs H, et al. Transcatheter closure of interatrial communications for secondary prevention of paradoxical embolism: single-center experience. Circulation. 2002;105:2845–8.
11. Braun MU, Fassbender D, Schoen SP, Haass M, Schraeder R, Scholtz W, et al. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. J Am Coll Cardiol. 2002;39:2019–25.
12. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med. 2003;139:753–60.
13. Silvestry FE, Naseer N, Wiegers SE, Hirshfeld JW, Herrmann HC. Percutaneous transcatheter closure of patent foramen ovale with the Amplatzer Cribriform septal occluder. Catheter Cardiovasc Interv. 2008;71:383–7.
14. Akhondi A, Gevorgyan R, Tseng CH, Slavin L, Dao C, Liebeskind DS, et al. The association of patent foramen ovale morphology and stroke size in patients with paradoxical embolism. Circ Cardiovasc Interv. 2010;3:506–10.
15. Ueno Y, Iguchi Y, Inoue T, Shibazaki K, Urabe T, Kimura K. Paradoxical brain embolism may not be uncommon—prospective study in acute ischemic stroke. J Neurol. 2007;254:763–6.
16. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation. 2002;105:2565–631.
17. Kizer JR, Devereux RB. Clinical practice. Patent foramen ovale in young adults with unexplained stroke. N Engl J Med. 2005;353:2361–72.
18. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med. 2007;357:2262–8.
19. Schwerzmann M, Windecker S, Wahl A, Mehta H, Nedeltchev K, Mattle H, et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart. 2004;90:186–90.
20. Braun M, Gliech V, Boscheri A, Schoen S, Gahn G, Reichmann H, et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. Eur Heart J. 2004;25:424–30.
21. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus JL, Karnicki K, et al. Patent foramen ovale: standards for a preclinical model of prevalence, structure, and histopathologic

comparability to human hearts. Catheter Cardiovasc Interv. 2007;69:266–73.
22. Zhang CJ, Huang YG, Huang XS, Huang T, Huang WH, Shen JJ. Transcatheter closure of patent foramen ovale in Chinese patients with paradoxical embolism. Immediate results and long-term follow-up. Circ J. 2011;75:1867–71.
23. Verma SK, Tobis JM. Explantation of patetent foramen ovale closure devices: a multicenter survey. JACC Cardiovasc Interv. 2011;4:579–85.
24. Spies C, Timmermanns I, Reissmann U, Van Essèn J, Schrader R. Patent foramen ovale closure with the Intrasept occluder: complete 6–56 months follow-up of 247 patients after presumed paradoxical embolism. Catheter Cardiovasc Interv. 2008;71: 390–5.
25. Windecker S, Wahl A, Nedeltchev K, Arnold M, Schwerzmann M, Seiler C, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. J Am Coll Cardiol. 2004;44:750–8.
26. Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. Int J Cardiol. 2005;101: 77–82.
27. Thanopoulos BV, Dardas PD, Karanasios E, Mezilis N. Transcatheter closure versus medical therapy of patent foramen ovale and cryptogenic stroke. Catheter Cardiovasc Interv. 2006;68: 741–6.
28. Wahl A, Jüni P, Mono ML, Kalesan B, Praz F, Geister L, et al. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. Circulation. 2012;125:803–12.
29. Agarwal S, Bajaj NS, Kumbhani DJ, Tuzcu EM, Kapadia SR. Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. JACC Cardiol Interv. 2012;5:777–89.
30. Rigatelli G, Dell'Avvocata F, Cardaioli P, Giordan M, Braggion G, Aggio S, et al. Permanent right-to-left shunt is the key factor in managing patent foramen ovale. J Am Coll Cardiol. 2011;58: 2257–61.

Outcomes in Patients With High-Degree Atrioventricular Block as the Initial Manifestation of Cardiac Sarcoidosis

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Although high-degree atrioventricular block (AVB) is a common initial manifestation of cardiac sarcoidosis, little is known about the outcomes. The aim of this study was to assess outcomes in patients with AVB as an initial manifestation of cardiac sarcoidosis compared with those in patients with ventricular tachyarrhythmia (VT) and/or heart failure (HF). Fifty-three consecutive patients with cardiac sarcoidosis, who had high-degree AVB (n = 22) or VT and/or HF (n = 31), were enrolled. The end point was defined as major adverse cardiac events, including cardiac death, ventricular fibrillation, sustained VT, and hospitalization for HF. Over a median follow-up period of 34 months, the outcomes of major adverse cardiac events were better in patients with high-degree AVB than in those with VT and/or HF (log-rank test, p = 0.046). However, this difference was due mainly to HF hospitalization. The outcomes of fatal cardiac events, including cardiac death, ventricular fibrillation, and sustained VT, were comparable between the 2 groups (log-rank test, p = 0.877). The fatal cardiac events in patients with high-degree AVB were not associated with the initiation of steroid treatment or left ventricular dysfunction. In conclusion, the outcomes of major adverse cardiac events are better in patients with high-degree AVB than in those with VT and/or HF. However, patients with high-degree AVB have a high rate of fatal cardiac events, similar to those with VT and/or HF. An indication for an implantable cardioverter-defibrillator, but not a pacemaker system, can be considered in patients with cardiac sarcoidosis manifested by high-degree AVB. (Am J Cardiol 2015;115:505–509)

Sarcoidosis is a systemic granulomatous disease of unknown origin.[1] Cardiac involvement is increasingly recognized because of adverse outcomes.[2–5] The principal initial manifestation of cardiac sarcoidosis is high-degree atrioventricular block (AVB), ventricular tachyarrhythmia (VT), or heart failure (HF).[5] Patients with VT have a high rate of recurrence of fatal VT or sudden cardiac death.[6–10] HF caused by left ventricular dysfunction is one of the most common causes of cardiac death.[11] Therefore, patients with VT and/or HF as the initial manifestation of cardiac sarcoidosis are regarded as at high risk for cardiac events, whereas outcomes in patients with high-degree AVB have not been well investigated. One study showed that patients with AVB caused by cardiac sarcoidosis had an increase in the risk for cardiac events compared with those with idiopathic AVB.[12] However, whether the outcomes are different according to the initial manifestation, such as high-degree AVB or VT and/or HF, remains unknown. Understanding the incidence of cardiac events in patients with high-degree AVB may be important for selecting the appropriate device (i.e., pacemaker system vs implantable cardioverter-defibrillator [ICD]). The aim of this study was to assess outcomes in patients with high-degree AVB as the initial manifestation of cardiac sarcoidosis compared with those in patients with VT and/or HF.

Methods

The study population consisted of 53 consecutive patients diagnosed with cardiac sarcoidosis in our institution from July 1998 to November 2013, who had high-degree AVB (n = 22) or VT and/or HF (n = 31) as the initial manifestation. Cardiac sarcoidosis was diagnosed according to Japanese Ministry of Health and Welfare guidelines, revised in 2006 by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders.[13,14] In brief, cardiac sarcoidosis is diagnosed on the basis of histologic findings or clinical findings. Histologic diagnosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas. Clinical diagnosis is confirmed in the absence of endomyocardial biopsy when extracardiac sarcoidosis is diagnosed and the following clinical cardiac criteria (>2 of 4 major criteria, or 1 of 4 major criteria and >2 of 5 minor criteria) is satisfied. Major criteria consist of advanced AVB, basal thinning of the interventricular septum, positive myocardial uptake of gallium-67 citrate (^{67}Ga) scintigraphy or ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET), and a left ventricular ejection fraction <50%. Minor criteria consist of abnormal electrocardiographic results, abnormal echocardiographic results, perfusion defect on thallium-201 or technetium-99m myocardial scintigraphy, delay enhancement of myocardium on gadolinium-enhanced

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See page 509 for disclosure information.

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0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.11.028

Table 1
Patient characteristics

	All (n = 53)	High-degree atrioventricular block (n = 22)	Ventricular tachyarrhythmia and/or heart failure (n = 31)	p
Age (years)	60 ± 13	60 ± 9	60 ± 15	0.948
Female	33 (62%)	16 (73%)	17 (55%)	0.193
Extracardiac organ involvements	43 (81%)	17 (77%)	26 (84%)	0.554
Lung	34 (64%)	13 (59%)	21 (68%)	0.527
Skin	11 (21%)	5 (27%)	6 (19%)	0.771
Eye	19 (36%)	9 (41%)	10 (32%)	0.527
Others	10 (19%)	4 (18%)	10 (32%)	0.475
New York Heart Association functional class III or IV	27 (51%)	6 (27%)	21 (68%)	0.003
Left ventricular end-diastolic diameter (mm)	55 ± 9	51 ± 7	57 ± 9	0.013
Left ventricular end-systolic diameter (mm)	43 ± 11	38 ± 10	46 ± 11	0.005
Left ventricular ejection fraction (%)	42 ± 16	48 ± 15	38 ± 15	0.012
Angiotensin-converting enzyme (IU/L)	15.1 ± 7.0	16.0 ± 6.8	14.4 ± 7.2	0.438
Log plasma B-type natriuretic peptide (pg/ml)	2.34 ± 0.50	2.16 ± 0.43	2.46 ± 0.52	0.035
Positive myocardial uptake of gallium-67 citrate or ^{18}F-fluoro-2-deoxyglucose	40 (75%)	19 (86%)	21 (68%)	0.125
Diagnosis at the time of initial manifestation	48 (91%)	17 (77%)	31 (100%)	0.005
Initiation of 30 or 40 mg prednisone daily	42 (79%)	17 (77%)	25 (81%)	0.771
Medications after initial manifestation				
Beta-blockers	33 (62%)	7 (32%)	26 (84%)	<0.001
angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	31 (58%)	11 (50%)	20 (65%)	0.300
Diuretics	25 (47%)	2 (9%)	23 (74%)	<0.001
Anti-arrhythmic drugs	14 (26%)	2 (9%)	12 (39%)	0.015
Implantable cardioverter defibrillator	12 (23%)	1 (5%)	11 (35%)	0.007
Cardiac resynchronization therapy with defibrillator	9 (17%)	1 (5%)	8 (26%)	0.043
Median follow-up period (months)	35	45	33	0.605

Data are presented as mean ± standard deviation or number (%).

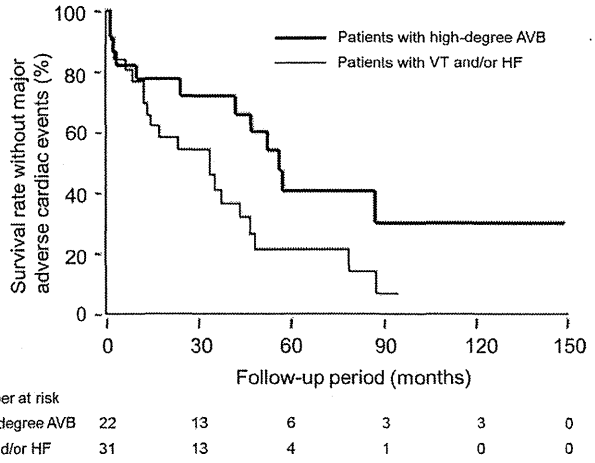


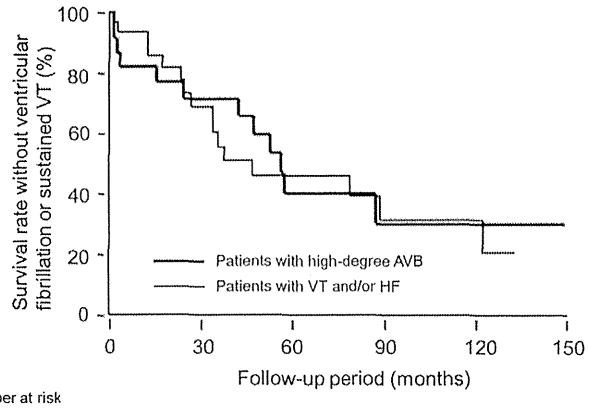
Figure 1. Survival rate without major adverse cardiac events in patients with high-degree AVB and in those with VT and/or HF.

cardiac magnetic resonance imaging, and interstitial fibrosis or monocyte infiltration on endomyocardial biopsy. This study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee.

This was a retrospective observational study. Patients with high-degree AVB were defined as having complete AVB or Mobitz II block at the time of initial manifestation of cardiac sarcoidosis. Patients with VT and/or HF were defined as having ventricular fibrillation or sustained VT and/or as being hospitalized for HF caused by left ventricular dysfunction without high-degree AVB, at the time of initial manifestation. Sustained VT was defined as spontaneous ventricular tachycardia at a rate of ≥120 beats/min that lasted ≥30 seconds. Steroid treatment was initiated at a dose of 30 or 40 mg/day of prednisone. Doses of prednisone were tapered over a period of 6 to 12 months to maintenance doses of 5 to 10 mg daily.

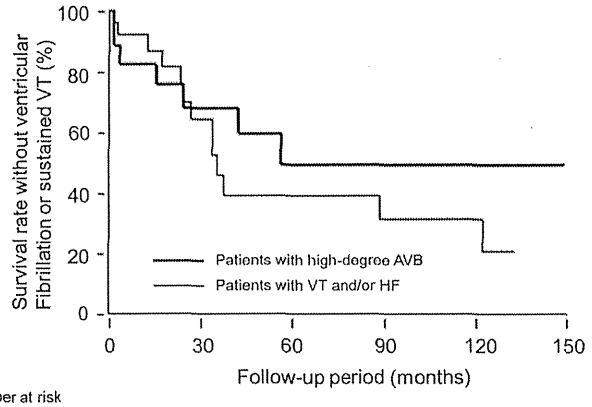
The end point was defined as major adverse cardiac events, including cardiac death, ventricular fibrillation, sustained VT, and hospitalization for HF. Patients were followed from the date of initial manifestation of cardiac sarcoidosis, such as high-degree AVB or VT and/or HF hospitalization, until the date of first documentation of cardiac events or the end of follow-up, whichever occurred first. The first documentation of cardiac events was assessed after the initial manifestation had been recovered. Follow-up information was obtained by medical records, contact with the patient's physicians, or telephone interview with the patient or, if deceased, with family members.

Gallium-67 citrate scintigraphy was performed in all patients. Fluorine-18-FDG PET was performed in 6 patients who were diagnosed after September 2010 and had no positive myocardial uptake of ^{67}Ga at baseline. On ^{18}F-FDG PET, patients were instructed to fast for ≥12 hours, blood glucose levels were determined to ensure a level of



Number at risk						
High-degree AVB	22	13	6	3	3	0
VT and/or HF	31	16	9	4	3	0

Figure 2. Survival rate without ventricular fibrillation or sustained VT in patients with high-degree AVB and in those with VT and/or HF.



Number at risk						
High-degree AVB	17	9	4	3	3	0
VT and/or HF	25	11	5	4	3	0

Figure 3. Survival rate without ventricular fibrillation or sustained VT in patients with high-degree AVB and in those with VT and/or HF, among patients treated with prednisone.

<150 mg/dl, and unfractionated heparin was preadministered. Increased uptake of ^{67}Ga or ^{18}F-FDG in the myocardium that was higher than background activity was regarded as positive myocardial uptake. After the initiation of steroid treatment, ^{67}Ga scintigraphy or ^{18}F-FDG PET was repeated to evaluate the resolution of active myocardial inflammation. Echocardiography was performed by cardiologists. Left ventricular ejection fraction was calculated by the disc summation technique. Plasma B-type natriuretic peptide levels (normal, ≤18.4 pg/ml) and serum angiotensin-converting enzyme levels (normal, ≤21.4 IU/L) were measured.

Data are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Statistically significant differences were analyzed using Student's *t* tests and Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. The event-free survival rate was estimated using Kaplan-Meier analysis, and the difference was analyzed using the log-rank test. Predictors of cardiac events in patients with high-degree AVB were analyzed using Cox proportional-hazard analysis. Variables for univariate analysis included age, gender, New York Heart Association functional class, the left ventricular ejection fraction, plasma B-type natriuretic peptide levels, and the initiation of steroid treatment. Variables with p values <0.10 in univariate analysis were entered into multivariate analysis. Hazard ratios are presented with 95% confidence intervals. Statistical analysis was performed with JMP version 8.0 (SAS Institute Inc., Cary, North Carolina), and significance was defined as $p < 0.05$.

Results

Patient characteristics are listed in Table 1. Twenty patients were diagnosed on the basis of histologic findings on endomyocardial biopsy, and the other 33 were diagnosed on the basis of clinical findings. Extracardiac organ involvements were observed in 43 patients, and the other 10 were classified as isolated cardiac sarcoidosis without extracardiac organ involvements. All 10 patients were diagnosed on the basis of histologic findings on endomyocardial biopsy that identified noncaseating epithelioid cell granulomas, but not necrosis or eosinophils.

Among the 22 patients with high-degree AVB, complete AVB was observed in 20, and Mobitz II block was observed in 2. Pacemaker systems were implanted in 20 patients, ICDs were implanted in 1, and a cardiac resynchronization therapy device with a defibrillator was implanted in 1. Seventeen patients were treated with prednisone 30 or 40 mg/day, and the other 5 were not treated, because they were not diagnosed with cardiac sarcoidosis at the time of initial manifestation and were diagnosed at a later date. Among the 31 patients with VT and/or HF, ventricular fibrillation was observed in 1, and sustained VT was observed in 13. All patients were diagnosed with cardiac sarcoidosis at the time of initial manifestation. ICDs were implanted in 11 patients, and cardiac resynchronization therapy devices with defibrillators were implanted in 8. Twenty-five patients were treated with prednisone 30 or 40 mg/day, and the other 6 were not treated, because of the decisions of attending physicians or patient refusal.

As expected, HF and left ventricular dysfunction were less severe in patients with high-degree AVB than in those with VT and/or HF. Patients with high-degree AVB less often received ICDs or cardiac resynchronization therapy devices with defibrillators. There were no significant differences in age, positive myocardial uptake of ^{67}Ga or ^{18}F-FDG, and the initiation of steroid treatment between the 2 groups.

Over a median follow-up period of 34 months (range 1 to 149), major adverse cardiac events occurred in 34 patients. Of the 22 patients with high-degree AVB, 12 (55%) had major adverse cardiac events: 2 had ventricular fibrillation and were resuscitated by bystander cardiopulmonary resuscitation and an automated external defibrillator, 9 had sustained VT, and 1 was hospitalized for HF. After the first events, 1 patient died from HF. Of the 31 patients with VT and/or HF, 22 (71%) had major adverse cardiac events: 12 were hospitalized for HF, and 10 had sustained VT. After the first events, 6 patients died from VT and/or HF.

Table 2
Predictors of fatal cardiac events in patients with high-degree atrioventricular block

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P
Age >60 years	0.59 (0.16-1.91)	0.389		
Female	0.78 (0.24-2.92)	0.684		
New York Heart Association functional class III or IV	6.98 (1.67-34.8)	0.008	4.83 (1.05-26.7)	0.044
Left ventricular ejection fraction <50%	2.47 (0.71-11.3)	0.158		
Plasma B-type natriuretic peptide >150 pg/ml	3.52 (1.06-13.5)	0.041	2.21 (0.57-9.33)	0.252
Initiation of 30 or 40 mg prednisone daily	0.51 (0.16-1.74)	0.269		

Kaplan-Meier analysis showed that the survival rate without major adverse cardiac events was better in patients with high-degree AVB than in those with VT and/or HF (log-rank test, $p = 0.046$; Figure 1). However, this difference in the outcomes between the 2 groups was due mainly to the difference in the incidence of HF hospitalization. We compared the incidence of fatal cardiac events, which included cardiac death, ventricular fibrillation, and sustained VT, between patients with high-degree AVB and those with VT and/or HF. The survival rate without ventricular fibrillation or sustained VT was similar between the 2 groups (log-rank test, $p = 0.877$; Figure 2).

Forty-two patients, including 17 with high-degree AVB and 25 with VT and/or HF, were treated with prednisone 30 or 40 mg/day at the time of initial manifestation. At the time of initial manifestation, 36 of the 42 patients had positive myocardial uptake of ^{67}Ga or ^{18}F-FDG. All of them showed complete disappearance of positive myocardial uptake on repeat ^{67}Ga scintigraphy or ^{18}F-FDG PET at a mean of 2 months after steroid treatment. All of these patients were considered to be responders of steroid treatment. During the follow-up period, fatal cardiac events occurred in 7 of the 17 patients (41%) with high-degree AVB and 13 of the 25 (52%) with VT and/or HF. The survival rate without ventricular fibrillation or sustained VT was not different between the 2 groups (log-rank test, $p = 0.391$; Figure 3). High-degree AVB recovered to normal or first-degree AVB in 7 of the 17 patients after the initiation of steroid treatment. Of the 7 patients, 3 had fatal cardiac events later.

Cox proportional-hazards analysis showed that the fatal cardiac events in patients with high-degree AVB were associated with New York Heart Association functional class III or IV at the time of initial manifestation, but not with the initiation of steroid treatment or left ventricular dysfunction (Table 2).

Discussion

The major findings of the present study are as follows: (1) the outcomes of major adverse cardiac events were better in patients with high-degree AVB as the initial manifestation of cardiac sarcoidosis than in those with VT and/or HF, but the outcomes of fatal cardiac events, which included cardiac death, ventricular fibrillation, and sustained VT, were similar between the 2 groups; (2) >1/2 of the patients with high-degree AVB had fatal cardiac events at a median follow-up of 34 months; and (3) the initiation of steroid treatment or left ventricular dysfunction was not associated with the fatal cardiac events in patients with high-degree AVB. Our findings suggest that an indication for implantation of an ICD, but not a pacemaker system, can be considered in patients with cardiac sarcoidosis manifested by high-degree AVB.

Although high-degree AVB is one of the most common initial manifestations of cardiac sarcoidosis,[5] little is known about the outcomes. Kandolin et al[12] showed that patients with AVB caused by cardiac sarcoidosis had adverse outcomes, but their outcomes were merely compared with those in patients with idiopathic AVB, and thus this finding is reasonable because cardiac sarcoidosis itself is at high risk for adverse outcomes.[2–5] Therefore, it remains unknown whether the outcomes in patients with high-degree AVB are better or worse among cardiac sarcoidosis. Our study showed that patients with high-degree AVB had a high rate of fatal cardiac events, including cardiac death, ventricular fibrillation, and sustained VT, compatible with that in patients with VT and/or HF, suggesting that the risk for fatal cardiac events is irrespective of the initial manifestation.

Because several studies showed that steroid treatment was particularly effective for patients with AVB, but not for those with VT or left ventricular dysfunction,[6,11,15–17] we focused on patients treated with prednisone at the time of initial manifestation and assessed their outcomes. In the present study, positive myocardial uptake of ^{67}Ga or ^{18}F-FDG disappeared after the initiation of steroid treatment in all patients, and high-degree AVB recovered in some patients, indicating that steroid treatment was effective.[17–19] However, about half of the patients with high-degree AVB had the fatal cardiac events, and the outcomes of fatal cardiac events in patients with high-degree AVB were not better than those in patients with VT and/or HF. Our findings indicated that steroid treatment might not be sufficient for preventing the fatal cardiac events in patients with high-degree AVB.

The present study has clinical implications. Our study showed that patients with high-degree AVB had a high rate of fatal cardiac events, similar to those with VT and/or HF. Importantly, 2 patients with high-degree AVB had ventricular fibrillation and were resuscitated by an automated external defibrillator. Furthermore, the fatal cardiac events in patients with high-degree AVB were not associated with the initiation of steroid treatment or left ventricular dysfunction, indicating that the prevention and prediction for these events might be difficult. Therefore, additional treatments, such as ICD implantation or a wearable ICD,

may be required even in patients with high-degree AVB. The current Heart Rhythm Society expert consensus statement has listed cardiac sarcoidosis as a class IIa indication for ICD implantation.[20] A few studies have also suggested that cardiac sarcoidosis with high-degree AVB is an indication for ICD implantation.[21,22] However, there is little evidence to support these recommendations. The present study adds important evidence that cardiac sarcoidosis manifested by high-degree AVB is an indication for implantation of an ICD, but not a pacemaker system.

There were several limitations to the present study. First, this was a retrospective observational study at a single center, and the number of patients was small. Second, arrhythmic events might have been underestimated, because patients who did not receive ICDs could not undergo any monitoring. However, although the frequency of ICD implantation was lower in patients with high-degree AVB than in those with VT and/or HF, the rate of arrhythmic events was similar between the 2 groups, indicating that this underestimation would not affect our conclusion. Third, cardiac sarcoidosis was diagnosed according to the Japanese Ministry of Health and Welfare guidelines, revised in 2006 by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders.[13,14] All of the patients were not confirmed to have cardiac sarcoidosis by histologic findings. Fourth, 6 patients with high-degree AVB had HF symptoms at the time of initial manifestation, with New York Heart Association functional class III. However, these HF symptoms were considered to be temporary caused by high-degree AVB because they improved immediately after cardiac pacing. Therefore, the 6 patients were classified as having high-degree AVB, but not VT and/or HF caused by left ventricular dysfunction without high-degree AVB. Finally, cardiac magnetic resonance imaging or programmed ventricular stimulation has been reported to be effective for risk stratification,[23,24] but these assessments were not performed.

Disclosures

The authors have no conflicts of interest to disclose.

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336:1224–1234.
2. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoidosis: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978;58:1204–1211.
3. Fleming HA, Bailey SM. The prognosis of sarcoid heart disease in the United Kingdom. *Ann N Y Acad Sci* 1986;465:543–550.
4. Roberts WC, McAllister HA Jr, 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;63:86–108.
5. Sekhri V, Sanal S, Delorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. *Arch Med Sci* 2011;7:546–554.
6. Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E, Gomes JA. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. *J Am Coll Cardiol* 1991;18: 937–943.
7. Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, Rosenfeld L, Mitiku TY, Cooper JM, Mehta D, Greenspon AJ, Ortman M, Delurgio DB, Valadri R, Narasimhan C, Swapna N, Singh JP, Danik S, Markowitz SM, Almquist AK, Krahn AD, Wolfe LG, Feinstein S, Ellenbogen KA. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. *Europace* 2013;15:347–354.
8. Aizer A, Stern EH, Gomes JA, Teirstein AS, Eckart RE, Mehta D. Usefulness of programmed ventricular stimulation in predicting future arrhythmic events in patients with cardiac sarcoidosis. *Am J Cardiol* 2005;96:276–282.
9. Uusimaa P, Ylitalo K, Anttonen O, Kerola T, Virtanen V, Paakko E, Raatikainen P. Ventricular tachyarrhythmia as a primary presentation of sarcoidosis. *Europace* 2008;10:760–766.
10. Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR, Sweiss NJ, Nguyen DT, Aleong RG, Varosy PD, Weinberger HD, Sauer WH. Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosos. *J Cadiovasc Electrophysiol* 2012;23: 925–929.
11. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi T, Sekiguchi M. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* 2001;88:1006–1010.
12. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol* 2011;4:303–309.
13. Hiraga H, Yuwai K, Hiroe M. Guideline for the diagnosis of cardiac sarcoidosis: study report on diffuse pulmonary disease [in Japanese]. *Jpn Ministry of Health Welfare* 1993:23–24.
14. Japanese Ministry of Health and Welfare. Diagnostic standard and guidelines for sarcoidosis. *Jpn J Sarcoidosis and Granulomatous Disorders* 2007;27:89–102.
15. Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, Ogo KO, Nishii N, Watanabe A, Nagase S, Sakuragi S, Ohe T. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. *Heart Rhythm* 2007;4:1292–1299.
16. Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M, Kitakaze M, Tomoike H, Miyatake K. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. *Am J Cardiol* 2005;95:143–146.
17. Kato Y, Morimoto S, Uemura A, Hiramitsu S, Ito T, Hishida H. Efficacy of corticosteroids in sarcoidosis presenting with atrioventricular block. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:133–137.
18. Okayama K, Kurata C, Tawarahara K, Wakabayashi Y, Chida K, Sato A. Diagnostic and prognostic value of myocardial scintigraphy with thallium-201 and gallium-67 in cardiac sarcoidosis. *Chest* 1995;107: 330–334.
19. Tadamura E, Yamamuro M, Kubo S, Kanao S, Hosokawa R, Kimura T, Kita T, Togashi K. Multimodality imaging of cardiac sarcoidosis before and after steroid therapy. *Circulation* 2006;113:e771–e773.
20. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvemoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;11:1305–1323.
21. Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. *Heart* 2011;97:2078–2087.
22. Mantini N, Williams B Jr, Stewart J, Rubinsztain L, Kacharava A. Cardiac sarcoidosis: a clinician's review on how to approach the patient with cardiac sarcoid. *Clin Cardiol* 2012;35:410–415.
23. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, Meine TJ, White JB, Elliott MD, Kim HW, Judd RM, Kim RJ. Detection of myocardial damage in patients with sarcoidosis. *Circulation* 2009;120:1969–1977.
24. Mehta D, Mori N, Goldbarg SH, Lubitz S, Wisnivesky JP, Teirstein A. Primary prevention of sudden cardiac death in silent cardiac sarcoidosis: role of programmed ventricular stimulation. *Circ Arrhythm Electrophysiol* 2011;4:43–48.

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PII: S1547-5271(14)01416-7
DOI: http://dx.doi.org/10.1016/j.hrthm.2014.12.009
Reference: HRTHM6045

To appear in: *Heart Rhythm*

Cite this article as: Koji Miyamoto MD, Takeshi Aiba MD, PhD, Hiromi Kimura MD, PhD, Hideki Hayashi MD, PhD, Seiko Ohno MD, PhD, Chie Yasuoka MD, PhD, Yoshihito Tanioka MD, PhD, Takeshi Tsuchiya MD, PhD, Yoko Yoshida MD, Hiroshi Hayashi MD, Ippei Tsuboi MD, Ikutaro Nakajima MD, Kohei Ishibashi MD, Hideo Okamura MD, Takashi Noda MD, PhD, Masaharu Ishihara MD, PhD, Toshihisa Anzai MD, PhD, Satoshi Yasuda MD, PhD, Yoshihiro Miyamoto MD, PhD, Shiro Kamakura MD, PhD, Kengo Kusano MD, PhD, Hisao Ogawa MD, PhD, Minoru Horie MD, PhD, Wataru Shimizu MD, PhD, Efficacy and Safety of Flecainide for Ventricular Arrhythmias in Patients with Andersen-Tawil Syndrome with *KCNJ2* Mutation, *Heart Rhythm,* http://dx.doi.org/10.1016/j.hrthm.2014.12.009

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Short title: Efficacy and safety of flecainide for Andersen-Tawil syndrome

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Total word count: 4879 words

Total number of Tables: 2 and Figures: 4

Sources of Funding
This work was supported by grants from a Grant-in-Aid for Scientific Research on Innovative Areas (22136011 A02, Aiba), a Grant-in-Aid for Scientific Research (C) (24591086 Aiba) from MEXT of Japan, and a Research Grant for Cardiovascular Diseases (H24-033, H26-040 T Aiba, Y Miyamoto, S Kamakura, M Horie, and W Shimizu) from the Ministry of Health, Labor and Welfare, Japan.

Conflict of Interest: None