Carvedilol Therapy Improved Left Ventricular Function in a Patient With Arrhythmogenic Right Ventricular Cardiomyopathy

Yukio HIROI,1 MD, Katsuhito FUJIU,1 MD, Shuhei KOMATSU,2 MD, Makoto SONODA,1 MD, Yasunari SAKOMURA,3 MD, Yasushi IMAI,1 MD, Yumi OISHI,1 MD, Fumitaka NAKAMURA,1 MD, Kohsuke AJIKI,1 MD, Noriyuki HAYAMI,1 MD, Yuji MURAKAWA,1 MD, Minoru OHNO,1 MD, Yasunobu HIRATA,1 MD, Kuni OHTOMO,2 MD, and Ryozo NAGAI,1 MD

SUMMARY

An asymptomatic 35 year-old man was referred to our hospital because of abnormal ECG findings. The ECG showed complete right bundle branch block and left anterior hemiblock. Echocardiography revealed a moderately enlarged right ventricle (RV) and an apical aneurysm. RV wall motion showed diffusely moderate impairment, while the systolic function of the left ventricle (LV) was slightly decreased. The ejection fractions (EF) of the RV and LV were calculated as 28.1% and 41.9% by Simpson's method using multiple cardiac computed tomography (CT) scans. A 24 hour ambulatory ECG showed only 372 single premature ventricular contractions (PVC). Cardiac catheterization revealed that the RV was enlarged with prominent trabeculation and decreased motion. In an electrophysiologic study, neither electrical stimulation of the RV nor electrical stimulation plus isoproterenol infusion could induce ventricular tachycardia. Pathological examination of a biopsy from the interventricular septum of the RV revealed fibrofatty change in the myocardium. Based on these results, we made a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) and administered 5 mg of carvedilol. Sixty days after the initiation of carvedilol therapy, we performed repeat cardiac CT. The EF of the LV was markedly improved from 41.9% to 62.0%, although the EF of the RV was not changed. The number of PVCs showed no change. This case suggests that carvedilol is not only useful for controlling arrhythmia but also for improving left ventricular function in some patients with ARVC. Sympathetic overactivity is reported to cause sudden death, so carvedilol may be a first-line drug for some patients with ARVC. (Jpn Heart J 2004; 45: 169-177)

Key words: Arrhythmogenic right ventricular cardiomyopathy, Carvedilol, CT
ARRHYTHMOGENIC right ventricular (RV) cardiomyopathy (ARVC) is a myocardial disease affecting primarily the RV and is characterized histologically by the gradual replacement of myocytes by adipose and fibrous tissue.\(^2\) ARVC often accompanies ventricular tachycardia (VT), which is an important cause of sudden death in young people, especially during exercise. This disease is typically inherited as an autosomal dominant trait with variable penetrance and incomplete expression. Eight chromosomal loci have been reported and two genes were identified.\(^3\) One is the cardiac ryanodine receptor gene (RyR2) which induces calcium release from the sarcoplasmic reticulum into the cytosol\(^4\) and the other is desmoplakin which binds to plakoglobin, a key component of desmosomes and adherens junctions.\(^3\) The autosomal recessive genes responsible for ARVC have also been identified.\(^3\) One is plakoglobin itself (Naxos disease)\(^5\) and the other is desmoplakin, both of which interact with intermediate filament.\(^6\)

The prognosis for ARVC is quite different between cases.\(^7\) Patients with Naxos disease experience a more severe course\(^8\) and some patients are diagnosed at an elderly age.\(^9\) Medical treatment should be initiated with beta-blockers, sotalol, or amiodarone in the presence of arrhythmia or symptoms and implantation of an automatic cardioverter defibrillator is necessary for drug resistant sustained VT. However, there are no studies evaluating treatments in asymptomatic patients with morphologic RV alterations and without VT. Beta-blocker therapy is a reasonable choice for reducing the possibility of adrenergically-stimulated arrhythmia. We report here an ARVC case without VT in which decreased left ventricular (LV) systolic function was improved after carvediol.

**CASE REPORT**

A completely asymptomatic 35 year-old Japanese man was referred to our hospital because of abnormal ECG findings in his health examination. On physical examination, his blood pressure was 116/56 mmHg and his pulse was regular, with a rate of 84 bpm. Heart sounds were normal with no audible murmur. Laboratory data were normal including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and a chest radiograph was normal with a cardiothoracic ratio of 48% (Figure 1). An ECG showed complete right bundle branch block (RBBB) and left anterior hemiblock without any epsilon waves (Figure 2). A 24 hour ambulatory ECG showed only 372 single premature ventricular contractions (PVC) per day. We performed echocardiography for screening, which revealed a moderately enlarged right ventricle (RV) and an apical aneurysm (Figure 3A, B). RV wall motion showed diffuse moderate impairment, while the systolic function of the LV was slightly decreased (Figure 3C). Thus, we suspected ARVC and performed cardiac computed tomography (CT) and magnetic resonance imaging.
Figure 1. Chest X-ray of posterior-anterior view (A) and right-left view (B). Both were normal and the cardiac thoracic ratio was 48%.

Figure 2. ECG obtained in the hospital. Complete right bundle branch block and left anterior bundle block are obvious. There were no epsilon waves.
Enlargement of the RV with thin wall was revealed on cardiac CT (Figure 4A-D). The ejection fractions (EF) of the RV and LV were calculated as 28.1% and 41.9%, respectively, by Simpson's method using multiple CT scans obtained at 5 mm intervals. Enlargement of the RV was also suspected on cardiac MRI but intramyocardial fat was not prominent (Figure 5).

Though our patient was asymptomatic, we recommended further examinations in order to make a diagnosis. Cardiac catheterization revealed his pulmonary arterial pressure was 13/6 mmHg and RV pressure 21/5 mmHg. The coronary arteries were normal (Figure 6A, B), but the RV was enlarged with prominent trabeculation and decreased motion (Figure 6C). In an electrophysiologic study (EPS), neither electrical stimulation of the RV nor electrical stimulation plus isoproterenol could induce VT. Pathological examination of a biopsy specimen from the interventricular septum of the RV revealed disarray and fibrofatty changes in the myocardium, a finding consistent with ARVC (Figure 7).
Figure 4. Cardiac CT scans obtained before therapy (A-D). Longitudinal diastolic (A) and systolic (B) images and short axis diastolic and systolic images (C,D). RV was enlarged moderately and the function of the RV was moderately impaired (EF = 28.1%), while systolic function of the LV was slightly decreased (EF = 41.9%). Cardiac CT images obtained after carvedilol therapy (E-H). Longitudinal diastolic (E) and systolic (F) images and short axis diastolic and systolic images (G,H). Motion of the LV was improved (EF = 62.0%), but the function of the RV was unchanged (EF = 26.5%).
Based on these results, we made a diagnosis of ARVC and administered a small dose of carvedilol (5 mg daily) to prevent VT. Sixty days after the initiation of carvedilol therapy, we performed cardiac CT again. Unexpectedly, the EF of the LV was markedly improved from 41.9% to 62.0% (Figure 4A-H), although the

Figure 5. Cardiac MRI. Enlargement of RV was obvious.

Figure 6. Coronary arteriography and right ventriculography. Coronary arteries were normal (A,B) and RV was enlarged with prominent trabeculation (C).
EF of the RV was not changed (from 28.1% to 26.5%). Echocardiography revealed the EF of the LV calculated by the Teicholtz method had increased from 42.7% to 59.7% (Figure 2C, D). The number of PVCs showed no change and there were no side effects associated with carvedilol such as hypotension and bradycardia.

**DISCUSSION**

The prevalence of ARVC in the general population is approximately 1 in 5000, but the disease is not well recognized because of the difficulty in making the diagnosis. The typical clinical onset of ARVC occurs in adolescence and young adulthood, although our case was 35 years-old and completely asymptomatic. A familial cause has been found in 30% of cases with ARVC. Our case is not married and has no relatives who have heart diseases or died suddenly, therefore, he might be a sporadic case.

T-wave inversion in leads V1 to V3 in the absence of a complete RBBB is a useful clue in patients > 12 years old with suspected ARVC though it is a minor diagnostic criterion, while epsilon waves are a major diagnostic criterion that are found in up to 30% cases of ARVC. Complete RBBB is found in approximately 15% of patients with ARVC and incomplete RBBB is observed in 18%. Importantly, almost half of their cases had a normal 12-lead ECG and 55% of affected patients had no ECG-documented ventricular arrhythmia in 37 ARVC families. In our case, the ECG showed complete RBBB and left anterior hemiblock with no epsilon waves (Figure 2) and a 24 hour ambulatory ECG showed only 372 PVCs per day. ECG and 24 hour ambulatory ECG are useful for the screening of cardiac
diseases but are not definitive in the diagnosis of fifty percent of patients with ARVC.

Echocardiography is extremely useful for the screening and diagnosis of many cardiac diseases. In the present case, it clearly revealed a moderately enlarged RV and an apical aneurysm (Figure 3A, B). It also showed diffuse moderate impairment of RV motion with slightly decreased LV function (Figure 3C). We should perform echocardiography for the screening of block and PVC even if the patient is asymptomatic.

CT and MRI are noninvasive and important methods for the diagnosis of ARVC. It is easy to confirm dilated RV and fibrofatty changes in the myocardium.\textsuperscript{12,13} Sometimes fibrofatty change is difficult to detect because the RV wall is thin and there is epicardial and pericardial fat,\textsuperscript{13} like in our case. Simpson's method using multiple CT scans obtained at 5 mm intervals and synchronized ECG were used to evaluate EF. This method is more accurate than Teicholtz's method and Simpson's method using only one scan. The evaluation of the EF of the RV is almost impossible using Teicholtz's method and Simpson's method using only one scan because the RV shape is complex. We believe CT and MRI are also useful methods with which to follow up the function of LV and RV in ARVC.

Cardiac catheterization is an important examination. An enlarged RV with prominent trabeculation with normal coronary arteries (Figure 6A-C) and normal RV pressure were consistent with ARVC. It is extremely important for prognosis and therapy to determine whether the patient has VT or not in asymptomatic ARVC. Neither electrical stimulation of the RV nor electrical stimulation plus isoproterenol could induce VT in our patient, indicating the risk of death by arrhythmia was low in our patient at this time. For the diagnosis of ARVC, especially in a sporadic case, a pathological examination is quite important and necessary. The RV inflow area, apex, and infundibulum are most frequently involved and fibrofatty replacement of the myocardium is a major diagnostic criterion.\textsuperscript{2} Because intramyocardial fat increases with age and to avoid overdiagnosis of ARVC, it has been proposed that more than 3\% fibrous tissue and more than 40\% fatty tissue are highly suggestive of ARVC.\textsuperscript{14} Our case is also consistent with this proposal (Figure 7).

Since we felt sympathetic overactivity would worsen the prognosis of this patient and beta-adrenergic blockers are useful for congestive heart failure, we administered a small dose of carvedilol to avoid side effects such as hypotension and bradycardia. The improvement in LV function was marked (Figure 3C, D, 4A-H) though the EF of the RV was not changed. We did not expect carvedilol to have an effect on RV and function because fibrofatty replacement is irreversible. This case suggests that blocking sympathetic overactivity is important not only
for controlling arrhythmia but also for improving LV function in some patients with ARVC, although not RV function. Therefore, carvedilol may be a first-line drug for ARVC with few complications.

REFERENCES