THE USEFULNESS OF EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY IN THE DIAGNOSIS OF ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA AND A REPORT OF CASES OF A FAMILIAL OCCURRENCE

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Arrhythmogenic right ventricular dysplasia (ARVD) is a recently identified clinical entity and its diagnosis rests on documentation of ventricular tachycardia (VT) of right ventricular origin and morphologic changes of the right ventricle. However, the diagnosis of ARVD is difficult noninvasively and often requires angiography. The usefulness of equilibrium radionuclide ventriculography as a noninvasive method for the diagnosis of ARVD has not been fully evaluated. We performed equilibrium radionuclide ventriculography in 7 patients with ARVD, 10 normal subjects and 9 patients with dilated cardiomyopathy (DCM). The right ventricular ejection fraction (EF) in patients with ARVD ($25 \pm 8\%$, mean $\pm$ SD) was lower ($p < 0.001$) than that in normal subjects ($56 \pm 7\%$) but was not significantly different from that in patients with DCM ($32 \pm 10\%$). The left ventricular EF in patients with ARVD ($57 \pm 12\%$) was lower ($p < 0.05$) than that in normal subjects ($70 \pm 7\%$), but higher ($p < 0.001$) than that in patients with DCM ($27 \pm 7\%$). These findings suggest that ARVD is a specific form of DCM which predominantly affects the right ventricle and that equilibrium radionuclide ventriculography may be a useful noninvasive method for the diagnosis of this disorder.

In addition, we present a family in which 3 of 6 siblings were affected by ARVD, suggesting that some genetic factors may be involved in the etiology of this disorder.

ARRHYTHMOGENIC right ventricular dysplasia (ARVD) is recognized clinically by recurrent ventricular tachycardia (VT) of right ventricular origin and by segmental or generalized right ventricular cardiomyopathy.¹⁻⁵ Since Frank et al first reported 4 cases of ARVD in 1978⁶ many cases have been reported and its characteristics

have been clarified.^{1,3,7-9} The diagnosis of ARVD is based on recurrent VT of the left bundle branch block morphology in the absence of clinical or angiographic evidence of coronary artery disease or other organic heart disease.^{1,3,5,8} Segmental or global right ventricular wall motion abnormalities were documented by angiography of the right ventricle^{10,11} and/or echocardiography.^{11,12} However, it is difficult to make the diagnosis of ARVD by the routine noninvasive methods. Equilibrium radionuclide ventriculography is a simple and noninvasive method which

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TABLE I SUMMARY OF DATA IN PATIENTS WITH ARVD

Patient	Age (years)	Sex	X-ray CTR (%)	Electrocardiogram		Echocardiogram				Angiogram		
				Inverted T in precordial leads	VT morphology	RV		LV		RV/LV ratio	LVEF (%)	RVEF (%)
						diastole	systole	diastole	systole			
1	54	M	63	V_1-V_6	LBBB	5.2	4.6	4.1	3.7	1.00	25	16
2	41	M	56	V_1	LBBB	3.1	2.5	3.6	3.1	0.99	58	29
3	16	M	42	V_1	LBBB	3.6	2.4	3.8	2.8	1.00	69	—
4	37	M	46	V_1-V_3	LBBB	4.2	3.0	4.0	3.0	0.98	74	38
5	37	M	54	V_1-V_5	LBBB	5.2	4.8	2.4	1.5	2.04	55	—
6	41	M	54	V_1-V_6	LBBB	4.6	4.0	3.7	2.5	1.15	70	37
7	26	M	56	V_1-V_6	LBBB	3.8	3.8	4.0	3.1	0.95	65	—

Control ECG

During Attack

Fig.1. ECG from patient 6. T-wave inversion in precordial leads was evident and right ventricular hypertrophy was suggested on the rest ECG. VT with the left bundle branch morphology was documented during attack.

is useful to determine the right ventricular ejection fraction (EF), independent of the geometry of the right ventricle.¹³⁻¹⁸ Therefore this method may be useful for the diagnosis of ARVD.

In this study, we examined right and left ventricular function in seven cases with ARVD using equilibrium radionuclide ventriculography. Because some investigators have suggested that this disorder is generalized cardiomyopathy,⁸ the results were compared with those in normal subjects and patients with dilated cardiomyopathy (DCM).

We also presented 3 siblings with ARVD occurring in a family. Familial occurrence suggests that some genetic factors may be involved in the etiology of ARVD.

METHODS

Patients (Table I)

The study group comprised 7 patients with ARVD, 10 normal subjects and 9 patients with DCM. ARVD was clinically diagnosed based on documentation of VT of right ventricular origin and the dilated right ventricle with reduced ejection fraction assessed by right ventricular angiography and/or 2-dimensional echocardiography (2DE). All patients with ARVD were male and their mean age was 36 ± 12 years (range, 16–54 years). Three patients were siblings. Chest X-rays showed moderate cardiac enlargement in 5 patients. The resting electrocardiograms (ECGs) showed T-wave inversion in the anterior precordial leads beyond V_3 in 5 patients. Postexcitation waves were not clearly identified. Spontaneous VT was documented in all patients on 12

Fig.2. Equilibrium radionuclide ventriculography in patient 5. The right ventricle is markedly enlarged and poorly contracts. The right and left ventricular ejection fractions in this patient are 28 and 62%, respectively.

leads ECG or by Holter ECG monitoring, which showed the left bundle branch block morphology. ECGs at rest and during an attack of VT in patient 6 are shown in Fig. 1. All patients had 2-dimensional echocardiographic (2DE) examination in the supine or left recumbent position using a Toshiba SSH-11 Sonolayergraph phased array sector scanner with 78° scanning angle, equipped with a 32-element transducer with the frequency of 2.4 MHz. The images of the right ventricle were obtained in the apical four chamber view. The right and left ventricular dimensions were determined in this view by measuring a maximal minor axis of each ventricle¹⁹ and the right ventricular/left ventricular diameter ratio was calculated from the end-diastolic data. Normal values in this view in our laboratory are 1.6–2.4 cm (2.0 ± 0.3 cm; end-systole of the right ventricle), 2.1–3.4 cm (2.5 ± 0.4 cm; end-diastole of the right ventricle), 2.1–3.2 cm (2.5 ± 0.3 cm; end-systole of the left ventricle) and 3.2–4.5 cm (3.7 ± 0.4 cm; end-diastole of the left ventricle). All patients showed right ventricular dilatation. The left ventricular dimensions were within normal limits except in patient 1 who was previously reported in our laboratory as having ARVD with both ventricular dysfunction in the course.²⁰ Patients 3, 5, and 7 without right ventricular angiography were diagnosed as having ARVD by echocardiography only. Coronary artery disease or valvular heart

disease was excluded by cardiac catheterization in all patients. Right ventricular angiography was performed in 4 patients and revealed the dilated and hypokinetic right ventricle. Electrophysiologic study (EPS) was performed in 4 of 7 patients and VT was induced in 1 patient.

Normal subjects comprised 8 males and 2 females, and the mean age was 33 ± 12 years (range, 20–55 years). Four were normal volunteers. The remaining 6 were patients who underwent diagnostic catheterization for chest pain. All had normal coronary arteriographic and hemodynamic results.

Patients with DCM were 7 males and 2 females, and the mean age was 45 ± 7 years (range, 33–54 years). DCM was diagnosed based on dilatation of the left ventricle with reduced EF of less than 40% determined by angiography. Coronary angiography showed normal coronary arteries or minimal coronary stenosis of $< 25\%$. No patient with DCM had hypertension, angina pectoris, previous myocardial infarction or pathologic Q waves on ECG. Treadmill exercise testing showed no ischemic ST change in any of these patients with DCM.

Radionuclide ventriculography

Multiple gated equilibrium radionuclide ventriculography was performed after an injection of 15 mCi ^{99m}Tc labeled human serum albumin using a gamma camera and a converging hole

Fig.3. Right and left ventricular EF values in normal subjects, in patients with ARVD and in patients with DCM. The mean right ventricular EF in patients with ARVD and DCM was lower than in normal subjects ($p < 0.001$). The mean left ventricular EF in patients with ARVD was slightly lower than in normal subjects ($p < 0.05$), but it was higher than in DCM ($p < 0.001$).

collimeter. The 45° left anterior oblique projection was used. Energy selection was set at 140 KeV with a 20% window. Gated images were collected with a computer (Shimadzu, Scintipac 1200) and an electrocardiographic synchronizer in a 64 × 64 matrix. The frame interval for each patient was < 40 msec.²¹ Ectopic beats were excluded from the data.²² Smoothing was performed using a spatial (9 point) and the temporal (3 point) filter. Background correction was estimated automatically by the computer using a linear interpolated technique similar to that described by Goris et al.²³ A right ventricular region of interest on the image of a composite cardiac cycle was drawn with a joy-stick to a width of 2–3 matrix elements from the right ventricular activity with care taken to avoid the inclusion of the pulmonary artery. An automated computer program then defined the right ventricular regions of interest for each frame of the composite cardiac cycle, determined the activity within each region of interest and generated a time activity curve based on the background corrected counts obtained from these varying regions of interest. The region of interest on each frame was drawn automatically and displayed on a cathode-ray tube (CRT). Its accuracy was examined by an operator. The computer program permitted the operator to observe the motion of

each cardiac chamber on a color CRT and helped to determine the proper end-diastolic region of interest. The right ventricular EF was determined by the computer from the time activity curve. The left ventricular EF and peak filling rate were determined by the same method.

In our laboratory, inter- and intraobserver variabilities were analyzed and there was a satisfactory reproducibility of right and left ventricular EF. There was also a good correlation between right ventricular EFs calculated by first pass and equilibrium method.^{14,15}

Statistical analysis

Statistical analysis was performed using analysis of variance and correction was made by the Bonferroni's method. P values less than 0.05 were considered significant. All values are expressed as mean ± SD.

RESULTS

Equilibrium radionuclide ventriculography

Figure 2 reveals the markedly enlarged and poorly contracting right ventricle in a patient with ARVD (patient 5) examined by equilibrium radionuclide ventriculography. Fig. 3 summarizes the data. In patients with ARVD, the right and left ventricular EFs were $25 \pm 8\%$ and $57 \pm 12\%$,

Fig.4. The family background of patients 5, 6, 7. Darkened symbols represent affected members. The striped symbol represents a possibly affected member.

respectively. In normal subjects, the right and left ventricular EFs were $56 \pm 7\%$ and $70 \pm 7\%$, respectively. Patients with ARVD had lower right ventricular EF than normal subjects ($p < 0.001$). In patients with DCM, the right ventricular EF was $32 \pm 10\%$ which was not different from that in patients with ARVD. The left ventricular EF in patients with ARVD was slightly but significantly lower than that in normal subjects ($p < 0.05$) and higher than that in patients with DCM ($p < 0.001$).

Familial occurrence of ARVD

In Table I, patients 5, 6, 7 were siblings; the family history is shown in Fig. 4. The father was healthy and did not have arrhythmias. The mother died at 56 years old because of heart disease but details were not known. Three of 6 siblings were diagnosed as having ARVD. They had syncope due to VT. Two were not examined because they lived far from our hospital but their ECGs at rest which were sent to us were within normal limits. The only woman of the 6 siblings had arrhythmias which were multiple premature ventricular complexes without VT by Holter ECG and she had no symptoms. Thus she was not included in Table I. She had equilibrium radionuclide ventriculographic examination and right ventricular EF was 19% and left ventricular EF was 39%.

DISCUSSION

Utility of equilibrium radionuclide ventriculography

The diagnosis of ARVD is based on recurrent VT originating in the right ventricle and some

morphologic changes.^{5,10,24} VT with left bundle branch block configuration can be assessed by ECG. However, morphologic abnormalities of the right ventricle were assessed mainly by angiography. Several reports have suggested that echocardiography could identify right ventricular morphologic abnormalities associated with this rare disorder.^{3,11,12} Marcus et al showed right ventricular enlargement in 6 patients³ and Baran et al reported findings by 2DE in 1 patient and found multiple outpouchings and sacculations of the right ventricle confirmed by angiography.¹² Quantitatively, the diagnosis of ARVD using M-mode echocardiography relied on the measurement of the right ventricular/left ventricular diameter ratio.³ Recently, 2DE findings in ARVD were compared with angiographic findings¹¹ and the usefulness of 2DE technique was explored. In our study, we used angiography and/or 2DE in the diagnosis of ARVD and dilatation of the right ventricle was detected in the apical four chamber view. However, there is considerable subjectivity in interpretation of right ventricular changes by 2DE and the absence of the established quantitative criteria for both M-mode and 2DE techniques is an important limitation. In addition, because of the anatomical structure, only a expert could detect the localized abnormalities.¹⁹

We used equilibrium radionuclide ventriculography in this study. This is a reliable and non-invasive method for evaluating the right and left ventricular EF.^{13-15,17,18} Our results indicated that the right ventricular EF was lower in patients with ARVD than in normal subjects and the left ventricular EF was slightly lower in patients with ARVD than in normal subjects. Purves et al

reported a case with ARVD which was detected by radionuclide ventriculography at rest and echocardiography failed to reveal definite right ventricular abnormalities.²⁵ Manyari et al also reported right ventricular hypofunction in 6 patients with ARVD by radionuclide ventriculography at rest and exercise.⁸ In these 2 studies, radionuclide ventriculography at rest clearly demonstrated hypofunction of the right ventricle. Our results are compatible with these previous studies and suggest that this method may be useful in the noninvasive diagnosis of ARVD. In the study by Manyari et al, the left ventricular EF in patients with ARVD did not increase during exercise. Therefore they suggested that ARVD may be a generalized cardiomyopathy. However, the left ventricular EF was not different at rest from that of normal subjects. In our laboratory, Higuchi et al reported a case of ARVD in which the patient manifested progressive left ventricular dysfunction.²⁰ Our study clearly demonstrated that the left ventricular EF by radionuclide ventriculography was slightly but significantly lower ($p < 0.05$) in patients with ARVD than that in normal subjects, but was higher than that in patients with DCM. The right ventricular EF was not different between ARVD and DCM. These findings suggest that ARVD may be a specific form of DCM which affects the right ventricle predominantly with minor involvement of the left ventricle. It is not known whether ARVD may result in severe left ventricular dysfunction in future and may be indistinguishable from DCM.

Familial occurrence of ARVD

The pathogenesis of ARVD is still unknown and genetic predisposition is also unclear. ARVD may closely resemble Uhl's anomaly which is a rare congenital cardiac malformation. However, unlike Uhl's anomaly, there is no absence of the myocardium. In ARVD, some areas of the myocardial wall are thinned and other areas are hypertrophied, but the endocardial, myocardial and epicardial layers are all identifiable. Fontaine et al suggested that ARVD is a result of an anomaly in the structure of myocardial fibers of the working myocardium already present in the embryo. This reasoning is based on the fact that ARVD was observed in other members of the same family (siblings or father), which suggests some genetic factors.⁵ There had been several reports of VT of the left bundle branch block morphology or of sudden death in relatives of

patients with ARVD.^{3,20,26,27} Although this was suggestive of a familial occurrence of ARVD, the definite evidence of organic disease of the right ventricle in these relatives has not been presented. Ruder et al first reported familial cases of ARVD documented by echocardiography or histologic examination of the hearts.²⁸ In the family examined in this study, 3 of 6 siblings were affected and 1 other sibling also might have had ARVD although she did not have documented VT.

These results suggest that this disorder may be inherited but not sex linked. Since patients with ARVD are susceptible to sudden death due to VT, all family members of a patient with ARVD should be examined. Equilibrium radionuclide ventriculography is a useful method to examine right ventricular function.

In summary, we reported 7 cases of ARVD in which we evaluated right and left ventricular function using equilibrium radionuclide ventriculography. The results suggest that ARVD is a specific form of DCM and this method may be useful to diagnose this disorder noninvasively. Our cases included 3 siblings, which suggests that this disorder may have some genetic factors.

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