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Long-term prognostic value of cardiac autonomic nervous activity in postoperative patients with congenital heart disease

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ABSTRACT

Background: Abnormal cardiac autonomic nervous activity (CANA) is not uncommon in postoperative patients with congenital heart disease (CHD).

Methods and results: We attempted to clarify the prognostic value of the CANA variables in postoperative CHD patients and prospectively evaluated the CANA variables in 292 consecutive biventricular and 91 Fontan repair patients. The CANA variables included the heart rate variability, arterial baroreflex sensitivity (BRS), washout ratio of the myocardial metaiodobenzylguanidine scintigraphy, and plasma norepinephrine level. With a follow-up of 10 ± 2 years, 98 total events that required hospitalization, including 13 deaths and 48 unscheduled cardiac events (UCEs), occurred. In all the CHD patients, all the CANA indices predicted the total events and UCEs. Of those, the NE level ($p = 0.0004$) and BRS ($p = 0.0373$) predicted the mortality. In a multivariate analysis, the BRS was an independent CANA-predictor for the total events ($p = 0.007$). In the biventricular patients, the plasma NE level, heart rate variability, and BRS predicted the total events and UCEs and the BRS was the only independent CANA-predictor for the total events ($p = 0.0329$). In the Fontan patients, the plasma NE level was the only predictor for the UCEs ($p = 0.0242$) and no other CANA variables were independent predictors of the total events or UCEs.

Conclusions: All CANA variables, especially the BRS, were useful predictors for future clinical events in biventricular CHD patients, whereas no CANA variables, except for the plasma NE level, predicted future clinical events in the Fontan patients.

1. Introduction

Abnormal cardiac autonomic nervous activity (CANA) commonly coexists with impaired hemodynamics in patients with heart failure [1] and the magnitude of the abnormal CANA correlates to the heart failure severity and predicts the adverse outcome in these patients [2]. Similarly, an abnormal CANA is relatively common in postoperative patients with congenital heart disease (CHD), such as a diminished heart rate variability and arterial baroreflex sensitivity (BRS) [3,4], and the impairment is more prominent in postoperative CHD patients than in heart failure patients without CHD partially due to the surgery-related cardiac denervation in the postoperative CHD patients [5]. In biventricular postoperative CHD patients, the abnormal CANA reflects, to some extent, the heart failure severity. In contrast, the abnormal CANA poorly correlates with the heart failure severity in Fontan and complex CHD patients who had required multiple surgical interventions [2–6]. However, there have been few studies that address the prognostic values of these CANA variables. Accordingly, the purpose of the present study was to clarify the prognostic value of the CANA variables in postoperative CHD patients after biventricular (BVR) and Fontan repairs.

2. Subjects

We prospectively studied 383 consecutive clinically stable postoperative CHD patients (Fontan = 91, BVR = 292, 17.4 ± 7.7 years, 1 to 40 years) and 54 with a history of Kawasaki disease as referents from December of 1995 to April of 2003. They included 116 adult subjects (≥18 years, 93 CHD, 23 referents). The details of the clinical characteristics, including their medical status, are shown in Table 1. The referent subjects were being followed at our institute because of a history of dilatation and/or aneurysm of the coronary arteries due to Kawasaki disease and showed no significant stenotic lesions of the coronary arteries [3–6], and their values of their hemodynamics, CANA and neurohormonal activity were used as a reference. The procedures in the patients after a right ventricular outflow tract reconstruction included tetralogy of Fallot in 87 patients, double outlet right ventricle in 15, transposition of the great arteries after Rastelli operation in 15, double switch operation (atrial switch and Rastelli type procedures) for atrioventricular discordance in 12, conventional repair in 9, and persistent truncus arteriosus in 7. The

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Table 1
Subject characteristics.

	Congenital heart disease	
Type of repair	Fontan repair	Biventricular repair
Number of cases	91	292
Male gender (%)	58	56
Age (year)	14±6	15±6
Age at first repair (year)	6±4	7±7
Follow-up (year)	7±4	6±6
NYHA class (I/II/III+IV)	27/54/10	218/59/15
SV morphology		
Non-LV (%)	59	3
No. of surgeries	2.6±1.2	1.9±1.1
Type of procedures		
A/VSD closure	–	70
RVOTR	–	145
ASO	–	15
Ross	–	28
Repair of CoA/IAA	–	30
Others	–	4
Fontan (APC/TCPC)	–	14/77
Previous or additional procedures at repair (%)		
APS	58	27
PAB	23	4
AVVP/R	14	3
AVR	0	5
PMI	0.3	2
Medications (%)		
Digoxin	9	8
Diuretics	47	20
Anticoagulant	56	21
Antiarrhythmia	1	2
ACEI/ARB	5	5
β blocker	3	z2

ACEI = angiotensin converting enzyme inhibitor, APC = antriopulmonary connection, APS = aortopulmonary shunt, ARB = aigiotensin II receptor blocker, A/VSD = atrial or ventricular septal defect, ASO = arterial switch operation, AVD = atrioventricular discordance, AVR = aortic valve replacement, AVVP/R = atrioventricular valve repair or replacement, CoA/TAA = coarctation/interruption of the aorta, FU = follow-up period, PAB = pulmonary artery banding, PMI = pacemaker implantation, RVOTR = right ventricular outflow tract reconstruction, SV = systemic ventricle. TCPC = total cavopulmonary connection. Values are mean ± SD.

follow-up period from the last operation to the time of the study was at least 3 months in the post-surgical patients. All patients were free from any intravenous medications and 44 patients had undergone a pacemaker implantation. We excluded the patients with unrepaired complex cyanotic CHD, Eisenmenger syndrome, and primary pulmonary hypertension from the present study.

3. Methods

3.1. Postoperative status based on the New York Heart Association classification

Because the New York Heart Association (NYHA) classification of the cardiac status applies to adult cardiac patients, a modification of the classification was used for our pediatric patients [7].

3.2. Systemic ventricular systolic function

Of the 383 CHD patients and 54 referents, cardiac catheterization with cineventriculography was performed in the 328 CHD patients (237 with BVR and 90 with Fontan) and 51 referents. The morphology of the systemic ventricle was determined angiographically and/or echocardiographically, then the patients were divided into 3 groups as previously described, i.e., those with 1) a dominant left ventricle with or without a rudimentary right ventricle; 2) the presence of both right and left ventricles; and 3) a dominant right ventricle with or without a rudimentary left ventricle [7], and then our patients were divided into 2 groups, i.e., those with a left ventricular type and those with a non-left ventricular type. In patients who underwent cineventriculography, the morphological right and left ventricular volumes were estimated using Simpson's rule and the systemic ventricular ejection fraction (SVEF) was calculated [3,4]. When cineventriculography was not available, the SVEF was estimated by echocardiography using Pombo's method in patients with left ventricular type systemic ventricles and a nuclear imaging technique was applied to estimate the SVEF in the CHD patients with right ventricular type systemic ventricle. Because of the inaccuracy of these estimations for the SVEF, our patients were further divided into 3 SVEF-based groups, i.e., groups with preserved (SVEF ≥ 50%), reduced (30% ≤ SVEF < 50%) and poor (SVEF < 30%) SVEF values, and were graded as 0, 1, and 2, respectively.

3.3. Neurohumoral activity

After at least 15 min of supine rest, the plasma norepinephrine and B-type natriuretic peptide levels (NE and BNP, respectively) were determined by high-performance liquid chromatography (367 subjects) [8] and (BNP, 371 subjects) were assayed by radioimmunoassay [9], respectively.

3.4. Heart rate variability and the BRS

The heart rate variability and BRS were measured in 347 and 340 subjects, respectively. The methods were reported previously [3,4]. Briefly, after a 15-minute supine rest, ECG signals were recorded for 5 min and the beat-to-beat fluctuations were transformed into frequency domains using a fast Fourier transformation. The spectral heart rate variability was expressed as a low frequency component (0.04 to 0.15 Hz) and a high frequency (HF) component (0.15 to 0.40 Hz) and the logarithmic values were used. A phenylephrine bolus method was used to measure the BRS (ms/mm Hg) [10]. The patients with a pacemaker implantation without sinus rhythm were excluded from these analyses.

3.5. [^{123}I] Metaiodobenzylguanidine scintigraphy

The methodology for this index was identical to that previously reported [3,4]. Metaiodobenzylguanidine scintigraphy (MIBG) was performed in 228 subjects to evaluate the myocardial adrenergic nervous activity. Myocardial images were acquired 4 h after a tracer injection and the heart to mediastinal activity ratio and myocardial washout ratio (WR) were calculated. The WR was defined as the percent change in the activity from the initial to the delayed images within the left ventricle and was calculated as follows: washout rate (%) = [(A − B/A)] × 100, where A is the average count per pixel in the left ventricle on the initial image and B is the average decay-corrected count per pixel in the same region on the delayed image. There were no definitive criteria for the subject selection and the reason why all patients did not undergo this scintigraphy was due to the capacity of our laboratory.

Informed consent was obtained from all patients and/or their parents. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee and approved by the Ethical Committee of the National Cardiovascular Center.

3.6. Prospective clinical events

Clinical events were divided into 2 categories, i.e., total events and unscheduled cardiac events (UCEs). The total events included scheduled hospitalizations for catheter and/or surgical intervention(s) and miscellaneous events, such as hemoptysis and infectious endocarditis. Scheduled catheter or surgical interventions included balloon dilatation for a stenotic pulmonary branch(s) or re-reconstruction of the right ventricular outflow tract due to progressive stenosis as well as a conversion from atriopulmonary connection to total cavopulmonary connection in Fontan patients. UCEs requiring hospitalizations included arrhythmias, heart failure, thromboembolisms, emergent catheter and/or surgical interventions and all-cause death. Protein losing enteropathy, including its relapse, and renal failure were categorized as heart failure. The diagnosis of enteropathy and the definition of heart failure were described previously [11,12]. Decisions for emergent catheter and/or surgical interventions for hemodynamic abnormalities were decided at our clinical conferences.

3.7. Statistical analysis

Data are expressed as the mean ± SD. Differences in the CANA variables, BNP, and hemodynamic variables were evaluated using an unpaired t test or one-way ANOVA with a Bonferroni post hoc test where appropriate. We used a univariate Cox's proportional hazards model to predict the associations of the clinical factors, i.e., age, gender, hemodynamic physiology (BVR or Fontan physiology) as well as the SVEF, CANA variables and BNP levels. To ease the interpretability of the results, hazard ratios were computed for intervals of 5 (years) for the age, 100 (pg/ml) for the NE and 10 (pg/ml) for the BNP. When the variables were statistically significant, the receiver–operator characteristic (ROC) curve analysis was applied to determine the cutoff values to identify an efficient prognostic prediction, i.e., the values with a maximal area under the ROC curve (AUC). The variables that proved to be significant predictors of the outcome in the univariate analysis ($p < 0.05$) were included in the multivariate analysis of the Cox's regression model to determine any independent outcome predictors. The MIBG findings were excluded from the multivariate analysis because of the smaller number of CHD patients who underwent the test when compared with the other CANA variables. A free status from total events, including all-cause death, was estimated using the Kaplan–Meier method and the differences in the event free status between the groups were assessed using log rank tests. A p value of <0.05 was considered statistically significant.

Table 2
Comparison of the hemodynamics, neurohormonal factors and exercise variables between Fontan and BVR patients.

Groups	Fontan repair	Biventricular repair	Reference	P value
SV systolic function				
SVEF grading	1.5 ± 0.6*!	1.9 ± 04*	2.0 ± 0.0	<0.0001
(Preserved/reduced/poor)	46/40/5	257/30/5	54/010	
Neurohormonal activity				
Norepinephrine (pg/ml)	258 ± 139*!	166 ± 83	157 ± 70	<0.0001
BNP (pg/ml)	41 ± 67*	35 ± 55*	4 ± 4	0.0003
Cardiac autonomic nervous activity				
log LF	1.6 ± 0.5*!	1.9 ± 0.5*	2.5 ± 0.4	<0.0001
log HF	1.3 ± 0.6*!	1.7 ± 0.5*	2.5 ± 0.5	<0.0001
BRS (ms/mm Hg)	3.2 ± 3.2*!	7.9 ± 5.7*	17.6 ± 6.3	<0.0001
H/M	1.7 ± 0.4*!	1.8 ± 0.5*	2.9 ± 0.5	<0.0001
WR (%)	56 ± 17*!	50 ± 19*	22 ± 10	<0.0001

BNP = brain natriuretic peptide, BRS = arterial baroreflex sensitivity, EDP = end-diastolic pressure, EDVI = end-diastolic volume index, EF = ejection fraction, H/M = heart to mediastinal metaiodobenzylguanidine activity ratio, PV = subpulmonary ventricle, Sp02 = arterial oxygen saturation, SP = systolic pressure, SV = systemic ventricle, LF and HF = low and high frequency component of heart rate variability, WR = myocardial metaiodobenzylguanidine washout ratio. The values are the mean ± SD. * and ! indicate a $p<0.05$, vs. the referent and biventricular groups, respectively.

4. Results

4.1. SVEF, BNP and CANA variables

The number of patients in NYHA I, II, and III + IV heart failure at the entry of the present study was 27, 54, and 10 in the Fontan group and 218, 59, and 15 in the BVR groups, respectively (Table 1). The data on those variables are shown in Table 2. The Fontan patients exhibited a relatively impaired CANA and systemic ventricular systolic function with high BNP levels.

4.2. Total events and UCEs

We lost 6 BVR and 2 Fontan patients during the follow-up and the remaining 375 CHD patients were analyzed. During a follow-up of 9.8 ± 2.1 years (6.5 to 14.1 years), 98 total events (66 with BVR, 32 with Fontan) and 48 UCEs (27 with BVR, 21 with Fontan) occurred. Of the 48 UCEs, arrhythmias occurred in 19 (13 with BVR, 6 with Fontan), heart failure in 23 (9 with BVR, 14 with Fontan), sudden death in 3, surgery-related death in 1, and one each for an emergent surgery and theoboembolism. Eventually, 13 patients (8 with BVR, 5 with Fontan) died due to heart failure in 7, sudden death in 3, surgery-associated complications in 1 and others in 2.

4.3. Prognostic power of the BNP and CANA variables

The significant prognostic variables from the univariate and multivariate Cox analyses in all CHD, BVR, and Fontan patients are summarized in Tables 3–5. Because of the smaller number of deaths, the statistical approach for the mortality was performed in only all of the CHD patients.

4.4. All CHD patients

In addition to the SVEF and BNP levels, all the CANA variables, except for the heart to mediastinal MIBG activity ratio for UCEs, could predict the total events and UCEs (Table 3). Regarding the mortality, of the CANA variables, the NE and BRS were the only significant predictors ($p = 0.0004$ and 0.0373, respectively).

In the multivariate analysis, the NYHA class and BRS independently predicted the total events ($p<0.05$ and 0.01, respectively). Regarding the UCEs and mortality, the NYHA class was the only independent predictor ($p<0.01$).

The Kaplan–Meier curves of the free status from total events for the 3 CANA variables (BRS, log HF, and WR) are shown in Fig. 1 and the curves for the NE and BNP are also shown in Fig. 2. When the variables were not significant predictors, the Kaplan–Meier curve was conducted based on the median value.

4.5. BVR physiology

In the univariate analysis, the BNP level, NE, heart rate variability, and BRS predicted the total events and UCEs. Of those, the age and BRS were the only independent predictors for total events ($p<0.05$), while a male gender and the NYHA class were independent predictors for

Table 3
Univariate and multivariate predictors of cardiac events and death in all CHD patients.

	Morbidity						Mortality		
	Total events			Unscheduled cardiac events			Death		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis									
Patients profiles (n = 375)									
Age (5 years)	1.197	1.017–1.409	0.0305	1.200	0.951–1.515	0.1245	0.985	0.605–1.605	0.9523
Male gender	1.588	1.048–2.408	0.0293	2.046	1.098–3.814	0.0242	4.493	0.996–20.27	0.0507
NYHA class	2.899	2.217–3.791	<0.0001	4.907	3.385–7.114	<0.0001	5.667	3.129–10.26	<0.0001
Fontan physiology	1.789	1.170–2.736	0.0072	2.898	1.633–5.144	0.0003	1.917	0.627–5.861	0.2537
Cardiac performance (n = 375)									
SVEF (0 = poor, 1 = red, 2 = nor)	0.380	0.280–0.516	0.0001	0.232	0.158–0.342	<0.0001	0.230	0.1130–0.468	<0.0001
Neurohormonal activity									
NE (100 pg/ml) (n = 367)	1.318	1.144–1.519	<0.0001	1.499	1.267–1.773	<0.0001	1.643	1.247–2.165	0.0004
BNP (10 pg/ml) (n = 371)	1.071	1.052–1.091	<0.0001	1.087	1.064–1.100	<0.0001	1.080	1.047–1.115	<0.0001
Cardiac autonomic nervous activity									
log HF (n = 347)	0.631	0.435–0.915	0.0153	0.553	0.328–0.933	0.0265	0.780	0.285–2.137	0.6295
BRS (n = 340)	0.879	0.836–0.924	<0.0001	0.869	0.806–0.938	0.0003	0.834	0.704–0.989	0.0373
H/M (n = 228)	0.530	0.305–0.920	0.0240	0.557	0.206–1.193	0.1321	0.617	0.125–3.053	0.5539
WR (n = 228)	1.018	1.005–1.031	0.0070	1.021	1.003–1.039	0.0215	1.018	0.981–1.057	0.3410
Multivariate analysis (n = 327)									
NYHA class	1.616	1.000–2.613	0.0501	2.345	1.160–4.739	0.0176	6.600	1.836–23.73	0.0038
BRS	0.974	0.846–0.974	0.0070	–	–	–	–	–	–

CI = confidence interval, red = reduced, nor = normal.

Table 4
Univariate and multivariate predictors of total and cardiac events in BVR patients.

	Morbidity					
	Total events			Unscheduled cardiac events		
	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis						
Patients profiles (n = 286)						
Age (5 years)	1.167	0.954–1.427	0.1343	1.168	0.851–1.602	0.3361
Male gender	1.620	0.976–2.689	0.0622	2.473	1.045–5.850	0.0393
NYHA class	2.896	2.113–3.971	<0.0001	4.994	3.172–7.863	<0.0001
Cardiac performance (n = 286)						
SVEF (0 = poor, 1 = red, 2 = nor)	0.337	0.231–0.492	<0.0001	0.202	0.124–0.329	<0.0001
Neurohormonal activity						
NE (100 pg/ml) (n = 280)	1.393	1.094–1.775	0.0073	1.499	1.054–2.133	0.0243
BNP (10 pg/ml) (n = 282)	1.064	1.040–1.088	<0.0001	1.083	1.055–1.112	<0.0001
Cardiac autonomic nervous activity						
log HF (n = 266)	0.525	0.319–0.865	0.0114	0.461	0.214–0.990	0.0472
BRS (n = 267)	0.878	0.828–0.932	<0.0001	0.888	0.810–0.973	0.0112
H/M (n = 173)	0.556	0.293–1.057	0.0732	0.602	0.226–1.605	0.3101
WR (n = 173)	1.016	1.001–1.032	0.0407	1.015	0.991–1.040	0.2115
Multivariate analysis (n = 254)						
Male gender	–	–	–	3459	1133–1056	0.0293
NYHA class	–	–	–	3.578	1.278–10.02	0.0152
BRS	0.918	0.849–0.993	0.0329	–	–	–

CI = confidence interval, red = reduced, nor = normal.

the UCEs ($p<0.05$ for both). The BNP was not an independent predictor for either of both events. The sensitivity and specificity of the BRS were 71.2% and 67.3% (AUC = 0.707, cutoff = 5.45) for the total events, and 87.0% and 44.7% (AUC = 0.667, cutoff = 8.48), for the UCEs, respectively.

4.6. Fontan physiology

In the univariate analysis, among all the CANA variables, the NE was the only predictor for the UCEs ($p<0.05$) and no other CANA variables independently predicted clinical events. In the multivariate analysis, the age and BNP were the independent predictors for total events and UCEs ($p<0.01$ for all). The sensitivity and specificity of the BNP were 75.0% and 71.9% (AUC = 0.756, cutoff = 20.3) for the total events (Fig. 2), and 76.2% and 64.7% (AUC = 0.735, cutoff = 20.3), for the UCEs, respectively.

5. Discussion

Our main findings from the present study were as follows: 1) all CANA variables could predict total events and UCEs in the total postoperative CHD patients. Of those, the NE and BRS predicted the mortality. However, 2) when the BVR and Fontan patients were separately analyzed, the prognostic values of the heart rate variability and BRS were limited to the BVR patients and no CANA variables, except for the NE, could predict clinical events in the Fontan patients. The BNP level, rather than the CANA variables, could predict total events and UCEs in the Fontan patients.

Table 5
Univariate and multivariate predictors of cardiac events and death in Fontan patients.

	Morbidity					
	Total events			Unscheduled cardiac events		
	HR	95% CI	P value	HR	95% CI	P value
Univariate analysis						
Patients profiles (n = 89)						
Age (5 years)	1.468	1.101–1.958	0.0090	1.515	1.064–2.156	0.0211
Male gender	1.429	0.688–2.968	0.3387	1.478	0.596–3.669	0.3993
NYHA class	2.683	1.488–4.839	0.0010	3.856	1.890–7.867	0.0002
Cardiac performance (n = 89)						
SVEF (0 = poor, 1 = red, 2 = nor)	0.568	0.318–1.013	0.0552	0.398	0.198–0.801	0.0099
Neurohormonal activity						
NE (100 pg/ml) (n = 87)	1.155	0.931–1.434	0.1894	1.305	1.035–1.646	0.0242
BNP (10 pg/ml) (n = 89)	1.099	1.061–1.139	<0.0001	1.105	1.061–1.150	<0.0001
Cardiac autonomic nervous activity						
log LF (n = 81)	1.506	0.784–2.893	0.2184	1.324	0.582–3.009	0.5032
log HF (n = 81)	1.363	0.702–2.646	0.3604	1.318	0.571–3.043	0.5170
BRS (n = 73)	0.940	0.830–1.065	0.3345	0.930	0.792–1.093	0.3804
H/M (n = 55)	0.606	0.187–1.968	0.4049	0.793	0.199–3.153	0.7418
WR (n = 55)	1.016	0.991–1.042	0.2198	1.020	0.990–1.051	0.1874
Multivariate analysis (n = 87)						
Age (5 years)	1.566	1.185–2.069	0.0016	1.684	1.196–2.270	0.0028
BNP (10 pg/ml)	1.081	1.032–1.132	0.0010	1.088	1.024–1.156	0.0063

CI = confidence interval, red = reduced, nor = normal.

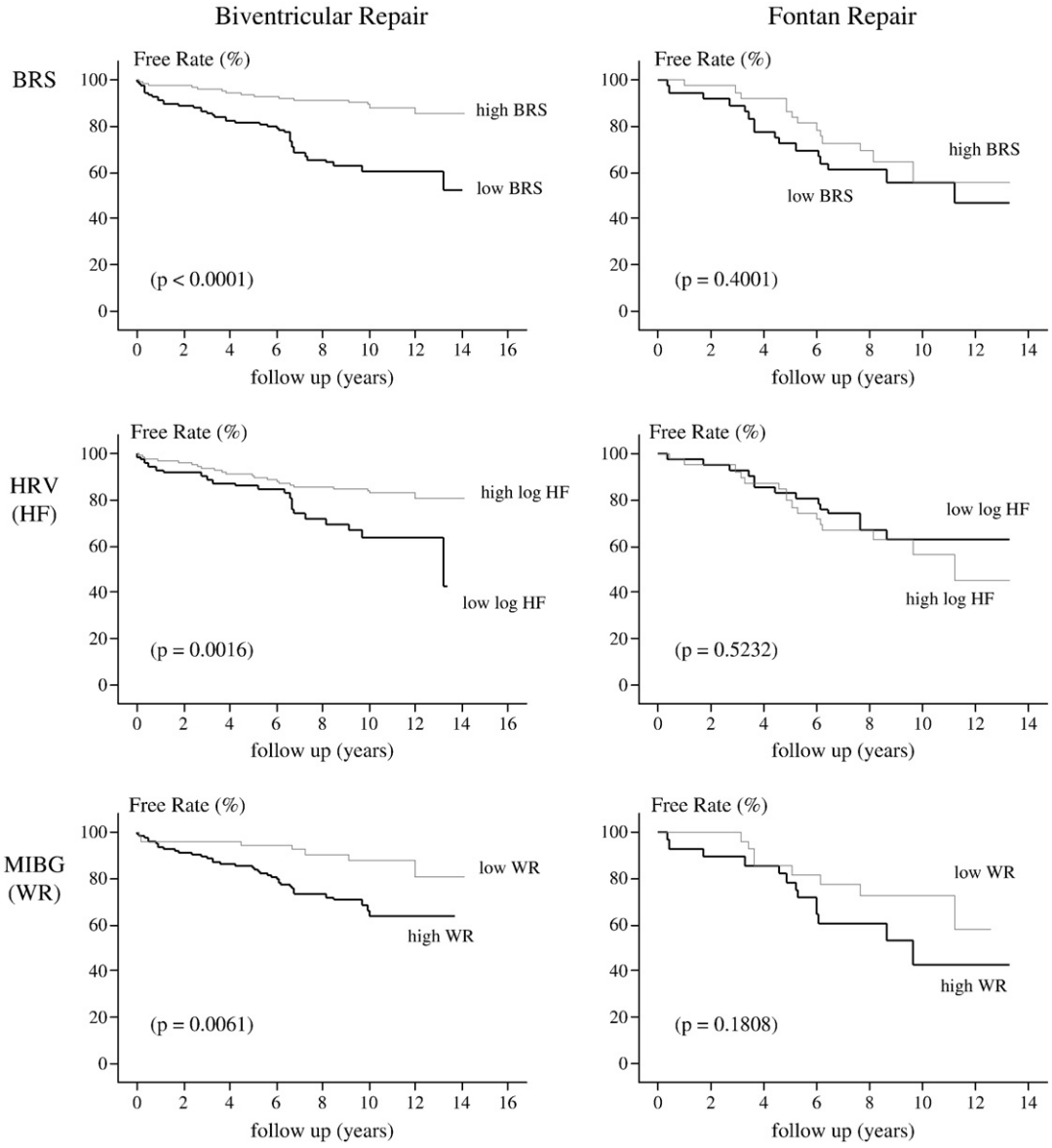

Fig. 1. The Kapalan-Meier total event free rate curves were stratified into 2 groups by the arterial baroreflex sensitivity (BRS), high frequency component of the heart rate variability (HRV, log HF), and myocardial washout ratio (WR) by metaiodobenzylguanidine myocardial scintigraphy in the postoperative biventricular (left) and Fontan (right) patients. In the biventricular patients, the Kapalan-Meier curves were divided by cutoff values according to area under the receiver-operator characteristic curve. In the Fontan patients, the Kapalan–Meier curves were divided by the median values. In the biventricular repair, the cutoff values for BRS, log HF, and WR were 5.45, 1.37, and 39.6, respectively.

5.1. Heart rate variability

Although the clinical meaning of the low frequency component of the heart rate variability remains unclear, the HF value reflects the basal parasympathetic cardiac nervous activity [13] and a lower HF value predicts adverse clinical events in patients with chronic heart failure [14]. The association of a diminished heart rate variability with a poor prognosis reflects an impaired CANA balance, i.e., diminished parasympathetic and increased sympathetic nervous activity in heart failure patients [1]. Relief of the inhibitory stimulus from the central nervous system to the sinus node during the inspiratory period, i.e., the stretch of the lungs, increases the HF component of the heart rate variability [13] and the impaired mechanism correlates, to some extent, with the severity of the heart failure in the non-postoperative patients. However, the close association between the respiratory system and heart rate control does not operate well in postoperative CHD patients with a denervated heart and a restrictive smaller lung due to the multiple open-heart surgeries. The denervated heart and restrictive lung cause a substantial discrepancy between the hemodynamic condition and heart rate variability. In fact, a smaller vital capacity is one of the independent determinants for the reduced heart rate variability in postoperative CHD patients [5]. This unique pathophysiology may limit the benefit of heart rate variability for the risk stratification in postoperative CHD patients. Inclusion of relatively simple CHD patients, such as closures of atrial or ventricular septal defects, may have strengthened the prognostic value in our BVR patients. However, in addition to the unique hemodynamics, the heart rate variability lost its prognostic value in our Fontan patients because of the severely impaired CANA with an even smaller variation [4].

5.2. BRS

In contrast to an inevitable respiration-associated nature of the heart rate variability, the BRS directly reflects the reflex function of the parasympathetic nerves irrespective of the surgery-related restrictive change in the lung. The respiration-independent nature of the BRS may have been, in part, responsible for the independent prognostic value and a study demonstrating the prognostic value of the heart rate turbulence,

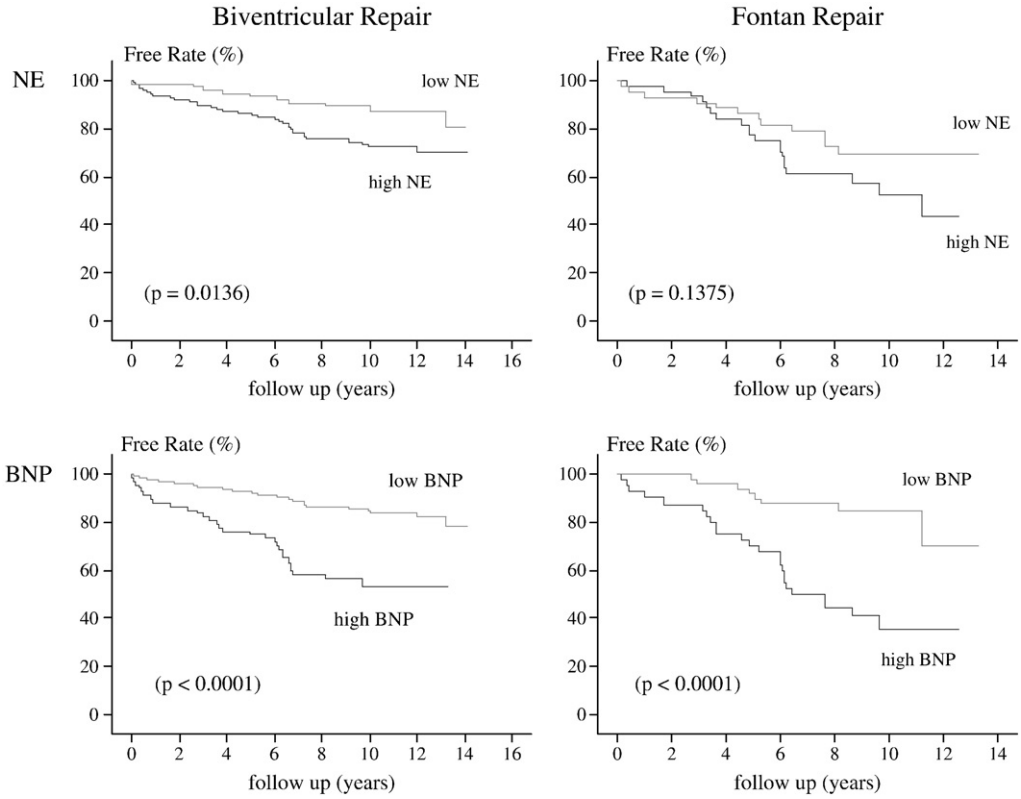

Fig. 2. The Kapalan-Meier total event free rate curves were stratified into 2 groups by the plasma norepinephrine (NE) and B-type natriuretic peptide levels (BNP) in the postoperative biventricular (left) and Fontan (right) patients. The Kapalan–Meier curves were divided by the cutoff values according to the area under the receiver-operator characteristic curve, except for the NE where the curves were divided by the median value. In the biventricular repair, the cutoff values for NE and BNP were 110 and 36.3, respectively. In the Fontan repair, the cutoff value for BNP was 20.3.

which is associated with the BRS, supports our results [15]. In addition, keeping an effective parasympathetic nerve stimulation through the preserved BRS may have a beneficial impact on the volume and/or pressure overloaded ventricular remodeling and/or oxidative stress modification [16–18] in postoperative CHD patients. However, the prognostic value may be limited in postoperative complex CHD patients because the parasympathetic nervous activity is originally much diminished in patients with severe heart failure [1,5,19] and postoperative complex CHD with severely denervated hearts.

5.3. NE and MIBG imaging

Elevated plasma NE levels reflect the activated sympathetic nervous system and predict adverse events in patients with chronic heart failure [20]. This story held true in our study and our MIBG findings also supported this idea in the BVR patients as demonstrated in the patients with chronic heart failure [21]. However, again, the prognostic value of the MIBG may be limited in postoperative HD patients with denervated hearts [5]. In fact, there were no relationships between the plasma NE levels and MIBG findings in the BVR patients. In contrast, the plasma NE levels correlated inversely with the heart to mediastinal MIBG activity ratio and positively with the WR ($r = -0.33$, $p = 0.015$, and $r = 0.37$, $p = 0.005$, respectively). The different severities of the heart failure, i.e., significantly high levels of the plasma NE in the Fontan patients, may explain our inconsistent results.

5.4. BNP and other variables

The plasma BNP level has a powerful prognostic value in pediatric and adult patients with chronic heart failure [22,23]. The present study expands the prognostic value to postoperative CHD patients, especially in the Fontan patients for the prediction of UCEs. Although our main purpose was not to evaluate the prognostic value of the plasma BNP level, a more detailed analysis of the neurohormal factors, including the plasma BNP level, is mandatory in future studies because of the limited prognostic value of our CANA variables in Fontan patients.

The NYHA functional class has been one of the more robust prognostic variables in patients with chronic heart failure. Further, this idea was also true in our CHD patients although the classification had some concerns, such as the objectivity and reproducibility [24].

The SVEF has been another robust prognostic variable in patients with chronic heart failure [25]. An accurate calculation of the SVEF is sometimes difficult in CHD patients with non-left ventricular type systemic ventricles. We divided our patients into 3 groups according to the SVEF and this analysis demonstrated a significant prognostic value irrespective of the hemodynamic conditions, i.e., a BVR or Fontan physiology, in our long-term follow-up.

5.5. Study limitations

First, the diversity of the diagnosis-based patient groups and the relatively small patient number of each group may be our major limitations and further more long-term studies with even a large number of postoperative CHD patients are necessary to confirm our results, especially the mortality. Second, a selection bias for the BVR patients should be given attention and our BVR patients were somewhat sicker than the stable BVR patients in our outpatient clinic. However, no such bias exists in our Fontan patients because we routinely check the hemodynamic status in all Fontan patients with only a few exceptions. Third, the RV function using cineventriculography may not be accurate and magnetic resonance imaging might be ideal although this modality is not always feasible for all CHD

patients. Finally, the present results may not be applicable in even older postoperative CHD patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [26].

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