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A β-Blocker may be Effective on Ventricular Contractile Mechanisms in Atrial Fibrillation Patients with Heart Failure with Preserved, but not Reduced, Ejection Fraction

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Abstract

Background: Ventricular contractile responses to β-blockers remain largely unknown in patients with Atrial Fibrillation (AF) and Heart Failure (HF), despite the recommended use of β-blockers as first-line pharmacotherapy for these patients. This study investigated β-blocker effects on ventricular contractile mechanisms, namely the Frank-Starling Mechanism (FSM), Mechanical Restitution (MR), and Postextrasystolic Potentiation (PESP), which are closely associated with ventricular contractile function, in AF patients with HF with preserved (HFpEF) versus reduced Ejection Fraction (HFrEF).

Methods: Twenty AF patients were divided into two groups based on EF: the HFpEF group (EF ≥ 50%, n=14) and the HFrEF group (EF<40%, n=6). Using impedance cardiography, an FSM-MR graph and a PESP graph were created by applying (dZ/dt) min values representing the peak velocity of aortic blood flow on the y-axis against preceding RR interval (RR1) or RR1/pre-preceding RR interval (RR2) ratio values on the x-axis at baseline and after administration of a β-blocker in AF patients with HFpEF versus HFrEF.

Results: With the β-blocker administration, rates of increase in median (dZ/dt) min values showed a significant positive correlation with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFpEF (ρ=0.88, P<0.001), in contrast to those with HFrEF (ρ=−0.43, P=0.40). PESP index values representing the extent of the effect of PESP were similarly and significantly decreased after administration of the β-blocker in both groups: AF patients with HFpEF (baseline: median 5.9 [Interquartile Range (IQR) 2.0-16.9] *vs.* after β-blocker: median 1.6 [IQR 0.62-7.2]; P=0.023), and AF patients with HFrEF (baseline: median 6.6 [IQR 0.66-22.6] *vs.* after β-blocker: median 1.2 [IQR 0.06-15.1]; P=0.028).

Conclusions: From the perspective of ventricular contractile mechanisms in AF, the β-blocker may be effective on the Frank-Starling mechanism and mechanical restitution in AF patients with HFpEF, but not HFrEF.

Keywords: Atrial fibrillation; Heart failure; Ventricular function; Beta-blocker; Impedance cardiography

Introduction

Due to the aging of society, the prevalence of patients with AF, HF, and co-existing AF and HF is increasing [1-4]. The current guidelines recommend that the use of β-blockers should be a cornerstone in the medical treatment of AF patients with HF [1-3].

However, ventricular contractile responses to β-blockers remain largely unknown in patients with AF and HF. The underlying cause may be that beat-to-beat variations characterized by irregular RR intervals in AF make it difficult to reproducibly assess ventricular contractile function [5]. Therefore, the author has developed a ventricular function graph reflecting ventricular contractile responses to beat-to-beat variations of RR intervals in AF using impedance cardiography [6-8] which is a non-invasive method for monitoring beat-to-beat cardiac function [9].

Furthermore, the involvement of three ventricular contractile mechanisms in ventricular contractile function of AF has been recognized. Two of them are dependent on the preceding RR interval (RR1), namely the Frank-Starling mechanism [10,11] and mechanical restitution [12,13]. The third is dependent on the pre-preceding RR interval (RR2), namely Postextrasystolic Potentiation (PESP) [12,13]. The author has also developed a method for visual and quantitative analysis of the degree of the involvement of these ventricular contractile mechanisms in AF using impedance measurements [6-8].

The purpose of this study was to investigate β-blocker effects on ventricular contractile mechanisms (i.e., FSM, MR, and PESP), which are closely associated with ventricular contractile function, in AF patients with concomitant heart failure with preserved ejection fraction (HFpEF) *vs.* reduced ejection fraction (HFrEF) using impedance cardiography and the analytical method of ventricular contractile mechanisms in AF.

Materials and Methods

Study patients

Twenty AF patients with both AF and HF were recruited from the Ushiroda Medical Clinic (Fukushima, Japan). Patients were eligible for the study based on the following criteria: 1) AF that had persisted for >1 year; 2) HF defined according to the American College of Cardiology Foundation/American Heart Association guideline [3] and HFpEF and HFrEF determined by Left Ventricular Ejection Fraction (LVEF) ≥50% and <40%, respectively (assessed by echocardiography); 3) New York Heart Association (NYHA) class I or II; 4) stable clinical condition, defined as no hospital admissions for greater than 1 year before study inclusion. Patients receiving current β-blocker therapy or with a cardiac implantable electronic device, severe chronic obstructive pulmonary disease, congenital heart disease with intracardiac shunt, hypertrophic obstructive cardiomyopathy, severe aortic valve stenosis, hypotension (systolic blood pressure ≤ 90 mm Hg), and bradycardia (heart rate<50 beats per minute) were excluded. This study conformed to the ethical guidelines of the Declaration of Helsinki and written informed consent was obtained from all patients.

Study protocol

The twenty AF patients were divided into two groups based on the LVEF, which was determined using the modified Simpson's method with 2-dimensional Doppler echocardiography (EUB-7500; Hitachi, Tokyo, Japan): the HFpEF group (n=14) and the HFrEF group (n=6). Each patient was placed in the supine position on the bed and was given 200 mL of a 0.9% saline solution by a constant intravenous drip infusion throughout the study to maintain intravenous access for a β-blocker administration. Electrocardiogram, heart rate, blood pressure, and various hemodynamic parameters were non-invasively and continuously measured during the study using impedance cardiography (Task Force Monitor: CNSystems, Graz, Austria). Five minutes after start of measurement, all patients received an intravenous bolus injection of 0.125 mg/kg landiolol hydrochloride (Corebeta, Ono Pharmaceutical Co., Osaka, Japan) in 0.9% saline solution over a median 75-second period [interquartile range (IQR) 60-90], followed by a constant drip infusion of the saline solution [14]. Landiolol hydrochloride is an ultra-short-acting (half-life: 4-minute) β-adrenergic receptor blocker that has high β1-selectivity (β1/β2=255) and can be administered intravenously. Four minutes of measurements were obtained from patients before the bolus injection of the β-blocker and beginning 2 minutes after administration of the β-blocker (Figure 1A-1C) to analyze ventricular contractile mechanisms of AF with HFpEF or HFrEF.

Methods for analyzing ventricular contractile mechanisms of AF based on thoracic impedance measurements

Previous described procedures were used as follows [6-8], and similarly calculations of hemodynamic measurements and the creation of various graphs and equations were performed using Excel software version 2013 (Microsoft, Redmond, WA, USA).

Creating a ventricular function graph in AF using impedance cardiography: The beat-to-beat measurements of RR intervals, namely RR1and RR2, and the corresponding (dZ/dt) min values representing the peak value of the first derivative of the heart-synchronous thoracic impedance changes indicated by delta Z (ΔZ) (Figure 1B), were obtained during 4 minutes at baseline and after administration of the β-blocker.

Application of (dZ/dt) min values obtained using impedance cardiography to create a ventricular function graph in AF is a theoretical method, because it has long been recognized that (dZ/dt) min values are strongly associated with the peak velocity of aortic blood flow ejected from the left ventricle and represent a surrogate for myocardial contractility [9,15,16].

A ventricular function graph representing ventricular contractile responses to irregular RR intervals in AF was therefore created by applying (dZ/dt) min values corresponding to RR1 values on the y-axis against RR1 values on the x-axis as a two-dimensional scatter plot. In addition, a ventricular function curve accompanied by both a logarithmic equation and a coefficient of determination (R2) fitted to this scatter plot was obtained by logarithmic regression using the least-squares method (Figures 2A-2H, and 3A-3H).

Analyses of ventricular contractile mechanisms in AF: With respect to ventricular contractile mechanisms (i.e., FSM, MR, and PESP) closely related to ventricular contractile function in AF, when RR1/RR2 ≤ 1 (Figure 1C(I)), a ventricular beat depends only on RR1-dependent mechanisms, namely FSM and MR. Both the functions of the FSM and MR (termed "FSM-MR") are briefly described as follows: as the RR1 increases, the strength of contraction of the ventricular beat corresponding to the RR1 increases.

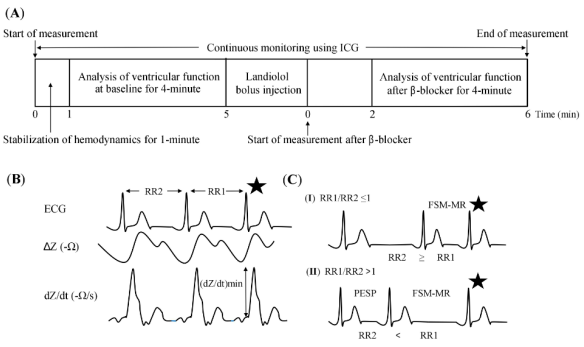
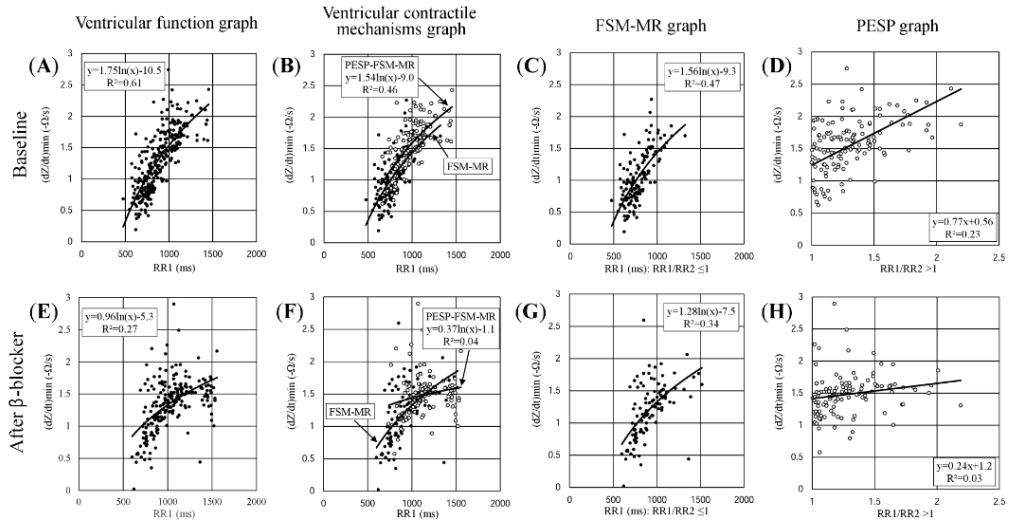
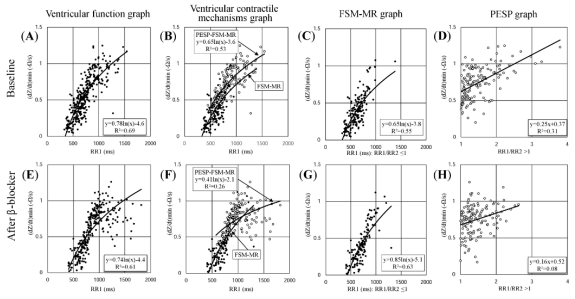


Figure 1: (A) Timeline of the study protocol. (B) Impedance cardiography in Atrial Fibrillation (AF). ECG: Electrocardiogram, ΔZ: heart-synchronous thoracic impedance changes, dZ/dt: first derivative of the ΔZ, (dZ/dt) min: peak value of the first derivative of the ΔZ, and the beat indicated by asterisk accompanied by preceding RR interval (RR1) and pre-preceding RR interval (RR2). (C) Ventricular contractile mechanisms in AF. (I) Contractility of the beat indicated by asterisk depends on the Frank-Starling Mechanism (FSM) and Mechanical Restitution (MR), namely FSM-MR when RR1 is less than or equal to RR2 (RR1/RR2 ≤ 1); (II) Contractility of the beat indicated by asterisk depends on not only FSM-MR but also Postextrasystolic Potentiation (PESP) when RR1 is greater than RR2 (RR1/RR2>1), namely PESP-FSM-MR.



Figures 2: Case 11 with AF and heart failure with preserved ejection fraction (HFpEF). (A) A ventricular function graph and a ventricular function curve at baseline; (B) a two-colored scatter plot is obtained by classifying points in the ventricular function graph (A) into two groups using RR1/RR2 ratios: an open circle (○) represents ventricular beat involved in PESP-FSM-MR and a closed circle (●) represents ventricular beat involved in FSM-MR, to which each logarithmic regression curve is fitted; (C) a FSM-MR graph with a logarithmic regression curve is selected from a two-colored scatter plot (B) using RR1/RR2 ratios ≤ 1 (i.e., closed circles (●) of the two-colored scatter plot); (D) a PESP graph with a regression line is created using RR1/RR2 ratios >1 in ventricular beats involved in PESP-FSM-MR (i.e., open circles (○) of the two-colored scatter plot); (E-H) changes in the each graph after administration of the β-blocker.



Figures 3: Case 15 with AF and heart failure with reduced ejection fraction (HFrEF). (A-D) At baseline; (E-H) after administration of the β-blocker.

The reason why functions of the FSM and MR were evaluated together in this study is that the FSM is investigated by changes in ventricular volume at a fixed stimulation interval, whereas the MR is investigated by changes in stimulation intervals at a fixed ventricular volume [17]; thus the method of this study using only RR1/RR2 ratios cannot distinguish between the function of the FSM and the function of the MR due to changes in the ventricular volume of the *in situ* human heart.

In contrast, when RR1/RR2>1 (Figure 1C(II)), a ventricular beat depends on not only RR1-dependent mechanisms mentioned above (i.e., FSM-MR), but also the RR2-dependent mechanism, namely PESP [18] (termed "PESP-FSM-MR"). The PESP has been characterized as enhanced myocardial contractility caused by a ventricular beat with a longer RR1 following a ventricular premature beat with a shorter RR2. It follows from the physiological point of view of the PESP that the RR1/RR2 ratio is always greater than 1 [12,13]. In addition, as the RR2 decreases (i.e., an increase in the ratio of RR1/RR2) the strength of contraction of the ventricular beat corresponding to the RR2 increases [12,13].

According to RR1/RR2 ratios described above, the two-colored scatter plots (Figures 2B, 2F, 3B and 3F) were created by classifying points representing ventricular beats on the ventricular function graphs (Figures 2A, 2E, 3A and 3E) into two groups: one group of points representing ventricular beats involved in the PESP-FSM-MR, and another group of points representing ventricular beats involved in the FSM-MR. Then, a logarithmic regression curve accompanied by both a logarithmic equation and a coefficient of determination (R2) fitted to the PESP-FSM-MR points, and those fitted to the FSM-MR points were obtained by the logarithmic regression using the least-squares method.

Moreover, the extent of the effect of PESP involved in the PESP-FSM-MR points was visually displayed on a two-dimensional scatter plot by applying (dZ/dt) min values corresponding to RR1/RR2 values on the y-axis against the RR1/RR2 values on the x-axis, even though RR1/RR2 values are maintained >1. A PESP-regression line accompanied by both a straight line equation and a coefficient of determination (R2) fitted to this scatter plot was obtained by linear regression using the least-squares method (Figures 2D, 2H, 3D, and 3H). The PESP-regression line makes it possible to assess quantitatively the extent of the effect of PESP (termed "PESP index value") by using the following formula: a slope of a PESP-regression line × a coefficient of determination (R2) × 100.

Statistical analyses

Continuous variables are presented as median and IQR. Categorical variables are expressed as numbers and percentages, and were evaluated using the Fisher' Exact test. Changes in heart rate, systolic and diastolic blood pressure, median (dZ/dt) min values, median RR1 values and PESP index values in the patients between baseline and after administration of the β-blocker were compared using the Wilcoxon signed-rank test. The percentage of change in each hemodynamic parameter from baseline to after administration of the β-blocker between AF patients with HFpEF and those with HFrEF, and baseline characteristics for continuous variables between two groups were examined using the Mann-Whitney U test. The correlation between two variables was estimated using Spearman rank-correlation coefficient. A P<0.05 (2-tailed) was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

Baseline patient characteristics

Twenty patients with AF and HF were divided into two groups based on LVEF: the AF with HFpEF group and the AF with HFrEF group (Table 1). The AF patients with HFpEF were older than those with HFrEF. Concerning echocardiography parameters, LV systolic and diastolic diameters in the AF with HFrEF group were larger than those in the AF with HFpEF group. LVEF and Fractional Shortening (FS) were significantly lower in the AF with HFrEF group compared with the AF with HFpEF group, whereas left atrial dimensions, E/e', and e' values were similar between the two groups. Moreover, sex, HF stage, NYHA classification, plasma Brain Natriuretic Peptide (BNP) values, and medications did not differ significantly between the two groups.

Hemodynamic responses to β-blocker in AF patients with HF

After administration of the β-blocker, systolic and diastolic blood pressure in the AF with HFpEF group and heart rate in the both groups were significantly decreased. However, the percentage of change in each hemodynamic parameter from baseline to after administration of the β-blocker was not significantly different between the two groups (Table 2).

Ventricular contractile mechanisms in AF patients with HFpEF

Figure 2 shows ventricular contractile mechanisms in case 11 involving a patient with AF and HFpEF. The median (dZ/dt) min value in the FSM-MR graph at baseline (Figure 2C) was significantly increased after administration of the β-blocker (Figure 2G) (median 0.970 –Ω/s [IQR 0.739-1.315] *vs.* median 1.220 –Ω/s [IQR 0.890-1.487]; P=0.005). The median RR1 value in the FSM-MR graph at baseline (Figure 2C) was also significantly increased after administration of the β-blocker (Figure 2G) (median 765 ms [IQR 684-872] *vs.* median 881 ms [IQR 767-1028]; P<0.001).

In addition, the PESP index value calculated using the above formula at baseline decreased from 17.7 to 0.72 after administration of the β-blocker (Figure 2D and 2H).

Baseline Characteristics		HFpEF (n=14)	HFrEF (n=6)	P-value
Age (years), median (IQR)		74 (65-81)	66 (62-70)	0.039
Male gender, n (%)		9 (64)	6 (100)	0.26
Stages of HF, n (%)				0.61
	B	10 (71)	3 (50)	
	C	4 (29)	3 (50)	
NYHA class, n (%)				0.52
	I	13 (93)	5 (83)	
	II	1 (7)	1 (17)	
Plasma BNP (pg/mL), median (IQR)		73 (29-130)	110 (73-126)	0.28
Echocardiography, median (IQR)				
LAD (mm)		41 (36-49)	41 (40-47)	0.84
LVDd (mm)		48 (45-52)	55 (52-60)	0.013
LVDs (mm)		28 (26-32)	40 (38-41)	0.003
LVEF (%)		64 (56-71)	38 (33-38)	<0.001
FS (%)		42 (33-44)	30 (26-32)	0.001
E/e'		11.4 (9.6-14.4)	10.4 (9.4-11.8)	0.41
e' (-cm/s)		7.6 (6.8-8.6)	6.8 (5.3-9.2)	0.62
Medications, n (%)				
ACEI/ARB		7 (50)	5 (83)	0.32
Loop diuretics		5 (36)	2 (33)	1
Spironolactone		5 (36)	1 (17)	0.61
Digoxin		6 (43)	3 (50)	1
Diltiazem		3 (21)	2 (33)	0.61

Table 1: Baseline atrial fibrillation patients' characteristics. Values are presented as the median and interquartile range (IQR) or as n (%). HF: Heart Failure; NYHA: New York Heart Association; BNP: Brain Natriuretic Peptide; LAD: Left Atrial Dimension; LVDd: Left Ventricular end-Diastolic diameter; LVDs: Left Ventricular end-systolic Diameter; LVEF: Left Ventricular Ejection Fraction; FS: Fractional Shortening; E: Early diastolic wave velocity; e': early diastolic mitral annual velocity, ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin II Receptor Blocker; HFpEF: Heart Failure with preserved Ejection Fraction, HFrEF: Heart Failure with reduced Ejection Fraction.

In the AF with HFpEF group (n=14), according to Table 3, when administering the β-blocker, the rates of increase in median (dZ/dt) min values strongly correlated with the rates of increase in median RR1 values as the functions of the FSM-MR (ρ=0.88, P<0.001), despite the fact that there were 6 patients with AF and HFpEF in whom each median (dZ/dt) min value at baseline was not significantly increased after administration of the β-blocker (Figure 4A and 4B).

	HFpEF (n=14)			HFrEF (n=6)		
	Baseline	**After β-blocker**	**P-value**	**Baseline**	**After β-blocker**	**P-value**
Parameter, median (IQR)						
Heart rate (/min)	77 (71-86)	68 (61-74)	0.001	81 (71-88)	69 (62-81)	0.028
Systolic blood pressure (mmHg)	116 (108-126)	108 (103-26)	0.008	116 (113-23)	112 (108-18)	0.058
Diastolic blood pressure (mmHg)	78 (68-92)	74 (68-86)	0.042	79 (77-92)	78 (72-84)	0.14
Percentage of change from baseline, median (IQR)						P-value
Heart rate (%)	14.5 (8.6-6.3)			14.6 (8.9-6.1)		0.87
Systolic blood pressure (%)	4.2 (0.3-7.5)			4.3 (0.7-6.5)		0.93
Diastolic blood pressure (%)	4.6 (-1.9-7.8)			5.2 (-1.3-2.6)		0.71

Table 2: Hemodynamic responses to β-blocker in AF patients with HF.

With respect to differences in responses to the β-blocker as the functions of the FSM-MR in AF patients with HFpEF, statistically significant differences between cases with a significant increase in median (dZ/dt) min value in each FSM-MR graph and cases with no significant increase in each FSM-MR graph, when administering the β-blocker, were observed only for the extent of the effect of PESP (i.e., the PESP index value) at baseline (Table 4).

Furthermore, according to Figure 5A, the PESP index values in AF patients with HFpEF at baseline were significantly decreased after administration of the β-blocker (median 5.9 [IQR 2.0-16.9] *vs.* median 1.6 [IQR 0.62-7.2]; P=0.023).

Ventricular contractile mechanisms in AF patients with HFrEF

Figure 3 shows ventricular contractile mechanisms in case 15 involving a patient with AF and HFrEF. The median (dZ/dt) min value in the FSM-MR graph at baseline (Figure 3C) was not significantly increased after administration of the β-blocker (Figure 3G) (median 0.363 –Ω/s [IQR 0.235-0.516] *vs.* median 0.357 –Ω/s [IQR 0.219-0.541]; P=0.69). However, the median RR1 value in the FSM-MR graph at baseline (Figure 3C) was significantly increased after administration of the β-blocker (Figure 3G) (median 633 ms [IQR 513-717] *vs.* median 698 ms [IQR 602-805]; P<0.001). In addition, a PESP index value calculated using the above formula at baseline decreased from 7.8 to 1.3 after administration of the β-blocker (Figure 3D and 3H).

In the AF with HFrEF group (n=6), according to Table 3, when administering the β-blocker, the rates of increase in median (dZ/dt) min values did not significantly correlate with the rates of increase in median RR1 values as the functions of the FSM-MR (ρ=−0.43, P=0.40) (Figure 4B).

However, according to Figure 5B, the PESP index values in AF patients with HFrEF at baseline were significantly decreased after administration of the β-blocker (median 6.6 [IQR 0.66-22.6] *vs.* median 1.2 [IQR 0.06-15.1]; P=0.028).

Discussion

This study is the first to demonstrate that when administering the β-blocker, first, the rates of increase in median (dZ/dt) min values showed a significant positive correlation with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFpEF. Second, the rates of increase in median (dZ/dt) min values did not significantly correlate with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFrEF. Third, the PESP index values in both AF patients with HFpEF and those with HFrEF were similarly and significantly decreased.

When administering the β-blocker, the rates of increase in median (dZ/dt) min values showed a significant positive correlation with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFpEF (Figure 4A). The mechanism of the FSM depends on stretched LV myocardium caused by an increase in LV diastolic volume related to the length of RR1. The MR is generally accounted for by recovery of myocardial contractility of a premature beat in proportion to an increase in a preceding relaxation time, because this mechanism is associated with the excitation-contraction coupling. However, β-blockers attenuate the extracellular Ca^{2+} influx related to the action of the sarcoplasmic reticulum Ca^{2+} release channel, resulting in decreased myocardial contractility (negative inotropic action) and heart rate (negative chronotropic action), as opposed to β-adrenoceptor stimulation [11].

The most likely explanation for an increase in the functions of the FSM-MR after administration of the β-blocker in AF patients with HFpEF would be that the negative chronotropic action of the β-blocker caused a significant decrease in heart rate (Table 2), thereby resulting in an increase in the median RR1 values, so that RR1-dependent mechanisms (i.e., FSM and MR) yielded an increase in the median (dZ/dt) min values as a surrogate for myocardial contractility (Figure 4A). Thus, these findings imply that myocardial contractility in AF patients with HFpEF accompanied by a significantly higher FS at baseline than that in AF patients with HFrEF (Table 1) might outweigh the negative inotropic action of the dosage of the β-blocker and might be strong enough to cause an increase in the functions of the FSM-MR in the present study. Interestingly, when administering the β-blocker in AF patients with HFpEF, differences between cases with a significant

increase in median (dZ/dt) min value in each FSM-MR graph and cases with no significant increase in each FSM-MR graph significantly depended only on the extent of the effect of PESP, namely PESP index value at baseline (Table 4).

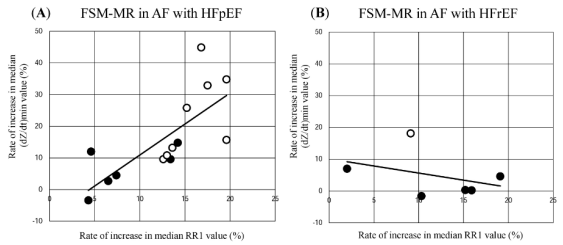
Case	Median (dZ/dt)min (-Ω/s)				Median RR1 (ms)				LVEF (%)
	Baseline	After β-blocker	Increase rate (%)	P-value	Baseline	After β-blocker	Increase rate (%)	P-value	
1	0.251	0.276	9.6	0.18	686	778	13.4	<0.001	54.4
2	0.328	0.317	-3.4	0.63	607	633	4.3	0.002	53.6
3	0.617	0.645	4.5	0.36	661	710	7.4	<0.001	60.4
4	0.557	0.572	2.7	0.74	754	803	6.5	<0.001	70.7
5	0.65	0.728	12	0.26	774	810	4.6	0.002	81
6	0.337	0.387	14.8	0.12	800	914	14.2	<0.001	56.3
7	0.178	0.24	34.8	0.001	636	761	19.6	<0.001	58.6
8	0.41	0.545	32.9	0.002	532	625	17.5	<0.001	81
9	1.261	1.459	15.7	<0.001	758	907	19.6	<0.001	72.5
10	0.766	0.867	13.2	0.017	631	717	13.6	<0.001	56.5
11	0.97	1.22	25.8	0.005	765	881	15.2	<0.001	68.7
12	0.632	0.693	9.6	0.036	714	804	12.6	<0.001	65.5
13	0.585	0.648	10.8	0.002	764	863	13	<0.001	62
14	0.363	0.526	44.9	<0.001	644	752	16.8	<0.001	71.1
15	0.363	0.357	-1.6	0.69	633	698	10.3	<0.001	39
16	0.306	0.32	4.6	0.09	571	680	19.1	<0.001	38
17	0.4	0.428	7	0.54	635	648	2	0.2	33.8
18	0.661	0.663	0.3	0.69	644	742	15.2	<0.001	38
19	0.665	0.666	0.2	0.09	819	949	15.9	<0.001	30.9
20	0.486	0.574	18.1	0.029	725	791	9.1	0.001	38.2

Table 3: Median (dZ/dt) min values and median RR1 values in the FSM-MR graphs at baseline and after administration of the β-blocker in AF patients with HF. FSM: Frank-Starling Mechanism, MR: Mechanical Restitution, (dZ/dt) min: peak value of the first derivative of the heart-synchronous thoracic impedance changes, RR1: preceding RR interval.

Therefore, these results strongly suggest that when the PESP index values at baseline are greatly increased, the β-blocker may be effective for an increase in the functions of the FSM-MR in AF patients with HFpEF.

When administering the β-blocker, the rates of increase in median (dZ/dt) min values did not significantly correlate with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFrEF (Figure 4B). One explanation for the malfunctions of the FSM-MR after administration of the β-blocker in AF patients with HFrEF would be that myocardial contractility in AF patients with HFrEF is accompanied by a significantly lower FS at baseline than that in AF patients with HFpEF (Table 1), and may be further depressed by the negative inotropic action of the β-blocker; consequently, the myocardial contractility in AF patients with HFrEF may not be strong enough to cause an increase in the functions of the FSM-MR in spite of a significantly decreased heart rate (Table 2) yielded by the negative chronotropic action of the β-blocker, in sharp contrast to AF patients with HFpEF. From the perspective of the functions of the FSM-MR described above, the results of the present study support, at least in part, several meta-analyses of trials in which the use of β-blockers did not result in a significant survival benefit in AF patients with HFrEF [19,20].

When administering the β-blocker, the PESP index values in both AF patients with HFpEF and those with HFrEF were similarly and significantly decreased (Figure 5A and 5B). The mechanism of PESP is also related to the excitation-contraction coupling, but not increased filling of the ventricle (i.e., FSM) [12,13]. Many studies have been performed to examine the mechanisms of PESP [13,21], whereas only a few studies have thus far investigated the influence of β-blockers on PESP in the *in vivo* heart.



Figures 4: The functions of the FSM-MR when administering the β-blocker. (A) The correlation between the rates of increase in median (dZ/dt) min values and the rates of increase in median RR1 values in AF patients with HFpEF; (B) those in AF patients with HFrEF. An open circle (○) represents a case with a significant increase in median (dZ/dt) min value and a closed circle (●) represents a case with no significant increase in median (dZ/dt) min value after administration of the β-blocker.

The effects of β-blockers on PESP in the *in situ* human heart were examined by atrial pacing during cardiac catheterization by Zhang, et al. [18], showing that β-blockers (metoprolol and sotalol) did not affect the extent of the effect of PESP in man. However, Cornelussen, et al. [22] demonstrated that a β-blocker (metoprolol) significantly decreased myocardial contractility related to PESP. These results were obtained from *in vivo* hearts of 7 anesthetized animals investigated by ventricular pacing during cardiac catheterization. In the present study, the β-blocker attenuated the extent of the effect of PESP in both AF patients with HFpEF and those with HFrEF. One possible explanation of these results would be that since the extent of the effect of PESP is likely to be affected by sympathetic nerve activity [21,23] and adrenaline [24] in the *in situ* heart, the present study attempted to avoid enhancing sympathetic nerve activity as thoroughly as possible using this non-invasive method; therefore, the β-blocker may weaken the function of the excitation-contraction coupling [11] related to PESP [13] under the conditions of this study, unlike prior studies using invasive methods in human participants [18,25]. It may be worth mentioning here that the present study is the first to demonstrate the response to the β-blocker on PESP in AF patients with HFpEF *vs.* HFrEF using the non-invasive method.

The present study has limitations. A PESP graph was created using RR1/RR2 ratios under consideration for RR1 because of the presence of irregular RR1 in the *in situ* human heart. Thus, variations in (dZ/dt) min values at the same RR1/RR2 value in the PESP graph were considered to be affected by RR1-dependent mechanisms, namely FSM-MR. However, to conclusively solve the limitations of this method using only RR1/RR2 ratios in the PESP graph, a new PESP graph accompanied by the involvement of RR1 is warranted [6].

Baseline patient characteristics	**Cases with a significant increase in median (dZ/dt) min value after β-blocker (n=8)**	**Cases with no significant increase in median (dZ/dt) min value after β-blocker (n=6)**	**P-value**
Age (years), median (IQR)	74 (67-80)	73 (63-82)	0.56
Male gender, n (%)	5 (62)	4 (67)	1
Stages of HF, n (%)			0.58
B	5 (62)	5 (83)	
C	3 (38)	1 (17)	
NYHA class, n (%)			0.43
I	8 (100)	5 (83)	
II	0 (0)	1 (17)	
Hemodynamic parameter, median (IQR)			
Heart rate (/min)	79 (71-86)	77 (71-86)	0.8
Systolic blood pressure (mmHg)	122 (110-133)	110 (106-120)	0.22
Diastolic blood pressure (mmHg)	80 (67-90)	76 (68-94)	0.95
Impedance cardiography, median (IQR)			
Median RR1 in FSM-MR (ms)	679 (632-762)	720 (648-780)	0.44
Median (dZ/dt) min in FSM-MR (-Ω/s)	0.608 (0.375-0.919)	0.447 (0.309-0.625)	0.24
Coefficient of ln(x) × R^2 × 100 in FSM-MR logarithmic regression curve	74.3 (38.3-95.7)	34.4 (10.2-51.5)	0.093
Slope of PESP-regression line × R^2 × 100 (PESP index value)	15.5 (5.12-23.1)	2.97 (0.57-6.95)	0.039

Echocardiography, median (IQR)			
LA (mm)	44 (40-49)	38 (34-48)	0.16
LVDd (mm)	50 (46-54)	45 (44-51)	0.27
LVDs (mm)	28 (26-32)	28 (25-34)	0.84
LVEF (%)	67 (59-72)	58 (54-73)	0.22
FS (%)	42 (39-45)	38 (32-43)	0.27
E/e'	10.5 (8.7-14.5)	11.9 (10.0-13.6)	0.44
e' (-cm/s)	7.6 (5.9-8.6)	7.6 (6.8-8.6)	0.85
Plasma BNP (pg/mL), median (IQR)	73 (30-98)	95 (26-235)	0.61
Medications, n (%)			
ACEI/ARB	4 (50)	3 (50)	1
Loop diuretics	4 (50)	1 (17)	0.3
Spironolactone	3 (38)	2 (33)	1
Digoxin and/or diltiazem	7 (88)	2 (33)	0.091

Table 4: Comparison of differences in response to β-blocker as the functions of the FSM-MR in AF patients with HFpEF. PESP: Postextrasystolic Potentiation, R2: a coefficient of determination in PESP regression line.

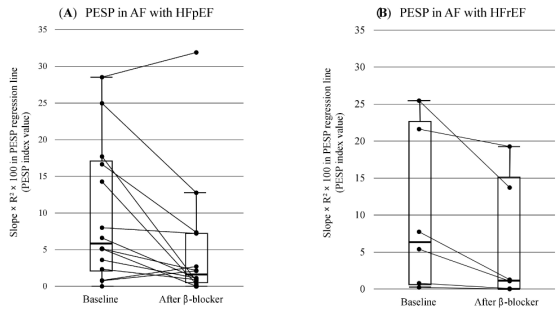


Figure 5: Box and whisker plots demonstrate the extent of the effect of PESP (PESP index value) at baseline and after administration of the β-blocker. (A) AF patients with HFpEF (n=14); (B) AF patients with HFrEF (n=6).

Conclusions

This study is the first to demonstrate that when administering the β-blocker, the rates of increase in median (dZ/dt) min values showed a significant positive correlation with the rates of increase in median RR1 values as the functions of the FSM-MR in AF patients with HFpEF, in contrast to those with HFrEF, and the PESP index values in both AF patients with HFpEF and those with HFrEF were similarly and significantly decreased. From the perspective of these ventricular contractile mechanisms, the β-blocker may be effective on the Frank-Starling mechanism and mechanical restitution in AF patients with HFpEF, but not HFrEF.

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