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Heart Failure

The Effects of Ivabradine on Left Ventricular Synchronization and Tei Index in Patients with Systolic Heart Failure

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Background: The aim of our study was to evaluate in stable outpatients with systolic heart failure (HF) the 3 months effect of ivabradine on LV synchronization and Tei index in stable outpatients with systolic HF.

Methods: We evaluated prospectively 40 (30 males, 10 females) patients with HF. All patients were evaluated before and after treatment by transthoracic M mode, two dimensional (2D), pulsed-wave (PW), continuous wave (CW), color flow and tissue Doppler imaging (TDI) and tissue synchronization imaging (TSI). Standard deviation of Ts of the 12 LV segments (Ts-SD-12) is the most widely used parameter of intra-LV asynchrony.

Results: Thirty men and 10 women with mean ± SD age of 64.7 ± 9.9 years were included in this study. Most of the patients benefitted from some degree of clinical improvement, 12/16 (75.0%) from NYHA III to II and 18/24 (75.0%) from II to I, respectively. Resting heart rate was significantly reduced after ivabradine treatment (84.3 ± 11.4 vs. 66.5 ± 11.5 bpm, $p < 0.001$). E/E' and Tei index were significantly changed after ivabradine treatment (17.3 ± 9.0 vs. 14.8 ± 7.1, $p = 0.02$ and 0.86 ± 0.74 vs. 0.81 ± 0.69, $p = 0.02$). Intra-LV synchrony parameters Ts-SD-12 and Ts-12 were significantly reduced after ivabradine (46.8 ± 13.6 vs. 42.7 ± 13.1, $p = 0.01$ and 142.5 ± 44.0 vs. 128.5 ± 45.2, $p = 0.009$).

Conclusions: The present study demonstrated that adding ivabradine to the standard therapy reduced HR and significantly improved LV ventricular asynchrony and Tei index in systolic HF patients.

Key Words: Heart failure • Ivabradine • Left ventricular function

INTRODUCTION

The heart rate reducing drug ivabradine, acts selectively on inward 'funny' (If) channels of the sinus node without affecting atrioventricular conduction or contractility.[1] The drug has been previously prescribed in a large population with chronic heart failure (HF). Systolic HF treatment with the If inhibitor ivabradine trial (SHIFT) revealed that its use was associated with significant reduction in major cardiovascular outcomes.[2] In patients with ivabradine added to optimal treatment, there were improved HF outcome, including reduced cardiovascular death and hospitalization.[3]

The optimized medical therapy for systolic HF includes several drug and cardiac resynchronization therapy for those with persistent symptoms.[4] Left ventricle (LV) negative remodeling is prevented by angiotensin-converting enzyme inhibitors, angiotensin receptors II blockers, β-blockers and spironolactone.[5-8] Heart rate

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(HR) reduction with ivabradine improves left ventricle filling by the prolongation of the diastolic time, and also increases stroke volume. In patients with systolic HF and resting HR > 70/ min, it improves event-free survival,[3] quality of life,[9] exercise capacity,[10] and promotes left ventricle reverse remodeling at 8 months.[11] However, it remains unclear what ivabradine's effect is on LV synchronization and Tei index. The aim of our study was to evaluate in stable outpatients with systolic HF the 3-month effect of ivabradine on LV synchronization and Tei index.

METHODS

The population for our study consisted of outpatients who came to the Cardiology Clinic of Abant Izzet Baysal University Hospital. We recruited men or women greater than 18 years of age with a established diagnosis of stable HF, with reduced left ventricular ejection fraction (≤ 35%) according to the New York Heart Association functional classes II to III, and at least 5 minutes after resting a 12-lead electrocardiogram (ECG) heart rate of 70 beats/min or higher as measured by the baseline heart rate. Candidates were excluded if in the last three months they had history of myocardial infarction, permanent pacemaker, atrial fibrillation or flutter and symptomatic hypotension. We evaluated prospectively 40 (30 males, 10 females) patients with HF between January 2013 and September 2013. All patients gave their written informed consent before inclusion, and this study was approved by the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee.

All patients received standard HF therapy (angiotensin-converting enzyme inhibitors, angiotensin II blockers, aldosterone receptor blockers, beta-adrenoreceptor blockers, diuretics, and digitalis) at their maximum doses tolerated. At the beginning of the study, subjects were started on ivabradine 5 mg twice daily. After seven days, if the resting heart rate was more than 60 bpm, the ivabradine dose was increased to 7.5 mg b.i.d. Thereafter depending upon the heart rate and tolerability, ivabradine dose was either reduced 2.5 mg b.i.d. or stopped. All patients underwent extensive clinical, electrocardiographic, and echocardiographic evaluation both before and after 1- and 3-month initiation of ivabradine treatment.

Electrocardiography

The 12-lead surface electrocardiogram (ECG) was obtained from all patients in the supine position using an ECG (Cardiofax M, Nihon Kohden, Tokyo, Japan) device. All ECG recordings were performed after resting for 5 minutes in a quiet room, in the supine position. For a standardized assessment of all patients, 25 mm/sec recording speed and 10 mm/mV amplitude ECG recordings were obtained.

Standard echocardiography

All patients were evaluated by transthoracic M mode, two-dimensional (2D), pulsed-wave (PW), continuous wave (CW), color flow and tissue Doppler imaging (TDI). All examinations were performed with the GEVivid-S6 system (GE Vingmed, Horten, Norway) with a 2-4 MHz transducer at a depth of 16 cm. During echocardiography, continuous single-lead ECG recording was obtained. All patient images were taken in the left lateral decubitus position. Additionally, 2D and conventional Doppler examinations were obtained in the parasternal and apical views, according to the guidelines of the American Society of Echocardiography.[12] LV diameters and wall thickness was measured by M-mode echocardiography and LV ejection fraction was calculated using the apical two- and four-chamber views by Simpson's method, according to American Society of Echocardiography guidelines.[12] The mitral valve inflow patterns [E-wave, A-wave, E-wave deceleration time (Dt), and E/A ratio] were measured using pulsed wave Doppler.[13]

Tissue Doppler echocardiography

Tissue Doppler imaging (TDI) was performed by transducer frequencies of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to acquire the Nyquist limit of 15 to- 20 cm/s was reached using minimal optimal gain. Myocardial TDI velocities [peak systolic (Sm), early diastolic (Em) and late diastolic velocities (Am)] were measured via spectral pulsed Doppler from as of the LV – free wall and also from the apical four chamber view.[13] TDI was performed using apical four-chamber, apical two-chamber and apical long-axis

views for motion of the ventricle. The Tei index was determined by using the following equation:

Tei index = [Isovolumetric contraction time (ICT) + isovolumic relaxation time (IVRT)]/Ejection time

The time interval from the end of the onset of mitral annular velocity pattern during diastole (a) was measured by TDI recordings. The duration of the Sm (b) was measured from the onset of the end of the Sm. The Tei index was calculated as (a – b)/b.[14]

Evaluation of intra-LV systolic asynchrony was performed by tissue synchronization imaging (TSI),[15] which was a parametric imaging tool derived by 2D TDI images. TSI exhibits regional asynchrony on 2D echocardiography and enables the evaluation of regional delay in systole. TSI is calculated automatically and color-codes for the time to peak tissue velocity (Ts) in each position in the image with reference to the QRS signal.[15-17] The algorithm of TSI defines positive velocity peaks within a specified time period, and the color coding ranges from green (first), yellow, orange and red (latest) within this period (Figure 1). Initially, the event timing tool was measured manually from the onset of the QRS to the aortic valve opening and closure and the separately recorded pulsed Doppler spectrum. The event timing tool allows the start and end times of TSI to be accurately measured. Then it is adjusted manually to align with the corresponding aortic valve opening and closure markers on ECG. Therefore, peak systolic velocities outside the ejection phase will be measured. In addition, for qualitative measurement, the wall with the most severe delay was identified on the basis of TSI at the three apical views. A quantitative measurement device allowed numerical calculation of the median time to peak velocity within a 6-mm sample volume manually positioned within the 2D TSI image for 12 LV. At least three consecutive beats were stored and the images were analyzed offline for TSI by a customized software package (EchoPac for PC, GE Vingmed Ultrasound). The six-basal and six mid-segmental model was used.[15-17] Four parameters of intra-LV asynchrony were recorded with only the ejection phase and included:

1) Standard deviation of Ts of the 12 LV segments (Ts-SD-12);
2) Maximal difference in Ts between any 2 of the 12 LV segments (Ts-12);
3) Standard deviation of TS of the 6 basal LV segments (Ts-SD-6);
4) Maximal difference in Ts between any of the 6 basal LV segments (Ts-6).[19]

Ts-SD-12 is the most widely used parameter of intra-LV asynchrony.[15-17] When Ts-SD-12 is more than 34.4, ms is defined as that intra-LV systolic asynchrony by TSI.[13] All measurements were performed by an experienced investigator, who was unaware of the subject's clinical status. Intra-observer variability was evaluated in 20 subjects selected randomly from the study population by repeating the measurements under the same basal conditions. Intra-observer variability was 4.4% for Tei index, 4.0% for Ts-SD-12, 4.7% for Ts-12, 4.9% for Ts-SD-6, 4.3% for Ts-6 and 4.7% for E/A, respectively. Also, all of measurements were assessed for 15 minutes.

Statistical analysis

All analyses were performed using the SPSS (SPSS for Windows 15.0) software package. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as the percentage. The Wilcoxon signed rank test was used for categorical variables, and the paired t-test was used for continuous variables. Additionally, the Wilcoxon signed rank test and paired sample t-test were used to compare the differences between the baseline and the third month of

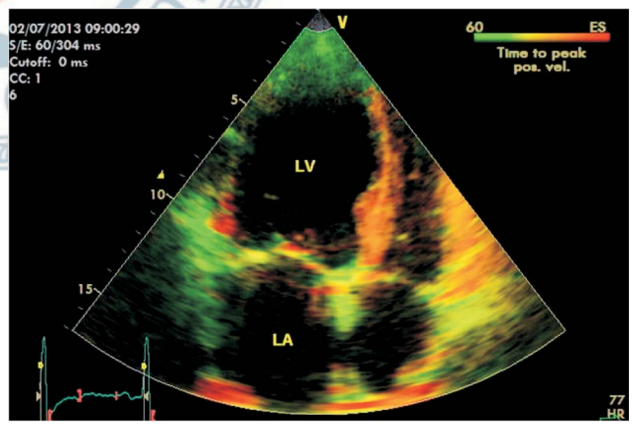

Figure 1. *Tissue synchronization imaging (TSI) image on apical four-chamber view showing the presence of septal wall delay in a heart failure patient with normal QRS duration. TSI was derived from 2D tissue Doppler imaging (TDI) images and automatically color-coded time to peak myocardial velocity (Ts) with reference to the QRS signal. The TSI algorithm color coding ranges from green (earliest) through yellow and orange to red (latest) within this interval. Ts of septal wall of LV more delayed when compared with apical wall.*

ivabradine administration. A value of $p < 0.05$ was considered statistically significant.

All sample sizes and power calculations were one-tailed with a probability level of 0.05. The anticipated effect size (Cohen's d) was 0.8, and the desired statistical power level was 80%. The result of sample size calculation for minimum total sample size was 38, which was in part why we included 40 individuals as part of our study.

RESULTS

Thirty men and 10 women with mean ± SD and 64.7 ± 9.9 years of age were included in this study. Coronary heart disease and arterial hypertension were the most common comorbidities with patients in functional classes (NYHA) II and III (Table 1). Concomitant medication was as follows: angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARB) (77.5%, 10%) and beta blocker (BB, 95%) agents were the most commonly employed; also, 37.5% received mineralocorticoid receptor antagonists and 40% furosemide (Table 1). During the study period, ivabradine dose was increased to 7.5 mg bid in 25 patients, and remained at 5 mg bid in 9 patients. The ivabradine dose was thereafter reduced to 2.5 mg bid in 6 patients during the study period so that bradycardia would not progress to the symptomatic bradycardia. Other adverse events were not observed.

All patients were in the NYHA class II and III, and resting heart rates were 84.3 ± 11.4 bpm on average with sinus rhythm. Most of patients exhibited some degree of clinical improvement, 12/16 (75.0%) from NYHA III to II and 18/24 (75.0%) from II to I, respectively. Resting heart rate was significantly reduced after ivabradine treatment (84.3 ± 11.4 vs. 66.5 ± 11.5 bpm, $p < 0.001$). There were no significant difference in IVRT and IKT before and after ivabradine treatment. However, LVEF, E/A, E/E' and Tei index were significantly changed after ivabradine treatment [28.98 (15-35) vs. 30.76 (15-40), $p = 0.013$, 0.94 (0.29-2.74) vs. 1.21 (0.31-2.96), $p = 0.001$, 17.3 ± 9.0 vs. 14.8 ± 7.1, $p = 0.02$ and 0.86 ± 0.74 vs. 0.81 ± 0.69, $p = 0.02$, respectively] (Table 2).

Intra-LV systolic synchrony parameters of TSI including Ts-SD-6 and Ts-6 were not changed after ivabradine treatment; however, Ts-SD-12 and Ts-12 were significantly reduced after ivabradine treatment (46.8 ± 13.6 vs. 42.7 ± 13.1, $p = 0.01$ and 142.5 ± 44.0 vs. 128.5 ± 45.2, $p = 0.009$, Table 3, Figure 2). The frequency of intra-LV systolic asynchrony defined as Ts-SD-12-ejection more than 34.4 ms was significantly lower after ivabradine treatment (80% vs. 50%, $p = 0.04$).

Results of the multivariate Cox regression analyses for Ts-SD-12 and Ts-12 were listed in Table 4. No one were found to have prognostic significance ($p > 0.05$).

DISCUSSION

It has been noted that heart rate is an important contributor in the pathophysiology of both CAD and HF, and is being increasingly acknowledged as a modifiable risk factor in patients with cardiovascular disease.[20,21] The ivabradine acts by selectively inhibiting the ionic current If, which modulates pacemaker activity in the sino-atrial node, provided there is pure heart rate diminution.[7] The results of the SHIFT study[2] clearly demonstrated that when If inhibitor ivabradineis added to con-

Table 1. Demographic, clinical characteristics and drugs of patients

	n = 40
Age, mean ± SD, yrs	64.7 ± 9.9
Sex, male/female	30/10
Arterial hypertension (%)	47.3
Diabetes mellitus (%)	32.3
CHD (%)	81.4
COPD (%)	20
Cigarette smoker (%)	12
BMI, mean ± SD	26.6 ± 4.2
Perindopril (5 mg/d), n (%)	16 (40.0)
Ramipril (10 mg/d), n (%)	12 (30)
Trandolapril (2 mg/d), n (%)	5 (12.5)
Candesartan (16 mg/d), n (%)	4 (10)
Karvedilol (25 mg/d), n (%)	28 (70)
Nebivolol (5 mg/d), n (%)	5 (12.5)
Metoprolol (50 mg/d), n (%)	5 (12.5)
Spironolactone (25 mg/d), n (%)	15 (37.5)
Furosemide (20 mg/d), n (%)	16 (40)
Digoksin (0.125 mg/d), n (%)	4 (10)
Statin (10 mg/d), n (%)	24 (60)

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; karvedilol was given 12.5 mg twice daily.

Table 2. Effects of ivabradine on clinic and echocardiographic characteristics

	Before ivabradine (mean ± SD, n%)	After ivabradine (mean ± SD, n%)	p
Heart rate at rest, bpm	84.3 ± 11.4	66.5 ± 11.5	< 0.001
Systolic blood pressure (mmHg)	127.9 ± 35.4	125.3 ± 25.6	0.49
Diastolic blood pressure (mmHg)	78.8 ± 15.2	75.7 ± 13.4	0.21
LVEDV (mL)	144.5 (44-325)	130.9 (75-280)	0.02
LVESV (mL)	93.3 ± 42.6	88.4 ± 46.8	0.31
LVEF (%)	28.98 (15-35)	30.76 (15-40)	0.01
IVS (mm)	9.8 ± 2.2	9.7 ± 2.0	0.19
PW (mm)	9.5 ± 2.1	9.5 ± 1.8	0.51
E/A	0.94 (0.29-2.74)	1.21 (0.31-2.96)	0.001
E/E'	17.3 ± 9.0	14.8 ± 7.1	0.02
IVRT (ms)	99.8 ± 26.9	97.9 ± 30.5	0.19
IKT (ms)	84.6 (47-296)	84.9 (41-251)	0.89
Tei index	0.86 (0.37-7.45)	0.81 (0.28-7.29)	0.02

Data are expressed as mean ± SD, median (minimum-maximum) values.
A, late diastolic mitral inflow velocity; DT, deceleration time; E, early diastolic mitral inflow velocity; E', early diastolic mitral annular velocity; IVRT, isovolumetric relaxation time; IVS, interventricular septum; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; PW, posterior wall.

Table 3. Effects of ivabradine on intra left ventricular synchronization

	Before ivabradine (mean ± SD)	After ivabradine (mean ± SD)	p
Ts-SD-12	46.8 ± 13.6	42.7 ± 13.1	0.01
Ts-12	142.5 ± 44.0	128.5 ± 45.2	0.009
Ts-SD-6	42.9 ± 16.9	42.8 ± 17.0	0.74
Ts-6	109.2 ± 38.7	109.9 ± 41.2	0.57

Ts, time to peak tissue velocity; Ts-6, maximal difference in Ts between any 2 of the 6 basal LV segments; Ts-SD-6, standard deviation of Ts of the 6 basal LV segments; Ts-12, maximal difference in Ts between any 2 of the 12 LV segments; Ts-SD-12, standard deviation of Ts of the 12 LV segments.

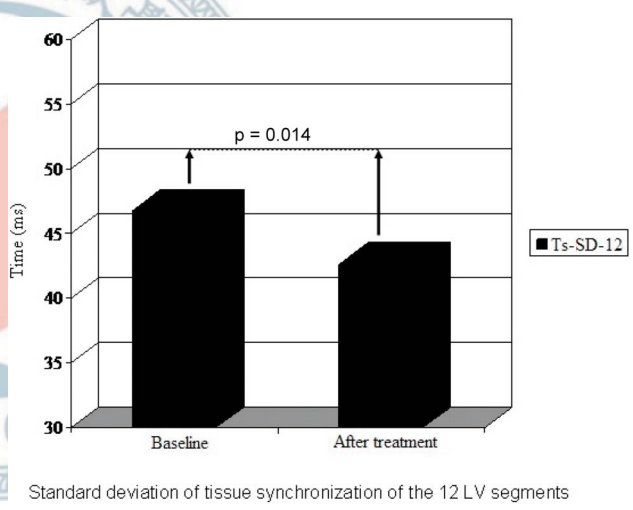

Figure 2. *Demonstrated that LV asynchrony before and after treatment of ivabradine.*

ventional therapy for the systolic HF, there was a related 18% reduction in the relative risk for the primary composite endpoint of cardiovascular death or hospitalization for worsening HF (p < 0.0001). Additionally, ivabradine had a positive effect on LV remodelling as noted in the echocardiographic results of the BEAUTIFUL (morBidity-mortality EvAlUa-Tion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study.[22] In our study, we established that when long-term treatment with ivabradine in outpatients with systolic HF on optimized medical therapy and resting HR > 70 beats/min is utilized, the estimated HR diminution with ivabradine added together improves significantly intra LV ventricular asynchrony and the Tei index after 3 months. Moreover, E/E' suggested that the LV filling pressure was significantly decreased with the HR reduction after ivabradine treatment.

Some studies demonstrated that ivabradine reduced fibrosis and improved endothelial function,[23-25] together with its anti-ischemic and anti-anginal effects.[25] In rats with chronic HF, long-term (3 month) HR reduction induced by the selective If inhibitor ivabradine improves LV function and increases stroke volume, preserving

Table 4. The results of regression analyses of Ts-SD-12 and Ts-12

	Ts-SD-12		Ts-12	
	Beta	p value	Beta	p value
Age	-0.120	0.68	0.152	0.44
Sex	-0.200	0.39	-0.081	0.66
Smoking	0.125	0.58	-0.147	0.41
CAD	-0.210	0.42	-0.123	0.14
Hypertension	0.248	0.34	-0.030	0.88
Diabetes mellitus	0.472	0.09	0.117	0.56
BMI	-0.038	0.89	0.308	0.12
Heart rate at rest	0.148	0.51	-0.028	0.90
Systolic blood pressure	-0.044	0.86	-0.231	0.21
Diastolic blood pressure	-0.201	0.39	-0.211	0.29
Glucose	0.254	0.33	-0.165	0.37
Creatinine	-0.252	0.33	-0.100	0.60
LVEF	-0.251	0.31	-0.226	0.27
LVEDV	0.014	0.96	0.152	0.44
Hgb	-0.106	0.70	-0.081	0.66
Plt	0.136	0.59	-0.147	0.41
Wbc	-0.131	0.64	-0.030	0.88

BMI, body mass index; CAD, coronary artery disease; Hgb, hemoglobin; LVEDV, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; Plt, platelet; Wbc, white blood count.

cardiac output despite the HR decrease.[23] These experimental study results could explain why our patients experienced improved left ventricular asynchrony and Tei index, possibly associated with decreased LV filling pressure. It may also be explained by the prolonged diastolic period (per cardiac beat and per minute). Moreover, we can speculate that enhanced cardiac function is associated not only with the HR decrease by itself, but also to modifications in the extracellular matrix and/or function of myocytes as a result of long-term HR reduction.[23,24]

As a result of left ventricular remodeling myocardium, most chronic of HF patients become ischemic and probably more prone to transient local hypoxia/ischemia/reperfusion injury, because of a diminished myocardial O2 supply linked to capillary rarefaction[26] and an amplified O2 consumption mainly associated with ventricular dilatation, an increase in LV end-diastolic pressure, and myocardial tension.[23-27] So, we can hypothesize that ivabradine administration would decrease HR, and increase the diastolic time of the cardiac cycle. Thus, it can play an important role leading to an enhanced coronary perfusion time and thus increasing myocardial perfusion, reduced ventricular wall tension, which possibly reflects improved coronary perfusion pressure (aortic mean pressure/coronary sinus ratio). Moreover, an increase in coronary perfusion owing to HR reduction would prevent the progress of coronary endothelial dysfunction. All of these factors implicated the deterioration of LV function/remodeling and intrinsic tissue structure.

Tei index can be used as a simple method to evaluate LV systolic and diastolic function, and it can be easily applied. The Tei index proposal combines both systolic and diastolic function of LV. The normal Tei index value has been reported to be 0.39 $\pm$ 0.05 in adults.[28] In our study, we found that the Tei index was significantly elevated in patients with chronic HF, and after 3 months treatment of ivabradine the Tei index was reduced significantly.

In HF patients, LV asynchrony can contribute to the worsening of HF. Also, the presence of LV asynchrony is an independent factor of deterioration of HF. Yu et al.[15] demonstrated that the systolic asynchrony index measured by tissue synchronization imaging was the only independent predictor of LV reverse remodeling after CRT. Ts-SD-12 more than 34.4 ms is defined by way of intra-LV systolic asynchrony by TSI.[13] Previous studies have suggested that measuring Ts from myocardial velocity curves of TDI were very useful for quantitative assessment of systolic asynchrony.[15-17] The results of our study demonstrated that If inhibitor ivabradine added to conventional therapy for the systolic HF was related to improving LV asynchrony and Tei index.

The limitations of the study

The major limitation of this study was its size, which was relatively small. Second, strain or strain rate was not performed for LV asynchrony. Nevertheless, strain and strain rate analysis are not applicable for routine clinical use and difficult to interpret strain images. In this study, we used TSI method which is reliable, practical and less time consuming.

CONCLUSIONS

For treatment with ivabradine in outpatients with

systolic HF on optimized medical therapy and resting HR > 70 beats/min, the estimated HR diminution with ivabradine added together significantly improves intra LV ventricular asynchrony and Tei index after 3 months. This improvement in LV function is possibly linked not only to the HR decrease by itself, but also to modifications in the extracellular matrix and/or function of myocytes as a result of long-term HR reduction.

POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SOURCES OF FUNDING

There were no external funding sources for this study.

STUDY ASSOCIATION

This study is not associated with any post-graduation program.

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