Excitation-Contraction Coupling Time is More Sensitive in Evaluating Cardiac Systolic Function

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Abstract

Background: Pressure overload-induced myocardial hypertrophy is a key step leading to heart failure. Previous cellular and animal studies demonstrated that deteriorated excitation–contraction coupling occurs as early as the compensated stage of hypertrophy before the global decrease in left ventricular ejection fraction (LVEF). This study was to evaluate the cardiac electromechanical coupling time in evaluating cardiac systolic function in the early stage of heart failure.

Methods: Twenty-six patients with Stage B heart failure (SBHF) and 31 healthy controls (CONs) were enrolled in this study. M-mode echocardiography was performed to measure LVEF. Tissue Doppler imaging (TDI) combined with electrocardiography (ECG) was used to measure cardiac electromechanical coupling time.

Results: There was no significant difference in LVEF between SBHF patients and CONs (64.23 ± 8.91% vs. 64.52 ± 5.90%; $P = 0.886$). However, all four electromechanical coupling time courses (Qsb: onset of Q wave on ECG to beginning of S wave on TDI, Qst: onset of Q wave on ECG to top of S wave on TDI, Rsb: top of R wave on ECG to beginning of S wave on TDI, and Rst: top of R wave on ECG to top of S wave on TDI) of SBHF patients were significantly longer than those of CONs (Qsb: 119.19 ± 35.68 ms vs. 80.30 ± 14.81 ms, $P < 0.001$; Qst: 165.42 ± 60.93 ms vs. 129.04 ± 16.97 ms, $P = 0.006$; Rsb: 82.43 ± 33.66 ms vs. 48.30 ± 15.18 ms, $P < 0.001$; and Rst: 122.37 ± 36.66 ms vs. 93.25 ± 16.72 ms, $P = 0.001$), and the Qsb, Rsb, and Rst time showed a significantly higher sensitivity than LVEF (Rst: $P = 0.032$; Rsb: $P = 0.003$; and Qsb: $P = 0.004$).

Conclusions: The cardiac electromechanical coupling time is more sensitive than LVEF in evaluating cardiac systolic function.

Key words: Excitation–Contraction Couplings; Heart Failure; Left Ventricular Dysfunction

Introduction

Heart failure is a major public health concern and the most common cause for hospitalization.[1] The standard treatment of heart failure fails to improve cardiac systolic function in more than a third of patients with Stage C or D heart failure.[2] Increasing evidence suggests that heart failure is preventable and treatable in the early stage.[3] Thus, it is important to develop an earlier and more sensitive evaluation index of cardiac systolic function during the early stage of heart failure.

Excitation–contraction (E-C) coupling is an important indicator of cardiomyocyte contractile function.[4] Our previous study suggests that the efficiency between a single L-type channel and its controlled-Ca^{2+}-release channels decrease before the appearance of cardiac systolic and cardiomyocyte contractile dysfunction at the early stage of heart failure in animal models.[5] The basic characteristics of E-C coupling are a series of stereotyped events that are responsible for the rapid mechanical contraction response of muscle fibers to an initial electrical event at the surface.[6-8]

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Thus, we speculated whether the electromechanical coupling of the cardiac muscle is a more sensitive indicator in the evaluation of cardiac systolic function compared with left ventricular ejection fraction (LVEF) in the early stage of heart failure patients.

Echocardiogram (echo) and electrocardiogram (ECG) are widely used to evaluate the structural changes and mechanical activity[9] and the electrical activity of the heart,[10] respectively. However, no specific medical test can detect the cardiac electromechanical coupling efficiency. The Q wave on ECG represents the beginning of ventricular electrical activity and the S wave on tissue Doppler imaging (TDI) represents the beginning of ventricular systolic activity. The time course from Q wave to S wave reflects the electromechanical coupling efficiency of left ventricular. Thus, we aimed to measure ventricular electromechanical coupling time course by combining TDI measurement of echo and ECG measurement and study its role in the evaluation of cardiac systolic function.

Methods

Ethical approval

The procedure was approved by the Ethics Committee of Peking University Third Hospital (Approval No. IRB00006761-2016125) and in accordance with the *Declaration of Helsinki* 1975, as revised in 2000. All individuals provided written informed consent before taking part in this study.

Study population

We consecutively evaluated 26 patients with Stage B heart failure (SBHF) and 31 age- and sex-matched healthy controls (CONs). All CONs were recruited before the initiation of the study. CONs did not have a history of hypertension, diabetes, cardiovascular disease, or cerebrovascular disease. SBHF patients were diagnosed with hypertensive myocardial hypertrophy by echo (interventricular septum [IVS] thickness ≥11 mm or left ventricular posterior wall [LVPW;d] ≥11 mm or left ventricular mass index [LVMI] ≥115 g/cm^2). Volunteers with inflammatory disease, with allergy, who are taking drugs that affect the immune or endocrine system, and/or with alcoholism were excluded from the study.

Echocardiographic measurement

Echo was performed as described previously.[11] A Vivid GE 7 color ultrasonic diagnostic instrument (GE, Fairfield, CT, USA) with a probe of 1.7–3.4 MHz frequency was used to measure the IVS, LVPW;d, Left ventricular end-diastolic dimension (LVEDD), and Left ventricular end-systolic dimension (LVESD) in M-mode echo. Relative wall thickness (RWT) was calculated using the following formula: RWT = (2 × LVPW;d)/LVEDD. The left ventricular mass (LVM) and LVMI were calculated according to the Devereux formula: LVM (g) = $0.8 \times 1.04 \times ([IVS + LVPW;d + LVEDD]^3 - LVEDD^3) + 0.6$, LVMI (g/m^2) = LVM/BSA, respectively, the body surface area (BSA) was calculated as follows: BSA = $0.0061 \times$ height (cm) + $0.0128 \times$ weight (kg) − 0.1529. LVEF was calculated by the Teicholz method. The values of three consecutive cardiac cycles were measured.

Electromechanical coupling time measurement

ECG was performed as described previously.[12] The TDI echo combined with ECG was used to evaluate the four time courses (Qsb, Qst, Rsb, and Rst) in all six walls of the left ventricle, namely the lateral wall (Lat), anterior wall (Ant), inferior wall (Inf), posterior wall (PW), posterior ventricular septum (Pivs), and anterior ventricular septum (Aivs). The time measurement module of Vivid GE 7 color ultrasonic diagnostic instrument was used to detect the time course of Qsb, Qst, Rsb, and Rst. Qsb time course is from the onset of Q wave on ECG to beginning of S wave on TDI. Qst time course is from the onset of Q wave on ECG to top of S wave on TDI. Rsb time course is from the top of R wave on ECG to beginning of S wave on TDI. Rst time course is from the top of R wave on ECG to top of S wave on TDI.

Statistical analysis

All statistical analyses were conducted using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). The data are expressed as mean ± standard deviation (SD). The results were compared using Student's *t*-test. A value of $P < 0.05$ was considered statistically significant. Sensitivity and specificity analyses were conducted using MedCalc version 14 software (MedCalc Inc., Ostend, Belgium), and a $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of Stage B heart failure patients and healthy controls

The clinical characteristics of SBHF patients and CONs are given in Table 1. There were no significant differences in age, body mass index (BMI), and heart rate (HR)

Table 1: Comparison of the general characteristics of study population

Items	CONs (n = 31)	SBHF patients (n = 26)	t	P
Age (year)	42.65 ± 13.61	46.00 ± 11.56	−1.006	0.319
BMI (kg/m^2)	23.75 ± 3.01	25.00 ± 3.12	−1.541	0.129
HR (beats/min)	72.35 ± 9.58	74.73 ± 13.75	−0.766	0.447
SBP (mmHg)	118.77 ± 8.88	156.23 ± 25.14	−7.229	<0.001
DBP (mmHg)	71.58 ± 9.07	93.04 ± 15.76	−6.426	<0.001

Data are expressed as mean ± SD. BMI: Body mass index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; CONs: Healthy controls; SBHF: Stage B heart failure.

between SBHF and CON groups (age: 46.00 ± 11.56 vs. 42.65 ± 13.61, $t = -1.006$, $P = 0.319$; BMI: 25.00 ± 3.12 vs. 23.75 ± 3.01, $t = -1.541$, $P = 0.129$, HR: 74.73 ± 13.75 vs. 72.35 ± 9.58 $t = -0.766$, $P < 0.001$). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) in SBHF patients were significantly higher than those of CONs (SBP: 156.23 ± 25.14 vs. 118.77 ± 8.88, $t = -7.299$, $P < 0.001$; DBP: 93.04 ± 15.76 vs. 71.58 ± 9.07, $t = -6.426$, $P < 0.001$) [Table 1].

Standard echocardiographic parameters of Stage B heart failure patients and healthy controls

Echocardiographic data showed that the indexes reflecting myocardial hypertrophy in SBHF patients were much higher than those in CONs. As shown in Table 2, the thickness of IVS and LVPW;d significantly increased in SBHF patients compared with those of CONS (IVS: 12.14 ± 1.17 vs. 8.09 ± 1.06, $t = -13.702$, $P < 0.001$; LVPW;d: 11.78 ± 0.94 vs. 8.13 ± 0.89, $t = -15.017$, $P < 0.001$). RWT and LVMI were significantly higher in SBHF patients than in CONs (RWT: 0.45 ± 0.04 vs. 0.34 ± 0.04, $t = -9.974$, $P < 0.001$; LVMI: 134.07 ± 30.37 vs. 75.96 ± 14.24, $t = -8.964$, $P < 0.001$). The average LVEDD and LVESD in SBHF patients were larger than those in CONs (LVEDD: 52.54 ± 4.71 vs. 48.1 ± 3.38, $t = -4.136$, $P < 0.001$, LVESD: 33.52 ± 5.28 vs. 29.84 ± 2.71, $t = -3.222$, $P = 0.003$). SBHF patients had significantly lower than those in CONs for the E/A and E/Em ratios (E/A: 0.98 ± 0.49 vs. 1.34 ± 0.40, $t = 3.053$, $P = 0.003$, E/Em: 10.28 ± 3.80 vs. 5.72 ± 0.65, $t = -5.687$, $P < 0.001$). However, there was no significant difference in LVEF between SBHF patients and CONs (64.23 ± 8.91 vs. 64.52 ± 5.90, $t = 0.145$, $P = 0.886$).

Electromechanical coupling time parameters of Stage B heart failure patients and healthy controls

Four cardiac electromechanical coupling time courses in Lat of the left ventricle (Lat-Rst, Lat-Rsb, Lat-Qst, and Lat-Qsb) of CONs [Figure 1a] and SBHF patients [Figure 1b] were evaluated by TDI echo combined with ECG. The measurement showed that the four electromechanical coupling parameters in SBHF patients were all longer than those in CONs [Lat-Rst: 122.37 ± 36.66 vs. 93.25 ± 16.72, $t = -3.696$, $P = 0.001$, Figure 1c; Lat-Rsb: 82.43 ± 33.66 vs. 48.30 ± 15.18, $t = -4.779$, $P < 0.001$, Figure 1d; Lat-Qst: 165.42 ± 60.93 vs. 129.04 ± 16.97, $t = -2.951$, $P = 0.006$,

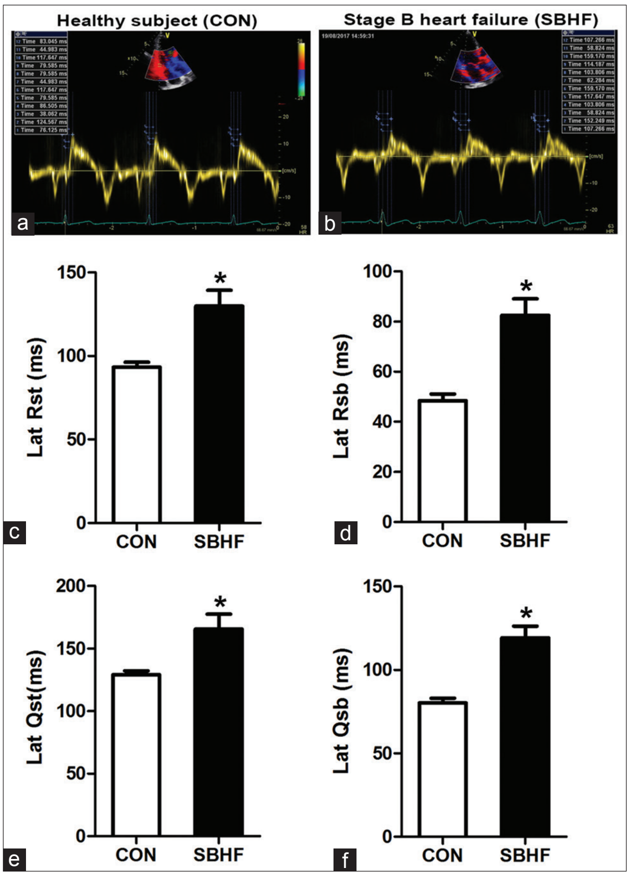

Figure 1: Cardiac electromechanical coupling time in SBHF patients and CONs. Representative images of TDI combined with ECG to measure the electromechanical coupling time in the lateral wall of the left ventricle (Lat) of CON subjects (a) and SBHF patients (b). Statistical data of Lat-Rst (c), Lat-Rsb (d), Lat-Qst (e), and Lat-Qsb (f) in SBHF patients group and CON group. Data are mean ± SD. *$P < 0.05$ versus CON. CONs: Healthy controls; TDI: Tissue Doppler imaging; ECG: Electrocardiography; SBHF: Stage B heart failure; Rst: From the top of R wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Qsb: From the onset of Q wave on ECG to the beginning of S wave on TDI; SD: Standard deviation.

Table 2: Comparison of M-mode echocardiographic measurement parameters

Items	CONs (n = 31)	SBHF patients (n = 26)	t	P
IVS (mm)	8.09 ± 1.06	12.14 ± 1.17	−13.702	<0.001
LVPW;d (mm)	8.13 ± 0.89	11.78 ± 0.94	−15.017	<0.001
LVEDD (ml)	48.10 ± 3.38	52.54 ± 4.71	−4.136	<0.001
LVESD (ml)	29.84 ± 2.71	33.52 ± 5.28	−3.222	0.003
RWT	0.34 ± 0.04	0.45 ± 0.04	−9.974	<0.001
LVMI (g/m^2)	75.96 ± 14.24	134.07 ± 30.37	−8.964	<0.001
LVEF (%)	64.52 ± 5.90	64.23 ± 8.91	0.145	0.886
E/A	1.34 ± 0.40	0.98 ± 0.49	3.053	0.003
E/Em	5.72 ± 1.65	10.28 ± 3.80	−5.687	<0.001

Data are expressed as mean ± SD. IVS: Inter-ventricular septum; LVPW;d: Left ventricular posterior wall; LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular end-systolic dimension; RWT: Relative wall thickness; LVMI: Left ventricular mass index; LVEF: Left ventricular ejection fraction; SD: Standard deviation; CONs: Healthy controls; SBHF: Stage B heart failure; ECG: Electrocardiography; TDI: Tissue Doppler imaging.

Figure 1e; Lat-Qsb: 119.19 ± 35.68 ms vs. 80.30 ± 14.81 ms, $t = -5.196$, $P < 0.001$, Figure 1f, respectively] [Table 3]. In addition, the sensitivity and specificity analyses showed that the Lat-Rst, Lat-Rsb, and Lat-Qsb were significantly better than LVEF [Rst: P = 0.032, Figure 2a; Rsb: P = 0.003, Figure 2b; and Qsb: P = 0.004, Figure 2d]. While, the sensitivity and specificity of Lat-Qst was not significantly different from the LVEF [P = 0.126, Figure 2c] similar trends were also observed in the Pivs, Ant, Inf, PW, and Aivs [Table 3].

Discussion

The results of our research suggested that the electromechanical coupling time is more sensitive and specific than LVEF in evaluating cardiac systolic function [Figure 2a, 2b, and 2d]. These results suggested that electromechanical coupling time is a potential index in evaluating cardiac systolic function in SBHF patients.

The Qsb time course was used to detect systolic asynchrony in patients with regional myocardial dysfunction.[13] In our study, the Qsb, Qst, Rsb, and Rst time course were chosen to evaluate the cardiac systolic function. S wave of TDI represents the beginning of systolic activity of left ventricular, and Q wave on ECG represents the beginning of mechanical activity of left ventricular. Hence, we detected the time course from the Q wave to the beginning of S wave to represent the efficiency that the electrical activity transferred into mechanical activity. As the beginning of S wave was sometimes unclear in TDI, therefore, we supplement the time course of Qst, which is from the Q wave on ECG to the top of S wave on TDI representing the efficiency of electromechanical coupling efficiency. In additional, Rsb and Rst time course were measured to avoid the uncertainty of the Q wave.

Regarding the effects of electromechanical coupling time, the following factors need to be discussed. First, HR is related with the electrical and mechanical activities of the heart.[14,15] To determine the effects of HR in electromechanical coupling time, the electromechanical coupling time with or without HR correction in SBHF patients and CONs was analyzed in our study. The results showed that the electromechanical coupling durations were all significant longer in SBHF patients than those in CONs with or without HR correction [Supplementary Table 1], which indicates that HR has no significant influence in the prolongation of electromechanical coupling in the SBHF group.

Second, the homogeneity of the heart might influence the electromechanical coupling time. In our study, we selected participants with pressure overload-induced heart failure, which is known to lead to homogenous cardiac remodeling.[16,17] We detected electromechanical coupling

Table 3: Comparison of cardiac E-C coupling measurement parameters of study population

Items	CONs (n = 31)	SBHF patients (n = 26)	t	P
Lat-Qsb (ms)	80.30 ± 14.81	119.19 ± 35.68	−5.196	<0.001
Lat-Qst (ms)	129.04 ± 16.97	165.42 ± 60.93	−2.951	0.006
Lat-Rsb (ms)	48.30 ± 15.18	82.43 ± 33.66	−4.779	<0.001
Lat-Rst (ms)	93.25 ± 16.72	122.37 ± 36.66	−3.696	0.001
Pivs-Qsb (ms)	80.32 ± 17.35	109.11 ± 28.35	−4.516	<0.001
Pivs-Qst (ms)	127.80 ± 20.45	154.07 ± 38.45	−3.131	0.003
Pivs-Rsb (ms)	48.87 ± 13.70	73.88 ± 22.45	−4.960	<0.001
Pivs-Rst (ms)	74.20 ± 11.57	92.96 ± 34.32	−2.663	0.012
Ant-Qsb (ms)	79.37 ± 12.47	114.89 ± 37.51	−4.619	<0.001
Ant-Qst (ms)	127.00 ± 16.13	162.46 ± 57.69	−3.037	0.005
Ant-Rsb (ms)	47.84 ± 12.94	79.86 ± 31.27	−4.882	<0.001
Ant-Rst (ms)	92.19 ± 16.13	125.29 ± 51.84	−3.132	0.004
Inf-Qsb (ms)	82.47 ± 17.81	106.22 ± 23.63	−4.323	<0.001
Inf-Qst (ms)	127.42 ± 22.58	153.41 ± 40.29	−2.926	0.006
Inf-Rsb (ms)	50.13 ± 16.60	74.23 ± 19.23	−5.078	<0.001
Inf-Rst (ms)	97.85 ± 22.51	119.5 ± 33.3	−2.914	0.005
PW-Qsb (ms)	81.89 ± 17.35	112.1 ± 30.53	−4.476	<0.001
PW-Qst (ms)	130.30 ± 17.76	160.96 ± 54.28	−2.759	0.010
PW-Rsb (ms)	49.28 ± 14.77	78.47 ± 27.37	−4.873	<0.001
PW-Rst (ms)	95.14 ± 17.73	128.76 ± 44.65	−3.608	0.001
Aivs-Qsb (ms)	83.33 ± 17.45	103.6 ± 25.1	−3.476	0.001
Aivs-Qst (ms)	125.10 ± 20.17	153.35 ± 36.64	−3.677	0.001
Aivs-Rsb (ms)	51.13 ± 13.84	70.78 ± 21.2	−4.056	<0.001
Aivs-Rst (ms)	93.34 ± 17.84	117.03 ± 32.22	−3.486	0.001

Data are expressed as mean ± SD. Lat: Lateral wall of left ventricle; Pivs: Posterior ventricular septum of left ventricle; Ant: Anterior wall of left ventricle; Inf: Inferior wall of left ventricle; PW: Posterior wall of left ventricle; Aivs: Anterior ventricular septum of left ventricle; Qsb: From the onset of Q wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Rst: From the top of R wave on ECG to the top of S wave on TDI; SD: Standard deviation; CONs: Healthy controls; SBHF: Stage B heart failure; ECG: Electrocardiography; TDI: Tissue Doppler imaging; E-C: Excitation-contraction.

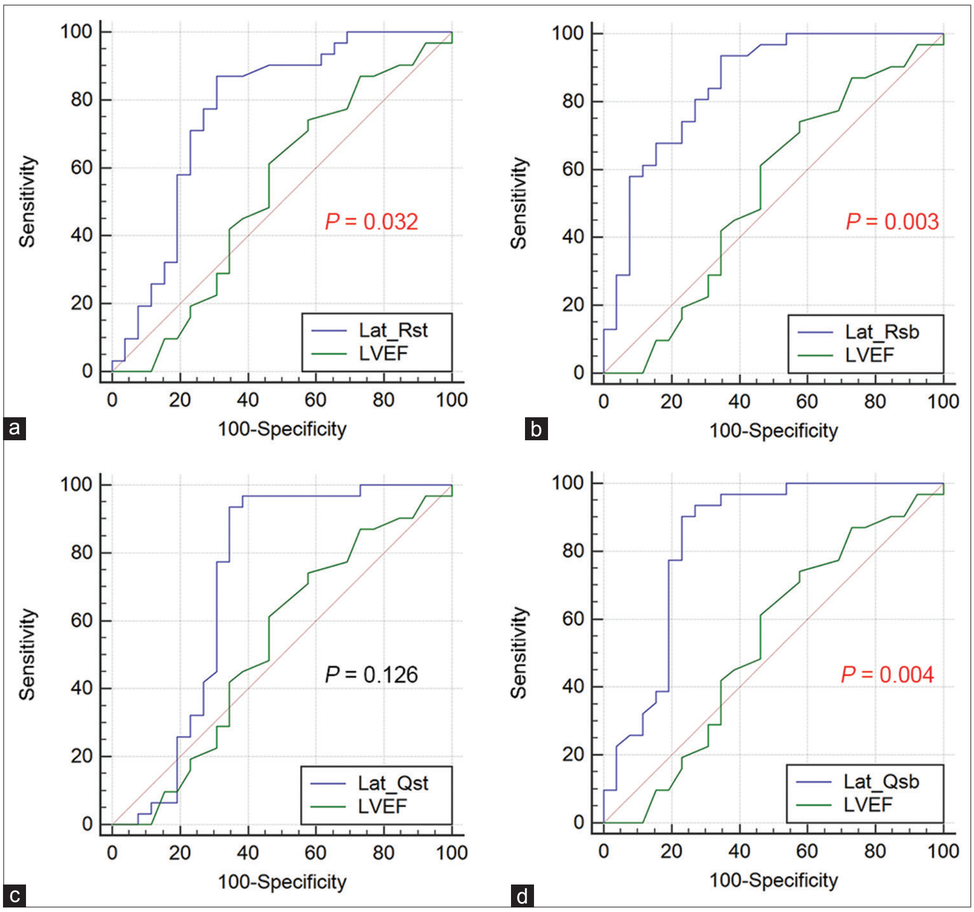

Figure 2: Comparison of sensitivity and specificity between Lat-Rst and LVEF, $P = 0.032$ (a), between Lat-Rsb and LVEF, $P = 0.003$ (b), between Lat-Qst and LVEF, $P = 0.126$ (c), and between Lat-Qsb and LVEF, $P = 0.004$ (d). LVEF: Left ventricular ejection fraction; Rst: From the top of R wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Qsb: From the onset of Q wave on ECG to the beginning of S wave on TDI.

time course in six walls of the left ventricle (including Lat, Ant, Inf, PW, Aivs, and Pivs) in SBHF patients and CONs, and the results showed that the indexes of electromechanical coupling time were all significantly longer than those of CONs in six walls of left ventricle [Table 3]. This suggested that, in pressure overload-induced SBHF, the electromechanical time would not be significantly influenced by the scanning position of TDI.

Third, age affects cardiac function and structure, especially cardiac diastolic function.[18,19] To determine the influence of age, we compared the electromechanical coupling time in two control groups with significant different ages. The results show that there is no significant difference in electromechanical coupling durations between these two groups [Supplementary Table 2]. Thus, it suggests that the electromechanical coupling duration is not influenced by age.

Finally, cardiac hypertrophy can be divided into pathological cardiac hypertrophy and physiological cardiac hypertrophy. To determine whether the electromechanical coupling time is associated with physiological cardiac hypertrophy, we detected the electromechanical coupling time in athletes with exercise-induced hypertrophy,[20,21] [Supplementary Tables 3 and 4]. The measurement results showed that the athletes' myocardium was characterized by hypertrophy, but their electromechanical coupling time was not significantly longer than that of CONs [Supplementary Table 5]. These results showed that the electromechanical coupling time course can be a potential index to distinguish between pathological cardiac hypertrophy and physiological cardiac hypertrophy.

E/A and E/Em were most used index in evaluating cardiac diastolic function. Aging and hypertension are remarkably related cardiac diastolic function, and cardiac diastolic dysfunction often occurs first in hypertension-induced cardiac hypertrophy.[22] In our study, cardiac diastolic function was significantly decreased in SBHF patients compared with CONs. This is reasonable, for the SBHF patients with remarkable cardiac hypertrophy. For the LVEF in SBHF patients was not significantly decreased, a more sensitive index for evaluating cardiac systolic function is urgently needed. The electromechanical coupling time course in our study related with the systolic mechanical activity of the heart, and our results showed that electromechanical coupling time course was significantly longer than CONs. In addition, the sensitivity and specificity of electromechanical coupling time are better than LVEF. These results showed that the electromechanical coupling time in our study was a potential index to evaluate cardiac systolic function but not the diastolic function.

However, there are still some limitations in our study. One limitation is the lack of follow-up study in humans. Moreover, the sample size is not big enough, and different types of heart failure need to be studied in the future.

In conclusion, SBHF patients have already prolonged electromechanical coupling time but with normal LVEF compared with CONs. Our study provides a potential index for evaluating cardiac systolic function in heart failure at a much earlier stage of heart failure.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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心肌电-机械耦联参数评价心脏收缩功能的优越性

摘要

背景：压力负荷引起的心肌肥厚是引起心力衰竭的重要因素之一，前期的细胞实验和动物实验表明在心脏收缩功能（左心室射血分数）下降之前，心肌细胞兴奋-收缩耦联效率已经发生下降。本研究的目的是为检测心肌电-机械耦联参数在心力衰竭早期对心脏收缩功能的评价作用。

方法：26名心力衰竭B期患者和31名健康志愿者纳入此研究中，使用M型超声心动图测量左心室射血分数（LVEF），超声心动图组织多普勒联合心电图用于测量心肌的电-机械耦联参数。

结果：与健康志愿者相比，心力衰竭B期患者的LVEF值未显著降低（64.23±8.91 vs. 64.52±5.90 %; *P*=0.886）。然而，心力衰竭B期患者心肌电-机械耦联参数均明显延长（Qsb：心电图Q波的波谷至组织多普勒S波起点的时间；Qst：心电图Q波的波谷至组织多普勒S波波峰的时间；Rsb：心电图R波的波峰至组织多普勒S波起点的时间；Rst：心电图上R波的波峰至组织多普勒上S波波峰的时间）（Qsb: 119.19 ± 35.68 vs. 80.30 ±14.81 ms, *P*<0.001; Qst: 165.42 ± 60.93 vs. 129.04 ± 16.97 ms, *P*=0.006; Rsb: 82.43 ± 33.66 vs. 48.30 ±15.18 ms, *P*<0.001; Rst: 122.37 ±36.66 vs. 93.25 ± 16.72 ms, *P*=0.001）。此外，Qsb，Rsb与Rst 的敏感性明显高于LVEF（Rst: *P*=0.032; Rsb: *P*=0.003; Qsb: *P*=0.004）。

结论：研究结果显示心肌电-机械耦联参数在评价心脏收缩功能方面比LVEF更加敏感。

Supplementary Table 1: Comparison of electromechanical coupling time measurement parameters without HR corrected

Items	CONs (n = 31)	SBHF patients (n = 26)	t	P
Lat-Qsb	67.68 ± 14.55	97.31 ± 29.62†	4.652	<0.001
Lat-Qst	108.2 ± 13.85	134 ± 41.85*	3.008	0.005
Lat-Rsb	40.92 ± 14.01	68.38 ± 29.06†	4.401	<0.001
Lat-Rst	78.19 ± 13.98	104.6 ± 36.10*	3.517	0.001
Pivs-Qsb	66.38 ± 12.68	95.88 ± 25.44†	5.38	<0.001
Pivs-Qst	106.3 ± 13.25	134.3 ± 32.89†	4.337	<0.001
Pivs-Rsb	41.83 ± 15.08	65.31 ± 21.40†	4.843	<0.001
Pivs-Rst	77.23 ± 14.04	99.58 ± 30.54†	3.646	<0.001
Ant-Qsb	67.6 ± 13.09	93.96 ± 30.09†	4.411	<0.001
Ant-Qst	106.7 ± 14.19	134.7 ± 46.99*	3.151	0.003
Ant-Rsb	41.46 ± 11.95	66.81 ± 27.73†	4.337	<0.001
Ant-Rst	77.63 ± 14.78	107.4 ± 43.25†	3.352	0.002
Inf-Qsb	69.17 ± 15.78	94.73 ± 24.40†	4.596	<0.001
Inf-Qst	107.6 ± 20.52	136.7 ± 35.00†	3.742	<0.001
Inf-Rsb	42.11 ± 15.42	66.08 ± 20.78†	4.992	<0.001
Inf-Rst	82.38 ± 19.56	106.8 ± 29.61†	3.604	<0.001
PW-Qsb	67.56 ± 15.56	92.73 ± 24.19†	4.572	<0.001
PW-Qst	108 ± 19.56	132.6 ± 40.56*	2.786	0.009
PW-Rsb	41.59 ± 13.09	64.27 ± 21.13†	4.759	<0.001
PW-Rst	79.71 ± 14.41	103.7 ± 33.49*	3.403	0.002
Aivs-Qsb	69.91 ± 15.42	94.62 ± 25.28†	4.351	<0.001
Aivs-Qst	104.8 ± 15.73	138 ± 36.46*	4.323	<0.001
Aivs-Rsb	43.07 ± 12.61	64.58 ± 21.1†	4.558	<0.001
Aivs-Rst	78.19 ± 13.98	104.6 ± 36.10*	4.155	<0.001

Data are expressed as mean ± SD. Lat: Lateral wall of left ventricle; Pivs: Posterior ventricular septum of left ventricle; Ant: Anterior wall of left ventricle; Inf: Inferior wall of left ventricle; PW: Posterior wall of left ventricle; Aivs: Anterior ventricular septum of left ventricle; Qsb: from the onset of Q wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Rst: From the top of R wave on ECG to the top of S wave on TDI; SD: Standard deviation; CONs: Healthy controls; SBHF: Stage B heart failure; ECG: Electrocardiography; TDI: Tissue Doppler imaging; *P<0.05; †: P<0.01.

Supplementary Table 2: Comparison of electromechanical coupling time measurement in CONs of SBHF patients and CONs of athletes

Items	CONs of SBHF patients ($n = 31$)	CONs of athletes ($n = 15$)	t	P
Age (year)	42.7 ± 13.6	28.87 ± 4.26	4.855	<0.001
Lat-Qsb (ms)	80.3 ± 14.81	79.14 ± 16.02	−0.044	0.965
Lat-Qst (ms)	129 ± 16.97	128.8 ± 20.2	−1.014	0.316
Lat-Rsb (ms)	48.3 ± 15.18	52.2 ± 12.73	0.308	0.759
Lat-Rst (ms)	93.25 ± 16.72	98.35 ± 15.09	−0.873	0.387
Pivs-Qsb (ms)	80.32 ± 17.35	82.19 ± 21.78	−0.303	0.764
Pivs-Qst (ms)	127.8 ± 20.45	137 ± 29.67	−1.21	0.233
Pivs-Rsb (ms)	48.87 ± 13.7	49.48 ± 16.31	−0.132	0.896
Pivs-Rst (ms)	74.2 ± 11.57	74.86 ± 10.33	−0.189	0.851
Ant-Qsb (ms)	79.37 ± 12.47	79.64 ± 14.27	−0.063	0.95
Ant-Qst (ms)	127 ± 16.13	132.4 ± 22.39	−0.911	0.367
Ant-Rsb (ms)	47.84 ± 12.94	47.87 ± 12.93	−0.006	0.995
Ant-Rst (ms)	92.19 ± 16.13	95.3 ± 18.2	−0.575	0.569
Inf-Qsb (ms)	82.47 ± 17.81	83.91 ± 26.23	−0.212	0.833
Inf-Qst (ms)	127.4 ± 22.58	136.7 ± 32.31	−1.068	0.292
Inf-Rsb (ms)	50.13 ± 16.6	50.33 ± 16.45	−0.035	0.972
Inf-Rst (ms)	97.85 ± 22.51	108.1 ± 27.27	−1.262	0.214
PW-Qsb (ms)	81.89 ± 17.35	83.01 ± 24.57	−0.159	0.874
PW-Qst (ms)	130.3 ± 17.76	138.3 ± 28.92	−1.057	0.297
PW-Rsb (ms)	49.28 ± 14.77	50.19 ± 12.69	−0.166	0.869
PW-Rst (ms)	95.14 ± 17.73	102.2 ± 23.91	−1.003	0.322
Aivs-Qsb (ms)	83.33 ± 17.45	85.18 ± 24.94	−0.269	0.79
Aivs-Qst (ms)	125.1 ± 20.17	132.3 ± 28.81	−0.899	0.374
Aivs-Rsb (ms)	51.13 ± 13.84	51.51 ± 10.19	−0.07	0.945
Aivs-Rst (ms)	93.34 ± 17.84	96.39 ± 24.43	−0.587	0.56

Data are expressed as mean ± SD. Lat: Lateral wall of left ventricle; Pivs: Posterior ventricular septum of left ventricle; Ant: Anterior wall of left ventricle; Inf: Inferior wall of left ventricle; PW: Posterior wall of left ventricle; Aivs: Anterior ventricular septum of left ventricle; Qsb: From the onset of Q wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Rst: From the top of R wave on ECG to the top of S wave on TDI; SD: Standard deviation; CONs: Healthy controls; SBHF: Stage B heart failure; ECG: Electrocardiography; TDI: Tissue Doppler imaging.

Supplementary Table 3: Comparison of the general characteristics

Items	CONs ($n = 15$)	Athletes ($n = 23$)	t	P
Age (year)	28.87 ± 4.26	21.09 ± 3.31	−6.318	<0.001
BMI (kg/m^2)	22.07 ± 1.59	21.86 ± 2.37	−0.288	0.775
HR (bpm)	76.13 ± 10.51	59.09 ± 7.92	−5.698	<0.001
SBP (mmHg)	117.14 ± 8.33	111.95 ± 8.89	−1.762	0.087
DBP (mmHg)	66.29 ± 8.64	69.35 ± 8.02	1.094	0.281

Data are expressed as mean ± SD. BMI: Body mass index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; CONs: Healthy controls.

Supplementary Table 4: Comparison of M-mode echocardiographic measurement parameters

Items	CONs ($n = 15$)	Athletes ($n = 23$)	t	P
IVS (mm)	8.17 ± 0.94	9.41 ± 1.23	3.323	0.002
LVPW;d (mm)	8.10 ± 0.76	9.44 ± 1.27	4.076	<0.001
LVEDD (ml)	49.56 ± 3.44	54.54 ± 3.51	4.314	<0.001
LVESD (ml)	31.09 ± 0.15	34.46 ± 3.11	3.199	0.003
RWT	0.33 ± 0.33	0.35 ± 0.49	1.360	0.182
LVMI	83.51 ± 14.88	109.06 ± 20.48	4.161	<0.001
LVEF (%)	60.33 ± 5.21	65.39 ± 4.21	3.298	0.002
E/A	1.60 ± 0.34	2.11 ± 0.13	2.912	0.006
E/Em	0.05 ± 0.01	0.05 ± 0.01	0.451	0.655

Data are expressed as mean ± SD. IVS: Inter-ventricular septum; LVPW;d: Left ventricular posterior wall; LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular end-systolic dimension; RWT: Relative wall thickness; LVMI: Left ventricular mass index; LVEF: Left ventricular ejection fraction; SD: Standard deviation; CONs: Healthy controls.

Supplementary Table 5: Comparison of electromechanical coupling time measurement parameters

Items	CONs ($n = 15$)	Athletes ($n = 23$)	t	P
Lat-Qsb	80.52 ± 18.65	79.41 ± 16.02	−0.197	0.845
Lat-Qst	135.62 ± 26.91	128.80 ± 20.20	−0.893	0.378
Lat-Rsb	46.83 ± 16.44	52.2 ± 12.73	1.136	0.264
Lat-Rst	98.58 ± 23.56	98.35 ± 15.09	−0.012	0.991
Pivs-Qsb	82.02 ± 22.67	82.46 ± 14.93	0.047	0.962
Pivs-Qst	137.76 ± 30.70	130.98 ± 20.3	−0.685	0.498
Pivs-Rsb	49.48 ± 16.31	56.29 ± 9.48	1.390	0.180
Pivs-Rst	75.43 ± 10.47	58.1 ± 7.78	−5.698	<0.001
Ant-Qsb	80.27 ± 14.65	81.96 ± 16.81	0.420	0.677
Ant-Qst	133.81 ± 22.60	130.19 ± 21.63	−0.283	0.779
Ant-Rsb	47.71 ± 13.45	55.35 ± 12.74	1.674	0.104
Ant-Rst	96.52 ± 18.33	99.15 ± 16.25	0.647	0.522
Inf-Qsb	83.91 ± 27.39	84.82 ± 16.37	0.123	0.903
Inf-Qst	136.55 ± 33.88	123.36 ± 35.11	−1.082	0.290
Inf-Rsb	50.37 ± 17.25	54.37 ± 11.37	0.810	0.424
Inf-Rst	107.62 ± 28.55	97.05 ± 16.27	−1.418	0.167
PW-Qsb	82.91 ± 26.05	83.42 ± 15.9	0.055	0.956
PW-Qst	140.21 ± 30.01	128.74 ± 28.48	−0.864	0.395
PW-Rsb	46.51 ± 16.88	57.08 ± 10.57	1.529	0.138
PW-Rst	104.22 ± 24.42	99.35 ± 16.12	−0.387	0.701
Aivs-Qsb	84.86 ± 26.27	83.68 ± 19.79	−0.184	0.855
Aivs-Qst	133.38 ± 30.12	134.94 ± 22.92	0.283	0.779
Aivs-Rsb	51.19 ± 19.26	56.06 ± 14.62	0.742	0.464
Aivs-Rst	97.19 ± 25.60	104.32 ± 19.74	1.618	0.116

Data are expressed as mean ± SD. Lat: Lateral wall of left ventricle; Pivs: Posterior ventricular septum of left ventricle; Ant: Anterior wall of left ventricle; Inf: Inferior wall of left ventricle; PW: Posterior wall of left ventricle; Aivs: Anterior ventricular septum of left ventricle; Qsb: From the onset of Q wave on ECG to the beginning of S wave on TDI; Qst: From the onset of Q wave on ECG to the top of S wave on TDI; Rsb: From the top of R wave on ECG to the beginning of S wave on TDI; Rst: From the top of R wave on ECG to the top of S wave on TDI; SD: Standard deviation; CONs: Healthy controls; ECG: Electrocardiography; TDI: Tissue Doppler imaging.