Original Article

Evaluation of Systolic Time Intervals in Patients of Ischemic Heart Disease with Clinical Heart Failure

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Abstract

Introduction: Left ventricular (LV) systolic function evaluation is based on ejection fraction assessment. Due to the great sensitivity of the examination and the ease of measurement, systolic time intervals (STIs) are ideally appropriate for studying the effects of pharmacologic agents upon the heart. In this context, the present study aimed to estimate and compare STI in patients with ischemic heart disease (IHD) with clinical heart failure and among control subjects without clinically established LV dysfunction based on their LV ejection fraction (LVEF). **Materials and Methods:** This case–control study included 33 IHD patients as cases and 32 healthy subjects as controls. All subjects underwent pulsed-Doppler echocardiogram to estimate STIs: total electromechanical systole (QS_2), preejection period (PEP), and LV ejection time (LVET). **Results:** A significant difference between PEP (145.23 ± 23.20 vs. 82.99 ± 8.63, $P < 0.00001$), LVET (231.34 ± 40.89 vs. 265.39 ± 31.98, $P = 0.000947$), and PEP/LVET ratio (0.63 ± 0.15 vs. 0.31 ± 0.08, $P < 0.00001$) between cases and controls was found. On subgroup analysis, a weak correlation was found in patients with LVEF ≤40% and PEP/LVET ($r = -0.3677$, $P = 0.1958$). In addition, a relatively strong correlation between LVET and heart rate ($r = -0.432$, $P = 0.012$) was found among the cases. **Conclusion:** The current study results showed that the differences in the values of STI among cases than in controls could be an indicator of LV systolic dysfunction. In addition, this method may have impending applications in the management of IHD.

Keywords: Echocardiography, ischemic heart disease, left ventricular function, myocardial infarction, systolic time intervals

Introduction

Nowadays, cardiovascular diseases (CVD) have become a prominent source of mortality in India. A quarter of all mortality is due to CVD. Ischemic heart disease (IHD) and stroke are the chief causes and are accountable for >80% of CVD deaths.[1]

CVD affects Indians, especially in their middle age, the utmost productive years of an individual's life. The quality of cardiovascular care in timely detection and accordingly variation in CVD treatment to halt the progression of disease is the paramount requirement. Hence, addition of effortlessly available techniques like STI measurements in primary and secondary health-care settings in India along with routine standard investigations is the need of the hour.

Systolic time interval (STI) measurement offers temporal depiction of the sequential phases of cardiac cycle which are influenced physiologically by variables such as heart rate (HR), preload, afterload, and myocardial inotropic state that affects the left ventricular (LV) performance.[2]

Even though the early introduction of simultaneous recording of the heart sounds, the central arterial pulse tracing, and the electrocardiogram (ECG) to define STIs in the cardiac cycle, their clinical application as an investigative tool received little attention until the early 1960s.[3] Methodological difficulties in recording phonocardiogram or indirect carotid pulse sometimes prevent the determination of the STI. Due

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to the great sensitivity of the examination and the practicality of measurement, STIs are ideally appropriate for studying the effects of pharmacologic agents upon the heart.[2] Furthermore, with the literature search, it was evident that so far, no study in India has evaluated STIs using pulsed-Doppler echocardiography in patients with IHD. Hence, this study aimed to estimate the STI among IHD patients and to compare the findings with the healthy controls based on LV ejection fraction (LVEF) using pulsed-Doppler echocardiography.

Materials and Methods

Study setting

This case–control study was conducted at the Department of Cardiology, R.L. Jalappa Hospital, in association with the Department of Physiology, attached to Sri Devaraj Urs Medical College, Kolar, Karnataka, India.

Ethical consideration

The study was approved by the Institutional Ethics Committee (IEC No. SDUMC/KLR/IEC/120/2019-20 dated 04-11-2019). Written informed consent was obtained from all the study participants.

Sample size was calculated[4] using Statistical Package for Social Sciences, version 22.0 (Chicago, IL). Out of 85 participants screened, 65 were found eligible and participated in the present study.

Study population

Inclusion criteria

Thirty-three consecutive IHD patients[5,6] (cases) from the Cardiology Outpatient Department, who prospectively underwent pulsed-Doppler echocardiography between November and January 2019, were included. Among the included, 27 (81.81%) patients had acute coronary syndrome, with the first acute myocardial infarction (ST-segment elevation myocardial infarction [STEMI], n = 21, and non-STEMI [NSTEMI], n = 6). The remaining six (18.18%) patients had old myocardial infarction.

Among 21 patients with STEMI, 36.36% had anterior wall MI, 41.78% had anterolateral wall MI, 3.47% had inferior wall MI, 4.35% had inferoposterior wall MI, 1.74% had inferolateral wall MI, 5.21% anteroseptal wall, and 1.10% of them had lateral wall MI. Furthermore, 78.78% of the patients had a history of angina and 30.30% had dyspnea. Heart failure (HF) patients with preserved/mid-range EF (HFpEF or HFmrEF)[7] being 47.16% ± 8.50% were considered.

Among 21 STEMI patients, reperfusion was successfully attained within 6 h of symptom onset with Percutaneous coronary intervention (PCI), and six NSTEMI patients underwent PCI within 24 h of symptom onset. The rest of the six patients had undergone PCI a month ago. Among STEMI/NSTEMI patients, predischarge or 24 h post PCI STI data were collected. In the case of old MI patients, 1 month post PCI STI values were noted.

A control group was chosen from a population of subjects without heart disease, diabetes mellitus, or hypertension. Besides, they presented with normal ECG and echocardiography with no regional wall motion abnormality[8] and LVEF around 60% (59.80 ± 1.68).

Exclusion criteria

Pregnant and lactating women, patients who were on cardiac stimulator, patients with atrial fibrillation, and patients with dysautonomia or hyperthyroidism were excluded from the study.

Study design

Selection of study participants was done by purposive sampling.

Methodology

A thorough history and clinical assessments were done for all the enrolled subjects. Height in centimeters (using Bio Plas Inc., Stadiometer, USA) and weight in kilograms (using KRUPS Weighing Scale, New Delhi, India) of the subjects were measured with shoes removed and minimal clothing on. Systolic and diastolic blood pressures were measured using sphygmomanometer (model BPDL 237, Dial BP: clock model by Industrial Electronic and Allied products) with the subjects seated in a chair comfortably. Twelve-lead ECG recording was done using GE Medical Systems Information Technologies (MAC 1200 ST electrocardiograph machine) to assess the changes of ST segment to confirm myocardial infarction (STEMI).

Echocardiography

All subjects underwent echocardiographic evaluation using Vivid S5 echocardiograph machine (GE Healthcare Systems, Israel, 2008) with a 2.0 to 3.6 MHz transducer. Doppler gains were attuned at a 100 mm/s sweep speed. Standard echocardiogram included assessment of LV parasternal long-axis view, parasternal short-axis view, and apical views (four-, two-, three-chamber views).

Subjects underwent an echocardiographic scan in the left lateral position. During quite breathing, STI measurement was done by pulsed-Doppler echocardiography. All measurements were performed offline, and averaged from three cardiac cycles on digital stored images manually.

STIs determined from the aortic valve echocardiogram based on pulsed-Doppler aortic acquisitions were as follows: the total electromechanical systole (QS_2) (interval from the commencement of the QRS complex on the ECG to the closure of the aortic valve on the echocardiogram), preejection period (PEP) (interval from the start of ventricular contraction to the start of aortic ejection), and LV ejection time (LVET) (interval ranging from the commencement to the end of aortic flow).

LVEF% assessment was done according to biplane Simpson method. LV end-diastolic diameter (LVEDD in mm) and LV end-systolic diameter (LVESD in mm) were measured using M-mode echocardiography. Consequently, stroke

volume was calculated using Teicholz method. Fractional shortening (FS) was calculated using the formula: FS (in %) = (LVEDD − LVESD)/LVEDD.

All values were presented as mean ± standard deviation. Independent *t*-test was done to compare the STIs between cases and controls. Kolmogorov–Smirnov test was done to test the normality of population characteristics. Pearson's correlation analysis was done to know the relationship between PEP, LVET, and PEP/LVET with the HR among the cases. A subgroup analysis was carried out wherein STI was evaluated in patients with LVEF ≤40% (n = 14) using Pearson's correlation analysis. Bivariate regression analyses were done to learn the association of body mass index with STIs. Multivariable analyses were performed to know the association of drugs with STI. IBM Statistical Product and Service Solutions (ver. 22.0) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Population characteristics

The study population composed of 33 IHD patients (59.6 ± 10.9 years; 69.69% of men) with LVEF% of 47.16 ± 8.50, with ischemic cardiomyopathy (n = 1; 3.03%; LVEF = 35%–40%), with mild-to-moderate mitral regurgitation (n = 32; 96.96%), with sclerosed aortic valve (n = 1; 3.03%), and with LV hypertrophy (n = 1; 3.03%). In addition, among 27 AMI patients, 10 patients were in early evolving phase of MI and 17 patients were in the later convalescent/evolved phase of MI (>6 h above the window period). Eighteen percent of them belonged to New York Heart Association (NYHA) class I, 63.33% were in NYHA class II, and 18.18% belonged to NYHA class III and all were stable on admission. Included patients were on antiplatelets (100%); 39% of patients received antianginal therapy; 12% were treated with β-blockers; 3% of them were on oral anticoagulants (OACs) (the indication for OAC was to prevent recurrent thrombosis); 82% were on statins; 46% were on diuretics; 27% were on oral hypoglycemic agents/insulin; 73% were on antihypertensives; 3% were on angiotensin receptor blockers (prescribed by a nephrologist to a patient with LV dysfunction and diabetic nephropathy); 3% were on calcium channel blockers; and 3% of them were on synthetic thyroid hormone supplements. Thirty-two control subjects were recruited (52.4 ± 10.4 years; 50% of men) [Table 1].

Echocardiography

With the initial echocardiography, the STIs (QS_2, PEP, and LVET) between cases and controls are given in Table 2.

Among the enrolled IHD patients, one IHD patient had sclerosed aortic valve. In whom, PEP was found to be 148 ms, LVET was 192 ms, LVET index (LVETI) was 372.2 ms, PEP/LVET was 0.77, and QS_2 index (QS_2I) was 562.6 ms.

Correlation analysis

Pearson's correlation analysis was performed to correlate PEP, LVET, and PEP/LVET with HR [Table 3].

Linear regression analyses were assumed to search for a possible correlation between STI and HR. No correlation was witnessed between PEP and HR [Figure 1a], whereas a relatively strong correlation was observed between LVET and HR (r = −0.432, P = 0.012) [Figure 1b]. Likewise, no significant correlation between PEP/LVET and HR was found [Figure 1c].

Pearson correlations were accomplished to compare STIs with LVEF. Weak correlations were observed between STI and LVEF (for PEP [r = 0.18, P = 0.325], for LVET [r = 0.05, P = 0.79], and for PEP/LVET [r = −0.15, P = 0.395]).

Furthermore, a subgroup analysis between STI and LVEF ≤ 40% was done. On Pearson's correlations, weak correlations were witnessed between PEP and LVEF ≤40% (r = −0.295, P = 0.305) and LVET and LVEF ≤40% (r = 0.18, P = 0.012). In addition, a relatively moderate correlation between PEP/LVET and LVEF ≤40% (r = −0.3677, P = 0.196) was found.

Bivariate analysis was done to observe the association of body mass index with STIs among the cases. BMI had no significant association with PEP (P = 0.374), with LVET (P = 0.564), and PEP/LVET (P = 0.394).

Multivariate tests were executed between drugs and STIs. No significant association of drugs with PEP and LVET was found [Table 4].

Discussion

In this study, a significant difference in STIs between cases and controls was found, which is in accordance with a study conducted in France,[4] wherein PEP was found to be significantly increased; LVET was significantly decreased,

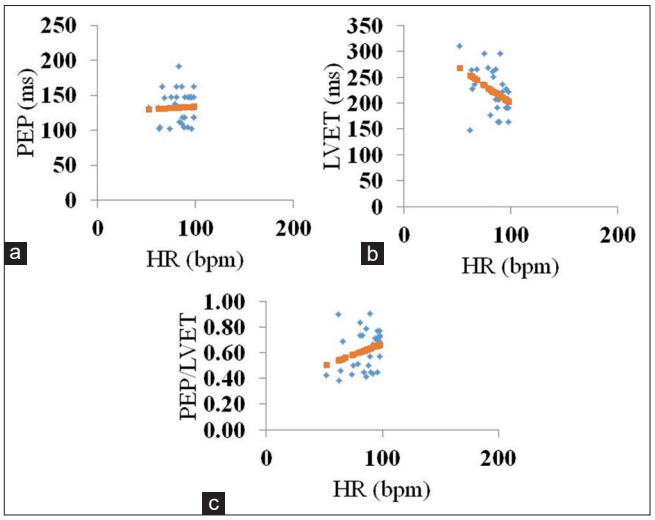

Figure 1: Linear regression analyses between systolic time intervals and heart rate. (a) Linear regression analysis between preejection period and heart rate. (b) Linear regression analysis between left ventricular ejection time and heart rate. (c) Linear regression analysis between PEP/LVET and heart rate. PEP/LVET: Preejection period/left ventricular ejection time.

Table 1: Population characteristics of two groups

	Mean±SD		*t*	*P*
	Cases (*n*=33)	Controls (*n*=32)		
Mean age (years)	59.6±10.9	52.4±10.4	2.724	0.08[a]
Gender (%)				
Men	69.69	50.0	2.626	0.105[b]
Women	30.30	50.0		
Height (cm)	164.6±8.5	159.3±10.1	2.284	0.026[a,*]
Weight (kg)	60.5±9.1	63±14.9	−0.794	0.430[a]
BMI (kg/m^2)	22.3±2.5	24.7±5	−2.569	0.013[a,*]
Systolic blood pressure (mm Hg)	125.8±14.4	123.4±12.3	0.697	0.488[a]
Diastolic blood pressure (mm Hg)	79.4±9.7	78.8±8.7	0.282	0.779[a]
Hemoglobin (g %)	13.7±2.3	12.8±1.2	1.933	0.058[a]
Serum creatinine (mg/dL)	1.0±0.3	1.0±0.18	−0.58	0.564[a]
LVEF (%)	47.16±8.50	59.80±1.68	10.275	0.0001[a,*]
HR (bpm)	81.56±12.52	77.37±11.74	1.33	0.187[a]
LVEDD (mm)	47.1±3.7	45.3±0.65	2.56	0.013[a,*]
LVESD (mm)	32.1±4.2	31.0±1.4	1.44	0.156[a]
Stroke volume (mL)	56.1±5.7	61.1±12.2	−2.12	0.038[a,*]
Fractional shortening (%)	31.9±5.1	31.6±3.5	0.22	0.83[a]
Pulmonary artery systolic pressure (mm Hg)	28.6±8	23.9±4.2	2.94	0.0046[a,*]

*Significance $P<0.05$, [a]Unpaired *t*-test and [b]Chi-square test. BMI: Body mass index, LVEF: Left ventricular ejection fraction, HR: Heart rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, SD: Standard deviation

Table 2: Comparison of total electromechanical systole, preejection period, left ventricular ejection time, and preejection period/left ventricular ejection time between cases and controls using independent *t*-test

	Mean±SD		*t*	*P*
	Cases (*n*=33)	Controls (*n*=32)		
QS_2 (ms)	376.6±47.8	348.4±29.9	1.244	0.218
PEP (ms)	145.23±23.20	82.99±8.63	10.086	<0.00001*
LVET (ms)	231.34±40.89	265.39±31.98	−3.469	0.000947*
PEP/LVET	0.63±0.15	0.31±0.08	8.633	<0.00001*

*Significance $P<0.05$. QS_2: Total electromechanical systole, PEP: Preejection period, LVET: Left ventricular ejection time, SD: Standard deviation

Table 3: Pearson correlations between heart rate and systolic time intervals among cases

	r, *P*		
	PEP (ms)	LVET (ms)	PEP/LVET
HR (bpm)	0.0408, 0.822	−0.432, 0.012*	0.281, 0.113

*Significance $P<0.05$. LVET=Left ventricular ejection time, PEP=Preejection period, HR: Heart rate

with the resultant significant increase in PEP/LVET ratio among HF patients using pulsed-Doppler echocardiography. In addition, the authors observed that a correlation between LVEF and PEP/LVET was found, with $r = -0.55$, $P < 0.001$, among HF patients. Similar results were found in our study with $r = -0.368$, $P = 0.196$, between LVEF ≤ 40% and PEP/LVET with regard to IHD patients.

A prospective observational study by Biering-Sørensen *et al*.[9] included African-Americans (n = 1980) of the Atherosclerosis Risk in Communities. Subjects underwent echocardiography, and LVET was measured using pulsed-wave Doppler. A short LVET was associated with younger age, in the case of men, increase in diastolic blood pressure, prevalence of diabetes, tachycardia, elevated blood sugar levels, and poorer FS. During a median follow-up of 17.6 years, 384 of them had the incidence of HF, 158 had a myocardial infarction, and 587 of them died. In univariate analysis, a lower LVET was significantly associated with increased risk of all events ($P < 0.05$ for all). Nevertheless, after multivariable adjustment for confounding variables, LVET persisted as an independent interpreter only of incident HF (hazard ratio 1.07, $P = 0.010$/10 ms decrease). In addition, LVET provided incremental prognostic information on the risk of future HF and death but not myocardial infarction.

Every component of STI fluctuates inversely with HR, thus corrections must be made,[4] resulting in PEP index, LVETI, and total electromechanical systole index (QS_2I). Although these changes are small, they are statistically significant and correction of the PEP for HR increases the sensitivity of the method, especially in clinical pharmacology.[10] In the current study, a relatively strong correlation of LVET with HR ($r = -0.432$, $P = 0.012$) was observed in the case of IHD patients.

Besides, we found normal STI among 32 IHD patients with mild-to-moderate mitral regurgitation, which was in accordance with previous findings.[2,11]

Table 4: Multivariable analysis between drugs and preejection period and left ventricular ejection time

Effect	Value	*F*	Hypothesis df	Error df	Significance	Partial Eta squared
Intercept	0.023	235.925	2.000	11.000	0.000	0.977
On antianginal drugs	0.912	0.529	2.000	11.000	0.604^{NS}	0.088
On beta-blockers	0.999	0.005	2.000	11.000	0.995^{NS}	0.001
On antiplatelets	0.777	1.576	2.000	11.000	0.250^{NS}	0.223
On diuretics	0.901	0.605	2.000	11.000	0.563^{NS}	0.099
On anticoagulants	0.955	0.701	2.000	30.000	0.504^{NS}	0.045
On statins	0.706	2.292	2.000	11.000	0.147^{NS}	0.294
On OHAs	0.679	2.601	2.000	11.000	0.119^{NS}	0.321
On antihypertensives	0.841	1.040	2.000	11.000	0.386^{NS}	0.159

NS: Not significant $P > 0.05$. OHA: Oral hypoglycemic agent

In a study by Ohte *et al*.,[12] LV performance among 51 patients (34 – acute MI and 17 –angina pectoris aged 38–82 years) was evaluated using the Q-V peak interval (composed of PEP and acceleration time of aortic ejection flow) using continuous-wave Doppler echocardiography, wherein Q-V peak interval correlated well with LVEF.

The presence of acute myocardial infarction (early) leads to shortening of PEP, LVETI, and QS_2I, late: long PEP and short LVETI.[2] Following acute MI, there will be shortening of QS_2I. In addition, alterations in PEP/LVET could be obvious between the 1st and 4th days.[11] Furthermore, after AMI, there will be shortening of QS_2 and the ejection time (ET). However, the PEP will either be normal or lengthy.[11] The current study had included 27 acute MI (10 early and 17 late) patients, wherein the STIs showed similar changes. Increase in the isovolumetric contraction time might have caused the prolongation of PEP. Identified factors which shorten the ET are increased HR, decreased cardiac contractility, and decreased stroke volume, administration of catecholamines, digitalis, and isoprenaline.[13]

Another study by Khanna *et al*.[14] examined the short-term effects of altered preload on STIs among 17 acute myocardial infarction patients and 7 subjects without AMI having normal hemodynamics. The authors found that in patients with AMI, effects of altered preload on STI could provide a more accurate index of LV function than the STI when measured alone.

According to a study by Parker and Just,[15] excellent correlations were shown between contractility indices and ejection fraction in the case of 36 male patients with electrocardiographically and angiographically evident coronary artery disease. However, STI was found to be not reliable indices of ventricular function. Hence, it is doubtful whether STIs are of value in the clinical assessment of coronary artery disease or not?

A total of 545 HF patients (171 with reduced EF, i.e., heart failure with reduced ejection fraction (HFrEF) of 30%, and 374 with preserved EF, i.e., HFpEF of 54%) met eligibility criteria in a study by Patel *et al*. Among patients with HFrEF vs. HFpEF, median LV systolic ET (SET) was found to be shorter (280 ms vs. 315 ms, $P < 0.001$), median PEP obtained was longer (114 ms vs. 89 ms, $P < 0.001$), and median relaxation time was shorter (78.7 ms vs. 93.3 ms, $P < 0.001$). Death or HF hospitalization occurred in the case of 26.9% ($n = 46$) of HFrEF and 11.8% ($n = 44$) of HFpEF patients. Multivariable logistic regression analyses showed that longer SET was independently associated with better outcomes among HFrEF but not HFpEF patients, suggesting a possible role for stabilizing SET as a helpful approach in patients with systolic dysfunction. Further research should be done to appreciate normal ranges for SET and to discover the history of SET with advanced systolic dysfunction.[16]

Limitations

PEP and PEP/LVET are related to QRS width; hence, corrections as described[13] must be applied, which was not addressed in the present investigation.

Patients with severe congestive HF (NYHA class IV) or pulmonary edema will be in respiratory distress or are even ventilated mechanically and thus the STI values could not be procured properly from them; therefore, they were left out from this study.

Furthermore, a follow-up study may yield better results regarding the prognostic value of STIs among IHD patients with clinical HF.

Conclusion

This study could precisely evaluate STIs as an index of LV systolic function in patients with IHD using pulsed-Doppler echocardiography. STIs, especially PEP/LVET, correlated well with conventional LV systolic performance indices like LVEF. Hence, this method could be useful, particularly in the case of IHD patients with LVEF ≤40%. In addition, close monitoring of STI may help to recognize subjects with early LV dysfunction and also in the management of IHD.

Ethics clearance

The study was approved by the Institutional Ethics Committee (IEC No. DUM/KLR/IEC/338/2021-22 dated 20-9-2021).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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