Review Article

A Narrative Review of Clinical Applications of Systolic Time Intervals

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Abstract

Systolic time interval (STI) estimation is an established noninvasive method for the quantifiable assessment of left ventricular (LV) performance in well-being and disease states; it stays valuable for clinical application and forms no burden to the subjects. This manuscript reviews the potential clinical applications and prognostic value of STI for the assessment of LV systolic function in cardiovascular disease (CVD). STIs could be obtained by several noninvasive imaging modalities such as transthoracic echocardiography, tissue Doppler imaging M-mode echocardiography, conventional echocardiography, and so on. In view of that, a literature review for studies reporting the clinical applications of STI in assessing LV systolic function among CVD patients was carried out using PubMed search. Accordingly, the current review describes how STI can be measured; reliability of cardiac time interval measurement in patients with CVD and its role in a clinical setting. With the advent of modern techniques, STI could be easily measured in a clinical setting. Likewise, STI parameter, particularly preejection period and LV ejection time ratio (PEP/LVET), has got the highest degree of correlation with LV ejection fraction (LVEF) in assessing LV performance. Furthermore, reproducibility of systolic ejection time (SET) achieved by the TDI M-mode method is outstanding and better when compared with the reproducibility of SET obtained by the conventional pulsed Doppler method. Furthermore, prolonged SET is independently related with enhanced outcomes among heart failure with reduced EF (HFrEF, i.e., EF ≤40%) but not HF with preserved EF (HFpEF, i.e., EF >40%) patients, indicating that stabilizing SET would be helpful in the case of systolic dysfunction. Clinically, tissue Doppler-derived time intervals could be beneficial to analyze abnormal cases in comparison with other invasive and noninvasive methods of ventricular function examination. Furthermore, phonoelectrocardiography-derived STI parameters, particularly electromechanical activation time-to-LVET ratio, may have a significant role in the diagnostic approach of heart failure (HF) in patients with undifferentiated dyspnea. In addition, in HF patients, PEP/LVET of >0.43 helps to detect LVEF <35% by pulsed Doppler echocardiography. Moreover, LVET continues to be an independent predictor of incident HF and provides incremental prognostic value on the future HF risk and death but not myocardial infarction. In conclusion, STI measurement could be useful, particularly in identifying LVEF <35% in the case of refractory HF patients. This could be beneficial in the selection of patients requiring cardiac resynchronization, specifically when accurate LVEF evaluation by echocardiography proves challenging in atrial fibrillation or if the evaluation is done by a trainee echocardiographer. Furthermore, the cardiac time intervals including SET can be acquired irrespective of rhythm. Good image quality is required for the assessment of LVEF. In contrast, evaluation of SET could be useful in the case of echocardiograms with poor quality images. As a final point, the present review suggests using an echocardiographic parameter like STIs to procure additional information regarding the risk of mortality in patients with HFrEF along with LVEF measurement.

Keywords: Cardiovascular disease, heart failure, left ventricular ejection fraction, left ventricular function, pulsed Doppler echocardiography, systolic time intervals

Introduction

Nowadays, cardiovascular diseases (CVD) have become the 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%

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of CVD deaths.[1] Hence, addition of cost-effective, easily available techniques like systolic time interval measurement in primary and secondary health-care settings in India along with routine standard investigations to supervise CVD is the need of the hour.

Systolic time intervals (STIs) offer a time-sensitive translation of the successive phases of a cardiac cycle which are impacted physiologically by heart rate (HR), preload, afterload, and myocardial inotropic state which thus influences the left ventricular (LV) performance.[2]

The term coronary artery disease (CAD), also called coronary heart disease and IHD,[3] includes the reduction of blood flow to the cardiac muscle due to atherosclerosis in the coronary arteries.[4-6] Coronary artery disease comprises stable angina, unstable angina, myocardial infarction, and sudden cardiac death.[7]

Objective

This manuscript reviews the potential clinical applications of STIs to assess LV performance among CVD patients.

Methodology

Literature search of MEDLINE database was done and included original studies and review articles reporting the assessment of LV performance using STIs. In view of that, 8836 studies with accessible full-length articles in English language from 1960 to 2021 were considered.

Articles available with only abstracts, short communications, editorials, conference abstracts, and discussion papers were excluded. After screening full-length articles related to myocardial ischemia, articles reporting the importance of STI measurement in the case of other diseases, for example, thyroid diseases, malignancies, chronic obstructive pulmonary diseases, deficiency of Vitamin D, and anemia, were not included in this review.

After going through the articles, 23 appropriate studies were included in the current review [Figure 1]. Accordingly, review was narrated as method to measure STIs, reliability of STI measurement in patients with CVD, and its role in a clinical setting besides established techniques to assess LV performance. Brief summaries of the included articles are précised [Table 1].

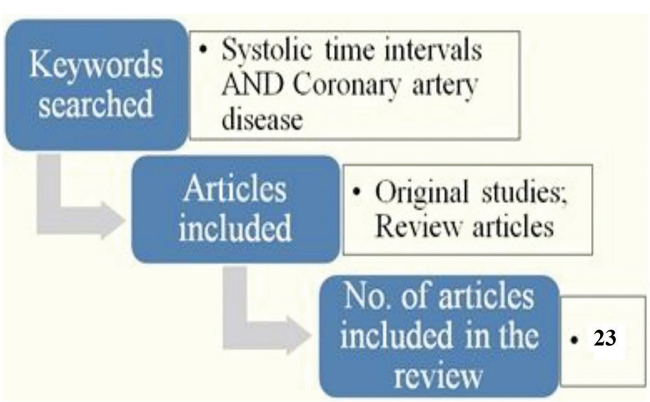

Figure 1: Schematic representation of literature search.

How systolic time interval is measured?

Weissler *et al*. 1961 obtained STIs with the simultaneous recording of the heart sounds (phonocardiogram), the central arterial pulse tracing (carotid pulse), and the electrocardiogram (ECG)[8] [Figure 3].

In our study, we measured STIs using pulsed Doppler echocardiography (using Vivid S5 echocardiograph machine developed by GE Healthcare, Israel, 2008) at cardiology outpatient department 1 week post percutaneous coronary intervention. Doppler gains were attuned at a sweep speed of 100 mm/s. Standard echocardiogram included assessment of LV parasternal long-axis view, parasternal short-axis (PSAX) view, and apical views (four-, two-, and three-chamber views). Accordingly, STIs determined from the aortic valve echocardiogram built on pulsed Doppler aortic acquisitions were as follows: the total electromechanical systole (QS_2) is the interval from the initiation of the QRS complex on the ECG to the closing of the aortic valve on the echocardiogram. Preejection period (PEP) is the interval from the start of ventricular contraction to the start of aortic ejection. LV ejection time (LVET) is the interval ranging from the commencement to the end of aortic flow[19] [Figure 4a and b].

Discussion

Physiological understanding of systolic time intervals

PEP/LVET ratio has been utilized as a degree of cardiovascular contractility; conversely, LVET and PEP/LVET are influenced by the HR as well as parasympathetic activity. Interestingly, PEP is not significantly changed by variations in HR. Accordingly, LVET and PEP/LVET should be revised for the basic HR (resulting in LV ejection time index [LVETI]), whereas the need for HR correction of PEP (i.e., PEP index) is pugnacious.[2]

Reliability and reproducibility of STI measurement in a clinical setting

A study conducted in France[20] included 134 heart failure (HF) patients and 43 control subjects. The authors found that with the progressively changed LV ejection fraction (LVEF), PEP was significantly prolonged, LVET was significantly shortened, and the ratio of PEP/LVET ($P < 0.001$) was increased. In the case of HF patients, a correlation between LVEF and PEP/LVET was found (with $r = 0.55$). Based on receiver operating characteristic curve analyses, the area under the curve was obtained as 0.91 for PEP/LVET >0.43, which permitted the authors to identify LVEF <35% with a sensitivity of 87% and a specificity of 84%. Thus, STI can be effortlessly and precisely measured in a clinical setting and it could be used for spotting LV systolic dysfunction. Likewise, this method is probable to have would-be applications in the supervision of HF patients.

Table 1: Brief summary of the included studies

Author, year of publication	Study design	Sample size (*n*)	Outcomes	Comments
Weissler *et al*., 1961[8]	Case–control study	Normal male subjects=60 Male patients with various heart diseases=61	ET varies inversely with heart rate and directly with stroke volume among normal individuals In patients with nonvalvular heart disease and HF, ET will be low relative to heart rate with respect to stroke volume Mean rate of LV ejection was within normal limits among patients with congestive HF ET will be prolonged in aortic insufficiency and in those with secluded aortic stenosis In patients with isolated mitral stenosis and in mild-to-moderate mitral regurgitation, ET found within the normal range in relation to stroke volume In the case of severe hypertension, ET was found to be within the normal or low normal range with respect to stroke volume	Hence, in patients with various cardiovascular disorders, real-world application of these techniques could be beneficial
Samson, 1970[9]	Follow-up study	Patients with AMI=31	After AMI, the QS_2 and the ET will be shortened The PEP will either be normal or prolonged. With the maximum shortening of QS_2 and ET, progressive improvement toward the normal will be seen	In this study, the shortened ET and the raised catecholamine levels had no direct relationship
Dowling *et al*., 1971[10]	Follow-up study	AMI patients=15	AMI causes shortening of QS_2 interval. Alterations in PEP/LVET could be evident between the 1st and 4th days	The application of various stressful situations like volume load or drug therapy could be carried out to reveal the proof of ventricular dysfunction
Bennett *et al*., 1971[11]	Follow-up study	AMI patients=24	Measurement of STI is valuable in assessing LV dysfunction after AMI	STI measurements seemed as a promising diagnostic and prognostic tool among AMI patients
Khanna *et al*., 1973[12]	Case–control study	17 AMI patients and 7 subjects without AMI having normal hemodynamics	Examined the short-term effects of altered preload on STI	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
Parker *et al*., 1974[13]	Correlative study	36 male patients with CAD	Excellent correlations were shown between contractility indices and EF in the case of male patients with CAD	But STIs were found to be not reliable indices of ventricular function
Weissler *et al*., 1976[14]	Case–control study	Patients who had recovered from a previous acute transmural myocardial infarction=37; normal subjects=25	Deviation from the normal PEP/LVET evidenced as the most promising index of LV dysfunction	This study documents the high degree of sensitivity of the noninvasive measures over clinical invasive or noninvasive methods for spotting abnormal LV performance
Lewis *et al*., 1976[15]	Review article	CAD patients	The STIs are useful in gauging both medical and surgical cure in CAD. In addition, the test can be executed repeatedly as a measure of LV performance and degree of adrenergic hyperactivity	Appraisal of therapy represents the most valuable application of STIs in a clinical settings
Boudoulas *et al*., 1978[16]	Comparative study	Patients with atrial fibrillation=40; patients with congestive HF=20; sinus rhythm=20	Prolonged PEP at faster heart rates; LVET will be comparatively constant at slower heart rates. In the case of increased heart rate, increase in PEP/LVET will be seen	This study result must be considered when STIs are measured in the case of atrial fibrillation patients
Gillilan *et al*., 1979[17]	Follow-up study	Patients with stable angina and proven obstructive coronary disease=85	In the resting preexercise state, the PEP/LVET ratio (0.40 ± 0.05 in survivors vs. $0.50 + 0.09$ in nonsurvivors) had significantly more prognostic value of mortality than the other STIs	STI is valid in identifying LV dysfunction in subjects with CAD. Besides, it retains its significant prognostic value very efficiently

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Table 1: Contd...

Author, year of publication	Study design	Sample size (*n*)	Outcomes	Comments
Hassan and Turner, 1983[2]	Review article	Patients with chronic myocardial dysfunction; AMI; aortic stenosis; aortic regurgitation; mitral stenosis; mitral regurgitation; left bundle branch block; hypothyroidism; hyperthyroidism; diabetes mellitus; chronic alcoholism	In the case of AMI, early: Short PEP, LVETI, and QS_2I, late: Long PEP and short LVETI will be seen	STI is a useful, noninvasive method to study the LV performance. Accordingly, STI should be looked at as a measure of LV function which is not in competition with other cardiac function tests
Cui *et al*., 2008[18]	Cross-sectional study	593 children (aged 1 day-18 years) with normal echocardiograms	IVCT, IVRT, ET, St, and Dt were measured using TDI [Figure 2]. In addition, TX and St/Dt were also calculated. Study sampled longitudinal directed TDI waves from three locations: Mitral annulus, tricuspid annulus, and basal interventricular septum from an apical four-chamber view. On univariate analysis, all the calculated time intervals at each of the three places correlated well with age, heart rate, and body surface area (P<0.001–P<0.003), except the mitral annulus TX (P=0.1). On multivariate analysis, IVCT, IVRT, and TX correlated very well with age at all three locations (P<0.001). Conversely, when the intervals were corrected for heart rate on dividing with square root of R-R interval, both corrected IVCT and corrected IVRT turned out to be constants at all three places	Throughout the pediatric population, normal values for TDI-derived corrected IVCT, corrected IVRT, and TX are basically constant. ET, St, Dt, and St/Dt normal values must be corrected for heart rate
Anavekar *et al*., 2009[19]	Review article	2D echocardiographic examination of the heart	Doppler echocardiography provides an exact hemodynamic evaluation of the heart	Thus, this method offers an insight into the structure and function of heart
Reant *et al*., 2010[20]	Case–control study	134 HF patients and 43 control subjects	Altered LVEF causes PEP to be significantly increased; LVET significantly decreased, with the resultant significant increase in PEP/LVET (P<0.001)	Measurement of STI can be easily and precisely done in clinical practice, and could be used for detecting LV systolic dysfunction. Furthermore, STI measurement is possible to have potential uses in the supervision of HF patients
Prabhakaran *et al*., 2016[1]	Epidemiological study	CVD patients	CVD is the major public health concern in India and often affects the most productive years of a person's life	Hence, age-old, reliable, noninvasive, cost-effective tests like STI measurements are needed to pause the progression of the CVD epidemic in India
Michael *et al*., 2017[21]	Review article	Effect of exercise dosage on autonomic indices during exercise and acute postexercise recovery	Simultaneous monitoring of HRV and STI could be a treasured noninvasive method to examine autonomic stress reactivity, with respect to exercise dosages	Limited research in response of PEP to exercise and recovery is in consistence with the understanding of cardiac sympathetic influences, the effects of different exercise dosages, predominantly in the course of recovery period
Biering-Sørensen *et al*., 2018[22]	Community based cohort study	African-Americans (n=1980) of the atherosclerosis risk in communities	Subjects underwent echocardiography, and LVET was measured using pulsed-wave Doppler	LVET persists as an independent interpreter only of incident HF. In addition, LVET provides incremental prognostic information on the risk of future HF and death but not myocardial infarction

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Table 1: Contd...

Author, year of publication	Study design	Sample size (*n*)	Outcomes	Comments
Sadaf *et al*., 2020[23]	Cohort study	Ninety-eight healthy MBBS students	Measurement of arterial blood pressures (in all four limbs) and the cardiac time interval determination (PEP, ET, UT, DT, PD, and ES) was done by PeriScope™	Since sex, anthropometric values, and blood pressure affect cardiac time intervals, these must be adjusted for when drawing conclusion about LV performance
Trabelsi *et al*., 2020[24]	Cohort study	855 patients with dyspnea and suspected HF	Echocardiographic measurements of LVEF, testing of BNP levels, and computerized phonoelectrocardiography to assess STI including EMAT, LVET, and EMAT/LVET ratio were done	STI measurement could identify HF in patients with acute dyspnea. It is particularly useful in patients with reduced EF and those with intermediate BNP level
Patel *et al*., 2020[25]	Retrospective, observational cohort study	545 HF patients	Among patients with HFrEF versus HFpEF, median LV SET was found to be shorter (P<0.001), median PEP obtained was longer (P<0.001), and median relaxation time was shorter (P<0.001) among patients with HFrEF versus HFpEF	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
Wiley *et al*., 2021[26]	Cohort study	158 healthy participants	CAR values were calculated using both HF-HRV and the RMSSD, along with PEP of STI and LVET	Accordingly, in future, researchers should consider calculating CAB and CAR using LVET and HF-HRV instead of calculating a combination of PEP and HF-HRV measures.
Bikia *et al*., 2021[27]	*In silico* model	Different hemodynamic cases=4645	An artificial intelligence-based method was proposed to evaluate LV E_{es} (a major factor determining the systolic function and ventricular-arterial interface) using PEP and ET. The authors developed a testing pattern using virtual subjects (n=4645) from a formerly validated *in silico* model	LV E_{es} can be accurately evaluated from the conventional arm pressure and echocardiographic PEP and ET parameters
Alhakak *et al*., 2021[28]	Cohort study	HFrEF patients=997	Patients went through echocardiographic examination. During the follow-up of 3.4 years, 165 (17%) patients expired. The mortality risk was increased by 9% per 10-ms reduction in SET (P<0.001)	In patients with HFrEF, SET can predict mortality in conjunction with established clinical predictors of mortality

AMI: Acute myocardial infarction, CAD: Coronary artery disease, ET: Ejection time, SET: Systolic ET, LVET: Left ventricular ET, LV: Left ventricular, LVETI: LVET index, EF: Ejection fraction, LVEF: LV ejection fraction, HRV: Heart rate variability, CAB: Cardiac autonomic balance, IVCT: Isovolumic contraction time, IVRT: Isovolumic relaxation time, St: Systolic time, Dt: Diastolic time, TDI: Tissue Doppler imaging, TX: Tei index, E_{es}: End-systolic elastance, BNP: B-type natriuretic peptide, STI: Systolic time interval, EMAT: Electromechanical activation time, RMSSD: Root mean square of successive differences, CVD: Cardiovascular disease, PEP: Preejection period, HF: Heart failure, HFrEF: HF with reduced EF, QS_2: Total electromechanical systole, HF-HRV: High-frequency HRV, CAR: Cardiac autonomic regulation, QS_2I: total electro-mechanical systole, UT: upstroke time, PD: pulse duration, DT: deceleration time, ES: ejection slope, HFpEF: heart failure with reduced ejection fraction

A study by Bennet *et al*. 1971[11] concluded that measurement of STI is valuable in assessing LV dysfunction after acute myocardial infarction (AMI) and it seemed promising as a diagnostic and prognostic tool among 24 AMI patients. Though, further study is needed to appreciate the mechanisms accountable for the shortened LVET and QS_2 intervals.

Another study by Khanna *et al*. 1973[12] examined the short-term effects of altered preload on STIs among 17 AMI 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 STIs when measured alone.

According to a study by Parker *et al*., 1974,[13] 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, STIs were 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 study was conducted on 593 children with normal echocardiogram results in Illinois.[18] Wherein, five time intervals were measured from tissue Doppler imaging (TDI), namely isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), ejection time (ET), systolic time (St), and diastolic time (Dt). Furthermore, Tei index (TX) and St/Dt were calculated. The study measured longitudinal directed TDI waves [Figure 2] from three places such as mitral annulus, tricuspid annulus, and basal interventricular septum from an apical four-chamber view. All seven time interval measures at all of the three sampling sites correlated well with age, HR, and body surface area ($P < 0.001$–$P < 0.003$),

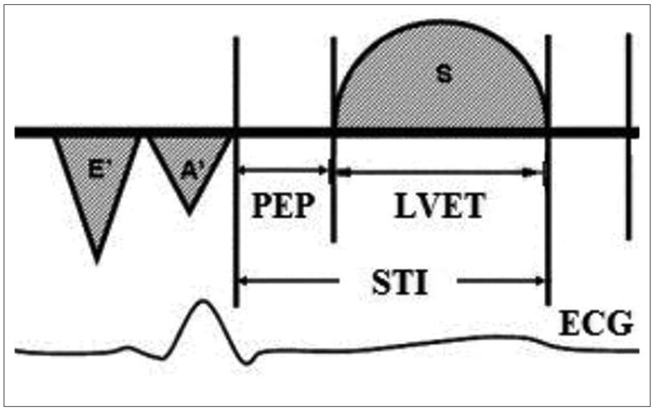

Figure 2: Line diagram depicting the measurements of preejection period and left ventricular ejection time from tissue Doppler imaging. STI: Systolic time interval; A': Late diastolic wave; E': Early diastolic wave; S: Systolic wave (adapted from: Cui, Wei and Roberson, David and Chen, Zhen and Madronero, Luisa and Cuneo, Bettina (2008). Systolic and Diastolic Time Intervals Measured from Doppler Tissue Imaging: Normal Values and Z-score Tables, and Effects of Age, Heart Rate, and Body Surface Area. *Journal of the American Society of Echocardiography*: official publication of the American Society of Echocardiography. 21. 361-70. 10.1016/j. echo. 2007.05.034).

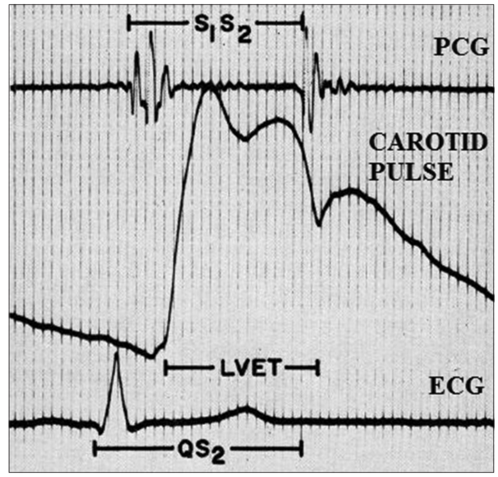

Figure 3: "Simultaneous recording of the heart sounds (phonocardiogram), carotid arterial pulse tracing, and the electrocardiogram in a normal subject (paper speed, 100 mm/s; time markers, 0.02 s). QS2 = Total electromechanical systole; SlS2 = Heart sound interval; LVET = Left ventricular ejection time; and PEP = Preejection period" (adapted from: Circulation, Volume XXXVII, February 1968).

except the mitral annulus TX ($P = 0.1$) on univariate analysis. On multivariate analysis, IVCT, IVRT, and TX correlated well with age at all three sites ($P < 0.001$). Conversely, when the intervals were corrected for HR on dividing by square root of R-R interval, both corrected IVCT and corrected IVRT turned out to be constants at all three locations. Thus, for real-world clinical applications, corrected IVCT, corrected IVRT, and TX were constant at all three places. In addition, ET, systolic time, diastolic time, and St/Dt correlated very well with HR at all three locations ($P < 0.001$). Moreover, at faster HRs, ET, St, and Dt all decreased, whereas St/Dt augmented at faster HRs.

A prospective observational study by Sorensen *et al*. 2018 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, and prevalence of diabetes, tachycardia, elevated blood sugar levels, and poorer fractional shortening. 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, $P = 0.010$ per 10-ms decrease). In addition, LVET provided incremental prognostic information on the risk of future HF and death but not myocardial infarction.[22]

Ninety-eight healthy MBBS students aged 19–21 years were included in a study by Sadaf *et al*. 2020. Measurement of arterial blood pressures (in all four limbs) and the cardiac time interval determination (PEP, ET, UT, DT, PD, and ES) was done by PeriScope™. The study concluded that since sex, anthropometric values, and blood pressure affect cardiac time intervals, these must be adjusted for when drawing conclusion about LV performance.[23]

A study by Trabelsi *et al*. 2020[24] included total of 855 patients with dyspnea and suspected HF. Echocardiographic measurements of LV ejection fraction (LVEF), testing of B-type natriuretic peptide (BNP) levels, and computerized phonoelectrocardiography to assess STIs including electromechanical activation time (EMAT), LVET, and EMAT/LVET ratio were done. STI diagnostic accuracy was calculated. A significantly higher EMAT and lower LVET was found in patients with HF ($n = 530$) compared to non-HF patients. Receiver operating characteristic curve c-statistic was 0.74, 0.72, and 0.78 for EMAT, LVET, and EMAT/LVET, respectively. The sensitivity and specificity of EMAT/LVET were 72% and 88%, respectively. EMAT/LVET ratio had the maximum correlation with LVEF ($r = 0.48$). Positive likelihood ratio was found to be 1.8 with BNP alone and was 3.6 with BNP along with EMAT/LVET ratio in patients with intermediate BNP. Patients without HF had STIs not significantly altered from those with preserved LVEF (≥45%). Hence, phonoelectrocardiography-derived STI parameters, particularly EMAT/LVET ratio, may have a significant role in the diagnostic approach of HF in patients with undifferentiated dyspnea.

A total of 545 HF patients (171 with reduced EF, i.e., HF with reduced EF (HFrEF) of 30%, and 374 with preserved EF, i.e., HFpEF of 54%) met eligibility criteria in a study by Patel *et al*. 2020. 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,

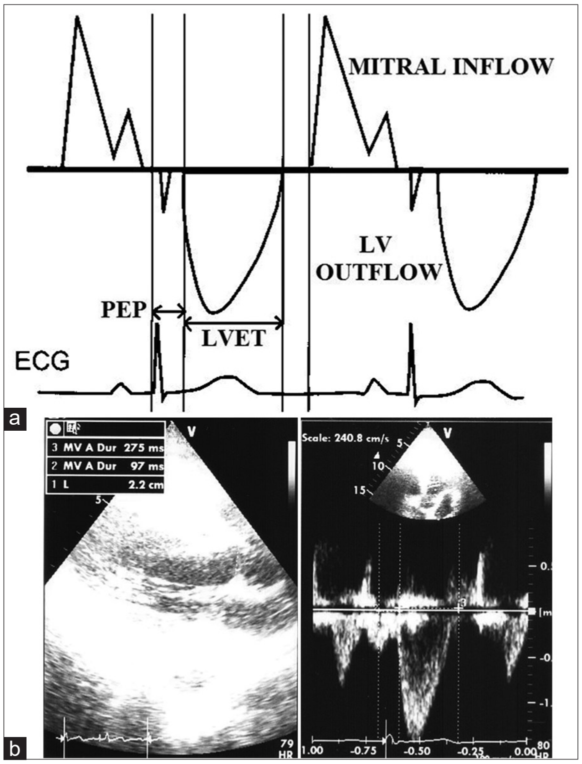

Figure 4: (a) Line diagram depicting the measurements of preejection period and left ventricular ejection time using pulsed Doppler echocardiography. (b). Measurements of preejection period and left ventricular ejection time in an ischemic heart disease patient 1 week post revascularization with percutaneous coronary intervention: PEP (2 MV A Dur) = 97 ms, left ventricular ejection time (3 MV A Dur) = 275 ms, PEP/LVET = 0.35. Cross-sectional area of aortic orifice (LVOT: Left ventricular outflow tract or 1 L) = 2.2 cm.

$P < 0.001$), 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% ($n = 46$) HFrEF and 11.8% ($n = 44$) 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.[25]

In a study by Wiley *et al*. 2021, data from 158 healthy participants (19.09 ± 1.84 years) were available for analyses. Cardiac autonomic balance (CAB) and cardiac autonomic regulation (CAR) values were calculated using both high-frequency HR variability (HF-HRV) and the root mean square of successive differences (RMSSD), along with PEP of STI and LVET. HR variability HF-HRV is a chronotropic measure (reflects parasympathetic nervous system activity) whereas PEP of STI has both chronotropic and inotropic activities (reflects sympathetic activity) and LVET (chronotropic measure). Analyses showed a significantly weaker correlation between CAB and CAR calculated using LVET for both HF-HRV ($z = 5.12$, $P < 0.001$) and RMSSD ($z = 5.26$, $P < 0.001$) than with PEP. Accordingly, researchers should consider calculating CAB and CAR using LVET and HF-HRV measures instead of calculating a combination of PEP and HF-HRV measures.[26]

A study conducted in Switzerland proposed an artificial intelligence-based method to evaluate LV end-systolic elastance (E_{es}) (a major factor determining the systolic function and ventricular-arterial interface) using PEP and ET. The authors developed a testing pattern using virtual subjects (different hemodynamic cases: $N = 4,645$) from a formerly validated *in silico* model. Results displayed that E_{es} could be prophesied with extreme precision attaining a normalized RMSE = 9.15% ($r = 0.92$) for a range of E_{es} values from 1.2 to 4.5 mmHg/ml. The suggested model had great sensitivity, with the measurement errors of ±10%–30% of the actual value in blood pressure, bestowed with low test errors for the diverse levels of noise (RMSE was not >0.32 mmHg/ml). A great sensitivity was stated for systolic timing feature measurement errors. Hence, it showed that E_{es} can be accurately evaluated from the conventional arm pressure and echocardiographic PEP and ET parameters.[27]

In another study, a total of 997 patients with HFrEF (mean age: 67 ± 11 years, 74% of males) went through echocardiographic scan including TDI. During a median follow-up of 3.4 years, 165 (17%) patients passed away. The mortality risk was increased by 9% per 10-ms decline in SET (per 10-ms decrease: HR – 1.09; 95% confidence interval [CI] [1.06–1.13], $P < 0.001$). The association could retain its significance even after multivariable adjustment for various clinical and echocardiographic parameters (per 10-ms decrease: HR – 1.06; 95% CI (1.01–1.11), $P = 0.030$). Reproducibility of SET achieved by the TDI M-mode echo was exceptional (intraclass correlation coefficient: 0.98 and interclass correlation coefficient: 0.95) and better compared to the reproducibility of SET attained by the traditional method (intraclass correlation coefficient: 0.93 and interclass correlation coefficient: 0.73). The reproducibility of LVEF was modest (intraclass correlation coefficient: 0.73 and interclass correlation coefficient: 0.63). In addition, the SET provided incremental prognostic information with regard to predicting mortality when combined with the established clinical predictors of mortality in patients with HFrEF.[28]

Conclusion

TDI-derived time intervals could be beneficial to analyze abnormal cases, in comparison with other invasive and noninvasive methods of ventricular function examination, in sensitivity, specificity, and predictive value assessment, and to determine its use clinically.

Furthermore, noninvasive STI measurement could recognize HF in patients admitted to emergency department with acute dyspnea. It is predominantly helpful in patients with reduced ejection fraction. Assuming its potential advantages, STI measurements should be practically considered when echocardiography is not readily available.

Furthermore, STI measurement could be useful, particularly in identifying LVEF <35% in the case of refractory HF patients. This could be beneficial in the selection of patients requiring cardiac resynchronization, specifically when accurate LVEF evaluation by echocardiography proves challenging in atrial fibrillation or if the evaluation is done by a trainee echocardiographer. Furthermore, STI measurement could be useful clinically among cardiovascular disease patients in assessing their LV performance. In addition, STIs retain its prognostic value during the course after acute myocardial illness. Accordingly, the present review suggests using STIs to procure additional information regarding the risk of mortality in patients with HFrEF along with LVEF measurement.

Ethics clearance

The study was approved by the Institutional Ethics Committee (IEC No. DMC/KLR/IEC/648/2021-22 dated 4-3-2022).

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Conflicts of interest

There are no conflicts of interest.

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