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Computerized Acoustic Cardiographic Electromechanical Activation Time Correlates with Invasive and Echocardiographic Parameters of Left Ventricular Contractility

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ABSTRACT

Background: Electromechanical activation time (EMAT) is a systolic time interval defined as the time from Q-wave onset to the peak first heart sound. We assessed the correlation between systolic dysfunction and EMAT calculated using computerized acoustic cardiography.

Methods: A total of 25 patients with heart failure contemporaneously underwent echocardiography, left-sided heart catheterization, and acoustic cardiography. Invasive pressure−volume hemodynamics included peak isovolumetric left ventricular (LV) pressure at the end-diastolic volume, end-diastolic pressure, dyssynchrony, and maximal +dP/dT. An EMAT/(R to R interval) (%EMAT) interval ≥ 0.15 was prospectively defined as abnormal.

Results: An abnormal %EMAT correlated with a lower LV ejection fraction (50.9% ± 18.6% with normal EMAT vs 32.0% ± 10.9% with abnormal EMAT, $P = .015$), end-systolic elastance (3.07 ± 1.56 mm Hg/mL vs 1.43 ± 0.83 mm Hg/mL, $P = .018$), and peak isovolumetric LV pressure at the end-diastolic volume (317 ± 90 mm Hg vs 222 ± 67 mm Hg, $P = .015$). An abnormal %EMAT was associated with a higher end-systolic volume index (33.6 ± 29.3 mL/m^2 vs 71.0 ± 35.8 mL/m^2, $P = .011$), end-diastolic volume index (61.2 ± 29.8 mL/m^2 vs 100.3 ± 40.8 mL/m^2, $P = .012$), and dyssynchrony (26.1% ± 6.0% vs 31.5% ± 3.5%, $P = .028$). There was no difference in end-diastolic pressure (20.3 ± 7.9 mm Hg vs 21.4 ± 12.3 mm Hg, $P = .78$).

Conclusions: An abnormal %EMAT was strongly associated with impaired LV contractility but had no association with LV filling pressures. This noninvasive, simple, point-of-care diagnostic test has potential applications when echocardiography cannot be obtained in a timely fashion to assess systolic function. (*J Cardiac Fail 2008;■:1−6*)

Key Words: Acoustic cardiography, hemodynamics, echocardiography, systolic time intervals.

Heart failure is the primary diagnosis in more than 1 million hospitalizations annually in the United States.[1] The physical examination for the diagnosis of heart failure remains inexact with considerable interobserver variability.[2] Despite the recent incorporation of B-type natriuretic peptide (BNP) measurement into clinical practice, the bedside diagnosis of left ventricular (LV) dysfunction remains a diagnostic challenge. Intermediate-range BNP levels between 100 and 500 pg/mL are not diagnostic.[3] Although echocardiography represents a noninvasive criterion standard in diagnosis for reduced ejection fraction, it requires a high level of skill for acquisition and interpretation, and is associated with cost and time that necessitate the selective use of this resource. The development of a simple inexpensive bedside test to aid in the diagnosis of LV dysfunction could help stratify which patients would benefit from a further, more detailed, diagnostic workup.

A validated noninvasive method of detecting LV dysfunction is the measurement of systolic time intervals (STIs),[4−12] combining data from electrocardiography, echocardiography, electrophonocardiography, and carotid pulse tracings. STIs have been extensively studied during the past 40 years, and abnormalities in STIs have been shown to correlate with LV end-diastolic volume,[4] stroke

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volume,[5,11] cardiac output,[12] and LV ejection fraction (LVEF).[4] Although STIs hold diagnostic potential, their bedside applicability in the past has been limited because of the necessity of skilled technicians and manual calculations. With the emergence of echocardiography, the diagnostic use of STIs has fallen out of favor. However, new automated computerized acoustic cardiographic methods of measuring STIs at the bedside use recently developed technology that requires no skill beyond placing a standard 12-lead electrocardiogram. The STI electromechanical activation time (EMAT) can be measured by computerized acoustic cardiography and has been shown to correlate with heart failure and LVEF measured by echocardiography.[13] We undertook a study to correlate EMAT detected by computerized acoustic cardiography with invasive and noninvasive measures of LV function in patients with heart failure.

Materials and Methods

Study Design and Patient Selection

This was a prospective cohort study that enrolled adults with a history of heart failure who were referred for right and left-sided heart catheterization and coronary angiography. All patients had a clinical history of symptomatic heart failure diagnosed by an experienced clinical cardiologist. Patients were required to have either systolic heart failure (LVEF $<$ 40%) or diastolic heart failure (LVEF $\geq$ 50%). Exclusion criteria included age $<$ 18 years, systolic blood pressure $<$ 95 mm Hg, heart rate $<$ 50 beats/min, intravenous vasopressor, inotropic or vasodilator pharmacotherapy, cardiac rhythm other than a sinus or paced atrial rhythm, severe stenotic valvular disease, complex congenital heart disease, hypertrophic or obstructive cardiomyopathy, constrictive pericarditis, severe precapillary pulmonary hypertension, and mechanical ventilation. Patients with bundle branch block were not excluded. All patients gave written informed consent before the procedure, and the protocol was approved by the Committee on Human Research.

Study Protocol

Left-sided heart catheterization was performed, and a baseline BNP (using a membrane immunofluorescence assay, Biosite Inc, San Diego, California) was drawn from the femoral venous sheath. Transthoracic echocardiography was performed for assessment of LV function. Computerized acoustic cardiography (Audicor, Inovise Medical, Inc, Portland, Oregon) was performed. A 4F high-fidelity micromanometer pressure–volume conductance pigtail catheter (CD Leycom/*CardioDynamics BV, Zoetermeer, The Netherlands*) was advanced to the left ventricle through a 6F guiding catheter for invasive pressure–volume measurements. All patients received 2 L/min of nasal cannula oxygen throughout the study period, and the level of conscious sedation was continued at a steady level throughout the study period. Invasive and noninvasive measurements were obtained within a 30-minute period in the cardiac catheterization laboratory.

Invasive Hemodynamic Assessment

The 4F pressure–volume catheter has 1 solid-state micromanometer pressure sensor and 12 electrodes with 6-mm spacing, and measures the volume from 7 segments (CD Leycom/*CardioDynamics BV, Zoetermeer, The Netherlands*). Under fluoroscopic guidance, the catheter was advanced to the ventricular apex. Volume segments that were not in the ventricle were not included in the analyses. Measurements from this catheter were recorded using the Leycom CFL 512 for offline analysis of cardiac function using the Conduct NT software (version 2.8, CD Leycom/*CardioDynamics BV*). We measured the LV end-diastolic pressure, maximum positive dP/dT, and calculated peak isovolumetric pressure (Pmax).[14] At each time point, a segmental signal was defined as dyssynchronous if its change (ie, dVseg/dt) was opposite to the simultaneous change in the total ventricular volume (dV/dt). Segmental dyssynchrony was quantified by calculating the percentage of time within the cardiac cycle that is dyssynchronous. Overall ventricular dyssynchrony was calculated as the mean of the segmental dyssynchronies.[15] Dyssynchrony was recorded during both the systolic and diastolic periods.

Echocardiography

Transthoracic echocardiography was performed (Acuson Sequoia, Siemens, Malvern, Pennsylvania), and echocardiographic contrast (Optison, Amersham, Little Chalfont, United Kingdom; 0.3 to 0.5 mL injected into a peripheral vein) was administered when required to improve endocardial border detection and enhance Doppler signals. End-diastolic and end-systolic volumes were calculated using the biplane method of discs and were then indexed to body surface area. These volumes were used to calculate LVEF. LV end-systolic elastance (Ees) was calculated by a modified single-beat method using systolic and diastolic arm-cuff pressures, echo-Doppler stroke volume, echo-derived ejection fraction, and an estimated normalized ventricular elastance at arterial end diastole.[16] Echocardiographic data were stored on magneto-optical disks and analyzed off-line by a single experienced reader. An LVEF $<$ 40% was prospectively defined as impaired LV systolic function.

Computerized Acoustic Cardiographic Analysis

A 3-minute acoustic cardiographic tracing (Audicor, Inovise Medical, Inc, Portland, Oregon) was obtained. Acoustic cardiographic sensors were attached in the V3 and V4 positions and connected to a Marquette MAC 5000 cardiograph (General Electric Healthcare Technologies, Waukesha, Wisconsin). The acoustic cardiographic data were stored electronically to a CD. A 10-second segment free of artifact was selected off-line by a technician blinded to any patient characteristics for a computer-generated report. The Q-S1 interval was measured from the initial deflection of the electrocardiographic Q wave to the peak component of the S1 phonocardiographic complex. This interval, divided by the R-R interval for heart rate correction, was designated as the %EMAT (Figure 1). A %EMAT $\geq$ 0.15 was prospectively defined as abnormal.[13]

Statistical Analysis

Data are presented as mean values and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed data, and proportions for categoric variables. Differences between continuous values were assessed using an unpaired 2-tailed *t* test for normally distributed continuous variables, the Mann-Whitney rank-sum test for skewed variables, and chi-square testing for nominal variables. Pearson product-moment correlation coefficients, receiver operator curve c-statistics, and multivariable linear regression were performed

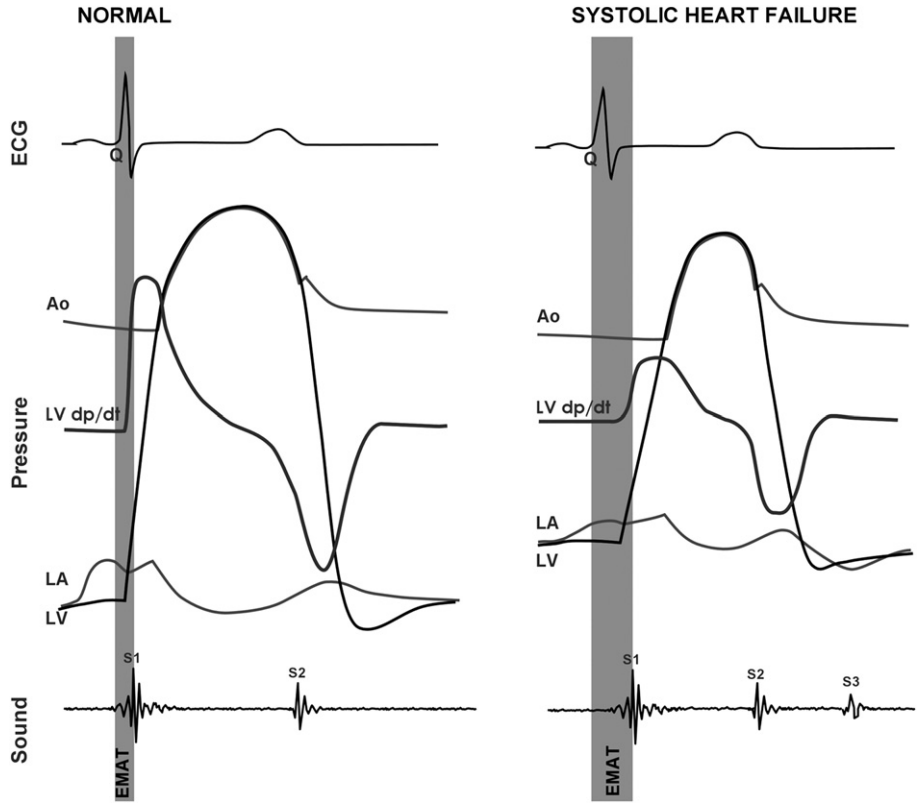

Fig. 1. EMAT in relation to the cardiac cycle via the electrocardiogram, cardiac pressure waveforms (aorta, left ventricle, and left atrium), change in pressure divided by change in time (dP/dT), and acoustic cardiography. In systolic dysfunction, there may be widening of the QRS complex, reduction in pulse pressure, elevation in LV diastolic pressure, and reduction in peak positive dP/dT, a third heart sound in early diastole, and a prolonged EMAT. *ECG,* Electrocardiogram; *Ao,* aorta; *LV,* left ventricular; *LA,* left atrial; *dP/dT,* change in pressure divided by change in time; *EMAT,* electromechanical activation time.

on %EMAT results. Two-tailed *P* values less than .05 were considered significant. All analyses were performed using STATA version 9.2 (StataCorp, College Station, Texas).

Results

Patient Population

In the study group of 25 patients, the mean age was 60 ± 11 years (range 38−80 years), and 12 patients (48%) were male. Sixteen patients (64%) had systemic hypertension, and 8 patients (32%) had diabetes mellitus. Fourteen patients (56%) had angiographic evidence of coronary artery disease, the mean body mass index was 29.0 ± 8.1 kg/m^2, and the mean creatinine was 1.5 ± 1.1 mg/dL. Ten patients had left bundle branch block, and 2 patients had right bundle branch block. The majority (80%) had New York Heart Association class 2 to 3 symptoms (Table 1).

Markers of LV Function and EMAT

Fifteen patients (60%) had an LVEF < 40%, and 10 patients (40%) had an LVEF ≥ 50%. In this study cohort, 8 patients (32%) had an abnormal %EMAT. Of the 10 patients with left bundle branch block, 8 had an LVEF < 40% and 5 had an abnormal %EMAT. An abnormal %EMAT had a strong association with parameters of LV dysfunction. An abnormal %EMAT correlated with measures of LV systolic dysfunction, including lower LVEF (50.9% ± 18.6% vs 32.0% ± 10.9%, *P* = .015), a significantly lower echocardiographic Ees (3.07 ± 1.56 mm Hg/mL vs 1.43 ± 0.83 mm Hg/mL, *P* = .018), and a lower invasive Pmax (317 ± 90 mm Hg vs 222 ± 67 mm Hg, *P* = .015; Table 2). An abnormal %EMAT was associated with a significantly higher LV volume and greater dyssynchrony (Table 2).

Table 1. Baseline Demographic and Clinical Characteristics (n = 25)

Age, y	60 ± 11 (range 38−80)
Male, n (%)	12 (48%)
Non-Caucasian, n (%)	13 (52%)
Body mass index, kg/m^2	29.0 ± 8.1
Diabetes mellitus, n (%)	8 (32%)
Coronary artery disease, n (%)	14 (56%)
Previous myocardial infarction, n (%)	9 (36%)
Hypertension, n (%)	16 (64%)
Hyperlipidemia, n (%)	17 (68%)
Current smoker, n (%)	1 (4%)
NYHA Class I, n (%)	3 (12%)
Class II	9 (36%)
Class III	11 (44%)
Class IV	2 (8%)
Creatinine, mg/dL	1.5 ± 1.1
BNP, pg/mL (median, interquartile range)	231 (94-687)

NYHA, New York Heart Association; *BNP,* B-type natriuretic peptide.

Table 2. Noninvasive and Invasive Hemodynamics and Electromechanical Activation Time

	Normal %EMAT < 0.15 N = 17	Abnormal %EMAT ≥ 0.15 N = 8	*P* value
Echocardiographic LVEF, %	50.9 ± 18.6	32.0 ± 10.9	.015
End-diastolic volume index, mL/m^2	61.2 ± 29.8	100.3 ± 40.8	.012
End-systolic volume index, mL/m^2	33.6 ± 29.3	71.0 ± 35.8	.011
End-systolic elastance, mm Hg/mL	3.07 ± 1.56	1.43 ± 0.83	.018
Invasive dyssynchrony, %	26.1 ± 6.0	31.5 ± 3.5	.028
Maximal +dP/dT, mm Hg/s	1036 ± 242	841 ± 244	.074
Pmax, mm Hg	317 ± 90	222 ± 67	.015
End-diastolic pressure, mm Hg	20.3 ± 7.9	21.4 ± 12.3	.78

EMAT, Electromechanical activation time; *LVEF,* left ventricular ejection fraction; *dP/dT,* change in pressure divided by change in time; *Pmax,* peak isovolumetric pressure.

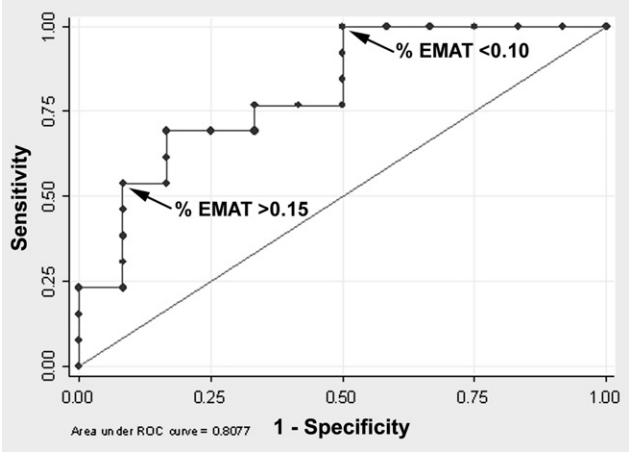

Fig. 2. Receiver operating characteristic curve for %EMAT to predict LV systolic dysfunction, defined as LVEF $< 40\%$. *EMAT,* Electromechanical activation time; *ROC,* receiver operating characteristic.

An abnormal %EMAT had the following diagnostic test characteristics for the diagnosis of systolic dysfunction (LVEF $< 40\%$): 54% sensitivity, 92% specificity, accuracy 72%, positive likelihood ratio 6.46, and negative likelihood ratio 0.50. The receiver operating characteristic analysis for %EMAT to predict systolic dysfunction has a c-statistic of 0.81 (95% confidence interval, 0.63−0.98; Figure 2). As seen in this figure, a %EMAT < 0.10 was observed in all patients with an LVEF $> 40\%$. In a multivariate model controlling for age, gender, BNP, QRS duration, and LV end-diastolic pressure, %EMAT was an independent predictor for LVEF ($P = .005$). For every 2% absolute decrease in LVEF, %EMAT increased by an absolute value of 0.01 (or 1% of the cardiac cycle; coefficient 1.97, standard error 0.96). Despite the significant differences in ventricular contractility and volume in patients with an abnormal %EMAT, there was no difference in ventricular diastolic pressures.

Discussion

In this prospective study of patients with either diastolic or systolic heart failure undergoing left-sided heart catheterization, echocardiography, and BNP measurement, noninvasive bedside EMAT assessment by computerized acoustic cardiography had a strong association with parameters of LV systolic function. A prolonged heart rate-adjusted EMAT displayed strong associations with decreased LVEF, Pmax, and Ees, in addition to increased end-systolic volume index, end-diastolic volume index, and LV dyssynchrony. This noninvasive point-of-care test was therefore able to identify patients with systolic heart failure; however, EMAT was not predictive of identifying patients with elevated LV diastolic pressure.

STIs have been validated for the detection of abnormal LV function.[4−12] These studies, mostly performed in the late 1960s to the early 1980s, showed strong correlations with direct measures of LV performance. The strongest correlation ($r = -0.90$) was between EMAT/LV ejection time (defined by carotid pulse tracing) and angiographically determined LVEF.[4] These observations held true regardless of the type of underlying heart disease. STIs with an EMAT/LV ejection time ≥ 0.42 were shown in a prospective study of 112 patients to display high sensitivities (88%) and specificities (96%) for detecting abnormal LVEF.[10] More recently, investigators[17−19] examined STIs derived from echocardiographic Doppler mitral inflow and LV outflow tracings. The Tei-index, defined as the sum of isovolumic contraction and relaxation times divided by ejection time, incorporates measures of both systolic and diastolic cardiac performance. This index was shown to be a reliable indicator of global cardiac dysfunction in patients with heart failure from either ischemic or dilated cardiomyopathy.[17−19]

Several studies have been performed to investigate the physiologic underpinnings of the relationship between STIs and measures of LV function. Studies in animal models demonstrated that changes in LV stroke volume caused by alterations in LV filling were accompanied by changes in the duration of STIs.[20,21] In human heart failure studies, the LV ejection time decreased while the pre-ejection period (from the initial deflection of the Q wave to the initial upward deflection of the carotid pulse tracing) lengthened.[5,11,12,22] Pre-ejection period prolongation was the subject of further investigation as a potential measure of myocardial contractile performance. These studies showed that LV end-diastolic pressure, aortic diastolic pressure, and the rate of LV pressure development affect the pre-ejection period.[23−25] In heart failure, the decrease in the rate of LV pressure development in the pre-ejection phase results in a prolonged isovolumic contraction time and a consequent lengthening of the pre-ejection time interval. This decrease in LV dP/dT during the pre-ejection phase and the consequent lengthening of the pre-ejection period reflect ineffective force generated by the left ventricle.[26]

The calculation of STIs in these early studies relied on combining phonocardiography, electrocardiography, and carotid pulse tracings to determine the pre-ejection period. The simultaneous acquisition of these 3 methods was

cumbersome and required a highly trained technician, thus limiting its widespread clinical applicability. In contrast, the computerized acoustic cardiographic device used in our study provides a simple, noninvasive method of evaluating useful clinical data at the bedside. This device generates a standard 12-lead electrocardiogram, where electrodes V3 and V4 are replaced with computerized acoustic cardiographic sensors, obviating the need to perform carotid pulse recordings. These recordings do not require any special training beyond that required for a 12-lead electrocardiogram. Moreover, these results may be immediately available on printing the computerized heart sound detection report.

Our correlations of the computerized acoustic cardiographically determined prolonged EMAT was associated with all the studied parameters of LV dysfunction, including decreased LVEF, Ees, and Pmax. Increased end-systolic volume index, end-diastolic volume index, and LV dyssynchrony were robust, along with a trend for a decreased maximum dP/dT. Previous investigators have attributed the lengthening of EMAT in LV dysfunction almost entirely to a prolonged isovolumic contraction time,[6,27] a measurement that can only be obtained through carotid pressure analysis or Doppler echocardiography by trained technicians. Although a %EMAT $\geq$ 0.15 was a specific finding to the diagnosis of LVEF $<$ 40%, a %EMAT $<$ 0.10 was 100% accurate in excluding LV systolic dysfunction.

Our study showed that a prolonged EMAT measured by computerized acoustic cardiography may be an effective, inexpensive, and noninvasive method to screen patients in rural medical facilities, emergency departments, or outpatient clinics where echocardiography is not immediately available and is associated with increased cost and time. This method does not require any specialized training; therefore, this method may be more widely applicable compared with portable echocardiography. Computerized acoustic cardiography may be used as a test to aid in the diagnosis of LV dysfunction and could help stratify which patients would benefit from a further, more detailed, diagnostic workup.

This study is limited by the small sample size. Further studies are required before these findings can be extrapolated to patients with conditions known to independently affect EMAT, including left bundle branch block, aortic valve disease, and the use of positive or negative inotropic agents. Our study did show that the association between EMAT and LVEF was independent of QRS duration. Last, by excluding patients with mildly reduced LVEF between 40% and 50%, we may have introduced a spectrum bias that may overestimate the diagnostic test characteristics observed with %EMAT. Further research is needed to assess the association between EMAT and systolic function in patients with mildly depressed ejection fraction.

Conclusions

An abnormal EMAT was strongly associated with invasive and noninvasive measures of impaired LV contractility. Although EMAT is an accurate measure of systolic performance, it did not differentiate patients with heart failure according to LV filling pressure. This point-of-care, noninvasive test may be useful to identify patients with reduced ejection fraction when access to echocardiography is not readily available.

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