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General Cardiology

Potential Linkage between High Normalized Electromechanical Activation Time (EMAT), an Early Systolic Time Interval Abnormality with Metabolic Syndrome

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Background: High electromechanical activation time (EMAT) is associated with paroxysmal atrial fibrillation and heart failure. Little is known about the association between EMAT and metabolic syndrome (MetS), a precursor of cardiovascular disease.

Objectives: To explore the association between EMAT and MetS.

Methods: A total of 429 male volunteers were divided into MetS (n = 135, age 60.3 ± 3.7 years) and non-MetS (n = 294, age 58.1 ± 26.6 years) groups in this cross-sectional study. A complete medical history, fasting blood analysis and phonoelectrocardiographic parameters were recorded. EMAT was defined as the time from the onset of Q-wave to the peak first heart sound (Q-S1 interval), and this interval divided by the R-R interval for heart rate correction was calculated as normalized EMAT (nEMAT).

Results: The subjects with MetS had a significantly higher rate of positive nEMAT (nEMAT ≥ 15%: 6.7% vs. 2%, p = 0.015), higher heart rate (HR, 71.9 ± 12.0 vs. 69.2 ± 11.1 bpm, p = 0.022) but shorter left ventricular ejection time (LVST = 312.4 ± 33.5 vs. 319.8 ± 31.8 msec, p = 0.029). However, the normalized LVST (nLVST) was not significantly different after adjusting for HR. In multivariate analysis, nEMAT was significantly associated with MetS (odds ratio = 3.43, 95% confidence interval = 1.195-9.837, p = 0.022).

Conclusion: Positive nEMAT, a prolonged early phase of contraction, was significantly associated with MetS in males. High nEMAT may be an earlier sign of cardiac function abnormality in MetS.

Key Words: Electromechanical activation time (EMAT) • Male • Metabolic syndrome • Phonography

INTRODUCTION

Electromechanical activation time (EMAT) is an important parameter of computerized acoustic cardiographic (phonoelectrocardiographic) analysis. It is a systolic time interval defined as the time from the onset of Q-wave to the peak first heart sound (Q-S1 interval), and this interval divided by the R-R interval for heart rate correction is calculated as normalized EMAT (nEMAT). An abnormal nEMAT value is defined as ≥ 15% (Figure 1).[1,2] High nEMAT is associated with organic heart disease including heart failure (HF)[3,4] and paroxysmal atrial fibrillation (PAF).[5] In addition, high nEMAT was also re-

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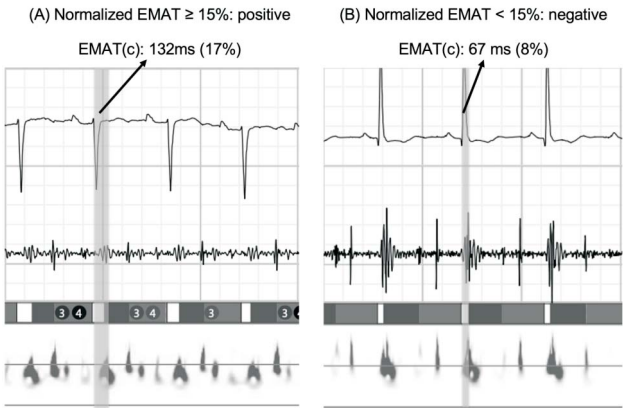

Figure 1. *Normalized electromechanical activation time (EMAT) (% EMAT): Abnormal with values ≥ 15%.*

ported to be a better guide than symptoms for medication adjustment in an outcome trial of acute HF.[6]

Metabolic syndrome (MetS) is also known to increase the risk of developing major cardiovascular events including coronary artery disease (CAD), cardiovascular disease (CVD)[7-14] and HF.[15] However, little is known about the association between phonoelectrocardiographic analysis, the combined information of phonography and electrocardiography (ECG) and MetS. In addition, if this association exists, it may be beneficial to have an easy and non-invasive tool such as phonoelectrocardiography to alert subjects with MetS to possible cardiac abnormalities. Therefore, the aim of the study was to explore associations between EMAT or nEMAT and other phonoelectrocardiographic parameters with MetS in a middle-aged Taiwanese male population.

METHODS

Subjects and study protocol (Figure 2)

The cross-sectional data of 429 Taiwanese males (age: 50-65 years) who lived in Kaohsiung City were collected from a free male health exam and screening activity held by our institution (Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan).[9,16] Ethical approval was authorized by the Institutional Research Ethics Committee of Kaohsiung Medical University Hospital, and informed written consent was obtained from each participant. The study was also conducted according to the Declaration of Helsinki. Men who had previously been diagnosed with hypertension, diabetes mellitus (DM), or hyperlipidemia (kept under control by regular medication) were included in the study. Men who were diagnosed as labile for hypertension, labile for diabetes, had current malignancy, advanced liver and/or renal disease or who were using hormones, antiandrogen treatment, antifungal drugs, or steroidal agents were excluded.

Data collection and definitions

Complete medical, surgical, and psychosexual histories and the results from detailed physical examinations, including body weight, height and blood pressure were recorded for each subject, and the medical histories were double-checked individually using the NHI Medi-Cloud system through NHI cards. Fasting blood samples were also taken for further biochemical analysis including cardiac markers of B-type natriuretic peptide (BNP) and

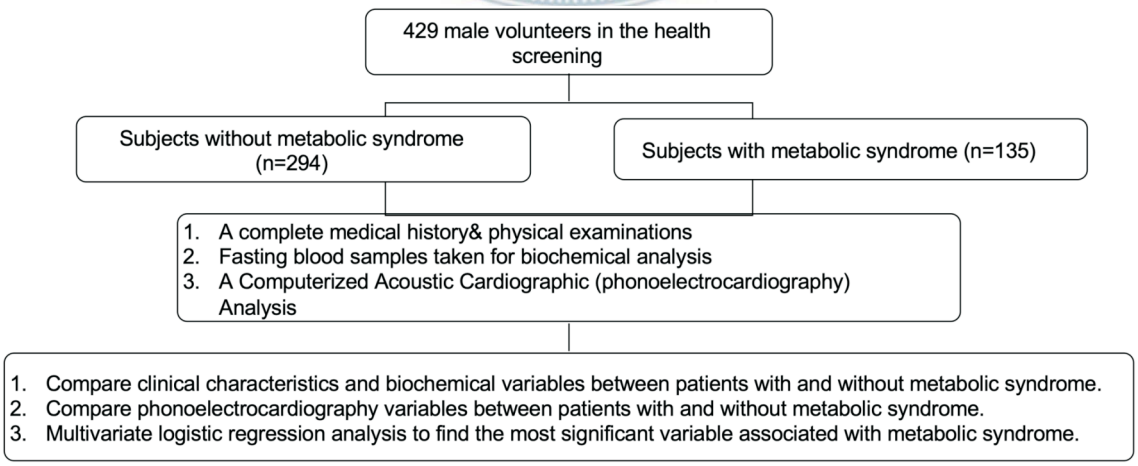

Figure 2. *Study flow.*

high-sensitivity troponin-T (hs-TnT). The subjects were classified as alcohol drinkers, cigarette smokers, or betel nut chewers if they had regularly consumed any alcoholic beverage ≥ 1 times per week, had smoked ≥ 10 cigarettes per week, or had chewed ≥ 7 betel quids per week, respectively, for at least 6 months prior to the commencement of the study.[17,18] Hypertension was defined as a systolic blood pressure (SBP) of ≥ 140 mmHg or a diastolic blood pressure (DBP) of ≥ 90 mmHg, and hyperlipidemia was defined as a total cholesterol level of ≥ 200 mg/dL or a triglyceride level of ≥ 200 mg/dL.[9,19] DM was diagnosed when the fasting blood glucose (FBG) level was ≥ 126 mg/dL. An individual was diagnosed with MetS if he was positive for at least three of the five following criteria: (1) waist circumference (WC) ≥ 90 cm; (2) high-density lipoprotein (HDL) cholesterol < 40 mg/ dL; (3) triglyceride level ≥ 150 mg/dL; (4) blood pressure (BP) ≥ 130/85 mmHg or diagnosed as hypertensive and receiving therapy; (5) FBG level ≥ 100 mg/dL or diagnosed with type 2 DM, in accordance with the modified criteria proposed by the Bureau of Health Promotion in Taiwan.[9,13,20]

Computerized acoustic cardiographic (phonoelectrocardiographic) 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 on a CD. A 10-second segment free of artifacts 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 (HR) correction was calculated as nEMAT. An nEMAT value > 15% was prospectively defined as being abnormal.

Statistical analysis

Quantitative demographic and laboratory data were presented as mean ± standard deviation. To quantify the differences between subjects with and without MetS, qualitative variables were compared using the chi-square test and Fisher's exact test, while quantitative variables were compared using the Student's *t* test. Any variables significantly associated with components of MetS in the initial analyses were further examined in multivariate logistic regression analysis to determine the independent risk factors for MetS. A p value of less than 0.05 was considered to be significant. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Baseline characteristics

The 429 men were divided into two groups according to the presence or absence of MetS. The baseline characteristics and biochemical data of the subjects with MetS (n = 135) and without MetS (n = 294) are summarized in Table 1 and Supplementary Table 1. The subjects with MetS had significantly higher WC and BP, FBG and rates of hypertension and DM compared to those without MetS. With regards to cardiac biomarkers, there were no significant differences in BNP and hs-TnT.

Associations between phonoelectrocardiographic parameters and MetS

The results of phonoelectrocardiography in the subjects with and without MetS are summarized in Table 2. The prevalence of high nEMAT (≥ 15%) was significantly higher in the subjects with MetS compared to those without MetS (6.7% vs. 2%, p = 0.015). In addition, the subjects with MetS had a significantly higher HR (71.9 ± 12.0 vs. 69.2 ± 11.1 bpm, p = 0.022) but significantly shorter left ventricular ejection time (LVST, 312.4 ± 33.5 vs. 319.8 ± 31.8 msec, p = 0.029) than those without MetS. However, the high normalized LVST (nLVST) was not significantly different between the two groups.

Multivariate logistic regression analysis to identify the independent factors

To examine why LVST but not normalized LVST was significantly shorter in the subjects with MetS, both HR and LVST were put into a regression model. The results showed that only HR was statistically significant (beta = 0.004, p = 0.022) (Table 3). Therefore, the reason why LVST was significantly shorter in the subjects with MetS

Table 1. Means ± standard deviations of the baseline characteristics and biochemical variables in the subjects with and without MetS

	Subjects without MetS (n = 294)	Subjects with MetS (n = 135)	p value
Age (yrs)	58.1 ± 26.6	60.3 ± 3.7	0.385
MetS scores	1.5 ± 0.6	3.3 ± 0.5	< 0.001*
CHA2DS2-VasC scores	0.4 ± 0.6	0.6 ± 0.8	0.002*
Waist circumference (cm)	84.1 ± 6.4	88.7 ± 7.8	< 0.001*
SBP (mm-Hg)	132.7 ± 13.4	140.2 ± 13.1	< 0.001*
DBP (mm-Hg)	89.4 ± 9.7	94.2 ± 8.9	< 0.001*
DM, n (%)	14 (4.7)	21 (15.8)	< 0.001*
Hypertension, n (%)	68 (23)	46 (34.3)	< 0.013*
Smoking, n (%)			0.098
Non-smokers	227 (78.5)	84 (67.7)	
Former smokers	43 (14.9)	27 (21.8)	
Current smokers	19 (6.5)	13 (10.5)	
Drinking, n (%)			0.084
Non-drinker	237 (81.2)	95 (75.4)	
Former drinkers	11 (3.8)	2 (1.6)	
Current drinkers	44 (15.1)	29 (30)	
Dyslipidemia history, n (%)	94 (31.6)	47 (35.1)	0.483
CAD history, n (%)	21 (7.1)	8 (6)	0.687
Stroke history, n (%)	1 (0.3)	1 (0.7)	0.563
Betel quid, n (%)			0.805
Never chewed	280 (96.6)	121 (96.8)	
Former chewers	9 (3.1)	4 (3.2)	
Current chewers	1 (0.3)	0 (0)	
Blood biochemistry			
Fasting glucose (mg/dl)	95.8 ± 16.0	104.4 ± 21.1	< 0.001*
TG (mg/L)	119.0 ± 72.7	127.9 ± 83.7	0.261
HDL-C (mg/dl)	51.4 ± 11.2	52.0 ± 14.6	0.614
BNP (pg/ml)	30.4 ± 42.5	26.6 ± 21.7	0.484
Hs-TnT (ng/L)	3.1 ± 5.8	3.4 ± 5.9	0.579

BNP, B-type natriuretic peptide; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high density lipoprotein; Hs-TnT, high-sensitivity troponin-T; MetS, metabolic syndrome; SBP, systolic blood pressure; TG, triglyceride.
* Significant difference ($p < 0.05$).

Table 2. The results in phonoelectrocardiography in the subjects with and without MetS

	Subjects without MetS (n = 294)	Subjects with MetS (n = 135)	p value
S3 (≥ 5, positve), n (%)	3 (1.0)	1 (0.7)	0.780
S4 (≥ 5, positve), n (%)	19 (6.5)	4 (3)	0.137
SDI (≥ 5, positve), n (%)	9 (3.1)	5 (3.7)	0.728
EMAT (≥ 120 msec, positve), n (%)	13 (4.4)	5 (3.7)	0.730
nEMAT (≥ 15%, positve), n (%)	6 (2.0)	9 (6.7)	0.015*
HR (bpm)	69.2 ± 11.1	71.9 ± 12.0	0.022*
QRS (msec)	95.0 ± 19.7	95.4 ± 20.3	0.853
QTc (msec)	387.6 ± 37.0	387.3 ± 26.5	0.932
PR (msec)	144.7 ± 29.3	144.3 ± 27.3	0.891
EMAT (msec)	89.9 ± 17.0	90.2 ± 16.7	0.874
nEMAT	10.0 ± 2.4	10.4 ± 2.8	0.069
LVST (msec)	319.8 ± 31.8	312.4 ± 33.5	0.029*
% LVST	36.2 ± 3.9	36.8 ± 4.1	0.168
S3	2.7 ± 0.9	2.7 ± 0.8	0.652
S4	3.5 ± 1.2	3.4 ± 1.1	0.738
SDI	3.0 ± 1.0	3.0 ± 1.0	0.420

EMAT, electromechanical activation time; HR, heart rate; LVST, left ventricular ejection time; MetS, metabolic syndrome; nEMAT, normalized EMAT; S3, the third heart sound; S4, the fourth heart sound; SDI, systolic dysfunction index.
* Significant difference ($p < 0.05$).

Table 3. Multivariate logistic regression analysis (conditional stepwise) with statistically significant data in phonography associated with MetS

Significant continuous variables only	p value	Unstandardized coefficients		Standardized coefficients	95% CI
		B	Std. error	Beta	
HR (bpm)	0.022*	0.004	0.002	0.11	0.001-0.008
LVST (msec)#	0.43				
Significant mixed variables	p value	SE	Wald X^2	Odds ratio	95% CI
nEMAT (≥ 15%, positve)	0.022*	0.538	5.25	3.43	1.195-9.837
HR (bpm)#	0.123				
LVST (msec)#	0.151				

CI,confidence interval; EMAT, electromechanical activation time; HR, heart rate; LVST, left ventricular ejection time; MetS, metabolic syndrome; NEMAT, normalized EMAT.
* Significant difference ($p < 0.05$). # Variables not significant in multivariate regression (those exempted from the equation).

was due to a higher HR. All significant parameters of phonoelectrocardiography were then entered into multivariate logistic regression analysis, and the only significant determinative factor was high nEMAT (≥ 15%) for MetS (odds ratio = 3.43, 95% confidence interval = 1.195-9.837, p = 0.022).

DISCUSSION

This cross-sectional study aimed to explore the associations of nEMAT and other phonoelectrocardiographic parameters with MetS in middle-aged Taiwanese males. Our results showed that the subjects with MetS had significantly higher positive nEMAT (≥ 15%) and HR, but significantly shorter LVST compared to those without MetS. However, after adjusting for HR, LVST became statistically non-significant, which also explained why normalized LVST was non-significant. When all significant phonoelectrocardiography parameters were entered into multivariate logistic regression analysis, the only significantly independent factor was high nEMAT (≥ 15%) for MetS.

Since MetS is well known to increase the risk of developing CAD, CVD[7-14] and HF,[15] it is important to find a feasible, easy and noninvasive tool to aggressively manage these risk factors to prevent major adverse cardiovascular events (MACEs). Prediabetes and DM have been independently associated with an increase in the development of subclinical myocardial damage compared to those without DM, as assessed by hs-TnT. In addition, subjects with evidence of subclinical damage have been reported to have the highest risk of clinical events.[21] Since there was no significant difference in hs-TnT between the two groups in our study, the subjects with MetS may have been free of subclinical damage. Therefore, high nEMAT (≥ 15%) may be an earlier sign of cardiac function abnormalities than hs-TnT. High EMAT parameters have been associated with HF[3,4] and PAF,[5] and they have been reported to be a good guide for medication adjustment in patients with acute HF.[6] Since the current study showed that high nEMAT was significantly prevalent in the subjects with MetS, high nEMAT may be a good predictor of the development of MACEs in future causality studies in patients with MetS.

An abnormal nEMAT (nEMAT = Q-S1 interval/R-R interval) value is defined as ≥ 15%,[1,2] and reflects the early phase of contraction abnormality.[22] Delayed contraction in early-to-mid systole of contraction is an early sign of left ventricular (LV) dysfunction in ischemia.[22-24] In addition, an increase in the duration of contraction has also been reported to be a sign of anthracycline-induced cardiotoxicity before HF.[14] The concept of nEMAT is similar to isovolumic contraction time/ejection time (the early phase of contraction) in our previous study,[14] which may be a more sensitive marker of cardiac stressors before the occurrence of HF.[22]

The notion of early contraction delay has also been reported in breast cancer patients who receive anthracycline-based chemotherapy, and it was an early indicator of cardiac injury in our previous study.[14] An abnormal nEMAT (≥ 15%) has been reported to have 54% sensitivity, 92% specificity, 72% accuracy, 6.46 positive likelihood ratio, and 0.50 negative likelihood ratio for the diagnosis of systolic dysfunction (left ventricular ejection fraction < 40%) with a c-statistic of 0.81 (95% CI =

0.63-0.98).[1] Furthermore, EMAT > 15% has also been reported to provide diagnostic information independently of BNP for detecting patients with LV dysfunction.[2] However, to the best of our knowledge, the present study is the first to report that men with MetS were significantly associated with high nEMAT (≥ 15%).

Study limitations

Since the current study is a cross-sectional study, there are some limitations. First, we could not determine the cause and effect, and we could only identify the associations and unequal subject numbers between the MetS and non-MetS groups which may have led to some bias in our findings. Second, the study may face some challenges while putting together the sampling pool based on the variables of the population being studied. However, our findings may provide a direction for future in-depth research. Future large cohort studies with an equal number of MetS subjects with and without high nEMAT (≥ 15%) are warranted to investigate the causality of the development of cardiovascular diseases, especially HF, in subjects with MetS and high nEMAT. Third, the results can only be applied to male subjects as all of our participants were male. Finally, computerized acoustic cardiography is not currently widely used as a screening tool in Taiwan, and it may not be feasible in clinical practice at this point. However, we found that nEMAT was significantly positively associated with Mets. Since nEMAT has been significantly associated with the occurrence of HF[3,4] and PAF,[5] we suggest that subjects with MetS and positive nEMAT should receive regular follow-up at CV clinics to avoid severe MACEs. This device is not expensive, it is easy to carry and more clinical importance is found in studies with certain parameters.[1-6] Therefore, the potential of computerized acoustic cardiography in clinical practice as well as in MetS studies is increasing.

CONCLUSIONS

High nEMAT (≥ 15%), which reflects early contraction delay, was significantly associated with MetS in middle-aged Taiwanese males. High nEMAT may be an earlier sign of cardiac function abnormalities in subjects with MetS. We recommend that subjects with high nEMAT and MetS should receive close regular follow-up in a CV clinic to mitigate the risk of CV events.

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AUTHOR CONTRIBUTIONS

The first author, Dr. Kai-Hung Cheng, participated in generating original ideas, in study design and analysis of data, in drafting of the manuscript, in revising it critically for important intellectual content and in final approval of the manuscript submitted. Other authors participate in 1) conception and design or analysis and interpretation of data, or both: JHG, CHL, CCL, CPW and SPH 2) drafting of the manuscript or revising it critically for important intellectual content: JHG and SPH; and 3) All authors provided final approval for publication and submission and critically revised the manuscript for important intellectual content.

DATA ANALYSIS

We thank Chao-Shih Chen for data analysis.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

DISCLOSURE SUMMARY

The authors have nothing to disclose.

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SUPPLEMENT

Supplemental Table 1. The associations of nEMAT with MetS individual component

	Negative nEMAT (n = 414)	Positive nEMAT (n = 15)	p value
WC (≥ 90 cm, positve), n (%)	106 (25.6)	6 (40.0)	0.212
HDL (< 40 mg/dL, positve), n (%)	58 (14.0)	2 (13.3)	0.941
TG (≥ 150 mg/dL, positve), n (%)	181 (43.7)	8 (53.3)	0.461
HBP (positive), n (%)	344 (83.1)	12 (80.0)	0.754
Hyperglycemia (positve), n (%)	144 (34.8)	8 (53.3)	0.140

HBP, high blood pressure (≥ 130/85 mmHg or diagnosed as hypertensive and on therapy); HDL, high density lipoprotein cholesterol; Hyperglycemia, fasting blood glucose (FBG) ≥ 100 mg/dL or diagnosed as type 2 DM; nEMAT, normalized electromechanical activation time; TG, triglyceride; WC, waist circumference.