

QT_c Heterogeneity in Rest Magnetocardiography is Sensitive to Detect Coronary Artery Disease: In Comparison with Stress Myocardial Perfusion Imaging

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Background: Stress nuclear myocardial perfusion imaging (MPI) is an established method for diagnosis and prognosis of coronary artery disease (CAD). However, radiation exposure limits its clinical application. Magnetocardiography (MCG) has been proposed as a non-contact, rapid and non-radiation technique with high reproducibility. The aim of the study was to evaluate the diagnostic efficacy of rest MCG in CAD comparing to stress MPI.

Methods: We prospectively enrolled 55 patients with suspected CAD (64 ± 10 years) who were scheduled for coronary angiography (CA). MCG, stress ²⁰¹Tl MPI and CA were performed within 3 months. The spatial distribution maps of QT_c interval (21×21 in resolution) were derived from a 64-channel MCG system (KRIS, Korea). T-wave propagation mapping, repolarization heterogeneity index with QT_c dispersion and smoothness index of QT_c (SI-QT_c) were analyzed, and the diagnostic criteria for CAD were developed based on the receiver operating characteristic (ROC) curve analysis.

Results: Patients with significant CAD ($\geq 70\%$ luminal stenosis, $n = 36$) had higher QT_c dispersion and SI-QT_c than controls (both $p < 0.05$). The diagnostic sensitivity and specificity were 0.8330, 0.6842 for QT_c dispersion ≥ 79 ms; 0.7778, 0.6842 for SI-QT_c ≥ 9.1 ms; and 0.8611, 0.6842 for combination. There was no difference of area under ROC curve by using criteria of QT_c dispersion ≥ 79 ms, SI-QT_c ≥ 9.1 ms or combination (0.7588, 0.7310, 0.7727, $p = \text{NS}$), and non-inferior to stress MPI ($p = \text{NS}$).

Conclusions: The QT_c heterogeneity parameters of rest MCG yield a good sensitivity and acceptable specificity for detection of CAD, and may provide an alternative to stress MPI without stress and radiation.

Key Words: Coronary artery disease (CAD) • Magnetocardiography (MCG) • Myocardial perfusion imaging (MPI) • Repolarization

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INTRODUCTION

The prevalence and incidence of cardiovascular disease and its manifestations increase as the global population ages, and have become a worldwide public health problem. Stress nuclear myocardial perfusion imaging (MPI) using single-photon emission tomography (SPECT) is an established method for assessment of the functional significance of coronary stenosis and has been shown to be useful in risk stratification for future cardiac events.¹⁻⁵ However, radiation exposure, high cost

and long examination time still limit its clinical application.

The electric current flowing through the heart generates a magnetic field surrounding the source of the current, and ischemia may alter the regional myocardial electrophysiological properties by depolarizing the cellular membrane, reducing excitability, shortening action potential duration, slowing conduction velocity and prolonging the refractoriness beyond repolarization.⁴⁻⁶ Recently, magnetocardiography (MCG) has been proposed as a non-invasive, contact-free, non-radiation technique with high reproducibility. Rest MCG has been reported to have a good diagnostic accuracy of 60-90% in subjects with acute chest pain⁷⁻¹² or stable coronary artery disease (CAD).¹³⁻²² However, interpretation of MCG remains a challenge since it requires highly experienced personnel and is time consuming, and the criteria for diagnosing CAD are still controversial. In addition, there are limited data comparing the diagnostic performance of stress MPI and rest MCG for detection of CAD.²³ The present study was designed to evaluate the diagnostic performance of MCG for subjects with suspected CAD, comparing with stress MPI which served as the reference standard.

MATERIALS AND METHODS

Study population

Between November 2006 and February 2011, consecutive patients with suspected or known stable CAD referred for stress MPI and coronary angiography (CA) were enrolled in this study. Participants were eligible if they had: (1) typical/atypical chest pain or ischemic equivalents (eg. dyspnea), (2) an interpretable baseline electrocardiography (ECG) and in sinus rhythm, (3) at least intermediate pretest CAD likelihood, (4) preserved left ventricular (LV) ejection fraction (EF) ($\geq 50\%$ by 2D echocardiography) and wall motion. Exclusion criteria were significant arrhythmias, recent (< 6 weeks) myocardial infarction, unstable angina pectoris, Q-wave on 12-lead ECG, and metallic prosthesis (including pacemaker and implantable cardioverter-defibrillator). Patients with surgical wires in the sternum were not excluded. For each subject, all procedures (ECG, echocardiography, MPI, MCG and CA) were performed within three months; information about their medical history

and coronary risk factors were collected at the time of coronary angiography. The protocol was approved by the institutional review board of National Taiwan University Hospital, and written informed consent was obtained from each patient before enrollment.

ECG

The QT interval was automatically measured from the onset of the QRS complex to the end of the T wave (defined as the return to the T-P isoelectric line), and the QT_c represented a QT interval corrected for the previous cardiac cycle length and was calculated automatically according to Bazett's formula: $(QT_c = QT/(R - R)^{1/2})$, where R-R interval in sec).

SQUID MCG procedures and analysis

All MCG measurements were obtained in a magnetically shielded room using a 64-channel superconducting quantum interference device (SQUID) system developed by the Korea Research Institute of Standards and Science (KRISS). The MCG signals were recorded within 100 seconds at a sampling rate of 500 Hz, with the patient in the supine position and the SQUID's two-dimensional arrayed sensors positioned close to, but not in contact with, the left chest wall. After baseline correction, data were averaged using R-peaks to obtain a time-averaged one-period magnetocardiac signal. The QT interval of MCG was automatically defined from the earliest onset of the QRS complex to the latest terminal portion of the T wave at each position from the time-averaged B_z -t curves by using overlapped MCG waveforms, then visually checked and manually corrected if necessary. The QT was used for the construction of the QT contour map, with a spatial resolution of 21×21 . Two parameters were generated to represent the repolarization heterogeneity as follows: (1) the QT_c dispersion, from the difference between the longest and shortest QT_c interval on the QT_c contour map; (2) the spatial smoothness index of QT_c (SI- QT_c), modified from Van Leeuwen et al.'s formula¹³ of the QT_c contour map via

$$SI-QT_c \equiv (1/S) \sum_S \{ (1/n) \sum_n [(QT_c)_k - (QT_c)_n] \},$$

where S is the total number of measured MCG points, \sum_S is summed over the total measured MCG points, n is the number of nearest neighbors for a fixed position k, and $(1/n) \sum_n [(QT_c)_k - (QT_c)_n]$ is the spatially averaged QT_c at a

fixed measured position k summed over the total number of nearest neighbors, n . Then, the time-dependent area ratio of the T wave propagation was analyzed, and the early occurrence of the $+T$ wave due to the shorter action potential of ischemic myocardium could be identified as previously described.^{18,19} Quality evaluation and analysis of ECG and MCG were performed by an independent investigator.

Echocardiography

M-mode and 2-dimensional echocardiography was performed with 2.5- to 3.75-MHz transducers (Hewlett-Packard 5500; Hewlett-Packard, Palo Alto, CA, USA). Conventional measurements of the left atrial and ventricular dimensions, the derived indices of function, and regional wall motion abnormalities were made according to standard criteria.²⁴

Myocardial perfusion imaging procedures and analysis

MPI procedures were standardized and consistent with the published guidelines.²⁵ Two kinds of stress were used for thallium-201 (²⁰¹Tl) SPECT. Standard ECG exercise treadmill testing was performed using a Bruce protocol. ²⁰¹Tl (3 mCi) was injected at peak exercise and exercise was continued for an additional minute. Pharmacologic stress ²⁰¹Tl SPECT was performed if patients were suspected of failing to exercise adequately. Dipyridamole (0.56 mg/kg over 4 minutes) was intravenously infused to induce coronary hyperemia. Three minutes after the completion of the infusion, ²⁰¹Tl was injected. Stress SPECT imaging was started within 5 minutes after the end of stress and redistribution images were acquired 4 hours later. In cases with irreversible defects shown at 4 hours, additional 1 mCi ²⁰¹Tl was injected and a third set of images was obtained 15 minutes after the reinjection. The stress produced techniques for image processing and reconstruction that have been previously described.²⁶ All MPI scans were interpreted with a 17-segment model in which each segment was scored using a 5-point scoring system (0 = normal perfusion to 4 = no uptake).²⁷ Summed scores were calculated from these segmental scores, including summed rest score (SRS: the sum of the 17 segmental rest scores), summed stress score (SSS: the sum of the 17 segmental stress scores) and summed difference

score (SDS: the difference between SSS and SRS). A normal, mildly abnormal, and moderate to severely abnormal MPI was defined as a summed stress score of < 4, 4 to 8, and > 8, respectively. Image interpretation according to these definitions was performed by 2 experienced readers who had no prior knowledge of either the clinical or MCG testing data with excellent intra- and inter-reader reproducibility ($r \geq 0.99$).²⁸ Diverging interpretations were classified by consensus.

Coronary angiography

In each patient, a diagnostic coronary angiogram was performed using standard techniques after pretreatment with intracoronary nitroglycerin to avoid vessel spasm; multiple projections of coronary arteries were recorded digitally. All angiograms were examined, and the degree of coronary stenoses was assessed using a computer-aided quantitative angiographic analysis (QCA) system (DCI-S Automated Coronary Analysis, Philips Medical Systems, Netherlands). Significant CAD was defined as angiographic left main (LM) $\geq 50\%$ or maximum lesions of $\geq 70\%$ luminal stenosis in at least one of the primary coronary arteries and their major branches.

The representative images of a QT contour map, T wave propagation and SPECT of subjects with and without significant coronary stenosis are shown in Figures 1 and 2, respectively.

Statistical analysis

All values were expressed as mean \pm SD. Comparisons were made using a Student's t -test for continuous variables, non-parametric tests, and chi-square tests or Fisher's exact test for categorical variables. One-way ANOVA with Bonferroni post-hoc analysis was performed to make pairwise comparisons among groups. The strength of associations was estimated by the Pearson correlation coefficient (r). Receiver-operating characteristic (ROC) curves were constructed to identify patients with significant CAD using MPI and MCG parameters. All analyses were performed using STATA 10.0 (StataCorp LP, College Station, TX, USA) statistical software. All statistical tests were 2-sided, and a p value of less than 0.05 was considered statistically significant. The diagnostic accuracy of stress MPI was estimated at 85%.^{29,30} In order to observe differences of at least 15% diagnostic accuracy between resting MCG and stress

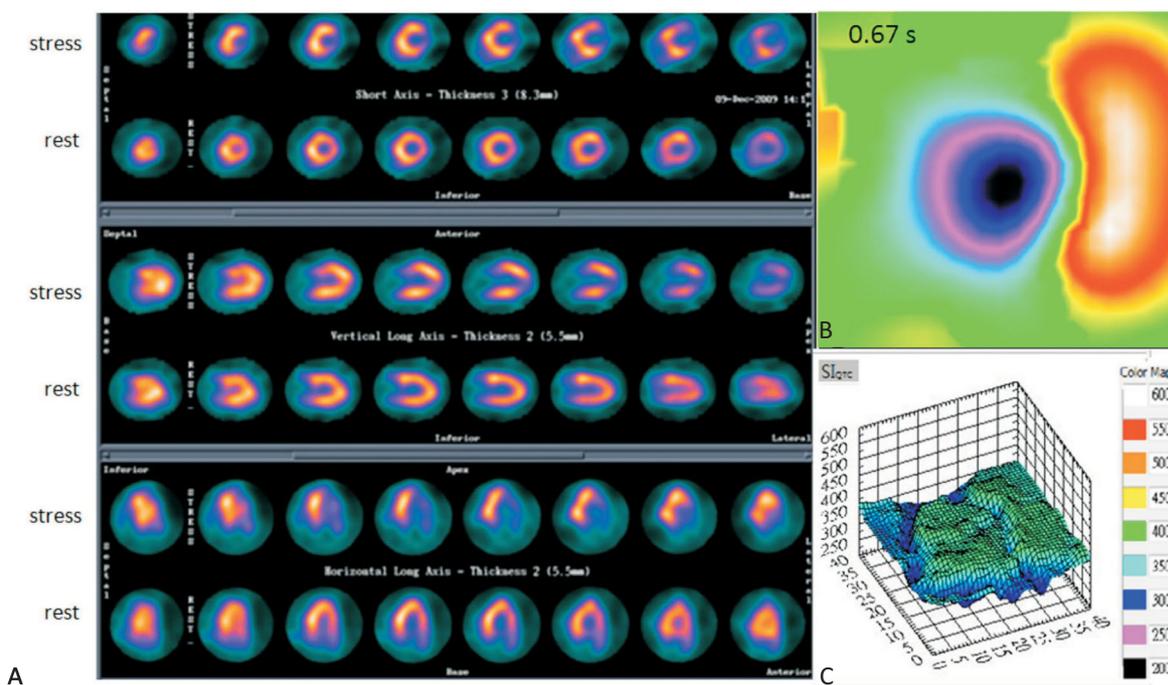


Figure 1. Stress and rest myocardial perfusion imaging in a 68-year-old man showed reversible perfusion defects in the lateral wall (A). An occurrence of +T wave was noted at around 0.67 s. Although absence of early occurrence of +T wave (B), magnetocardiography QT contour map was constructed from the repolarization map (C) which showed increased heterogeneity indices (QT_c dispersion = 93.7 ms, $SI-QT_c$ = 9.7 ms). His coronary angiogram showed near total occlusion in the left circumflex artery.

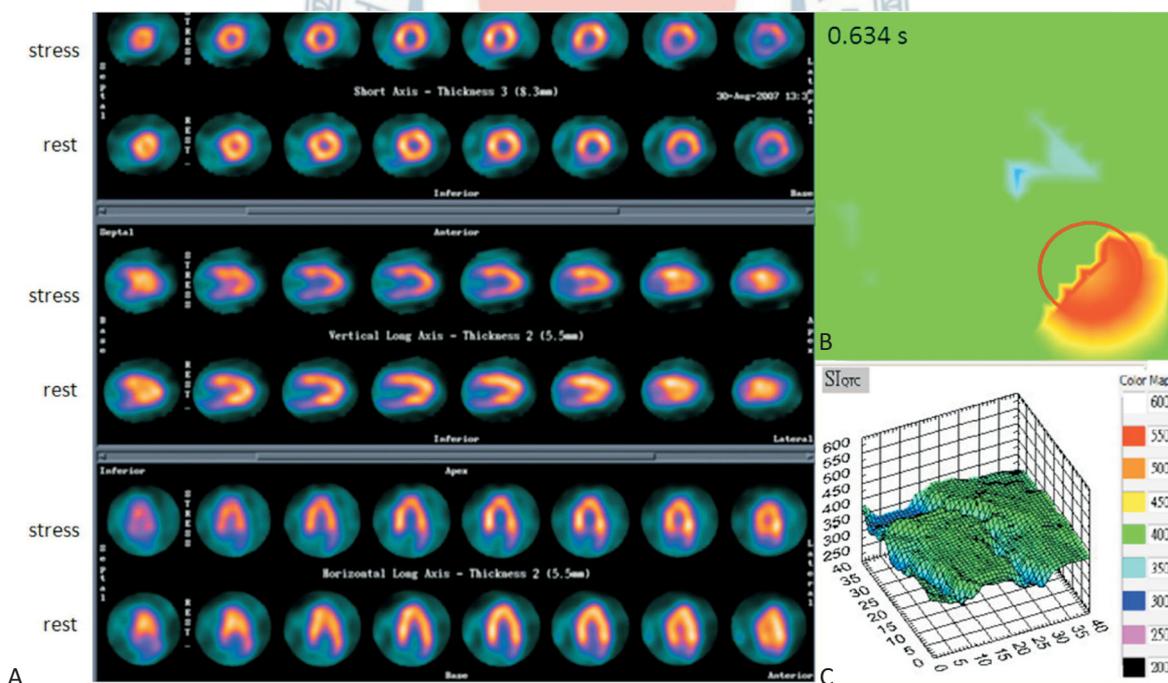


Figure 2. Stress and rest myocardial perfusion imaging in a 60-year-old man showed only mild reversible perfusion abnormalities in anterior and inferior walls (A). Although an early occurrence of +T wave could be detected in 0.634 s in 2D mapping (B), magnetocardiography heterogeneity indices generated from QT contour map (C) were within normal ranges (QT_c dispersion = 69.0 ms, $SI-QT_c$ = 7.8 ms). His coronary angiogram showed no significant coronary stenosis.

MPI for CAD on coronary angiography in subjects with intermediate and high likelihood of CAD, a minimum of 43 patients were required for a 1-side value of $p < 0.05$ with a power ($1-\beta$) of 80% in the non-inferior study design. Nevertheless, in order to improve power, our aim was to recruit a minimum of 50 patients in this pilot study.

RESULTS

A total of 55 subjects were included in the study. Fifteen patients (27%) had a history of coronary revas-

cularization. Based on the coronary angiogram, there were 36 patients with angiographically significant CAD; nine had single-vessel disease, 13 had 2-vessel disease, and the remaining 14 patients had 3-vessel disease. Participants were predominantly middle-aged (mean 65 years), with the majority being male and hypertensive. The frequency of hyperlipidemia was significantly higher in subjects with significant CAD (78% vs. 42%). A high prevalence of statin use was noted in patients with hyperlipidemia, even in the control group. Additional details about the study population are shown in Table 1.

Treadmill ²⁰¹Tl SPECT was performed on 19 patients and all achieved 85% of age-predicted maximum heart

Table 1. Patient characteristics

n = 55	With CAD (n = 36)	Without CAD (n = 19)	p value
Age (y)	64 ± 10	65 ± 9	0.96
Gender (male, %)	33 (92%)	15 (79%)	0.18
Hypertension	32 (89%)	15 (79%)	0.33
Diabetes mellitus	14 (39%)	5 (26%)	0.36
Hyperlipidemia	28 (78%)	8 (42%)	0.0075
Statin	21 (75%)	7 (71%)	
Fibrate	0 (0%)	1 (13%)	
Smoking (current/former)	14 (39%)	4 (21%)	0.15
Prior revascularization	12 (33%)	3 (16%)	0.17
Echocardiography			
IVS (mm)	11.7 ± 2.0	11.2 ± 1.8	0.57
PW (mm)	11.4 ± 1.6	10.3 ± 1.9	0.13
LVEDD (mm)	49.6 ± 4.6	46.6 ± 1.9	0.067
LVESD (mm)	32.8 ± 5.6	27.7 ± 2.2	0.01
LVEF (%)	62.4 ± 11.0	70.7 ± 4.4	0.038
MPI			
SSS	15.4 ± 9.8	3.8 ± 2.8	< 0.0001
SRS	4.6 ± 5.9	1.0 ± 2.4	0.0115
SDS	10.8 ± 8.6	2.8 ± 2.4	0.0002
SSS ≥ 4	32 (89%)	10 (52%)	0.0021
SDS ≥ 4	31 (86%)	7 (37%)	0.0010
SSS > 8	25 (69%)	1 (5%)	< 0.0001
ECG QT _c (ms)	422.8 ± 46.7	406.3 ± 29.1	0.168
MCG			
Early TW peak	30 (83%)	11 (58%)	0.04
QT _c (ms)	382.5 ± 32.0	376.8 ± 23.7	0.499
QT _c disp (ms)	95.53 ± 23.93	77.35 ± 17.58	0.0052
SI-QT _c (ms)	10.81 ± 2.29	9.06 ± 2.99	0.0193
QTc dispersion ≥ 79 or SI-QTc ≥ 9.1 ms	41 (86%)	6 (32%)	< 0.0001

Variables are presented as mean ± SD or number of patients (%).

CAD, coronary artery disease; ECG, electrocardiography; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; IVS, interventricular septum; LV, left ventricular; LVD, LV dilatation; MCG, magnetocardiography; MPI, myocardial perfusion imaging; PW, posterior wall; QT_c disp, QT_c dispersion; SDS, summed difference score; SI, smooth index; SRS, summed rest score; SSS, summed stress score; TW, T wave.

rate, indicating intact effort intolerance and adequate stress. Dipyridamole ^{201}Tl SPECT was performed on the remaining 36 subjects. No major adverse events developed during the study period.

In the overall study population, the MPI results were normal in 18%, mildly abnormal in 31%, and moderate to severely abnormal in 51% of subjects. The values of SSS, SRS and SDS on MPI were positively correlated with the number of stenosed coronary arteries. In addition, SRS was associated with lower LVEF ($r = -0.46$, $p = 0.011$).

Patients with CAD had significantly larger LV end-systolic dimension (ESD), lower LV EF, a high prevalence of perfusion abnormalities on MPI, and higher values of repolarization heterogeneity parameters on MCG. QT_c derived from ECG. Also, MCG tended to be higher in patients with CAD, but not reaching statistical significance.

A good correlation between QT_c dispersion and SI-QT_c ($r = 0.72$, $p < 0.0001$) derived from MCG was noted. However, there was no significant correlation between QT_c of ECG and MCG parameters (including QT_c , QT_c dispersion, SI-QT_c). The early occurrence of +T wave propagation could be identified in 29 (81%) patients with significant CAD, but no specific correlation between location of angiographic distribution, perfusion abnormalities on MPI and early +T wave peak on MCG could be defined. In addition, lack of correlation between QT_c dispersion and SI-QT_c derived from MCG and the number of stenosed coronary arteries was noted.

Table 2 describes the results of ROC curves, sensitivity, specificity and overall accuracy of MPI and MCG parameters for the identification of significant CAD. There was no statistically significant correlation between summed scores of MPI and heterogeneity index of MCG. However, using the area under ROC curve (AUC), SI-QT_c had comparable diagnostic performance as SSS for the detection of significant CAD. On the other hand, QT_c dispersion and the presence of early occurrence +T wave were less accurate. There was no significant difference of AUC in CAD detection by using criteria of QT_c dispersion ≥ 79 ms, $\text{SI-QT}_c \geq 9.1$ ms or in combination (0.7588, 0.7310, 0.7727, $p = \text{NS}$). The diagnostic sensitivity, specificity, and accuracy were 0.8330, 0.6842, and 0.7818 for QT_c dispersion ≥ 79 ms, 0.7778, 0.6842, 0.7455 for $\text{SI-QT}_c \geq 9.1$ ms, and 0.8611, 0.6842, 0.8000 for combination, respectively. Using the criteria of combination of QT_c dispersion ≥ 79 ms or $\text{SI-QT}_c \geq 9.1$ ms, the diagnostic performance was acceptable for the detection of CAD. There was no significant difference in comparison with the cut-off values of $\text{SSS} \geq 4$, $\text{SDS} \geq 4$ or $\text{SSS} > 8$ on semiquantitative MPI.

DISCUSSION

Exercise stress ECG is the most common screening test used to detect CAD; however, lower diagnostic accuracy has been reported in low risk group, women,

Table 2. The results of ROC curves, sensitivity, specificity and overall accuracy of MPI and MCG parameters for the identification of significant CAD

	ROC area	Std. Err.	Sensitivity	Specificity	Accuracy	p value
MPI						
SSS (as standard)	0.8772	0.0449				
SRS	0.6930	0.0675				0.0019
SDS	0.8121	0.0576				0.1283
$\text{SSS} \geq 4$	0.6813	0.0646	0.8889	0.4737	0.7455	< 0.0001
$\text{SDS} \geq 4$	0.7463	0.0639	0.8611	0.6316	0.7818	0.0066
$\text{SSS} > 8$	0.8209	0.047	0.6944	0.9474	0.7818	0.1075
MCG						
Early TW peak	0.6272	0.0662	0.8333	0.4118	0.6981	0.0014
QT_c disp (ms)	0.7383	0.0719				0.0461
SI-QT_c (ms)	0.7551	0.0767				0.1131
QT_c disp ≥ 79 ms	0.7588	0.0632	0.8330	0.6842	0.7818	0.0611
$\text{SI-QT}_c \geq 9.1$ ms	0.7310	0.0651	0.7778	0.6842	0.7455	0.035
QT_c disp ≥ 79 ms or $\text{SI-QT}_c \geq 9.1$ ms	0.7727	0.0621	0.8611	0.6842	0.8000	0.1042

MCG, magnetocardiography; MPI, myocardial perfusion imaging; QT_c disp, QT_c dispersion; ROC, receiver operating characteristic; SDS, summed difference score; SI, smooth index; SRS, summed rest score; SSS, summed stress score; TW, T wave.

subjects with greater functional impairment or after revascularization procedures.^{30,31} The use of SPECT with exercise or pharmacologic stress is superior to exercise ECG test alone, particularly in patients unable to reach an adequate level of stress. This technique has been proven to have good prognostic values for the development of subsequent cardiac events and the need for revascularization. A strategy incorporating stress MPI as the initial test for detecting CAD and assessing prognosis in subjects with intermediate to high pretest likelihood of CAD is recommended,¹⁻³ but not indicated in unselected, asymptomatic individuals or symptomatic subjects with low pretest CAD probability because of its ionizing radiation and high expense.^{2,3} Factors reducing the sensitivity of SPECT MPI are a small LV chamber, single vessel disease (vs. multivessel CAD), mild stenosis and balanced ischemia in the presence of three-vessel CAD.³² Additionally, specificity is reduced when attenuation or motion artifacts are read as indicating CAD. Therefore, the diagnostic accuracy of MPI in women is adversely affected by several gender-specific factors, including breast attenuation, small LV chamber size, and the high prevalence of single-vessel disease.³³⁻³⁵

MCG has been proposed as a non-contact, non-invasive, rapid and non-radiation technique with high reproducibility for functional diagnosis of various heart diseases, which could be easily adapted to routine medical examination among the general population. Increased repolarization heterogeneity of the diseased heart can be either anatomic, due to infarction, fibrosis, or structural remodeling, or electrophysiological, due to ischemia, electrical remodeling, drugs, genetic defects or heterogeneous autonomic innervations.³⁵ Many MCG studies have attempted to investigate the repolarization abnormalities in subjects with myocardial infarction,³⁶⁻³⁹ acute chest pain,⁷⁻¹² stable CAD after stress⁴⁰⁻⁴² or only at rest.¹³⁻²⁰ The diagnostic accuracy for MCG has been reported to be similar to the efficacy of those of existing noninvasive modalities for diagnosing CAD,^{21,22} whereas limited in head-to-head comparison with stress MPI.²³ We previously revealed the early occurrence +T-wave propagation of electromagnetic signals could detect myocardial ischemia in the resting state, and thereafter be improved soon after successful revascularization.¹⁸ We also demonstrated QT heterogeneity index were better than the early occurrence of +T-wave in detection

of CAD as well as cardiac allograft vasculopathy.¹⁹ Furthermore, the present study showed a good diagnostic performance of QT heterogeneity index derived from resting MCG in diagnosis of CAD, and even non-inferior in comparison to stress MPI.

MCG detects cardiac magnetic fields and has advantages over stress MPI or computed tomography coronary angiography.^{43,44} First, MCG is non-radiation in nature which can be conducted with a rapidity that allows high-throughput examination and thus is more feasible for daily practice. Second, MCG records magnetic fields that originate directly from the primary cardiac current and has no need to come into contact with patients during the examination, resulting in minimal signal distortion and attenuation, and thus are less affected by the body composition, including women and obese subjects. In addition, the possibility of underestimation of disease severity due to balanced ischemia could be reduced. Here we demonstrated the MCG heterogeneity index could successfully detect significant CAD even at resting state, and thus could be much safer and more suitable for elderly and subjects with poor functional status. Although the MCG system is relatively expensive and presently requires a magnetically shielded room, it could be widely adapted to a routine examination in daily practice. Due to the positive factors of safety, non-radiation and high reproducibility, the application of MCG as a screening modality in the general population is suitable, even in the asymptomatic or low risk subjects.

We could not establish the correlation between QT_c heterogeneity indices from MCG, and severity of perfusion abnormalities on MPI, or the number of stenosed CAD. The location of early T peak on MCG did not match well with the ischemic region on MPI. These could be partially explained with the high prevalence of multivessel obstructive CAD and history of prior interventions in this study. Further development of new MCG parameters and 3-dimensional mapping are mandatory for better detection and localization of myocardial ischemia and scar formation.

QT heterogeneity detected via ECG could also be reported as a useful predictor of CAD.⁴⁵ In the current study, patients with CAD had significantly higher values of repolarization heterogeneity parameters from MCG. Values of QT_c derived from ECG or MCG tended to be higher in CAD patients in comparison to the controls, although not

reaching statistical significance. This might suggest that repolarization heterogeneity parameters on MCG are more sensitive than QT_c , either using surface ECG or MCG.¹⁹

To the best of our knowledge, this is the first study to evaluate the efficacy of resting MCG in comparison with stress MPI as a non-invasive assessment of CAD. It suggests that resting MCG is a good diagnostic screening tool for the detection of significant CAD. Although stress MPI or computed tomography coronary angiography may be more sensitive than MCG in the detection of CAD, they are not indicated in unselected, asymptomatic individuals or symptomatic subjects with low pretest CAD probability arising from their ionizing radiation and high expense. A negative MCG may obviate the necessity for stress MPI, computed tomography coronary angiography, even invasive coronary angiography.

Study limitations

There are several limitations of this study. ²⁰¹Tl instead of ^{99m}Tc-labeled perfusion tracer is used. In the current study, SPECT with attenuation correction or ECG gating techniques, which could improve the specificity of MPI, was not applied. However, the protocol actually reflects the true clinical practice scenario in Taiwan, with clinically acceptable diagnostic performance of stress MPI.^{3,25,27,34} The sensitivity, specificity and overall accuracy of stress SPECT in the study were comparable to prior reports.²⁹⁻³¹ The study population is rather small and heterogeneous. Because the actual difference of diagnostic accuracy between stress MPI and rest MCG was less than 10%, the sample size which was needed to show significance should be 2-fold larger than the current study. Finally, the frequency of coronary risk factors was high in the enrolled subjects, and we only enrolled subjects with normal sinus rhythm and preserved LV systolic function. This might limit the generalization for clinical application of MCG, especially for the low risk subjects. Therefore, further validation in a larger population with wide range of CAD likelihood, and evaluation of prognostic impact is warranted.

CONCLUSIONS

The repolarization heterogeneity index detected with resting MCG is a sensitive screening tool for ob-

structive CAD.

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REFERENCES

1. Gibbons RJ, Balady GJ, Bricker JT, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106:1883-92.
2. Hendel RC, Berman DS, Di Carli MF, et al. American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Nuclear Cardiology; American College of Radiology; American Heart Association; American Society of Echocardiography; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; Society of Nuclear Medicine. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *Circulation* 2009;119:e561-87.
3. Shen TY, Chang MC, Hung GU, et al. Prognostic value of functional variables as assessed by gated thallium-201 myocardial perfusion single photon emission computed tomography for major adverse cardiac events in patients with coronary artery disease. *Acta Cardiol Sin* 2013;29:243-50.
4. Taggart P, Sutton PM, Boyett MR, et al. Human ventricular action potential duration during short and long cycles. Rapid modulation by ischemia. *Circulation* 1996;94:2526-34.
5. Shaw RM, Rudy Y. Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration. *Cardiovasc Res* 1997;35:256-72.
6. Lazzara R, Scherlag BJ. Electrophysiologic basis for arrhythmias in ischemic heart disease. *Am J Cardiol* 1984;53:1B-7B.
7. Park JW, Hill PM, Chung N, et al. Magnetocardiography predicts

- coronary artery disease in patients with acute chest pain. *Ann Noninvasive Electrocardiol* 2005;10:312-23.
8. Tolstrup K, Madsen BE, Ruiz JA, et al. Non-invasive resting magnetocardiographic imaging for the rapid detection of ischemia in subjects presenting with chest pain. *Cardiology* 2006; 106:270-6.
 9. Park JW, Leithäuser B, Hill P, Jung F. Resting magnetocardiography predicts 3-year mortality in patients presenting with acute chest pain without ST segment elevation. *Ann Noninvasive Electrocardiol* 2008;13:171-9.
 10. Lim HK, Kwon H, Chung N, et al. Usefulness of magnetocardiogram to detect unstable angina pectoris and non-ST elevation myocardial infarction. *Am J Cardiol* 2009;103:448-54.
 11. Kwon H, Kim K, Lee YH, et al. Non-invasive magnetocardiography for the early diagnosis of coronary artery disease in patients presenting with acute chest pain. *Circ J* 2010;74:1224-430.
 12. Leithäuser B, Park JW, Hill P, et al. Magnetocardiography in patients with acute chest pain and bundle branch block. *Int J Cardiol* 2013. doi: 10.1016/j.ijcard.2013.01.254. [Epub ahead of print].
 13. Van Leeuwen P, Hailer B, Lange S, Grönemeyer D. Spatial distribution of repolarization times in patients with coronary artery disease. *Pacing Clin Electrophysiol* 2003;26:1706-14.
 14. Hailer B, Chaikovsky I, Auth-Eisernitz S, et al. The value of magnetocardiography in patients with and without relevant stenoses of the coronary arteries using an unshielded system. *Pacing Clin Electrophysiol* 2005;28:8-16.
 15. Gapelyuk A, Wessel N, Fischer R, et al. Detection of patients with coronary artery disease using cardiac magnetic field mapping at rest. *J Electrocardiol* 2007;40:401-7.
 16. On K, Watanabe S, Yamada S, et al. Integral value of JT interval in magnetocardiography is sensitive to coronary stenosis and improves soon after coronary revascularization. *Circ J* 2007; 71:1586-92.
 17. Tantimongcolwat T, Naenna T, Isarankura-Na-Ayudhya C, et al. Identification of ischemic heart disease via machine learning analysis on magnetocardiograms. *Comput Biol Med* 2008;38: 817-25.
 18. Wu CC, Lin LY, Lin LC, et al. Two-dimensional propagations of magnetocardiatic T wave signals for characterizing myocardial ischemia. *Appl Phys Lett* 2008;92:194104-13.
 19. Wu YW, Lee CM, Liu YB, et al. The usefulness of magnetocardiography to detect coronary artery disease and cardiac allograft vasculopathy. *Circ J* 2013;77:1783-90.
 20. Ogata K, Kandori A, Watanabe Y, et al. Repolarization spatial-time current abnormalities in patients with coronary heart disease. *Pacing Clin Electrophysiol* 2009;32:516-24.
 21. Agarwal R, Saini A, Alyousef T, Umscheid CA. Magnetocardiography for the diagnosis of coronary artery disease: a systematic review and meta-analysis. *Ann Noninvasive Electrocardiol* 2012; 17:291-8.
 22. Kwong JS, Leithäuser B, Park JW, Yu CM. Diagnostic value of magnetocardiography in coronary artery disease and cardiac arrhythmias: a review of clinical data. *Int J Cardiol* 2013;167: 1835-42.
 23. Tolstrup K, Brisinda D, Meloni AM, et al. Comparison of resting magnetocardiography with stress single photon emission computed tomography in patients with stable and unstable angina. *J Am Coll Cardiol* 2006;47:176
 24. Oh JK, Seward JB, Tajik AJ. The echo manual 3rd ed. 2007. Philadelphia: Lippincott Williams & Wilkins.
 25. Hansen CL, Goldstein RA, Akinboboye OO, et al. Myocardial perfusion and function: single photon emission computed tomography. *J Nucl Cardiol* 2007;14:e39-60.
 26. Wu YW, Yen RF, Chieng PU, Huang PJ. TI-201 myocardial SPECT in differentiation of ischemic from nonischemic dilated cardiomyopathy in patients with left ventricular dysfunction. *J Nucl Cardiol* 2003;10:369-74.
 27. Douglas PS, Hendel RC, Cummings JE, et al. ACCF/ACR/AHA/ASE/ASNC/HRS/NASCI/RSNA/SAIP/SCAI/SCCT/SCMR 2008 Health Policy Statement on Structured Reporting in Cardiovascular Imaging. Endorsed by the Society of Nuclear Medicine [added]. *Circulation* 2009;119:187-200.
 28. Wang SY, Cheng MF, Hwang JJ, et al. Sex-specific normal limits of left ventricular ejection fraction and volumes estimated by gated myocardial perfusion imaging in adult patients in Taiwan: a comparison between two quantitative methods. *Nucl Med Commun* 2011;32:113-20.
 29. Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. *Int J Clin Pract* 2012;66:477-92.
 30. Miller TD. Stress testing: the case for the standard treadmill test. *Curr Opin Cardiol* 2011;26:363-9.
 31. Beller GA. Underestimation of coronary artery disease with SPECT. *J Am Coll Cardiol* 2008;15:151-3.
 32. Mieres JH, Rosman DR, Shaw LJ. The role of myocardial perfusion imaging in special populations: women, diabetes, and heart failure. *Semin Nucl Med* 2005;35:52-61.
 33. Shaw LJ, Mieres JH, Hendel RH, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease. Results from the what is the optimal method for ischemia evaluation in women (WOMEN) trial. *Circulation* 2011;124:1239-49.
 34. Ho YL, Wu CC, Huang PJ, et al. Assessment of coronary artery disease in women by dobutamine stress echocardiography: comparison with stress thallium-201 single-photon emission computed tomography and exercise electrocardiography. *Am Heart J* 1998;135:655-62.
 35. Weiss JN, Chen PS, Qu Z, et al. Ventricular fibrillation: how do we stop the waves from breaking? *Circ Res* 2000;87:1103-7.
 36. Nomura M, Nakaya Y, Fujino K, et al. Magnetocardiographic studies of ventricular repolarization in old inferior myocardial infarction. *Eur Heart J* 1989;10:8-15.
 37. Goernig M, Haueisen J, Schreiber J, et al. Comparison of current

- density viability imaging at rest with FDG-PET in patients after myocardial infarction. *Comput Med Imaging Graph* 2009; 33:1-6.
38. Van Leeuwen P, Hailer B, Beck A, et al. Changes in dipolar structure of cardiac magnetic field maps after ST elevation myocardial infarction. *Ann Noninvasive Electrocardiol* 2011;16:379-87.
39. Lim HK, Chung N, Kim K, et al. Can magnetocardiography detect patients with non-ST-segment elevation myocardial infarction? *Ann Med* 2007;39:617-27.
40. Takala P, Hänninen H, Montonen J, et al. Heart rate adjustment of magnetic field map rotation in detection of myocardial ischemia in exercise magnetocardiography. *Basic Res Cardiol* 2002;97: 88-96.
41. Hänninen H, Takala P, Mäkijärvi M, et al. Recording locations in multichannel magnetocardiography and body surface potential mapping sensitive for regional exercise-induced myocardial ischemia. *Basic Res Cardiol* 2001;96:405-14.
42. Park JW, Leithäuser B, Vrsansky M, Jung F. Dobutamine stress magnetocardiography for the detection of significant coronary artery stenoses - a prospective study in comparison with simultaneous 12-lead electrocardiography. *Clin Hemorheol Microcirc* 2008;39:21-32.
43. Perrone-Filardi P, Achenbach S, Mohlenkamp S, et al. Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology. *Eur Heart J* 2011;32:1986-93.
44. Chua SK, Hung HF, Cheng JJ, et al. Diagnostic performance of 64-versus 256-Slice computed tomography coronary angiography compared with conventional coronary angiography in patients with suspected coronary artery disease. *Acta Cardiol Sin* 2013; 29:151-9.
45. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000;36: 1749-66.

