Usefulness of Magnetocardiography to Detect Coronary Artery Disease and Cardiac Allograft Vasculopathy

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**Background:** Electrophysiological information as well as anatomic information are important for the detection of coronary artery lesions. The aim of this study was to assess the efficacy of resting magnetocardiography (MCG) in stable coronary artery disease (CAD) and cardiac allograft vasculopathy (CAV).

**Methods and Results:** MCG and coronary angiography were performed within 1 month in 75 patients with suspected CAD and in 26 subjects after orthotopic heart transplantation (OHT). Plaque volumes were additionally measured on intravascular ultrasound in OHT recipients. The spatially distributed QTc interval maps were constructed with 64-channel MCG. A T-wave propagation map and QTc heterogeneity index including QTc dispersion and smoothness index of QTc (SI-QTc) were derived for ischemia detection and localization. CAD patients had higher QTc dispersion and SI-QTc. Receiver operating characteristic curve analysis identified SI-QTc ≥9ms, QTc dispersion ≥79ms as the optimal cut-off for detecting CAD (diagnostic accuracy, 0.7953, 0.7819), better than T-wave propagation (0.6594, P<0.05). There was no significant difference of QTc dispersion between CAD and OHT subjects. In OHT recipients, QTc dispersion positively correlated with plaque volume, and SI-QTc progressively increased after transplantation. Using T-wave propagation mapping, regionally increased dispersion could be demonstrated in CAD patients, but increased dispersion was noted in fewer OHT recipients.

**Conclusions:** MCG is clinically feasible as a non-invasive tool for diagnosis of CAD, and could be used as a surrogate marker of CAV. *(Circ J 2013; 77: 1783–1790)*

**Key Words:** Cardiac allograft vasculopathy; Coronary artery disease; Heart transplantation; Magnetocardiogram

Techniques for diagnosing and estimating the severity of coronary artery disease (CAD) are important. Exercise electrocardiography (ECG) test is the most common screening test, but lower diagnostic accuracy has been reported, especially in women, in subjects with greater functional impairment or after revascularization procedures. The use of stress single-photon emission computed tomography (SPECT) or CT coronary angiography is superior to exercise ECG test, but are not indicated in unselected, asymptomatic individuals or symptomatic subjects with low pretest CAD probability because of the ionizing radiation and cost. Cardiac allograft vasculopathy (CAV) is the leading cause of late mortality in recipients of heart transplantation. It is characterized by a diffuse, concentric, intimal thickening of both the epicardial and intramyocardial arteries. Intravascular ultrasound (IVUS) has been considered a much more sensitive method in the diagnosis of CAV, but invasiveness and cost limit its clinical application. Stress ECG and myocardial SPECT often underestimate the extent and severity of CAV due to the diffuse nature of the disease and balanced ischemia. Dys-
has not been established. The aim of the present study was therefore to assess the diagnostic efficacy of MCG in the evaluation of subjects with suspected CAD or CAV.

Methods

Subjects
Between November 2006 and February 2011, 75 patients with suspected CAD and 26 recipients of orthotopic heart transplantation (OHT) with preserved left ventricular (LV) systolic function (ejection fraction [EF] ≥ 50%) were enrolled. All participants had a physical examination and 12-lead resting ECG. Exclusion criteria were significant arrhythmias, known MI history or Q wave on surface 12-lead ECG, unstable angina pectoris, significant valvular heart disease, metallic prosthesis (including pacemaker and implantable cardioverter defibrillator). Patients with surgical wires in the sternum were not excluded. All OHT recipients were treated with standard immunosuppressive therapies as previously described. An endomyocardial biopsy (EMB) was performed weekly in the first month; once every 3 months in the first 6 months; at 1 year; and then annually thereafter. Coronary angiography was performed at 1 month after transplantation, then annually. For each subject,
left chest wall. After baseline correction, data were averaged using R-peaks to obtain a time-averaged 1-period magnetocardiographic signal. The spatiotemporal analysis of repolarization heterogeneity was determined from the spatial distribution of the QT intervals (Figure 1A). The QT interval 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 Bz-t curves by using overlapped MCG waveforms, then visually checked and manually corrected if necessary (Figure 1B). The QT was used for the construction of the QT contour map, with a spatial resolution of 21×21 (Figure 1C).

We derived 2 parameters from the QT contour map to represent the myocardial repolarization heterogeneity. First, the QT dispersion was derived from the difference between the longest and shortest QT interval on the QT contour map. Second, we derived the spatial smoothness index of QT (SI-QT), modified from Van Leeuwen et al.,22 from the QT contour map via:

$$SI_{QT} = \left( \frac{1}{S} \right) \sum_s \left( \frac{1}{n} \right) \sum_n [(QT_s)_k - (QT_s)_n]$$

where S is the total number of measured MCG points, Ss is summed over the total measured MCG points, n is the number of nearest neighbors for a fixed position k, and (1/n) Σn [(QT_s)_k - (QT_s)_n] is the spatially averaged QT at a fixed measured position k summed over the total number of nearest neigh-

Figure 2. Examples of (Left) QT contour map and (Right) T-wave propagation in subjects with significant coronary stenosis. The time-dependent area ratio of positive (+) T to negative (–) T waves is analyzed. Yellow-to-red, +T waves; blue-to-black, –T waves. The earliest area of the +T waves could be located in the ischemic myocardium: (A) left anterior descending artery (LAD); (B) left circumflex artery (LCX); and (C) right coronary artery (RCA).
The early occurrence of the $+T$ wave could be attributed to the shorter action potential of ischemic myocardium, and the vascular distribution was defined by the 2-D mapping around the occurrence of the peak. The representative images of QT contour map and $T$-wave propagation in subjects with significant coronary stenosis are given in Figure 2. Quality evaluation and analysis of ECG and MCG were performed by an independent investigator.

**Echocardiography**

Echocardiography was performed with 2.5–3.75-MHz transducers (Hewlett-Packard 5500; Hewlett-Packard, Palo Alto, CA, USA) according to standard criteria. Peak velocities of early filling (E), atrial filling (A), and deceleration time (DT) were determined by using pulsed-wave Doppler from an apical 4-chamber view. Tricuspid regurgitation velocity was obtained on continuous-wave Doppler, which reflects the pressure difference during systole between the right ventricle and the right atrium ($4 \times$ tricuspid regurgitation velocity)$^2$. Restrictive physiology was defined as LVEF $>50\%$, E/A ratio $>2$ and shorter DT ($<150$ ms) or restrictive hemodynamic parameters (estimated pulmonary capillary wedge pressure $>25$ mmHg)$^3$.

**Cardiac Catheterization and EMB**

Starting the first or second week after transplantation, EMB were done. Histologic and immunofluorescence findings were recorded, and semi-quantitative scales were used to report an antibody-mediated rejection (AMR) and acute cellular rejection (ACR)$^3$.

Diagnostic coronary angiogram was performed using standard techniques after pretreatment with i.c. nitroglycerin to avoid vessel spasm; multiple projections of coronary arteries were recorded digitally, and the degree of coronary stenosis was assessed using a computer-aided quantitative angiographic analysis system (DCI-S Automated Coronary Analysis; Philips Medical Systems, The Netherlands). Significant CAD was defined as angiographic maximum lesions $\geq 50\%$ luminal stenosis in the left main (LM), or $\geq 70\%$ in at least one of the primary coronary arteries and their major branches. In OHT patients, CAV status was further classified in accordance with International Society for Heart and Lung Transplantation (ISHLT) recommended nomenclature as follows: not significant, CAV0; mild, CAV1; moderate, CAV2; or severe, CAV3$^3$.

In OHT subjects, additional IVUS (Atlantis SR Pro 2.5F, 40-MHz; Boston Scientific) of the left anterior descending coronary artery (LAD) was performed after the coronary angiography$^5$ using the resident software (Galax system; Boston Scientific). The percentage of maximum area stenosis was calculated as (maximum plaque area/vessel volume)$\times 100\%$, and percentage of atheroma volume (PAV) was defined as (total plaque volume/vessel volume)$\times 100\%$, which normalized the individual variations of the vessel and vessel length.

**Statistical Analysis**

All data are given as mean $\pm$ SD. Comparisons were made using Student’s t-test for continuous variables and chi-square analysis for categorical variables. ANOVA was performed to detect any associations between 2 or more variables. In the subgroup of cardiac transplant recipients, IVUS measurements were compared with MCG variables on linear regression analysis. The
strength of associations was estimated with the Pearson correlation coefficient (r). Diagnostic criteria of CAD using QTc on 12-lead ECG and MCG, the presence of early peaking of T-wave propagation, QTc dispersion and SI-QTc on MCG were developed based on receiver operating characteristic (ROC) analysis. Logistic regression was used to evaluate the statistical significance of different cut-offs of QTc dispersion and SI-QTc in predicting CAD. All analyses were performed using STATA (release 10.0; StataCorp LP). All statistical tests were 2-sided, and P<0.05 was considered statistically significant.

Results

A total of 75 subjects with known or suspected CAD and 26 OHT recipients were included in the study. The clinical characteristics are summarized in Table 1.

Of 75 subjects with known or suspected CAD, there were 51 patients with significant CAD based on coronary angiogram; 16 had single-vessel disease, 17 had 2-vessel disease, and the remaining 18 patients had LM or 3-vessel disease. There was good correlation between QTc dispersion and SI-QTc (r=0.70, P<0.0001). The early occurrence of +T-wave propagation was also correlated with higher SI-QTc (P=0.049), but not QTc dispersion. There was no significant association between clinical characteristics (including age, gender and cardiovascular risk factors) and these MCG parameters. Only QTc dispersion was positively correlated with LV end-systolic dimensions (P=0.038).

There was no significant difference of QTc on ECG (P=0.14) or MCG (P=0.25) between subjects with CAD and those without. Patients with significant CAD had significantly larger LV dimensions, higher prevalence of early occurrence of time-dependent area ratio of +T-wave propagation and increased heterogeneity (QTc dispersion and SI-QTc) on MCG (all P<0.05). ROC curve analysis identified SI-QTc ≥9 ms, QTc dispersion ≥79 ms as the optimal cut-off for detecting CAD. There were no significant differences between areas under the ROC curve when using a single criterion or a combination of QTc dispersion and SI-QTc criteria (Figure 3).

Although the heterogeneity indicators were consistently more

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<th>Table 2. MCG Parameters in Detection of Significant CAD</th>
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<td><strong>Early TW peak</strong></td>
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CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SI, smoothness index. Other abbreviations as in Table 1.
mined on IVUS agrees well with myocardial perfusion reserve assessed on PET in OHT recipients, it can be used as a marker of inducible ischemia burden and disease severity. In the present study, QTc on ECG and MCG was significantly higher in OHT patients than in those with patent coronary angiogram (both P<0.0001), but did not correlate well with any IVUS parameters. In contrast, only QTc dispersion derived from MCG was positively correlated with PAV (r=0.49, P=0.021) and maximum area stenosis (r=0.37, P=0.049). The OHT recipients with QTc dispersion $\geq$79 ms or SI-QTc $\geq$9 ms, the criteria for detecting significant CAD, had significantly higher PAV than those with lower QTc dispersion or SI-QTc (27.8 $\pm$ 10.8%, n=15 vs. 16.9 $\pm$ 9.8%, n=11, P=0.014). Although SI-QTc was not correlated well with plaque volume in OHT patients, it still marginally increased with the post-transplantation time (P=0.05; Figure 4).

Discussion

Spatial electrical heterogeneity within the ventricular myocardium has been demonstrated in previous studies. The spatial heterogeneity of repolarization could be amplified during pathological condition. Increased repolarization heterogeneity of the diseased heart can be either anatomic, due to infarction, fibrosis, or structural remodeling; or electrophysiological, due to electrical remodeling, drugs, genetic defects, or heterogeneous autonomic innervations. Chronic myocardial disease could result in both electrophysiological and structural remodeling of the heart, and both could affect the repolarization heterogeneity of ventricular myocardium.

Many MCG studies investigated repolarization abnormal-
ties in subjects with acute chest pain,17-21 or stable CAD after stress,22,23 or at rest.22-28 Those studies have focused either on exercise-induced ischemia or on ischemia and the infarct scar at rest. Different parameters have been developed based on signal intensity/vector, time intervals, or magnetic field map analysis. In a previous study, we have also utilized a 64-channel MCG system to detect the time-dependent area ratio of T-wave propagation that is spatially distributed over the heart, for screening and localizing the myocardial ischemia.24 There was no clear separation, however, of patients with CAD from those with patent coronary arteries using these MCG parameters. Even with a combination of multiple MCG parameters, the sensitivity was approximately 75–85% and the specificity was approximately 70–80% for diagnosis of CAD based on post-hoc analysis. The evaluation of spatial QT dispersion on MCG, reflecting regional heterogeneity of repolarization, may improve the identification of CAD patients.18,38 In this study, we demonstrated not only that the patients with significant CAD had significantly higher prevalence of early occurrence of +T-wave propagation and increased heterogeneity (QT$_c$-index), but also that the repolarization heterogeneity index has superior diagnostic accuracy to T-wave propagation mapping in the patients with suspected CAD (0.79 vs. 0.65; P=0.036).

The ECG of a transplanted or native heart are different which may be due to anatomically different position. Most grafts develop right ventricular distension and tricuspid insufficiency, and changes in QRS morphology and T-wave configuration may be diffuse, non-specific or absent. A progressive increase in the QT interval is considered to be a prognostic indicator after heart transplantation associated with allograft rejection or CAV, and can be reversed after statin treatment.2 In the present study, none of the OHT subjects had a history of acute rejection. This study has shown that QT$_c$-dispersion determined on MCG correlated well with coronary morphological changes on IVUS, suggesting that the development of CAV is associated with an increase in QT dispersion. This suggests that QT$_c$-dispersion may be a useful marker or predictor of cardiovascular events due to ischemia or arrhythmia. These findings imply that CAV is a progressive process. The SI-QT$_c$-scores in OHT patients increased gradually over time, similar to the progression of inhomogeneity scores on SPECT.6

The present study has a practical implication in that the addressed MCG heterogeneity scores for CAD would be useful for distinguishing the patients with significant CAD in rest state, and the best cut-off values for these criteria was established. In addition, 2-D T-wave propagation could be used to identify the most ischemic zones, and QT$_c$-dispersion may be a useful marker for the development of CAV after OHT. All of the present patients, however, were in sinus rhythm and none had left bundle branch block, so it should be stressed that the present observations are limited to patients with sinus rhythm and without left bundle branch block.

Due to the low prevalence of higher grade of acute rejection at the time of MCG, the relationship between severity of acute rejection and MCG parameters was not clear. Also, CAV, diastolic dysfunction due to increased interstitial fibrosis, is another main prognostic factor after heart transplantation. The present OHT recipients had preserved LV systolic function, but significantly higher E/A ratio and shorter DT compared to subjects with known or suspected CAD (Table 1). Overall, 19% (5/26) were classified as restrictive physiology status on echocardiography criteria. Although we did not find the associations between episodes of ACR or AMR, progressive and heterogenous interstitial fibrosis may exist. It is possible that not only myocardial ischemia but also increased interstitial cellularity or extracellular matrix accumulation could affect repolarization heterogeneity. Other methods such as delayed enhanced magnetic resonance imaging could be considered for comparison. Furthermore, we performed IVUS only in the LAD vessel, but the real extent and severity of CAV in these patients cannot be assessed in vivo.

To the best of our knowledge, this is the first study to evaluate the efficacy of using MCG in the resting state as a non-invasive assessment of CAD and CAV. The present study suggests that MCG is clinically feasible as a diagnostic tool in the detection of CAD. A negative or stable MCG may obviate the necessity for invasive coronary angiography and IVUS surveillance in transplant recipients. The limitations of this study include the following factors: the subject group was small and heterogeneous, and the study was cross-sectional in design. Variable factors, especially in the OHT group (including donor demographic factors, donor ischemic time, immunosuppressive regimen and history of acute rejection), may weaken the association between the study variables and the MCG results. Little information on the relationship with arrhythmia was addressed due to study design. Also, the predictive value of MCG for long-term clinical outcome is not available. A large-scale prospective longitudinal follow-up study is warranted to further elucidate at what point the elevated QT$_c$-heterogeneity is associated with significant CAD or CAV, complex arrhythmias or LV dysfunction.

**Conclusion**

We have developed a new method for quantitative estimation of repolarization heterogeneity using MCG, which had good diagnostic accuracy in significant CAD and good correlation with plaque volume on IVUS in CAV. The repolarization heterogeneity index determined on MCG is clinically feasible as a diagnostic tool for the non-invasive examination of significant CAD, and could be used as a surrogate marker for CAV.

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**Disclosures**

Conflict of Interest: None declared.

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