



# Magnetocardiographic recognition of abnormal depolarization and repolarization in patients with coronary artery lesions caused by Kawasaki disease

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## Abstract

Myocardial ischemia changes the electrophysiological properties of the myocardium, but it is difficult to detect the abnormalities of depolarization and repolarization noninvasively in patients with coronary artery disease. Depolarization and repolarization abnormalities were retrospectively investigated in 61 patients (48 males and 13 females) with coronary artery lesions (CALs) caused by Kawasaki disease (KD) from 2007 to 2014 using magnetocardiography (MCG). CAL had been diagnosed by selective coronary angiography. The integral value was computed for each channel, and isointegral maps were constructed during depolarization and repolarization. The MCG findings were compared between the stenotic lesions group (SL group) and the non-stenotic lesions group (non-SL group). The incidence of MCG abnormalities was significantly higher in the SL group than in the non-SL group ( $p < 0.0001$ ). The incidence of abnormal repolarization was significantly higher than that of abnormal depolarization ( $p < 0.0001$ ). The number of coronary artery occlusions significantly affected the severity of abnormal repolarization ( $p = 0.02$ ). Six (75%) of the patients with abnormal depolarization had a previous anteroseptal myocardial infarction. The transmural myocardial infarction affects on abnormalities of depolarization, and the non-transmural myocardial infarction might relate on abnormalities of repolarization. The myocardial electrical properties were preserved in patients except very severe coronary stenosis. MCG is possible to detect electrical myocardial abnormalities noninvasively in patients with CALs caused by KD.

**Keywords** Magnetocardiography · Kawasaki disease · Coronary artery occlusion · Depolarization · Repolarization

## Introduction

Sudden death due to a fatal ventricular arrhythmia can occur in patients with coronary artery lesions (CALs) caused by Kawasaki disease (KD) [1]. Myocardial ischemia changes the electrophysiological properties of the myocardium. Therefore, it is important to follow-up the electrical

abnormalities in ischemic heart disease. However, noninvasive recognition of abnormalities of depolarization and repolarization in patients with coronary artery disease is difficult. Magnetocardiography (MCG) is a noninvasive and noncontact mapping technique for recording action currents in cardiac tissues, and it produces waveforms which are morphologically similar to that of an electrocardiogram (ECG) [2]. Several investigators have studied the detection of myocardial involvement and arrhythmias with MCG [3, 4]. Thus, depolarization and repolarization abnormalities were investigated in patients with CALs due to KD using MCG.

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## Materials and methods

### Study population

The MCG findings of patients with CALs caused by KD from 2007 to 2014 at the National Cerebral and Cardiovascular

Center in Japan were retrospectively investigated. A total of 61 patients (48 males and 13 females) who had undergone selective coronary angiography (CAG) by cardiac catheterization were selected. Informed consent was obtained from all the children's parents. The ethical committee of our institution approved this retrospective study. The age at MCG ranged from 3 to 39 years (median 19 years), and the age at the onset of KD was from 2 months to 11 years (median 2 years 4 months). The interval from the onset of KD to MCG ranged from 1 to 38 years (median 13 years). The median interval from MCG to CAG was 165 days. Forty-nine patients (80%) had undergone CAG within 3 years of the MCG examination. Although 12 (20%) patients had undergone MCG more than 3 years since the previous CAG, they had undergone coronary angiography by dual-source computed tomography within 3 years of the MCG examination. There were no cardiac events such as myocardial infarction (MI) between the MCG and CAG examinations in all patients. Four patients had a history of non-sustained ventricular tachycardia.

Antiplatelet agents were administered to 59 patients (97%), and 14 (23%) patients were taking warfarin. Beta-blockers and angiotensin-converting enzyme inhibitors were being taken by 10 patients and 3 patients, respectively. Sotalol and a calcium antagonist were being taken by one patient each.

The patients were divided into two groups determined by the presence of stenotic lesions on CAG: the stenotic lesions group (SL group) and the non-stenotic lesions group (non-SL group). In this study, the SL group included complete occlusion, segmental stenosis, and localized stenosis  $\geq 75\%$ . In the SL group, whether a previous MI had occurred was determined based on the medical records. The non-SL group included regressed aneurysms, aneurysms, and localized stenosis  $< 75\%$ .

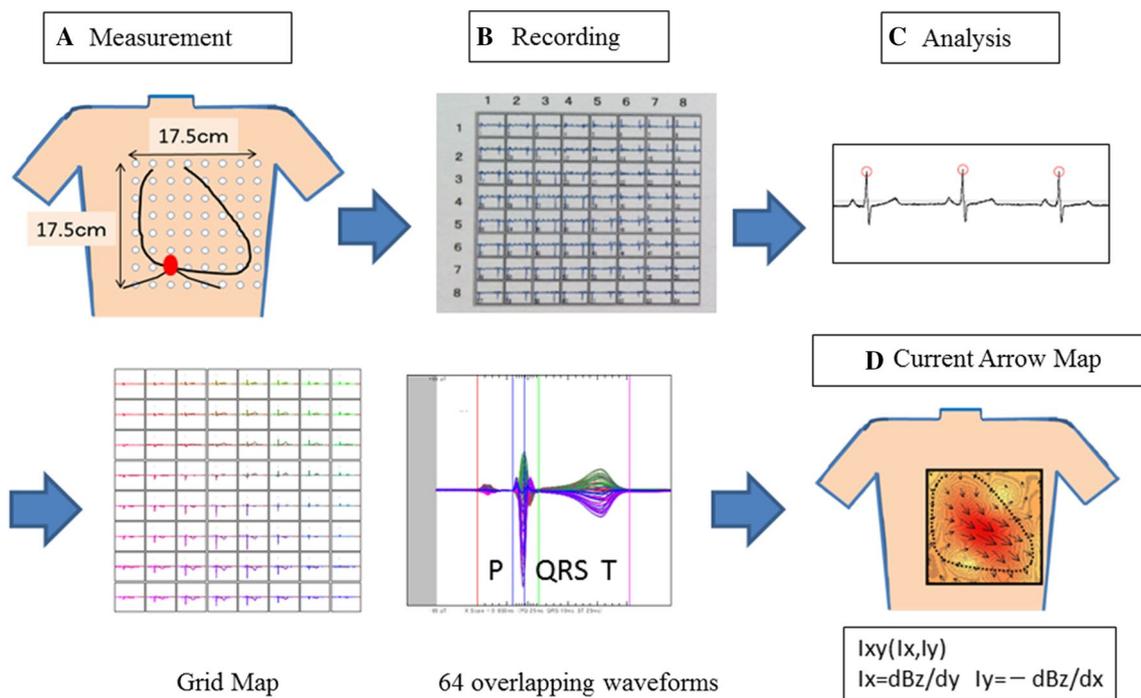
### MCG system and data acquisition

MCG was done inside a magnetically shielded room (MSR) using a multichannel superconducting quantum interference device (SQUID) system. The system had 64-channel magnetic sensors (MC-6400; Hitachi High-Technologies Corp., Tokyo, Japan) inside the dewar, and each magnetic sensor probe incorporated a first-order gradiometer. A probe was placed at each of the 64 sites in an  $8 \times 8$  matrix with 25-mm intervals, giving a measurement area of  $175 \times 175 \text{ mm}^2$ . This area could cover the entire heart. Subjects with gowns on lay on a bed inside the MSR, and all metallic objects were removed. The dewar containing the SQUID sensors was placed as close as possible to the anterior chest without touching it. Each sensor was set to its exact position, with the xiphoid process as the reference landmark using a laser marker (Fig. 1). The normal ( $B_z$ ) component of the magnetic field vertical to the torso was measured for 30 s.

The signals could be viewed on a real-time display, and the data were stored and analyzed by a personal computer. The electrocardiogram (ECG) signals were also obtained as reference signals. The MCG signals ( $> 20$  beats) were averaged with simultaneously digitalized ECG, which was also used to synchronized 2-D current arrow mapping (CAM) for each recording. The acquired MCG signals were passed through a bandpass filter (0.1–100 Hz) and an analog notch filter (60 Hz) and signal-averaged using the ECG R wave peak. MCG measurement data were converted to a current arrow map, which indicates pseudocurrents ( $I_x$  and  $I_y$ ) from the derivatives of the normal component ( $B_z$ ) of the MCG signals as  $I_x = dB_z/dy$  and  $I_y = -dB_z/dx$  (Fig. 1).

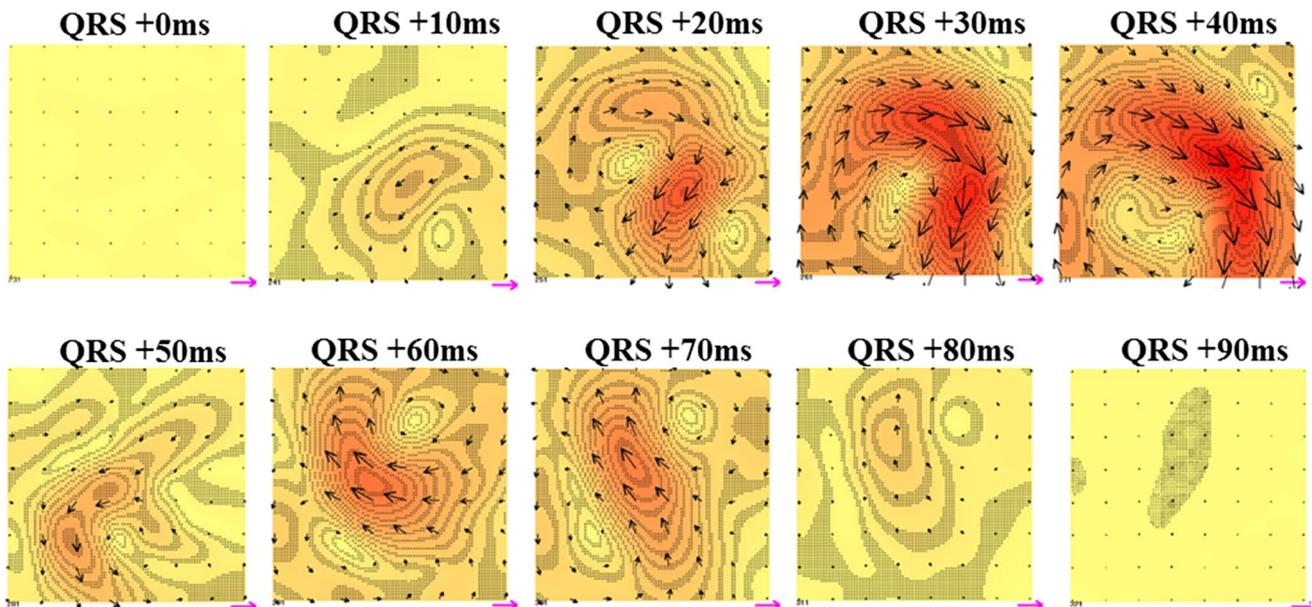
### Definitions of depolarization and repolarization abnormalities

In normal subjects, the peak magnetic fields can be recognized on the frontal 2-D CAM, which has been reported in previous studies [6–8]. The activation time course can also be recognized and confirmed using 64 overlapping waveforms. There are three main portions on the 64 overlapping waveforms for the QRS process. For the first depolarization process of the interventricular septum (septal Q), a weak current arrow with lower-right direction appears in the lower-left chest. The activation is indicated by a septal vector from the left ventricle to the right ventricle. For the second depolarization of whole left ventricular activation after breakthrough, the activation changes dynamically (25 ms after QRS onset). There is then immediately large left ventricular activation with the main current flow toward the apex. The CAM of the R wave has a current that starts from the middle right, flows across the center, and flows down along the left. For the third depolarization of the right ventricle (mainly the right ventricular outflow tract), there is weak activation with an upper-right direction (Fig. 2). As for the ST-T process, it is simple. There is no current for the ST process, the main current begins to flows toward the apex (lower-left direction) from the T process, and this pattern is almost similar to that during activation (Fig. 3). The depolarization and repolarization abnormalities were analyzed by observing 2-D CAM for the depolarization process (QRS) and the RE process (ST-T) (Figs. 4, 5). As for the depolarization and repolarization processes, CAM was classified using a classification system with a scale from 0 (normal), 1 (slightly abnormal), 2 (abnormal), to 3 (grossly abnormal) (Figs. 4, 5) [5]. Briefly, the classification system is based on the notion that, during normal repolarization, the underlying electrical activity will be coordinated, and the current distributions represented in the CAM will be primarily characterized by currents in a left and downward direction. Disturbances in repolarization will affect the symmetry of the maps, and these asymmetries are quantified on the basis of the weighted sums of the directions of the vectors. Normal CAM is classified as



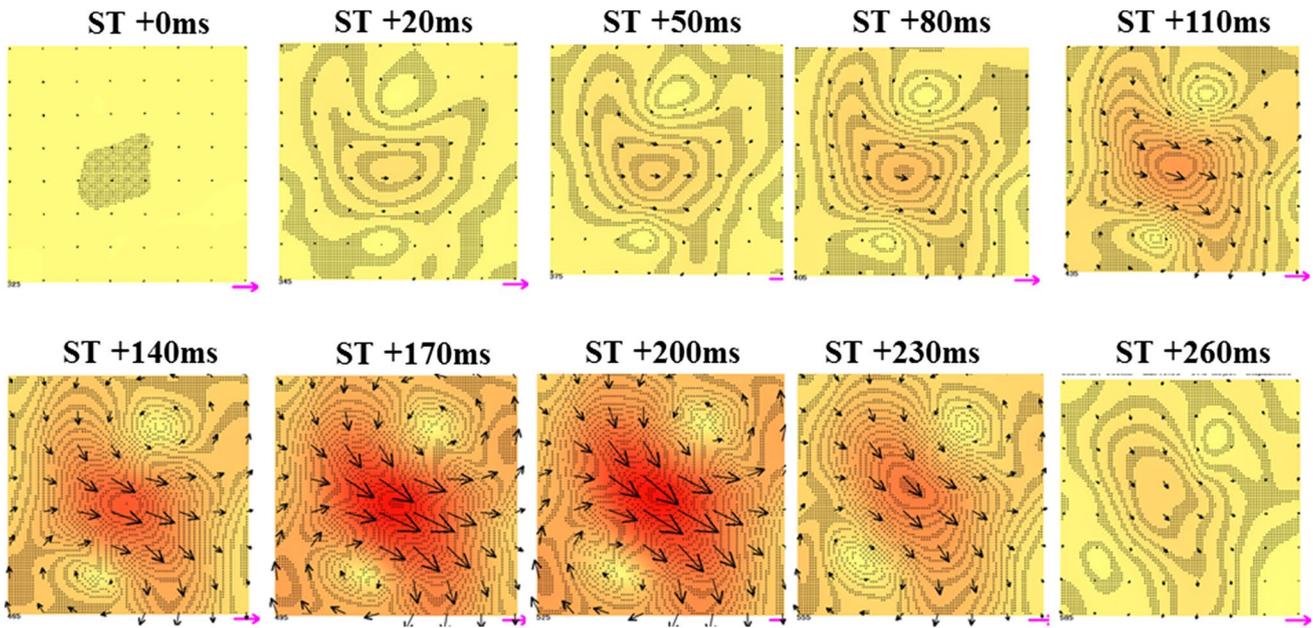
**Fig. 1** Magnetocardiography (MCG) study. **a** A laser marker (red point) is placed on the xiphoid process to adjust the supine patient's heart with the sensor area. **b** The MCG signals are recorded. **c** Signals are ECG-gated and averaged and corrected for baseline. A grid

map and 64 overlapping waveforms are then produced. **d** A current arrow map is made from the MCG grid map whose normal components of magnetic vectors are converted to tangential components

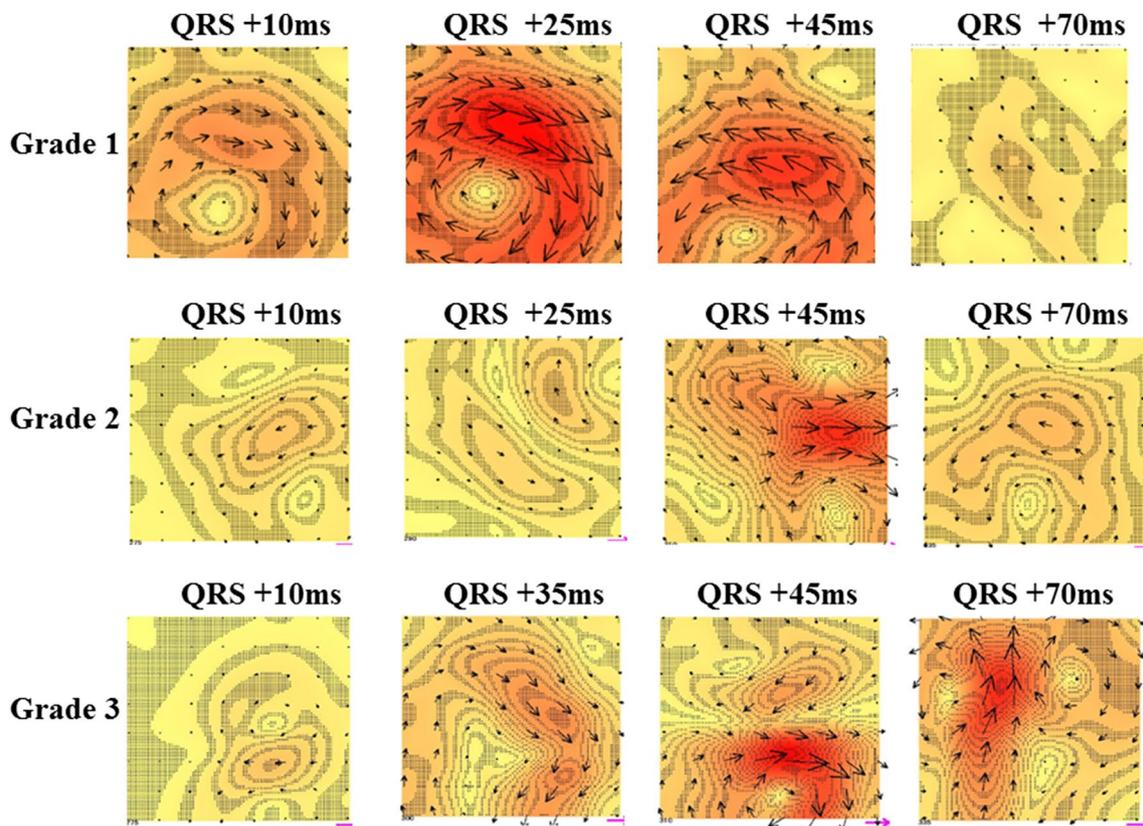


**Fig. 2** Depolarization for the QRS process. There are three main portions on the 64 overlapping waveforms for the QRS process: the first depolarization of the interventricular septum (septal Q), the second

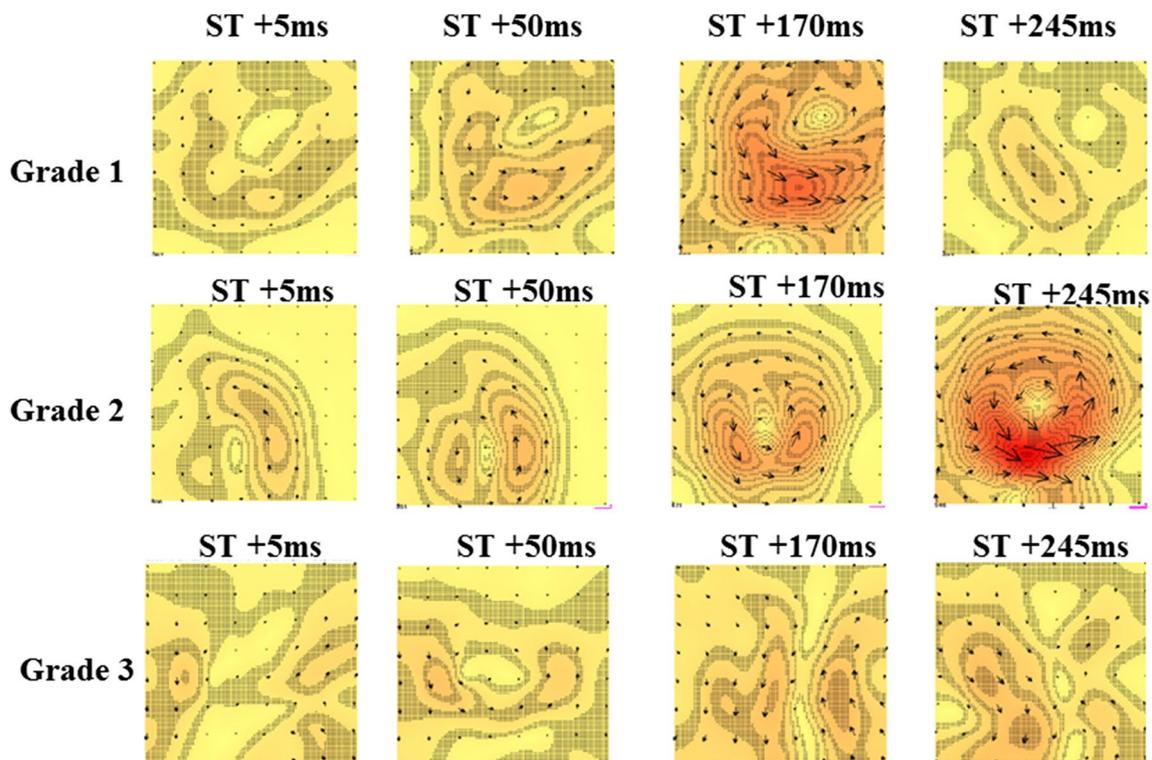
depolarization of whole left ventricular activation after breakthrough, and the third depolarization of the right ventricle



**Fig. 3** Repolarization for the ST-T process. The main current begin to flows toward the apex (lower-left direction) from the T process, and this pattern is almost similar to that during activation



**Fig. 4** Abnormalities of depolarization



**Fig. 5** Abnormalities of repolarization

0, with classes 1–3 indicating an increasing deviation from the normal direction, forming a dipolar pattern.

The incidence of abnormal depolarization and abnormal repolarization was retrospectively analyzed. The findings of MCG were classified into three groups: none; the appearance of repolarization; and the appearance of depolarization and repolarization. The incidences of abnormalities in MCG findings were compared between the SL group and the non-SL group on CAG using the Chi-square test. Next, the relationship between the number of coronary artery occlusions and the degree of abnormal repolarization was investigated using logistic analysis. Finally, the incidence of abnormal depolarization was compared among the three groups of respective coronary artery occlusions using the Chi-square test.

### Statistical analysis

Statistical analysis was performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA). A  $p < 0.05$  was considered significant.

### Results

In the patients with CALs caused by KD, abnormalities of depolarization and repolarization were seen on MCG (Table 1). Abnormal repolarization and abnormal

depolarization were detected in 21 patients and 8 patients, respectively. The incidence of abnormal repolarization was significantly higher than that of abnormal depolarization ( $p < 0.0001$ ). All eight patients with abnormal depolarization had abnormal repolarization  $\geq$  Grade 2 (Fig. 6). Further, all eight patients with abnormal depolarization had coronary artery occlusion or stenosis in the left anterior descending coronary artery. In four patients with non-sustained ventricular tachycardia, abnormal repolarization was detected in two patients, and abnormal depolarization and repolarization were detected in two patients.

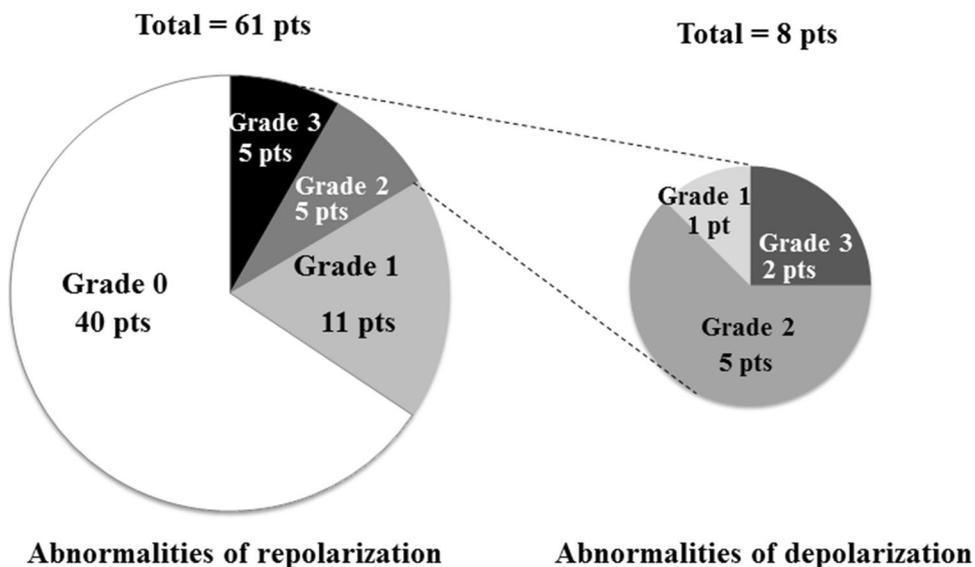
There were 42 patients in the SL group and 19 patients in the non-SL group. In the SL group, 11 patients had a previous MI, and 21 had at least one asymptomatic occlusion of a major coronary artery branch. Ten patients had at least one localized stenosis  $\geq 75\%$  in a major coronary branch. In the SL group, abnormal repolarization and abnormal depolarization and repolarization were detected in 12 patients (29%) and 8 patients (19%), respectively (Fig. 7 left). On the other hand, abnormal RE (Grade 1) was detected in three patients (16%) in the non-SL group. The distributions of abnormal MCG findings in the SL group and the non-SL group are shown in Fig. 7 (right). The incidence of MCG abnormalities was significantly higher in the SL group than in the non-SL group ( $p < 0.0001$ ).

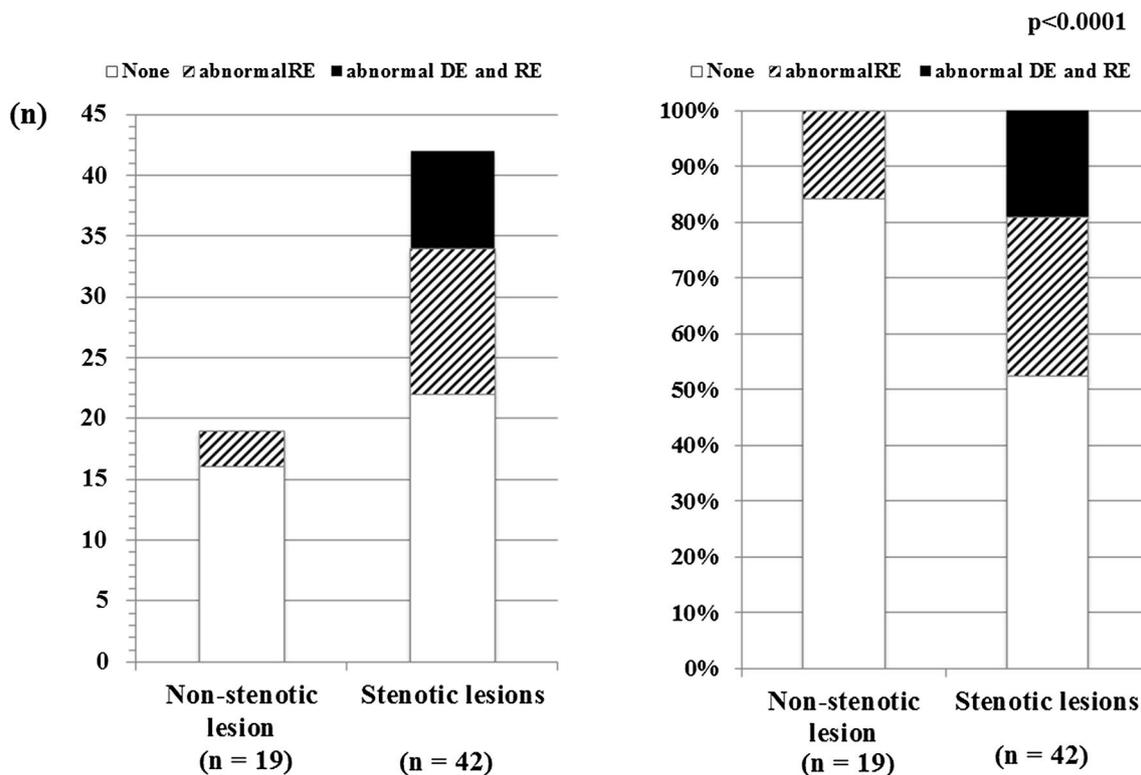
**Table 1** Abnormalities of magnetocardiogram in respective group

Group	Affected branches	n (pts)	Abnormalities of MCG					
			Depolarization			Repolarization		
			Grade			Grade		
			1	2	3	1	2	3
<i>Stenotic lesions</i>								
MI (n = 11)	RCA	6						1
	LAD	3	1	1	1	1		1
	RCA LAD	2		2		1		1
Asymptomatic OC (or SS) (n = 21)	RCA	14				5	1	
	LAD	3		1				1
	RCA LAD	4					1	1
LS ≥ 75% (n = 10)	RCA	2				1	1	
	LAD	4						
	LMT	1		1				1
	RCA LAD	1						1
	RCA LAD LCX	2			1		1	
<i>Non-stenotic lesions</i>								
AN (n = 18)	RCA	6					3	
LS < 75%	LAD	2						
	LCA	1						
	RCA LAD	3						
	RCA LCA	5						
	RCA LCA LAD	1						
Regression (n = 1)	RCA	1						
<b>Total</b>		<b>61</b>	<b>1</b>	<b>5</b>	<b>2</b>	<b>11</b>	<b>5</b>	<b>5</b>

MCG magnetocardiogram, MI previous myocardial infarction, OC coronary artery asymptomatic occlusion, SS segmental stenosis, LS localized stenosis, AN aneurysm, RCA right coronary artery, LAD left anterior descending artery, LMT left main truncus, LCX left circumflex, LCA bifurcation at the left coronary artery

**Fig. 6** Abnormalities of repolarization and depolarization detected by MCG (left). The grade and the number of abnormal repolarization (right). The grade and the number of abnormal depolarization





**Fig. 7** Magnetocardiogram abnormalities and stenotic lesions. *RE* repolarization, *DE* depolarization

The number of coronary artery occlusions was significantly related to the severity of abnormal repolarization ( $p=0.02$ ) (Table 1). Furthermore, six (75%) of the patients with abnormal depolarization had a previous anteroseptal MI. The incidence of abnormal depolarization was significantly higher in patients with occlusion of the left anterior descending artery than in patients with occlusion of the right coronary artery ( $p < 0.05$ ) (Fig. 8).

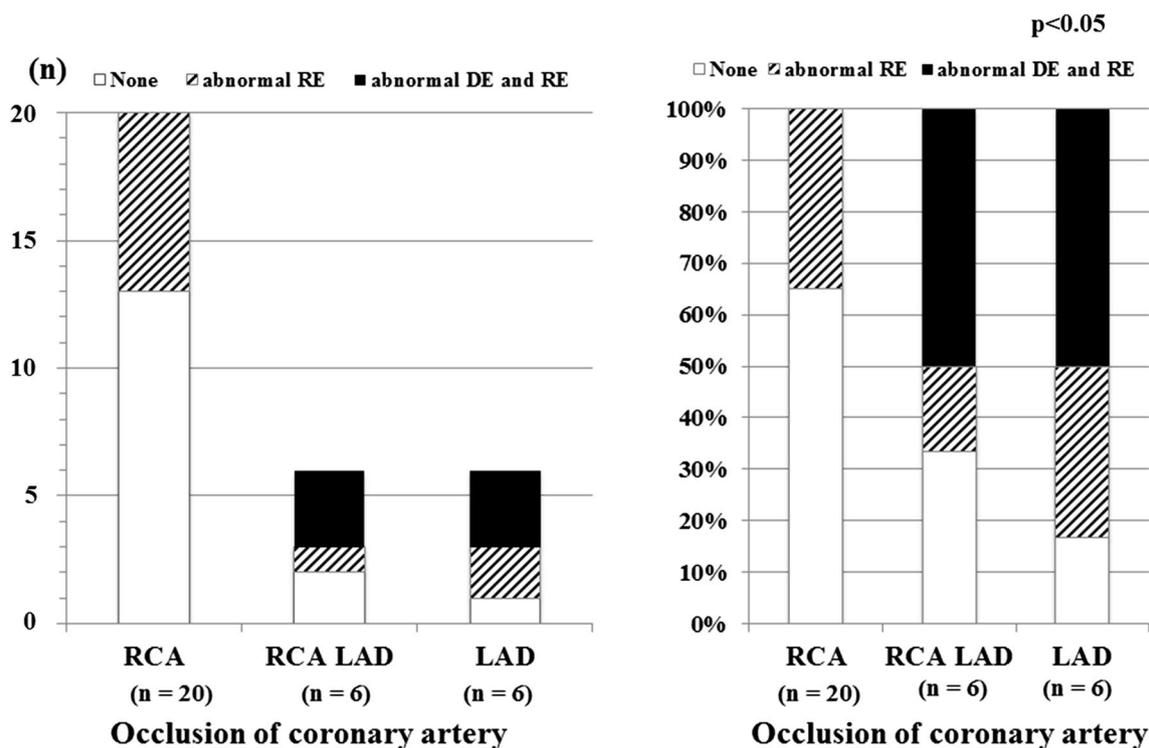
## Discussion

MCG abnormalities were found during the repolarization phase and the depolarization phase in patients with stenotic lesions caused by KD [8]. Repolarization abnormalities were more likely to appear than depolarization abnormalities in patients with ischemic heart disease. Repolarization abnormalities could be detected in patients with asymptomatic coronary occlusion. Asymptomatic coronary occlusion caused by KD is not necessarily rare in this population [9]. In our study by magnetic resonance, the depth of late gadolinium enhancement in most patients of asymptomatic coronary occlusion caused by KD was  $< 50\%$  in the myocardial wall [10]. It is suspected that repolarization abnormalities can occur even with non-severe myocardial involvement such as non-transmural infarction. Using the visualization

methods, it was easy to identify abnormal repolarization. The abnormalities of CAM could be classified into three patterns. In the normal myocardium, the current flow was almost uniform during repolarization. When there was an ischemic site, the current flow seemed to become random. Although why these abnormalities appear in ischemic heart disease is unclear, they are thought to be caused by the inhomogeneous repolarization currents [11].

Abnormal MCG findings are related to myocardial involvement [12, 13]. In the present study, MCG abnormalities were detected in most patients with a previous MI, especially anteroseptal infarction. Severe myocardial involvement due to symptomatic myocardial infarction is related to electrical myocardial abnormalities, especially depolarization abnormalities. Abnormal depolarization appeared in patients with abnormal repolarization of grade 2. Depolarization abnormalities were thought to appear in cases with severe myocardial involvement. Abnormal depolarization might appear in cases with transmural infarction rather than subendomyocardial infarction. To recognize MCG abnormalities, further studies comparing with other modalities are needed. Follow-up by MCG is useful, because it is possible to evaluate myocardial involvement which induces electrical abnormalities.

The findings of MCG abnormalities differed depending on the coronary artery branch occluded. Occlusion of the left



**Fig. 8** Relationship between coronary artery occlusion and magnetocardiogram abnormalities. *RCA* right coronary artery, *LAD* left anterior descending artery, *RE* repolarization, *DE* depolarization

anterior descending artery has a major effect on depolarization abnormalities. However, occlusion of the right coronary artery was not related to depolarization abnormalities. This difference might depend on the area affected due to occlusion of each coronary artery.

### Study limitations

The interval between the MCG examination and the CAG examination varied, because this was a retrospective study.

### Conclusion

The transmural myocardial infarction affects on abnormalities of depolarization, and the non-transmural myocardial infarction might relate on abnormalities of repolarization. The myocardial electrophysiological properties were preserved in patients except very severe coronary stenosis. MCG is possible to detect electrical myocardial abnormalities noninvasively in patients with CALs caused by KD.

**Funding** This study had no financial support.

### Compliance with ethical standards

**Conflict of interest** The authors state that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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