Animal magnetocardiography using superconducting quantum interference device gradiometers assisted with magnetic nanoparticle injection: A sensitive method for early detecting electromagnetic changes induced by hypercholesterolemia

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In this work, the authors used a superconducting quantum interference device (SQUID) magnetocardiography (MCG) system consisted of 64-channel low-transition-temperature SQUID gradiometers to detect the MCG signals of hypercholesterolemic rabbits. In addition, the MCG signals were recorded before and after the injection of magnetic nanoparticles into the rabbits' ear veins to investigate the effects of magnetic nanoparticles on the MCG signals. These MCG data were compared to those of normal rabbits to reveal the feasibility for early detection of the electromagnetic changes induced by hypercholesterolemia using MCG with the assistance of magnetic nanoparticle injection. © 2007 American Institute of Physics. [DOI: 10.1063/1.2433036]

Due to its ultrahigh sensitivity in magnetic flux, superconducting quantum interference devices (SQUIDs) are widely applied to detect small magnetic signals.^{1–3} One of the important applications is to detect the spatial and temporal biomagnetic signals of the heart, so-called magnetocardiography (MCG),^{4–7} which are generated by the electric activities of beating hearts. Several groups have reported the relationships between the MCG and the physiology of heart.^{4–6} Furthermore, the diagnostic models on animals having heart diseases using SQUID MCG systems have been established.⁷ These published papers show advantages such as high sensitivity, high accuracy, noncontact, noninvasive, and high convenience for diagnosing heart diseases using SQUID MCG data. Hence, the developments of SQUID MCG in aspects of technologies and clinical trials have been attracting lots of interests of engineers, scientists, and even medical doctors.

On the other hand, nanoparticles are very useful in achieving bioimage. For example, biofunctionalized semiconductor quantum dots are used as markers for imaging

specific organs, lymph nodes, and of other beings *in vivo*.^{8,9} Contrast to optical bioimages using semiconductor quantum dots, magnetic nanoparticles may contribute to magnetic-related biosignals via utilizing its magnetism. In addition, with the superparamagnetism, magnetic nanoparticles may be applied not only to static but also to dynamic magneto-bioimaging. These motivated us to investigate the effects of magnetic nanoparticles on the MCG signals, especially of the disease models. To do this, a low-transition-temperature (low- T_c) SQUID MCG system was used to detect the MCG signals of rabbits injected intravenously with magnetic nanoparticles. The MCG signals before and after nanoparticle injection were compared to clarify the effects of magnetic nanoparticles on the MCG signals. The MCG data from normal and hypercholesterolemic rabbits were compared to test the feasibility for early detection of the electromagnetic changes induced by hypercholesterolemia using MCG with the assistance of magnetic nanoparticle injection.

The SQUID MCG system consisted of 64 low- T_c SQUID gradiometers, which was developed by Korea Research Institute of Standards and Science. The MCG system was set up inside a magnetically shielded room (MSR). Inside the MSR, the SQUID gradiometers exhibit a noise level of about 50 fT/Hz^{1/2} at 1 Hz.

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FIG. 1. (Color online) (a) Picture to show the chest area, which is enveloped with suprasternal, right axillar, and left axillar, for MCG measurement. Typical MCG contour map for Q wave of a hypercholesterolemic rabbit (b) before and (c) after being injected with magnetic fluid.

Three normal and another three hypercholesterolemic rabbits were used for MCG studies. To make the rabbits hypercholesterolemic, we fed the rabbits with standard rabbit chow enriched with 0.5% cholesterol, 0.2% vitamins, 0.8% minerals, and 12.1% coconut oil for 3 weeks. Statistically, the serum concentrations of cholesterol were around 500 and 50 mg/dL for hypercholesterolemic and normal rabbits, respectively. For MCG measurement, each rabbit was anesthetized. The MCG measurement was performed just before the injection of magnetic nanoparticles. The following MCG measurement was done immediately after the injection. The following MCG measurements were conducted every 20 min. The other normal rabbit was used for magnetic resonance imaging (MRI) study before and after the injection of magnetic nanoparticles. Experiments on rabbits were performed in accordance with the regulations set by the National Taiwan University Animal Care and Use Committee and approved by National Taiwan University.

The injected magnetic nanoparticles are dextran-coated Fe_3O_4 nanoparticles (GABC Co.), which are homogeneously dispersed in water. The mean diameter of the nanoparticles is 52 nm. The saturated magnetization of the magnetic fluid

FIG. 2. Temporal variations in the normalized peak-to-peak magnetic signal, $\Delta B/\Delta B_0$, in the MCG contour map for (a) P , (b) Q , (c) R , (d) S , and (e) T waves of normal rabbits injected with magnetic fluid (dashed lines) and pure dextran solution (solid lines).

containing magnetic nanoparticles is 0.3 emu/g. The volume of magnetic fluid injected into each rabbit was 2 ml. The magnetic fluid was injected into the rabbits' ear vein. Hemodynamically, the injected magnetic fluid flow from the right to the left heart, and then perfused the myocardium through the coronary arteries. It was observed that the magnetic fluid flow into the heart in a short period of time after injection, as evidenced by the MRI study (not shown here).

The MCG signals within the chest area of a hypercholesterolemic rabbit were detected, as shown in Fig. 1(a). The typical averaged MCG contour map within the detected area for a certain instant, say, Q wave, is plotted in Fig. 1(b). The maximum intensity $B_{\max}$ was observed at the lower-right part, and the minimum intensity $B_{\min}$ occurred at the upper-left part. After the injection of magnetic fluid, the MCG contour map of Q wave is probed, as shown in Fig. 1(c). It was found that the $B_{\max}$ became higher than that before the injection. To quantitatively describe the variation in the intensities of MCG contour maps due to the injection of magnetic fluid, the peak-to-peak magnetic signal ΔB , defined as $B_{\max} - B_{\min}$, was analyzed as a function of time after the injection of magnetic fluid into rabbits. To eliminate the individual difference among rabbits, the ΔB was normalized to ΔB_0 , which corresponds to $B_{\max} - B_{\min}$ just before the injection of magnetic fluid. Since the magnetic nanoparticles Fe_3O_4 are coated with dextran, the effect on ΔB may be attributed to the Fe_3O_4 magnetic nanoparticles or dextran. To clarify this point, the time-dependent $\Delta B/\Delta B_0$ for the rabbits injected with pure dextran solution was also investigated. The time-dependent normalized values, $\Delta B/\Delta B_0$, for P , Q , R , S , and T

FIG. 3. Temporal variations in the normalized peak-to-peak magnetic signal, $\Delta B/\Delta B_0$, in the MCG contour map for (a) *P*, (b) *Q*, (c) *R*, (d) *S*, and (e) *T* waves of hypercholesterolemic rabbits injected with magnetic fluid (dashed lines) and pure dextran solution (solid lines).

waves for normal and hypercholesterolemic rabbits are plotted in Figs. 2 and 3, respectively. The data at time being zero correspond to $\Delta B/\Delta B_0$'s before the injection of magnetic fluid. The squares and solid lines represent for the data after dextran injection, and the circles and dashed lines for those after magnetic fluid injection, respectively.

In order to identify any effect on ΔB of the *P*, *Q*, *R*, and *S* waves, the MCG contour map of normal rabbits injected with magnetic fluid or pure dextran solution were measured. Furthermore, the $\Delta B/\Delta B_0$ as a function of time was analyzed and is shown in Fig. 2. It is obvious that both dashed lines and solid lines in Figs. 2(a)–2(d) for *P*, *Q*, *R*, and *S* waves overlap and are kept at a constant value of 1. This means that both magnetic fluid and pure dextran solution hardly affect the cardiac electromagnetic activities during *P* to *S* wave. However, the data shown in Fig. 2(c) reveal that the ΔB in the MCG contour map for *T* wave was depressed when normal rabbits were injected with magnetic fluid. The suppressed ΔB was probable due to most of the magnetic nanoparticles flowing downstream through the coronary arteries during the cardiac diastolic phase, which was compatible with *T* wave on MCG tracings.

In contrast, it could be observed in Fig. 3 that, except that of *T* wave, the time-dependent $\Delta B/\Delta B_0$ curves for *P*, *Q*,

R, and *S* waves exhibited a similar behavior. The $\Delta B/\Delta B_0$'s became higher than 1 after the injection of magnetic fluid. This result implies that the difference between $B_{\max}$ and $B_{\min}$ in the MCG contour map was enhanced for hypercholesterolemic rabbits after the injection of magnetic fluids. The results are shown with solid lines in Figs. 3(a)–3(e) for *P*, *Q*, *R*, *S*, and *T* waves, respectively. Remarkably, the $\Delta B/\Delta B_0$ almost remains at 1 for the solid lines in Figs. 3(a)–3(e). This reveals that the enhancement in ΔB in the MCG contour map for *P*, *Q*, *R*, and *S* waves of hypercholesterolemic rabbits was caused only by the Fe_3O_4 magnetic nanoparticles. Although the detailed mechanism responsible for the enhancement in ΔB of MCG contour map is not clear, it is strongly suggested that the Fe_3O_4 magnetic nanoparticles leaking from the coronary arteries into myocardium through tiny clefts of the coronary arteries of hypercholesterolemic rabbits may be the most possible candidate. Thus, the electromagnetic signals generated by the action potential of myocardium are modified with the surrounding magnetic nanoparticles.

Through comparing the magnetic-fluid induced variations in ΔB of MCG contour maps in Figs. 2 and 3, a significantly different behavior between normal and hypercholesterolemic rabbits was obtained. It is worthy to note that the conventional diagnosis such as electrocardiography cannot distinguish the difference between normal and hypercholesterolemic rabbits until having been hypercholesterolemic for 6 weeks.¹⁰ However, according to the results shown in Figs. 2 and 3, an abnormal magnetic-fluid induced ΔB of MCG contour map could be observed in rabbits having hypercholesterolemia only for 3 weeks. Therefore, the measurement of magnetic-fluid induced ΔB in MCG is promising for the early-stage diagnosis for hypercholesterolemic rabbits.

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