Introduction to Magnetocardiography (MCG)

A breakthrough in cardiology:

"<u>detect heart-attacks safely and quickly before they happen</u>"

Magnetocardiography (MCG) Diagnostic Equipment

The detection of biomagnetic signals generated from the heart (Magnetocardiography, MCG) is an advanced diagnostic technology for early diagnosis of numerous heart diseases.

- The MCG System is capable of carrying out a non-invasive, safe, quick and harmless diagnostic test for the early detection of heart diseases, in particular coronary artery disease (CAD).
- The CS MAG II MCG System is the most advanced MCG system worldwide and is developed, refined and maintained by German engineers.
- The MCG System includes a 64-channel sensor array, a liquid helium dewar, a gantry and bed, as well as electronics inside the shielded room, and analog signal processing outside the shielded room. Furthermore it has a power supply, data acquisition boards and a computer for measuring and analyzing MCG data. An additional unique part of the CS MAG II system is the non-magnetic ergometer, which enables a physical stress MCG investigation.

- 3 MCG Systems are currently installed in 2 hospitals in Germany and 1 clinic in Hong Kong. So far tests have been done for the detection of CAD on over 5,000 patients. No adverse event has been reported.
- The test requires only 10-15 minutes with an accuracy of over 90%[i] compared to other screening examinations. It is harmless, since it does not require any insertion of catheters and is free from radiation or contrast agents. Thus it is suitable for patients requiring frequent monitoring of the functionality of the heart after treatment. Another breakthrough is that the MCG enables the accurate diagnosis of patients who have received stenting, for whom the CTA's diagnostic accuracy is limited.
- The MCG Systems reliably and accurately detect coronary artery diseases at an early stage, at which the patient is normally either asymptomatic or has mild or atypical symptoms.
- For those patients the MCG System is the best choice to frequently monitor their heart's functionality to reduce a disease recurrence.

Technology Highlights for Stress MCG

Stress Magnetocardiography Technique

- Stress magnetocardiography (Stress MCG[i]) is a non-invasive technique to detect and display the local magnetic field signals generated by the electrical activity of the heart during exercise.
- Stress MCG is a safe, quick and harmless test, which is very useful for the early detection of heart diseases, in particular coronary artery disease.
- In order to detect these very weak cardiac magnetic signals, the subject will need to perform cycling exercises in a shielding room, where the subtle changes of cardiac magnetic activities during exercise will be measured by very sensitive magnetic sensors, commonly known as the SQUID (Superconducting QUantum Interference Device) sensors.

Proven Proprietary Technology – *F A S T*

- The CS MAG II (or MCG System) is US FDA (510k) and EU CE approved and registered.
- Clinical papers[i] have shown the MCG System as a useful, non-invasive strategy for the diagnosis and assessment of ischemia in patients with suspected CAD or after a percutaneous coronary intervention (PCI).
- ***Fast****:* It takes only 10-15 minutes to carry out a test.
- ***Accurate****:* It has comparable accuracy (>90%[i]) to other screening tests like Computed Tomography Coronary Angiogram (CTA).
- ***Safe****:* Does not require insertion of catheters and is free from radiation or contrast agents.
- ***Tolerable****:* Useful for patients that require frequent monitoring of their heart's condition after treatment.



Multiple Uses of the MCG System

- Screening for CAD in patients with risk factors (e.g. DM, HT), but without symptoms[i].
- Diagnosis of CAD patients with symptoms (e.g. chest pain), especially for emergency cases[ii].
- To guide treatment decisions for patients with equivocal CT findings (e.g. if the CTA showed 50% narrowing in one vessel, the patient would need stenting in the case that the MCG System showed the presence of functional ischemia.)[iii].
- Magneto-electro-cardiography in the case of arrhythmia[iv]: non-invasive recording (mapping) of atrial fibrillation, ventricular mapping, mapping of accessory pathways.
- Monitoring of the recurrence of a disease after revascularization treatment (e.g. post-stenting or post CABG open heart surgery)[v].
- Risk stratification for sudden cardiac death: analysis of the fragmentation of the QRS complex at rest and during exercise; micro-re-entry recognition[vi].
- Fetal magnetocardiography[vii].
- Surveillance of patients with congestive heart failure[viii].
- Sports medicine (quantification of myocardial functional reserve)[ix].

MCG is the most convenient technology for the patient

- **high diagnostic accuracy**[i] (higher than that of ECG, Echo, SPECT)
- **fast** (resting MCG 1 min, exercise MCG 12 min)
- **no radiation** (as CT, SPECT, PET, or coronary angiography)
- **no contrast agents** (as CT, coronary angiography or MRI)
- **no radioactive substances** (as SPECT, PET)
- **no vessel puncture** (venous or arterial as SPECT, CT, MRI, coronary angiography)
- **no pain** (potentially in SPECT, CT, MRI, PET, coronary angiography)
- **no drug application** (as MRI, SPECT, coronary angiography)
- **no claustrophobia** (potentially in CT and MRI)
- **no noise** (as MRI)

MCG is the ideal first-line diagnosis for the patient

	diagnostic accuracy[i,v]	*spacial resolution*	*time resolution*	*investigation speed*
MCG	+ + +	+ +	+ + +	+ + +
ECG	+	*(+)*	+ + +	+ + +
Echo	+ +	+ +	+ +	+ +
SPECT	+ +	+	-	-
CT	+ +	+ + +	+	++
MRI	+ + +	+ +	+	-
PET	+ + +	+ +	-	-

Clinical Applications and Publications

i

High accuracy (>90%) of MCG in the diagnosis of chronic CAD:

A significant number of publications are available regarding the MCG diagnosis of CAD in medical literature (selected examples at the bottom). However, the limitation of these studies is the lack of MCG information during stress-induced myocardial ischemia. From 2010 to 2013 BMP invented, patented, and developed a non-magnetic bicycle, which allows a physical stress protocol with a stepwise increment of workload and a 12-lead ECG recording simultaneously with the 64-channel MCG. The integration of the non-magnetic bicycle and the 12-lead ECG into the BMP 64-channel MCG system represents the robust CS MAG II MCG system from BMP for routine clinical use. If the patient is unable to ride the bicycle, a pharmacological stress protocol using dobutamine/atropine is performed.

Our clinical evidence of the CS MAG II as a robust non-invasive diagnostic tool is based on the investigations of approx. 5,000 stable patients from 2 German and 1 Hong Kong centers undergoing stress MCG test for CAD diagnosis. So far we have performed and published 3 prospective, clinical studies on 243 patients:

Study A:
Dobutamine stress MCG vs coronary angiography, 100 patients, sensitivity 98%, specificity 82%.

Study B:
Exercise stress MCG vs invasive FFR, 47 patients, sensitivity 91%, specificity 92%.

Study C:
Exercise stress MCG vs coronary angiography, 96 patients, sensitivity 85%, specificity 88%. Combination of 2 MCG parameters improved C-statistics, indicating the enhancement of diagnostic performance in the detection of significant CAD (0.790 to 0.930; $p < 0.001$).

Study A: Park J-W, Leithäuser B, Vrsansky M, and Jung F. Dobutamine stress magnetocardiography for the detection of significant coronary artery stenoses – A prospective study in comparison with simultaneous 12-lead electrocardiography. Clinical Hemorheology and Microcirculation 2008;39(1-4):21-32.

Study B: Park J-W, Shin E-S, Ann SH, Gödde M, Park LS-I, Brachmann J, Vidal-Lopez S, Wierzbinski J, Lam Y-Y, and Jung F. Validation of Magnetocardiography versus Fractional Flow Reserve for Detection of Coronary Artery Disease. Clin Hemorheol Microcirc. 2015;59:267-281.

Study C: Shin E-S, Lam Y-Y, Her A-Y, Brachmann J, Jung F, Park J-W. Incremental diagnostic value of combined quantitative and qualitative parameters of magnetocardiography to detect coronary artery disease. Int J Cardiol 2017; 228:948-952.

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ii

1-minute resting MCG detects Acute Coronary Syndromes (ACS) with a high accuracy (>90%) and predicts patient´s prognosis:

Only a small number of publications are available in regards to the MCG diagnosis of a ACS in the emergency department (literature at the bottom). The scientific group of the Yonsei University in Seoul studied prospectively more than 300 patients with unstable angina applying a resting MCG protocol[5-8]. A recent publication of the same group (124 patients with acute myocardial infarction) revealed that the MCG predicted a long-term prognosis in patients with acute myocardial infarction[9-10].

Our clinical evidence of the MCG value for the emergency department is based on 2 prospective studies (402 patients) of patients presenting with acute chest pain without a ST segment elevation in the ECG[1,2]. A resting MCG at hospital admission predicted ACS as the cause of chest pain with a sensitivity of 95% and a specificity of 93% (sensitivity of 12-lead ECG, Troponin I, and Echo were 34%, 43%, and 51%, respectively). The 3-year mortality of patients with a pathological resting MCG at hospital admission was significantly higher than the mortality of patients with a normal resting MCG (17.3% vs 3.77%, relative risk 4.58 (95% CI 1.68 – 12.42)). Our studies confirm the findings of the Yonsei University group that the resting MCG at hospital admission predicts a long-term prognosis of patients presenting with ACS. The MCG is valuable for identifying high-risk chest pain patients.

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iii

CS MAG II in comparison with other tools

Limitations of various tests as *first-line* investigative tool for chronic coronary artery disease

Test	Sensitivity	Specificity	Expertise dependency	Specific limitations
Exercise ECG (First-line Test)	45-50%	85-90%	+	Lower accuracy
Stress-Echo	79-85%	80-88%	+++	Echo-window dependent Operator dependent
CT coronary artery	85-99%	64-83%	+++	HR dependent, radiation, calcified lesions, multiple stents
Cardiac MR	87-91%	80-83%	++++	Claustrophobia
SPECT (Nuclear)	87-89%	73-75%	++++	radiation
Exercise MCG	**90.5%**	**92.3%**	**+**	**No side effects**

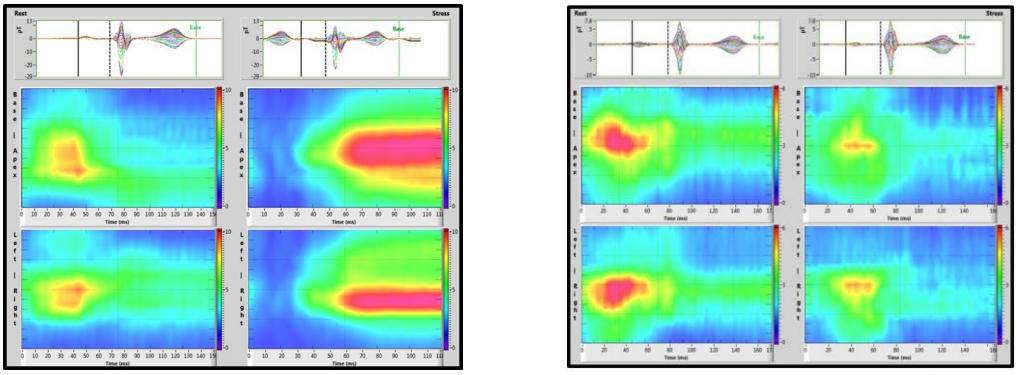
Engel LC et al. Kardiologie up2date 2015;11:177-187 (modified).
Park J-W et al. Clin Hemorheol Microcirc 2015;59:267-281.
Shin E-S et al. Int J Cardiol 2017;228:948-952.

iv

Role of the CS MAG II in electrophysiology[1-21]

The CS MAG II application in the field of electrophysiology shows huge potential, because electro-anatomical mapping can be performed non-invasively and also during exercise. Our current main priorities are:

- Electro-magnetic mapping of the atria in patients with paroxysmal atrial fibrillation at rest and during exercise
- Detection of left atrial fibrosis
- Non-invasive mapping of WPW syndromes
- Ventricular mapping (scar, aneurysm, stem cell therapy control, etc.)
- Pre-operative identification of non-responder scheduled for CRT therapy



Spatio-Temporal Activation Graph (STAG).

Left: In the left atrial posterior wall of this healthy volunteer a strong, homogenous increase of the pseudo-current is measured during exercise (STAG value: +3)

Right: In the left atrial posterior wall of this AFib patient with a twice failed PVI, the pseudo-current decreases during exercise (STAG value: -1) (Unpublished data)

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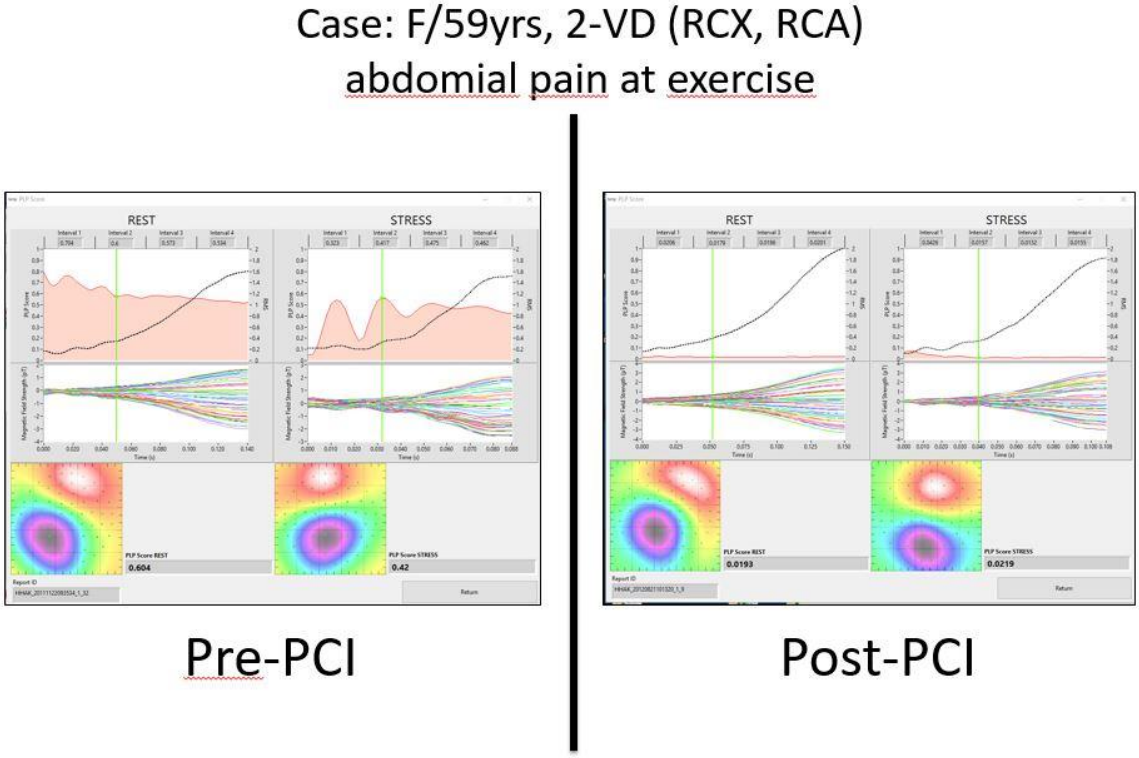
v

Monitoring of the recurrence of disease after revascularization (surveillance post-stenting or post CABG).

On-going exercise MCG study in 50 patients pre- and post-stenting.

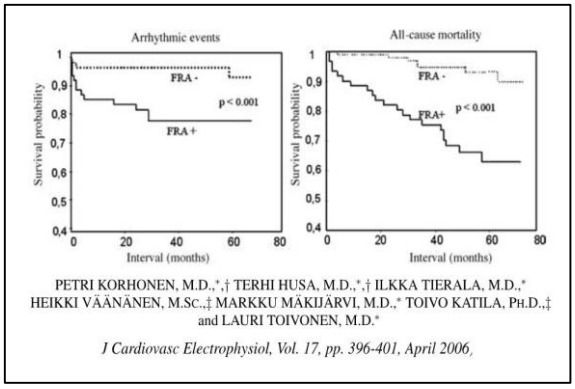


The so-called PLP2-curve (Tbeg-Tmax, 0 = dipole, 1 = monopole) shows a significant imbalance of the dipole (left) pre-PCI indicating electro-magnetic vulnerability at rest and myocardial ischemia during exercise. In the control exercise MCG eight months post PCI a balanced dipole at rest and exercise presents itself(right)

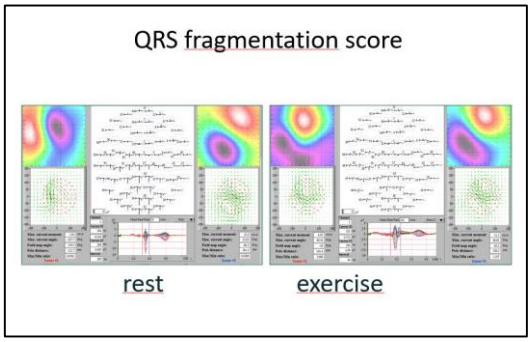
vi

Risk assessment sudden cardiac death (SCD) and ventricular arrhythmia by CS MAG II

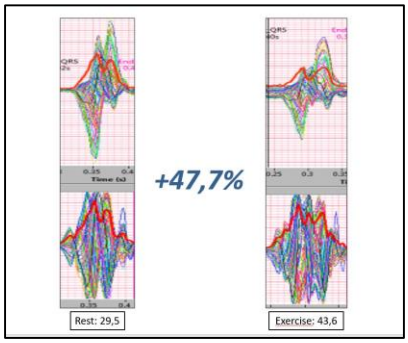
The MCG derived intraQRS-fragmentation-score correlates with the risk of SCD and ventricular arrhythmia.



The CS MAG II can additionally measure the IntraQRS-fragmentation-score during exercise and unmask the underlying conduction disturbance.



Unpublished data



Unpublished data

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vii

Fetal MCG with CS MAG II

Fetal MCG is the MCG application with the best acceptance by medical associations[1-17]. Fetal MCG is already introduced in the recommendations of the AHA guidelines[1].

Advanced Techniques

13. Advanced techniques that currently are research tools but are reasonable to use in clinical practice for specific indications include cardiac MRI (for assessment of heterotaxy, venous anatomy, and extracardiac anomalies), tissue Doppler (for time interval and rhythm assessment), fetal electrocardiography (for fetal monitoring after rupture of membranes), and fMCG (for assessment of cardiac conduction and rhythm in fetuses with known or suspected conduction system abnormalities) (*Class IIa; Level of Evidence B/C*).

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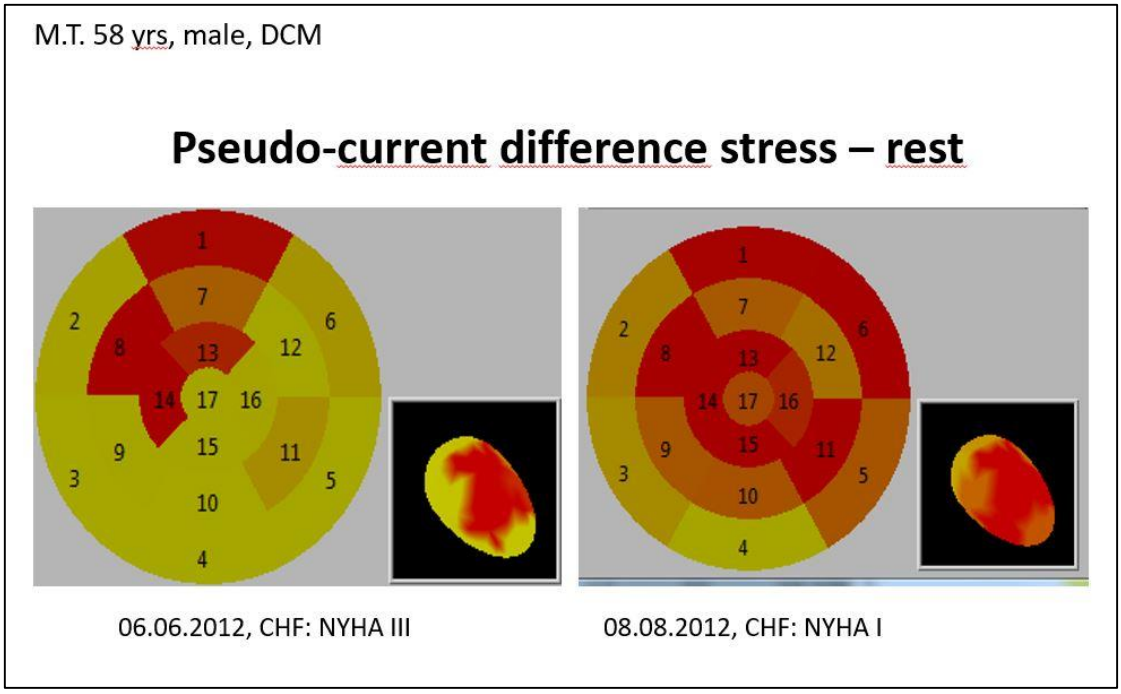
viii

Surveillance of patients with congestive heart failure with the CS MAG II

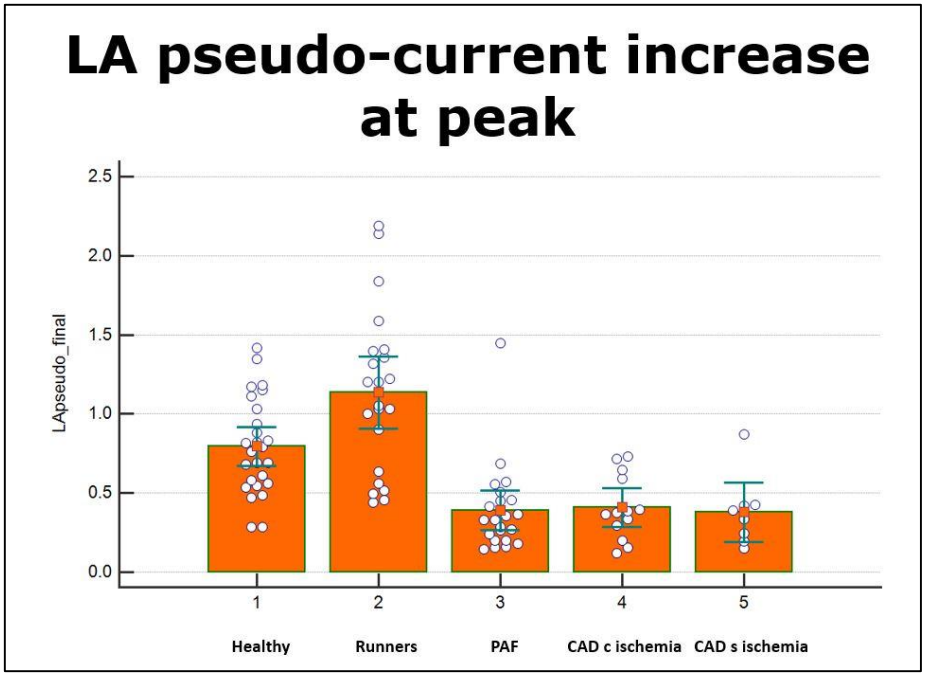


Exercise induced global pseudo-current increase before (left) and after (right) heart failure treatment in a patient with severe dilated cardiomyopathy (unpublished data)

ix

CS MAG II in sports medicine

Because of the correlation between the exercise induced left ventricular contractility and the pseudo-current increase, the CS MAG II parameters may become objective assessment tools for the cardiac function of athletes (quantification of myocardial functional reserve).



Amateur runners developed a significantly higher pseudo-current increase during exercise than healthy volunteers, patients with paroxysmal atrial fibrillation, CAD patients with or without ischemia. (unpublished data)