Magnetocardiographic Imaging of Ventricular Repolarization in Rett Syndrome[1]

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Abstract. Rett syndrome (RS) is a severe neurological disorder, predominant in females, with higher risk of sudden death (SD). So far for risk-assessment, heart rate variability (HRV), QT duration and its dispersion (QTd) were measured with ECG. However SD has occurred in RS also in absence of ECG abnormality. We aimed to evaluate the feasibility of magnetocardiographic (MCG) mapping as an alternative to study ventricular repolarization (VR) alteration in RS patients. 9 female (age: 1-34 years) RS patients were studied with an unshielded 36-channels MCG system. To assess VR, heart rate (HR)-corrected $JT_{peak,}$ JT_{end}, $QT_{end,}$ $T_{peak-end}$ intervals and QTd, were measured from both MCG and ECG signals. Moreover the magnetic field (MF) gradient orientation (α-angle) during the ST segment and three MF dynamic parameters were automatically evaluated from MCG T-wave. HRV parameters were evaluated from 12-lead Holter ECG. 15 age-matched normal controls (NC) were studied for comparison. HR-corrected JT_{peak}, JT_{end}, QT_{end} and $T_{peak-end}$ intervals, and QTd were longer in RS than in NC. The differences were more evident with clinical impairment (stage IV). MF gradient orientation and MF dynamic parameters were abnormal in RS patients. As compared to NC, HRV parameters were altered in the time-domain, although still within normal range in the frequency-domain. In RS, ECG recordings are often noisy and BSPM is difficult. On the contrary MCG mapping is easily feasible and discovers VR alteration not evident at the ECG. The diagnostic value of MCG in RS remains to be defined.

1 Introduction

Rett syndrome (RS) is a severe progressive neurodevelopment disorder, occurring almost exclusively in females, characterized by cortical atrophy, psychomotor regression, mental retardation, irregular breathing, hyperventilation[1-2] caused by dominant mutation of the MeCP2 gene, encoding the transcriptional repressor methyl-CpG-binding protein 2, related to Xq28 locus[3]. *RS Diagnostic Criteria World Group*[4-5]

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differentiates four stages of clinical evolution (*Stage I-IV*), which are characterized by progressive deterioration of neural, respiratory and cardiac functions. Life expectancy of RS patients is uncertain. The survival rate drops to 70% by age thirty-five, and for the profoundly mentally retarded, it drops to 27%, due to autonomic nervous system (ANS) abnormality with associated cardiac, gastrointestinal and breathing problems[6]. In RS incidence of sudden death (SD) is greater than that in the general population[7-8], likely due to cardiac electrical instability, associated with ANS activity abnormality[9] and with reduced level of nerve growth factor (NGF) leading to a decline in number of choline acetyltransferase (ChAT)-positive cells that are necessary for the production of acetylcholine[10-11]. So far, HR-corrected QT interval duration (QTc), its dispersion (QTd) measured from 12-lead ECG and heart rate variability (HRV) parameters have been used as markers of electrical instability in RS[12-15]. However SD has been reported in RS pts also in the absence of ventricular repolarization (VR) alterations at the ECG[16]. Furthermore, being the RS pts restless, movement artifacts often disturb the ECG recordings and impair precise measurements of ECG parameters. For the same reason body surface electric mapping has never been attempted so far in RS. Alternatively to ECG, contactless magnetocardiography, which provides accurate multisite mapping of cardiac electrical activity without movement artifacts[17], can be used. Previous studies suggest that magnetocardiographic (MCG) recordings might contain information additional to 12-lead ECG[18-19]. Moreover it has been shown that MCG mapping is useful for precise quantitative evaluation of VR abnormalities and to identify markers of arrhythmogenic risk[20-21]. The aim of this study was limited to evaluate the feasibility of multichannel MCG mapping in RS pts, and its reliability to detect VR abnormalities, associated or not to alteration of HRV parameters, in the absence of significant ECG alterations.

2 Methods

2.1 Patients

9 female RS pts, aged 1 to 34 years, clinically classified in stage II (2), in stage III (4), and in stage IV (3)[4] were investigated, after parental written informed. consent. 15 age-matched normal controls (NC) were studied for comparison.

2.2 Study Protocol

The cardiac magnetic field (MF) component perpendicular to the sensor array surface was mapped in the supine position, from a 6 x 6 grid covering an area of 20 x 20 cm (Figure 1), with a 36-channel system, featuring DC-SQUID sensors, coupled to second-order axial gradiometers, with pick-up coil diameter of 19 mm, baselines of 50-70 mm, and intrinsic sensitivity of 20 fT / √Hz, in the frequency range of interest for clinical MCG signals (DC to 100 Hz)[22] (*CardioMag Imaging Inc*. Schenectady, NY) (Figure 1 A).

MCG signals (low-pass filtered at 100 Hz) were digitally recorded at 1 kHz (with 24 bits resolution). The relative position of the patient in respect of the sensors was defined with three laser pointers. Each MCG mapping lasted typically 90 seconds and was repeated twice to test for reproducibility. 12-lead ECG was simultaneously

recorded (bandwidth: 0.05-100 Hz), with amagnetic electrodes. HRV parameters were calculated, in the time (TD) and frequency (FD) domains, according to standard protocols[23], from 12-lead ECG Holter *(H-scribe Digital Holter, Mortara Instruments, Inc.).*

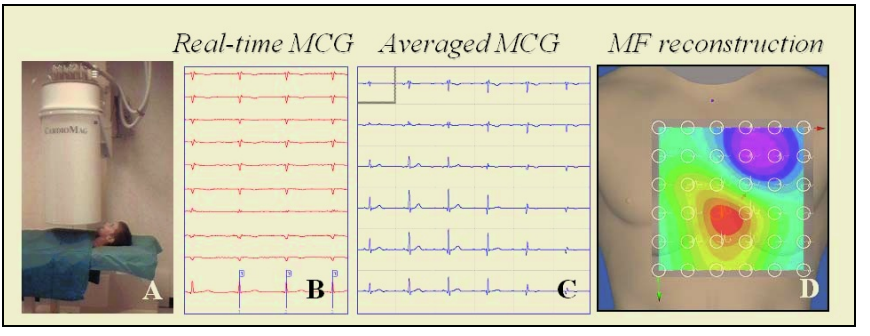

Fig. 1. Typical positioning of the patient under the MCG mapping system (A). Real–time MCG signals with one reference ECG (B). MCG averaged waveforms (C). Magnetic field reconstruction (D)

2.3 MCG Signal Processing and Analysis

MCG signals were automatically processed and analyzed with a ***Windows-based*** software (*CardioMag Image Inc)* and with the ***UNIX-based*** software developed by the Helsinki University of Technology (*NEUROMAG)*, as described elsewhere[20,24-26]. Briefly, MCG signals were adaptively filtered (Figure 1 B) and averaged (Figure 1 C) to eliminate the 50 Hz noise and improve the Signal/Noise ratio. After automatic (and/or interactive) baseline selection, MCG signals were analyzed as waveforms in the time domain and used to construct isofield contour maps by automatic interpolation, with a time resolution of 1 millisecond (msec). Contour maps were also constructed after time integration of specific intervals of interest (Figure 1 D). The software provides automatic measurements of ventricular time intervals. However, the Q wave onset, the J point, the T_{peak} and the T_{end} were also interactively edited, using a "butterfly" superposition of all MCG signals amplified at the resolution of 10 mm/pT (picoTesla) with a time scale of 200 mm/sec (Figure 2 A) and morphological analysis of the time evolution of the MF maps (Figure 2 B) to improve the timing accuracy.

2.4 Ventricular Repolarization Parameters

To assess VR, the following quantitative MCG parameters were evaluated:

1. The $\mathbf{JT_{peak}}$, $\mathbf{JT_{end}}$, $\mathbf{QT_{end}}$, **and** $\mathbf{T_{peak\text{-}end}}$ intervals (Figure 2 A), all corrected for the heart rate (HR), and the $\mathbf{QT_{dispersion}}$, measured automatically from MCG and manually from ECG signals. In order to correct to HR, the values were divided by the square root of the averaged R-R interval measured in seconds [corrected value = measured value (ms) / √ RR (sec)].

2. The **MF gradient (MFG) orientation,** measured at the integral of the second quarter from the J-point to the T_{peak} and at the T_{peak}, as the angles (**α**) between the direction of the largest MF gradient (vector between the maximum positive and negative magnetic poles) and the patient's right-left axis[26] (Figure 3).
3. The **dynamics of MF distribution**, in any floating time windows of 30 ms during the T-wave (starting when the MF strength is equal to 1/3 of that at the T_{peak}, arbitrarily defined T_{onset}, until the T_{peak}), quantified as: a) changes of the angle between + pole and - pole (abnormal if > 45 degrees); b) changes of the distance between + pole and - pole (abnormal if > 20 mm); c) changes of the ratio between the strength of + pole and - pole (abnormal if > 0.3)[25] (Figure 4).

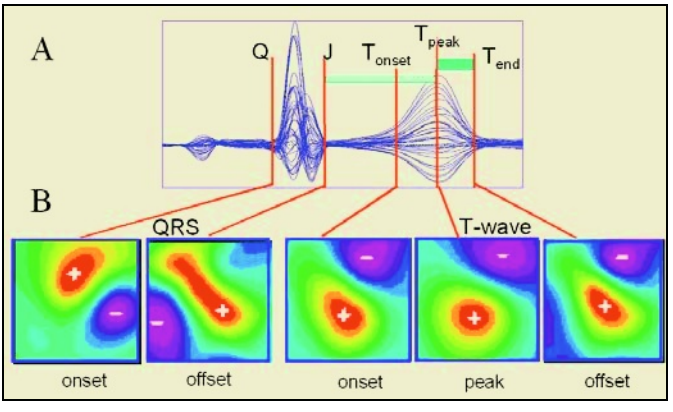

Fig. 2. "Butterfly" superposition of the 36 MCG averaged waveforms (A). Typical MF distribution at the onset and offset of the QRS, and at the onset, peak and offset of the T-wave (B)

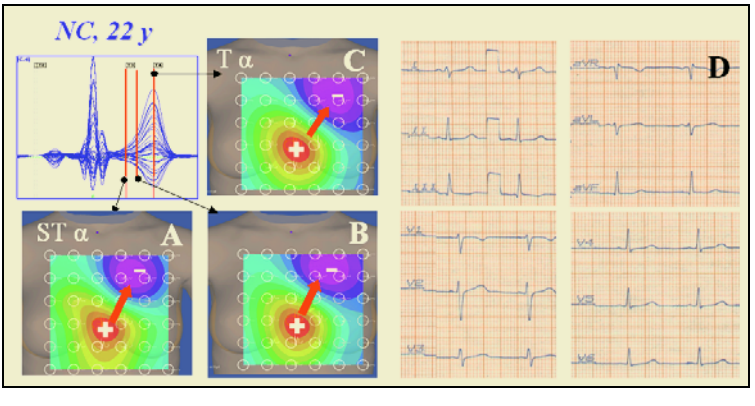

Fig. 3. Normal control (22 years old female). Examples of typical stability of the MF distribution and of the MF gradient orientation (angle α), measured at the second quarter of the ST (A), at the T-wave onset (B) and at the T-wave peak (C). In (D), 12-lead ECG

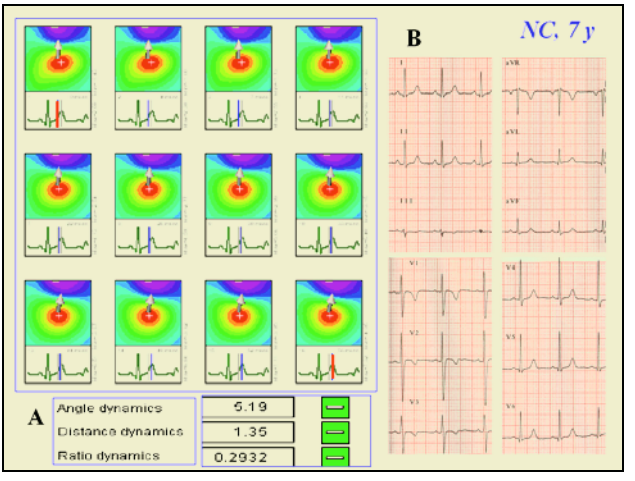

Fig. 4. Normal control (7 years old female). Example of automatic score analysis based on the MF dynamics during the T_{onset} -T_{peak} interval (A). In spite of the "juvenile" repolarization pattern at the 12-lead ECG (negative T-wave in V2 and V3) (B), all T-wave MF dynamic parameters are within normal range. The automatic classification is negative (green flags)

2.5 HRV Parameters

The following standardized parameters[23] were calculated:
pNN 50%: NN50 count divided by the total number of all NN intervals; **SDNN** (msec): Standard deviation of all NN intervals; **SDANN** (msec) Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording; **r-MSSD** (msec): the square root of the mean of the sum of the squares of differences between adjacent NN intervals; **LF/HF ratio**: Low Frequency/High Frequency Ratio: LF [$msec^2$]/HF [$msec^2$].

2.6 Statistical Methods

Data are reported as mean ± S.D. Statistical analysis was performed with the unpaired two-tails Student t-test. A value of $p < .05$ was considered significant.

3 Results

3.1 Ventricular Repolarization

Average values of HR-corrected JT_{peak}, JT_{end}, QT_{end} and $T_{peak-end}$ intervals and of QTd are summarized in Table 1.

In general, all MCG intervals were shorter (p = n.s.) than corresponding ECG ones. In spite of the limited number of cases, significant differences were found between RS pts and NC for all parameters except JT_{peak}. However, only MCG evidenced significantly longer values of $T_{peak-end}$ and of QTd.

Table 1. MCG and ECG intervals in Rett syndrome patients and in NC. Data are presented as mean ± SD

	MCG			ECG		
HR-corrected	**Rett**	**Normals**	***P***	**Rett**	**Normals**	***P***
JT_{peak}	240.4±26.8	223.9±18.0	n.s.	248 ± 48.8	215.7 ± 26	0.05
JT_{end}	312.3±29.9	281.1±11.8	< 0.01	342.2 ± 43	307.9 ± 21	<0.02
QT_{end}	402.7±29.8	378.05 ± 15	< 0.02	428 ± 42.7	388.7 ± 21	<0.01
$T_{peak-end}$	71.8± 23.6	57.02 ± 10	< 0.05	94.2 ± 23.6	92.2 ± 20.9	n.s.
QT_d	18.6 ± 9.3	7.28 ± 1.46	< 0.001	33.8 ± 14.1	33.1 ± 17.3	n.s.

Table 2. MF orientation (α angle) and MF dynamics in RS patients and in NC. Data are presented as mean ± SD

	Rett	**Normals**	***P* value**
ST α angle *(degrees)*	135.6±79	55.9±23.3	< 0.01
T α angle *(degrees)*	72.1 ± 2.9	60.8± 13.08	n.s.
MF +/- poles angle dynamics *(degrees)*	29.4 ± 38.3	4.8 ± 2.9	< 0.02
MF +/- distance dynamics *(mm)*	27.1 ± 28.1	7.6 ± 5.6	< 0.02
MF +/- ratio dynamics	0.68 ± 0.36	0.018 ± 0.09	< 0.01

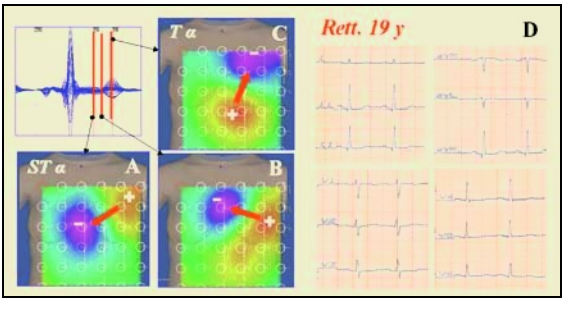

Fig. 5. Rett syndrome stage IV, (19 years old female). MCG mapping evidences clear-cut alteration of the MF gradient, during the ST interval (A and B), in spite of the absence of significant VR abnormalities at the 12-lead ECG at rest (D). The MF gradient at the T-wave peak is still within normal limits (C)

Taking into account the different degree of clinical impairment, a trend toward prolongation of JT_{end} and of QT_{end} values was found in stage IV patients, in respect of stage II and III patients. Among other MCG parameters (Table 2), the ST α-angle

(Figure 5) and the three T-wave MF dynamic parameters were significantly abnormal in RS patients (Figure 6), although only non-significant repolarization abnormalities were observed at the 12-lead ECG.

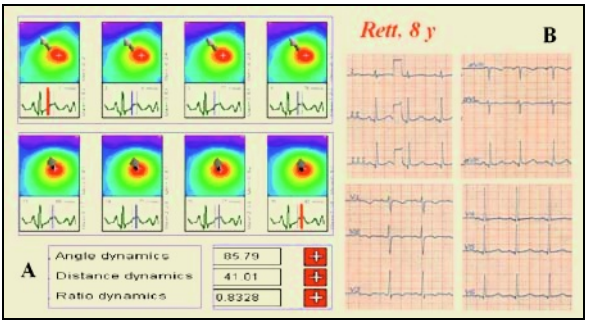

Fig. 6. Rett syndrome stage IV, (8 years old female). All MF dynamics parameters, during the T_{onset} -T_{peak} interval, are abnormal (red flags) (A), in spite of non-significant VR alterations (negative T wave in V2 and V3) at the 12-lead ECG (B), similar to those of the age-matched control (shown in Figure 4 B)

3.2 HRV Analysis

In all RS pts, independently of the clinical stage, HRV analysis in the time domain (pNN50%, SDNN, SDANN, r-MSSD) evidenced lower values as compared with normal age-matched subjects[27-28] (Table 3).

Table 3. HRV parameters in Rett Syndrome patients. Data are presented as mean ± SD

Stage	pNN50%	SDNN	SDANN	r-MSSD	LF/HF *(day)*	LF/HF *(night)*
II	3.13 ± 2.2	59.4±14.7	51.0± 12.7	22.7 ± 3.8	1.46 ± 0.4	2.5± 1.2
III	1.6 ± 0.8	62 ±17.9	51.5 ± 8.6	18.1 ± 4.6	4.1 ± 1.4	2.8± 1.2
IV	6.9 ± 0.6	109.8±7.4	93.1 ± 1.8	31.3 ± 3.1	2.0 ± 0.7	1.2± 0.1

In the FD, the total power was higher then 1900 $msec^2$ in all patients; however in stage II patients the LF/HF ratio was higher during the night than during daytime, whereas in stage III and IV, an inversion was observed, being the LF/HF ratio higher in daytime.

4 Discussion

RS is a severe neurodevelopmental disorder associated to higher risk of SD than in general population[7]. Cardiac electrical instability has been hypothesized as the potential mechanism for SD, in few studies, carried out with 12 lead-ECG or 24

hours ECG Holter monitoring[12-15], in which a reduced HRV and/or prolonged QTc interval were found. Although the ECG is the most widely used method to detect VR abnormalities, to assess the arrhythmogenic risk and predict cardiac death, especially in patients with ischemic heart disease (IHD) or long-QT syndrome[29-32], recent work has shown that MCG mapping is more sensitive than rest ECG in detecting VR alterations and markers for risk of SD in patients with IHD and with dilated cardiomyopathy (CMP)[20-21,33-34]. In this study, we demonstrated the feasibility of unshielded MCG mapping in RS patients. Indeed in some cases, although it was difficult to maintain the patient immobile during the recording, limbs movement did not affect significantly the quality of the MCG signals, good enough for quantitative analysis of VR, even when ECG was unreliable for artifacts. In agreement with previous studies[11-15], a prolongation of all HR-corrected JT_{peak}, JT_{end}, QT_{end} and $T_{peak-end}$ intervals was observed in RS patients in comparison with NC, measured independently from MCG and ECG recordings. Moreover a trend was observed toward more prolonged values in patients in stage IV. Absolute values of MCG VR intervals were shorter than those measured from ECG. This might be due to the partially different definition of the T-wave end by automatic MCG analysis as compared to manual ECG measurements. However MCG measurements evidenced significant differences for $T_{peak-end}$ and QTd, between RS patients and NC, which were not appreciable with ECG. This suggests that, as previously observed in patients with ischemic or dilated CMP[20-21,33], MCG mapping might be more sensitive than ECG in detecting early signs of VR dispersion in RS. Moreover abnormalities of ST α-angle and of MF dynamics, similar to those demonstrated in IHD and CMP, were found in RS patients in more advanced stages[4]. As concern HRV, we found that independently of the clinical stage of disease, TD parameters in RS were lower as compared with age-matched NC[27-28]. This might be a sign of parasympathetic impairment. However the FD parameters were still within normal range, although a non-physiological behavior of the LF/HF ratio was observed in patients in stage II. The evident limitation of this study is that the number of patients is too small to draw any conclusion about the statistical significance of the results. This is due to the fact that it was not easy to collect RS patients, in the condition to collaborate for the additional MCG procedure, unless with some sedation. On the other hand this was a feasibility study and we did not considered ethical to include patients needing sedation, without the “a priori” knowledge that MCG mapping could provide information useful for their risk stratification.

5 Conclusion

This is the first study reporting non-invasive MCG evaluation of RS patients. The MCG method provides easy and quick multi-site mapping of cardiac electromagnetic activity, without any contact or the need to undress the patient, thus avoiding some of the pitfalls, which impede sometime the recording of good quality ECG in non-collaborative patients. In conclusion, although the number of cases investigated in this feasibility study is too small to conclude that MCG mapping is more sensitive that ECG, it was observed that the MCG method evidence abnormality of VR dynamics, not detected by the 12-lead ECG. Thus MCG mapping might provide additional

electrophysiological information, clinically useful for early non-invasive risk assessment, especially of uncooperative and restless RS pts, and to select more appropriate diagnostic and therapeutic approaches. The only limitation to a widespread use of MCG mapping is at the moment the cost of LT SQUID-based instrumentations. However low-cost MCG non-cryogenic systems, such as laser-pumped optic magnetometer[35], are under development and should be commercially available rather soon.

References

1. Jellinger KA. Rett syndrome- an update. *J Neural Transm*. 110: 681-701, 2003.
2. Dunn HG, MacLeod PM. Rett syndrome: review of biological abnormalities. *Can J Neurol Sci.* 28(1): 16-29, 2001.
3. Rosenberg C, Wouters CH, Szuhai K, Dorland R, Pearson P, Tien Poll-The B, Colombijn RM, Breuning M, Lindhout D. A Rett syndrome patient with a ring X chromosome: further evidence for skewing of X inactivation and heterogeneity in the aetiology of the disease. *Eur J Hum Genet.* 9(3): 171-177, 2001.
4. Hagberg BA, Witt-Engerstrom I. Rett Syndrome: A suggested staging system for describing impairment profile with increasing age towards adolescence. *American J Med genetics.* 24: 47-59, 1986.
5. Trevathan F. The Rett syndrome Diagnosis Criteria Working Group. Diagnostic criteria for Rett syndrome. *Ann Neurol.* 23: 425-428, 1988.
6. Naidu S. Rett syndrome. A disorder affecting early brain growth. *Ann Neurol*; 42 (1) :3-10, 1997.
7. Kerr AM, Armstrong DD, Prescott RJ, Doyle D, Kearney DL. Rett syndrome: analysis of deaths in the British survey. *Eur Child Adolesc Psychiatry.* 6 (suppl 1): 71-74, 1997.
8. Driscoll DJ, Edwards WD. Sudden unexpected death in children and adolescents. *J Am Coll Cardiol* 1985;5(6 Suppl):118B-121B.
9. Julu P, Kerr AM, Apartopoulos F, Alrawas S, Witt Engerstrom I, Jamal GA, Hansen S. Characterization of breathing and associated central autonomic dysfunction in the Rett disorder. *Arch Dis Child*. 85: 29-37, 2001.
10. Wenk GL, Hauss-Wegrzyniak B. Altered cholinergic function in the basal forebrain of girls with Rett syndrome. *Neuropediatrics.* 30 (3): 125-129, 1999.
11. Guideri F, Acampa M, Calamandrei G, Aloe L, Zappella M, Hayek Y. Nerve Growth Factor Plasma Levels and Ventricular Repolarization in Rett Syndrome. *Pediatr Cardiol.* 25(4): 394-396, 2004.
12. Sekul EA, Moak JP, Schultz RJ, Glaze D, Dunn JK, Percy AK. Electrocardiographic findings in Rett Syndrome: an explanation for sudden death? *The Journal of Pediatrics.*125: 80-82, 1994.
13. Ellaway CJ, Sholler G, Leonard H, Christodoulou J. Prolonged QT interval in Rett syndrome. *Arch Dis Child.* 80: 470-472, 1999.
14. Guideri F, Acampa M, Hayek G, Zappella M, Di Perri T. Reduced heart rate variability in patients affected with Rett sindrome. A possible explanation of sudden death. *Neuropediatrics*. 30: 146-148, 1999.
15. Guideri F, Acampa M, Di Perri T, Zappella M, Hayek Y. Progressive cardiac disautonomia observed in patients affected by classic Rett syndrome and not preserved speech variant. *J Child Neurol*. 16: 370-373, 2001.

16. Dearlove OR, Walker RWM. Anesthesia for Rett syndrome. *Pediatr Anaesth*. 6:155-158, 1996.
17. Tavarozzi I, Comani S, Del Gatta C, Di Luzio S, Romani GL, Gallina S, Zimarino M, Brisinda D, Fenici R, De Caterina R. Magnetocardiography: current status and perspectives. Part II: Clinical applications. *Italian Heart J.* 3(2):151-165, 2002.
18. Wikswo JP, Barach J. Possible sources of new information in the magnetocardiogram. *Journal of Theoretical Biology*. 95:721-729, 1982.
19. Brockmeier K, Schmitz L, Bobadilla Chavez JD, Burghoff M, Koch H, Zimmermann R, Trahms L. Magnetocardiography and 32-lead potential mapping: repolarization in normal subjects during pharmacologically induced stress. *J Cardiovasc Electrophysiol*. 18: 615-626, 1997.
20. Korhonen P, Väänanen H, Mäkijärvi M, Katila T, Toivonen L. Repolarization abnormalities detected by magnetocardiography in patients with dilated cardiomyopathy and ventricular arrhythmias. *J Cardiovasc Electrophysio.*12: 772-777, 2001.
21. Korhonen P, Pesola K, Jarvinen A, Makijarvi M, Katila T, Toivonen L. Relation of magnetocardiographic arrhythmia risk parameters to delayed ventricular conduction in postinfarction ventricular tachycardia. *Pacing Clin Electrophysiol*. 25(9): 1339-1345, 2002.
22. Fenici R, Brisinda D, Meloni AM, Fenici P. First 36-channel System for Clinical Magnetocardiography in Unshielded Hospital Laboratory for Cardiac Electrophysiology. *International Journal of Bioelectromagnetism.* 5(1): 80-83, 2003.
23. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability standards of measurement, physiological interpretation and clinical use. *Circulation.* 93: 1043-1065, 1996.
24. Brisinda D, Meloni AM, Fenici R. First 36-channel Magnetocardiographic Study of CAD Patients in an Unshielded Laboratory for Interventional and Intensive Cardiac Care. In Magnin I, et al, eds. *Lecture Notes in Computer Science.* 2674:122-131, 2003.
25. Brisinda D, Meloni A.M, Fenici P, Fenici R. Unshielded Multichannel Magnetocardiographic Study of Ventricular Repolarization in Healthy Subjects. *Biomed Tech*. 48(2): 165-167, 2004.
26. Hänninen H, Takala P, Mäkijärvi M, Montonen J, Korhronen P, Oikarinen L, Nenonen J, Katila T, Toivonen L. Detection of exercise induced myocardial ischemia by multichannel magnetocardiography in patients with single vessel coronary artery disease. *Ann. Noninv Electrocardiology.* 5: 147-157, 2000.
27. Goto M, Nagashima M, Baba R, Nagano Y, Yokota M, Nishibata K, Tsuji A. Analysis of heart rate variability demonstrates effects of development on vagal modulation of heart rate in healthy children. *The Journal of pediatrics.* 130(5): 725-729, 1997.
28. Umetani K, Singer D, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol*. 31: 593-601, 1998.
29. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J*. 24: 1357-1364, 2003.
30. Kannel WB, Anderson K, McGee DL, Degatano LS, Stampfer MJ. Non-specific electrocardiographic abnormality as a predictor of coronary heart disease. The Framingham Study. *Am Heart J.* 113:370-376, 1987.
31. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE**.** Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 20:278-284, 1999.

32. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and Electrocardiographic manifestation of the Long-QT syndrome. *Circulation.* 98:1928-1936, 1998.
33. Oikarinen L, Viitasalo M, Korhonen P, Vaananen H, Hanninen H, Montonen J, Makijarvi M, Katila T, Toivonen L. Postmyocardial infarction patients susceptible to ventricular tachycardia show increased T wave dispersion independent of delayed ventricular conduction. *J Cardiovasc Electrophysiol.* 12:1115-1120, 2001.
34. Steinberg BA, Roguin A, Allen E, Wahl DR, Smith CS, St John M. Reproducibility and interpretation of MCG maps in detecting ischemia. (Personal Communication, ACC March 2004].
35. Fenici R, Bison G, Wynands R, Brisinda D, Meloni AM, Weis A. Comparison of Magnetocardiographic Mapping with SQUID-based and Laser-pumped Magnetometers in Normal Subjects. Biomed Tech. 48(Suppl 2):192-194, 2004.