The Multiphase Functional Cardiogram
A Clinical Overview

Abstract

MCG, the Multifunction Cardiogram, is a revolutionary approach to diagnosing cardiac conditions. It goes beyond a traditional ECG by incorporating aspects of computational biology and systems theory to build a functional mathematical model of the cardiac system – the heart, blood and circulatory system – from which a more accurate diagnosis can be drawn.

This white paper discusses the theoretical background underlying the MCG system and presents supporting results from Premier Heart's clinical trials. Additional technical and clinical information regarding the MCG system can be found at Premier Heart's web site (http://www.premierheart.com)

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Overview

MCG (Multifunction Cardiogram) analysis process is part of an emerging trend in medicine: the clinical application of advances in computational biology. By combining mathematical modeling and functional measurements of the heart's electrical activity with an extensive empirical digital database MCG is able to detect coronary ischemia within 90% of the accuracy of an angiogram[1], using a method that is rapid, non-invasive, and does not expose the patient to radiation or physical stress.

Where traditional ECG technology has taken a reductionistic approach – simplifying the cardiac system by plotting ECG signals as a virtual dipole in a voltage-over-time graph – MCG takes an integrative approach, building upon a mathematical model that embraces the complexity of the cardiac system, including the interaction between heart muscle and blood flow. The MCG model, founded upon a LaGrange-Euler complex, considers all the physical properties of the heart[2] and blood[3] embraces the complexity of the cardiac system.

The MCG model is combined with ECG signals from two left ventricular leads (V5 and II), and via digital signal transformations a sequence of indices is produced which quantify abnormalities in the ECG. Clusters of these indexes have been correlated to cardiac conditions and represent potential diagnoses, and a statistical analysis these index clusters is used to determine the likelihood that a condition is present and produce a final diagnosis.

Systems Analysis and ECG Signals

The Premier Heart approach is based on systems theory, in which mathematical modeling is used in the analysis of complex systems. The mathematical modeling of organ systems is based on computational physiology research such as the Physiome Project[4]. This approach is becoming increasingly popular as advances in computer processing power make the analysis of large datasets, such as those produced by medical devices, more feasible. Efforts in computational physiology, such as the Physiome Project, and computational electro-physiology, such as MCG for surface resting ECG, have proven useful in academia and clinical practice.

An analog signal such as an ECG can be digitized and then processed by standard digital signal processing techniques. When two signals are recorded from the same source, these techniques can be used to examine

[1] Based upon Premier Heart's clinical trials. See http://www.premierheart.com/trials

[2] viscoelasticity of the muscle, kinetic energy of cells/groups of cells, the irregularly shaped chambers of the heart and the complex electrical signals generated along the heart's conduction pathways

[3] non-Newtonian (semi-compressible) nature, viscosity & how blood flow is influenced by its environment

[4] http://www.physiome.org/

the relationships between the signals and infer information about the source. This type of analysis allows a complex system emitting signals to be modeled as mathematical functions, where one signal is treated as the input and the other the output of the system. The functions represent a virtual or idealized system that embodies the relationship between the two signals, and is used to examine the relationship as a meaningful component of the more complex system.

The system modeled by such a function could be a series of cardiac cycles, a flow of blood from chamber to chamber, or a depolarization and repolarization cycle from one part of the heart to another part of the heart. A conventional 2-D ECG plot is the summation of all of the complex periodic electrical activity throughout a cardiac cycle of a human heart, and can be broken down into discernible components in systems analysis approach. Once the complex waveform is broken into simpler mathematical functions it can be studied quantitatively, obtaining and examining the functional characteristics of signals sampled from healthy and diseased patients and revealing latent information not visible in the conventional 2-D plots.

Digital Signal Processing and ECG Analysis

In a traditional 12-lead ECG, six limb and six precordial leads represent the vectors of the heart as an electrical power-generating source, reduced to a dipole with a pair of + & - signs. Conventionally, each lead is sampled at a rate of 200-500Hz, and then analyzed individually and sequentially in the time domain. This produces a simple model of the heart – a signal of millivolts over microseconds – which reveals arrhythmias clearly, however the model neglects the dynamic multidimensional electrical field changes due to the stress and strain of the interaction between the myocardium and the blood circulating through the cardiac cycle of the heart[5].

In the MCG system two leads are used: the V5 lead, a precordial lead that represents electrical activity in the left ventricle, and lead II, a limb lead that represents electrical activity from right arm to left ankle along the left ventricular axis. The sampling rate is calculated to target frequency domain components that fall between 1 Hz (a 60 bpm heart rate) and 35 Hz[6]. Multiple cardiac cycles for the two leads are sampled to provide a view of cardiac function over time, and mathematical models of the cardiac system are used to determine which digital signal processing methods are appropriate, and where in the output significant characteristics are likely to be found. For example, the ECG data on individual leads is well-suited to power spectrum analysis, while systems models derived from the interactions of the two leads can be analyzed as an impulse-response relationship.

The MCG system employs a multidimensional analysis examining the ECG signal in the frequency domain in addition to the traditional time domain analysis. The frequency domain is commonly used in analysis of mechanical systems to detect component wear or deterioration by monitoring a signal for changes in amplitude at a specific frequency. The approach is easily adapted to signals from biological systems by considering the system as a mechanism whose components oscillate at specific frequencies. In the specific case of the heart, the components of interest are the left and right atria and ventricles.

The ECG is a periodic waveform, and therefore can be represented in the frequency domain as a Fourier series with the heart rate as its fundamental frequency (or first harmonic). The harmonics of the heart rate frequency are the basis for further analysis: as with all periodic waveforms each harmonic component has a characteristic amplitude and phase angle. Correlation analysis uses the amplitudes and phase rotation angles between two leads to determine the relationship to those leads.

Empirically Derived Clinical Indices

MCG Analysis performs DSP transformations on the Fourier series of the two leads, and using signal analysis techniques derived from our research produces values for a set of empirically derived indices.

These quantifiable and reproducible indices are based on latent data not observable in conventional ECG plots which becomes visible in frequency-domain analysis of individual and paired leads. The indices represent clinically significant abnormalities can be identified in the ECG waveform which have been quantified through

[5]Feng G. EKG and EEG Multiphase Information Analysis. First Edition. New York: American Medical Publishers; 1992.

[6]Premier Heart's empirical research has shown that 85-90% of the power output of a normal human heart occurs below 35Hz. The sampling rate for MCG is targeted to capture frequencies up to 50Hz.

empirical research. The clinical relevance of individual indices alone is not normally significant, however patterns or clusters of indices have been found to have strong correlation to specific diseases.

The results of this stage of analysis can indicate abnormalities of the heart that have been found empirically to represent early (i.e., sub-critical coronary artery narrowing due to atherosclerosis of as little as 40% in single vessel disease) to later (severe multiple vessel disease due to critical stenosis) stages of myocardial pathologies. In particular, the power spectra analysis, impulse response, phase shift, and cross correlation data have been found to be highly sensitive to the changes in heart mechanical and/or electrical functions as a result of ischemia due to coronary supply and myocardium demand imbalances. Empirical research has lead to thresholds for each index, providing crossing points for normal versus abnormal patterns, and for degrees of abnormality within an index where applicable.

Statistical Analysis and Weighting

The statistical analysis phase generates differential diagnoses and severity scores from the empirically derived indices. The diagnoses are generated by comparing index clusters against a database population of index patterns from patients with known disease diagnoses as well as healthy patients.

The potential differential diagnoses are weighted against the quality of the match (degree of conformance to a disease pattern) and the quantity of confirmed cases matching the pattern. Diagnoses that exceed a set confidence threshold are reported to the physician for further investigation.

Continual Improvement

In addition to the underlying techniques described above the MCG system relies upon a large-scale database of empirically and clinically validated tests and results. This database is broken down into three overlapping populations:

The General Population consists of all MCG tests ever performed. All other populations are subsets of this group.

The Qualitative Population contains tests which have been exhaustively reviewed and whose patients have consented to their use in our ongoing research. This population is used for improving the mathematical model and the analysis functions.

The Quantitative Population consists of tests from the Qualitative and General populations whose results have been confirmed by two independent physician experts and whose patients have consented to their use in our ongoing research. This population and is used to generate the statistical weights used in diagnosis as well as for improving the mathematical model and analysis functions. The current Quantitative Population includes approximately 40,000 patients between the ages of 14 and 95, of which 20% are clinically normal and the remaining 80% have been diagnosed with various pathologies.

These three populations allow for the accumulation of a large body of clinical data on which to base the mathematical models and subsequent statistical analysis. By permitting only verified and validated tests in the quantitative population to be used in the generation of disease diagnoses we are able to continually improve the accuracy of the technology. Furthermore both the quantitative and qualitative populations can be mined to develop analysis functions to detect additional diseases or improve the accuracy of the system on currently targeted conditions.

Reporting and Physician Follow-up

An MCG report consists of three classes of diagnosis (primary, secondary and tertiary), along with a disease severity score representing the overall risk of heart disease for the patient. The Primary Diagnosis class has been validated through extensive clinical trials and are considered extremely reliable. The Secondary and Tertiary classifications have been strongly correlated, however as they have not been formally validated through clinical trials they are considered suggestions for further investigation.

The Primary Diagnosis produces a result for coronary ischemia, which may be negative, borderline, local or global.

The Severity Score combines with the primary diagnosis to indicate the severity of the patient's disease burden. Lower scores in asymptomatic patients can usually be managed through medication and lifestyle changes with continued monitoring, while higher scores indicate the need for a thorough follow up and possible interventional procedures.

The Secondary Diagnoses produce positive or negative results for myocardial infarction, ventricular hypertrophy, myocarditis congenital heart disease, myocarditis, rheumatic heart disease,ventricular fibrillation, atrial-fibrillation, cardiomyopathy, and pulmonary heart disease.

The Tertiary Diagnoses produce positive or negative results for power failure, decreased ejection fraction, bradycardia, tachycardia, increased and decreased myocardial compliance, myocardial remodeling, and local or global asynchrony.

Clinical Accuracy

Premier Heart has developed the MCG technology through extensive in-house research and validated the ability of MCG to detect coronary artery disease through rigorous double-blind clinical trials encompassing over 1000 patients at leading heart centers around the world. An analysis of our trial data shows the accuracy of MCG testing approaches that of coronary angiography, and when performed in accordance with our clinical quality guidelines is unaffected by age, gender, testing center or ethnicity.

A summary of our trial data is presented in Table 1 below[7]. For extensive information on Premier Heart's clinical trials, including published articles, please see http://www.premierheart.com/trials .

												ROC AUC						Odds Ratio		
	n	TP	TN	FP	FN	Sens.	Spec.	PPV	NPV	Correct	a piori	ROC AUC	lower CI	upper CI	PPV (Bayes)	NPV (Bayes)	LR+	LR-	Odds Ratio	lower CI	upper CI
Combined Analysis																				
Total	1076	426	515	94	41	0.912	0.846	0.819	0.926	0.875	0.434	0.881	0.860	0.903	0.777	0.942	5.910	0.104	56.925	38.594	83.963
USA	136	72	45	17	2	0.973	0.726	0.809	0.957	0.860	0.544	0.886	0.825	0.946	0.835	0.950	3.548	0.037	95.294	21.014	432.131
Asia	189	73	97	15	4	0.948	0.866	0.784	0.971	0.899	0.407	0.914	0.868	0.961	0.770	0.972	7.079	0.060	118.017	37.594	370.482
Germany	751	281	373	62	35	0.889	0.857	0.819	0.914	0.871	0.421	0.873	0.846	0.900	0.767	0.936	6.239	0.129	48.301	31.034	75.175
female	390	121	221	38	10	0.924	0.853	0.761	0.957	0.877	0.336	0.885	0.849	0.920	0.617	0.978	6.296	0.089	70.371	33.878	146.172
male	686	305	294	56	31	0.908	0.840	0.845	0.905	0.873	0.490	0.881	0.853	0.908	0.839	0.908	5.673	0.110	51.653	32.377	82.405
< 65 years	623	216	332	47	28	0.885	0.876	0.821	0.922	0.880	0.392	0.892	0.865	0.920	0.747	0.948	7.138	0.131	54.492	33.108	89.688
65+ years	453	210	183	47	13	0.942	0.796	0.817	0.934	0.868	0.492	0.858	0.821	0.896	0.812	0.936	4.608	0.073	62.897	32.987	119.926
Female, < 65 years	184	43	121	12	8	0.843	0.910	0.782	0.938	0.891	0.277	0.896	0.838	0.953	0.579	0.975	9.345	0.172	54.198	20.754	141.533
Female, 65+ years	206	78	100	26	2	0.975	0.794	0.750	0.980	0.864	0.388	0.857	0.803	0.911	0.656	0.987	4.725	0.032	150.000	34.545	651.330
Male, < 65 years	439	173	211	35	20	0.896	0.858	0.832	0.913	0.875	0.440	0.886	0.853	0.920	0.795	0.931	6.300	0.121	52.147	29.051	93.605
Male, 65+ years	247	132	83	21	11	0.923	0.798	0.863	0.883	0.870	0.579	0.865	0.814	0.915	0.896	0.846	4.571	0.096	47.429	21.754	103.407
No Revasc	827	351	367	74	35	0.909	0.832	0.826	0.913	0.868	0.467	0.873	0.847	0.899	0.806	0.923	5.419	0.109	49.736	32.423	76.295
PCI	188	47	120	15	6	0.887	0.889	0.758	0.952	0.888	0.282	0.894	0.841	0.947	0.552	0.981	7.981	0.127	62.667	22.938	171.205
CABG	61	28	28	5	0	1.000	0.848	0.848	1.000	0.918	0.459	0.902	0.814	0.989	0.826	1.000	6.600	0.000	NaN	NaN	NaN
Revasc of any type	249	75	148	20	6	0.926	0.881	0.789	0.961	0.896	0.325	0.902	0.860	0.944	0.644	0.981	7.778	0.084	92.500	35.642	240.058

Table 1: Premier Heart Trial Results (Summary)

[7]Data from *International Journal of Medical Sciences*, 2009; 6(4): 143-155