The Multiphase Functional Cardiogram
Diagnostic Technology 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 diagnostic technology underlying the MCG system. 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

The MCG approach is based on systems theory, in which mathematical modeling is used in the analysis of complex systems and the interaction of the internal and external environment with those systems. In the case of the heart analysis is performed on the signals emitted by the heart, such as the electrical signal measured by an ECG. An analog signal such as the ECG can be digitized and then processed by signal analysis algorithms. When these algorithms operate on two signals recorded from the same source, such as communication signals from two antennae or ECG signals from two leads, they can be used to infer information about the source by examining the relationships between the signals. The correlation of the antennae signals can be used to obtain a more accurate copy of the transmission; the correlation of the ECG signals can be used to obtain more accurate measurements of the multidimensional cyclic oscillations of the chambers of a living heart and its complex interactions with its equally complex internal and external environments.

In the MCG system the ECG signals are not analyzed conventionally, evaluating individual cardiac cycle (P-QRS-T waveform) on individual leads. Instead, multiple cardiac cycles from two ECG leads are sampled, digitized and analyzed both individually and in relation to each other. This allows MCG to focus on the variations of heart harmonics in the frequency domain from each lead independently and also on other non-linear correlations between the two leads in both frequency and time domain, relating them through a mathematical model of a living heart.

Systems Analysis and Idealized Systems

A complex system emitting signals, such as the heart emitting electrical activity recorded on an ECG, can be modeled as a mathematical function. In the case of the heart, leads can be paired with one lead considered a functional *input* and the other an *output*. This mathematical function is a virtual model of a heart, embodying the ideal relationship between the two signals, which is termed an *idealized system*.

The idealized system is intended to represent the interplay between the ECG leads, taking into account the complexities of the heart's conduction system which relies on cell-to-cell and chamber-to-chamber communication throughout the entire organ. By evaluating the real-world data using the idealized system as a model MCG is able to draw conclusions about the overall function of the cardiac system. Several investigational studies using aspects of the MCG technology to draw such conclusions have been published[1][2].

[1]Suzanne L. Dawson, Thompson G. Robinson, Jane H. Yodel, et. al. "Older subjects show no age-related decrease in cardiac barorecptor sensitivity". *Age and Aging*, 1999;28:347-353

[2]B. Kocsis, et. al. "Basis for differential coupling between rhythmic discharges of sympathetic efferent nerves". *Am. J.*

The MCG Diagnostic Technology

Premier Heart's MCG technology digitally records a resting ECG signal from two left ventricular leads (II and V5) over a brief period. This signal is then converted to the frequency domain, and the frequency-domain data processed through post-FFT signal averaging to maximize the signal-to-noise ratio[3]. This frequency domain data is then processed through a series of signal analysis functions and evaluated against empirically validated patterns in the mathematical model to reveal abnormalities in the ECG signal which are not expressed by conventional ECG methods.

MCG then derives a series of functional indices which quantify the detected abnormalities, and matches clusters of those indices against a database containing clinically validated patterns from thousands of normal and abnormal patients to produce a diagnosis for myocardial ischemia (including an evaluation of severity, representing the amount of the myocardium acting abnormally). The diagnosis of myocardial ischemia and the quantitative severity score have been rigorously validated in prospective, double-blind clinical studies, and MCG has consistently demonstrated high sensitivity ($\geq$90%), and specificity (80%), with the ability to detect myocardial ischemia due to coronary artery disease with as little as 40% occlusion in a single vessel.

It is important to note that in many cases the abnormalities detected through the MCG analysis have been linked with pathologies through empirical research (allowing their use as diagnostic indicators) however the physiological processes involved may not be fully understood, presenting an avenue for further research and the potential development of new or improved treatment regimens.

ECG Sampling Method

An ECG lead signal is a measurement of amplitude over time, and can only demonstrate fluctuations of voltage that occur in the time domain (arrhythmias). Assuming the heart is a single dipole generator of electrical current, the invisible or virtual dipole has an input and an output current that is then projected into three- dimensional vectorized space as the leads of a conventional 12-lead system. The limb precordial leads represent the vectors of the electrical projections of the myocardium in vivo.

Traditional ECG systems analyze the leads individually and sequentially to extract observable abnormal fluctuations of the waveforms based on empirical experience, e.g. S-T wave segment depression or elevations. This approach has not been fruitful in providing an accurate tool for use in diagnosing heart disease: traditional ECG methods have poor sensitivity (20%) in detection of myocardial abnormality as result of hemodynamically significant ischemia, and equally poor sensitivity (~50%) in detecting myocardial infarction[4].

In order to uncover complex anomalies of the heart that are not apparent in the time domain, such as humero-myocardial interactions and structural remodeling, it is necessary to process two or more leads in other domains (such as the frequency domain) and evaluate them using a systems analysis approach. The two leads used in the MCG system are the V5 lead, a precordial lead which represents electrical activity in the left ventricle, and lead II, a limb lead which represents electrical activity from the right arm to the left leg or from head to toe along the left ventricular axis.

As MCG analysis operates on data in the frequency domain the sampling of the ECG signal focuses on frequencies up to 50 Hz in order to capture frequency domain components that fall between 1 Hz (a 60 bpm heart rate) and 35 Hz[5] (allowing the signal analysis to focus on the harmonics of a resting heart rate). To accomplish this MCG sampling is performed at 100 Hz, the Nyquist frequency or Nyquist limit: this is the highest frequency that can be coded at a given sampling rate in order to be able to fully reconstruct the analog ECG signal.

Physol. Regulatory Integrative Comp. Physiol. 1994;267:1008-1019

[3]Note that this is in contrast to "Signal-Averaged ECG" systems, which perform their averaging on the raw ECG data over an extended period of time, potentially losing minor harmonics in the signal. MCG employs signal averaging to eliminate noise introduced by the FFT algorithms.

[4]Welch RD, Zalenski RJ, Malmgren JA, et al. "Prognostic Value of a Normal or Nonspecific Initial Electrocardiogram in Acute Myocardial Infarction". *JAMA* 2001; 286:1-2.

[5]Premier Heart's empirical research as shown that 85-90% of the power output of a normal human heart occurs at frequencies below 35Hz.

Signal Analysis

The systems analysis approach treats the heart as a complex system emitting periodic signals which are captured by the ECG leads. These signals are inter-related, with the relationship carrying information about the function of the heart which are not visible in conventional ECG representations. This latent information includes anomalies which can be caused by a variety of pathologies, including myocardial oxidative stress due to reduced blood or oxygen supply, or myocardial cellular hypertrophy due to increased systemic resistance, consequences of systemic hypertension or imbalance in supply-and-demand due to ischemic heart disease.

MCG analysis considers the ECG signals in three phases:

1. The leads are analyzed independently, generating amplitude and frequency data which provides information similar to a traditional ECG
2. The leads are analyzed in relation to each other, generating cross-correlation and coherence data (latent and not visible with traditional ECG technology)
3. The leads are analyzed as the input and output of a system, generating phase angle shift, impulse-response and transfer function data (also latent and not visible on a traditional ECG)

The results of this three phase analysis can indicate abnormalities of the heart, which have been found empirically to represent early (i.e. subcritical coronary artery athromas as little as 40% single vessel disease) to later stages (severe multiple vessel diseases due to critical stenosis) 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 result of ischemia.

It is very important to note that the information from each function can not be used directly to derive a diagnosis While patterns are indicative of potential diagnoses only the integrated clusters of abnormal expressions across all of the functions can be used to represent the system's behavior. These are the functional indices used by MCG to achieve its high level of accuracy.

The Diagnostic Functions

MCG analysis can be viewed as a series of layered abstractions representing the cardiac data:

- The raw ECG data
- Amplitude Data
- Frequency Data
- Transfer Data (the relationship between two leads in the frequency domain)
- Correlation Data (the relationship of the amplitude and transfer data between two leads)

Amplitude Analysis - The amplitude histogram

The *amplitude histogram* represents he statistical distribution, or frequency of occurrence, of the voltage in the ECG signal. The histogram depicts the beat-to-beat variations in amplitude for each lead, which can provide information on chronic conditions, ventricular voltage distribution, and non-uniform, variable or unstable amplitude in the cardiac cycle.

Frequency Analysis - The Auto-Power Spectrum

The *auto power spectrum* is a measure of the power in watts of each frequency of an ECG signal. The peak with the lowest frequency in the auto power spectrum represents the heart rate, which is generally between 1Hz and 1.2Hz (60-72 bpm); higher frequency peaks will generally have less power than lower frequency peaks, with the signal generally fading out at approximately 35 Hz.

The auto power spectrum data can be used to identify pathological conditions such as fast or slow heart rate, arrhythmias, and fibrillation. In addition, the peak-to-peak power amplitude abnormal distribution correlates well with clinical conditions such as myocardial ischemia, hypertensive heart disease, congestive heart failure or Cardiogenic Shock.

Transfer Analysis - The Transfer Function, Impulse-Response and Phase Angle Shift

The transfer function is used to quantify the relationship between two ECG leads. This relationship is purely in the frequency domain: the transfer function determines the ratio of the auto power spectra of the two leads to their cross power spectrum. The result is a number whose components represent the amplitude ratio and the angle of the phase shift between the two ECG signals.

The *transfer* or *process frequency response* function is the operation of the heart, which generates the output signal from the input signal: it embodies the relationship between the two signals. When the two leads have a close relationship, i.e. when the transfer function output is determined largely by the input, then interference is low and the system is "normal"[6]. When the leads are not closely related, i.e. the output of the transfer function is determined by many factors in addition to the input, then interference is high and the system is abnormal[7], based on what we observed from abnormal population data.

The *impulse response* function measures the continuous activation and response of the cardiac system between input and output. It is derived from the transfer function using a reverse Fourier Transform, and is expressed in the time domain as the latency for each amplitude peak in millivolts.
The impulse response function uses the V5 lead as system input and lead II as system output; this makes the impulse response function an idealized system which generates Lead II from Lead V5 in response to a unit impulse. Since the heart is constantly in motion, the input/output systems approach becomes essential for expressing impulse response.
The impulse response function is used to measure the quality of the system: high amplitudes with latency greater than 10 ms indicate excessive oscillation, which suggests a degraded system. Impulse response data can be used to detect changes in the cardiac muscle and in blood flow, including ventricular remodeling, increases or decreases in myocardial compliance, conduction blockage or delays, and potential arrhythmia. In addition, distortion in the impulse response can indicate part of the cardiac cycle not visible in the conventional ECG signal, including hidden arrhythmias.

The *phase angle shift* function is the comparison of an actual waveform (the auto power spectrum of each lead) to an ideal waveform (the cross power spectrum of the two leads). This is expressed as the angle in degrees of the phase shift for each frequency: essentially, the relative angles of the harmonics at a specific frequency to each other. The angle represents the delay between the two leads, so that a greater angle is evidence of higher degrees of asynchronization; positive angles indicate angle shift favoring the input lead (V5), and negative angles indicate angle shift favoring the output lead (II). Asynchrony between the leads may be due to infarction, myocardial ischemia, and myocardial hypertrophies.

Correlative Analysis The Coherence and Cross Correlation Functions

The correlative analysis of the ECG leads is based on the frequency domain, time domain and transfer function analysis. Each of the heart rate harmonics is characterized by its phase shift and amplitude, and the correlation analysis uses these to determine the systemic relationship between the ECG leads.

The *coherence* or *condensation* function represents the correspondence of the amplitude, frequency, and phase shift of two ECG leads[8]. Coherence is expressed as the amplitude ratio of the two leads squared for each frequency; the result is a measure of the correspondence of the output energy of the two leads. The coherence function is primarily useful in the frequency band of the heart harmonics as higher frequencies exhibit little variation in amplitude ratio. During analysis, the coherence of the frequency of the highest peak in both the auto power spectrum and the amplitude ratio of the transfer function is examined. Low coherence for a heart rate harmonic indicates decreased output energy, and correlates well with low ejection fractions: if both frequencies have low coherence, the ejection fraction is likely to be below 40% in more than 80% of patients[9].

The *cross correlation* of the auto power spectra of two ECG leads provides the linear relation between the R-waves of the ECG signals, expressed as the measure of amplitude in millivolts over time. This correlation

[6] As determined by empirical observation of subjects who have been clinically validated as free of pathology.

[7] As determined by empirical observation of subjects with clinically validated pathologies, and compared to subjects free of pathology.

[8] Because each harmonic of the heart rate is characterized by its frequency, amplitude, and phase shift, the coherence function can be viewed as a measure of what distinguishes each harmonic component. This allows the harmonics of the heart rate to be directly compared.

[9] Premier Heart bases the correlation of ejection fraction to coherence on empirical research.

generally takes the form of a periodic curve, which shows the degree to which electrical activity corresponds in different areas of the heart. The cross correlation data can be used to find evidence of dysfunction in cardiac electrical conduction patterns or cellular responses adapting to abnormal blood supply, particularly in relation to myocardial remodeling such as ventricular hypertrophy and myocardial infarction, surgical injuries or blunt chest trauma causing contusion.

Index Generation and Statistical Analysis

Each transformation described above has an associated set of indexes determined through empirical research. These indexes are used to represent significant characteristics of the waveform which are found during analysis. While individual indexes generally have no conclusive clinical meaning patterns of indices have been found to have a high probability of indicating a specific disease; these patterns are known as *disease index patterns*.

Statistical analysis of the disease index patterns is used to generate probabilities for each disease diagnosis, as well as to aid in the calculation of disease severity. the statistical weights are calculated using patterns from patients who have been independently verified as being free of pathology, or who have clinically validated conditions. These results are additionally weighted according to *disease control factors*, including physical characteristics (e.g. age, gender), medical history (e.g. diabetes) and lifestyle factors (substance abuse, frequency of exercise, diet) to determine the degree to which each index or pattern will contribute to the overall diagnosis.

The disease index patterns and statistical data used in MCG analysis have been repeatedly verified and validated through trials to correlate with possible clinical conditions.

Final Diagnosis and Severity Scoring

The final diagnosis and severity scoring phase of analysis uses the results of the statistical analysis to produce a diagnosis. This involves summing the probabilities associated with detected disease patterns to produce overall disease probabilities and performing additional tests to quantify the severity of any disease present.

The MCG final diagnosis includes a clinically validated result for ischemia, along with a clinically validated *severity score* which may be used in conjunction with published guidance to assist in determining a course of treatment.

MCG results also include a series of secondary and tertiary results which have not been formally validated, but which are provided based on our research to be considered as *rule-out* diagnostic suggestions.