A POTENTIALLY POWERFUL NEW TOOL FOR NONINVASIVE DIAGNOSIS OF CARDIAC ABNORMALITIES: THE CUPID® SYSTEM FOR ANALYSIS OF ELECTROCARDIOGRAMS IN THE FREQUENCY DOMAIN

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ORIGINAL RESEARCH: PRELIMINARY REPORT

A Potentially Powerful New Tool for Noninvasive Diagnosis of Cardiac Abnormalities: The CUPID® System for Analysis of Electrocardiograms in the Frequency Domain

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Clinical correlation of frequency-domain characteristics of electrocardiograms with specific disease entities of thousands of patients has produced a simple, noninvasive diagnostic system capable of detecting many cardiac abnormalities with specificity and sensitivity exceeding 90%. This system, a proprietary product called CUPID®, is now undergoing clinical trials in Europe, South America, and the United States. The author discusses the physiologic basis of electrocardiography and the development of the CUPID system, and reviews the results of the trials that have been completed. The system appears to hold promise for fast, inexpensive, and accurate screening of patients for cardiac disease without somatic invasion. (BIOMEDICAL INSTRUMENTATION & TECHNOLOGY 1998; 32:387-400)

For most of the 20th century, electrocardiography has been an essential first-line diagnostic modality for evaluation of patients presenting with manifestations of cardiac disease. It was first demonstrated at the University of Leiden in The Netherlands by Willem Einthoven[1] (1860-1927), who, in 1903, devised the string galvanometer to indicate and graphically record the changes of electric potential at various points on the exterior surface of the human body caused by contractions of the myocardium. He was the coiner of the term *electrocardiogram* (now usually designated by the acronym ECG). The string galvanometer was later replaced by the d'Arsonval galvanometer, then combined with the familiar strip-chart recorder to constitute the electrocardiograph, and ultimately coupled with solid-state electronic amplifiers, analog-digital converters, and microprocessors in the sophisticated ECG analyzers now widely used. The present-day standard limb leads were originally used and described by Einthoven.

Voluminous treatises[2] on the interpretation of ECG tracings have been written, all aimed at enabling the cardiologist to evaluate the physiologic conditions underlying the time waveform of the ECG, or at least to guide the choice of subsequent diagnostic modalities for fur-

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ther testing of the patient. Such disease entities as chamber hypertrophy, bundle-branch block, arrhythmias, aberrant ventricular conduction, myocardial infarction, and severe myocardial ischemia can be detected by an experienced cardiographer interpreting the ECG, taken both at rest and after strenuous exertion. The sensitivity and specificity of the ECG as an indicator of the foregoing abnormalities are very dependent on the experience and skill of the cardiac diagnostician, however. Such disease entities as moderate atherosclerosis of the coro-naries and so-called "silent" myocardial ischemia are essentially undetectable by standard electrocardiography, and in early stages are not readily discernible by minimally invasive modalities such as contrast angiog-raphy and radioisotope scintigraphy. Moderately invasive diagnostic modalities such as angioscopy and intravascular ultrasonography are capable of accurate, definitive visualization of early coronary atherosclerosis, but they carry significant morbidity, which restricts their use to patients who have already presented with overt symptoms of cardiac disease. The sheer number of texts[3] on cardiac disease and its diagnosis eloquently attests to the difficulty of the problem.

It has long been known that periodic or quasi-periodic functions of time can be mathematically transformed from the time domain to the frequency domain by Fourier analysis, which replaces a complex time waveform by a

spectrum of sinusoidal waveforms whose frequencies, amplitudes, and phases are uniquely related to the time waves from which they are derived. In particular, the technique of autocorrelation and Fourier transformation of the autocorrelation function enables a time wave such as an electrocardiogram to be represented by a spectral power-density function, which is often more revealing of subtle changes in the wave shape than is direct inspection in the time domain. These mathematical techniques were largely of theoretic interest until the advent of compact, powerful computers made their use feasible for everyday analysis of time-domain signals such as electrocardiograms.

Clinical correlation of frequency-domain characteristics of electrocardiograms with specific disease entities of thousands of patients has produced a simple, non-invasive diagnostic system capable of detecting many cardiac abnormalities with specificity and sensitivity exceeding 90%. This system, a proprietary product called CUPID®,* holds promise for fast, inexpensive, and accurate screening of patients for cardiac disease without somatic invasion. CUPID is an acronym for Cardiac Ultra Phase Information Diagnosis. In this context, the term "phase" refers to any one of the mathematical functions that may be derived by sophisticated analysis of either the time wave of the electrocardiogram or its spectrum in the frequency domain. The CUPID system is now undergoing clinical trials in Europe, South America, and the United States.

PMOR ATTEMPTS AT CARDIAC DIAGNOSIS BY FREQUENCY-DOMAIN ANALYSIS OF THE ECG

Over the past 40 years or more, many fragmentary attempts have been made to discover clinically useful correlations between various frequency-domain parameters derived from ECGs and specific cardiovascular abnormalities. Until the development of the CUPID system, however, none of these had achieved any significant clinical utility or recognition by the community of cardiovascular physicians and surgeons. There were three major reasons why frequency-domain analysis of the ECG failed to become a clinically useful diagnostic modality: first, it was, and is, a technique that is esoteric to many physicians and surgeons because of their lack of training in advanced mathematics; second, it lacked a database of patients who had been studied by both spectral analysis and conventional cardiovascular methods such as angiography, s.p.e.c.t thallium, ultrasonography, an-gioscopy, and serum cardiac enzymes; and third, the calculations required were unpractically difficult and time-consuming operations until the advent of powerful computers at moderate prices. (The bibliography at the end of the article lists, in chronologic order, some early attempts at spectral analysis of the ECG.[12-18])

*The CUPID® system is a proprietary product of Auragenics, Incorporated, of New York, NY.

THE PHYSIOLOGIC BASIS OF ELECTROCARDIOGRAPHY

The biophysical phenomenon responsible for the generation of small electric potentials at various points on the surface of the human body associated with the beating heart is the cyclic polarization and depolarization of various segments of the myocardium. In a resting state, each muscle cell has a uniform distribution of positive electric charges externally around the membrane, bound by a comparable distribution of negative charges inside the membrane. When the sinoatrial (SA) node of the cardiac conduction system fires, its impulse is conducted in about 0.03 second to the atrioventricular (AV) node, causing atrial contraction along the three intern-odal tracts. At the AV node it is delayed by 0.07 to 0.10 second to allow the ventricles to fill with blood expelled by the contracting atria. After this delay in the SA node, the impulse travels via the bundle of His to its bifurcation into the right and left bundle branches, which run down opposite faces of the interventricular septum. The fascicles of both bundle branches divide into fine filaments, called the Purkinje network, which distribute the signal to the ventricular muscle fibers to cause contraction. About 0.03 to 0.04 second is required for the impulse to travel from the bundle of His to the ventricular fibers.

Contraction of muscle fibers occurs as the wave of depolarization sweeps along, caused by the entrance of positive sodium and calcium ions into the muscle cells through their membranes, so that the potential difference across each membrane is reversed in polarity, becoming negative externally and positive internally. The net external effect is that of an electric dipole moving along each muscle cell. Because the elongated muscle cells are parallel to the long direction of each muscle fiber, the whole fiber produces an external electric field equivalent to that of a moving electric dipole. The totality ofmyocardial fibers depolarizing simultaneously and sequentially produces an electric field outside the heart that varies in intensity and direction at all points in the somatic space surrounding the myocardium.

Because the human body consists of about 80% water in which various electrolytes are dissolved, the varying electric field external to the heart produces a complex spatial

pattern of electric currents and potential differences throughout the body, which can be detected superficially by electrodes placed at various points on the skin, after impregnating the stratum corneum with an electrolytic gel at each site. Because the significant frequencies present in the Fourier spectrum at the ECG are low, inductive and capacitive effects within the body around the beating heart are negligible by comparison with resistive phenomena, so the cardio-electric field at any point within the body is describable by Maxwell's equation

$$E = p\, i \text{ volts/meter} \quad (1)$$

where E is the vector of electric-field intensity and i is the vector of electric current density at any point within the quasi-liquid medium, whose resistivity is p.

From the analytic point of view, it is sufficient to regard the heart merely as a generator of repetitive waveforms of voltage that can be recorded by an oscilloscope connected to any pair of the ten standard electrodes used in electrocardiography: right wrist, left wrist, right ankle, left ankle, and thoracic electrodes V^, ¥3, Уз, ¥4, Уз, and Vg. A description of the ECG waveforms observed between various pairs of these electrodes as resulting from moving myocardial dipoles is mentally satisfying to the electrocardiologist, but quite unnecessary to a diagnostician studying the electric signals generated by the human heart.

RATIONALE FOR MATHEMATICAL ANALYSIS OF THE ECG

The diagnostic method of the CUPID system is based upon two postulates for any given individual in a patient population: 1) that the time waveshape of the ECG, including any minor perturbations in amplitude and period of repetition, as observed between any pair of the ten electrodes, is uniquely determined by the physiologic events occurring within the heart and by the spatial location of that electrode pair relative to the heart; and 2) that any change in the physiology of the heart will cause a unique corresponding change in the waveform of the ECG under observation. Underlying these postulates is the assumption that the ECG is recorded for a length of time sufficient to include all of the variations of amplitude vs time that occur for a given individual who is not experiencing acute, rapidly changing intracardiac events that can cause sudden morbidity or mortality.

The validity of the foregoing postulates has never been specifically tested by an experiment designed expressly for that purpose, but has been indirectly verified by cardiologic studies of millions of patients by means of ECG. Such studies do not definitively exclude the possibility that two individuals with different physiologic states of their hearts might produce ECGs that were identical between all possible electrode pairs, or the possibility that a given individual might produce ECGs identical between all possible electrode pairs, respectively, before and after developing some cardiac abnormality. However, such possibilities have very low probabilities.

ANALYTIC MECHANISM OF ECG DIAGNOSIS BY CUPID

In the early part of the nineteenth century, the French mathematician Jean Baptiste Joseph Fourier demonstrated that any periodic function of time satisfying the Dirichlet conditions can be represented by the sum of a spectrum of sinusoidal waves whose frequencies are integer multiples of the frequency of repetition of the original wave. The Dirichlet conditions specify that the original time function must be single-valued, have a finite number of maxima and minima, and have a finite number of finite discontinuities (jumps) in amplitude within any one period of repetition. All periodic biologic phenomena in the real world fulfill these conditions, and hence are Fourier-analyzable.

The typical ECG is not truly periodic, because a healthy subject will show some beat-to-beat variations in heart rate and in the amplitudes of the several "waves," designated by the letters P, Q, R, S, T, and U. However, a Fourier spectrum is still computable from observations of a finite record of such an ECG. If the beat-to-beat variations are significant, the Fourier spectrum will show peaks of finite width on the frequency scale, rather than the line spectrum that is characteristic of a true periodic function. The cyclic fluctuations can be regarded as noise, which, in general, has a continuous spectrum of amplitude and power vs frequency. When a spectrum is continuous, it is a plot of amplitude density, or voltage per unit of bandwidth, rather than a distinct amplitude for each discrete frequency. Similarly, the continuous power spectrum is a plot of power density, or power per unit of bandwidth, vs frequency. The noise is uniquely related to the physiologic events occurring within the heart and to somatic influences acting on the heart via the sympathetic and parasympathetic nervous systems. If an individual is engaging in physical exercise of any kind, myoelectric noise may be comparable in amplitude to the ECG signals. Therefore, it is essential that patients undergoing CUPID testing be maintained in a quiescent state before and during the analysis of ECG waveforms.

SPECIFIC INDICES OF MYOCARDIAL FUNCTION AND PHYSIOLOGY

The spectral power-density function corresponding to the time wave of the electrocardiogram measured between any pair of Einthoven's electrodes may be interpreted as a plot of the electric power per unit of bandwidth dissipated in a resistive load connected between those two electrodes, vs frequency of the sinu-soidal waves in the Fourier spectrum of the ECG. By convention, the resistance of this load is equal to the internal resistance of the cardiac source generating the time wave, so that the power dissipated externally is the maximum available from the source.

The transformation of the time-varying cardiac signal into a frequency spectrum allows the well-developed principles of harmonic analysis to be used in studying the dynamics of the heart. In the frequency domain, a si-nusoidal signal can be modified by passing it through a linear, time-invariant processing device, such as a passive filter, which, in general, will change its amplitude and phase but not its frequency. Such a device can be characterized by a *transfer function,* g(f):

$$g(0 = S,/S, \quad (2)$$

where the symbols in boldface denote *phasor* quantities, i.e., sinusoidal functions of time, each of which has both amplitude and phase, at a given fixed frequency. In equation 2, So is the phasor representing the output signal from the processing device and S, is the phasor of the input signal. In general, the transfer function of the proces-sor may be written in complex phasor notation as

$$g(f) = g(f)eie \quad (3)$$

where g(f) is the amplitude ratio of the transfer function, j is *the* square root of (-1), 6 is the phase shift caused by passing the signal through the processor, and e is the base of the natural logarithms (6 = 2.71828———). In general, both g(f) and 9 are functions of the frequency, f.

It is diagnostically useful to regard the heart as a signal processor that converts the cyclic electric impulses of the sinoatrial node to the ECG observable between any pair of the ten standard electrodes. Because the ECG observed between any one pair of Einthoven electrodes is different from that observed between any other pair, the cardiac-signal processor must be thought of as a multi-port processor having several distinct output signals concurrently derived from the input signal of the sinoatrial node. The biophysical complexity of the heart does not invalidate this concept, even though each segment of the heart may not be truly linear in the sense that output amplitude is always related to input amplitude by a factor of proportionality that is constant for any one frequency.

The cardiac diagnostician can not attach electrodes di-rectly to the heart of a human patient during routine testing, so it is not possible to measure the whole cardiac-transfer function by applying a prescribed stimulus to the sinoatrial node and measuring the several resulting epidermal waveforms of the ECG. However, it is possible to compute this transfer function indirectly and segmentally by regarding the ECG recorded between any given pair of electrodes as being the signal input to a portion of the cardiac signal processor, and the ECG between another pair as the output of that portion. Diagnostically, this is equivalent to postulating that each of the non-redundant ECG waveforms measurable between all possible pairs of the ten electrodes has a distinct Fourier spectrum that is related to every other such spectrum by a transfer function that is unique and constant for any given individual in a fixed state of cardiac health or disease.

Mathematically, ten electrodes combined two at a time will produce 100 pairs. Ten of these are null: electrode 1 paired with itself has no potential *difference,* and so on. Only 45 of the remaining 90 dual combinations are unique: electrode 1 paired with electrode 2 is the reverse of 2 paired with 1, etc. The standard Einthoven "leads," as they are called in cardiographic terminology, are actually just 12 of the 45 unique electrode pairs (Table 1). These "leads", or electrode pairs, are not necessarily the optimum set for frequency-domain studies of the ECG, but they are now deeply embedded in cardiologic tradi-

Table 1. Standard Einthoven "Leads"

Lead I	Left wrist + and right arm -
Lead II	Left ankle + and right arm -
Lead III	Left ankle + and left arm -
aVR	Right wrist + and right ankle -
aVL	Left wrist + and right ankle -
aVF	Left ankle + and right ankle -
V^	4th right costal interspace + and right ankle -
Vg	4th left costal interspace + and right ankle -
У3	Midpoint between chest 3 and chest 4 + and right ankle -V4 5th left interspace, midclavicular, + and right ankle -¥5 Level of ¥4, anterior axillary line, + and right ankle -VgLevel of ¥4, midaxillary line, + and right ankle

tion, so the CUPID system utilizes only leads included in this group.

For example, if the ECG at lead II is considered to be an input, S,(f), to part of the cardiac signal processor, and the ECG at lead ¥5, So(f), is considered to be the output of that part of the processor, then the frequency-domain relationship between these two versions of the ECG is

$$So(0 = S.(f)g(f) \quad (4)$$

where the linear transfer function g(f), as defined by equation 3, is understood to be applied individually and simultaneously to every frequency-domain component ofSi(f).

If the shape and period of the ECG waveform at each "lead" were time-invariant, then its Fourier spectrum would consist only of vertical lines on a plot of amplitude (ordinate) vs frequency (abscissa), and each such line would be located at a frequency n/(At), where Д1 is the duration of one heartbeat, and n = 1,2,3,4,5,————. For a real heart, however, there is always stochastic variation in At and in the amplitude of each *"wave"* (P, Q, R, S, T, or U). As stated earlier, the frequency-domain effect of this phenomenon is to broaden each line of the spectrum from a spike of zero abscissal width into a peak of finite ab-scissal width that includes a band of frequencies, whether the ordinate is amplitude density or power density.

Two mathematical procedures are fundamental to frequency-domain studies of time-domain signals: computation of the autocorrelation function of a single time-varying signal, and Fourier transformation of the autocorrelation function to yield the spectral power density of that signal.[4] For analog signals that can be digitized, these procedures are readily accomplished with a suitably programmed desktop computer. The autocorrelation of a function of time S(t) is defined as

$$C,(\tau) = \lim_{T\to\infty} (1/T); \int_0 [S(t)-S(t+T)]\,dt \quad (5)$$

where T is the interval of integration and represents the maximum value of lag time т for which the integrand in equation 5 can be computed. In the real world, no function of time, S(t), continues or can be inspected for an infinite length of time. Therefore, Сд(т) can not be computed exactly. In practice, it is usually sufficient to calculate the integral for a time T that is large by comparison with the reciprocal of the lowest frequency in the spectrum of S(t), and it is usually undesirable to use lags longer than 10% of the length of the record.[4] *The* lowest frequency in the Fourier spectrum of a normal human ECG is in the order of 1 hertz; for a patient with bradycardia it can fall to a fraction of a hertz.

In order to avoid the phenomenon of aliasing, the sampling rate of the analog-digital converter in the computer should be at least twice the highest significant frequency in the ECG, or about 100 samples per second for a pulse rate of one beat per second, and proportionately higher for increased heart rates. In the actual diagnosis of cardiac abnormalities by the CUPID system, frequencies higher than 25 hertz seldom are significant. Therefore, a sampling rate of 100 hertz is more than adequate.

The Fourier transform of the autocorrelation yields the spectral power-density function of the time signal:

(6)

Conversely, the autocorrelation function may be expressed as the inverse Fourier transform of the spectral power density:

(7)

Equations 6 and 7 are known as the Wiener-Khintchine relations.

Cross-correlation of two separate signals can be performed, and Fourier transformation of the cross-correlation will show whether there is any coherence of one signal with the other. If the two signals are Si(t) and 83(0, the cross-correlation function is

$$C,(\tau) = \lim (1/T);\int Si(t).S2(t+T)\,dt \quad (8)$$

The Fourier transform of C<;(т) is computed according to equation 6 to give the cross-spectral power-density function, Pc(f), of time signals Si(t) and Sgft). If there is coherence between these signals, then Pp(f) will show one or more peaks on a plot of power density vs frequency. However, if there is no synchronism between the signals, P^(f) will be zero, except for errors caused by evaluating Сд(т) and Pp(f) over finite lengths of time. This is so because the product of two sinusoidal functions of time having different frequencies, or having the same average frequency but drifting cyclically in phase, is a pair of sinusoidal functions of time having, respectively, the sum and difference of the frequencies of the two signals. The long-term average of such a pair is zero.

The amplitude-vs-frequency characteristic of a seg-mental transfer function, computed from equation 2 by using, say, the ECG at lead Vg as Si(t) and the ECG at lead II as Sg (t), or vice versa, can be used to compute the impulse response of that segment of the myocardial signal processor. The impulse response is defined as the time-domain output of a linear signal processor that re-

suits when a Dirac impulse function is applied at its input. Although a cardiac diagnostician can not literally apply such an impulse to one of the Einthoven leads and record the response at another such lead, the computed impulse response is of considerable diagnostic value.

Although it is impossible to generate an exact Dirac impulse in the real world, it is a useful concept in the analysis of linear systems in both the frequency domain and the time domain. Mathematically, a Dirac impulse is the first derivative with respect to time of a step function. A step function is defined as

$$SF(t) = \begin{cases} [A, t > t_{\text{„}} \\ [0, t < t, \end{cases} \quad (9)$$

where A is a constant. The Dirac impulse function is d[SF(t)]/dt.

The frequency-domain transfer function of a segment of the cardiac signal processor is g(f) = g(f)6^. The amplitude characteristic of this transfer function is g(f). The Fourier transform ofg(f) is the impulse response of this segment of the cardiac processor:

$$Ь(т) = f\, g(f)'cos2^{-}df \quad (10)$$

where т is time elapsed from the instant at which the Dirac impulse is applied. Conversely, the amplitude-vs-frequency characteristic of the transfer function is the inverse Fourier transform of the impulse-response function:

$$g(f) = .fh(т)^{»}cos2^{<}тгfт•dт \quad (11)$$

For purposes of calculation, the integrals in equations 10 and 11 can be evaluated as one-sided transforms, i.e., from zero to infinity.

The analytic utility of the impulse-response function is that it can be used to calculate the time-domain response, So(t), of the signal processor to any input function of time, S;(t):

(12)

The coherence, or synchronism, of the input and output signals, S}(t) and So(t), for any segment of the my-ocardial signal processor can be judged by a coherence parameter ^(f):

$$^{IPcioWP/tPaiOO-Pao^)]} \quad (13)$$

where Pcio(0 is fhe cross-spectral power-density function of S,(t) and So(t), and P^(f) and Pao(f) are the respective spectral power-density functions of S, (t) and 8д (t). The numerical value of "/^ will lie between zero and unity. If the transfer function of the cardiac signal processor relating Sj(t) and So(t) is such that it causes a phase shift of 90° *(mm/2* radians) between every sinusoidal component of the input-signal spectrum and the corresponding component of the output-signal spectrum, then the cross-power spectrum, Pao(f), will be zero. If the transfer function is such that So(t) is zero, and only noise appears at the output, Pcio(f) will be zero. Although neither of these mathematical extremes is likely to be observed in a human heart, mere is always sufficient phase shift and physiologic noise to make "^ less than unity.

A final index of myocardial function and physiology that is useful in the CUPID system is the *amplitude histogram* of the heights of the three waves designated P, R, and T, measured over a finite time interval of observation long enough that the shape of the histogram is not changing significantly from beat to beat. The histogram is evaluated for leads that present P, R, and T as positive-going waves: e.g., Vg and II. This is a true histogram, as defined in texts[5] on medical statistics. Its horizontal axis is a scale of amplitude in millivolts (or millimeters on a standard ECG) on which the base of each bar of the histogram has the same width, equal to some small fraction of the maximum amplitude recorded. Its vertical axis is a scale on which the height of each bar is the number of beats during which the wave under observation has an amplitude falling within the base width of the bar, divided by the width of the bar. Thus it is a bar graph of

Table 2. Indicators Utilized by the CUPID System

1. Spectral power density at each of the 12 leads This is Pa(0, as given by equation 6.
2. Amplitude characteristic of transfer function, leads IIandVg This is g(f), from equation 3.
3. Phase shift of transfer function, leads II and Vg This is 9, from equation 3.
4. Cross-correlation function, leads II and *У*^ This is C^(т), from equation 8.
5. Impulse response, leads II and Уз This is п(т), from equation 10.
6. Coherence parameter, leads II and ¥5 This is -Yio, from equation 13.
7. Amplitude histogram, lead II or Уз Measured for P, R, and T waves.

amplitude density, in which the *area* inside each bar represents the total number of beats during which the wave under observation has an amplitude falling within the base width of the bar. If the base width of each bar is made progressively smaller and the sampling is carried out for a very long interval of time, the histogram approaches a continuous curve, similar to that of spectral power density.

The indicators of myocardial function and physiology upon which the diagnosis for a given patient is made are summarized in Table 2.

CLINICAL CORREIATION OF MYOCARDIAL INDICES WITH RECOGNIZED DISEASE ENTITIES

This was originally accomplished over a period of nine years by CUPID evaluation[6] of each of 20,000 patients. Of these, 5,000 were "normal" in the traditional cardie-logic meaning of the word: the blood pressure, heart rate, left-ventricular ejection fraction, valvular function, and volumetric cardiac output were within accepted limits for each patient's age and gender, and they did not suffer from angina pectoris. The remaining 15,000 were diagnosed by traditional techniques, such as contrast an-giography, s.p.e.c.t. thallium scintigraphy at rest and after stress, intensity of angina, Kamofsky performance status, and cardiac ultrasonography for valvular disease, as having recognized cardiac abnormalities. The ECG-derived indices listed above were then carefully compared with the recognized pathologic conditions to determine the existence, and the degree, of correlation of the indices with the conventionally demonstrated cardiac-disease entities. This laborious statistical study is constantly ongoing, and the correlative association of the frequency-domain parameters with traditional cardiac-disease states are being steadily refined on the basis of accumulating experience. Independent clinical studies conducted in medical centers in the United States and Brazil have shown that both the sensitivity and the specificity of the CUPID system are above 90%. A recent study[7] conducted at the New York Hospital Medical Center of Queens showed that sensitivity and specificity were both about 95%. That study is summarized in Appendix D. Several earlier studies were done in Western countries.[8-11]

The letter in Appendix D, from William J. Tenet, MD, an investigator in the New York Hospital Study, states "of course, the CUPID is not able to indicate the location of a coronary artery stenosis, but. . . ." That was true when the letter was written, on July 7, 1997. However, since then, refinements in the computation of the seven cardiac indices and the diagnostic algorithms derived from them suggest that it may be possible to locate significant stenoses in one or more of the major coronaries.

OUTPUT OF THE CUPID SYSTEM (APPENDICES A-C)

Algorithms Used to Detect and Quantify States of Cardiac Disease

For obvious reasons, the proprietary algorithms used in CUPID have not been divulged to the author by Auragenics, Inc. However, they are based upon the ordinates (amplitudes) and abscissal locations of various peaks in the waveforms of the seven indices listed in Table 2.

Waveform Printouts and Diagnostic Tables

The waveforms are printed out, as shown in Appendices A, B, and C, by the CUPID instrument's computer, to supplement a "Diagnosis Table" that is concomitantiy printed out in the format shown. The Diagnosis Table consists of a set of eight parameters that are evaluated for each of the 12 standard leads of the ECG; each is displayed as either a plus (+) or a minus (-) sign, indicating, respectively, a positive or a negative diagnostic response. At the bottom of the table, a "suggestion" is printed to indicate the cardiac condition at the time of testing, and to guide the clinician or the technician in the choice of further testing modalities, if such are deemed necessary.

Appendix A shows the diagnostic table and waveforms for a cardiac-normal patient. Appendix B is for a "borderline" patient. Such a patient could have an intrinsic cardiac abnormality but might be suffering temporarily from an abnormal condition in one or more of the somatic systems that have influence on cardiac function. Appendix C shows the results for a patient whose result are very abnormal. The patients whose test results are summarized in these three appendices were evaluated with the CUPID system at the Casa de Salud Hospital in Livramento, State of Rio Grande do Sul, Brazil, by Fernando Guadalupe, MD, Assistant to the Minister of Health of the State of Rio Grande do Sul.

Figure 1 shows a patient being tested by the CUPID system. The total time required for the test after attachment of the electrodes is 21 minutes and 28 seconds.

Explanation of Acronyms in the Diagnostic Tables

The acronyms listed horizontally at the top of each diagnostic table relate to the auto power spectrum, as given by equation 6. Those listed horizontally at the bottom of the table relate to data derived from the impulse

Figure 1. A patient resting in the supine position with ECG leads attached, while the CUPID® system is performing its analysis of ECG waveforms at the 12 standard leads. The operator is giving instructions via the computer's keyboard to guide the system through the menu of algorithms.

response, equation 10; the cross-correlation function, equation 8; the amplitude characteristic of the transfer function, equation 3; the coherence parameter, equation 13; and the phase shift, equation 3. The parameters in the bottom row are evaluated for leads II and ¥5, and those in the top row are evaluated for each of the leads in the left-hand column of the table. The messages represented by the acronyms are as follows:

Auto Spectral Power Density R21 The second peak is greater than the first peak.
Myocardial ischemia. R43 The fourth peak is greater than the third peak.
Myocardial ischemia.
R51 The fifth peak is greater than the first peak. Myocardial ischemia, but some autocompensation. R53 The fifth peak is greater than the third peak.
Myocardial ischemia. L01 First peak is low. Previous injury of myocardium. L03 Third peak is low. Previous injury of myocardium. LOA Average amplitude of first four peaks is low.
Myocardial ischemia. HIA Average amplitude of first four peaks is high.
Ventricular hypertrophy. *Impulse Response* PDN The main peak of impulse response is inverted.
Poor conduction.
MUP Multiple main peaks. Poor conduction and <>or malfunction of left ventricle. *Cross Correlation, Transfer Function Magnitude, and Coherence* RSR Myocardial ischemia. CSR Occasional arrhythmia. *Phase Shift*
PHS Large fluctuations of phase shift. Poor flow rate of blood to myocardium. Abnormal hemody-namics.

A plus (+) sign in the body of the diagnostic table indicates a positive diagnosis, and a minus (-) sign signifies a negative diagnosis for the particular combination of lead and pathologic condition represented by that position in the table. A large number of plus signs corresponds to a severely diseased heart, and vice versa.

Cardiac Abnormalities Diagnosable by the System

Eight cardiovascular morbidities are currently diagnosable by the system:

1. Coronary artery disease
2. Corpulmonale
3. Congenital cardiac disease
4. Bacterial valvular disease
5. Ventricular hypertrophy
6. Cardiomyopathy
7. Bacterial, viral myocarditis
8. Arrhythmias, atrial and ventricular

It should be noted that other abnormalities of the cardiovascular system are probably detectable with suitable additions to the database of patients who have them.

DISCUSSION OF RESULTS SHOWN IN APPENDICES A-C

The CUPID system presents its diagnostic results in the tabular format shown in Appendices A, B, and C. The meanings of the acronyms at the tops of the columns are explained above. On the basis of the relative numbers and tabular locations of the plus (+) and minus (-) signs, the proprietary algorithms of the system generate a computerized diagnostic assessment of the patient's cardiovascular condition and display that assessment on the video monitor at the bottom of the table, below a number showing the heart rate **(HR)** in beats/minute, as **SUGGESTION: CAD** (the acronym for coronary artery disease), for example. Other general diagnostic suggestions are **NORMAL, BORDERUNE,** and more specific expressions, as follows:

C Insufficient blood supply to the heart, including coronary dysfunction, long-term anemia, anoxia, hypoxemia, hypoalimentation, hypocythemia, hypoglycemia, hypohemia, and hypoten-sion, etc; and cardiac ischemia and coronary atherosclerosis. Insufficient blood supply to the heart, including all the abnormalities under C, plus infarction, and elevated blood viscosity (hyperliposis, hypercholesterolemia.hyperlipemia, hyperadiposis), abnormal hemody-namics, etc. Any scar, artificial valve, or myocardial trauma that affects cardiac functions and causes symptoms similar to those of myocardial ischemia or infarction may be suggested by **C(I).**

C(I)

ARRHYTHMIA Any irregularity of heart rate causing the interval between successive R-waves to vary by more than 0.1 second.

OCCASIONAL ARRHYTHMIA Sometimes the R-R interval varies by less than 0.1 second, sometimes by more.

BRADYCARDIA The heart rate is 60 beats per minute or lower.

TACHYCARDIA The heart rate is 100 beats per minute or higher.

A Ventricular hypertrophy or hypertensive cardiac disease. Rheumatic cardiac disease, such as valvular dysfunction. Congenital cardiac disease or factors that may cause cardiac dysfunction. Myocarditis or frequent onset of serious arrhythmia, or infarction. Fibrillation, occasional or potential. Cardiac disease related to pulmonary factors, such as smoking, emphysema, bronchitis, pneumonia, or pulmonary hypertension. Myocardiopathy, including myocardial dysfunction caused by coronary disease, viral infection, or injury caused by surgery, fever, trauma, etc.

F

G

K

N **U**

M

The diagnostic legend **BORDERUNE** indicates regulatory disturbances of the sympathetic and parasympathetic nervous systems, or endocrine irregularities. The patient probably does not suffer from cardiac disease, but is experiencing some temporary functional abnormality resulting from exhaustion by exercise, extreme fatigue, hyposomnia, emotional stress, fear, alcoholism, epileptic sequelae, anesthesia, hemiplegia, apoplexy, puberty, menopause, disorder of the central nervous system, psychiatric disorder, neurasthenia, menstruation, etc.

After appropriate instructions via the keyboard, the CUPID system can differentiate between atrial and ventricular tachycardia, and can indicate whether a K or C diagnosis is more important when either of these legends is displayed.

It should be noted that the presence of any implanted cardiac prosthesis (valve, pacemaker, etc.) may invalidate the diagnostic suggestions of the system.

The system has been designed to allow a nurse, paramedic, instrument technician, or primary care physician to make an intelligent recommendation to the patient (or to the patient's cardiologist) for further testing by more invasive means. *The* total elapsed time is less than 25 minutes:
15 minutes for the patient to rest in a supine position before the electrodes are applied or automatic computer countdown of 20 minutes after the electrodes are connected, and an 88-second period of data acquisition before the system displays the diagnostic legends described above.

CLINICAL INVESTIGATION NOW UNDER WAY IN THE UNITED STATES

On December 8,1997, a prospective randomized, double-blind study of the CUPID system was started at Yale-Bridgeport Hospital in Connecticut, under the direction of Keith Bradley, MD, who is Chief of Emergency Medicine at that institution, and Stuart W. Zarich, MD, Chief of Cardiology at Yale-Bridgeport Hospital and Assistant Clinical Professor of Cardiology at Yale University Medical School. This study will ultimately include at least 700 patients who are admitted to the emergency department at Yale-Bridgeport Hospital with complaints of chest pain and elevated myocardial enzymes. Neither the emergency physicians nor the patients will know the results of the CUPID analyses until several hundred patients have been tested.

In May 1995, the U.S. Food and Drug Administration granted 510 (k) approval of the CUPID system for noninvasive cardiac testing, after reviewing 2,848 cases from the original correlative studies.

EXAMPLE OF THE POWER OF SPECTRAL ANALYSIS

From the science of oceanography comes a superb example of the ability of spectral analysis to detect minute changes in time waves. The following is from the preface to Blackman and Tukey.[4]

This account was written as an extended journal article, not as an introduction to the beauties of spectral analysis. Thus, there is no discussion of why one might want to estimate (power) spectra, and no catalog of the wondrous results thus obtained. We cannot refrain, however, from quoting one wondrous result (from a letter from Walter E. Munk to one of the authors): "... we were able to discover in the general wave record a very weak low-frequency peak which would surely have escaped our attention without spectral analysis. This peak, it turns out, is almost certainly due to a swell from the Indian Ocean, 10,000 miles distant. Physical dimensions are: 1 mm high, a kilometer long.

REFERENCES AND NOTES

1. *Encyclopedia Britannica, 15th ed, vol 4, 1991, p 403.*
2. *Marriott HJL. ECG/PDQ. Baltimore, MD: Williams & Wilkins, 1987.*
3. *Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. Vols 1 and 2. Philadelphia, PA: W. B. Sounders, 1992.*
4. *Blackman RB, TukeyJW. The Measurement of Power Spectra. New York: Dover, 1958.*
5. *Cotton T. Statistics in Medicine. Boston, MA: Little, Brown, 1974.*
6. *Feng G, and Beijing Municipal Committee of Science and Technology: Appraisal ofEKG and EEC Multiphase Information Diagnosis System. File No. Academia Sinica 88, Chen-Jei 026, Institute of Biophysics, Academia Sinica, Beijing, China, May 4, 1988.*
7. *Tenet Wf. Research Protocol No. 1261096,106 patients. The New York Hospital Medical Center of Queens, Flushing, NY, Sept-Nov 1996. Available from the hospital.*
8. *Feng G, GodinJF, Reissen L. Clinical Trials of CUPID at Bichat Hospital, Paris, France, 1989; 79 patients. Differentiation ofnormal from abnormal patients: 90%. Differential diagnoses of 8 cardiac abnormalities: 85%. Available from the hospital.*
9. *Feng G, Huston J. Clinical Trials of CUPIDS at Riverside Methodist Hospital, Columbus, Ohio, 1990; 54 patients. Study monitored by Maggio B, for the PDA. Differentiation of normal from abnormal patients: 90%. Differential diagnosis of 8 cardiac abnormalities: 89%. Available from the hospital.*
10. *Feng G, SungR. Clinical Trials of CUPID® system at Stan-ford University Medical Center, Palo Alto, California, 1993; 48 patients. Study monitored by Maggio B, for the FDA. Differentiation of normal from abnormal patients: 90%. Differential diagnosis of 8 cardiac abnormalities: 83%. Available from the medical center.*
11. *de Freitas Gomez M, Vaz R. Clinical Trials of CUPID® system at the Institute of Cardiology Foundation, University of Cardiology, Porto Allegre, Brazil, June 1996; 43 patients. Differentiation of normal from abnormal patients: 94%. Differential diagnosis of 8 cardiac abnormalities: 94%. Available from the foundation.*

BIBLIOGRAPHY

12. *Murthy VK, et al. Analysis of power spectral densities of electrocardiograms. Math Biol. 1971;12:41-51.*
13. *Saltzburg S, Haywood J. ECG monitoring and waveform analysis utilizing interactive computer graphics. JAssocAdv MedInstr. 1971;5:91-6.*
14. *Murthy VK, et al. Clinical usefulness of ECG frequency spectrum analysis. IEEE Trans BiomedEng. 1978:610-2.*
15. *Teichholz LE, et al. The Omnicardiogram: Early Detection of Abnormalities of the Electrical Signal of the Heart. Computers in Cardiology, Long Beach, CA; IEEE Computer Society, 1980, p 277.*
16. *Feng G. Theory and Practice of EKG and EEC Computer Analysis. Beijing, China: Scientific Press, 1986 [in Chinese].*
17. *Kelly GJ, et al. Effects of analyzed signal duration and phase on the results of fast Fourier transform analysis of the surface electrocardiogram in subjects with and without late potentials. J Am Coil Cardiol. 1987:60: 1282.*
18. *WillemsJL, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. N EnglJMed. 1991:325:1767.*