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Algorithm for Quantitative 3 Dimensional Analysis of ECG Signals Improves Myocardial Diagnosis over Cardiologists in Diabetic Patients

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Abstract - **Acute myocardial infarction (AMI) diagnosis in type II diabetes (DM2) patients is difficult and ECG findings are often non-diagnostic or inconclusive. We developed computer algorithms to process standard 12-lead ECG input data for quantitative 3-dimensional (3D) analysis (my3KGTM), and hypothesized that use of the my3KGTM's array of over 100 3D-based AMI diagnostic markers may improve diagnostic accuracy for AMI in DM2 patients.**

Methods: We identified 155 consecutive DM2 patients age >25 yrs with chest discomfort or shortness of breath who were evaluated at an urban emergency department (130 patients (pts)) or the cardiac catheterization laboratory (25 pts) for possible AMI. The first digital 12-lead ECG for each patient, obtained within 30 min of presentation, was evaluated by (1) 2 blinded expert cardiologists, and (2) my3KGTM. In each case, the ECG was classified as either likely AMI or likely non-AMI. "Gold standard" was the final clinical diagnosis. Statistical analysis was McNemar's test with continuity correction.

Results: The 155 DM2 patients were 50% male, mean age 56.8 ± 12.0 yrs; 44 pts had a final clinical diagnosis of AMI (17 ST Elevation Myocardial Infarctions (STEMI), 27 Non-ST Elevation Myocardial Infarctions (NSTEMI)) and 111 had no AMI.

Conclusions: Relative to standard 12L ECG read by cardiologists, quantitative 3D ECG analysis showed significant and substantial gains in sensitivity for AMI diagnosis in DM2 patients, without loss in specificity. Sensitivity gains were particularly high in patients exhibiting NSTEMI, the most common form of AMI in DM2.

Index Terms - Electrocardiography, Diabetes Mellitus, Acute myocardial infarction

I. Introduction

The standard 12-lead electrocardiogram (ECG) is invaluable for initial diagnosis of suspected heart disease, but is limited by relatively low diagnostic sensitivity and specificity [1]. In part, these limitations can be attributed to the fact that the ECG provides a 2-dimensional (2D) representation of cardiac electrical activity, an inherently 3-dimensional (3D) event. In addition, inaccurate physician interpretation of ECGs remains a significant issue; studies have demonstrated errors of "major proportions" in 4% to 32% of routine ECG interpretations [2]. Such interpretive errors can lead to clinical mismanagement, such as failure to detect and appropriately treat patients with acute myocardial ischemia.

Over the years, various efforts have been made to address the diagnostic limitations of the ECG, including but not limited to vectorcardiography, body surface mapping, and magnetocardiography [3-5]. One of the earliest examples of such efforts was vectorcardiography and primarily used from 1940s to the 1970s. A vectorcardiogram (VCG) is a spatial representation of magnitude and direction of the electrical currents of the heart analyzed in three orthogonal planes. Like the ECG, the VCG records and presents information about the electrical potential difference between the body surface and an electrical dipole in the approximate center of the heart. However, in the ECG, signal waveforms are presented individually as recorded from individual leads, whereas in the VCG, measurement points are positioned so that the three derived signals correspond to the three orthogonal axes (X, Y, & Z).

In spite of its diagnostic promise, vectorcardiography declined considerably by the 1970s. The decline was fueled by the technique's limitations, including complexity, the need for special leads and equipment, and – because of the era's technological limitations - a relatively small yield of diagnostic information. However, even with limited technology, VCG proved at least as powerful as the ECG in diagnosing a number of important conditions, including myocardial infarction, chamber enlargement, conduction abnormalities, and pre-excitation [3].

Remarkable gains in computational power create an opportunity to extract substantially more diagnostically valuable 3D information from the ECG signal, significantly enhance the ECG's diagnostic utility, and make it easier to use for the medical professional. We developed a set of algorithms and tools, named my3KG^{TM}, that provide a comprehensive method to describe cardiac electrical activity in time and 3D space. my3KG^{TM} extracts additional information from standard 12-lead ECG signals and uses it to generate a 3D representation of cardiac electrical activity as a function of time. The my3KG^{TM} also includes algorithms for real-time vectorial analysis and normalization tools to ensure accurate and balanced representation of all

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heart regions.

I. Methods

The my3KG™ approach comprises 4 main steps [6]:

1. *Transform* input from the standard 12 lead ECG into X,Y,Z components of the heart vector
2. *Normalize* the lead vectors to equalize electrical representation from all regions of the heart.
3. *Characterize* the lead vectors to extract useful information regarding the presence or absence of acute myocardial infarction
4. *Classify* patients as either having acute myocardial infarction or not having myocardial infarction

Transforming ECG input into X, Y, Z components of the heart vector. Several algorithms are available for converting 12 lead ECG data to orthogonal components of the heart vector [7-9]. One such algorithm is the inverse Dower matrix (ID), which is applied to ECG signals recorded from the standard positions of the leads [10]. The heart vector is calculated:

$$\vec{H} = ID \cdot \vec{V} \quad . \tag{1}$$

The X, Y, and Z components of the heart vector ($\vec{H}$) may be solved at any time point by applying the ECG data ($\vec{V}$) into the above equation.

Normalize the lead vectors. The my3KG™ includes a suite of algorithms to correct the problem of regional variation in electrical attenuation. Each lead attenuation factor is normalized to a standard or common attenuation factor. Individual lead attenuation factors (ρ_i) are calculated for each of the six precordial leads, the calculated individual ρ_i's are used to derive a single attenuation factor ρ, and ρ is then used as the common attenuation factor for all precordial leads. The frontal leads do not normalization due to the distal electrode positions.

Precordial lead vector magnitudes are calculated as follows, where $V_i(t)$ is the recorded voltage over time from a lead and $Vd_i(t)$ is the derived voltage for each of the ECG leads. Derived lead voltages are calculated as a scalar product of the heart vector H and a lead vector, L, or alternatively

$$Vd_i(t) = \vec{H}(t) \cdot \vec{L}_i \cdot \rho_i \quad , \tag{2}$$

Where $\vec{H}$ denotes the heart vector and $\vec{L_i}$ is the unit lead vector defined by the direction of the position of the i*th* electrode (e.g., precordial electrode 1 to 6), and ρ_i is the unknown lead attenuation factor for each electrode. Using the least squares method, the unknown attenuation factor ρ_i for every lead can therefore be calculated as a minimum of the function: time averaged difference of derived ECG lead and corresponding measured lead

$$F_i = \int_0^T \left[V_i(t) - \vec{H}(t) \cdot \vec{L}_i \cdot \rho_i \right]^2 dt \quad , \tag{3}$$

where T is the recording time. From this, we derive the relationship as:

$$\rho_i = \frac{\int_0^T V_i(t) \cdot [\vec{H}(t) \cdot \vec{L}_i] dt}{\int_0^T [\vec{H}(t) \cdot \vec{L}_i]^2 dt} \quad . \tag{4}$$

Each measured attenuation factor ρ_i is calculated by solving for the minimum value of the least-squares difference between the actual ECG waveform and a derived ECG waveform calculated from the heart vector at that point. The normalized attenuation factor, ρ, is selected from the range of individual attenuation factors (ρ_i) for measured leads. Each individual attenuation factor is approximately equal to the ratio between a virtual cardiac signal derived from the heart vector for a given lead over some time period, and an actual cardiac signal recorded at the same lead for the same time period of time. In this manner, the normalized attenuation factor, ρ, is chosen to minimize the difference between the derived signal and the signal as actually recorded across all precordial leads.

Using the normalized attenuation factor, one can derive the time dependent voltage in any virtual lead at any time:

$$Vd(t) = \vec{H}(t) \cdot \vec{L}_i \cdot \rho \quad . \tag{5}$$

The normalization factor can be used to draw a virtual "sphere" of equal signal attenuation around the heart, and can be used to calculate a derived voltage at any point on the virtual sphere (Fig 1), whether or not that point corresponds to a measured lead.

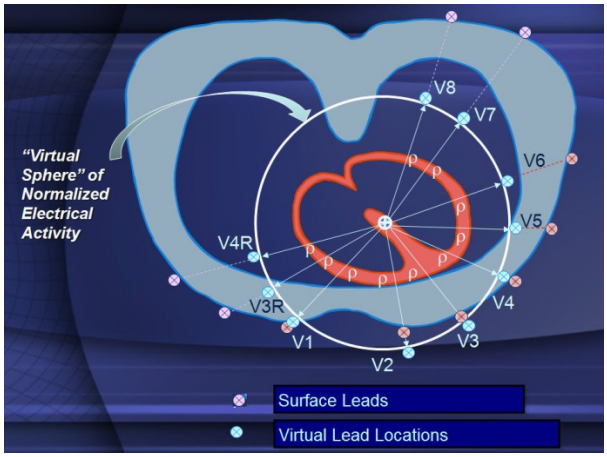

Fig. 1. Calculation of a "virtual sphere" of normalized cardiac electrical activity. See text for discussion. V3R, V4R, V7, and V8 are additional electrode location that may be used in an ECG recording.

For example, as shown in Fig. 1, it is possible to calculate virtual leads corresponding to V3R, V4R, V7 and V8 even though there is no corresponding measured value. Importantly, normalization assures that the derived voltages may be directly compared to any other normalized voltages on the virtual sphere. Thus, for example, 1 mm of ST segment deviation in any of the derived leads is directly comparable to 1 mm of ST segment deviation in any of the normalized precordial leads.

In this manner, normalization allows direct comparison of

cardiac voltage levels anywhere around the heart (Fig. 2). Thus, it is particularly helpful for ECG-based diagnostic markers that rely in part on the magnitude of recorded cardiac electrical signals (for example, ST segment shift in ischemia, R wave voltage in left ventricular hypertrophy, P wave voltage in atrial enlargement, etc).

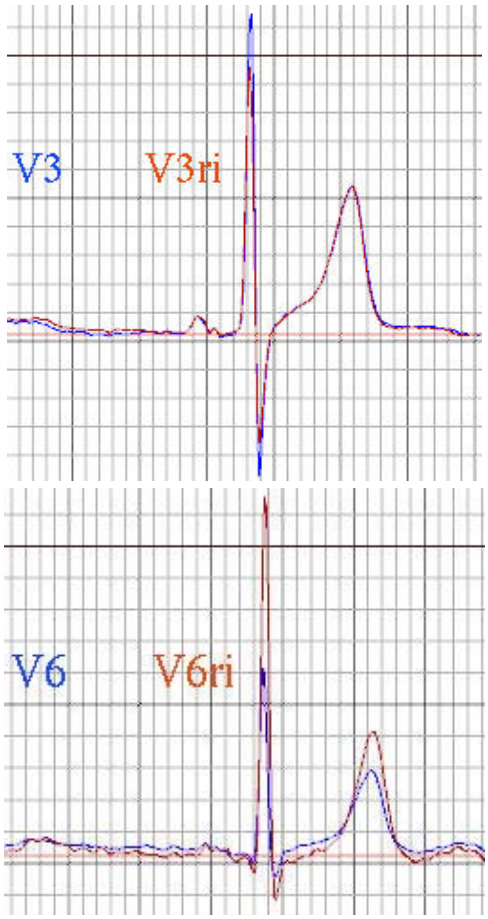

Fig. 2. Using a common attenuation factor to normalize lead voltages. In this figure, both the measured voltages in V3 and V6 (blue lines) and derived voltages (V3ri and V6ri, red lines) are shown superimposed. The derived voltages are calculated by use of the common attenuation factor as described. Note that in lead in V3, the measured voltages generally larger than the derived voltage, whereas in lead V6, the derived voltage is generally larger than the measured voltage. The derived voltages are calculated so that they would fall on the "virtual sphere" (Fig. 1).

Characterization of the lead vectors. After the leads are normalized, useful characteristics need to be extracted from these normalized leads in order to determine the presence or absence of acute myocardial infarction (AMI). These characteristics, called markers, can be used to specifically characterize AMI or other ECG diagnosis. For instance, one of the markers is the ST elevation. Some AMI patients have a characteristic ST elevation myocardial infarction. However, patients with left ventricular hypertrophy (LVH), right bundle branch block (RBBB), benign early repolarization (BER), among other all exhibit ST elevation. Some patients can have multiple diagnoses such LVH with AMI or RBBB with AMI. Since these patients can have multiple diagnoses and each diagnosis have overlapping characteristics, many markers are used to classify patients with AMI. These markers included: ratiometric (e.g., R peak to ST elevation), angular (e.g. angle QRS to T loops) or cluster-specific (e.g. BER, RBBB specific clusters). There are a total of 15 proprietary markers derived from the normalized leads and the heart vector used in the current version of my3KG.

Classifying patients. After all markers for the given ECG are generated, these markers are used to diagnose the patients. The classification scheme is a hierarchical approach with individual decision made through quadratic discriminate analysis classifiers. The output of this algorithm is a single AMI or non-AMI response.

The classifier was developed on a set of approximately 800 ECGs recording from emergency department, catheterization laboratory, and cardiac clinics. These recordings contained both STEMI and NSTEMI ECGs as wells as ECGs with pseudo-ischemia. Pseudo-ischemia's are ECGs with characteristics of an AMI, but the patient does not have AMI. These ECGs include patients with BBB, LVH, pericarditis, myocarditis, Wolf-Parkinson-Wolf syndrome, and others. The patients in the current study are not patients in the 800 ECG training set.

II. Results

University of Kansas Medical Center Study in AMI

The study included 155 consecutive patients who: presented to either University of Kansas Medical Center (KU, Kansas City, KS) Emergency Department with chest discomfort or shortness of breath; were admitted to KU cardiac catheterization laboratory for suspected myocardial infarction; received an ECG recording within 30 minutes of admission; had cardiac troponin I levels measured within 90 minutes of admission; and had Type II diabetes Mellitus (DM2).

The primary endpoint of the study was to compare the sensitivity and specificity of my3KG™ software to expert cardiologists. There are two cardiologists with experience reading ECGs. Their results (true positives, false positives, true negatives, and false negatives) were averaged to obtain one set of results. Both my3KG™ and the cardiologists were given the same ECGs and both had to label the patient as either having AMI or not having AMI. my3KG™ was blinded to the patients' age, sex, signs, symptoms, and clinical history. The cardiologists did know that the patients in this data set arrived at an emergency department with chest discomfort or shortness of breath, received an ECG recordings within 30 minutes of admission, and had troponin I levels measured within 90 minutes of admission. The cardiologists were blinded to other clinic symptoms, the patients' age, sex, signs, clinical history, and the results of any tests. The proportions of ECGs categorized as AMI or non-AMI by both methods were compared using McNemar's test with continuity correction.

Of the 155 patients, 78 patients were male. The mean age of the 155 patients was 56.8 ± 12.0 years. 26 patients had LVH; 6 patients had RBBB; and 4 had atrial fibrillation, atrial flutter, and/or supraventricular tachycardia. 44

patients had a final clinical diagnosis of AMI with 17 of these 44 patients having ST elevation myocardial infarction (STEMI) and 27 having non-ST elevation myocardial infarction (NSTEMI). 111 patients did not have AMI.

The sensitivity (true positives detection divided by total number of patients with AMI) and specificity (true negative detection divided by total number of patients without AMI) were recorded for both the algorithm and the cardiologists and compared (Table 1). The sensitivity for my3KG™ and the cardiologists was 68% and 48%, respectively. The AMI patients can be subdivided into STEMI and NSTEMI. The sensitivity for my3KG™ was 82% and 59% for STEMI and NSTEMI, respectively. The sensitivity for cardiologists was 65% and 37% for STEMI and NSTEMI, respectively. The specificity for my3KG™ and the cardiologists was 87% and 86%, respectively. my3KG™ performed statistically better in sensitivity without compromising the specificity.

Table 1. The sensitivity and specificity of detecting acute myocardial infarction (AMI) in diabetic patients. The cardiologists generally performed worse in detecting AMI than the my3KG™ algorithm. The cardiologists' specificity was comparable to the my3KG™ algorithm.

		Cardiologists	my3KG	Relative Gain
Sensitivity	All AMI	48% (21 TP / 44 Total)	68% (30 TP / 44 Total)	43% p < 0.01
	STEMI	65% (11 TP / 17 Total)	82% (14 TP / 17 Total)	27% p = NS
	NSTEMI	37% (10 TP / 27 Total)	59% (16 TP / 27 Total)	60% p < 0.05
Specificity	No AMI	86% (95 TN / 111 Total)	87% (96 TN / 111 Total)	1% p = NS

III. Conclusion

The purpose of this study was to determine if the my3KG™ algorithm could detect acute myocardial infarction with greater accuracy than the expert cardiologists in patients with type II diabetes mellitus. AMI diagnosis in DM2 patients is difficult and ECG findings are often inclusive.

In this study, 2 expert cardiologists diagnosis were compared with the my3KG™ diagnosis. my3KG™ was able to diagnosis more AMI correctly without suffering any loss in specificity. The largest relative gain in sensitivity was a result of the increased detection of NSTEMI AMI. In NSTEMI, patients' ECGs do not exhibit the characteristic ST elevation that is commonly associated with AMI making the ECG harder to diagnose. DM2 patients generally have a higher occurrence of NSTEMI than a patient without DM2 [11, 12]. The algorithm had a lower, non-significant relative gain in detecting STEMI AMI compared to the cardiologists.

One limitation of this study is its relatively low sample size. The all AMI and NSTEMI difference were large enough that a significant statistical test could be determined. However, the STEMI population size was too small to show statistical difference between the two results. A larger study needs to be conducted to determine if these results hold true.

Relative to standard 12L ECG read by cardiologists, my3KG™ showed significant gains in sensitivity for AMI diagnosis in DM2 patients, without loss in specificity. Sensitivity gains were particularly high in patients exhibiting NSTEMI, the most common form of AMI in DM2.

References

[1] D. M. Mirvis and A. L. Goldberger, "Electrocardiography," Chapter 12 in Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Eighth Edition 2008, Libby P Ed.

[2] S. M. Salerno, P. C. Alguire, H. S. Waxman, "Competency in interpretation of 12 lead electrocardiograms: a summary and appraisal of the published evidence," *Annals of Internal Medicine*; vol. 138, pp. 751-759, 2003.

[3] AR Perez Riera, *et al.*, "Significance of vectorcardiogram in the cardiological diagnosis of the 21st-century," *Clinical Cardiology* vol. 30, pp. 319-323, 2007.

[4] W. H. Self, *et al*. "Body surface mapping in the ED evaluation of the patient with chest pain: use of the 80-lead electrocardiogram system." *The American Journal of Emergency Medicine*, vol. 24, pp. 87-112, 2006.

[5] J-W Park, P. M. Hill, N. Chung, P. G. Hugenholtz, F. Jung. "Magnetocardiography Predicts Coronary Artery Disease in Patients with Acute Chest Pain." *Ann Nonivasive Electrocardiol* vol. 10, pp. 312-323, 2006.

[6] B. Bojovic, L. Hadzievski, P. Belicev. "Visual three dimensional presentation of ECG data". International Patent Application PCT/US2005/001239, WIPO Publication No. WO/2005/072607, 2005

[7] H. E. Burger, & J. B. van Milaan, "Heart Vector and Leads." *Brit Heart J,* vol. 10, pp. 229, 1948.

[10] L. Edenbrandt, & O. Pahlm. "Vectorcardiogram Synthesized from a 12-Lead ECG: Superiority of the Inverse Dower Matrix." *J Electrocardiol* vol. 21, pp. 361-367, 1988.

[11] A. K. Gitt, *et al*. "Similar high rates of newly diagnosed abnormal glucose metabolism in STEMI and NSTEMI in clinical practice: Results of the German SWEETHEART Registry." *Circulation* vol. 122, A20980, 2010.

[12] S. M. Donahoe, *et al*. "Diabetes and mortality following acute coronary syndromes." *JAMA* vol. 298, pp. 765-775, 2007.