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Development of an Automated Method for Display of Ischemic Myocardium from Simulated Electrocardiograms (DIMS-ECG)

Short title: Display of Ischemic Myocardium from Simulated ECGs

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Abstract

Background: Knowledge of the size and location of ischemic myocardium during acute coronary occlusion could provide decision support prior to reperfusion therapy. ECG scores based on the number of leads and the sum of ST-segment elevation have been unreliable in quantifying ischemia. We aimed to develop a new method to graphically Display Ischemic Myocardium from Simulated Electrocardiograms (DIMS-ECG) associated with known ischemic regions.

Methods: Twenty-one patterns of ischemia based on normal coronary anatomy were programmed into the freely available program ECGSIM (www.ecgsim.org). Minor variations of these patterns and five levels of ischemia severity produced 45,455 ECGs; 1,000 normal ECGs were also added. Given a *de novo* ECG (an ECG from a patient), ST-segment and T-wave measurements are compared to ECG measurements in the database. The closest 200 matches are selected and the corresponding ischemic areas are "averaged" to create a graphical display of the ischemic myocardium.

Results: Three patients are presented who underwent elective coronary angioplasty with continuous ECG recording and scintigraphically defined ischemic myocardium. Based on ECG analysis, the program graphically displays the ischemic myocardium with close agreement to the scintigraphic images. The program's source code and the ECG database will be made freely available.

Conclusions: The DIMS-ECG method graphically displays ischemic myocardium from information contained in the 12-lead ECG based on a novel approach to use a large simulated database instead of rule or score based method. Following further development and testing, the DIMS-ECG method could be used to risk-stratify patients with acute myocardial infarction.

Key Words: ischemia, ECG simulation, display, database

Introduction

Following acute coronary artery occlusion, the final infarct size depends on the duration of occlusion, the size of ischemic myocardium at risk and collateral coronary flow to the ischemic region (1,2). Acute myocardial infarction can be treated by invasive primary percutaneous coronary intervention (PCI) or noninvasive trombolytic agents, depending on the availability of PCI centers (*i.e.* prehospital or community hospital thrombolytics or transfer to a PCI center) (3,4). Knowing the size of myocardium at risk of infarction upon patient presentation could stimulate further research into which subsets of patients might benefit more from certain therapeutic strategies.

In humans, myocardium at risk can be measured with single photon emission computed tomography (SPECT) (5). A radioactive technetium-based tracer is injected before opening of the occluded vessel, and SPECT imaging is performed within 3 hours. However, this requires continuous availability of a radioactive tracer, injection of the tracer in the setting of acute coronary occlusion, and scanning with a gamma camera (usually after reperfusion), which could interfere with patient care. Although the tracer is injected before opening of the artery, the location and size of the myocardium at risk is often not determined until after reperfusion therapy has been administered. Therefore, new clinical methods that quantify myocardium at risk before treatment need to be developed.

The standard 12-lead electrocardiogram (ECG), which is inexpensive and widely available, is the most frequently used diagnostic tool for detecting both acute and healed myocardial infarction. Prior studies have used the presence or absence and the sum of ST-

segment deviation in the 12-lead ECG to quantify myocardium at risk (6), however, the results have been unreliable when compared with SPECT (7). These approaches do not take into account the complex interactions that affect the body-surface electrocardiogram, which include that certain ventricular walls have greater effects on the ECG than others, that individual leads are at different distances from the heart and that electrical cancellation can occur (8).

In order to make sense of these complex interactions to quantify chronic infarcts, Selvester and colleagues used computer simulation of the electrical activity of the heart to develop a 12-lead ECG QRS-scoring system to quantify different size infarcts throughout the left ventricle (9). A new, freely-available simulation program, ECGSim (www.ecgsim.org) uses a heart and thorax model measured by magnetic resonance images and takes into account the complex geometry and differences in conductivity between the myocardium, blood pool and lungs (10). We hypothesized that simulations using ECGSim could be used to study acute ischemia and develop methods to quantify myocardium at risk of infarction. The aim of the paper was to develop an automated method that Graphically Displays Ischemic Myocardium associated with a patient ECG, from here on denoted as *de novo* ECG by comparing the electrocardiogram to a database of Simulated Electrocardiograms (DIMS-ECG method).

Methods

In this study, we generated a database of simulated 12-lead ECGs associated with known areas of ischemia. Then, given a *de novo* ECG, measurements of ST-segment elevation and T-wave amplitude from each lead are extracted and compared to the same measurements from all ECGs in the database. The closest matches are combined and presented graphically on a polar plot, which is a method of displaying the LV. Figure 1 shows the relationship between displaying

ischemic myocardium (shaded area) from a left anterior descending (LAD) artery occlusion on a "Mercator projection" (Figure 1A) and a polar plot (Figure 1B). Each image shows the typical distribution of the coronary arteries and the division of the left ventricle into four walls. The same region of ischemia is shown on a three-dimensional depiction of the left and right ventricles in Figure 2 (right).

Development of the DIMS-ECG database

We used the freely available simulation program ECGSIM (www.ecgsim.org) (10) to simulate ischemia and produce a database of the corresponding ECGs. ECGSIM allows the user to alter the transmembrane (action) potentials on the endocardium and epicardium in 257 nodes on the left and right ventricles (Figure 2). ECGSIM does take into account the position of the heart in the chest and that electrical cancellation can occur. Parameters for each node can be set manually or can be retrieved from a file. The resulting electrical changes can be viewed on body surface maps and 12-lead ECGs that can be saved to files. Ischemia was simulated by changing the action potentials to yield a delayed initiation of action potential upstroke (delayed depolarization), a depolarized resting potential (resulting in reduced action potential amplitude) and earlier repolarization (reduced action potential duration). Of note, two additional changes do occur during acute ischemia. There is a decrease in the action potential upstroke velocity (which is separate from the delay in the initiation of the upstroke) and a decrease in the maximum potential to which the cell depolarizes (further reducing action potential amplitude in addition to the depolarized resting potential) (11-13). The process of creating the DIMS-ECG database is shown in Figure 3 and can be summarized as follows:

1. *Defining different levels of ischemia*

   Five different levels of ischemia severity were simulated; the different levels included both delaying depolarization time by 15, 15, 10, 10 and 8 milliseconds, reducing action potential duration, and reducing action potential amplitude to 50%, 80%, 85%, 90% and 93% of normal.

2. *Establishing basic ischemic regions*

   Simulating all possible ischemic patterns with 257 nodes would result in 6^{257} potential combinations (one normal level and 5 different levels of ischemia). This amount of simulation is not possible to handle and therefore limitations were set. As a first step, we decided which physiologically ischemic regions should be included in the database. The location and size of the simulated ischemic regions were selected based on coronary artery distributions as previously defined by Selvester (Figure 1) (9). We divided the coronary artery distributions into 10 basic regions. These were combined to produce small, medium and large regions of ischemia to obtain a total of 23 regions (Table 1).

3. *Expanding ischemic regions*

   Variations of the regions were developed by slightly expanding the size of the ischemic area outside of the basic regions. The region was allowed to include one of the neighbour nodes to the nodes within the basic region. This resulted in 9091 unique patterns and in each of these patterns five different levels of ischemia were simulated, resulting in a total of 45,455 ECGs. In addition, 1,000 “normal” ECGs were added to the database by introducing small random modifications of the normal action potentials. Given a normal *de novo* ECG, the program has to be able to find enough normal samples in the database to correctly classify the ECG.

Using the DIMS-ECG database

The steps involved in using the DIMS-ECG database are shown in Figure 4 and can be summarized as follows:

1. Given a *de novo* ECG, maximum and minimum T-wave amplitude and ST-segment amplitude at the J-point, J + 40 ms and J + 80 ms were extracted for each lead, which resulted in a total of 60 measurements (5 parameters in 12 leads) for that particular ECG. In the current implementation, additional parameters can be chosen from a set of 27 possible parameters. The same measurements were extracted from each ECG in the database. The parameter-extraction routine was based on the SignalAnalysis software developed by the Signal Processing Group (Department of Applied Electronics, Lund University, Lund, Sweden) (14).
2. A simple approach would be to compare the 60 *de novo* ECG measurements with the corresponding measurements for each ECG in the database. However, many of these 60 measurements are highly correlated and, therefore, this approach would not result in an accurate method of matching two ECGs. Instead, the database was compressed by the use of Principal Component Analysis (PCA) (15). PCA finds orthogonal modes of variation in the database so that the 60 measurements from one ECG can accurately be described using only 3-5 parameters (principal components). In the current implementation of the algorithm the user can select the number of principal components to use.
3. The *de novo* ECG is compared to each ECG in the database by calculating the Euclidean distance between their principal coordinates. The closest 200 matches are selected and the regions of ischemia associated with the retrieved 200 matches are “averaged” to

obtain one image representing the myocardium at risk of infarction. This number of matches in the algorithm was selected to be approximately 5‰ of the number of ECGs in the database so that the matches would not exceed the number of combinations in one basic region. In addition, a percentage representing how many of the matched ECGs belonged to each basic region is calculated. This can be interpreted as the likelihood that the *de novo* ECG belongs to each basic region.

Testing the simulated ECG database

In order to test the applicability of the DIMS-ECG database, three patients were selected from the STAFF studies investigations (14,16). These individuals had stable coronary disease and were referred for prolonged percutaneous transluminal coronary angioplasty with nonperfusion balloons at the Charleston Area Medical Center (Charleston, West Virginia). The 3 patients were selected to have one example from each of the main coronary arteries that meets American College of Cardiology/American Heart Association ECG criteria for acute ST-elevation myocardial ischemia. Patient #1 had a left circumflex (LCX) occlusion, patient #2 had a right coronary artery (RCA) occlusion and patient #3 had a left anterior descending (LAD) occlusion. They underwent two SPECT studies, one with sestamibi injection during prolonged balloon occlusion and one control study on the following day (16). The method for SPECT imaging acquisition and analysis was described previously (16). Twelve-lead ECGs were recorded continuously before, during and after angioplasty (14). For this study, we used ECGs recorded just before balloon deflation. The STAFF studies were approved by the investigational review board and informed consent was obtained from each subject.

Results

Figure 5 shows the ECGs and Figure 6 shows the SPECT and DIMS-ECG polar plots for three patients who underwent prolonged coronary angioplasty. Patients #1 and #2 both have ECGs with ST-elevation in the inferior leads (II, III and aVF) and ST-depression in the anterior precordial leads (primarily V2 and V3). The DIMS-ECG algorithm correctly predicted that Patient #1 had an LCX occlusion and Patient #2 had an RCA occlusion. The DIMS-ECG polar plot output of Patient #1 predicted ischemia in the posterolateral and inferior walls, which is concordant with the SPECT ischemic region. The 200 ECGs in the DIMS-ECG database that were most similar to the ECG of Patient #1 consisted of 78% dominant LCX, 11% nondominant LCX and 11% RCA. The DIMS-ECG polar plot output of Patient #2 predicted ischemia limited to the inferior wall, which is in agreement with SPECT. The DIMS-ECG distribution of most-similar ECGs were 84% RCA and 16% dominant LCX. The LAD occlusion of Patient #3 produced ST-elevation in leads V2, V3, V4, I and aVL and ST-depression in leads III and aVF. The DIMS-ECG polar plot predicted ischemia in the anterosuperior and anteroseptal left ventricular wall, which is in agreement with SPECT. The 200 most similar ECGs (100%) were from LAD occlusion.

The entire algorithm is written in Matlab (http://www.mathworks.com) and will be made freely available in open source form upon the time of publication at http://www.heiberg.se/dims-ecg. This will also include the database with the 46,455 ECGs together with their classification and perfusion defect territories. The user can easily define a wide range of ECG parameters to include in the analysis and it is easy to recompute the PCA. The parameters can then be explored quantitatively. It is also possible to load ECGs and visualize their parametric time series.

Discussion

We have developed an automated algorithm to quantify and graphically display ischemic myocardium at risk of infarction. The novel DIMS-ECG method uses the freely available ECG simulation program ECGSIM to create a database of approximately 45,000 ECGs paired with graphical displays of ischemia. Given a *de novo* ECG, ST-segment and T-wave amplitude measurements are compared with those of the ECGs in the database. Similar ECGs are identified and their graphical displays of ischemia are averaged to show the estimated ischemic area for the *de novo* ECG. Following further development and testing, this DIMS-ECG method could be implemented in commercial ECG machines and used to risk-stratify patients with acute myocardial infarction in the prehospital or emergency department setting.

Physicians and researchers have been using the ECG to diagnose myocardial ischemia and infarction for almost 100 years. However, it is difficult to unscramble the complex interactions that affect the body-surface ECG. In the 1950s-1960s there were conflicting studies in the literature regarding the ability of the ECG to diagnose chronic infarcts (17). However, computer simulation of electrical depolarization by Selvester and colleagues showed that infarcts in all parts of the heart produced quantifiable changes in the body-surface ECG (17,18). This led to the development of the 53-criteria, 32-point Selvester QRS-score to quantify and localize infarcts (9). While the ECG is routinely used to diagnose acute myocardial ischemia, there have been conflicting reports regarding its ability to quantify the size of ischemic myocardium (6,7). Prior approaches have not been based on systematic simulation of ischemia and have used simplistic approaches where ST-segment deviation in each lead is given equal weight. This does not take into account that individual ECG leads are at different distances from the heart and that

certain ventricular walls have greater effects on the ECG. Thus, we sought to develop a more sophisticated algorithm by simulating different sizes and severities of ischemia throughout the LV. However, unlike the rule-based approach developed by Selvester (18), we have created a database of approximately 45,000 simulated ECGs connected to maps of the associated ischemic region. The automated computer algorithm (DIMS-ECG) uses PCA to compare a *de novo* ECG to all ECGs in the database and identifies the 200 closest ECGs. DIMS-ECG then superimposes the 200 ischemia maps to display the predicted ischemia location and the predicted coronary artery that is occluded.

The freely available DIMS-ECG algorithm together with the ECG database may be useful for a large number of studies. The software will allow other researchers to continue the approach of simulating ECGs to test various analysis schemes and to explore different parameters for quantifying and graphically displaying ischemic myocardium. For example, as ischemia continues and necrosis develops, ST-segment and T-wave changes may decrease in magnitude, and QRS changes such as pathological Q waves will likely develop. This would result in underestimation of the ischemia region by the current DIMS-ECG algorithm. Future work should include simulation of electrically inactive cells and analysis of QRS complex measurements to simulate effects of confounding prior infarcts. Such an approach may allow prediction and graphical display of myocardium that is already dead and myocardium that is ischemic, but potentially salvageable following reperfusion. Prior studies have indicated that information regarding the potential for myocardial salvage is contained in the 12-lead ECG (19).

Limitations of the current version of the DIMS-ECG database are that it was based on simulations from a single heart's and thorax's geometry. Simulating ECGs using different heart positions, angles and geometries may improve the ability of the DIMS-ECG algorithm to

quantify and localize ischemic myocardium. In addition, the normal values for 12-lead ECGs are known to differ by age, gender and race (20). Inputting normal ECGs into the database classified by these variables, and then adding these as input variables when analyzing a *de novo* ECG, may improve the algorithm's performance. Finally, further study is required to validate the DIMS-ECG method against other measures of ischemic myocardium (*e.g.* SPECT) in patients. Unfortunately, SPECT imaging has its own limitations and, thus, any method to quantify and display ischemic myocardium should be prospectively studied to determine if it provides additional value in risk-stratifying patients with acute myocardial infarction.

In conclusion, we have presented a method where an ECG from a patient with potential ischemia can be compared to a database of simulated ECGs associated with known areas of ischemia. This DIMS-ECG program identifies similar ECGs in the database and outputs a graphical display of the predicted ischemic myocardium for the *de novo* ECG. The program and associated database will be made freely available for further development and testing.

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Figure Legends

Figure 1. (A) Mercator projection of the LV. The LV has been divided into 10 basic regions that can potentially be infarcted based on regional coronary anatomy. The highlighted region shows the ischemic area (sections 1, 2 and 10) from an LAD occlusion that is distal to the first diagonal artery but proximal to the first septal perforator artery. (B) A polar plot of the LV. The same ischemic area from (A) is highlighted. LAD=left anterior descending, LCX=left circumflex, RCA=right coronary artery, PDA=posterior descending artery.

Figure 2. (A) Representation of the thorax, ventricles and action potentials from an epicardial node from ECGSIM (www.ecgsim.org). The left side shows a normal heart and action potential. The right side shows an ischemic area highlighted in green that is equivalent to the ischemic area from Figure 1. The ischemic action potential has delayed depolarization, early repolarization and decreased amplitude. (B) 12-lead ECGs resulting from the normal simulation (blue) and the ischemic simulation from the LAD occlusion depicted in (A). LV=left ventricle; RV=right ventricle; LAD=left anterior descending.

Figure 3. Development of the DIMS-ECG database. The 10 ischemic regions were combined to create 21 basic ischemic regions (see Table 1). Minor alterations were made to the basic ischemic regions to create 8819 ischemic patterns. Five different ischemia severity levels were simulated in each unique pattern to create 44,095 ECGs paired with known ischemia regions. LAD=left anterior descending; RCA=right coronary artery.

Figure 4. Using the DIMS-ECG database. ST-segment and T-wave amplitude measurements are extracted from the *de novo* ECG and compared to the same measurements from each ECG in the database using principal component analysis (PCA). The 200 closest ECG matches are identified and the corresponding ischemia maps are superimposed to create a map showing the predicted ischemia location. The percentage of the 200 matches from each coronary artery territory is also presented that can be used to predict the location of the occlusion.

Figure 5. 12 lead ECGs for 3 patients who underwent prolonged coronary angioplasty. ECGs were recorded prior to balloon deflation. Patient #1 had an left circumflex occlusion, Patient #2 had an right coronary artery occlusion and Patient #3 had an left anterior descending occlusion.

Figure 6. SPECT (left column) and DIMS-ECG (right column) polar plots for the same 3 patients as in Figure 5. Color scales show the distribution of ischemic to nonischemic myocardium for SPECT and the predicted ischemic to nonischemic scale for DIMS-ECG.

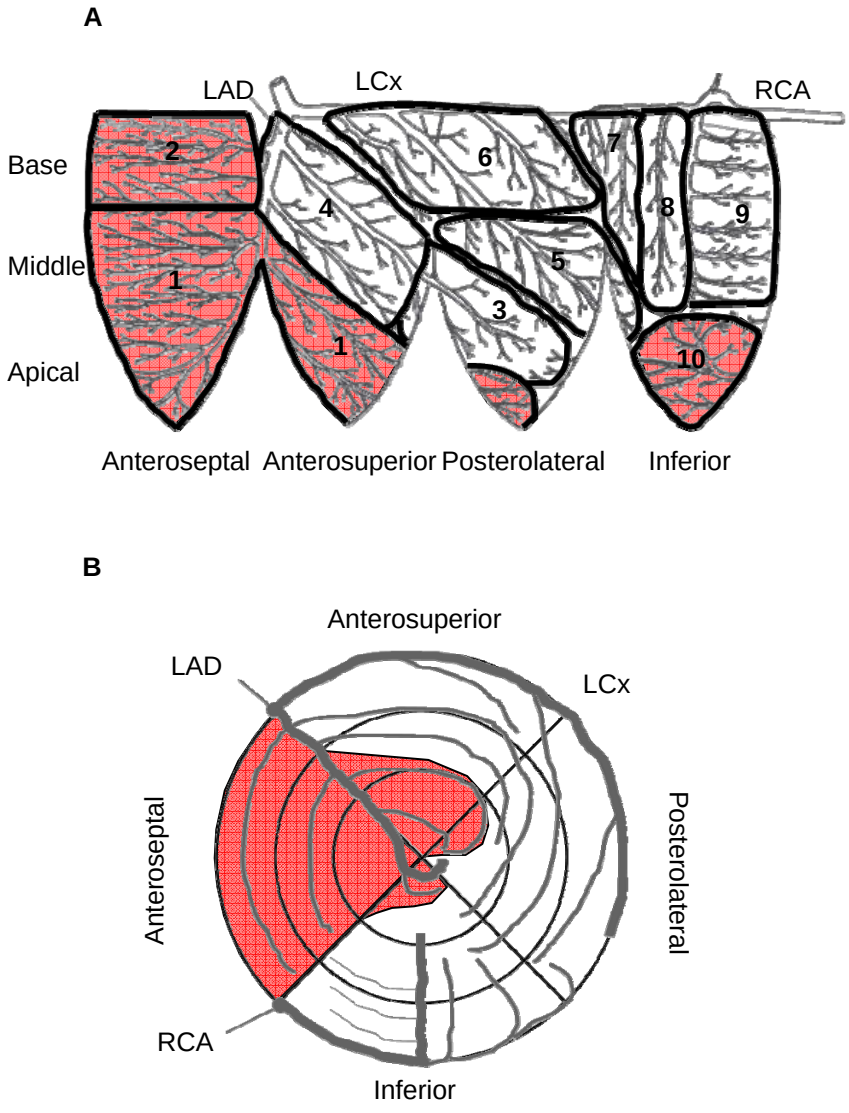
A
LAD
LCx
RCA
Base
Middle
Apical
2
6
7
4
8
9
1
5
3
1
10
Anteroseptal
Anterosuperior
Posterolateral
Inferior
B
Anterosuperior
LAD
LCx
Anteroseptal
Posterolateral
RCA
Inferior

Figure 1.

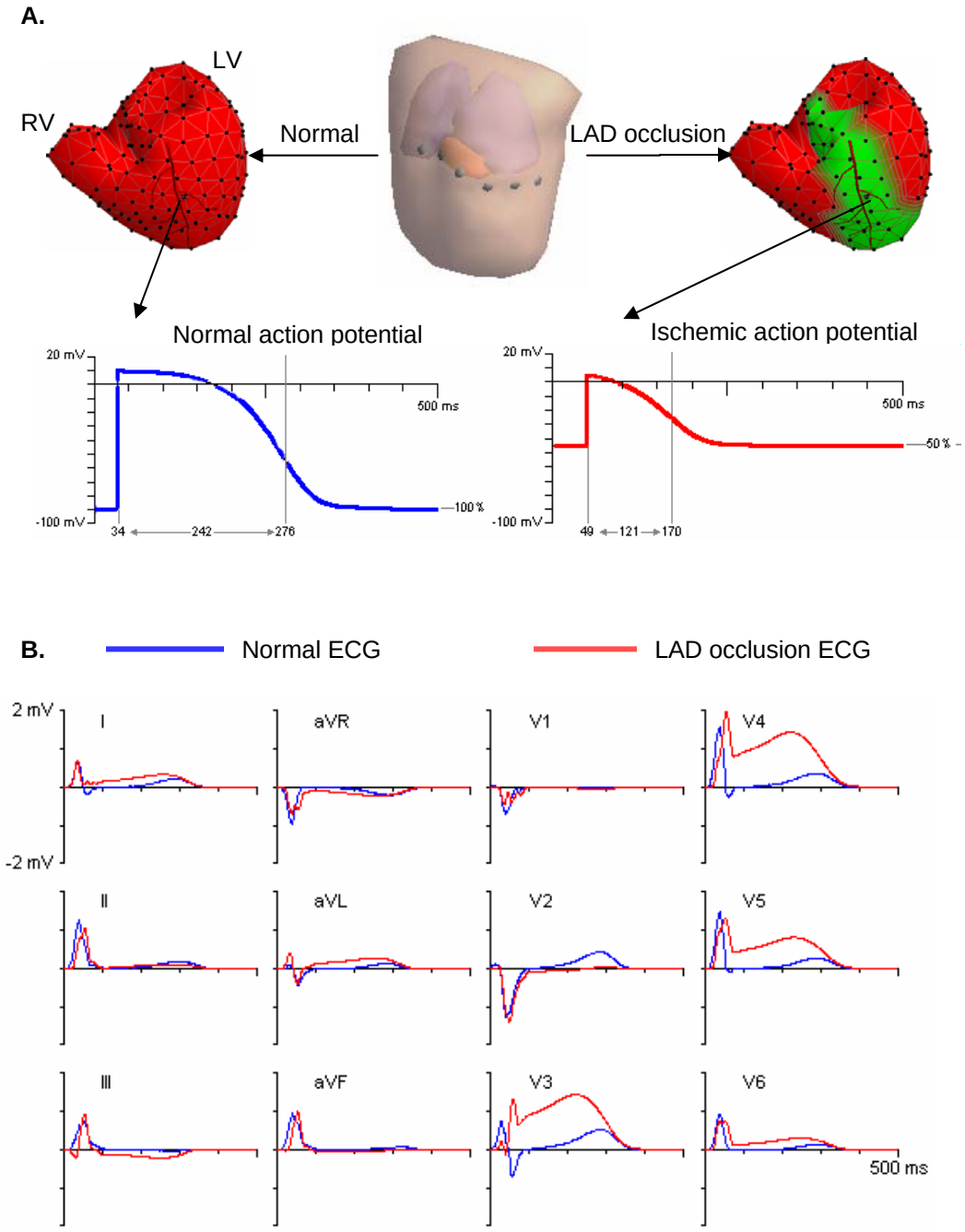
A.
LV
RV
Normal
LAD occlusion
Normal action potential
Ischemic action potential
20 mV
-100 mV
500 ms
100 %
50 %
34
242
276
49
121
170
B.
Normal ECG
LAD occlusion ECG
2 mV
-2 mV
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
500 ms

Figure 2.

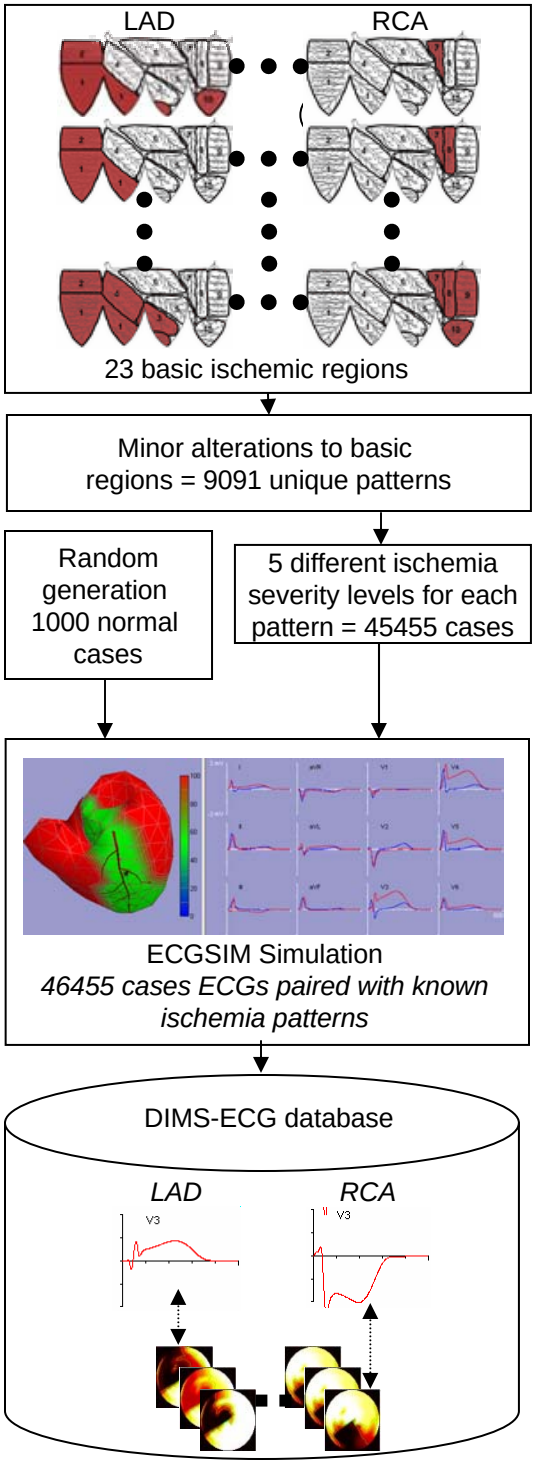
LAD
RCA
23 basic ischemic regions
Minor alterations to basic regions = 9091 unique patterns
Random generation 1000 normal cases
5 different ischemia severity levels for each pattern = 45455 cases
ECGSIM Simulation
46455 cases ECGs paired with known ischemia patterns
DIMS-ECG database
LAD
RCA
V3
V3

Figure 3.

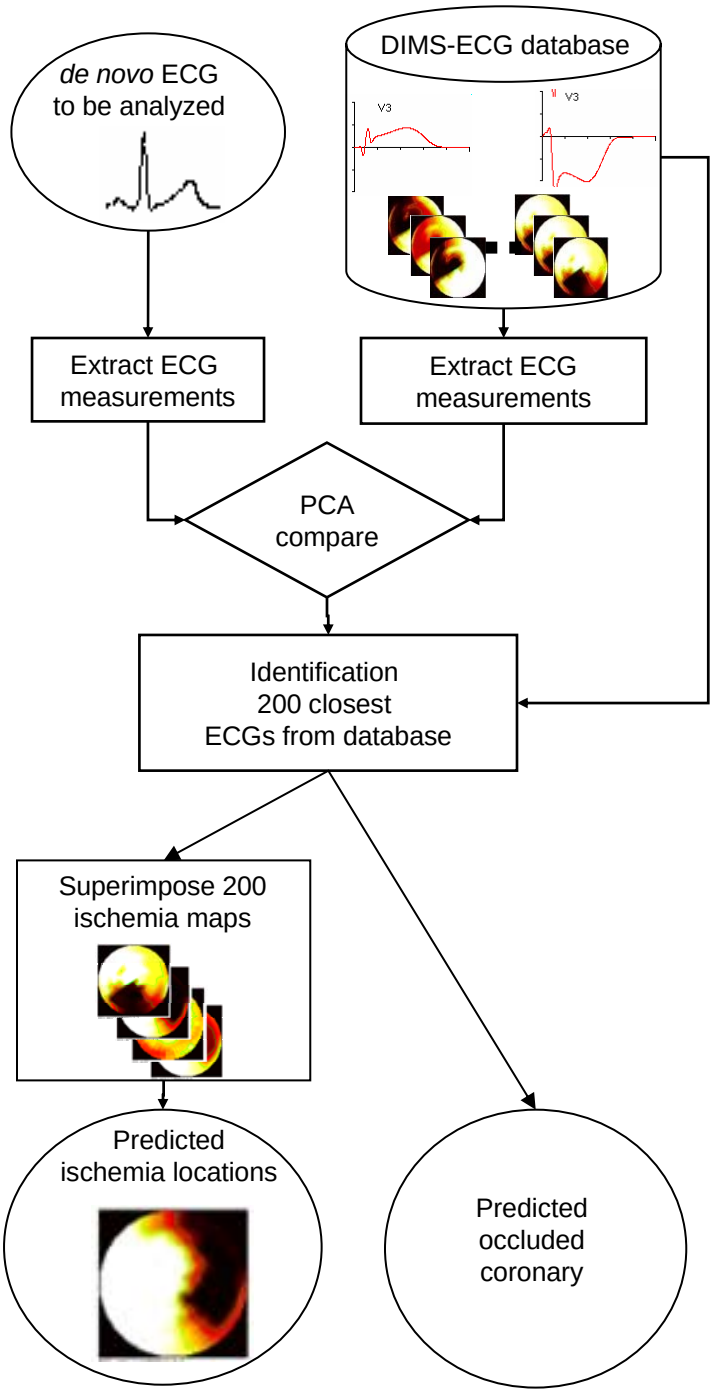
DIMS-ECG database
V3
V3
de novo ECG
to be analyzed
Extract ECG
measurements
Extract ECG
measurements
PCA
compare
Identification
200 closest
ECGs from database
Superimpose 200
ischemia maps
Predicted
ischemia locations
Predicted
occluded
coronary

Figure 4.

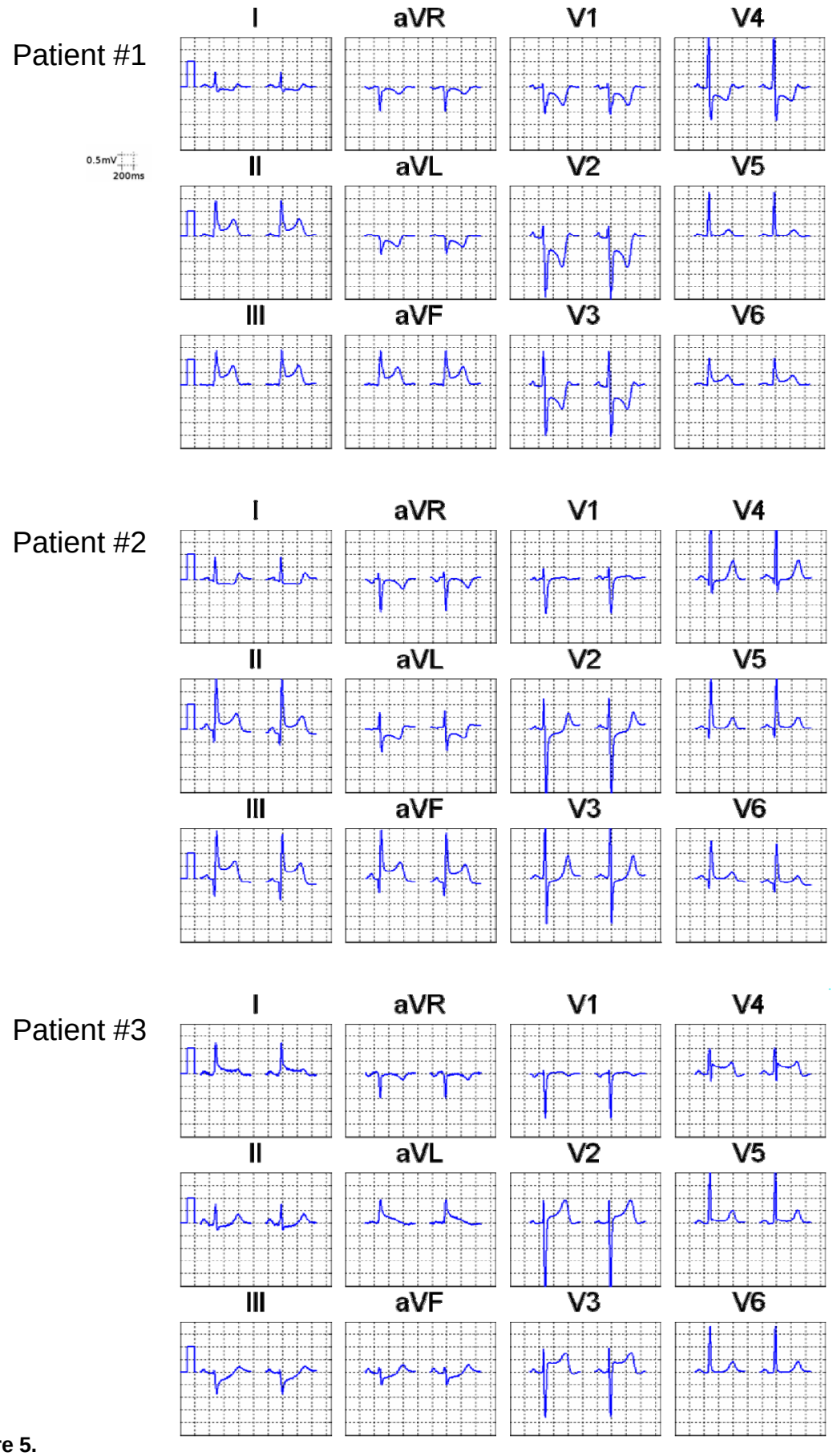
Patient #1
I
aVR
V1
V4
0.5mV
200ms
II
aVL
V2
V5
III
aVF
V3
V6
Patient #2
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
Patient #3
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Figure 5.

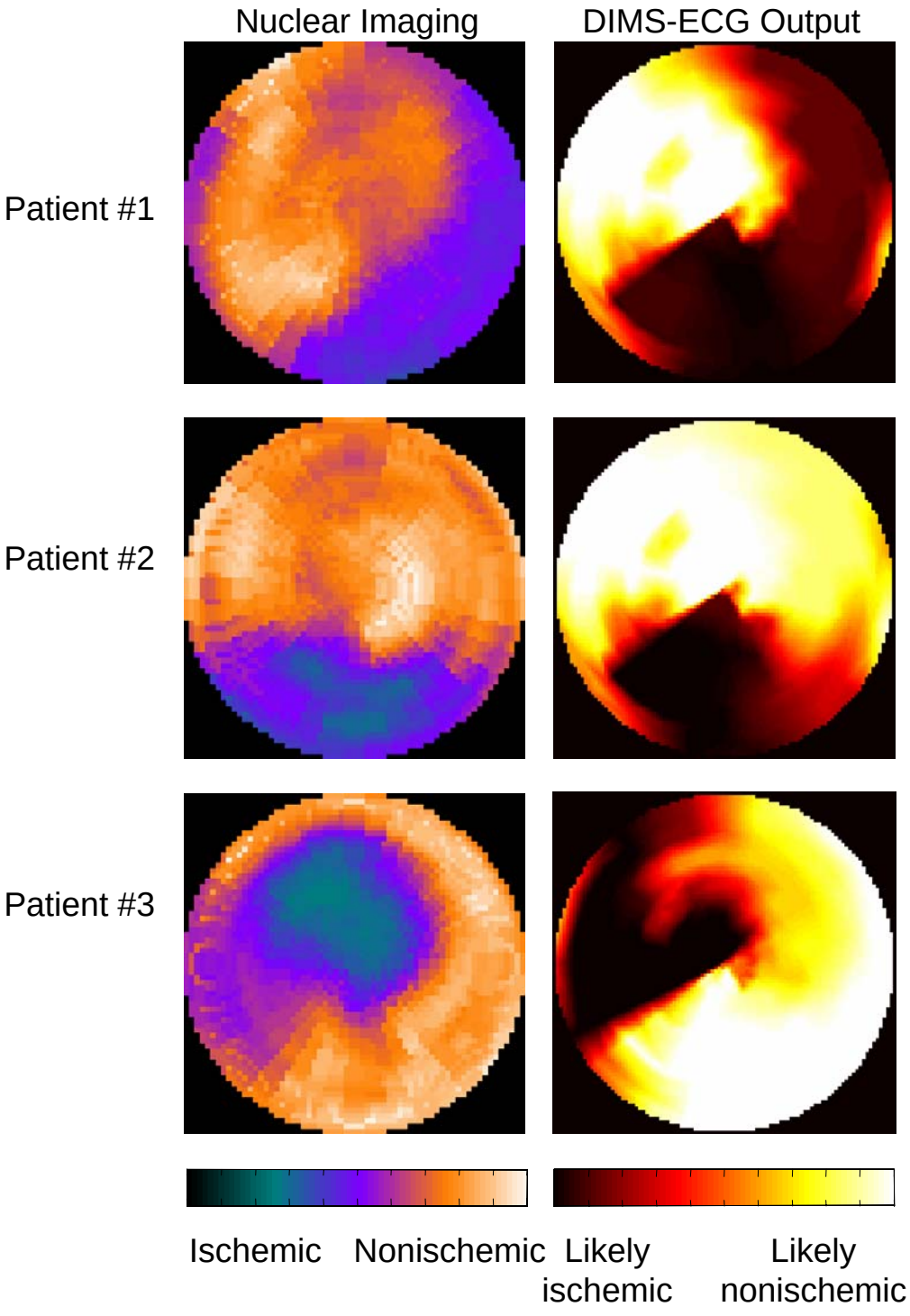
Nuclear Imaging
DIMS-ECG Output
Patient #1
Patient #2
Patient #3
Ischemic
Nonischemic
Likely ischemic
Likely nonischemic

Figure 6.