News on cardiac arrhythmias - Part II

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METHODS FOR PREDICTIVE CLASSIFICATION AND MOLECULAR PROFILING FROM DNA MICROARRAY DATA

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We present an experimental application of the entropy-based recursive feature elimination-support vector machine learning system for the molecular profiling of cardiogenomics data. The predictive methodology is applied to obtain the automatic ranking and selection of a panel of genes for a Mouse Model dataset of DNA expressions provided by the Genomics of Cardiovascular Development, Adaptation, and Remodeling, NHLBI Program for Genomic Applications.

We applied the entropy-based recursive feature elimination-support vector machine (ERFE-SVM) methodology for molecular gene profiling for gene expression microarrays described in Furlanello et al.[1,2] to the dataset of the Mouse Model of Myocardial Infarction, published as public data by the Cardiogenomics PGA[3] (http://cardiogenomics.med.harvard.edu/groups/proj1/pages/mi_home.html) as available in October 2003.

The ERFE system was developed for gene profiling in supervised classification problems[1]. The system integrates a procedure for gene ranking and selection within a complete experimental structure for training SVM classification models. It selects the best models with an internal cross-validation scheme and estimates the accuracy with an external resampling scheme. This two-strata structure has been designed to control the selection bias effect, a pervasive problem in gene profiling studies[4,5]. The ranking is obtained by a recursive feature elimination (RFE) process[6]: at each RFE step, a gene is discarded from the active variables of an SVM classification model. The features are eliminated according to a criterion related to their support to the discrimination function and the SVM is recomputed at each step. Due to the requirement of replicating the feature ranking process on many train/test set combinations, a complete RFE experiment is computationally intensive. We have thus modified RFE into the entropy-based procedure ERFE and obtained a significant reduction of computation steps (genes are eliminated in chunks). However, tasks as those discussed in this paper require the use of a high performance computing facility: for the Mouse Model classification study on a 12 488 × 36 Affymetrix (MGU74AV1/MGU74AV2/MU11KA-B) array, a total of 350 000 SVM models was constructed in 400 runs of the resampling scheme on our Open Mosix high performance computing facility (38 computing nodes).

Table I. Data and model parameters

Classification task	Infarcted (positive) vs non-infarcted (negative) region of the left ventricular free wall in left coronary artery ligated mice
Microarray technology	Affymetrix oligonucleotide
Positive-negative samples	18-18
No. genes	12 488 (MGU74AV1/MGU74AV2/MU11KA-B)
Preprocessing steps	Normalization of gene vectors (mean = 0, SD = 1)
Feature ranking method	ERFE
No. CV folds (K) in ONF	3
No. replicates (B) in VAL	400
Train-test split proportion in replicates	3/4-1/4

The entire procedure described in Furlanello et al.[1] has been applied to the Murine Myocardial Infarction database from the Cardiogenomics PGA[3]. The database consists of 36 samples of left ventricular wall tissue, 18 infarcted and 18 non-infarcted. A more precise description of the data set can be found in the Cardiogenomics PGA[3]. In table I the parameters used in the classification task are listed.

Results

In the analysis, we used SVM as the classifier, and ERFE as the feature ranker. The results are calculated over 400 experiments and are summarized in tables II and III.

The number (n*) is the optimal number of features as selected by the ranking methods, ATE is the average estimated test error, computed over the 400 runs of the VAL module, for differently sized subsets of genes, extracted by ERFE ranking procedure.

In summary, a 4.4% classification predictive error is estimated for this dataset with an optimal number of 60 (SD = 24) candidate genes as biomarkers.

A list of the best 100 ranked genes together with their multiplicity rank scores (number of extractions in the repeated experiments) is available as supplementary material at the web reference http://mpa.itc.it.

Table II. Average estimated test error (ATE) at increasing no. of genes for the Murine Myocardial Infarction dataset, 400 runs.

No. genes	ATE
10	7.6
20	5.3
50	4.1
100	4.2
300	4.3
500	4.5
1000	5.1
12 488	6.6

Table III. Optimal number of features (n*) and corresponding cross-validation test error (TE) for the Murine Myocardial Infarction dataset (global model).

n*	TE
60	4.4

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FAMILIAL OCCURRENCE OF NON-COMPACTION CARDIOMYOPATHY

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Isolated left ventricular non-compaction cardiomyopathy (LVNC) is characterized by altered structure of the myocardial wall due to intrauterine arrest of compaction of myocardial fibers in the absence of coexisting congenital malformation. LVNC is complicated by heart failure, thromboembolic events, and arrhythmias including ventricular tachycardia and cardiac arrest. During a follow-up of 3.5 years a 35% mortality (sudden death 50%) has been described. Family members may be affected due to an autosomal dominant or X-linked recessive inheritance.

Purpose. Identification of LVNC in families.

Methods. LVNC was diagnosed if end-systolic non-compacted subendocardial layer of the left ventricular wall was at least twice the thickness of the subepicardial compacted layer (two-dimensional echocardiogram and/or magnetic resonance imaging). This was studied in 13 patients in two families (A and B).

Results. LVNC was found in 3/11 patients in family A. The affected grandmother (79 years) was asymptomatic (Fig. 1). Her affected daughter (55 years) had recurrent syncope, persistent atrial fibrillation and heart failure (Fig. 2).

Treatment included amiodarone, anticoagulant therapy and cardioverter-defibrillator implantation. Her daughter, the affected granddaughter, had a cardiac transplant because of heart failure at age of 14 years. In family B LVNC was found in 2 patients, a father (58

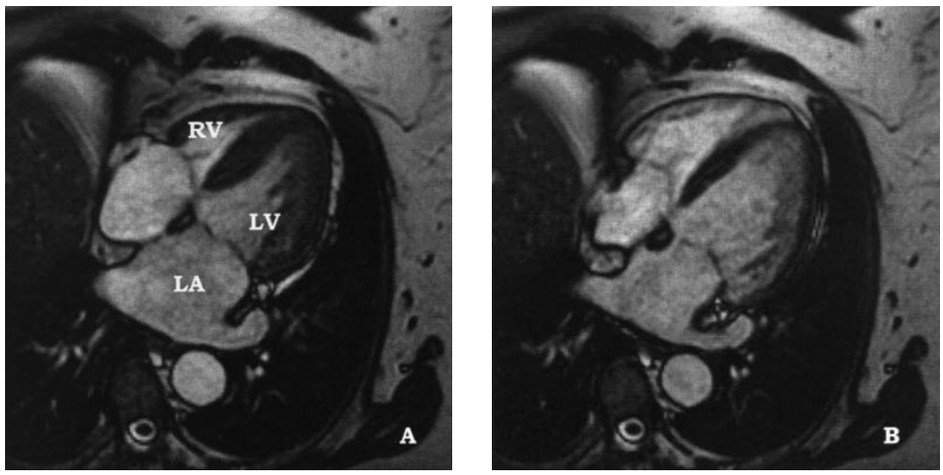

Figure 1. *Magnetic resonance imaging in affected asymptomatic grandmother in family A during systole* (A) *and during diastole* (B). *LA = left atrium; LV = left ventricle; RV = right ventricle.*

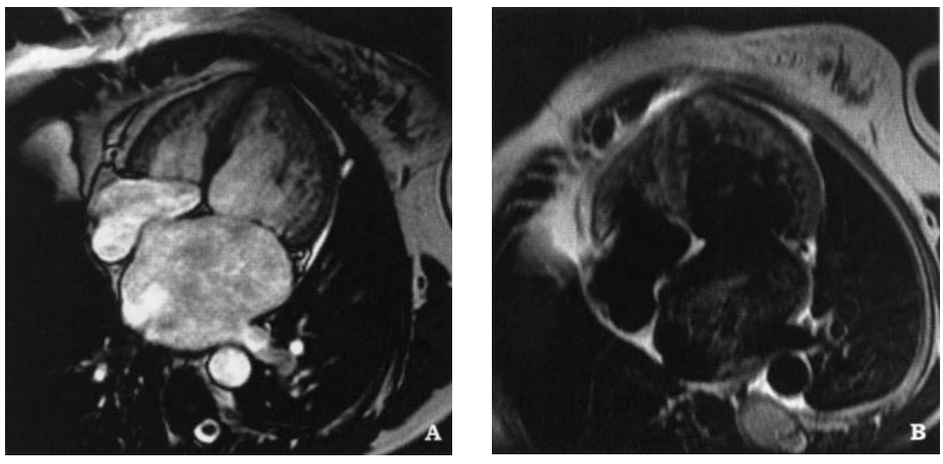

Figure 2. *Magnetic resonance imaging in affected daughter in family A during systole* (A) *and during diastole* (B).

years) and his son (33 years) and presumed in a brother and sister of the father who both died suddenly at the age of 15 and 21 years, respectively. The father survived cardiac arrest at the age of 42 years, preceded by syncopal attacks starting at the age of 14 years. Rapid monomorphic ventricular tachycardia was induced by programmed electrical stimulation. Treatment with amiodarone was successful, but at a later stage he had atrial arrhythmias and heart failure. His son had prolonged syncope treated with amiodarone. In all symptomatic patients, proven LVNC was previously misdiagnosed as hypertrophic or dilated cardiomyopathy.

Conclusions. 1) LVNC was identified in two families in 7 patients (5 proven, 2 presumed), 2) life-threatening complications and sudden death occurred at young age, but asymptomatic survival to old age is possible, 3) family screening may unmask affected family members for primary prevention including anticoagulation and implantable cardioverter-defibrillator therapy, 4) misdiagnosis may postpone directed molecular genetic analysis.

Thoracoscopic, robot-guided epicardial treatment of atrial fibrillation: first Italian experience

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Background. Surgical treatment of atrial fibrillation (AF) has been found to be 70-95% successful in valvular, coronary artery disease and lone AF. The procedure would be more beneficial if applied using minimally invasive techniques on the beating heart.

Methods. Following animal experience, epicardial pulmonary vein isolation was attempted on one patient via a three right thoracoscopic ports using a totally endoscopic approach with robotic assistance. Using microwave energy, a continuous lesion was created on

the posterior left atrium encircling all the pulmonary veins.

Patient and results. A 60-year-old man with daily episodes of paroxysmal-persistent AF, in the absence of cardiac disease, was extensively evaluated including transthoracic-transesophageal echocardiography, supra-aortic vessel echo-Doppler, pulmonary function tests. He was not responsive to different antiarrhythmic drug regimens (four drugs including amiodarone), and chronic oral anticoagulation therapy with INR range 2-3 was administered during 3 months. He was scheduled for catheter ablation, but he accepted to undergo the new thoracoscopic procedure. The entire procedure was successfully carried out in 3 hours. Brief episodes of self-terminating atrial flutter were recorded during the post-operative hospital stay (hospital stay lasting 7 days), but after a follow-up of 2 months he showed persistent sinus rhythm with oral beta-blocking agents and amiodarone.

Conclusion. Thoracoscopic, robot-guided epicardial isolation of pulmonary veins by means of microwave energy is a new promising procedure for AF treatment. In canines, isolation of all the pulmonary veins, using a 0.07" OD antennae can repeatedly create electrical isolation. At our knowledge, few human cases have been treated with this technique (10 cases in the United States, 7 cases in Europe). Our case represents the first and sole Italian experience.