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The Validity Value of Electrical Restitution Curve in Prediction of Ventricular Fibrillation Induction Using ANFIS

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***Abstract* – Detection of arrhythmias by different methods of neural network and Fuzzy algorithm has been investigated intensively in recent years. Electrical restitution curve (ERC) and some other ventricular electro-physiological properties which are discussing matter in prediction of cardiac arrhythmias in medical sciences were presented to an adaptive neuro-fuzzy inference system (ANFIS). These features were obtained from action potential signal which was recorded from isolated rabbit heart. This algorithm can detect steep part of this curve which is an indicator of ventricular fibrillation (VF) induction with high accuracy of 96.6%. Then in second step these features applied for detection of VF or stimulation block. The result shows that this curve can't predict inducibility of VF individually and it should be considered with other properties such as conduction velocity and memory effects.**

***Keywords* – Electrical Restitution Curve, Electro-Physiological Properties, Ventricular Fibrillation, Adaptive Neuro-Fuzzy Inference System.**

I. Introduction

The most common sustained arrhythmia that leads to ventricular fibrillation (VF) is re-entrant ventricular tachycardia (VT). However, despite more than a century of research, the mechanism(s) of the transition re-entrant VT to VF has not been determined (Samie *et al.*, 2001). It is established that ventricular fibrillation (VF) originated from wavelength (WL) oscillations which related to both action potential duration (APD) (Franz, 2003; Osadchii *et al.*, 2010; Sabir *et al.*, 2008). Destabilization of wave fronts and the subsequent initiation of re-entrant excitation can result from both intrinsic and dynamical heterogeneity of ventricular refractoriness (Gilmour *et al.*, 2007). Dynamical heterogeneity arises primarily from electrical restitution properties, ie, the dependence of action potential duration (APD) on the preceding diastolic interval (DI) which is the rest time between repolarization and the next action potential excitation. The electrical restitution curve (ERC), for first time defined by Bass in 1975 and studied extensively by other researchers in recent years (Franz, 2003). Traditionally, there is a belief that the slope of restitution curve dynamicity could be used to predict sudden cardiac death, based on what is called the restitution hypothesis (Franz, 2003). Animal studies showing that the slope of the restitution curve during ventricular fibrillation is >1 and some others showing that reducing the restitution slope converted ventricular fibrillation to ventricular tachycardia gave further support to the idea that restitution slope was an important factor in the generation of arrhythmias (Franz, 2003; Sabir *et al.*, 2008). ERC defines action potential duration (APD) as a function of previous diastolic interval (DI). Computer simulations and theoretical analysis from nonlinear dynamics determined that a steep (>1) electrical restitution slope promotes wavebreaks, thus contributes to electrical instability (Gelzer *et al.*, 2008).

Fig. 1 shows the mono-phasic action potential signal which APD_{90} and DI are mentioned on it. APD_{90} is defined the time interval between peak of action potential and 90% of repolarization. For computing previous diastolic interval, APD is reduced from time interval of two successive stimulus. The following equation shows how to calculate it:

$$DI_{n-1} = S_1S_2 - APD_{90(n-1)} \qquad (1)$$

In this equation DI_{n-1} is DI before premature stimulus. S_1S_2 represents time interval between the premature stimulus and its previous. $APD_{90(n-1)}$ is action potential duration before premature stimulus. Following figure specifies these intervals clearly.

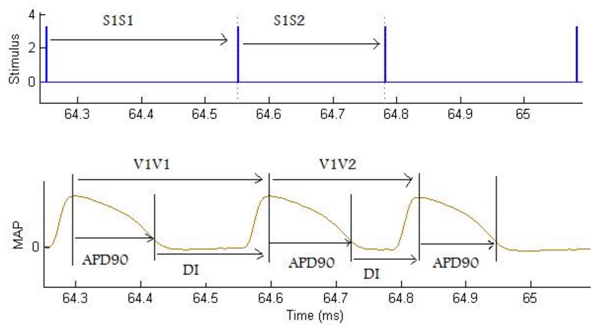

Fig.1. Monophasic action potential signal

Electrical restitution curve which is shown in Fig. 2 has two phases with standard stimulation protocol. The first phase starts with steep slope in shorter DIs and has final asymptotically increase to its flat phase in longer DIs. In this figure, the maximum slope of restitution was 1.23 at diastolic interval of 18.3 ms which was achieved at ERP.

This curve can be approximated with increasing mono-exponential function as follow:

$$y = y_0 + A(1 - e^{-\frac{x}{\tau}}) \qquad (2)$$

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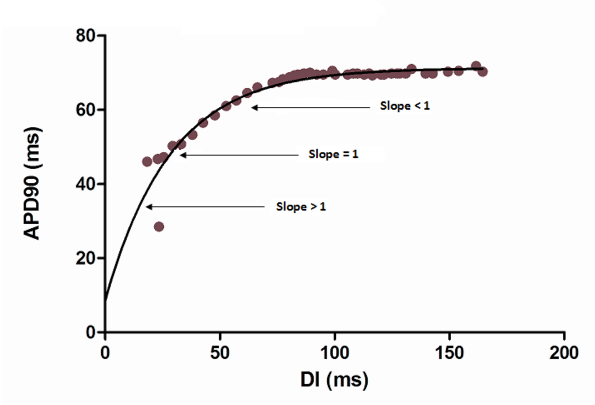

Fig.2. Electrical restitution curve which shows the dependency of action potentential duration

Where y is APD_{90} and x represent the diastolic interval. A, y_0 and τ are constant values that are obtained with the method of fitting least squares to the experimental values.

In this study it is proposed that ventricular fibrillation would originate from different electrophysiological properties of cardiomyocytes which manifested in various cycle lengths. It was hypothesized that electrical restitution is the combination of the result of some different bioelectric entities each of which has specific individual electrophysiologic kinetics and manifest during different smooth and steep parts of restitution curve. Consequently, the transition of VT to VF that occurs during short stimulation cycle length may be more complex and that instead of homogenous mono component (steep part) of APD curves. Experimental and mathematical modeling studies also have shown that although the slope analysis of ERC is a fundamental indicator, but it isn't enough reason to predicting the VF occurrence. Actually decreasing the premature stimulation time progressively in short BCLs may cause block occurrence or lead to VF. When block occurs, the slope may not be greater than 1, but arising or diminishing of stimulation response, depends on the value of slope relative to 1 (Gilmour *et al.*, 2007). Some research emphasizes on considering the role of conduction velocity (CV) (Gilmour *et al.*, 2007; Wu *et al.*, 2002) effective refractory period (ERP) (Osadchii *et al.*, 2010) and memory effects (Cherry *et al.*, 2012) in combination with ERC. Whereas the main cause of ventricular fibrillation has not been yet specified, predicting the VF occurrence and control it by drug leads to an interesting scientific area that cause extensive research has been done on the ventricular action potential signal during recent years.

The aim of this study is the detection of which ERC based on rate dependency terminated to VF and which one finished by block. Hence, in order to avoid difficult analysis of numerous properties together by human, electrophysiological properties of cardiomyocytes were presented as input vectors of ANFIS system and the ERC which lead to VF or stimulation block as outputs. By this algorithm the role of ERC components in prediction of VT to VF transition will be determined.

II. Literature Review

Cardiac arrhythmia detection using neuro-fuzzy algorithms has been considerate in recent years. Most research used ECG as a non-invasive signal due to the various limitations. Hence, in this section some neural networks and neuron-fuzzy methods which were used ECG in arrhythmia classification, are reviewed. However, these methods also have the same results for action potential classification because QT interval and its previous TQ interval of ECG are similar to APD and its previous DI in action potential (Cabasson *et al.*, 2012). Minami et al. pro-posed an algorithm that classifies VT and VF from ECG and intracardiac electrogram (EGM) signals. First, QRS complex is extracted by this algorithm. Then each QRS transfers to Fourier spectrum and finally, each spectrum classifies to three rhythms; (1) Supraventricular rhythm, (2) Ventricular rhythm includes VT and premature ventricular contraction (PVC) and (3) VF. Neural network algorithm is trained by backpropagation (BP). This method has sensivity and spesifity higher than 98% (Minami *et al.*, 1999). Heidari et al. compared a supervised algorithm, radial basis function (RBF) with an unsupervised one, fuzzy c-mean for classification of VT from VF. Sensivity and specifity were obtained respectively 92.3%, 71.4% for RBF and 84.6%, 71.4% for fuzzy c-mean. They believe that using an unsupervised algorithm is more reliable than supervised, because the most advantages of unsupervised algorithm is to find similar data characters, hence cluster them appropriately (Heidari *et al.*, 1998). A novel hybrid neural network presented by Dokur et al. classifies 10 types of ECG beats successfully. Eight-dimensional feature space are extracted by fourier and wavelet analysis, and then determined by dynamic programming according to the divergence value. This algorithm is trained by the genetic algorithm (GA) in order to increase the classification performance. This novel hybrid network which is named increasing sphere (Ins) has accuracy of 96% (Dokur *et al.*, 2001). Engin proposed a fuzzy-hybrid neural network which is composed of fuzzy c-mean as a pre-classifier and multi-layer perceptron (MLP) as the final classifier. These two networks are connected in cascade. This network has sensivity of 99.6%, specifity of 95.3% and accuracy of 93.5% (Engin *et al.*, 2004). Lim presented a method using the neural network with weighted fuzzy membership functions (NEWFMs) to classify PVC and normal beats by the trained bounded sum of weighted fuzzy membership functions (BSWFMs) using wavelet transformed coefficients. The eight generalized coefficients are used for the three PVC data sets with reliable accuracy rates of 99.80%, 99.21%, and 98.78%, respectively (Lim, 2009). Nazmi et al in 2010 presented an ANFIS model for classification of ECG signals. They extracted features as inputs classifier using Independent Component Analysis (ICA) and Power spectrum, together with the RR interval. Normal sinus rhythm and five types of arrhythmias were detected with accuracy level of more than 97%. They compared the proposed method with an ANFIS without

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special technique for feature extraction that had only less than 1% decrease in accuracy (Nazmy *et al.*, 2010).

Given all above technique used in previous studies, it is obvious that the use of neuron-fuzzy techniques have been successful from other techniques that used only neural network. Moreover, there are two reasons that make fuzzy decision systems applicable in medical reasoning because definition of crisp membership function in disease detection that has a qualitative process may due to inappropriate results. Also fuzzy algorithms are fast and easy tools for input spaces with high dimension and solve complicated calculations in short time. Therefore, using ANFIS is proposed, which combines the low-level computational power of a Neural Network with high-level reasoning capabilities of the fuzzy inference system (Silipo *et al.*, 1999).

III. Analysis Method

Jang believed that "System modeling based on the conventional mathematical tools (e.g., differential equations) is not well suited for dealing with ill-defined and uncertain systems". Hence, in 1993 he proposed ANFIS, a fuzzy inference system that models the qualitative aspects of human knowledge in to the rule base and database of a fuzzy inference system (FIS). Also, reasoning processes is done without employing exact quantitative analyses. Inputs are graded by the membership functions (MF's) in order to minimize the output error measure or maximize performance of system (Jang *et al.*, 1993). ANFIS is a hybrid Neuro-Fuzzy Inference expert systems that works in Takagi-Sugeno-type Fuzzy Inference System. This system also is a kind of adaptive with supervised learning algorithm that determined how the parameters should be changed in order to obtain minimum least square. It takes a given input/output dataset and constructs a fuzzy inference system whose membership function parameters are tuned, or adjusted, using either a backpropagation algorithm which is the only limitation of this network (Jang *et al.*, 1993; Nazmy *et al.*, 2010).

A. ANFIS Structure

ANFIS has a similar architecture to a Multilayer Feed Forward Neural Network but the links in an ANFIS which is shown in Fig. 3 only indicate the flow direction of signals between nodes that no weights are associated with these links (Nazmy *et al.*, 2010). ANFIS architecture has five layers of nodes. The first and the fourth layers consist of adaptive nodes while the other layers consist of fixed nodes. The adaptive nodes are associated with their respective parameters, get duly updated with each subsequent iteration while the fixed nodes are devoid of any parameters (Jang *et al.*, 1993).

To present the ANFIS architecture, two fuzzy if–then rules based on a first-order Sugeno model are considered

Rule 1: If (x is A1) and (y is B1) then (f1 = p1x+ q1y + r1)

Rule 2: If (x is A2) and (y is B2) then (f2 = p2x+ q2y + r2)

Where x and y are the inputs, A_i and B_i are the fuzzy sets, f_i are the outputs within the fuzzy region specified by the fuzzy rule, p_i, q_i and r_i are the design parameters that are determined during the training process. In Fig. 3, the circles indicate a fixed node, whereas the squares indicate an adaptive node.

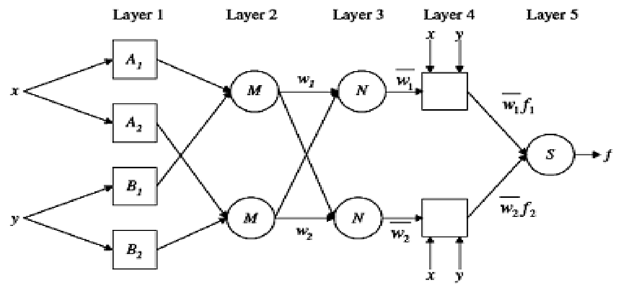

Fig.3. ANFIS Structure (Nazmy *et al.*, 2010).

Layer 1 (*fuzzification layer*): Every node I in the layer 1 is an adaptive node. The outputs of this layer are the fuzzy membership grade of the inputs, which are given by:

$$O_i^1 = \mu_{Ai}(x), \quad i = 1,2$$
$$O_i^1 = \mu_{Bi-2}(y), \quad i = 3,4 \tag{3}$$

Where x and y are the inputs to node i, where A is a linguistic label (small, large) and where $\mu_{Ai}(x)$, $\mu_{Bi-2}(y)$ can adopt any fuzzy membership function. Usually we choose $\mu_{Ai}(x)$ to be bell-shaped with maximum equal to 1 and minimum equal to 0, such as:

$$\mu_{Ai}(x) = \frac{1}{1+\left\{\left(x - {}^{c_i}\!/_{a_i}\right)^2\right\}^{b_i}} \tag{4}$$

Where $(a_i, b_i$ and $c_i)$ are the parameters of the membership function. Parameters are referred to as premise parameters.

Layer 2 (*rule layer*): this layer consists of fixed node labelled M whose output is the product of all the incoming signals, the outputs of this layer can be represented as:

$$O_i^2 = w_i = \mu_{Ai}(x)\mu_{Bi}(y), \quad i = 1,2 \tag{5}$$

Layer 3 (*normalization layer*): This layer are also fixed node is a circle node labelled N.

$$O_i^3 = \bar{w}_i = \frac{w_i}{(w_1 + w_2)}, \quad i = 1,2 \tag{6}$$

Layer 4 (*defuzzification layer*): Every node i in this layer is a square node. The output of each node in this layer is simply the product of the normalized firing strength and a first order polynomial.

$$O_i^4 = \bar{w}_i f_i = w_i(p_i x + q_i y + r_i), \quad i = 1,2 \tag{7}$$

Layer 5 (*summation neuron*): The final layer is a fixed node which computes the overall output as the summation of all incoming signals.

$$O_i^5 = \sum_{i=1}^{2} \bar{w}_i f_i = \sum_{i=1}^{2} w_i f_i / (w_1 + w_2) \tag{8}$$

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IV. Data Acquisition

In this section experimental method of rabbit heart preparation and MAP signal recording will be explained. Fig. 4 shows the block diagram of this research process.

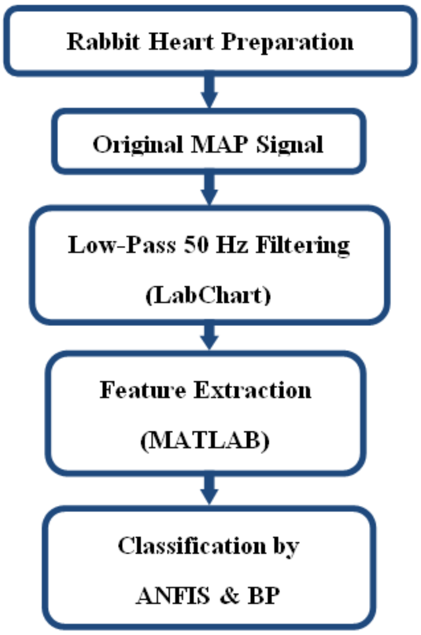

Fig.4. Block diagram of research process

The practical hypothesis of this study was that maximizing dynamic heterogeneity by delivering a set of premature stimuli would suffice to predictably induce VF in vitro. A wide range of pacing rate was used to investigate the rate dependency of ERC because it shows different behaviour in slow and rapid rate. In the first stage rabbit heart was prepared for recording signals. Then heart was stimulated by pacing protocols in different rates. In the next stage electrophysiological properties were extracted from MAP signal and finally these properties were presented as feature vectors to the classification algorithms in order to classify which protocol terminates to VF and which receive to block.

A. Experimental Methods

All experiments were performed on an isolated, perfused rabbit cardiac preparations obtained from hearts of male New Zealand white rabbits (1.8-2.8 kg). Anaesthesia was induced with pentobarbital (40 mg/kg); heparin (200 IU/kg) was used as an anticoagulant. Ethical approval and animal care are in accordance with the principles set forth in the regulations at the Golestan University of Medical Sciences, Gorgan, Iran. Data was recorded on an electrophysiology recording system (PowerLab, AD Instrument) and analyzed with MATLAB.

B. Ventricular MAP

Monophasic action potentials (MAPs) were recorded from the basal left ventricular endocardium. A small access window was created in the interventricular septum to allow access to the left ventricular endocardium. A custom-made endocardial MAP Teflon-coated silver wire of 0.25 mm diameter (100 micron, AMI Co.) was constructed. The Teflon coat was removed from the distal 1 mm of the electrode, which was then galvanically chlorided to eliminate DC offset, inserted and placed against the septal endocardial surface. MAPs were amplified, band-pass-filtered (0.5 Hz to 1 kHz) and recorded at a sampling frequency of 4 kHz.

Ventricular stimulation was performed through the MAP catheter using rectangular pulses of 2 ms duration at twice the diastolic threshold. ECG was simultaneously recorded by two Ag-AgCl electrodes fitted in a mounting ring placed in the perfusate-filled chamber just below the heart preparation.

C. Pacing Protocol

The dependence of APD on the preceding DI determined with the use of a standard S_1S_2 protocol. Single test pulses (S_2) which were named premature delivered after every 20th basic pulse (S_1) at a basic cycle length (BCL) which was started 500 ms. The S_1S_2 coupling interval was progressively shortened in steps of 50 ms starting from 450 to 200 ms and then was decreased in steps of 10–20 ms until the premature response block. Thereafter S_1S_2 interval was increased by 20 ms to restore capture and was subsequently shortened in 1–2 ms decrements until S2 response block. Furthermore pacing rates were decreased until 2:1 block occurred in BCL. The action potential duration was measured from action potential peak to 90% of repolarization (APD_{90}) in time scale. At all pacing cycle lengths used, the *ERP* was defined as the longest S_1S_2 interval at which a premature extrastimulus failed to elicit a propagating response. To enable measurements at long cycle lengths, the atrium was removed, and the atrioventricular (AV) node was mechanically crashed with forceps to slow down the intrinsic beating rate. The presence of complete AV block was verified by ECG recordings showing prolongation of the R-R interval.

V. Feature Extraction

MAP signals can be contaminated with noise, so a 50 Hz low pass filter was used to remove the unwanted noise. Then the main electrophysiological properties of MAP signals were extracted such as APD, DI, action potential peak amplitude, peak interval to present them to ANFIS algorithm as a features vector. Because of the rate dependency of some features for efficiency improvement of ANFIS, it is better to divide them to the stimulation rate. These features are APD, DI and peak interval. In this study direct feature extraction method was used instead of transform due to the presentation of restitution curve as a feature vector. Extracted electrophysiological properties are explained as below.

A. Electrical Restitution Curve

The electrical restitution curve traditionally describes the recovery of APD as a function of the interbeat interval or, more correctly, DI. In order to present the dynamical aspect of ERC, it is defined as a function of DI. Fig. 3

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shows the restitution points which were fitted by a mono exponential curve. The curve was fitted by GraphPad Prism 5. This protocol was executed in BCL of 130 ms. The slope of restitution curve which was fitted to square points, in shorter DIs or steep part of ERC is more than 1 and in longer DIs that constructed the flat part, is less than 1 but the protocol didn't terminate VF. In contrast, the protocol of circle points received to VF but the slope of ERC remains in flat part.

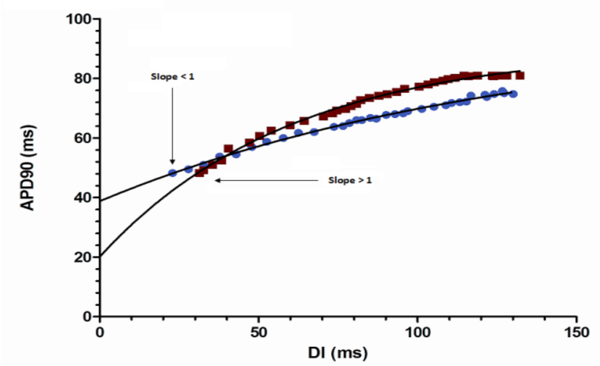

Fig.5. ERC of two separate protocols with BCL of 130 ms. The slope of curve fitted to square points receives to 1 and block occurred, but another curve which is terminated VF remains in flat part.

Two figures below shows the experiments that lead to VF and block. Fig. 6 shows a part of a protocol with decreasing extrastimulus premature that finally failed to elicit the propagating response and block occurred. But Fig. 7 shows another protocol with different rate that terminated to VF. As it is obvious there is no certain marker before VF or block occurrence. In previous studies action potential duration alternans has been determined as a precursor of VF induction. It occurs when slope of restitution exceed 1 (Koller *et al.*, 1998).

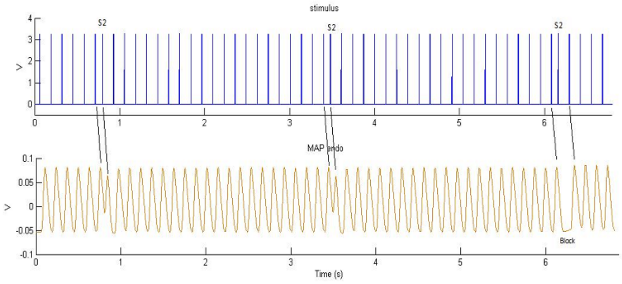

Fig.5. A part of protocol with stimulation rate of 130 ms that last premature response has blocked.

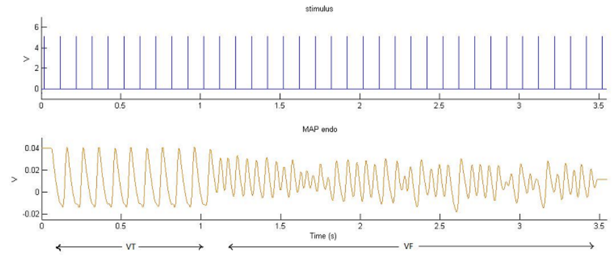

Fig.6. A part of pacing protocol with constant rate of 100 ms that terminated to VF.

VI. Results

Five features of MAP signal were extracted using direct method to present them to ANFIS algorithm as input vectors. A total of 50 datasets for two classes, which 65% of datasets were used for training and 35% of them used for testing. ANFIS can detect the steep slope of restitution curve with high accuracy of 96.6%. Fig. 7. demonstrates the accuracy for different percent of training dataset by sugeno type fuzzy inference system For different percent of training data .

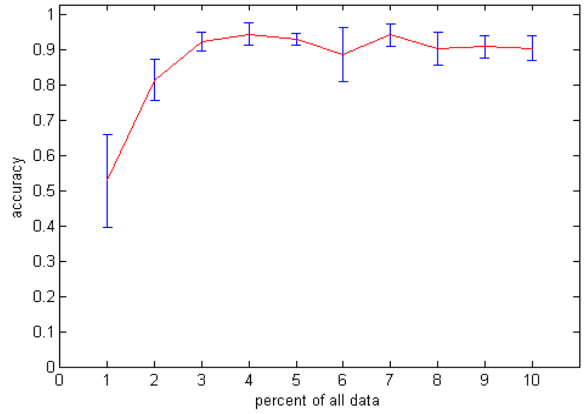

Fig.7. The accuracy of ANFIS algorithm to detect steep part of ERC for different percent of data which is selected randomly.

Fig. 8 shows the difference between mamdani and sugeno type fuzzy inference system according to the number of rules. Higher accuracy was achieved by sugeno type.

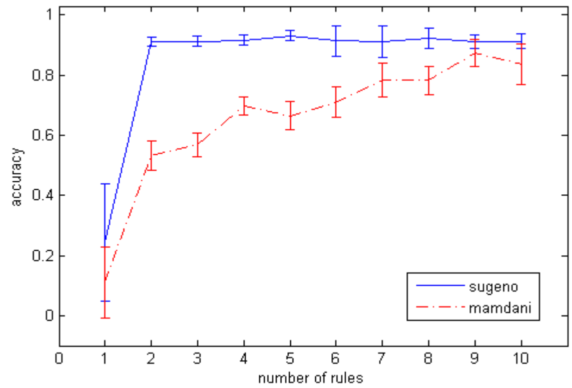

Fig.8. The accuracy difference of mamdani and sugeno type of FIS for detection of steep part of ERC.

By these electrophysiological that can detect steep part of ERC with high accuracy, we define its output as VF induction and block occurrence. The validity of this system has been checked with sensivity and specifity which is defined the next section.

A. Validity of algorithm

Sensitivity and specificity are used to measure the validity of the model to evaluate the classifier performance, because clinical research often investigates the accuracy by statistical relationship. In this paper the validity of algorithms is inspected by three factors; sensivity, specifity and accuracy which are described as below.

Sensivity is defined the probability of VF appearance. This value is equal to following equation:

$$Se(\%) = \frac{TP}{TP + FN} \times 100 \qquad (9)$$

Specificity is defined as the probability that propagating response failed to elicit.

$$Sp(\%) = \frac{TN}{TN + FP} \times 100 \qquad (10)$$

The parameters are defined as below:
True positive (TP): non-VF being detected non- VF;
True negative (TN): VF being detected VF;
False positive (FP): VF being detected non- VF;
False negative (FN): non- VF being detected VF;

Table 1: The validity of two algorithms; ANFIS and BP in detection of VT to VF transition.

	Sensivity	Specifity	Accuracy
ANFIS	38.1%	96.6%	85.2%
BP	59.53%	64.56%	62.27%

Table 1 shows the validity of ANFIS that for 5 features include S_1S_2 coupling interval, difference between V_1V_2 interval, APD_{90}, DI according to S_1S_2 and V_1V_2 interval. Sensivity of 38.1% demonstrates that ANFIS can't detect properly which protocol lead to VF. Also this model can detect well which protocol remains without VF induction which is shown by high specifity. This collection of features has the accuracy of 85.2%. Indeed, with this feature set the protocols which were terminated without VF are detectable well. Hence the accuracy didn't fall intensively. A neural network algorithm which was also applied in order to compare with ANFIS as a neuron-fuzzy system, is back-propagation. Although sensivity of back-propagation algorithm is higher than ANFIS, both specifity and accuracy are lower. Furthermore, back-propagation algorithm takes much time during learning, also may be caught by local minima, which decreases network performance. Another disadvantage of this algorithm is defining the number of nodes in the hidden layers before the training, because its structure is not automatically determined by the training algorithm (Dokur *et al.*, 2001). Actually ANFIS combines the advantages of fuzzy systems and neural networks, while reducing their difficulties. ANFIS uses the power of neural network to classify data while keeps the advantages of fuzzy expert system. Also Less tendency in memorizing errors is one of the other advantages of ANFIS in comparison with neural network (Nazmy *et al.*, 2010).

VII. Conclusion

In this paper, VT to VF transition detected using an ANFIS and back-propagation algorithm based on the features which are extracted from electrophysiological properties of MAP signal. This method can solve the difficulty of VF prediction by presentation of electrophysiological properties of cardiomyocytes include the components of APD, DI according to stimulus interval and action potential peak interval, magnitude of action potential peaks and time interval between two action potential peaks. These properties are discussing in recent papers because the steep slope of ERC traditionally was supposed to be an indicator of re-entrant arrhythmia or chaotic behaviour, while VF can occur in flat part. Also steep part of restitution may terminate to block. So, it can't predict VF occurrence individually. ANFIS and back-propagation algorithm showed that the electrical restitution curve can't predict inducing of VF properly. Therefore, other electrophysiological properties should be considered to enhance the accuracy of VF prediction.

Furthermore, between two applied algorithms, ANFIS is faster and has better and also more reliable results in predicting VF induction. ANFIS demonstrated accuracy of 85.2% that is higher than back-propagation.

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