Prediction of maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation by non-deterministic modelling

Petra Žohar a, M. Kočič b, M. Brezocnik b, Matej Podbregar c,*

a Cardiology Department, Hospital Celje, Slovenia
b Laboratory for Intelligent Manufacturing Systems, Faculty of Mechanical Engineering, Maribor, Slovenia
c Department for Intensive Internal Medicine, General Hospital Celje, Oblakova 5 3000 Celje, Slovenia

Submitted 30 March 2004, and accepted after revision 18 April 2005
Available online 14 July 2005

KEYWORDS
atrial fibrillation; electrical cardioversion; prediction

Abstract Aims Atrial fibrillation (AF) is the most common rhythm disorder. Because of the high recurrence rate of AF after cardioversion and because of potential side effects of electrical cardioversion, it is clinically important to predict persistence of sinus rhythm after electrical cardioversion before it is attempted. The aim of our study was the development of a mathematical model by “genetic” programming (GP), a non-deterministic modelling technique, which would predict maintenance of sinus rhythm after electrical cardioversion of persistent AF.

Patients and methods Ninety-seven patients with persistent AF lasting more than 48 h, undergoing the first attempt at transthoracic cardioversion were included in this prospective study. Persistence of AF before the cardioversion attempt, amiodarone treatment, left atrial dimension, mean, standard deviation and approximate entropy of ECG R–R intervals were collected. The data of 53 patients were randomly selected from the database and used for GP modelling; the other 44 data sets were used for model testing.

Results In 23 patients sinus rhythm persisted at 3 months. In the other 21 patients sinus rhythm was not achieved or its duration was less than 3 months. The model developed by GP failed to predict maintenance of sinus rhythm at 3 months in one patient and in six patients falsely predicted maintenance of sinus rhythm. Positive and negative likelihood ratios of the model for testing data were 4.32 and 0.05, respectively. Using this model 15 of 21 (71.4%) cardioversions not resulting in sinus rhythm at 3 months would have been avoided, whereas 22 of 23 (95.6%) cardioversions resulting in sinus rhythm at 3 months would have been administered.

* Corresponding author. Tel.: +386 34233000; fax: +386 35481204.
E-mail address: matej.podbregar@guest.arnes.si (M. Podbregar).
Introduction

Atrial fibrillation is the most commonly sustained cardiac arrhythmia in clinical practice; it is characterized by rapid ineffective atrial activity with irregular ventricular contractions [1]. AF may cause systemic thromboembolic complications, decrease exercise capacity, impair ventricular function, reduce quality of life and incur significant health care costs [2,3]. After adjusting for the underlying cardiac condition, AF is associated with a 1.5–1.9-fold increase in risk of mortality in both men and women across a wide spectrum of ages [4].

For many patients, maintenance of sinus rhythm is the main therapeutic goal. In patients with persistent AF repeated electrical cardioversions and prophylactic antiarrhythmic drugs are used to maintain sinus rhythm [5]. The success rate of electrical cardioversions ranges from 64% to 96% [6]. Although the success rate of electrical cardioversion is high, recurrence of AF is common, especially during the first 2 weeks following the procedure [7]. The percentage of recurrences of AF within 2 min after electrical cardioversion is 10% [8]. Electrical cardioversion has the potential of causing severe side effects, such as postshock bradycardia, malignant ventricular arrhythmias [9], arterial thromboembolism [10] and complications related to anaesthesia [11]. It has also minor complications such as local skin irritation or reversible muscle pain [12]. Because of the high recurrence rate of AF and because of potential side effects of electrical cardioversion, it would be clinically useful to be able to predict persistence of sinus rhythm after electrical cardioversion before it is attempted.

There are essentially two kinds of predictive models: deterministic (mathematical models, empirical models, and computer simulation models) and non-deterministic (models developed by genetic methods, neural network models, and models based on chaos theory and soft logic theory), and each has its advantages and disadvantages [13]. In general, when deterministic modelling is used the models obtained are the result of strict mathematical rules or they are set in advance. In that case, the goal is merely to discover a set of numerical coefficients for a model whose form has been pre-specified. However, nowadays more and more processes and systems are modelled and optimized using non-deterministic approaches. This is due to the high degree of complexity of the systems, and consequently, the inability to study them successfully with conventional methods only. In non-deterministic modelling of systems, there are no precise, strict mathematical rules. For example, in “genetic” programming (GP), no assumptions about the form, size, and complexity of models are made in advance. They are left to stochastic, self-organized, intelligent, and non-centralized evolutionary processes [14].

The aim of our study was to develop a mathematical model by GP, which would predict maintenance of sinus rhythm after electrical cardioversion of persistent AF.

Methods

Patients

Ninety seven patients with persistent AF lasting more than 48 h, during a 1-year period (January 2001 to January 2002), undergoing the first attempt at transthoracic electrical cardioversion were included in this prospective study. They were all treated at the cardiology department in a 860-bed Community General and Teaching Hospital. The study was approved by the Institutional Review Board. The patients gave informed consent.

Transthoracic echocardiography was performed in all patients before cardioversion. Wet polymer gel pads (M3502A, Agilent Technologies, Andover, MA, USA) were applied to the standard antero-lateral position. The anterior pad was placed at the upper right sternal border and the lateral pad over the cardiac apex.

Patients received damped sine wave monophasic sequential shocks of 100, 200, 300 and 360 J (Code Master XL+, Hewlett Packard, USA). All shocks were delivered during exhalation. During the procedure the patients were sedated with midazolam. For the purpose of the study cardioversion was considered successful if atrial-P waves were unmistakably identified ≥2 min after the shock.

Appropriate anticoagulation for at least 3 weeks or transoesophageal echocardiography to exclude
the presence of atrial thrombi before the procedure and anticoagulation with a therapeutic International Normalized Ratio (INR) of 2.0 to 3.0 for at least 4 weeks after the procedure was mandatory. All patients were required to have 12-lead ECG within 1 and 3 months of the cardioversion.

Patients were considered ineligible for the study if they were pregnant, were <18 years of age, were having AF of less than 48 h, had suffered from acute coronary syndrome within 3 weeks prior to cardioversion or if pharmacological cardioversion had been tried prior to electrical cardioversion.

**Signal recording and analysis**

A monophasic defibrillator was used for cardioversion and simultaneous on-line ECG recording. ECG signals of atrial fibrillation in length of 25 s before cardioversion were analyzed using MatLab R12 (MathWorks, USA).

Measurement of R–R (beat to beat) intervals was made from the original time-domain ECG signal by calculating the difference between different consecutive R spikes using the same computer programme.

Mean and standard deviation of consecutive R–R intervals were calculated.

Approximate entropy (ApEn), which is used in nonlinear analysis of R–R, was calculated from the same R–R intervals. ApEn measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the subsequent incremental comparison. A series containing many repetitive patterns has a relatively small ApEn; conversely, more random data produce higher values. Details of this method have been previously described [15].

**“Genetic” programming**

To avoid unnecessarily high classification performance of our model, data were divided into training and testing data sets. Data of 53 patients were randomized from the database and used for GP modelling. The theory of GP can be found in many books and articles that deal with evolutionary computation [16,17] (please see Appendix for more details).

In our study, computer programmes are in fact mathematical expressions (i.e. prediction models). The terminal genes (i.e. independent input variables) were persistence of AF before cardioversion attempt (1 = less than 3 month, 2 = between 3 and 6 months, 3 = between 6 and 12 months, 4 = more than 1 year), amiodarone treatment (yes = 1, no = 0), left atrial dimension (LA) (mm), mean (s) and SD (s) of R–R intervals and ApEn. The dependant output variable was persistence of sinus rhythm at 3 months after cardioversion (1 = sinus rhythm persisted at 3 months, 0 = atrial fibrillation). The function genes were basic arithmetical operations (functions of addition, subtraction, division, and multiplication).

With selected terminal and function genes the evolutionary attempts were made to construct, over several generations, as accurate a model as possible for prediction of sinus rhythm persistence at 3 months after cardioversion. The best model developed by GP from the training data was retested with the residual testing data of the 44 patients not included in the training set.

**Statistics**

Results were expressed as mean ± SD unless otherwise specified. Comparisons of dichotomous and continuous variables between different groups were calculated using χ² or nonparametric Kruskal–Wallis test and Student’s t test, respectively. SPSS 10.0 for Windows (SPSS Inc., USA) was used. A 2-tailed value of P < 0.05 was considered statistically significant. Classification of the performance of the decision model was determined by Bayesian analysis (true positive (TP), true negative (TN), false positive (FP), false negative (FN)) applying sensitivity (SENS) = TP/(TP + FN), specificity (SPEC) = TN/(FP + TN), positive predictive value = TP/(TP + FP), negative predictive value = TN/(FN + TN), positive likelihood ratio = SENS/(1–SPEC), and negative likelihood ratio = (1–SENS)/SPEC [18].

**Results**

Ninety-seven electrical cardioversion procedures were attempted. Sinus rhythm persisted in 89.9% of patients at 24 h after cardioversion, in 54.1% at 1 month and in 49.0% of patients at 3 months after cardioversion. The characteristics of patients are shown in Table 1. At 3 months sinus rhythm persisted more often in patients receiving amiodarone (22/48 vs. 7/49, P = 0.022). Maintenance of sinus rhythm was influenced by AF duration. At 3 months AF was registered more often compared with sinus rhythm in patients with AF duration of more than 12 months (24/49 vs. 9/48, P = 0.044). The predictive model developed by GP has not excluded any of six variables included at the start of programming. The equation of the predictive model is presented in Fig. 1. The following rules...
were used: the result of equation more than zero predicted persistence of sinus rhythm at 3 months after the cardioversion attempt, otherwise the rhythm was predicted not to be sinus.

The testing data included 44 data sets before cardioversion. In 23 patients sinus rhythm persisted at 3 months. In the other 21 patients sinus rhythm was not achieved or it persisted for less than 3 months.

The model developed by GP failed to predict persistence of sinus rhythm at 3 months in one patient (false negative result) and in six patients falsely predicted (false positive result) persistence of sinus rhythm. The classification of performance of the model developed by GP on testing data is shown in Table 2.

Discussion

In this study the prediction power of a non-deterministic model developed by GP to predict persistence of sinus rhythm at 3 months after cardioversion of persistent atrial fibrillation was studied. High positive and low negative likelihood ratios of the GP model indicate that the model may have a very substantial impact on clinical decision-making through meaningful revision of performance of cardioversion [19].

In all patients, six variables from the time-domain (persistence of atrial fibrillation, mean R–R interval before cardioversion, SD of R–R intervals, ApEn = approximate entropy), echocardiographic data (left atrial dimension, treatment (amiodarone) and nonlinear dynamics properties of R–R intervals (ApEn) were collected. On the basis of these data alone, amiodarone and shorter duration of AF before cardioversion attempt treatment were associated with a higher rate of sinus rhythm maintenance as was previously shown [20].

All independent input variables included in our model developed by GP had already been studied as predictors of persistence of sinus rhythm after cardioversion or as predictors of the onset of paroxysmal atrial fibrillation [6,21]. Electrical cardioversion is the most effective method for termination of
Figure 1  Model developed by genetic programming. Independent input variables: $T$ = duration of AF before cardioversion attempt (1 = less than 3 month, 2 = between 3 and 6 months, 3 = between 6 and 12 months, 4 = more than 1 year), CORD = amiodarone treatment (yes = 1, no = 0), LA = left atrial dimension parasternal long-axis (mm), $M$ = mean (s) of R–R time series, SD = standard deviation (s) of R–R time series, APEN = approximate entropy.
persistent atrial fibrillation. Rates of transthoracic cardioversion of chronic atrial fibrillation vary from 70% to more than 90%. Success rate is influenced by duration of atrial fibrillation, transthoracic impedance, initial energy selection and type of shock waveform [22–26]. We have previously reported that the type of shock waveform does not influence the success rate of cardioversion in atrial fibrillation which has persisted for more than a year [27]. It was also previously shown that amiodarone reduces procedures and cost related to atrial fibrillation and it reduces recurrences of atrial fibrillation after an electrical cardioversion [28–30]. Left atrial function and size are also independent predictors of atrial fibrillation recurrence [31,32]. The autonomic nervous system may play an important role as a trigger for spontaneous onset of paroxysmal atrial fibrillation [33]. Analysis of heart rate variability has become an important, non-invasive tool for assessing autonomic influence on the heart [34]. It was recently shown that a decrease of the complexity of RR intervals and altered fractal properties (ApnE) in short-term RR interval dynamics precedes the spontaneous onset of atrial fibrillation in patients with no structural heart disease.

In our study the data were separated into training and testing data, so the “best-fit” threshold values were not used in prediction to obviate artificially good sensitivity and specificity.

The present study has at least three major limitations. First, the number of cardioversions was low. Second, a 25-s period of ECG signal just prior to cardioversion was analyzed rather than classical long term ECG signal analysis [35]. The third weakness of our model is that it does not include data which potentially influence prediction of sinus rhythm maintenance after electrical conversion such as presence or absence of hypertension, level of C-reactive protein, presence or absence of heart failure etc. We have focused our data mainly on the ECG to develop computer programmes which could be simply integrated into defibrillators.

We have demonstrated that a non-deterministic model called genetic programming is able to develop a model, using clinical data, ECG data from the time-domain and nonlinear dynamics, which could predict maintenance of sinus rhythm after cardioversion of chronic atrial fibrillation with high positive and low negative likelihood ratios. Further research is needed to determine the utility of this model or an expanded version.

**Acknowledgments**

We thank the patients who participated in the study and Drs Mojca Bervar, Matej Marinski, Dragan Kovacic, Mojca Perkolj-Bicanic, Nanika Skrabl-Mocnik, Albina Dokler-Glavnik for treating the patients.

**Appendix**

**Genetic programming**

GP is probably the most general approach of evolutionary computational methods. In GP the structures subject to adaptation are the hierarchically organized computer programmes (organisms) the size and form of which dynamically change during simulated evolution. Computer programmes can be mathematical expressions, control strategies, plans, decision trees, state-transition rules, etc. Possible solutions in GP are all the possible computer programmes that can be composed in a recursive manner from a set of function genes and a set of terminal genes describing the problem area to be studied. The set of function genes can include e.g. arithmetical functions, Boolean functions, relation functions, program flow control functions, where the set of terminal genes, e.g., numerical constants, logical constants, variables. The aim of GP is to find the computer programme that best solves the problem.

The initial population is obtained with the creation of random computer programmes consisting of the available function and terminal genes. The next step is the evaluation of population (i.e. calculation of fitness for each organism). On the basis of fit, alternation of computer programmes with genetic operations follows. In GP the computer programs alter, in particular, with reproduction and crossover. The reproduction operation gives a higher probability of selection to more successful organisms. They are copied unchanged into the next generation. The crossover operation ensures the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Classification of performance of the model developed by genetic programming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic method</td>
<td>SENS (%)</td>
</tr>
<tr>
<td>Genetic programming</td>
<td>95.8</td>
</tr>
</tbody>
</table>

SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+,, likelihood ratio for a positive test result; LR−,, likelihood ratio for a negative test result.
Figure 2 Crossover of two computer programmes, which are in fact mathematical expressions (parent — mathematical expression before mathematical operation, child — mathematical expression after mathematical operation).

exchange of genetic material between computer programmes. Fig. 2 shows the operation of cross-over of two computer programmes, which are in fact mathematical expressions. Two randomly selected parts of two parental organisms (in boldface) are interchanged. Thus two offspring are created.

After finishing the first cycle which includes: (1) the creation of initial population, (2) calculation of fit for each individual of the population, and (3) genetic alternation of contents of the computer programmes, an iterative repetition of points 2 and 3 follows. The evolution is terminated when a termination criterion is fulfilled. This can be a prescribed maximum number of generations or a sufficient quality of the solution.

References


\[
\frac{x_1 + x_2}{5.6 x_3} + x_1 x_3 = \frac{(1 - x_2 x_3)}{5.6 x_3} + x_1 x_3
\]
Sinus rhythm persistence after cardioversion


