Predicting coronary artery disease using different artificial neural network models

Koroner arter hastalığının değişik yapay sinir ağı modelleri ile tahmini

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ABSTRACT

Objective: Eight different learning algorithms used for creating artificial neural network (ANN) models and the different ANN models in the prediction of coronary artery disease (CAD) are introduced.
Methods: This work was carried out as a retrospective case-control study. Overall, 124 consecutive patients who had been diagnosed with CAD by coronary angiography (at least 1 coronary stenosis > 50% in major epicardial arteries) were enrolled in the work. Angiographically, the 113 people (group 2) with normal coronary arteries were taken as control subjects. Multi-layered perceptrons ANN architecture were applied. The ANN models trained with different learning algorithms were performed in 237 records, divided into training (n=171) and testing (n=66) data sets. The performance of prediction was evaluated by sensitivity, specificity and accuracy values based on standard definitions.
Results: The results have demonstrated that ANN models trained with eight different learning algorithms are promising because of high (greater than 71%) sensitivity, specificity and accuracy values in the prediction of CAD. Accuracy, sensitivity and specificity values varied between 83.63% - 100%, 86.46% - 100% and 74.67% - 100% for training, respectively. For testing, the values were more than 71% for sensitivity, 76% for specificity and 81% for accuracy.
Conclusions: It may be proposed that the use of different learning algorithms other than backpropagation and larger sample sizes can improve the performance of prediction. The proposed ANN models trained with these learning algorithms could be used a promising approach for predicting CAD without the need for invasive diagnostic methods and could help in the prognostic clinical decision. *(Anadolu Kardiyol Derg 2008; 8: 249-54)*
Key words: Artificial neural network, prediction, coronary artery disease, learning algorithms

ÖZET

Amaç: Bu çalışmada, koroner arter hastalığının (KAH) tahmin edilebilmesi için değişik sekiz öğrenme algoritması ile farklı yapay sinir ağı modelleri oluşturulmuş ve tanıtılması amaçlanmıştır.
Yöntemler: Bu çalışma geriye dönük bir vaka kontrol araştırması olarak gerçekleştirilmiştir. Çalışmaya, anjiyografik olarak majör epikardiyal arterlerin en az bir tanesinde %50'den fazla darlığı olan 124 ardışık birey dâhil edildi. Anjiyografik olarak normal koroner arterlere sahip olan 113 birey ise kontrol grubu olarak alınmıştır. Çok katmanlı "perseptron" yapay sinir ağları uygulandı. Değişik sekiz öğrenme algoritması ile eğitilen farklı yapay sinir ağı modelleri, toplam 237 kayıtta, 171'i eğitimde ve 66'sı ise teste kullanılarak oluşturuldu. Tahminin performansı, duyarlılık, seçicilik ve doğruluk oranlarına dayalı olarak değerlendirilmiştir.
Bulgular: Çalışmanın sonuçları, oluşturulan yapay sinir ağı modelleri ile KAH'ın tahmininde yüksek oranda (%71.0'den daha yüksek) duyarlılık, seçicilik ve doğruluk oranları elde edildiği için modellerin performansının iyi olduğunu göstermiştir. Doğruluk, duyarlılık ve seçicilik değerleri eğitimde sırasıyla %83.63 - %100, %86.46 - %100 ve %74.67 - %100 arasında iken, testte ise duyarlılık %71'den daha büyük, seçicilik %76'dan daha büyük ve doğruluk %81'den daha büyük olarak elde edilmiştir.
Sonuç: Geriye yayılım algoritmasından başka farklı öğrenme algoritmalarının ve daha büyük örnek çaplarının kullanılması, tahminin performansını artırabilir. Değişik sekiz öğrenme algoritması ile eğitilen farklı yapay sinir ağı modelleri, KAH'ın tahmin edilmesinde ümit verici sonuçlar vermektedir ve ileriye yönelik klinik tanı sürecinde kullanılabilir. *(Anadolu Kardiyol Derg 2008; 8: 249-54)*
Anahtar kelimeler: Yapay sinir ağları, tahmin, koroner arter hastalığı, öğrenme algoritmaları

Introduction

Artificial neural networks (ANNs) are the computer programs, which are biologically inspired to design to simulate human brain processes information. Artificial neural networks gather their knowledge from input-output relationships in data and learn through experience, not from programming. Artificial neural networks can be used as a statistical analysis tool to build behavior models starting from a collection of examples (defined by a series of numeric or textual descriptive variables) of this

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behavior. The success of ANNs depends on the architecture, the learning algorithm and its parameters, the transfer function, the number of layers and processing elements (neurons) (1, 2).

For the last years, several studies have been reported pertaining to ANN approach in the prediction and classification of coronary artery disease (CAD) (3-7). In these studies, multilayered perceptrons (MLP) trained with backpropagation learning algorithm were mostly used for prediction. Still, the use of various learning algorithms other than backpropagation for training MLP can improve the performance of the classification and prediction.

This paper presents eight ANN models to the prediction of CAD. Eight learning algorithms, Levenberg-Marquardt, quasi-Newton (Broyden, Fletcher, Goldfarb, and Shannon (BFGS)), quasi-Newton (one step secant), conjugate gradients (CGs) of scaled, Polak-Ribiére, Fletcher-Reeves and Powell-Beale, and backpropagation (BP) with momentum have been used to train ANN structures to improve the training performance of the ANN models for CAD prediction.

Methods

Subject selection

This work was carried out as a retrospective case-control study. In İnönü University Faculty of Medicine, Malatya, Turkey, 237 consecutive people who had been referred for the department of Cardiology were studied in the year of 2001. Overall, 124 consecutive patients (Group 1) who had been diagnosed with CAD by coronary angiography (at least 1 coronary stenosis >50% in major epicardial arteries) were enrolled in the work. Angiographically, the 113 people (Group 2) with normal coronary arteries were taken as control subjects. The criteria of angiographically normal coronary arteries are absence of plaque in major epicardial arteries, absence of spasm and/or coronary ecstasy, and existence of TIMI-3 flow according to the TIMI flow score.

The predictive variables used in the analysis for predicting CAD or no CAD are as follows: sex (women/men), age (years), hypertension (diastolic blood pressure >90 mmHg and/or systolic blood pressure >140mmHg) (8), diabetes mellitus (Type 2 diabetes based on the criterions reported by World Health Organization) (9, 10), family history, smoking, stress, physical activity, obesity (body mass index-BMI > 30) (11), hemoglobin, white blood cells, uric acid, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), direct bilirubin, and total bilirubin. The predictive variables were similar to CAD risk factors used in the previous works (12-14).

Creation of the artificial neural network models

In this ANN application, 17 input variables were the predictive variables given earlier and the output (outcome variable) was CAD or no CAD. The predictors were used for predicting the outcome variable. ANN models were created and trained with different learning algorithms (Levenberg-Marquardt (15, 16), quasi-Newton (Broyden, Fletcher, Goldfarb, and Shannon (BFGS)) (17), quasi-Newton (one step secant) (18), conjugate gradients (CGs) of scaled, Polak-Ribiére, Fletcher-Reeves and Powell-Beale (19, 20), and backpropagation (BP) with momentum (21)) on training data set (171 records). After training, each ANN models were tested by a set of data, which were not used in the training process. As a result, it became clear whether the network had really learned or had just memorized. Briefly, the cross-validation approach was used for this process. The accuracy of the technique was evaluated by splitting data into two data sets: the training data set and the testing data set. When learning is stopped optimally, the network is evaluated with the data from the testing data set. Generally, more than 10% of the whole data set may be taken as testing data set (22). In our work, 66 of the 237 records, that is, nearly 28% of the whole data was used to test the models. Multi-layered perceptrons ANN architecture were applied in the current work. ANN models trained with different parameters and eight different learning algorithms were tested. Denote these proposed ANN models with ANN, where "i" is an integer and $1 \leq i \leq 8$. Table 1 tabulates the information about topologies of the networks and the methods that were used for training with the definitions. The performance of prediction was evaluated by sensitivity, specificity and accuracy based on standard definitions. The definitions are described in Table 2.

Statistical analysis

Values are given as Mean±Standard Deviation or percentage. Normality was tested by performing a Shapiro-Wilk test. The independent samples t test and Chi-square test were used based on statistical assumptions. Values of $p<0.05$ were considered statistically significant.

Table 1. ANN models used in CAD prediction

Model	I_n	H_n	O_n	F_1	F_2	LA
ANN_1	17	8	1	HT	Sigmoid	LM
ANN_2	17	15	1	Sigmoid	Sigmoid	Scaled CGs
ANN_3	17	12	1	Sigmoid	Sigmoid	QN (BFGS)
ANN_4	17	17	1	Sigmoid	Sigmoid	QN (one step secant)
ANN_5	17	15	1	Sigmoid	Sigmoid	CGs (Polak-Ribiére)
ANN_6	17	7	1	Sigmoid	Sigmoid	CGs (Powell-Beale)
ANN_7	17	17	1	Sigmoid	Sigmoid	CGs (Fletcher-Reeves)
ANN_8	17	17	1	Sigmoid	Sigmoid	BP with Momentum

ANN- artificial learning algorithm, BFGS- Broyden, Fletcher, Goldfarb, and Shannon, BP- backpropagation learning algorithm, CAD- coronary artery disease, CG- conjugate gradient, F_1- activation function between the input layer and the hidden layer, F_2- activation function between the hidden layer and the output layer, H_n - number of neurons in the hidden layer, HT- hyperbolic tangent transfer function, I_n- number of neurons in the input layer, LA- learning algorithm, LM- Levenberg-Marquardt learning algorithm, -O_n- number of neurons in the output layer, QN- quasi-Newton

Results

Clinical characteristics of the groups are shown in Table 3. The mean ages of Group 1 and Group 2 for men were 58.98±7.75 and 51.86±6.63 years. The percentages of men for Group 1 and Group 2 were 69.4% and 68.1%, respectively. There was a statistically significant difference for ages among the groups. The variables that were found to show a significant difference between the groups were hypertension, diabetes mellitus, family history, smoking, stress, physical activity, obesity, white blood cells, uric acid, triglyceride, high density lipoprotein (HDL), low-density lipoprotein (LDL), direct bilirubin and total bilirubin ($p<0.05$ for all).

The training of ANN models were carried out on 171 records. The results obtained from ANN models are given in Table 4. The accuracy, sensitivity and specificity values were among 83.63% - 100%, 86.46% - 100% and 74.67% - 100%, respectively.

The testing results having 66 records achieved from ANN models trained with eight different learning algorithms for the prediction of CAD are given in Table 4. Most of ANNs performed the tasks more than 71% for sensitivity, 76% for specificity and 81% for accuracy in the CAD prediction.

When the ANN models are compared based on the testing results, the highest sensitivity values were obtained from ANN_8 / ANN_1, ANN_2 / ANN_6, ANN_3 / ANN_4, ANN_7 and ANN_5 models were followed the prediction performance. The details of the training and testing results are presented in Table 4. For a clear expression, ANN structures, training / testing sample sizes, transfer functions used for ANN designs were compared to the reported results as given in Table 5.

Discussion

In the current study, ANN models, which can be used as non-invasive technique, trained with eight different learning algorithms were considered. The present results demonstrate that ANN models (ANN_1-ANN_8) performed CAD prediction with considerably high sensitivity, specificity and accuracy. When the ANN models are compared, the highest sensitivity, specificity and accuracy values were obtained from the network (ANN_8) in

Table 2. Accuracy test definitions

Diagnostic test	GS		Total
	Nondiseased (GS=0)	Diseased (GS=1)	
Negative (Dx=0)	A=true negatives	B=false negatives	A+B=test negatives
Positive (Dx=1)	C=false positives	D=true positives	C+D=test positives
Total	A+C=nondiseased	B+D=diseased	A+B+C+D=total sample size

Accuracy=(A+D)/(A+B+C+D), GS - gold standard, Specificity=true negative rate=A/(A+C), Sensitivity=true positive rate=D/(B+D)

Table 3. Clinical characteristics of the groups

Variables	Group 1 (n=124)	Group 2 (n=113)	p
Age, years	58.98±7.75	51.86±6.63	<0.001*
Sex, (men)	69.4	68.1	0.840**
Diabetes mellitus, %	49.2	19.5	<0.001**
Hypertension, %	53.2	20.4	<0.001**
Family history, %	43.5	15.9	<0.001**
Smoking, %	74.2	27.4	<0.001**
Obesity, %	49.2	20.4	<0.001**
Stress, %	88.7	52.2	<0.001**
Physical activity, %	3.2	25.7	<0.001**
Triglyceride, mg/dl	177.10±41.81	118.52±29.11	<0.001*
LDL, mg/dl	141.66±18.53	116.19±22.09	<0.001*
HDL, mg/dl	36.37±7.58	38.93±7.98	<0.001*
Uric acid, mg/dl	5.41±1.48	4.84±0.86	<0.001*
White blood cells, mg/dl	7897.58±1481.67	6869.20±1016.89	<0.001*
Hemoglobin, mg/dl	14.00±2.10	13.77±1.38	0.320*
Direct bilirubin, mg/dl	0.19±0.09	0.15±0.08	0.010*
Total bilirubin, mg/dl	0.81±0.23	0.73±0.27	<0.01*

Data are presented as percentages and Mean±SD
*- unpaired t test; ** -Chi-square test
HDL- high-density lipoprotein; LDL- low-density lipoprotein

training. ANN_1, ANN_3, ANN_4 and ANN_2 models were followed this performance. When the sensitivity testing results were considered, the success of ANN models could be sequentially ranked as ANN_1/ANN_8, ANN_6/ANN_2, ANN_4/ANN_3, ANN_7 and ANN5. Among the learning algorithms, BP with momentum and Levenberg-Marquardt were found as the most successful algorithms. The worst was conjugate gradients (Polak-Ribiére) algorithm based on sensitivity. The other findings of this study are that different learning algorithms can increase sensitivity, specificity and accuracy, selecting sigmoid function in ANN structures were also increased the performance. Tangent hyperbolic function is also effective in having high accuracy.

From the clinical point of view, CAD and its thrombotic complications are the leading cause of morbidity and mortality in the industrialized countries. It is expected that the rate of CAD will accelerate in the next decade, contributed to by aging of the population, alarming increases in the worldwide prevalence of obesity, type 2 diabetes and metabolic syndrome as well as a rise in cardiovascular risk factors among younger generations (23-25). Each year brings dramatic new developments in detection of CAD. Principally, there are two diagnostic techniques for detection of CAD; non-invasive and invasive techniques. Non-invasive tests including exercise electrocardiography (ECG), echocardiography, stress echocardiography, PET (positron emission tomography), magnetic resonance imaging (MRI) and electron beam computerized tomography (EBCT) can provide useful and often indispensable information to establish the diagnosis and estimate the prognosis in patients with CAD. Exercise electrocardiography (ECG), remains to be the most widely used method for assessment of the presence and severity of CAD although this method has some limitation for detection of CAD (26). Clinical confidence in the exercise ECG has been eroded by the limited sensitivity and predictive value of standard ST segment depression criteria and by the over-application of Bayesian principals to interpretation of the exercise ECG in comparison with other noninvasive modalities (26). On the other hand, interpretation of stress echocardiography is still subjective (27, 28). In the past decade, use of nuclear imaging methods has evolved as a preeminent technique to asses CAD. Nevertheless,

Table 4. Training and testing results for CAD prediction

Models	Training			Testing		
	Accuracy, %	Sensitivity, %	Specificity, %	Accuracy, %	Sensitivity, %	Specificity, %
ANN_1	97.08	96.88	97.33	92	96	89
ANN_2	95.91	98.96	92	87	89	86
ANN_3	97.08	96.88	97.33	86	85	86
ANN_4	96.49	97.92	94.67	86	85	86
ANN_5	88.89	90.63	86.67	84	71	94
ANN_6	83.63	90.63	74.67	81	89	76
ANN_7	84.21	86.46	81.33	78	78	78
ANN_8	100	100	100	87	96	91

ANN- artificial neural network, CAD- coronary artery disease

Table 5. Results of comparative studies

Works Literature / presented	Sample size in		ANN structure	LA	TF	Sensitivity, %	Specificity, %	Accuracy, %
	training	testing						
Allison et al. (4)	109	37	MLP	BP	Logistic	69-94	78-93	N/A
Bigi et al. (33)	496	-	MLP	BP	N/A	28-70	47-83	50-70
Lindahl et al. (34)	203	68	MLP	BP	?	92-98	62-81	N/A
Mobley et al. (35)	332	100	MLP	BP	Logistic	100	47.37	N/A
Lindahl et al. (36)	338	34	MLP	BP	Sigmoid	59-91	N/A	N/A
Present method	171	66	MLP	LM	HT	96	89	92
Present method	171	66	MLP	Scaled CGs	Sigmoid	89	86	87
Present method	171	66	MLP	QN (BFGS)	Sigmoid	85	86	86
Present method	171	66	MLP	QN (one step secant)	Sigmoid	85	86	86
Present method	171	66	MLP	CGs (Polak-Ribiére)	Sigmoid	71	94	84
Present method	171	66	MLP	CGs (Powell-Beale)	Sigmoid	89	76	81
Present method	171	66	MLP	CGs (Fletcher-Reeves)	Sigmoid	78	78	78
Present method	171	66	MLP	BP	Sigmoid	87	96	91

ANN - artificial neural network, BP - backpropagation learning algorithm, CG - conjugate gradient, HT - hyperbolic tangent transfer function, LA - learning algorithm, LM - Levenberg-Marquardt learning algorithm, MLP - multilayered perceptrons, N/A - not applicable, QN- quasi-Newton, TF - transfer function

this method is also limited due to false positive and negative results (29, 30). In addition, novel non–invasive methods such as MRI and EBCT have not yet found widespread application for the diagnosis and classification of CAD, because of demanding nature of the technique, high cost, time-consuming or not readily available in all coronary laboratories (31, 32). Accordingly, there is need to newer and reproducible techniques for definition and prediction of CAD. Recently, efforts have been made to develop reliable non-invasive diagnostic methods that would allow a broader use, as well as decreasing the risk linked to an invasive examination (32).

To our knowledge, few previous studies have investigated combining the cardiovascular risk factors to predict the extent of CAD. Therefore, using an artificial neural network model, a non-invasive method, for the first time we attempted to predict CAD combining seventeen cardiovascular risk factors mentioned above. From the clinical viewpoint, the collection of risk factor data, combined with surveillance for CAD events over several years, has led to the development of algorithms that estimate the risk for initial and recurrent CAD events. Strategies to identify persons at risk for CAD allow stratification of patients and are useful for clinicians. In high-risk patients, this will facilitate the targeting of modifiable risk factors that are present in excess and for which modification is likely to result in a reduction in risk. Additionally, for the patient it presents a clear picture of risks faced over the next 5 to 10 years. This information can improve compliance with treatment.

For a clear discussion, ANN structures, training and testing sample sizes, transfer functions used and so forth for ANN designs were compared to the literature results as given in Table 5. The obtained prediction results of the present study are mostly higher based on sensitivity, specificity and accuracy as compared to the results of the reported studies (4, 33-36) given in Table 5.

Limitations of the study

This study has a few limitations. First, the sample size of 237 (171 for training, 66 for testing) might be small for a robust test. Second, time, cost and obtaining the clinical parameters pertaining to patients difficultly may affect this study. Third, further studies should be done prospectively with larger data samples and different ANN structures/learning algorithms.

Conclusions

The present results and the reviewed studies have clearly demonstrated that ANNs are now not only promising but also an acceptable approach for prediction of the diseases like CAD. The use of different learning algorithms other than backpropagation and larger sample sizes can improve the success of CAD prediction. The proposed ANN models could be used a promising approach for predicting CAD without the need for invasive diagnostic methods and could help in the prognostic clinical decision.

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Beni çok hüzünlendiren bu fotoğraf 1943 yılında sevgili yurdumun bir köşesinde çekilmiş. Mehmetçik, dağ tepe dolaşarak, cumhuriyetimizin emanet edildiği geleceğin gençlerini eğitiyor. Yarı çıplak çocuklarla konuşan benim babacığım. O günlere gidebilmeyi ve "çocuklar ne olur çok dikkatli olun, ülkenize, cumhuriyetinize, Atatürk ilke ve devrimlerine yani aydınlık geleceğinize sahip çıkın" diye binlerce kez haykırabilmeyi yürekten istiyorum.

Esmeray Acartürk