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Relationship of Plasma Creatine Kinase and Cardiovascular Function in Myocardial Infarction

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Maximal plasma creatine kinase (CPK) values are often used as an enzymatic test in acute myocardial infarction. The cardiovascular functional ability (FA) is a reliable parameter, which may define the lesion of the cardiovascular system following myocardial infarction. We have applied the Cubist machine learning tool to set up a model that defines the residual cardiovascular functional ability after a myocardial infarction by means of the maximal CPK in the acute phase of the disease. Cubist models numeric data and generates values by means of a collection of rules associated with the linear expression for computing target values. Based on the literature data set of Mirić *et al.*,[1] we have derived and tested a reliable and accurate Cubist model for acute inferior and anteroseptal myocardial infarction consisting of three simple rules. The rules enable simple prediction of the expected cardiovascular functional ability in myocardial infarction following recovery. The model is based on two clinical parameters related to the disease, maximal CPK in the acute phase of the myocardial lesion, and anteroseptal or inferior cardial localisation of the infarction. Strong correlation (r anteroseptal = 1.00, r inferior = 0.94, n = 56), insignificant differences of real and predicted values, and low average error of the leave-one-out test (anteroseptal 1.72, inferior 3.54) confirm the accuracy of the method and its applicability in clinical medicine. In addition to the prognostic and diagnostic application, the extracted rules enable more efficient evaluation of new drugs and therapeutic procedures in Cardiology.

Key words: CPK, myocardial infarction, localisation, cardiovascular function, Cubist, machine learning, model.

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INTRODUCTION

Heart disease has become a major health hazard in middle life and in old age. Myocardial infarction, as a consequence of the heart disease, usually leads to a number of complications resulting in a decreased cardiovascular functional ability (FA). In this study, we model the relationship of plasma creatine kinase levels (CPK) and decreased cardiovascular functional ability in anteroseptal and inferior infarction. These two localisations are found in 80% of all patients with myocardial infarction.[1]

Determination of maximal CPK values reflects the degree of myocardial damage at the beginning of infarction, and cardiovascular functional ability defines the capacity of the cardiovascular system following the recovery.[1,2] We applied the Cubist machine learning tool to predict the decrease of cardiovascular functional ability on the basis of maximal CPK levels in acute anteroseptal and inferior myocardial infarction. The latter is important for the prediction of the heart disease outcome following the infarction, and for the evaluation of new therapeutic procedures in Cardiology.

MATERIAL AND METHODS

Data Set and Measurements

The analysed data set for modelling the relationship of CPK values and cardiovascular functional ability (FA) in myocardial infarction was obtained from the data presented in Figure 2 and Figure 3 of Mirić *et al.*[1] using of the Origin software (www.OriginLab.com), which is capable of extracting data coordinates from imported pictures. A total of 56 different cases of anteroseptal and inferior infarction localisations were extracted from the figures. Maximal CPK values in iU L^{-1} were measured in the standard manner, every 8 hours during the first 48 hours of acute myocardial infarction.[1–6] The cardiovascular functional ability, expressed as the percentage of oxygen uptake (FA in %), was measured on a tread-mill according to the Bruce protocol in the same patients with anteroseptal or inferior localisation of myocardial infarction 4 months after the onset of the disease (and CPK determination).[1–6]

Cubist Machine Learning System

The Cubist machine learning system, version 1.09 (www.Rulequest.com), was used for the generation of a rule-based predictive model of CPK and cardiovascular functional ability (FA) in anteroseptal and inferior myocardial infarction. In contrast to its sister model C5.0 (outgrowth of the classic C4.5) that predicts categories,[7–9] Cubist models numeric data and generates values. It extracts the collection of rules, each of which is associated with a linear expression for computing target values. Therefore, the Cubist model resembles a piecewise linear model (except that the rules can sometimes overlap). Cubist can also construct multiple models and combine rule-based models with instance-based (nearest neighbour) models. The Cubist ap-

plication consists of a collection of text files that define attributes, describe the analysed cases and provide new cases to test the produced models.

RESULTS AND DISCUSSION

The prognostic value of CPK determination in acute myocardial infarction was observed considering its influence on the cardiovascular functional ability and the localisation of infarction (Table I). Maximal CPK values in acute myocardial infarction are thought to be a reliable laboratory enzymatic parameter that defines the myocardial damage.[1,2] Normal CPK values are 10–15 iU L^{-1} and in myocardial infarction CPK are often >10 times higher than in the controls.[2,6]

TABLE I

Training set of the maximal plasma creatine kinase (CPK / iU L^{-1}) values and cardiovascular functional ability (FA / %) in anteroseptal and inferior myocardial infarction. The data were extracted from Mirić *et al.*[1] by means of the Origin software. The Cubist machine learning system release 1.09 was used to (a) define the prognostic value of CPK levels measured in acute anteroseptal and inferior myocardial infarction, (b) predict the cardiovascular functional ability following the recovery (FAC). Rules of the models are presented in Table II.

Anteroseptal Infarction			Inferior Infarction		
CPK[†] / iU L^{-1}	FA[§] / %	FAC* / %	CPK[†] / iU L^{-1}	FA[§] / %	FAC* / %
484	94.9	95.3	320	96	83.4
492	94.9	93.9	326	89.7	83.9
502	95	92.3	337	84.8	84
496	89.7	93.8	353	84.9	82.6
508	84.4	84.8	305	82	86.2
518	84.6	83.4	324	79.9	85.4
532	79.7	81.9	357	79.8	83.1
544	79.7	80.2	392	74.9	80.6
564	77.8	77.8	451	74.6	76.5
578	69.5	68.5	465	74.9	75.6
588	69.5	68.1	471	71.7	67.5
598	69.5	68	522	68.8	68
584	67.5	68.6	549	68	67.7
705	66.3	66.4	569	67.7	68
750	64.8	65.6	677	67.7	65.9

TABLE I (cont.)

	Anteroseptal Infarction			Inferior Infarction		
	CPK† / iU L^{-1}	FA§ / %	FAC* / %	CPK† / iU L^{-1}	FA§ / %	FAC* / %
	794	64.6	64.6	686	67.7	65.7
	867	63.6	63.8	686	64.8	66.3
	1000	61.5	60.6	702	64.8	66.2
	1020	59.7	60.8	753	64.7	65.4
	1139	59.8	58.7	822	64.6	64.6
	1208	57.4	57.5	878	64.6	64
	1242	57.4	56.8	914	64.6	64
	1278	56.4	56	1180	64.6	66.2
	1290	54.6	56.3	1259	64.6	64.1
	1478	54.5	54.8	1277	64.6	63.5
	1524	54.3	54	2035	43	43.4
	1571	54.2	53.8	–	–	–
	1685	53	52	–	–	–
	1825	48.9	50.5	–	–	–
	1934	48.8	48.5	–	–	–
x	943.27	67.88	67.91	677.31	71.46	71.22
SD	456.66	14.20	14.25	401.42	10.71	10.10
r**			1			0.94

* Predicted by Cubist from CPK of the myocardial infarction localisations.
† $p = 0.0255$ ($t = -2.30$).
§ FA and FAC* groups do not differ ($p > 0.93$, $t < 0.25$).
** Correlated to FA.

The Cubist based rules that define the relationship of maximal CPK values and the remaining cardiovascular functional ability following the recovery of anteroseptal and inferior myocardial infarction are presented in Table II. Table I presents the results of individual functional ability values and those predicted from the maximal CPK during the acute phase of the disease. The accuracy and applicability of the prediction method are confirmed by the insignificant differences, strong correlations and low error rates of the leave-one-out cross-validation tests, when the real and predicted cardiovascular functional ability data are compared (Table I, Figure 1).

The Cubist rule based model confirms that anteroseptal infarction is associated with a greater decrease in functional ability than the inferior one

TABLE II

Rules for the relationship of the cardiovascular functional (FA) ability and maximal plasma creatine kinase values (CPK) in anteroseptal and inferior myocardial infarction, obtained by means of the Cubist machine learning system (release 1.09)

Anteroseptal Myocardial Infarction	Inferior Myocardial Infarction
Rule 1: if CPK > 564 then FA = 76.92 – 0.0152 CPK	*Rule 1:* if CPK > 914 then FA = 97.73 – 0.0268 CPK
Rule 2: if CPK > 502 CPK ≤ 564 then FA = 150.61 – 0.1301 CPK	*Rule 2:* if CPK > 465 CPK ≤ 914 then FA = 76.11 – 0.0138 CPK
Rule 3: if CPK ≤ 502 then FA = 176.29 – 0.1675 CPK	*Rule 3:* if CPK ≤ 465 then FA = 99.9 – 0.0489 CPK

(Table I), which is in line with the previously observed results of Štambuk[5,6] for the nonlinear hyperbolic model of CPK and cardiovascular functional ability in infarction. This may be partly due to the extensive necrosis with higher deterioration in the left ventricular contractility.[1] Therefore, our results obtained by the Cubist based rules confirm that the site of infarction is a contributing factor responsible for the cardiovascular functional ability remaining after the recovery. The latter is also confirmed by 96.43% accurate discrimination of cases with anteroseptal and inferior infarction localisations obtained for CPK and functional ability parameters by means of the classification tree (Figure 2).

Low misclassification error rates of the tree, and the jack-knife test confirm the validity of the tree and parameter dependence (Figure 2). Tree-based models are statistical procedures that provide an alternative to linear and additive models for regression problems and to linear and additive logistic models for classification problems.[10] The rules are obtained by recur-

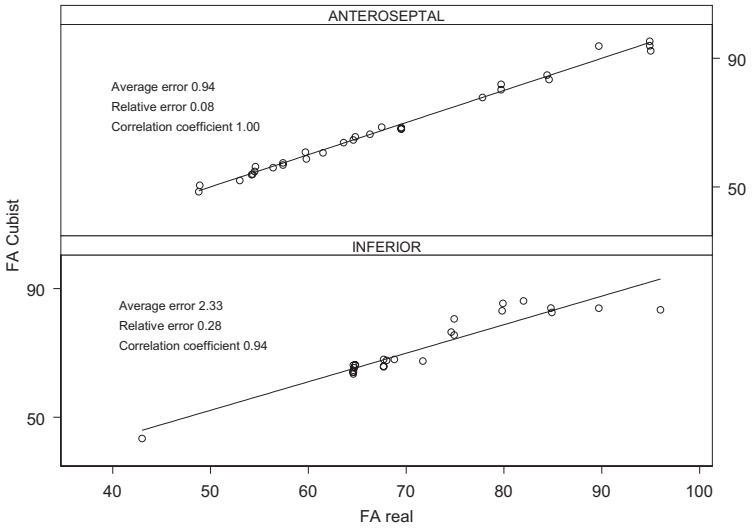

Figure 1. Correlation of the cardiovascular functional ability for the real and Cubist predicted values in anteroseptal and inferior myocardial infarction. Leave-one-out cross-validation procedure for the anteroseptal and inferior localisation had average errors of 1.72 and 3.54, relative errors of 0.14 and 0.41, and correlation coefficient (r) of 0.98 and 0.85, respectively.

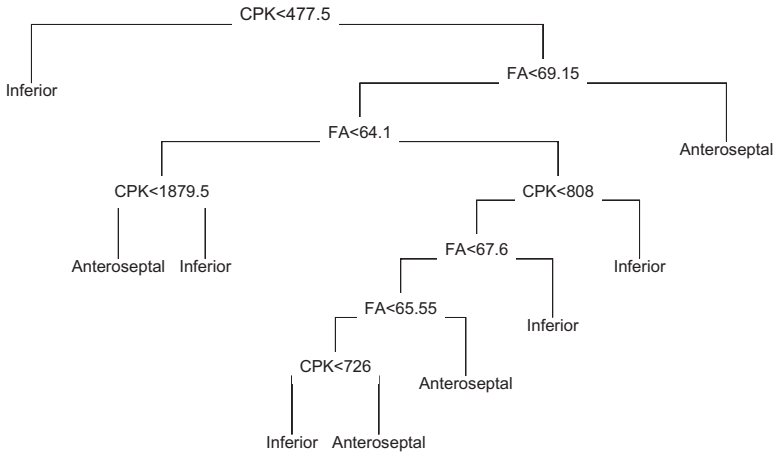

Figure 2. Classification tree discriminates between the groups of patients with anteroseptal and inferior localisation of the myocardial infarction on the basis of CPK and cardiovascular functional ability parameters. Low misclassification error rate of 0.0357 (2 cases misclassified out of 56), low residual mean deviation of 0.1492 and jack-knife testing of the procedure (mean error 2.03, SE 1.96) confirm the validity of the tree and parameter dependence.

sive partitioning.[10] The S-Plus 2000 software package was used for this type of statistical analysis.[10]

The rules obtained by means of the Cubist machine learning procedure provide accurate prediction of the cardiovascular functional ability following the anteroseptal and inferior myocardial infarction on the basis of routine CPK determination during the acute phase of the disease. The presented method, therefore, represents a potent predictive tool for the clinical and experimental trials in Cardiology. In addition to its prognostic (and diagnostic) applications, the extracted algorithms enable a more efficient evaluation of new drugs and therapeutic procedures for the myocardial infarction.

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SAŽETAK

Vrijednosti kreatin-kinaze plazme i kardiovaskularna funkcijska sposobnost u infarktu miokarda

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Najviše vrijednosti kreatin-kinaze plazme (CPK) često se rabe kao enzimski test u akutnom infarktu miokarda. Kardiovaskularna funkcijska sposobnost (FA) pouzdan je čimbenik kojim se može definirati oštećenje krvožilnog sustava nakon infarkta. Program strojnog učenja Cubist uporabili smo za izradbu modela koji s pomoću najviše izmjerene vrijednosti CPK tijekom akutnog infarkta miokarda definira ostatnu kardiovaskularnu funkcijsku sposobnost nakon infarkta. Cubist modelira numeričke pokazatelje i generira vrijednosti s pomoću skupa pravila koja lineariziraju

zadani skup. Koristeći se u literaturi navedenim podacima mjerenja Mirića i sur.[1], s pomoću programa Cubist izrađen je i testiran precizan model od tri jednostavna pravila odnosa spomenutih pokazatelja u akutnom infarktu miokarda. Pravila omogućuju jednostavno predviđanje ostatne funkcijske sposobnosti krvožilnog sustava nakon oporavka od infarkta. Model se zasniva na dva klinička pokazatelja povezana s bolešću, najvišim vrijednostima CPK na početku bolesti te anteroseptalnom ili inferiornom lokalizacijom infarkta. Točnost modela i mogućnost njegove primjene u kliničkoj medicini potvrđena je visokom korelacijom (r (anteroseptalni) = 1,00, r (inferiorni) = 0,94; n = 56) te minimalnim razlikama između stvarno izmjerenih i modelom predviđenih vrijednosti, kao i vrlo niskom pogreškom modela izmjerenom testom unakrsne validacije (anteroseptalni 1,72, inferiorni 3,54). Pored prognostičkih i dijagnostičkih primjena, izdvojena pravila omogućuju i učinkovitiju procjenu novih kardioloških lijekova i terapijskih postupaka.