

FUZZIFICATION, WEIGHT AND SUMMATION OF RISK FACTORS IN A PATIENT IMPROVES THE PREDICTION OF RISK FOR CARDIAC DEATH

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A b s t r a c t

Patients surviving myocardial infarction are at risk of cardiac death. The predictive value of non-invasive risk factors (ejection fraction <40%, positive late potentials, a frequency of ventricular premature complexes >10/hour, baroreflex sensitivity <3ms/mmHg or low heart rate variability – SDNN index <30ms, SDANN <50 ms) is insufficient. New methods for the stratification of patients at risk were developed: 1. fuzzy method, which takes into account that the borderline between a risky and non-risky value of a risk factor is not crisp, 2. weighted method, which quantifies the significance of different risk factors, and 3. new individual indices of risk based on summation of fuzzified, and weighted risk factors respectively, (Fuzzy Sum r.f., Fuzzy-Weighted Sum r.f.) were introduced. By this method, sensitivity 44% and specificity 97% of prediction of cardiac death were reached at a positive predictive value of 50%.

Key words

Myocardial infarction, Cardiac death, Risk stratification, Fuzzy method, Weighted method

Abbreviations used

BRS, baroreflex sensitivity; c.v., critical values; EF, ejection fraction; ICD, implantable cardioverter-defibrillator device; LP, late potentials; PPV, positive predictive value; SDANN, standard deviation of 5-minute average RR intervals in 24 hours; SDNN index, mean of 5-minute standard deviations of RRs in 24 hours; VPCs, ventricular premature complexes

INTRODUCTION

Patients surviving myocardial infarction are at risk of cardiac death. Patients at risk can be treated with an implantable cardioverter-defibrillator device (ICD) and they must be selected carefully for this therapy. In the 90th, the non-invasive risk factors as ejection fraction - EF <40% (1), positive late potentials - LP (2), a frequency of ventricular premature complexes - VPCs >10/hour (3), a decreased heart rate variability (SDNN index – mean of 5-minute standard deviations of RRs in 24 hours <30 ms; SDANN – standard deviation of 5-minute average RR intervals <50 ms) (4) or baroreflex sensitivity - BRS <3 ms/mmHg were

determined (5,6). The prognostic quality of risk factors was expressed by their sensitivity, specificity and positive predictive value (PPV). Prediction of risk based on a usage of critical values mentioned above has not been discriminating sufficiently, because high sensitivity at PPV of 50% is desirable to avoid an unnecessary treatment (7). Current indications for ICD implantation in primary prevention are based on results of the Multicenter automatic Defibrillator Implantation Trial MADIT (8), and MADIT II respectively. The invasive electrophysiological examination in patients with EF 35% and documented episode of asymptomatic unsustained ventricular tachycardia is used. Despite progress in the strategy for risk prediction, sudden cardiac death remains a major clinical and public problem (9).

The aim of this study was to develop a method for the evaluation of risk for cardiac death in patients after myocardial infarction, which will improve the quality of prediction on the bases of standard risk factors, but with respect to a pathophysiologic relevance of information in particular factors.

First, we took into account a physiologic assumption that a borderline between a risky and non-risky value of each factor is not crisp by fuzzification of the critical values. Second, for comparison of predictive quality of different risk factors we applied a weighted approach. Third, because risk for cardiac death of patients increases with number of risk factors in one patient (10), we determined a new index of the patient's individual risk calculated as summation of fuzzified, and weighted risk factors respectively, in each patient. Thus we took into account a measure of a discriminating quality of each factor together with a positive occurrence of different risk factors in particular patients. We determined critical values of risk for cardiac death for these new indices of risk and calculated sensitivity, specificity and a positive predictive value of the prediction of the risk based on these new factors.

METHODS

SUBJECTS

We examined 290 patients 7–21 days after having a myocardial infarction, 18 patients of whom died for cardiac death in the course of period of 22 month. Patients who died because of other causes were not included into statistics.

The Ethics Committee of Masaryk University approved of this study and all patients gave their informed consent.

PROTOCOL

The Holter monitoring, BRS determination, echocardiographic investigation and signal averaged ECG recording were done before the discharge from the hospital.

Recordings of a two-channel, 24-hour ECG recording (Oxford Excell) were manually edited, artefacts were removed. Arrhythmias were evaluated and classified (ventricular ectopic beats – simple, bigeminal, multiform, repetitive or R on T), and the count of ventricular ectopic beats was determined as *VPCs* (number/hour). *Heart rate variability* was expressed as the *SDNN* index – the

mean of standard deviations of normal-to-normal RR intervals determined in 5-minute periods during 24 hour ECG recording and *SDANN* – the standard deviation of mean RR intervals determined in 5-minute periods during 24 hour ECG recording.

Indirect continuous blood pressure recordings from finger arteries (Finapres, Ohmeda) lasting for 3 min, were performed in sitting, resting patients, between 9 a.m. and noon. Recordings were taken during breathing controlled at 20 per min by metronome, (0.33 Hz). Beat-to-beat values of systolic blood pressure and of pulse intervals were measured for further analysis. *Baroreflex sensitivity* was determined by spectral method (11).

The evaluation of left ventricular *ejection fraction* was performed using a 2-dimensional echocardiogram (Acuson 128 XP/10 unit).

Late potentials were evaluated using the HIPEC – analyser ECG Averaging System. Filtering at 40 Hz was used and 200 beats were averaged to achieve a final noise less than 0.3 V. The presence of late potentials was defined as positive if two of the three criteria were met: the filtered QRS complex longer than 120 ms, root mean square voltage of the last 40 msec of the filtered QRS complex less than 25 micro volts and duration of low-amplitude signals less than 40 micro volts in the terminal portion of the QRS complex longer than 40 msec. A prolonged QRS was not considered a positive criterion if the QRS duration measured from the standard ECG was greater than 120 msec.

NEW APPROACHES TO THE RISK STRATIFICATION

The weighted method for comparison of predictive quality of different risk factors

We developed a weighted method for comparison of a predictive quality of different risk factors which is based on the Bubble sort method (12) commonly known as a sorting method in computing. The output of our process is a weight of any risk factor calculated in the range 0 to 1, e.g. a quantified measure of a predictive quality of risk factors with a maximal risk equal to 1. We explain this method for comparison of a predictive quality of different risk factors on a following example. Let us mark survivors (o) and those who died (+). Then *the sequence of patients, ordered by values of factor tested*, can be as follows (+o+oo). *The completely sorted patients* (e.g. data file) *with respect to surviving* means the sequence (++ooo). The comparison of these two sequences gives the accuracy and also the weight of discriminating quality of a given risk factor. The sorting quality rate is determined by number of steps (*no_steps*), which the Bubble sort method needs to sort completely the data file. In our example, we need just one step to sort completely the data file (swap the third and second elements). If the completely sorted data (++ooo) is sorted in an opposite direction (ooo++) the number of sorting steps will be maximum (*max_steps*). In our example *max_steps* equals 6. *The weight* of the risk factor is then determined by the formula (*max_steps-no_steps*)/(*max_steps*). In our example a *weight* equals (6-1)/6, which is approx. 0.83. Consequently, the weight of the risk estimated by chosen factor is 0.83.

The fuzzy method

At present, the crisp limits of values of risk factors are used to determine patients at risk of cardiac death. The fuzzification of critical values smoothes the transient between the values of factor which are supposed to mean a maximal or no risk for cardiac death. We explain our method on an example. Let us imagine a risk factor with the critical value equal 5. In a mentioned crisp-limits approach which has been used until now, the value 5 would be classified as non-risk and 4.9 would be considered as risk one. A small difference in the factor value could result in a contradictory prediction. In a real life, the probability of risk for cardiac death of patients after myocardial infarction increases (or decreases) with an increasing (or decreasing) factor value. But this assessment is not precise enough, because the risk of cardiac death needs to be determined in range of 0 to 1 values. To express the uncertainty of the risk factor limit, the fuzzy method was used (13). The fuzzy method enables us to express better the real-life situation – the transition between the risk and non-risk extremes, than the method which divides the values of given risk factor into two groups – risk or no risk (Fig. 1).

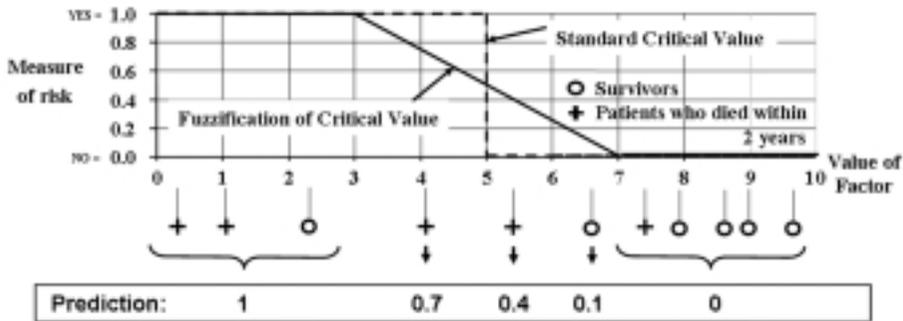


Fig. 1

Fuzzification of critical values; the sorting quality rate is determined as a number of steps needed by the Bubble sort method to complete sorting with respect to surviving.

For example, the sorting of our group of patients by the crisp critical value has for the VPCs the sorting quality rate (weight) equal 0.66. A fuzzy function can be used instead of a crisp transition. By the fuzzification we can reach the other extreme – the patients sized by the fuzzy function in the same sequence as for the VPCs values only (the weight equals to 0.77). The aim of an optimal approach is to find the compromise between these two extremes that means to find an optimal range of fuzzified values.

The fuzzy-weighted method

By combination of the two methods introduced above we get the new one called *the fuzzy-weighted method* in the following way: The risk of cardiac death determined by the fuzzy method is multiplied by the weight of the risk factor. In fact the factor's risk range 0 to 1 changes into the range 0 to the factor's weight.

New indices of risk for cardiac death – Fuzzy Sum r.f. and Fuzzy-Weighted Sum r.f.

Clinical praxis needs “binary” outputs in decision whether a patient is at risk or not and therefore we cannot use a single fuzzified risk factor to get a better quality of a prediction of the risk of individual patient. Our solution of this problem was in an introduction of a new risk factor in each patient based on summation of his/her fuzzified risk factors (*Fuzzy Sum r.f.*) or of his/her fuzzified-weighted risk factors (*Fuzzy-Weighted Sum r.f.*).

STATISTICS

Optimal limits for the critical values of newly introduced summation indices Fuzzy Sum r.f. and Fuzzy-Weighted Sum r.f. were determined for: 1. maximum achievable sensitivity and specificity, and 2. sensitivity at PPV 50%.

Moving critical values (c.v.) in steps with the aim to determine sensitivity for c.v. at which PPV reached 50% was used also for standard risk factors. Sensitivity, specificity and PPV of each index

Table 1

Comparison of the weight of standard and fuzzified risk factors, and of indeces based on summation of fuzzified and weighted risk factors in each patient.

Parameter	Weight	Parameter	Weight
BRS	0.679	Fuzzy BRS	0.708
EF	0.758	Fuzzy EF	0.761
LP	0.673	-	-
SDANN	0.619	Fuzzy SDANN	0.663
SDNN	0.625	Fuzzy SDNN	0.719
VPCs	0.660	Fuzzy VPCs	0.772
Fuzzy Sum r.f.	0.843	Fuzzy-Weighted Sum r.f.	0.859

Legends: BRS, baroreflex sensitivity; EF, ejection fraction; LP, late potentials; r.f., risk factor; SDANN, standard deviation of 5-minute average RR intervals in 24 hours; SDNN, mean of 5-minute standard deviations of RRs in 24 hours; VPCs, ventricular premature complexes

were calculated for optimal c.v. and for c.v. at which PPV reached 50% and predictive qualities of all factors were compared.

RESULTS

In the *Table 1* the weight of the standard and the fuzzified risk factors is compared. The weight increased after fuzzification but besides this the sequence of the factors according to their weights slightly changes. New individual risk factor based on summation of risk factors in each patient improved further the weight; it was the highest for Fuzzy-Weighted Sum r.f.

In the *Table 2* sensitivity, specificity and positive predictive value calculated for standard critical values for each particular risk factor and also for new risk factors based on summation of risk factors (with fuzzified and fuzzy-weighted limits) are shown. Summation and fuzzification improved the complex predictive quality. With respect to the demand of the clinical praxis on high sensitivity and specificity at PPV 50% all these values were calculated at proper critical value. Both, Fuzzy Sum r.f. and Fuzzy-Weighted Sum r.f. gives very good predictive quality, specificity over 97% and sensitivity tended to 50%.

DISCUSSION

New studies based on several non-invasive risk predictors are performed (14). Nowadays, not only positive predictive accuracy, but also the cost-effectiveness ratio of the ICD is discussed (15, 16). Even a high positive predictive value cannot

Table 2

Comparison of the predictive quality of risk factors (BRS, EF, LP, SDANN, SDNN, VPCs) at standard critical values and of indices of risk (Fuzzy Sum r.f. and Fuzzy-Weighted Sum r.f.) at optimal critical values (left) and at critical values for PPV=50% (right)

Parameter	Sensitivity [%]	Specificity [%]	PPV [%]	PPV = 50 [%]	
				Sensitivity [%]	Specificity [%]
BRS	66.7	69.1	12.5	5.6	98.9
EF	66.7	84.9	22.6	5.6	99.6
LP	50.0	15.4	3.8	–	–
SDANN	61.1	71.3	12.4	11.1	99.3
SDNN	38.9	86.0	15.6	16.7	98.2
VPCs	44.4	87.9	19.5	–	–
Fuzzy Sum r.f.	77.8	86.4	27.5	44.4	97.1
Fuzzy-Weighted Sum r.f.	83.3	79.0	20.8	44.4	97.1

Legends: PPV, positive predictive value; other abbreviations see in Table 1.

be expected when the rate of events is low and arrhythmic mortality is progressively shrinking (17, 18), our new approach brought evidence that PPV can be improved by new mathematical tools. Our methodology is new in several aspects.

Fuzzification of a critical value enables to determine a measure of risk of a patient in the range 0 to 1 in case, his/her value of clinical test is at the border of critical value.

Weight determined by Bubble sort method (12) enables to compare a predicting quality of any risk factor.

New individual risk factors based on summation of risk factors (Fuzzy Sum r.f. or Fuzzy-Weighted Sum r.f.) were introduced.

The aim of the weighted approach is to determine a weight of each risk factor that means, how precisely it predicts cardiac death. The use of statistical methods based on regression models is more complicated for this purpose. The quality of the prediction depends on the optimal choice of the regression function. Many other methods like entropy or standard evaluation of risk factors for postinfarction risk stratification are of the same principle and anticipate some knowledge to be evaluated. But what we know is just that the risk of cardiac death increases/decreases with the value of any observed factor and that the relation between dependent and explanatory variable is non-linear for all of these factors.

That is why a new method for evaluating of the measure of risk based on values of standard risk factors was developed. This method exploits the Bubble sort method commonly known as a sorting method in computing and its output - weight - is in the range 0 to 1. The problem of summation of risk factors with respect to their value near to a critical value was not introduced till now.

Application of our new mathematic analysis including fuzzification, weighted approach and summation of risk factors in each patient of 290 patients improved the prediction of their risk as was confirmed by comparison with a prediction quality by standard method. The highest sensitivity and specificity at positive predictive value 50% was determined for indices Fuzzy-Weighted Sum r.f. and Fuzzy Sum r.f.

The method of fuzzification has a general importance and can be used in similar discriminating processes.

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FUZZIFIKACE, VÁHA A SUMACE RIZIKOVÝCH FAKTORŮ U PACIENTA ZLEPŠUJE PREDIKCI RIZIKA SRDEČNÍ SMRTI

S o u h r n

Pacienti po infarktu myokardu jsou ohroženi náhlou srdeční smrtí. Prediktivní hodnota neinvazivních rizikových faktorů (ejekční frakce<40%, pozitivní pozdní potenciály, počet extrasystol za hodinu>10, baroreflexní sensitivita<3ms/mmHg a nízká variabilita tepové frekvence – SDNN index<30ms, SDANN<50 ms) není dostačující. Vypracovali jsme nové metody rizikové stratifikace pacientů: 1. fuzzy metodu, která berou v úvahu skutečnost, že hranice mezi rizikovou a nerizikovou hodnotou faktoru je neostrá, 2. váhování, které kvantifikuje význam jednotlivých rizikových faktorů, a 3. zavedli jsme nové individuální rizikové ukazatele založené na sumaci fuzzifikovaných, respektive váhovaných, rizikových faktorů (Fuzzy Sum r.f. a Fuzzy-Weighted Sum r.f.). Těmito metodami byla dosažena senzitivita 44% a specificita 97% predikce rizika srdeční smrti při pozitivní prediktivní hodnotě 50%.

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