# Noninvasive prediction of sudden death and sustained ventricular tachycardia after acute myocardial infarction using a neural network algorithm

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*Key words:*
**Myocardial infarction; Postinfarction risk stratification; Sudden death; Ventricular tachyarrhythmias.**

*Background.* **The early and accurate noninvasive identification of postinfarction patients at risk of sudden death and sustained ventricular tachycardia (arrhythmic events) still remains an unsolved problem. The aim of the present study was to identify the combination of clinical and laboratory noninvasive variables, easy to obtain in most patients, that best predicts the occurrence of arrhythmic events after an acute myocardial infarction.**

*Methods.* **Four hundred and four consecutive patients with acute myocardial infarction were enrolled and followed for a median period of 21.4 months. In each patient, 61 clinical and laboratory noninvasive variables were collected before hospital discharge and used for the prediction of arrhythmic events using an artificial neural network.**

*Results.* **During follow-up, 13 (3.2%) patients died suddenly and 11 (2.5%) had sustained ventricular tachycardia. The neural network showed that the combination best predicting arrhythmic events included: left ventricular failure during coronary care stay, ventricular dyskinesis, late potentials, number of ventricular premature depolarizations/hour, nonsustained ventricular tachycardia, left ventricular ejection fraction, bundle branch block and digoxin therapy at discharge. The neural network algorithm allowed identification of a small high-risk patient subgroup (12% of the study population) with an arrhythmic event rate of 46%. The sensitivity and specificity of the test were 96 and 93% respectively.**

*Conclusions.* **These results suggest that, in postinfarction patients, it is possible to predict early and accurately arrhythmic events by noninvasive variables easily obtainable in most patients. Patients identified as being at risk are candidates for prophylactic antiarrhythmic therapy.**

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## Introduction

In the first year following acute myocardial infarction, sudden death, usually due to ventricular tachyarrhythmias[1], and spontaneous sustained ventricular tachycardia occur in 3-5% of the patients discharged alive from hospital[2,3]. The accurate identification of patients at risk of such arrhythmic events would allow treatment with adequate antiarrhythmic therapy in only selected patients. In previous studies, numerous noninvasive and invasive variables were found to be significantly associated with the occurrence of postinfarction arrhythmic events. These included a previous history of myocardial infarction, high Killip classes, left ventricular dysfunction, segmental ventricular dyskinesia, impaired heart rate variability, spontaneous complex ventricular arrhythmias, ventricular late potentials and inducible sustained ventricular tachycardia at programmed ventricular stimulation. Unfortunately, none of these variables, either singly or in combination, allowed the accurate prediction of arrhythmic events[2-11]. Thus, the prediction of arrhythmic events after acute myocardial infarction still remains a major challenge for cardiologists. Such unsatisfactory results may be due to a number of reasons including: a) the systematic use of parametric statistical methods (i.e. classical linear discriminant analyses)[2-10] that are inadequate to treat nongaussian variables and to predict the individual risk of developing selected events; b) the small number of variables (generally two or three) on which the predictive indexes were constructed[2-10], and c) the use of complex diagnostic procedures, often not obtainable, generally causing a marked reduction of the study population size[7,9,10].

The aim of the present study was to identify a combination of clinical and laboratory noninvasive variables, easy to obtain in the vast majority of patients, able to accurately

predict the occurrence of arrhythmic events during a period of 2 years following acute myocardial infarction. To achieve such a goal, more than 400 consecutive postinfarction patients were enrolled, and approximately 60 noninvasive variables collected for each patient were used to perform an artificial neural network.

## Methods

**Study population.** Between July 1993 and April 1995, 503 consecutive patients with acute myocardial infarction were admitted to the coronary care unit at the Galliera Hospital. The diagnosis of myocardial infarction was made in the presence of at least two of the following conditions: typical prolonged chest pain, typical electrocardiographic changes (development of new Q waves or alterations in the ST segment or T wave), and a significant increase in the serum levels of creatine kinase and creatine kinase-MB isoenzyme. Before hospital discharge, 51 patients (10%) died. Among the 452 survivors, 39 (8.6%) were excluded from further evaluation because of the following reasons: uncontrolled heart failure despite adequate medical therapy, persistent myocardial ischemia requiring predischarge myocardial revascularization, sustained ventricular tachyarrhythmias occurring after the first 48 hours of the acute event, congenital cardiac disease, acquired valvular disease, cardiac preexcitation and end-stage disease of other organ systems. Nine additional patients (1.8%) were excluded from the study because of nonmedical problems. Hence, 404 patients (mean age 64 ± 13 years, range 29 to 84 years) were enrolled and evaluated prospectively; 317 (78%) were men.

**Data acquisition.** During the hospital stay and the follow-up period, in each of the 404 enrolled patients, 61 clinical and laboratory noninvasive variables were collected. These variables included: demographics, risk factors for ischemic heart disease, past history of ischemic heart disease, thrombolytic therapy, clinical course and rhythm disturbances during coronary care stay, echocardiographic findings, radionuclide left ventricular ejection fraction, exercise test results, spontaneous ventricular arrhythmias after coronary care discharge, medical therapy and some selected clinical and electrocardiographic findings at hospital discharge (see Appendix).

**Continuous 24-hour electrocardiographic recording.** A technically satisfactory electrocardiographic recording was obtained in 401 patients (99%). It was performed between days 7 and 9 after acute myocardial infarction using a two-channel portable electrocardiographic magnetic tape recorder (DMS, Dynacord model 419A, Irvine, CA, USA). Two chest-modified bipolar leads were used: CM5 and CM1. Each tape was analyzed automatically by computer (Del Mar model 500, Irvine, CA, USA) with manual overread.

**Signal-averaged electrocardiogram.** Signal averaging of the surface QRS complexes was obtained in 397 patients (98%) between days 7 and 9 after myocardial infarction. It was performed by using a Fidelity Medical Device model LP3000 (Haifa, Israel). The signal-averaged electrocardiogram was analyzed by standard time-domain methods. The electrocardiogram was recorded in sinus rhythm. In each patient, more than 200 beats were averaged to achieve a final noise level < 0.7 μV. Data were analyzed at filter frequencies of 25 to 250 Hz and 40 to 250 Hz. A signal-averaged electrocardiogram was defined as abnormal if any two of the three following criteria were present: total filtered QRS duration > 114 ms, root-mean-square voltage during the last 40 ms of the filtered QRS complex < 20 μV, and duration of the filtered QRS complex after voltage decreases to 40 μV > 38 ms[12]. In the presence of bundle branch block, late potentials were diagnosed at filter frequencies of 40-250 Hz if any one of the three criteria suggested by Buckingham et al.[13] was satisfied: total filtered QRS duration ≥ 145 ms, root-mean-square voltage during the last 40 ms of the filtered QRS complex ≤ 17 μV, and duration of the filtered QRS complex after voltage decreases to 40 μV ≥ 45 ms.

**Radionuclide ventriculography.** Radionuclide ventriculography was performed between days 10 and 21 after myocardial infarction. Data were collected as previously described[14]; the left ventricular ejection fraction was assessed at rest in 396 patients (98%) and during exercise in 242 (60%).

**Exercise test.** A maximal symptom-limited exercise test was performed in 281 patients (69%) between days 10 and 23 after myocardial infarction according to the protocol of the Gruppo Italiano per la Valutazione Funzionale e la Riabilitazione del Cardiopatico[15]. The occurrence of angina or the presence of an exercise-induced ST-segment depression ≥ 1 mm were considered indicative of residual myocardial ischemia.

**Echocardiogram.** Echocardiographic studies were performed between days 10 to 17 after myocardial infarction in 401 patients (99%) by means of a Hewlett-Packard model 77025A (Palo Alto, CA, USA) mechanical sector scanner. The measurement technique recommended by the American Society of Echocardiography was followed[16].

**Other data.** Left ventricular failure was diagnosed in the presence of at least one of the following: rales in more than one third of the lung fields, third sound and X-ray images of pulmonary congestion. The QT interval was calculated in 332 (82%) patients in the absence of bundle branch block, atrial fibrillation and antiarrhythmic or digitalis therapy; the adjustment for heart rate was made according to Bazzet's formula: QT corrected = $QT/\sqrt{RR}$. Creatine kinase and creatine kinase-MB serum peak levels were available in 347 (86%) patients.

**Follow-up.** In all cases follow-up consisted of either physical examination or of a phone call at 3 and 6 months after acute myocardial infarction, and then every 6 months up to the 24th month. At each follow-up contact, the following events were considered: a) death; b) cardiac death; c) sudden death (instantaneous or unexpected during sleep and not preceded by symptoms indicative of myocardial ischemia); d) spontaneous documented sustained ventricular tachycardia (rate ≥ 120 b/min, lasting ≥ 30 s) not preceded by symptoms indicative of myocardial ischemia; e) witnessed syncope in patients in whom, in the absence of other identifiable causes of syncope, programmed ventricular stimulation was able to induce a sustained ventricular tachycardia or any other symptomatic ventricular tachyarrhythmia. In the present study, endpoint events c), d), and e) were defined as arrhythmic events. Information about the endpoint events was obtained from the private physician, from family members, or from the hospital charts of patients admitted to other institutions. On the basis of the findings of the tests used for the risk stratification no patient received antiarrhythmic therapy at hospital discharge. After hospital discharge, treatment was left to the discretion of the attending physicians. Those patients who died, those who had nonfatal reinfarction, cardiac surgery, coronary angioplasty, and those lost to follow-up were censored from the statistical analysis of survival at the date of these events. The median follow-up period was 21.4 months; 313 (77%) patients were followed for 24 months.

**Statistical analysis.** Continuous data are presented as mean ± 1 SD. Differences among continuous variables were analyzed by the unpaired Student's t test, and those among discrete variables by the $\chi^2$ test with Yates correction, where appropriate. Comparison among groups for qualitative data was performed by *r*x*c* contingency tables[17]. To identify the combination of clinical and laboratory noninvasive variables best predicting arrhythmic events, each collected variable available in > 90% of our patients (this value was chosen arbitrarily to allow a complete evaluation of most of the enrolled patients) was used to perform, as previously described[18], an artificial neural network based on the method of Madansky[19]. Patients with arrhythmic events were labeled as +1 and those without as -1. Data of the first 96 enrolled patients (training set) were used to calculate the mathematical forecasting model that was subsequently validated in the remaining 308 patients (test set). More in detail, the weight of each variable of interest was first calculated on the training set and used to provide an activation index (ranging from -1 to +1) for each patient; subsequently, the same weights were used to estimate the activation index of the unknown patients of the test set. The activation index was calculated as follows:

$$AI_i = w_o + \sum_{J=1}^{k} w_j v_{ij}$$

where $AI_i$ is the activation index of the *i*th patient, $w_o$ is the threshold, k is the number of the variables of interest, $w_j$ is the weight of the *j*th variable, and $v_{ij}$ is the value of the *j*th variable of the *i*th patient. According to this algorithm, a patient was correctly identified when both the label and activation index shared the same sign: positive = event yes, negative = no event. The size of the training set was established by adding to the set a new patient at a time and recalculating, at each new entry, the weights of the variables of interest. The training phase was concluded when the 96th patient was introduced in the set since, after this entry, the weights of the variables became stable and the addition of further cases did not significantly improve the performance of the neural network. The survival curves were plotted as Kaplan-Meier curves[20], and the probabilities of endpoints between subgroups were tested by the Mantel-Haenszel test[21]. A p value < 0.05 was considered statistically significant.

**Ethical approval.** The study protocol was approved by the Ethical Committee of our Institution. All patients gave their informed consent to the study.

## Results

**Follow-up.** During the follow-up period, 34 (8.4%) patients died of cardiac and 9 (2.2%) of noncardiac causes (stroke in 4, cancer in 2, pneumonia in 1, renal failure in 1, and pulmonary embolism in 1). Among the 34 patients who died of cardiac causes, 13 (3.2%) died suddenly (in 2 a ventricular fibrillation was documented), 14 (3.5%) of heart failure, and 7 (1.7%) of reinfarction. Forty-one (10%) additional patients underwent a coronary artery bypass grafting, 18 (4.4%) a coronary angioplasty, and 19 (4.7%) experienced a nonfatal reinfarction. Nine patients had a spontaneous sustained ventricular tachycardia and 2 with inducibility of symptomatic ventricular tachycardia at programmed ventricular stimulation an unexplained syncope. Therefore arrhythmic events occurred in 24 patients (5.9%). Among the 13 patients who died suddenly, 10 (76%) died within the sixth month of acute myocardial infarction. Spontaneous sustained ventricular tachycardia and/or syncope occurred in 7 (63%) of the 11 patients within the sixth month of acute myocardial infarction.

**Clinical characteristics of the patients with and without arrhythmic events: relationship between noninvasive variables and arrhythmic events.** Of the 404 enrolled patients, 61 (15%) had had a previous myocardial infarction, 199 (49%) an anterior myocardial infarction, and 269 (67%) a Q-wave myocardial infarction. During the coronary care stay, 69 (17%) patients were in Killip class ≥ 2, and 181 (44%) received thrombolytic therapy. In addition, 51 (12%) patients showed

left ventricular failure, 16 (4%) had reversible II or III degree atrioventricular block, 27 (6.6%) ventricular fibrillation or sustained ventricular tachycardia, and 27 (6.6%) sustained atrial tachyarrhythmias.

Patients with arrhythmic events differed significantly from those without in age, history of a previous myocardial infarction, site of acute myocardial infarction, occurrence of left ventricular failure during the coronary care stay, frequency of late potentials and echocardiographic segmental left ventricular dyskinesis, presence of bundle branch block on the predischarge electrocardiogram, and the use of digitalis or angiotensin-converting enzyme inhibitors or diuretics at hospital discharge. In addition, patients with arrhythmic events had more complex spontaneous ventricular arrhythmias, a higher daily mean heart rate, longer QT corrected intervals and lower values of the left ventricular ejection fraction. No significant difference was present in the two patient subgroups with regard to gender, ischemic heart disease risk factors, thrombolytic or beta-blocking therapy, rhythm disturbances during the coronary care stay and predischarge exercise test results (Table I).

**Neural network results.** Among the 61 variables collected in each patient, the creatine kinase, creatine kinase-MB isoenzyme levels and the QT corrected interval were excluded from the set of variables used to perform the neural network since they were available in < 90% of the patients. The neural network allowed the identification of a combination of 8 variables best predicting arrhythmic events; this combination included, in order of importance: 1) the occurrence of left ventricular failure during the coronary care stay, 2) digoxin therapy at hospital discharge, 3) segmental left ventricular dyskinesis, 4) late potentials, 5) the number of ventricular premature depolarizations/hour, 6) the left ventricular ejection fraction, 7) nonsustained ventricular tachycardia, and 8) bundle branch block on the predischarge electrocardiogram. The inclusion of other variables did not improve prediction. The weight of each variable is shown in table II. On the training set, the system correctly recognized 81 of the 89 patients without arrhythmic events and 6 of the 7 patients with arrhythmic events (Fig. 1A). On the test set, the network correctly identified 255 of the 274 patients without arrhythmic events and all the 17 patients with arrhythmic events (Fig. 1B). Thus, the all-case analysis showed that the neural network algorithm correctly identified 336 (93%) of the 363 patients without arrhythmic events, and 23 (96%) of the 24 with arrhythmic events ($p < 0.0001$) (Table II). The sensitivity, specificity, and positive predictive value of the test were 96, 93 and 46%, respectively. The risk patient subgroup consisted only of 50 (12%) subjects, 23 (46%) of whom had an arrhythmic event. Conversely, only 1 (0.3%) of the 337 patients identified as not being at risk had arrhythmic events. The network allowed evaluation of 387 (96 in the training set and 291 in the test set) (96%) of the 404 patients enrolled for the study.

Survival curves showed that in the 2 years following acute myocardial infarction, the probability of being free of arrhythmic events was 47% in the risk patient sub-

**Table I.** Clinical characteristics of patients with and without arrhythmic events.

| Variable | Arrhythmic events (n=24) | No arrhythmic events (n=380) | p |
|---|---|---|---|
| Age (years) | 66 ± 9 | 63 ± 12 | < 0.025 |
| Previous AMI | 8 | 53 | < 0.025 |
| Anterior AMI | 19 | 181 | < 0.01 |
| Thrombolysis | 7 | 174 | NS |
| Killip class ≥ 2 | 17 | 52 | < 0.0001 |
| LV failure in CC | 17 | 34 | < 0.0001 |
| Peak creatine kinase-MB (U/l) | 329 ± 270 | 227 ± 181 | < 0.001 |
| VPD (no./hour) | 59 ± 81 | 14 ± 43 | < 0.0001 |
| Couplets of VPD | 15 | 73 | < 0.0001 |
| Nonsustained VT | 7 | 34 | < 0.005 |
| Daily mean heart rate (b/min) | 81 ± 13 | 71 ± 12 | < 0.001 |
| LV ejection fraction (%) | 28 ± 9 | 49 ± 13 | < 0.0001 |
| QT corrected interval (ms) | 446 ± 39 | 423 ± 35 | < 0.001 |
| LV segmental dyskinesis | 13 | 45 | < 0.0001 |
| Late potential (40-250 Hz) | 14 | 99 | < 0.005 |
| ACE-inhibitors | 20 | 200 | < 0.01 |
| Digitalis | 14 | 22 | < 0.0001 |
| Beta-blockers | 3 | 71 | NS |
| Diuretics | 21 | 61 | < 0.0001 |
| Bundle branch block | 5 | 22 | < 0.025 |

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CC = coronary care; LV = left ventricular; VPD = ventricular premature depolarizations; VT = ventricular tachycardia.

**Table II.** Results of the artificial neural network (all-case analysis).

| Variable | Weights |
|---|---|
| Threshold | -0.00309 |
| Left ventricular failure in CC | 0.00398 |
| Digitalis therapy at discharge | 0.00037 |
| Left ventricular dyskinesis | 0.00202 |
| Late potential (40-250 Hz) | 0.00516 |
| VPD (no./hour) | 0.00003 |
| LV ejection fraction | -0.00012 |
| Nonsustained VT | 0.00034 |
| Bundle branch block | 0.00318 |

| | Patients identified not at risk | Patients identified at risk | Total |
|---|---|---|---|
| Patients without AE | 336 | 27 | 363 |
| Patients with AE | 1 | 23 | 24 |
| Total | 337 | 50 | 387 |

AE = arrhythmic events. Other abbreviations as in table I.

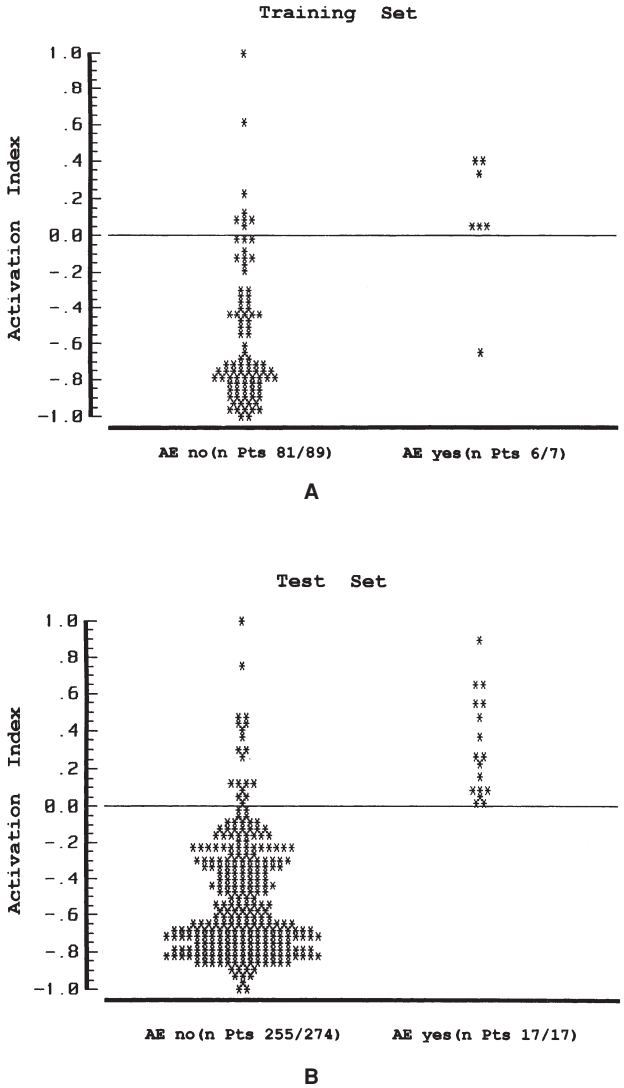


**Figure 1.** A: *training set;* B: *test set. Positive activation indexes were normalized for the occurrence of arrhythmic events (AE) between zero and +1, and negative activation indexes were normalized for the absence of AE between zero and -1.*

group, and 99% in the remainder ($p < 0.000001$) (Fig. 2A). In these two subgroups the relative risk of having arrhythmic events was 9.5:1 and .05:1 respectively.

The network algorithm was also a good predictor of cardiac death. In those patients identified as being at risk, the 2-year cardiac mortality rate was 42% (21 of 50) compared to 3.6% (12 of 337) in the remainder. In addition, the survival curves showed that the 2-year probability of remaining free of cardiac death was 57% in the former subgroup and 96% in the latter ($p = 0.0008$) (Fig. 2B). The relative risk of dying of cardiac causes was 5.3:1 and 0.4:1 respectively.

**Medical treatment.** At hospital discharge, among the 387 patients assessed by the neural network, 74 (19%) received beta-blockers, 220 (57%) angiotensin-converting enzyme inhibitors, 351 (91%) aspirin, and 7 (2%) antiarrhythmic drugs (5 amiodarone, 2 propafenone). At the end of follow-up, among the remaining 281 patients, 3 (1%) still received antiarrhythmic drugs and 55 (20%) beta-blockers. At the time of the endpoint events, 2 (28%) (both were under amiodarone treatment) of the 7 patients receiving and 22 (6%) of the 380 not receiving antiarrhythmic drugs had arrhythmic events, whereas 3 (4%) of the 74 patients receiving and 21 (7%) of the 313 not receiving beta-blockers had arrhythmic events. In both cases the difference was not significant.

## Discussion

**Prediction of arrhythmic events after acute myocardial infarction: considerations on the poor predictive accuracy of previous indexes.** In the past years, the risk stratification for postinfarction arrhythmic events has been the subject of intense investigation.

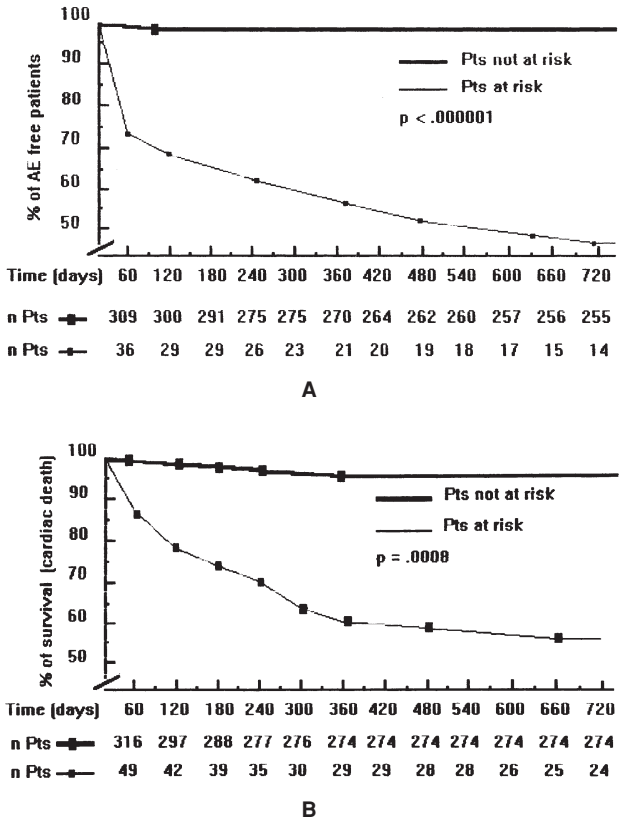


**Figure 2.** A: *survival curves for arrhythmic events (AE);* B: *survival curves for cardiac death.*

Nevertheless, the capability of predicting this event was unsatisfactory. One of the reasons of such unsatisfactory results may be the significant reduction that occurred in the last decade in the annual incidence of cardiac death and postinfarction arrhythmic events (7-14% and 1.5-3% in the '80s and '90s respectively)[4-6,22] (results of the present study). A second reason, and probably the main reason of such unsatisfactory results may be the large use of parametric statistical methods in most of the previous studies. Such statistical methods, in fact, are not the ideal computational technique for the analysis of biological and pathophysiological phenomena because they do not allow achievement of a linear complete subdivision of populations into well defined categories[23]. Unfortunately, until the end of the '80s, parametric statistical analyses were the most commonly used methods for the evaluation of medical problems since more appropriate electronic data processing techniques such as artificial intelligence were too complex, unable to solve simple problems and generally used in academic research and industrial applications[24]. Recently, however, artificial neural network research has been revitalized by the advent of new and low-cost learning models that have encouraged investigators to extend the use of such techniques even to clinical medicine. At present, the results of the available studies seem to confirm the optimistic expectations[23,24]. On the basis of these considerations, therefore, for the first time in the setting of postinfarction risk stratification, we tried to improve the prediction of late arrhythmic events using an artificial neural network. Additionally, in the attempt to make the risk stratification procedure more cost-effective, we only used selected variables easy to obtain in the vast majority of patients. Following such a strategy, we could evaluate 96% of the enrolled patients and identify a combination of variables able to accurately predict arrhythmic events.

**Clinical characteristics and follow-up of patients with arrhythmic events.** At the end of the 2-year follow-up, the cardiac mortality rate (8.4%) and arrhythmic event rate (5.9%) were similar to those reported in previous studies in which the study populations were similar to ours[2,3]. Even the temporal distribution of the arrhythmic events was similar to that reported previously, showing the maximal frequency within 6 months of the acute event[4,6,9]. This further increases the necessity of stratifying the risk before hospital discharge.

In agreement with the results of previous investigations, our findings confirm that postinfarction patients at risk for arrhythmic events are more likely to have a larger infarct size, severe left ventricular dysfunction, spontaneous ventricular electrical instability, and inhomogeneous conduction through the scarred myocardium.

**Prediction of arrhythmic events.** The combination of 8 variables resulting from the network algorithm allowed identification of a subgroup of patients at very high risk not only of arrhythmic events, but also of cardiac death. The predictive sensitivity and the predictive specificity for arrhythmic events of the discriminant score were 96 and 93% respectively, with a positive predictive value of 46%. In particular, the network allowed segregation of a small high-risk patient subgroup equivalent to only 12% of the entire study population. This patient subgroup showed a relative risk of developing arrhythmic events 18 times higher than in the remaining patients. All these results are placed at the highest value reported[2-11].

Our findings show that only 3 of the 8 variables included in the predictive index (number of ventricular premature depolarizations/hour, nonsustained ventricular tachycardia and late potentials) are factors directly involved in the genesis of arrhythmias. The former two represent the trigger mechanism, the latter the substrate for reentrant tachyarrhythmias. Although the remaining variables (left ventricular failure during the coronary care stay, left ventricular ejection fraction, segmental left ventricular dyskinesis, digoxin therapy, and bundle branch block) are well known single indicators of the extent of necrosis, of a larger border zone of myocardial scar tissue and of left ventricular dysfunction, it cannot be excluded that these variables may have provided additional, not apparent, information on the likelihood of developing life threatening arrhythmias. In

fact, the border zone of myocardial scar tissue is not only the site of anatomical and electrophysiologic abnormalities favoring reentrant circuits, but also the site of acute and chronic ischemic processes (ischemic burden) favoring abnormal automaticity and triggered activity[25,26]. Our findings confirm the results of other investigators on the importance of clinical data for the risk stratification of postinfarction patients[2,8,27].

**Comparison with previous studies.** The results of the present study differ from those of previous investigations in that our predictive index is simultaneously characterized by a high sensitivity (96%), specificity (93%), and positive predictive value (46%). In 1984, the MILIS Study Group Investigators found that the concomitant presence of left ventricular dysfunction and frequent ventricular premature depolarizations was able to segregate, just before hospital discharge, a high-risk patient subgroup with a sensitivity, a specificity and a positive predictive value of 24, 93 and 21% respectively[28]. Subsequently, at the end of the '80s, three different groups of investigators showed that combinations of two or three variables among ventricular late potentials, left ventricular dysfunction and spontaneous complex ventricular arrhythmias, allowed the identification of those patients at risk with a sensitivity, a specificity and a positive predictive value ranging from 33 to 80%, 89 to 98% and 29 to 57% respectively[4-6]. Some years later, using combinations of two or three variables including the classical three above-mentioned risk markers of arrhythmic events and the impairment of heart rate variability, Farrell et al.[3] did not significantly improve prediction (sensitivity 25-58%, specificity 91-99%, and positive predictive value 15-58%). More recently, similar results were also reported by De Chillou et al.[22] who used the perfusion status of the infarct-related coronary artery as a new predictor of arrhythmic events, and by McClements and Adgey[2] who suggested a combination of four variables (digoxin therapy, history of angina and/or myocardial infarction, late potentials) as a predictive index. Besides, the use of programmed ventricular stimulation either in nonselected or in selected patients failed to improve prediction since the induction of sustained monomorphic ventricular tachycardia allowed the identification of risk patient subgroups with a high specificity (97-99%), a satisfactory positive predictive value (30-67%), but a low sensitivity (53-55%)[9,10].

**Study limitations.** In the present study, medical therapy was not randomized. In addition, the percentage of patients treated with beta-blockers was lower than that reported in other previous studies similar to ours[2,3]. Thus, the use of antiarrhythmic drugs (although restricted to only a few patients) and the limited use of beta-blockers may have influenced both the arrhythmic event rate and the predictive accuracy of the neural network algorithm. This suggests that our satisfactory results might not be entirely reproducible in a population submitted to different medical treatment regimens.

A second potential limitation of the present study is the exclusion of the determination of heart rate variability from the set of variables used to assess the study population. The reason for such a choice was that, in the setting of the risk stratification for postinfarction arrhythmic events, approximately one fourth of high-risk patients is usually excluded from any analysis of heart rate variability because of clinical or technical problems[29]. This would have been in contrast with our strategy of stratifying postinfarction patients using only noninvasive variables easily obtainable in the vast majority of cases.

**Clinical implications.** The results of our study show that in postinfarction patients it is possible to predict sudden death and sustained ventricular tachycardia occurring during the 2 years following the acute event early and accurately. This is achievable exclusively using clinical and laboratory noninvasive variables, easy to obtain in the vast majority of patients.

The combination of the 8 variables resulting from the neural network algorithm allows the identification of two well defined subgroups of patients at a different risk of developing arrhythmic events: the first at a very high risk (event rate 46%), representing only 12% of the entire population, and the second at a very low risk (event rate 0.3%). This suggests that only patients included in the first subgroup may be considered candidates for prophylactic medical (beta-blockers, amiodarone) or electrical (automatic implantable cardioverter-defibrillator) antiarrhythmic therapy. In the light of the high costs of the implantable cardioverter-defibrillator devices, such a risk stratification procedure might be an effective solution, with a favorable cost-benefit ratio, of the still unsolved problem of the primary prevention of postinfarction sudden death. Trials of various pharmacological and nonpharmacological antiarrhythmic therapeutic strategies will have to be performed in such high-risk patient subgroups in an attempt to reduce the arrhythmic event rate and to assess the cost-benefit ratio of each different therapeutic approach.

## Appendix

Variables collected on each patient:

- demographic data: (1) sex, (2) age;
- risk factors for coronary artery disease: (3) systemic hypertension, (4) cigarette smoking, (5) high levels of serum cholesterol, (6) diabetes mellitus;
- previous history of coronary artery disease: (7) none, (8) angina, (9) myocardial infarction;
- site of acute myocardial infarction: (10) anterior-lateral, (11) inferior-posterior;
- type of acute myocardial infarction: (12) Q-wave, (13) non Q-wave;

- (14) thrombolytic therapy;
- cardiac serum enzyme peak levels: (15) creatine kinase, (16) creatine kinase-MB isoenzyme;
- clinical status during the coronary care stay: (17) Killip class, 18) left ventricular failure, (19) sinus tachycardia ≥ 100 b/min;
- bradyarrhythmias detected by electrocardiographic monitoring within the first 48 hours of acute myocardial infarction: (20) sinus pauses ≥ 3000 ms, (21) sinus bradycardia ≤ 40 b/min, (22) II degree atrioventricular block, (23) III degree atrioventricular block, (24) new bundle branch block;
- tachyarrhythmias detected by electrocardiographic monitoring within the first 48 hours of acute myocardial infarction: (25) sustained atrial tachycardia, atrial flutter or fibrillation, (26) ventricular fibrillation, sustained ventricular tachycardia (lasting ≥ 30 s), (27) nonsustained ventricular tachycardia (lasting ≥ 3 beats and ending spontaneously in ≤ 30 s);
- bradyarrhythmias detected by electrocardiographic monitoring after the first 48 hours of acute myocardial infarction: (28) sinus pauses ≥ 3000 ms, (29) sinus bradycardia ≤ 40 b/min, (30) II degree atrioventricular block, (31) III degree atrioventricular block, (32) new bundle branch block;
- tachyarrhythmias detected by electrocardiographic monitoring after the first 48 hours of acute myocardial infarction: (33) sustained atrial tachycardia, atrial flutter or fibrillation, (34) ventricular fibrillation, sustained ventricular tachycardia (see variable 26), (35) nonsutained ventricular tachycardia (see variable 27);
- spontaneous ventricular arrhythmias on the 24-hour electrocardiographic recording: (36) number of ventricular premature depolarizations/hour, (37) couplets of ventricular premature depolarizations, (38) nonsustained ventricular tachycardia (see variable 27), (39) sustained ventricular tachycardia (see variable 26), (40) mean heart rate during the entire electrocardiographic recording;
- (41) postinfarction angina;
- echocardiographic data: (42) segmental left ventricular dyskinesis, (43) left ventricular end-diastolic dimensions, (44) left ventricular end-systolic dimensions;
- ventricular late potential: (45) band pass filtering 25-250 Hz, (46) band pass filtering 40-250 Hz;
- exercise stress test: (47) inducible myocardial ischemia, (48) inducible ventricular arrhythmias (repetitive ventricular premature depolarizations, nonsustained or sustained ventricular tachycardia), (49) ineligibility to exercise test;
- radionuclide left ventricular ejection fraction: (50) at rest, (51) during exercise test;
- chest X-ray: (51) cardiothoracic ratio;
- electrocardiogram at hospital discharge: (52) bundle branch block, (53) QT corrected interval;
- therapy at hospital discharge: (55) beta-blockers, (56) acetylsalicylic acid, (57) nitrates, (58) angiotensin-converting enzyme inhibitors, (59) digitalis, (60) diuretics, (61) antiarrhythmic drugs.

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