Arrhythmia Risk Stratification after Myocardial Infarction

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ABSTRACT Summary Post-myocardial infarction ventricular arrhythmia and sudden cardiac death risk remain important issues in these patients. In high-risk post-myocardial infarction (MI) patients prophylactic implantable cardioverter defibrillators (ICD) may significantly improve survival. Risk stratification studies of post-MI patients will allow ICD therapy to be applied in a more cost-effective manner. We present some key features of non-invasive and invasive methods of risk assessment relevant to the assessment of the arrhythmic risk after myocardial infarction.

KEY WORDS keywords Arrhythmia, myocardial infarction, risk assessment

General Considerations

In case of all sustained arrhythmias, diagnosed or documented by ECG and in certain diseases without any present or past arrhythmic manifestation it is necessary to evaluate the risk of apparition or reoccurrence of a rhythm disturbance especially ventricular tachycardia (VT) or ventricular fibrillation (VF) as potentially lethal events [1].

Arrhythmia risk evaluation (or, by extension, of vital risk in case of VT/VF) includes, beside the careful reading of standard ECG, a series of useful more or less routine investigations (table 1).

Table 1. Useful investigations for the evaluation of arrhythmic risk

1. Standard ECG
2. Stress ECG, looking for:
   - effort induced arrhythmias
   - premature beats (behavior in certain effort stages)
   - QT interval (adaptation to heart rate)
   - Heart rate adaptation to effort (maximum value, return to normal rhythm)
3. Bedside ECG
4. Ambulatory ECG monitoring (Holter), analyzing:
   - eventual sustained or unsustained arrhythmias
   - number of PVB
   - heart rate variability
   - heart rhythm turbulence
   - QT variability
5. Long term monitoring with implantable devices
6. Signal averaged ECG (High resolution ECG or SAECG - signal averaged electrocardiography)
   - applied to the P wave
   - applied to the QRS complex
7. Evaluation of T wave alternans (or MTWA - microvolt T wave alternans)
8. Evaluation of the baroreceptor reflex sensitivity
9. Electrophysiological exploration (with programmed stimulation)

The complexity of these investigations resides not only in their depth (the best example is the type and number of the standard ECG derived parameters – table 2) but also the degree of sophistication of the equipment (which implies high costs) as well as the level of professional training of the medical staff.

Table 2. Standard ECG data useful in the assessment of arrhythmic risk

<table>
<thead>
<tr>
<th>Description</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>P waves with duration &gt; 0.12 s in the absence of LA</td>
<td></td>
</tr>
<tr>
<td>P waves with Bachmann’s bundle block</td>
<td></td>
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<tr>
<td>Frequent PVB or with deep altered morphology or with short coupling</td>
<td></td>
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<tr>
<td>compared to the base rhythm</td>
<td></td>
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<tr>
<td>Frequent ventricular couplets, polymorph, with short coupled V′-V″</td>
<td></td>
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<tr>
<td>Episodes of NSVT (randomly detected)</td>
<td></td>
</tr>
<tr>
<td>Accelerated idioventricular rhythm with HR &gt; 100/min*</td>
<td></td>
</tr>
<tr>
<td>Basic rest sinus cycle &lt; 750-800 ms (preferably one should assess the</td>
<td></td>
</tr>
<tr>
<td>mean/24 hours on Holter ECG</td>
<td></td>
</tr>
<tr>
<td>Signs of important LV hypertrophy</td>
<td></td>
</tr>
<tr>
<td>QRS duration &gt; 120 ms (bi- and trifascicular blocks or unspecific</td>
<td></td>
</tr>
<tr>
<td>intraventricular conduction disturbance)**</td>
<td></td>
</tr>
<tr>
<td>QRS duration &gt; 160 ms in those with left bundle branch block</td>
<td></td>
</tr>
<tr>
<td>Right bundle branch block with elevated ST in V₁-V₃</td>
<td></td>
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<tr>
<td>Obvious T wave alternans (millivolts)</td>
<td></td>
</tr>
<tr>
<td>Corrected QT &gt; 500 ms (450 ms ?)</td>
<td></td>
</tr>
<tr>
<td>QT dispersion interval &gt; 100 ms</td>
<td></td>
</tr>
<tr>
<td>ε wave (± QRS widening in V₁-V₂ with negative T waves)</td>
<td></td>
</tr>
</tbody>
</table>

* only in patients with acute myocardial infarction
** patients with chronic heart failure

Most investigations offer data, which to be significant must have a good positive predictive value, but in case of signal averaged electrocardiography (SAECG) and microvolt T-wave alternans (MTWA) the negative predictive value of 97-99% is that of practical importance. The clinical translation of the negative results by the two investigations for the patients with identified cardiac diseases consists in the exclusion of need for further investigations or antiarrhythmic therapeutical interventions.

The reality is not quite as simple, because the arrhythmic risk as assessed at a particular time does not remain at the same level throughout life, but it has a possible variability dependent on many factors, which may or may not be influenced by medical interventions (table 3).
Table 3. Arrhythmic risk variability

1. Substrate dependent variability (internosological) = arrhythmic risk in varying sizes from one disease to another and intensity variations and significance of a given arrhythmic risk parameter according to disease;
2. Share variability (intranosological interindividual), at the same type and severity of structural disease, depending on:
   - morbid fund associations;
   - individual habits (consumption of alcohol, coffee, illicit drugs);
   - degree and type of exercise (occupational or habitual);
   - age;
   - race;
   - sex;
   - level of education;
   - professional stress;
   - genetic factors (interindividual gene expression variations, polymorphisms);
   - weather biosensitivity (?);
3. Intrinsic variability (intraindividual), according to:
   - evolutionary moments of the heart (worsening or spontaneous improvement, episodes of acute coronary ischemia, occurrence of new diseases or effects of therapeutical interventions);
   - the degree of impairment of the heart pump function in evolution;
   - changes in autonomic balance (circadian and noncircadian);
   - psychiatric disorders (depression, anxiety), acute emotional demands;
   - variations in fluid and electrolyte metabolism (and acid-base);
   - different intercurrent conditions (fever, acute poisoning etc.);
   - continuous or intermittent drug therapy;
   - circadian biorhythm (and circanual?) vegetative interdependent (of coagulation and fibrinolysis etc.).

Of course arrhythmic risk assessment is not without controversy, but a major part is placed under the dominance of practice guidelines that cover statistics and major evidence in the light of the majority of situations in practice.

Ventricular arrhythmia risk assessment methods

We present some key features of non-invasive and invasive methods of risk assessment relevant to investigate the arrhythmic risk post-myocardial infarction [2].

ECG data with significance of ventricular arrhythmia risk

Standard ECG, in celebration of 100 years of use, continues to be an excellent noninvasive cardiology evaluation, mainly by its wide accessibility and the extensive support with data accumulated over time.

Items of interest are primarily those aimed to ventricular arrhythmias:
- Premature ventricular beats (PVB) / with profoundly altered morphology / polymorphic / short coupled;
- Frequent ventricular doublets, polymorphic, short-coupled;
- non-sustained VT (NSVT) episodes accidentally caught;
- Increased idioventricular rhythm with heart rate > 100/min;
- Signs of significant left ventricular hypertrophy (LVH);
- QRS duration > 120 ms (two-and trifascicular blocks) in patients with chronic heart failure (CHF);
- QRS duration > 160 ms in patients with complete left bundle branch block (LBBB);
- Alternation of T wave amplitude (of microvolts);
- QT dispersion > 100 ms.

Ambulatory electrocardiography

The use of continuous or intermittent ambulatory recording techniques can be very useful in diagnosing a suspected arrhythmia, determining the frequency of symptoms and reporting them to the presence of arrhythmia. Episodes of silent myocardial ischemia can be detected.

A continuous 24-48 hours Holter recording is appropriate when the known or suspected arrhythmia occurs at least once a day. For sporadic episodes that produce palpitations, dizziness or syncope, conventional event monitoring devices are appropriate because they can record for longer periods of time.

Newer implantable recording devices are capable of monitoring the pace and can be activated by the patient or automatically for predetermined criteria. Although these devices require surgical implantation they are extremely useful for diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life-threatening symptoms such as syncope.

The most important stratification instrument resulted from Holter recording is heart rate variability (HRV).

In normal heart, the heart rhythm is not regular but is determined by the balance between sympathetic and parasympathetic activity. HRV is a measure of this modulation. Analysis of HRV is a non-invasive method that determines the influence of autonomic nervous system activity on heart rate in the sinus node.

In recent years, it has been revealed that impaired autonomic nervous system plays an important role in the genesis of ventricular arrhythmias.

HRV can be analyzed in time and frequency domain using a 24 hour Holter ECG recording; the most used parameter is SDNN = standard deviation of all normal RR intervals over 24 hours.
The predictive value of HRV for risk stratification post-MI is limited. HRV is strongly reduced in the first weeks post-MI and tends to return during the first year, but not to normal values.

Currently, to improve the predictive value of HRV it is necessary to combine it with other risk factors, despite its independent value as risk factor predicting mortality and arrhythmic complications.

Multivariate analysis showed that the most sensitive combination of arrhythmic events predictors is the association between reduced HRV and positive SAECG (positive LP).

HRV is not affected by thrombolytic therapy. The ATRAMI study (Autonomous Tone and Reflexes in Acute Myocardial Infarction) [3] confirmed that HRV (and BRS - baroreflex sensitivity) remains a significant predictor of cardiac mortality in patients after AMI (< 28 days) even in the thrombolytic era.

Also according to the ATRAMI study, the combination of low values of HRV (SDNN < 70 ms) and reduced left ventricular ejection fraction (LVEF) is useful for sudden cardiac death (SCD) risk stratification in patients after AMI.

Heart rate turbulence – HRT, is represented by variations in sinus rhythm cycle length determined by a PVB. The validity of HRT as a risk marker for SCD was confirmed in ATRAMI study [4].

### Assessment of baroreflex sensitivity

It is a test used to assess the autonomic nervous system’s ability to respond to a stimulus by increasing the release of acetylcholine (by vagal reflex activation); there are several methods but the most used is the observation of reflex heart rate response to the physiological activation/deactivation of the baroreceptors following blood pressure changes caused by a vasoactive drug (phenylephrine).

The ATRAMI study shows that values of BRS < 3 ms/mmHg had a positive predictive power for cardiac mortality highly significant and independent of the depressed parameters of HRV [5].

### Ventricular late potentials

SAECG - signal averaged electrocardiography, allows the highlighting of small amplitude potentials, of the order of microvolts, possibly present at the end of QRS complex, representing the depolarization of some ventricle areas (areas of slow conduction) from which could be triggered reentrant arrhythmias.

The standard parameters used and their normal values (with the lower limit of the filter at 40 Hz) are:

- The total duration of filtered vector fQRS (fQRSrd) < 114 ms;
- Signal amplitude in the last 40ms (root mean square - RMS40) > 20 μV;
- Duration of the signal at the end fQRS signal amplitude < 40 ms (high frequency low-amplitude signal – HFLA, or low amplitude signal - LAS) < 38 ms.

The presence of these conditions is labeled as late potential present / positive SAECG.

Present LP in post-MI patients (in which the morphological substrate is the impaired depolarization - slow conduction areas - considered predisposing to reentrant arrhythmias) were expected to have an overwhelmingly positive predictive value for arrhythmic activity.

Numerous studies have concluded that under these conditions the positive predictive value of SAECG is only 17-22%, but with an impressive negative predictive value.

The association of positive LP with low LVEF is superior as a predictor for SCD.

Cain studied the prevalence of abnormal SAECG in normal subjects and patients with recent or old myocardial infarction with or without ventricular tachyarrhythmias (table 4) [6].

<table>
<thead>
<tr>
<th>Study group</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Time domain</td>
<td>Frequency domain</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>0-10</td>
</tr>
<tr>
<td>Recent MI (&lt; 2 weeks) no VT</td>
<td>14-29</td>
</tr>
<tr>
<td>Old MI (&gt; 1 month) no VT</td>
<td>18-33</td>
</tr>
<tr>
<td>Old MI (&gt; 1 month) with VT</td>
<td>52-80</td>
</tr>
</tbody>
</table>

In patients with myocardial infarction and ventricular tachyarrhythmias the prevalence of abnormal SAECG is significantly increased, compared to other groups, but it varies greatly, and this can be explained by differences in diagnostic criteria for late potentials, in infracted region, as well as the time of SAECG recording.

In another study, El Sherif and colleagues have observed that the incidence of abnormal SAECG recordings varied greatly in the first 60 days after myocardial infarction, the presence of late potentials between 6-30 days after myocardial infarction having a significant relationship with...
arrhythmic events in the first year after myocardial infarction [7].

Gomes showed that late potentials appear more frequently in patients with inferior myocardial infarction than in patients with anterior myocardial infarction [8].

The explanation could be that the left ventricular inferoposterior segment depolarizes later than anterior and anteroseptal segments.

Thus, in patients with myocardial infarction, activation of the abnormal region will exceed the normal depolarization and appears as late potentials after the end of the QRS complex. On the other hand, in patients with anterior myocardial infarction, the abnormal cardiac region is activated early, and late potentials are partially "hidden" in the QRS complex.

Several prospective studies have confirmed the increased likelihood of malignant ventricular tachyarrhythmias and sudden cardiac death post-myocardial infarction in patients with abnormalities of the SAECG. A study conducted by El-Sherif [9] offers the best predictive criteria SAECG in post-myocardial infarction period. A total of 1158 patients were recruited into the study and followed for a period of 10 ± 3 months. 45 patients (4%) of the studied group suffered serious arrhythmic events. SAECG parameters were found with independent predictive value, the most significant being the QRS duration at 40 Hz. Abnormal QRS duration at 40 Hz was defined as > 120 ms and it was found in 12% of the study group. The positive, negative and overall predictive value of SAECG abnormalities was found in 17%, 98% and respectively 88%. It is possible that, the criteria for late potentials, that are associated with monomorphic ventricular tachycardia may not very useful in post-myocardial infarction, where most arrhythmic events were polymorphic ventricular tachycardia and ventricular fibrillation. On the other hand, a prolonged QRS duration reflects the slow and uneven conduction of a large mass of ventricular myocardium, which predisposes to polymorphic ventricular tachycardia/ventricular fibrillation.

Sorgato and colleagues [10] have summarized the data of the prognostic value of SAECG in time domain based on the results of 14 prospective studies, totaling 4993 patients in the post - myocardial infarction period. In these studies, SAECG was performed in the first month post - myocardial infarction, and mean follow-up period was 13 months. SAECG was abnormal in 29% of patients, while arrhythmic events were encountered in 7% of patients. The positive predictive value was low (average 17%, range 8-29%), while the negative predictive value was high (average 96% with a range 81-99%).

Due to the low predictive value in patients post - myocardial infarction, no action is justified if based solely on the presence of late potential 36. One factor contributing to the negative predictive value of SAECG in post - myocardial infarction period was the high prevalence of false-positive results occurred in patients with inferior myocardial infarction.

On the other hand, analysis of the spectral turbulence is characterized by a number of false positive results in patients with previous myocardial infarction. By combining time domain and the analysis of spectral turbulence it is possible to improve predictive accuracy of SAECG for arrhythmic events in the post - myocardial infarction period. This was demonstrated in a prospective study that included 262 patients with myocardial infarction, followed up for 10 ± 2 months, as in the study of Copie [11], in which 603 patients were followed for 2 years. A multicenter european study (Post-infarction Late Potential - PILP) [12] enrolled 778 survivors after myocardial infarction who were followed for 6 months. The combination of late potentials and spectral analysis has the highest predictive power of arrhythmic events. The predictive value of SAECG increases, if its results are corroborated with other data: left ventricular ejection fraction, degree of ventricular ectopy, heart rate variability and response to programmed ventricular stimulation. El-Sherif's study showed that the rate of cardiac events in post-myocardial infarction patients was 23%, while SAECG was abnormal, and increased to 57%, when they combined SAECG, left ventricular dysfunction and a high level of ventricular ectopy.

**Electrophysiologic study**

It is used in diagnostic purposes and for arrhythmia risk stratification, particularly if other noninvasive tests were positive [13].

Although electrophysiologic (EP) study was considered the gold standard in predicting the arrhythmic risk after myocardial infarction, its current status remains uncertain in patients without prior arrhythmic events but with one ore more noninvasive positive tests (low LVEF, low HRV, positive LP, or positive MTWA); it is not clear if data obtained by EP imposes arrhythmia ablation or ICD implant.

Testing the effectiveness of antiarrhythmic therapy by EP study was generally abandoned; it was required in older studies (MADIT, MUSTT,
BEST-ICD), but not in MADIT II, SCD-HeFT, AVID.

Ventricular tachycardia inducibility in patients with NSVT at Holter monitoring identified a population with high risk for VT/VF in MADIT, in which ICD was implanted.

In a MUSTT substudy, NSVT characteristics (frequency, duration, time of onset) were not correlated with EP inducibility. Survival was lower for patients in hospital NSVT, suggesting the necessity for different criteria for in- and out-patients.

In a MADIT II substudy inducibility was 36%. Lower resting heart rate, lower LVEF, and a longer time interval between the myocardial infarction and EP test, correlated with inducibility.

In patients with ischemic heart disease, asymptomatic NSVT and LVEF < 40%, SVT inducibility varies between 20 and 40%.116 Absence of inducibility is associated with low risk in MADIT-like patients; however, these patients were in large proportion remitted for PCI. In patients with low LVEF (< 30%) non-inducibility does not imply a good prognosis.

EP study-guided medical antiarrhythmic therapy in patients with NSVT and inducible VT had no benefit.

Left ventricular ejection fraction

Left ventricular systolic dysfunction was the most powerful noninvasive predictor of post-MI arrhythmia and prognosis.

Bigger et al showed that in patients with LVEF < 30%, SCD and arrhythmia risk is 3.5 higher than in patients with LVEF > 30% [14].

In TIMI studies LVEF remained an important predictor of total and cardiac mortality in the thrombolytic era.

For cardiac mortality prediction LVEF < 35% had a sensitivity of 40%, a specificity of 78% and a positive predictive value of 14%.

LVEF remains a powerful predictor of post-MI 2-year mortality (EMIAT, SWORID, TRACE, DIAMOND - MI).

References