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Late Ventricular Potentials in Cardiac and Extracardiac Diseases

Ioana Mozoș, Corina Șerban and Rodica Mihăescu
*"Victor Babeș" University of Medicine and Pharmacy, Timisoara
 Romania*

1. Introduction

Late ventricular potentials (LVPs) are low amplitude, high frequency waveforms, appearing in the terminal part of the QRS complex of the electrocardiogram (Barbosa et al, 2002; Olinic & Zdrengha, 1998), generated by diseased myocardium. They may extend in the ST segment (Zimmermann et al, 1983). Late ventricular potentials may be also defined as fragmented electrical activity, appearing in heterogeneous tissue areas, located at the border zone of a myocardial infarction (Fetsch, 1999). They are markers of an electrophysiological substrate for reentry ventricular tachycardia (VT) and sudden cardiac death (SCD) (Zipes et al, 2006).

Most of the clinical research in this field is focused on risk stratification of patients with a history of myocardial infarction (MI), but the role of LVPs in other cardiac and extracardiac diseases is also discussed. At present, there is considerable interest on improved tests for risk stratification of sudden cardiac death and appropriate selection of prophylactic implantable cardioverter defibrillator recipients.

2. History

Late ventricular potentials were first reported by Berberi and Simson in dogs (Engel et al, 2004). Berbari et al. (Berbari et al., 1978) first demonstrated that, using high-gain amplification, filtering and signal averaging, late potentials could be recorded. Initially, LVPs were obtained directly from the endocardium or epicardium, but they can be recorded from the body surface, as well. The amplitude of LVPs is too low to be detected on the standard surface ECG, requiring an amplified high-resolution ECG recording. Simson and Breithardt et al. first showed the clinical value of ventricular signal averaged electrocardiography (SAECG) for identification of patients with sustained VT (Breithardt et al., 1981; Simson, 1981).

By the end of the 1980s, LVPs were helpful for the diagnosis, risk stratification and therapy of patients with ventricular arrhythmias. The initial enthusiasm diminished over time due to variability in the sensitivity, but lately, its predictive value for VT and fibrillation (VF) has been re-evaluated (Frances, 2010).

SAECG was originally developed for use in patients with coronary artery disease and VT, but it has been subsequently applied to other groups of patients (Goldberger et al., 1994).

3. Recording of LVPs

The amplitude of LVPs is in the order of microvolts and can not be detected on the standard surface ECG, requiring an amplified high-resolution ECG recording for their identification (Santangeli et al, 2008). Thus, LVPs are recorded using SAECG (Olinic & Zdrengha, 1998). The leads are different from those used in standard 12-lead ECG. Most investigators use an XYZ lead system, made of three orthogonal bipolar electrode combinations (Engel et al, 2004) and high-pass filtering. The leads are combined into a vector magnitude, a measure that sums up the high frequency information contained in all these leads. This vector magnitude is called filtered QRS complex (Santangeli et al, 2008). Considering the low intensity of LVPs, averaging of approximately 300 ECG cycles is needed, in order to minimize the level of noise (Santangeli et al, 2008). The signal-to-noise ratio increases with the number of averaged beats (Gottfridsson et al, 2011). Recording of LVPs using body surface mapping is, also, possible (Linnenbank et al, 2001).

3.1 Diagnosis criteria

LVPs are present, if, according to an international convention (Goldberger et al, 2008), 2 of the following criteria (variables of the filtered QRS) (Fig. 1) are positive:

- **SAECG-QRS** duration (**SA-QRS**)>120 ms. Other authors consider SA-QRS>114 ms (Breithardt et al, 1991; Lander et al, 1993)
- **LAS40**: low amplitude signal (duration of the terminal part of the QRS complex with an amplitude below 40 μ V) >38 ms
- **RMS40**: root mean square signal amplitude of the last 40 ms of the signal < 20 μ V.

Each laboratory should define its own normal values (Breithardt et al, 1991). Other authors (Askenazi et al, 1978) use two sets of criteria to classify SAECD results. SAECD-I criteria are positive if one or more variables are abnormal, and SAECD-II criteria are positive if two or more variables are abnormal.

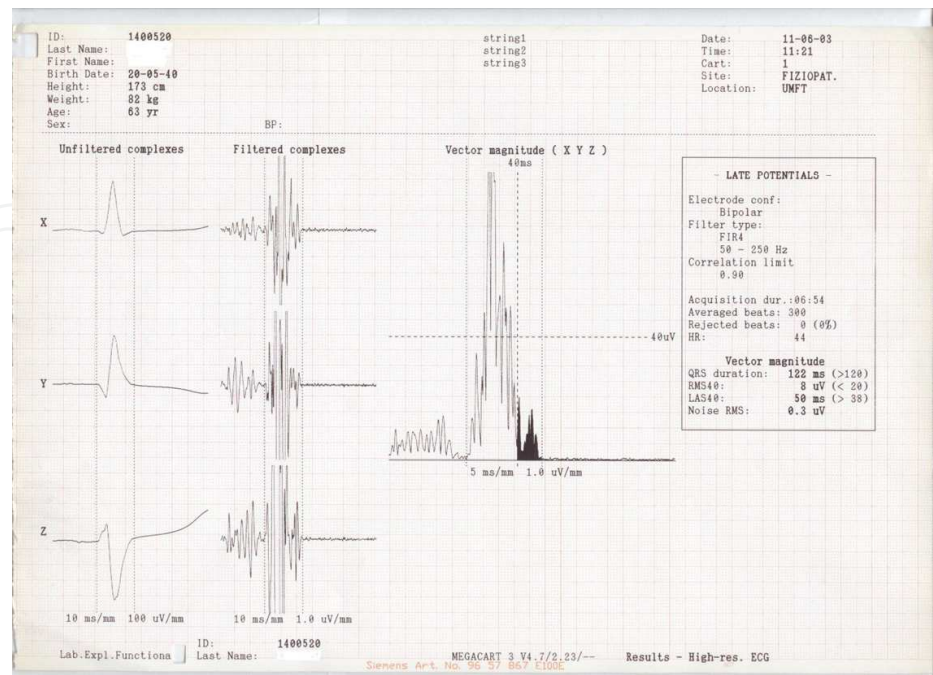


Fig. 1. Late ventricular potentials in a patient with an old inferior myocardial infarction.

Besides temporal domain analysis, frequency domain analysis allows identification of arrhythmia risk considering changes of ECG frequency components. Frequency domain analysis was not validated in clinical practice.

3.2 Limits

The amplitude of the signals is low, and averaging the electrocardiogram, amplifying it and filtering out the low frequencies is needed (Mehta & Camm, 1989; Santangeli et al, 2008). Several noise sources may appear in highly amplified recordings: artifacts from respiratory muscles, electronic noise arising from the electrodes, electrical power lines and other nearby electronic equipment (Engel et al, 2004). Despite technical improvement of the devices, electrical interferences and preexistent electrophysiological changes may cause false negative results. High-pass filters may attenuate or abolish LVPs (Santangeli et al, 2008).

Noise level was considered an important technical aspect influencing the results of the test. Steinberg and Bigger stated that the 0.3 μV level improves detection of late potentials (Steinberg & Bigger, 1989). The sensitivity of SAECG may be increased, by using a very low noise level (0.1 μV) (Frances, 2010). On the other hand, Engel et al. suggested that noise does not influence the SAECG variables and Christiansen et al. concluded that LVPs appear in healthy subjects at low noise levels (Christiansen et al, 1995; Engel et al, 1993).

The weakness of LVPs is the low positive predictive value. However, their negative predictive value for arrhythmic events is very high (Santangeli et al, 2008).

Difficulties may appear in detecting LVPs in patients with an anterior MI. Because of the early activation of the anterior regions during the normal sequence of electrical activation of the ventricles, delayed depolarization potentials of these regions after an anterior MI may not outlast the QRS complex, and therefore may be hidden within the QRS complex and not detected by SAECG (Santangeli et al, 2008).

Patients with a prolonged QRS complex duration, due to a bundle-branch block (BBB) or intraventricular conduction defect, have late-occurring depolarization potentials caused by these conduction disorders (Galinier et al, 1996). Separate LVPs criteria were used for patients with BBB: SA-QRS ≥ 145 ms, LAS40 ≥ 55 ms and RMS40 ≤ 17 μV (Galinier et al, 1996). Assessment of LVPs using multiple channel electrocardiographs, allows the use of the method in patients with wide QRS complexes, identifying the origin of LVPs.

4. Predictive value of LVPs

LVPs characterize ventricular depolarisation and its signal is more stable and easy reproducible compared to the repolarisation process (Askenazi et al, 1978).

The positive predictive accuracy for malignant ventricular arrhythmias, in patients recovering from MI, of LVPs, ranges only from 8% to 29% (Santangeli et al, 2008). A high negative predictive value (90%) is mentioned for LVPs.

5. Pathophysiology of LVPs

LVPs represent delayed conduction through a diseased myocardium and indicate the presence of a potential **anatomical substrate** for **macroreentry** ventricular arrhythmias (Olinic & Zdrenghea 1998, Santangeli et al, 2008).

LVPs appear as a consequence of late ventricular depolarisation due to delayed impulse conduction in certain myocardial regions (Olinic & Zdrenghea 1998; Engel et al, 2004).

Decremental conduction appears in coronary heart disease due to decreased conduction speed in ischemic myocardium or due to a prolonged impulse propagation path (Breithardt et al, 1991).

Certain conditions must be met by the area that provides LVPs. First, **conduction must be slow** enough to enable reentry in the healthy tissue. Second, a 1/1 conduction should be maintained at **high frequencies**; otherwise a bidirectional block appears and reentry is impossible. Third, an **unidirectional block** is needed, to allow depolarisation of the decremental zone in a single direction (Olinic & Zdrengea, 1998).

If the length of the reentry circuit is not long enough, the amplitude of the potentials can not be detected on the surface ECG and LVPs are absent despite arrhythmia favorable conditions. This explains the reduced positive predictive value of LVPs for ventricular arrhythmia (Olinic & Zdrengea, 1998).

In old MI, disorganised and asynchronous electrical activity arises from areas of surviving muscle at the border of a MI (Breithardt et. al, 1991; Savard et. al, 1997). Such areas are separated from each other by fibrous tissue, creating a disorganized, disconnected, heterogeneous network (Cain et al, 1996; Clayton, 2003). Considering other opinions, LVPs arise in the viable cells inside the necrotic and fibrotic mass, or in the injured myocardial fibers, with slow conduction (Cain et al, 1996; La Vecchia et al, 1998; Turrini et al, 1999).

An anatomical substrate, able to cause delayed conduction and produce LVPs, was reported in several other clinical conditions: dilated cardiomyopathy (Mancini et al, 1993), hypertrophic cardiomyopathy (Cripps et al, 1990), myocarditis, and infiltrative heart disease (Santangeli et al, 2008).

LVPs are favored by modified tissue architecture due to: necrosis, fibrosis or dystrophy, causing a delayed and fragmented depolarization. Fibrosis disturbs ventricular activity, separates myocardial bundles and prolongs conduction pathways (Cain et al, 1996). Anisotropic reentry is the result of fibrosis in addition to the density and distribution of gap junctions, which are responsible for variations in the conduction velocity (Kitamura et al, 2003; Peters et al, 1997). Some authors have demonstrated a close link between the distribution of the gap junctions, the specialized intercellular connections, and the development of reentrant arrhythmia in patients with healed MI and nonischemic dilated cardiomyopathy (Kitamura et al, 2003; Peters et al, 1997). The slow and discontinuous conduction caused by abnormalities in gap junction distribution and function form a **functional**, rather than anatomical, **substrate** for reentry (Santangeli et al, 2008).

To generate an arrhythmia needs a substrate (LVPs), but also a trigger and maintenance (Santangeli et al, 2008).

Arrhythmia triggers, such as acute ischemia, imbalance in autonomic tone, or the onset of clinical heart failure, may provide the link between the presence of LVPs and occurrence of spontaneous VT (Santangeli et al, 2008).

When sympathetic tone to the heart is augmented, vagal activation exerts a protective effect on ventricular vulnerability. Sympathetic stimulation unopposed by vagal activity induces ventricular electrical instability, increases susceptibility to ventricular fibrillation, resulting in a high risk of arrhythmia and SCD (Gussak & Antzelevitch, 2008). Myocardial infarction may damage nerve pathways, thereby limiting the potential of the vagus nerve to be activated (Gussak & Antzelevitch, 2008).

QRS prolongation may be explained by: intraventricular conduction disturbances and ventricular dilation, known to prolong ventricular conduction; and ventricular remodeling,

which increases tissue mass and slows conduction velocity. A correlation was found between QRS duration and end-diastolic volume after a few weeks after a MI. Some authors suggest that arrhythmias are due to left ventricular dysfunction and do not depend on its etiology, considering that no differences were found in patients with myocardial ischemia or idiopathic cardiomyopathy (Kondo et al, 2001).

Reentry explains the appearance of LVPs mainly in old myocardial infarctions, due to scarring. An **abnormal automatism** due to a recurrent acute MI can also cause LVPs. A significant proportion of deaths occurring after discharge are caused by an arrhythmia focus due to acute ischemia, hence the lack of sensitivity of LVPs in predicting SCD (Savard et al, 1997). A prolonged QRS duration was suggested to be predictive for arrhythmia SCD, regardless of arrhythmia mechanism.

LVPs extend beyond the normal QRS complex due to the low velocity, and may be detected in the ST segment, as well (Barbosa et al, 2002; Cain et al, 1996). Abnormal intra-QRS potentials, as markers of reentry, may also appear (Lander et al, 1993).

6. Analysis of SAEKG variables

Positivity criteria for LVPs (SA-QRS, LAS40 and RMS40) are significantly influenced by several factors: age, gender and myocardial infarction location (Barbosa et al, 2002; Savard et al, 1997). Criteria adjusted for sex, age and myocardial infarction location were developed only for SA-QRS, due to its higher predictive value for arrhythmic events (Lander et al, 1993).

SA-QRS measured by SAEKG is higher in men than in women. This can be attributed to the greater myocardial mass. The significant increase of SA-QRS in aging MI patients was attributed to degenerative processes affecting conduction (Mozos, 2007).

All three SAEKG variables showed significant predictive power for ventricular arrhythmic events. Several authors consider SA-QRS to have higher accuracy for arrhythmic events than any other combination of SAEKG parameters (Ammann et al, 2004; Lander et al, 1993). Other authors concluded that RMS40 has the highest predictive value for ventricular arrhythmia (Nakai et al, 1988).

In patients with inferior myocardial infarction and documented episodes of sustained VT, all variables were significantly different (lower voltages, longer durations) compared to patients with anterior infarction (Barbosa et al, 2002). LVPs can be better identified at higher frequencies, confirming the high frequency of these signals.

7. The role of SAEKG

The predictive value of SAEKG for arrhythmic events after a MI (Savard et al, 1997) exceeds that of other tests such as left ventricular ejection fraction (LVEF) or ambulatory ECG. The existence of LVPs increases 6 to 8 times the risk of arrhythmic events after a MI and it is considered the best non-invasive method to identify postinfarction VT risk (Ho et al, 1993).

The widespread use of thrombolytic therapy, beta-blockers, antiplatelet therapy and revascularisation, lifetime changes and risk factor management, improved post-infarction survival. In this context and considering the proarrhythmic effects of antiarrhythmic drugs, it is important to identify patients with low risk. Due to its high negative predictive value, LVPs can play an important role in selecting patients for interventional studies. The role of SAEKG as a screening test is limited due to the low positive predictive accuracy.

The behavior of LVPs on the body surface during programmed stimulation was evaluated by Ho et al (Ho et al, 1996), concluding that LVPs detected during sinus rhythm but lost after ventricular extrastimuli are often clinically irrelevant and may explain the false positive results and the reduced specificity of SAECEG. LVPs revealed by ventricular extrastimuli but concealed during sinus rhythm may be clinically relevant and may explain some of the false negative results and the reduced sensitivity of SAECEG.

8. Myocardial infarction (MI)

SAECEG is still a very useful method to identify MI patients at risk for lethal arrhythmic events (Huebner, 2010). In patients with **acute MI**, the electrophysiological substrate for LVPs gradually develop in the first 2 weeks of the acute event. LVPs were found in the first 3 hours after MI onset and their prevalence increased in the next 7-10 days. LVPs recorded in the first week were associated with subsequent ventricular dilation and may be due to cell slides (Zaman et al, 1993).

Once established, LVPs seem to remain indefinitely in most patients (Santangeli et al, 2008). LVPs can also disappear in the first year after an acute MI. Yang et al. consider that the prevalence of LVPs in the first week of a MI increases from 32% in the first day to 52% in the days 7-10 (Yang et al, 1990).

Time-dependent changes have been also attributed to cell death in the border zone of the MI or resolution of myocardial ischemia (Goldberger et al, 1994).

In the second week and in **old myocardial infarction**, prevalence stabilizes at 25-35%. Savard et al. (Savard et al, 1997) consider that LVPs recorded after 5-15 days from an acute MI, are the best predictors of ventricular arrhythmia appearing in the first year. If LVPs are missing at hospital discharge, their subsequent appearance is unlikely (Kuchar et al, 1986). LVPs may disappear later due to reshuffle of the myocardial scar.

In the first year after a transmural infarction, the predictive value of LVPs is low for SCD, because factors like: unidirectional block, heart rate and autonomic imbalance are triggering repetitive arrhythmias.

Patients with two MI (inferior and right ventricle) have a high prevalence of LVPs, independent of LVEF, and a high arrhythmia risk should be considered in those patients (Iltumur et al, 2001).

Prevalence of LVP is 7-10% in coronary heart disease without myocardial infarction.

Most studies on LVPs in MI patients were performed before the reperfusion era (Steinberg & Berbari, 1996). Studies investigating the effects of thrombolysis on LVPs reported controversial results. Bauer et al. (Bauer et al, 2005) suggested that LVP are of limited use for risk stratification in post infarction patients who received reperfusion/revascularization therapy. Zipes et al. considered that repermeabilisation of infarct related artery modifies the arrhythmogenic substrate and reduces the predictive power of LVPs (Zipes et al, 2006). The evidence for a benefit of thrombolysis on LVPs prevalence depended on the success of thrombolysis in achieving early and full coronary blood flow restoration (Hohnloser et al, 1994). LVPs were found in 25% to 65% of patients with an occluded infarct-related artery despite thrombolysis, but in only 6% to 34% of those with a patent infarct-related artery after thrombolytic therapy (Chew et al, 1990). Malik et al. showed that the usefulness of LVPs to predict subsequent arrhythmic events was significantly worse in patients who received thrombolytic therapy than in those who did not receive thrombolytic therapy (Malik et al, 1992). The controversial results may be due to the differences in therapy, lack of

adequate randomization and controlled studies, different techniques of recording SA-ECG and criteria to define LVPs. Savard et al. demonstrated that the prevalence of arrhythmic events declined from 9.6% to 5.8% after thrombolysis. Both the low positive predictive value (about 20%) and the high negative predictive value (97%) remained unchanged (Savard et al, 1997).

Percutaneous coronary interventions (PCIs) are associated with a significant reduction of the prevalence of LVPs (Santangeli et al, 2008). Bauer et al. showed that LVPs were significantly associated with SCD (Bauer et al, 2005). Ikeda et al. reported no significant prognostic role of LVPs for SCD/resuscitated cardiac arrest at a short-term follow-up of 3 to 6 months, but LVPs were independent predictors of sustained VT (Ikeda et al, 2002).

Reperfusion of severely ischemic myocardium may also lead to hemorrhages in the infarct core by extravasations of red blood cells through the damaged endothelium (Mather et al, 2010). The presence of hemorrhage was associated with a prolonged SA-QRS in patients with first ST-elevation acute MI, treated successfully with PCIs.

LVPs persist in patients not undergoing reperfusion, and may be caused by ventricular remodeling, involving fibrosis, redistribution of the fibers in the damaged region and one side left ventricular hypertrophy (LVH).

9. Cardiomyopathies

Cardiomyopathies are an important cause of SCD in young people.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is an inherited myocardial disease, characterized by fibro-fatty substitution of the right ventricle (Corrado & Thiene, 2006). The fibro-fatty areas can create reentry circuits, the substrate for repetitive ventricular arrhythmias and a delayed, fragmented activation front (Folino et al, 2006). The typical clinical manifestations are ventricular arrhythmias with left BBB pattern. LVPs were observed in more than 50% of patients with ARVC, and are minor diagnostic criteria in this setting (Santangeli et al, 2008). SAECD has shown particular reliability in ARVC, considering the classical location of the myocardial alterations in the right ventricle, which induce a delayed potential only in the terminal portion of QRS (Folino et al, 2006). Folino et al. (Folino et al, 2006) detected a progressive increase in delayed ventricular conduction, not associated with significant echocardiographic changes in patients with ARVC, and concluded that the baseline SAECD and echocardiographic parameters are useful in identifying patients with sustained VT. It was, also, hypothesized that the progression of the disease with an extension of fibro-fatty degeneration could completely isolate some infiltrated areas, with appearance of different preferential pathways of activation and reduction in late potentials (Folino et al, 2006).

A close correlation was found between SAECD and extent of disease (Nava et al, 2000). Turrini et al, found an increased percentage of fibrous tissue and a high risk for sustained ventricular arrhythmias in patients with LVPs and ARVC (Turrini et al, 1999). The sensitivity of SAECD for diagnosis of ARVC increased by using only 1 of 3 criteria (Kamath et al, 2011).

Santangeli et al (Santangeli et al, 2010) tested the association between noninvasive diagnostic criteria for ARVC and low voltage areas, detected at electroanatomic voltage mapping. SAECD abnormalities correlated with the presence of low voltage areas selectively in the right ventricular outflow tract, supporting the appropriateness of its inclusion among ARVC diagnostic criteria.

The prediction of sudden cardiac death is a major goal in the management of patients with **hypertrophic cardiomyopathy** (Cripps et al, 1990). Abnormal SAECGs were more prevalent in patients with hypertrophic cardiomyopathy compared to healthy controls, and were significantly associated with nonsustained VT on 48 h ECG Holter monitoring, but not with a family history of premature sudden cardiac death or a history of syncope (Cripps et al, 1990).

Fauchier et al. found a significantly higher incidence of severe ventricular premature beats in patients with **idiopathic dilated cardiomyopathy** (IDCM) and late ventricular potentials (Fauchier et al, 1991). Ohnishi et al. (Ohnishi et al, 1990) and Mancini et al. (Mancini et al, 1993) mentioned a high incidence of prospective arrhythmias and SCD in patients with a IDCM and abnormal SAECG. Kitamura et al (Kitamura et al, 2003) concluded that the heterogeneous expression of connexin 43 protein may contribute to impaired ventricular conduction and LVPs detected on SAECG in patients with IDCM. Patchy interstitial fibrosis adjacent to viable myocardium is commonly seen in dilated cardiomyopathy. Fibrosis decreases electrical coupling, slows the propagation of impulses between myocytes and can become the anatomical substrate for reentrant VT. Alterations of the gap junctions are accompanied by discontinuity of tissue structure, which includes the naturally occurring myocardial cell orientation and the collagen matrix formed by the fibrosis (Kitamura et al, 2003). The expression of connexin 43 was more decreased in patients with late ventricular potentials than in those without LVPs (Kitamura et al, 2003), but the degree of fibrosis seem not to influence the results.

10. Congenital heart defects

The predictive value of LVPs after repair of tetralogy of Fallot has been controversial. Al Balkhi et al. reported LVPs only 1 month after surgery in patients with tetralogy of Fallot, probably as a result of scarring (Al Balkhi et al, 2004). Zimmermann et al. found a correlation between inducibility of VT and LVPs (Zimmermann et al, 1991), but Giroud et al (Giroud et al, 1994) and Daliento et al. (Daliento et al, 1995) could not demonstrate a predictive value of LVPs alone in their studies. Janousek et al. found LVPs, and especially RMS40, to be predictive of spontaneous or induced VT in patients who underwent surgical correction of congenital cardiac disease (Janousek et al, 1995).

11. Heart failure (HF)

Patients with HF have a high SCD risk, despite therapeutic advances. Ventricular arrhythmias and SCD result from an interaction between a trigger and a substrate with neurohumoral factors (Bounhoure et al, 2010). The identification of the mechanisms of SCD in patients with HF is complicated by the different causes of HF. SCD risk correlates with the severity of congestive HF (Wilson et al, 1983). The high electrical instability in patients with post-infarction HF is due to structural inhomogeneities: patchy areas of fibrous tissue interdigitating with viable myocardium and scars. Interstitial fibrosis and hypertrophy are frequently seen on endomyocardial biopsies in patients with congestive HF. This can result in complex electrophysiological changes: abnormal impulse conduction with slow ventricular activation, changes in the refractory period responsible for ventricular arrhythmias (Bounhoure et al, 2010; Galinier et al, 1996).

There are conflicting results regarding the predictive value of LVPs for ventricular arrhythmias in HF patients. Small patient population studies (Meinertz et al, 1985; Middlekauff et al, 1990; Silverman et al, 1995) did not find SAECG to be predictive for SCD or ventricular arrhythmias in chronic HF. The studies by Mancini et al. and Galinier et al. found that the SAECG identified patients with congestive HF at high risk for death and/or ventricular tachycardia (Manicini et al, 1993; Galinier et al, 1996).

According to current guidelines, most patients with left ventricular dysfunction and symptomatic HF may benefit from implanted devices and resynchronization therapy. It is important but difficult to identify patients at risk, and LVPs, combined with other electrocardiographic stratification methods, etiologic and clinical information, may help to select the candidates (Bounhoure et al, 2010).

12. Brugada syndrome

Brugada syndrome is characterized by abnormal repolarization in the right ventricle, detected as ST elevation in the right precordial leads, and depolarization abnormality, detected as right bundle branch block and LVPs (Morita et al, 2008). Repolarization heterogeneity within the epicardium of the right ventricular outflow tract seems to be the origin of reentry arrhythmia (Morita et al, 2007). A reduced sodium current, due to mutations of the sodium channel gene SCN5A, slows the conduction velocity and causes conduction abnormalities. Conduction abnormalities provide a substrate for the degeneration of polymorphic VT into VF (Meregalli et al, 2005).

LVPs have been found in patients with the Brugada syndrome and might be helpful to identify patients at a higher risk of life-threatening arrhythmic events (Ikeda et al, 2001; Santangeli et al, 2008).

Kutsuzawa et al. (Kutsuzawa et al, 2011) reported two patients with Brugada syndrome and hypokalemia induced lethal events. Normalization of serum potassium concealed the typical ECG pattern, but LVPs persisted even at 18-month follow-up.

SAECG can detect not only LVPs, but also conduction abnormalities within the QRS complex: fragmented QRS (multiple spikes within the QRS complex) (Morita et al, 2008). It is considered that delayed activation within a small mass of ventricular tissue could produce LVPs and delayed activation in a larger ventricular mass can cause multiple spikes within the QRS complex. Fragmented QRS predicts syncope and VF in patients with Brugada syndrome (Morita et al, 2008).

13. Syncope

In patients with syncope of unknown cause, SAECG, combined with patient history and other diagnostic tests, can help identify or exclude a mechanism of VT as a cause of the syncope (Gang, et al, 1986; Santangeli et al, 2008).

14. Atrial fibrillation and flutter

It was hypothesized that the chaotic atrial activation in atrial fibrillation causes false-positive LVPs, making the analysis of SAECG very difficult (Buckingham et al, 1993; Halimi et al, 1994). But, atrial fibrillation rarely creates problems with time-domain analysis of the SAECG (Fitzgerald et al, 1996; Halimi et al, 1994). LVPs analysis provides similar results in

atrial fibrillation and sinus rhythm, was concluded by Gottfridsson et al. (Gottfridsson et al, 2011) in a study including 82 patients with atrial fibrillation, undergoing electrical cardioversion, despite decrease of heart rate and prolongation of SA-QRS. Conflicting results were obtained by different authors, analyzing SAECG variables after cardioversion. Halimi et al (Halimi et al, 1994) mentioned significant changes of LAS40 and RMS40 after cardioversion. Buckingham et al (Buckingham et al, 1993) found no significant changes of SA-ECG parameters.

Atrial flutter waves occur during ventricular systole and mimic LVPs (Gatzoulis et al, 1993). In conclusion, atrial flutter can create significant errors in the automated time-domain analysis of the SAECG, and patients with atrial flutter should not undergo SAECG for postinfarction risk assessment (Fitzgerald et al, 1996).

15. Bundle branch block (BBB)

Increased QRS duration has been previously associated with increased mortality in patients with coronary heart disease and hypertensive patients (Brembilla-Perrot et al, 2001; Liew, 2011). Syncope and dizziness may be related either to atrio-ventricular conduction disturbances or to ventricular arrhythmias. On the other hand, the presence of intraventricular conduction defects interferes with the detection of LVPs (Brembilla-Perrot et al, 2001; Englund et al, 1995), and, thus, patients with BBB are often excluded from the SAECG studies. Therefore, the management of these patients needs special attention.

BBB decreased the specificity of the SAECG to predict VT risk in patients with dilated cardiomyopathy (Brembilla-Perrot et al, 1997). Among noninvasive parameters, only a prolonged SA-QRS (>165 ms) was a significant predictor of cardiac mortality (Brembilla-Perrot et al, 2001).

Delayed terminal conduction observed in incomplete right BBB may cause false positive LVPs (Manolis et al, 1997). In order to prevent false positive results, separate LVPs criteria were used for patients with BBB (Galinier et al, 1996).

16. Hypertension (HT)

A significant association has been demonstrated between hypertension and SCD (Yildirim et al, 2002). The risk of SCD due to ventricular arrhythmias was demonstrated by a prolonged QT interval or LVPs. The most important mechanisms by which HT predisposes to SCD are: the degree of left ventricular hypertrophy (LVH), interstitial fibrosis, myocardial or subendocardial scars, silent myocardial ischemia, diastolic dysfunction and disturbances in cardiac autonomic balance (Galinier et al, 1997; Kaftan AH & Kaftan O, 2000; Palatini et al, 1995; Yildirim et al, 2002). Coronary artery disease may interact with LVH in the genesis of ventricular arrhythmias and SCD (Galinier et al, 1997).

LVPs were found by several authors in HT (Brune et al, 1991; Vester et al, 1992). Galinier et al. (Galinier et al, 1992) and Franchi et al. (Franchi et al, 1992) found a greater prevalence of LVPs in subjects with eccentric LVH than in those with concentric hypertrophy. Non-sustained VT has been found to have a prognostic value in HT patients (Galinier et al, 1997). Vardas et al. (Vardas et al, 1994) and Palatini et al (Palatini et al, 1995) confirmed that a high prevalence of ventricular arrhythmias was associated with LVPs in HT patients. Only the E/A ratios were related to the presence of either LVPs or VT, and they were far lower in patients with LVPs (Palatini et al, 1995).

The initial reports of the Framingham Heart Study demonstrated the deleterious effect on survival of LVH (Kannel & Abbot, 1986; Levy et al, 1990). A downward trend in the prevalence of LVH was noticed in the last decades, which coincided with improved HT control (Priori et al, 2001). A lack of a relation between left ventricular mass and the occurrence of LVPs has been also reported by some authors (Panagides et al, 1990; Prisant et al, 1993; Rizzo et al, 2000).

Experimentally, LVH delays ventricular conduction and prolongs action potential duration. Electrocardiographic QRS duration and QT interval measures reflect these changes (Oikarinen et al, 2004). The increased QRS duration may be attributed to the increased thickness of the left ventricle wall and to intramural fibrosis, which distorts and prolongs transmural impulse propagation, or it could be a manifestation of intraventricular or interventricular conduction delay or block (Hancock et al, 2009). Alterations in ion channels due to hypertrophy were also mentioned as possible causes of QT interval prolongation in LVH (Hancock et al, 2009).

LVPs were present in both dippers and nondippers, and the values were significantly lower in dippers for SA-QRS and LAS40, and nondipper pattern was not linked to a worse arrhythmogenic substrate (Rizzo et al, 2000).

There is no study with power to show prognostic significance of LVPs in HT patients. All studies on LVPs in hypertensive patients have all been small scale, with short follow up.

17. Dyslipidemia and metabolic syndrome

The epidemiological association between elevated LDL cholesterol and risk of all manifestations of coronary artery disease including SCD is well established (Priori et al, 2001). A relation between **dyslipidemia** and electrical instability has been hypothesized. Gimaev et al. (Gimaev et al, 2009) evaluated the effect of disturbed lipid metabolism on SAECG characteristics and found LVPs in patients with high, moderately elevated, low and normal serum cholesterol. Hypercholesterolemia has been reported to induce proarrhythmic sympathetic neural sprouting and ventricular electrophysiologic remodeling, and an increased vulnerability to VF in a high-fat-fed animal model (Liu et al, 2003).

A significant correlation was found between serum cholesterol and SAQRS, LAS40 and RMS40 in patients with an old MI (Mozos & Hancu, 2010).

Clinical trials of lipid lowering in the primary prevention of coronary artery disease have not evaluated SCD risk, and have not sufficient statistical power to identify a significant reduction (Priori et al, 2001). Statins seem to have antiarrhythmic properties in addition to their lipid-lowering effects (Chu et al 2007; Abuissa et al, 2009).

Isolated **metabolic syndrome** is associated with an increase in left ventricular mass index and diastolic dysfunction, increasing the risk of cardiovascular disease (Aijaz et al, 2008). The prevalence of increased QT interval duration has been investigated with respect to single components of the metabolic syndrome (Strohmer et al, 2007).

18. Obesity

Patients with morbid obesity have high rates of sudden, unexpected cardiac death (Duflou et al, 1995). An increased prevalence of abnormal SAECG results has been found in obese patients without known clinical heart disease, and body mass index (BMI) can be considered as an independent predictor of abnormal SAECG results (Lalani et al, 2000). Mizia-Stec et al .

(Mizia-Stec et al, 2000) found an increased QT dispersion (QTd) in obese women, associated with LVH and significantly higher QTd in patients with late ventricular potentials.

The mechanism of death in these patients remains uncertain. Parasympathetic withdrawal, occurring with increasing obesity, conduction abnormalities, cardiomyopathy of obesity, the lipotoxicity of the myocardium induced by free fatty acids, released from hypertrophied adipocytes in obese persons with myocardial steatosis, structural heterogeneity due to fatty infiltration of the heart, myocyte hypertrophy, focal myocardial disarray, fibrosis and mononuclear cell infiltration could be involved (Alexander, 1985; Bharati & Lev, 1995; Duflou et al, 1995; Lalani et al, 2000). Particularly, with a concentric pattern of LVH, the prevalence of ventricular ectopic beats is substantially elevated in obese patients (Schunkert, 2002). The cardiomyopathy of morbid obesity, the most common cause of SCD in these patients, is characterized by cardiomegaly, left ventricular dilatation, and myocyte hypertrophy in the absence of interstitial fibrosis.

A BMI associated increase in chronic MI patients' SCD risk was mentioned by Mozos et al. and SAECG-QRS and LAS40 correlated with BMI in patients with an old MI (Mozos et al, 2007).

19. Diabetes mellitus and hyperglycemia

There is controversy in the literature as to whether glucose intolerance or diabetes mellitus are independent risk factors for SCD (Priori et al, 2001). Streptozocin experimentally induced diabetes impairs both depolarization and repolarization (Pacher et al, 1999). QT interval prolongation in diabetic patients has been attributed to autonomic neuropathy and insulin resistance, and in healthy non-diabetic subjects with high plasma glucose, to increased cytosolic calcium content, oxidative stress and enhanced sympathetic activity (Muntean et al, 2009).

Kowalewski et al. (Kowalewski et al, 2002) included 72 children with type 1 diabetes mellitus in his study and found an increased prevalence of abnormal SAECGs and LVPs. Diabetic children with LVPs had thicker left ventricular posterior wall and longer diabetes duration time than children without LVPs. Nonlinear regression model showed that duration of diabetes, cardiac autonomic neuropathy, and left ventricular posterior wall were the strongest independent parameters of LVPs occurrence.

An association between hyperglycemia on admission in patients with acute ST elevation MI and arrhythmias during hospitalization has been observed (Sanjuan et al, 2011). Stress hyperglycemia on admission was found to be a predictor of mortality and arrhythmias in patients with acute ST elevation MI and could be used in the stratification of risk in these patients (Pinto et al, 2008; Sanjuan et al, 2011).

20. End-stage renal failure and hemodialysis

Cardiac disease is the major cause of death in dialysis patients (Herzog et al, 2008). LVH with interstitial fibrosis, deposition of calcium and aluminum salts in the heart tissue often occur in patients with end-stage renal disease (ESRD) (Morales et al, 1998). Autonomic neuropathy and impairment of left ventricular functions have been frequently encountered in chronic renal failure and depend on the disease duration (Karayaylali et al, 2003). SCD risk due to ventricular arrhythmias is high in ESRD patients on hemodialysis (HD) (Dubrava et al, 2003; Sakhuja et al, 2009). SAECG parameters are abnormal in a significant

proportion of patients with chronic renal failure (Girgis et al, 1999). The mentioned histological changes could represent a potential substrate for LVPs. LVH was already considered as SA-QRS prolonging factor in hypertensive patients (Vester et al, 1992) and associated with a high prevalence of LVPs in post-infarction HF patients (Mozos et al, 2009). This explanation appears unlikely in renal failure. Morales et al. did not detect significant differences in left ventricular mass between end-stage renal failure patients with and without late ventricular potentials before HD (Morales et al, 1998). Roithinger et al. did not find a significant association between mortality and LVPs or structural myocardial changes in HD patients, but a tendency towards an excess mortality of patients with coronary artery disease and compromised left ventricular function (Roithinger et al, 1992). On the other hand, Girgis et al. concluded that SAECG parameters improve with HD, and, decreased left ventricular dimensions, because of fluid removal during HD, (Girgis et al, 1999).

Volume, electrolyte, acid-base balance, heart rate and blood pressure changes appearing during HD, can trigger supraventricular and ventricular arrhythmias (Dubrava et al, 2003; Morales et al, 1998). Most of the studies performed in HD patients have focused on QRS amplitude and T wave (Morales et al, 1998). Abnormalities in SAECG were also mentioned in patients undergoing HD and peritoneal dialysis (Girgis et al, 1999; Ichikawa et al, 1997; Morales et al, 1998; Roithinger et al, 1992).

The prevalence of late ventricular potentials was 25% in the study of Morales et. al (Morales et al, 1998), including patients with a known history of myocardial infarction, and only 14% in another study including younger patients, with a lower prevalence of coronary heart disease (Roithinger et al, 1992). Ichikawa et al reported no LVPs before HD and abnormal SAECGs in only 2.4% of the patients (Ichikawa et al, 1997). Late ventricular potentials were attributed to underlying coronary heart disease with left ventricular dysfunction (Morales et al, 1998). Most of the studies reported improved SAECGs after HD.

Morales et al and Ichikawa et al reported a prolongation of SA-QRS duration after dialysis (Ichikawa et al, 1997; Morales et al, 1998), probably due to widening of the initial portion of the QRS, related to the acute reduction in serum potassium (Morales et al, 1998). Girgis et al. showed that only LAS40 and RMS40 change significantly after hemodialysis (Girgis et al, 1999). LAS40 was also significantly increased postdialysis in a study of Ichikawa et al, and the changes in LAS40 correlated with the changes in potassium in the high-K group (Ichikawa et al, 1997). Larger studies are needed to verify the effect of HD on time-domain SAECG parameters.

Animal studies demonstrated that hypokalemia-induced arrhythmogenicity is due to slowed conduction, prolonged ventricular repolarisation (caused by inhibition of outward potassium currents) and abnormal pacemaker activity (Osadchii, 2010). Hypokalemia effect on repolarisation is not uniform, causing amplified spatial repolarisation gradients and an unidirectional conduction block (Osadchii, 2010). Prolongation of action potential may be associated with shortening of the effective refractory period, facilitating reentry. Serum potassium between 4.6 and 5.3 mEq/l was associated with best survival in HD patients, and potassium <4 or ≥5.6 mEq/l was associated with increased mortality (Kovesdy et al, 2007). An insufficient decrease of serum potassium by hemodialysis was suggested to be an arrhythmogenic factor (Ichikawa et al, 1997).

21. Alcoholism

Acute alcoholic states, binge drinking, the “holiday heart syndrome” and liver cirrhosis are associated with prolonged QT intervals and an increased prevalence of cardiac arrhythmias

and SCD (Day et al, 1993; Genovesi et al, 2008; Wever & Robles de Medina, 2004;). In contrast, case-control studies have demonstrated a protective effect of moderate alcohol consumption against sudden cardiac death (Priori et al, 2001; Vreede-Swagemakers et al, 1999). Alcohol inhibits the Na-K-ATPase, which alters the resting membrane potential, delays calcium binding and transport by the cardiac sarcoplasmic reticulum and impairs calcium channels (Lorsheyd & de Lange, 2005).

Life-threatening ventricular arrhythmias are found in alcoholics without heart disease (Moushmoush et al, 1991). Alcoholic cardiomyopathy is associated with localized delays in intraventricular conduction and nonuniform myocardial involvement (Luca, 1979).

Koskinen & Kupari did not find LVPs in chronic alcoholics without detectable heart disease (Koskinen & Kupari, 1993). The absence of LVPs does not exclude nonuniformity of alcohol induced myocardial changes.

Chronic heavy alcohol consumption increases left ventricular mass and may cause subclinical impairment in left ventricular function (Luca, 1979).

Pochmalicki et al. found LVPs in chronic alcoholics (Pochmalicki et al, 1997) and concluded that chronic alcohol intake, sufficient to cause histologically significant fatty liver, is associated with LVPs. LVPs could reveal early, preclinical myocardial lesions, and help to identify alcoholic patients at high risk of lethal arrhythmias.

22. Chronic obstructive pulmonary disease (COPD)

COPD is an independent risk factor for cardiovascular morbidity and mortality (Celli et al, 2010). Potential explanations for this association include: smoking, negative cardiac consequences of dynamic hyperinflation, exercise limitations and hypoxemia (Celli et al, 2010; Priori et al, 2001).

Carjea (Carjea, 2003) studied the prevalence and characteristics of late ventricular potentials in 90 patients with COPD compared to healthy subjects and found significant differences. The highest prevalence was noticed in moderate to severe cases.

23. Acromegaly

The heart is an end-organ of growth hormone action. A high prevalence of complex ventricular arrhythmias has been mentioned in patients with acromegaly, possible as a result of disordered left ventricular architecture and ventricular remodeling (Clayton, 2003).

The frequency of premature ventricular complexes increased with duration of acromegaly, and the severity of arrhythmia correlated with left ventricular mass but not with growth hormone levels (Kahaly et al, 1992). Structural heterogeneity in acromegalic heart is due to areas of hypertrophied myocytes, separated by fibrosis and cellular infiltrations (Clayton, 2003). Late ventricular potentials are frequently seen in active acromegaly, are associated with disease activity and may represent an early and sensitive parameter to detect myocardial injury (Herrmann et al, 2001). No association was found between presence of late ventricular potentials and left ventricular mass index. Longitudinal studies are needed to determine whether therapy changes the electrophysiological abnormalities.

Earlier studies showed that arrhythmias were as frequent before and after treatment of acromegaly, implying that fibrous tissue infiltration caused irreversible scarring (Hayward et al, 1987; Rodrigues et al, 1989).

24. Thalassemia

Beta-thalassemia, the impaired production of the beta hemoglobin chain, is associated with significant changes in heterogeneity of cardiac ventricular repolarization and SCD (Russo et al, 2011). In the late stages, frequent premature ventricular contractions and sustained ventricular tachycardia have been mentioned, related to cardiac death. Thalassemia patients require intensive blood transfusions due to severe anemia, and an increase in body iron burden occurs both in patients who are or are not receiving transfusions (Lekawanvijit & Chattipakorn, 2009).

The role of iron overload in causing conduction delays in the thalassemic heart is well documented and iron overload thalassemic cardiomyopathy may explain the occurrence of LVPs (Isma'eel et al, 2007), as well as changes in QRS duration and RMS40 voltage. The patchy nature of cardiac iron deposition may provide substrates for re-entry and risk of fatal arrhythmias (Lekawanvijit & Chattipakorn, 2009). Iron-overloaded cardiomyocytes have a smaller overshoot potential and shorter action potential duration than iron-free cardiomyocytes in the same heart and reduced Na^+ currents may be an underlying mechanism (Lekawanvijit & Chattipakorn, 2009). Further mechanisms related to tachyarrhythmias and SCD are changes in calcium homeostasis, elevated prostaglandin E2 to prostacyclin ratio, increased interleukin 1 level and lipid peroxidation.

Future large populations, long-term follow-up studies are needed to demonstrate further clinical consequences in iron overload cardiomyopathy.

25. Connective tissue and systemic diseases

Cardiovascular involvement is common in connective tissue diseases (Lazzerini et al, 2006), but myocardial involvement is seldom recognized clinically (Stanescu & Dan, 1992). Ventricular arrhythmias represent a major cause of SCD in autoimmune rheumatic diseases (Sefarovic et al, 2006). The mechanisms are probably multiple and myocardial fibrosis seems to play a pivotal role (Lazzerini et al, 2006). Lazzerini et al (Lazzerini et al, 2007) concluded that anti-Ro/SSA positive patients have a particularly high risk of developing ventricular arrhythmias.

The heart is one of the major organs involved in scleroderma. Ventricular arrhythmias are common among asymptomatic patients with **systemic sclerosis**, especially: premature ventricular contractions and non-sustained VT (Sefarovic et al, 2006). Patchy myocardial fibrosis represents an ideal substrate for reentry tachyarrhythmias. LVPs occurred in patients with diffuse progressive systemic sclerosis; a lower myocardial involvement was noticed in the CREST syndrome (Paradiso et al, 1996). Diffuse abnormalities of the cardiac tissue detected by SAECG may be present in patients with systemic sclerosis without cardiac symptoms and higher skin scores correlated with the presence of LVPs (Paradiso et al, 2002). Pignone et al (Pignone et al, 1994) found no correlation between LVPs and immunologic patterns, cutaneous and pulmonary involvement in 26 patients with systemic sclerosis.

Myocardial lesions in **systemic lupus erythematosus** are characterized by an increase in interstitial connective tissue and myocardial scarring (Paradiso et al, 2001). The most important cardiac manifestations of systemic lupus erythematosus are: pericarditis, lesions of valves, myocardium and coronary artery disease (Gomez-Leon Manduiano & Amezcua-Guerra, 2008). Sinus and atrial arrhythmias are more prevalent, but QT interval

prolongation, abnormalities in the autonomic tone and LVPs indicate high risk of developing life-threatening ventricular arrhythmias (Sefarovic et al, 2006). LVPs were recorded in patients with systemic lupus (Paradiso et al, 2001; Wranicz et al, 2001), and the depolarization abnormalities revealed by SAECG reflect a longer extent of myocardial fibrosis and echocardiography and SAECG alterations are markers of subclinical myocardial involvement. Increasing evidence suggest that anti-Ro/SSA antibodies may trigger rhythm disturbances due to an inhibiting cross-reaction with several cardiac calcium and potassium ionic channels (Lazzerini et al, 2010).

So far, the evidence related to electrocardiographic disturbances in this setting is restricted to studies with small number of patients (Teixeira, et al, 2010). The mechanisms of arrhythmias are related to the inflammatory process of pericarditis and myocarditis, atherosclerotic myocardial ischemia, increased sympathetic activity, vasculitis of small vessels with collagen deposits and anti-Ro/SSA antibodies (Lazzerini et al, 2010; Teixeira, et al, 2010).

Cardiac **sarcoidosis** affects the myocardium, pericardium and endocardium, and the disease may present with: atrioventricular and intraventricular conduction disturbances, ventricular arrhythmias and HF. Ventricular arrhythmias are among the main causes of SCD in cardiac sarcoidosis. LVPs on SAECG were mentioned and they were abolished after steroid therapy (Yodogawa et al, 2011).

26. Schizophrenia

Schizophrenia patients were also found to be positive for LVPs. Cardiac autonomic dysregulation in schizophrenia patients and use of psychiatric and/or non-psychiatric medications that affect conduction, may account for LVPs (Nashoni et al, 2010).

27. Influence of therapy on LVPs

LVPs are influenced by antiarrhythmic therapy, trombolytic drugs, anevrismectomy, percutaneous coronary interventions, coronary artery bypass surgery, statins, steroids.

The effect on the prevalence of LVPs of modern pharmacologic therapy in patients with acute MI has been assessed in several studies (Santangeli et al, 2008). Class I, II and III antiarrhythmics may reduce the prevalence of LVPs. Class IV antiarrhythmics (Verapamil) do not influence LVPs. Some class III antiarrhythmic drugs are able to prolong SA-QRS and LAS40, and may be associated with the occurrence of LVPs.

Freedman and Steinberg showed that sodium channel blockers (quinidine, procainamide, imipramide) have preferential effects on slowly conducting tissue in patients with a history of VT, causing an important prolongation of LVPs (Freedman & Steinberg, 1991).

Santarelli et al, reported that LVPs were less frequent in acute MI patients treated with betablockers compared with those not treated with betablockers during hospitalization. This effect was found only in patients with a preserved LVEF (Santarelli et al, 1993).

No significant SAECG changes have been observed after Sotalol.

Adrenergic stimulation with adrenaline and isoprenaline, and parasympatholytic agents such as atropine, lead to significant changes in the signal averaged electrocardiogram in healthy subjects (Goldberger et al, 1994). Beta-adrenergic stimulation with isoproterenol led to a significant shortening of SA-QRS, and epinephrine prolonged the QRS duration. Increased alfa-adrenergic stimulation with phenylephrine and parasympathetic stimulation

did not affect the SAECG. Parasympathetic blockade caused a mild decrease in the QRS duration. Changes in the RMS40 and LAS40 paralleled those of the QRS duration (Goldberger et al, 1994).

Junker et al, found in a substudy of the CONSENSUS II trial, a reduced prevalence of LVPs after the angiotensin converting enzyme inhibitor enalapril (Junker et al, 1995).

Lipid-lowering interventions reduce coronary events, VT/VF episodes, SCD and all-cause mortality (Liu et al, 2009). Recent studies have demonstrated that statins have antiarrhythmic properties in addition to their lipid-lowering effects (Abuissa et al, 2009; Chu et al 2007; Liu et al, 2009). Kayikcioglu et al. found a significant decrease of the prevalence of LVPs and ventricular arrhythmias in acute MI patients receiving pravastatin, irrespective of lipid level (Kayikcioglu et al, 2003). Pre-treatment with statin could reduce the reperfusion arrhythmias after acute myocardial infarction (Zhao et al, 2008). Most of the antiarrhythmic benefits after statin therapy observed in high cardiovascular risk patients might be explained by statins' pleiotropic effects: anti-ischemia, anti-inflammation, antihypertrophy, angiogenic and sympathetic effects (Chu et al, 2007). Statins achieve their antiarrhythmic drug action in part by preventing or reversing electrophysiologic remodeling induced by hypercholesterolemia, but they also have an independent antiarrhythmic effect (Liu et al, 2009).

The ratio between QTc and QRS changes caused by several antiarrhythmic drugs identifies patients with sustained VT risk, which appear despite therapy (Cain et al, 1996).

LVPs may disappear after coronary artery bypass surgery in acute MI patients (Bigger et al, 1997). Aneurisectomy is also known to reduce the prevalence of LVPs.

Corticosteroid therapy may be effective for ventricular arrhythmias in the early stage of cardiac sarcoidosis (Yodogawa et al, 2011).

28. Correlation and combination with other ECG methods

Several studies have mentioned correlations between surface standard 12-lead ECG and SAECG parameters. The relation between LVP and **QT dispersion** (QTd) (Ducceschi et al, 1996; Mozos, 2006), suggested that the existence of some slow conducting myocardial areas, related to positive LVPs, is associated with a higher inhomogeneity of ventricular repolarisation, expressed as a higher QTd. LAS40 and SA-QRS correlated with QT dispersion (Ducceschi et al, 1998).

QT intervals and Tpeak-Tend intervals were prolonged in post-infarction HF patients with LVPs. LVPs and SAECG parameters can be predicted using 12-lead ECG: QT intervals, QRS duration, T wave variables (Mozos et al, 2011). The significant association between SA-QRS and Tpeak-Tend interval and T wave amplitude was attributed to the extension of LVP into the ST segment.

Breithardt et al. (Breithardt et al, 1990) showed that the presence of LVPs was positively correlated with an **ECG score** based on R and Q wave duration and R/S ratio in MI patients with or without a history of sustained VT.

LVPs were not related to the frequency of **ventricular ectopic activity** and malignant premature ventricular contractions because each test assesses different components of arrhythmia susceptibility. The combination of the two abnormalities may identify a high-risk group for SCD (Middelkauff et al, 1990; Fauchier et al, 1991).

The combination of **T wave alternans** and SAECG, increases sensitivity, specificity, positive and negative predictive value for VT risk (Kondo et al, 2001).

SAECG and **body surface mapping** (BSM) provide complementary information in patients with an old MI, and an important, significant correlation was found between isointegral QRST maximum and LAS40 and RMS40 (Mozos et al, 2008). SAECG may be assessed using BSM, increasing its sensitivity in anterior and inferior MI (Ho, 1993). BSM may detect LVPs, undetected by SAECG, even if the underlying substrate is relative small or the electrodes are placed outside that area (Linnenbank et al, 2001). Analysis of isopotential maps of the terminal part of the QRS complex may provide additional information regarding LVPs distribution, slow conducting areas and VT origin (Faugere et al, 1986).

29. LVPs and other ventricular arrhythmia predictors

Despite the significant predictive value for arrhythmic events, LVPs show a low positive predictive accuracy, thus resulting in limited usefulness as a single variable to identify patients at high risk (Santangeli et al, 2008). Significantly impaired LVEF is an established predictor of SCD and is included in the current guidelines for primary prevention of SCD. But patients with a preserved LVEF are not included in the current guidelines (Liew, 2011).

Combination of LVPs with LVEF (Jain & Avasthi, 1992; Konta et al, Kudaiberdieva et al, 2003), ventricular volumes (Pollak et al, 1985), heart rate variability (Gomes et al, 2001), ventricular dyskinesia (Olinic & Zdrenghea, 1998), programmed ventricular stimulation (Ho et al, 1996), atrial pacing (Steinbigler et al, 1999), a high Killip class (3 or 4) in a patient with a history of a MI, may improve the predictive value of LVPs for ventricular arrhythmias.

Kudaiberdieva et al (Kudaiberdieva et al, 2003) investigated incidence of ventricular tachycardia/ventricular fibrillation in relation with noninvasive arrhythmia risk markers in 54 patients with an old myocardial infarction. Logistic regression analysis revealed that the highest association with ventricular tachyarrhythmia had combination of LVPs and increased QT variability index, followed by combination of LVPs and left ventricular ejection fraction.

Standard methods fail to reveal late potentials in 20 to 30% of patients with ventricular arrhythmias after myocardial infarction (Steinbigler et al, 1999). Increase in heart rate may unmask late potentials in patients prone to malignant ventricular arrhythmias, because conduction in the arrhythmogenic area is critically slowed by an increased heart rate. Functional late potential analysis, with non-invasive clinical stress tests, should be performed in order to identify patients at risk of malignant ventricular arrhythmias, not identified with conventional late potential analysis (Steinbigler et al, 1999).

Epicardial mapping has demonstrated that during sinus rhythm, activation of the tissue critical to ventricular tachycardia is completed before the end of the QRS complex and is not detectable within the ST segment (Steinbigler et al, 1999). A shift of septal mid-QRS potentials toward the terminal QRS complex by critical slowing of conduction during increased heart rate, could explain the appearance of new late ventricular potentials. Different findings may be due to myocardial infarction location: an increase of QRS duration in patients with anterior infarction and an increase of magnitude and LAS40 in patients after inferior infarctions (Steinbigler et al, 1999).

Combining electrocardiography methods with other methods may help to select the candidates for pharmacological therapy, defibrillator implantation and resynchronization, in order to reduce overall mortality and SCD.

30. Conclusions

Sudden cardiac death, caused mainly by fatal ventricular arrhythmias, can be predicted using a practical and low-cost tool: SAECCG. LVPs represent slowed conduction through a diseased myocardium and may form the substrate for life-threatening ventricular arrhythmias in patients with cardiac and extracardiac pathology. SAECCG is altered due to a variety of physiological and pharmacologic conditions. Antiarrhythmic therapy, thrombolytic drugs, aneurysmectomy, percutaneous coronary interventions, coronary artery bypass surgery, statins and steroid therapy are able to influence LVPs. Late ventricular potentials have a high negative predictive value. When positive, LVPs help better stratify the arrhythmic risk of patients, alone or in combination with other methods, in several clinical settings.

31. References

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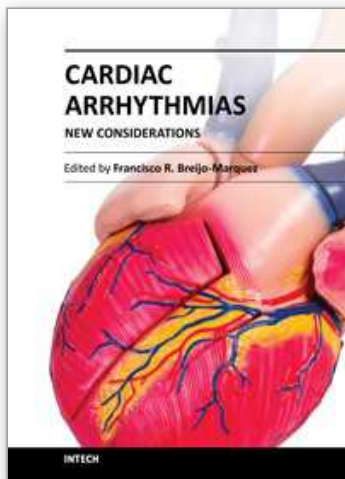
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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographic features, ion channel alterations, heart diseases still unknown, and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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University Campus STeP Ri
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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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Phone: +86-21-62489820
Fax: +86-21-62489821

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