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Signal-Averaged ECG: Basics to Current Issues

Ioana Mozos and Dana Stoian

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<http://dx.doi.org/10.5772/intechopen.69279>

Abstract

Signal-averaged ECG (SAECG) is a high-resolution, noninvasive electrocardiographic method enabling detection of late ventricular potentials (LVP), which are low-amplitude and high-frequency signals, predicting reentry ventricular arrhythmias, and sudden cardiac death (SCD). Three criteria are used to detect late ventricular potentials as follows: signal-averaged ECG QRS duration (SAECG-QRS), the duration of the terminal part of the QRS complex with an amplitude below 40 μV (LAS40) and the root mean square (RMS) signal amplitude of the last 40 ms of the signal < 20 μV (RMS40). Late ventricular potentials can be detected not only at the end of a QRS complex but also as intra-QRS (IQRS) potentials. Signal-averaged ECG was modified to enable the analysis of the P-wave and to detect atrial late potentials (ALPs), low-amplitude potentials at the terminal part of the filtered P-wave, and predictors of atrial fibrillation (AF). Late atrial and ventricular potentials originate from areas of delayed, fragmented, and heterogeneous conduction within atrial or ventricular myocardium. This chapter reviews the most important mechanisms explaining the occurrence of late ventricular, intra-QRS, and atrial potentials; their predictive value for arrhythmia, focusing on recent clinical data, long-term follow-up, and outcome; and analysis of SAECG variables in cardiac and noncardiac diseases.

Keywords: late ventricular potentials, atrial late potentials, ventricular arrhythmia risk, atrial fibrillation

1. Introduction

Cardiovascular disorders are leading mortality causes worldwide. Prophylactic methods and early detection deserve special attention. The standard 12-lead electrocardiogram (ECG) is a simple, reliable, and cost-effective method, used in clinical practice and trials for sudden cardiac death (SCD) risk stratification, considering QT and QRS duration, fragmented QRS complexes, and Tpeak-tend interval. Signal-averaged ECG (SAECG) can detect very small, subtle signals (microvolt level), which are not visible when using standard 12-lead ECG, by

averaging and filtering multiple ECG complexes [1–3]. The high-resolution or signal-averaged ECG has been recommended by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology as a useful tool to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or those at risk of developing life-threatening ventricular arrhythmias [4].

The substrate for SCD varies from advanced cardiomyopathic injuries, myocardial infarction scars to no obvious sign of structural damage [4]. The most common cause of SCD is coronary heart disease, but several cardiomyopathies, heart failure, and genetic influences, as well as myocarditis, pericardial diseases, pulmonary arterial hypertension, rheumatic disease, end-stage renal failure, endocrine disorders, obesity, anorexia, hypertension, lipid abnormalities, diabetes mellitus, several drugs, and physical and toxic agents can also be involved [4]. Several inherited abnormalities, including long and short QT interval, Brugada syndrome, and catecholaminergic ventricular tachycardia (VT), can precipitate SCD without any structural changes in the heart, triggered by external events [4].

Atrial fibrillation (AF) is the most frequent arrhythmia in the general population, with poorly understood underlying mechanisms of structural and electrical atrial remodeling [5]. It is associated with an increased risk of stroke, heart failure, and mortality [5].

The aim of this chapter is to review the most important mechanisms explaining the occurrence of late ventricular, intra-QRS (IQRS), and atrial potentials; their predictive value for arrhythmia, focusing on recent studies, long-term follow-up, and outcome; and analysis of SAECG variables in cardiac and noncardiac diseases.

2. Late ventricular potentials

LVPs are low-amplitude, high-frequency signals, occurring in the terminal part of the QRS complex, as markers of electrophysiological cardiac substrates for reentry ventricular arrhythmia, favored by structural heterogeneity due to myocardial necrosis, fibrosis, or dystrophy [6]. LVPs appear if conduction is slow enough to enable reentry and a unidirectional block is present [6]. They assess ventricular depolarization, and the signal is more stable and reproducible than the repolarization process [6]. Arrhythmia triggers are autonomic imbalances (increased sympathetic activity), acute ischemia, or electrolyte disorders. Temporal and frequency domain analysis can be performed to detect arrhythmia risk.

Three criteria are used to detect LVPs as follows: SAECG-QRS duration, the duration of the terminal part of the QRS complex with an amplitude below $40\ \mu\text{V}$ (LAS40), and the root mean square signal amplitude of the last 40 ms of the signal $< 20\ \mu\text{V}$ (RMS40) [7].

SAECG-QRS was considered prolonged if it exceeds 120 [7] or 114 ms according to other authors [8, 9]. LAS40 is pathological if exceeding 38 ms and RMS40 if less than $20\ \mu\text{V}$ [7]. Late

ventricular potentials are defined by the presence of one or two of the mentioned positive criteria (**Figures 1, 2**) [7, 10].

Considering their low amplitude, LVPs can only be detected if amplified, filtered, and averaged using high-resolution SAECG or body surface mapping. Electronic filters can further reduce signal noise by eliminating high-frequency signals such as skeletal muscle potentials [3]. The filters used in SAECG provide different numerical and diagnostic results, with a higher sensitivity for 40–250-Hz filters compared to 40-Hz filters [1]. The authors of the present chapter have experience only with 50–250 Hz filters. ECG signals are collected for 5–20 min, followed by averaging the QRS complexes through the temporal technique to reduce the signal-to-noise ratio [3].

The most important limitations in SAECG are related to electrical interference causing false results and the low positive predictive value for arrhythmic events [6, 11, 12]. However, they have a high negative predictive value for arrhythmic events [12]. Their presence predicts inducibility of ventricular tachycardia at invasive electrophysiology studies, and if they are combined with low ejection fraction, they enable detection of patients at high risk of sudden cardiac death [3].

Besides time-domain (TD) analysis of SAECG, frequency domain analysis may also provide valuable data. Abrupt changes in the frequency contents between adjacent overlapping segments of the QRS complex are the markers of the arrhythmogenic substrate in spectral turbulent analysis (STA) [13].

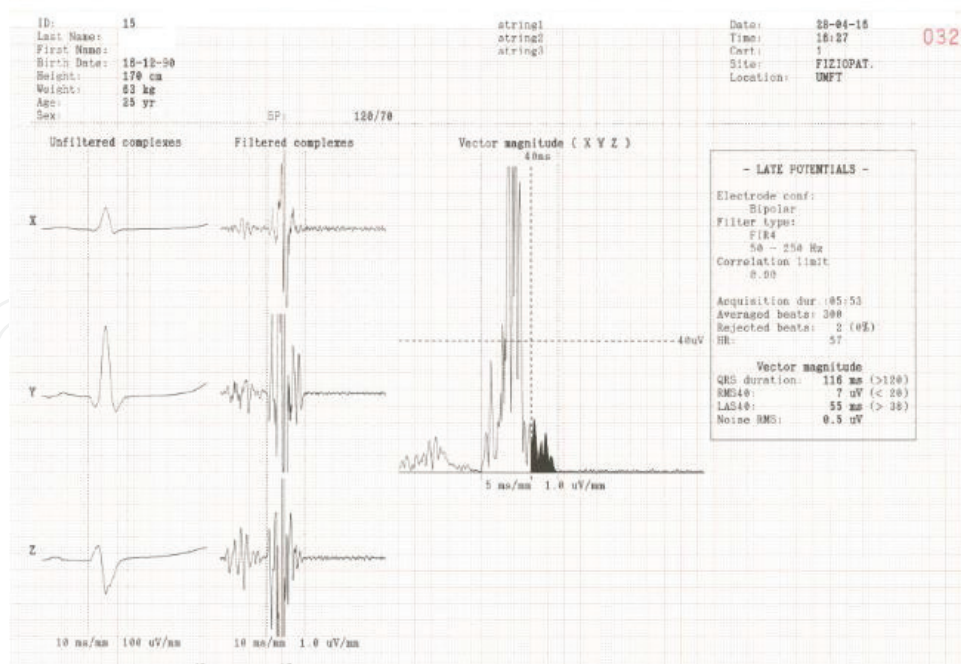


Figure 1. Late ventricular potentials with two positive criteria (LAS40 and RMS40).

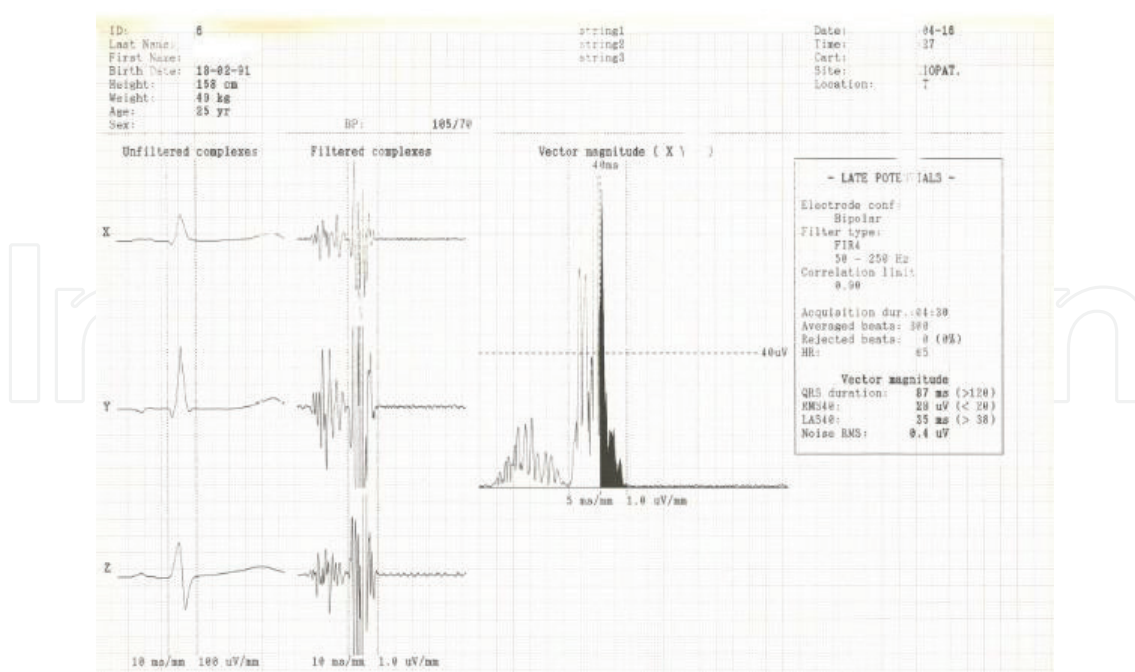


Figure 2. Normal SAECD and no late ventricular potentials.

The sensitivity of SAECD is higher compared to standard 12-lead ECG for identifying patients with acute coronary syndrome [14]. LVPs were initially used in patients with myocardial infarction. They appear in the heterogenous tissue at the border of a myocardial infarction scar [6], very frequent in nonseptal myocardial segments, and were abolished in most patients with myocardial infarction after ventricular tachycardia ablation, associated with scar homogenization and a low recurrence rate [15]. The utility of SAECD was questioned in the post-percutaneous coronary intervention era [3]. LVPs have been recorded in several other cardiac disorders, especially cardiomyopathies, myocarditis, infiltrative heart disease, arrhythmogenic right ventricular dysplasia, congenital heart defects, heart failure, left ventricular hypertrophy, Brugada syndrome, early repolarization, bundle branch block, and atrial fibrillation [6, 16–18]. Despite improved postinfarction survival due to lifestyle changes, thrombolytic, antiplatelet therapy, beta-blockers, and revascularization, LVPs can still be used in selecting patients for interventional studies [6]. Dinov et al. [19] found a positive correlation between endocardial scar area and filtered QRS in patients with ischemic VT, normalization of SAECD after catheter ablation (CA), and abnormal SAECD after CA as a predictor for VT recurrence (**Table 1**). Conduction delay contributed to ventricular dyssynchrony, regardless of LVPs in patients with heart failure, and LVPs did not play an important role in ventricular dyssynchrony [16]. Several SAECD studies have been performed in patients who underwent heart transplant [20–22]. SAECD distinguished between heart transplant patients with or without rejection, especially LAS40 and RMS40 [22]. The association between LVPs and rejection of heart transplant is explained by occurrence of areas of myocardial fibrosis, due to cell changes caused by alloreactive T lymphocytes against graft antigens and ischemia-reperfusion injuries as soon as the blood flow is reestablished [22].

Study population	Results	Follow up	References
52 psychiatric patients 30 healthy controls	The prevalence of LVPs was significantly higher in psychiatric patients, not influenced by age, gender, and therapy	46 months, 3 SCD	Antoniou et al. [28]
50 patients with ischemic VT undergoing CA	A significant correlation was found between the surface SAECD and endocardial scar size in patients with ischemic VTs. A successful CA can result in normalization of SAECD and more favorable long-term outcomes. SAECD can predict the procedural success of VT ablation		Dinov et al. [19]
28 heart transplant patients	The presence of fibrosis with increased LAS40 and decreased RMS40 showed a good ability to distinguish between patients with and without rejection		Mendes et al. [22]
100 postmyocardial infarction patients undergoing electroanatomical mapping-based VT ablation	LVPs were abolished in 51% improving outcome		Tsiachris et al. [15]
41 patients with COPD and 63 patients without any history of pulmonary disease, matched for age and hypertension history	SAECD parameters and LVPs have little value in risk stratification for ventricular arrhythmias in COPD patients		Buzea et al. [27]
26 patients with newly diagnosed epilepsy, and no clinical evidence of heart disease were examined with SAECD and standard ECG. 15 patients were treated with lamotrigine and 10 with carbamazepine	Lack of antiepileptic drug-induced electrocardiographic abnormalities	3–9 months	Svalheim et al. [31]
45 patients with epilepsy and 19 healthy volunteers, younger than 46 years	Epilepsy patients more frequently display abnormal SAECDs with LVPs compared to the control group, and their presence correlates with the disease duration, refractory epilepsy, and polytherapy		Rejdak et al. [23]
64 patients with interventricular and intraventricular dyssynchronies	Filtered QRS duration provides more information to estimate ventricular dyssynchrony in patients with reduced ejection fraction than simple QRS duration; LVPs did not correlate with ventricular dyssynchrony		Tahara et al. [16]
20 young heart transplant patients	SAECD is not effective in detecting heart transplant rejection in young patients		Horenstein et al. [21]

Study population	Results	Follow up	References
70 acromegalic patients and 70 control subjects, age- and sex-matched	A higher prevalence of LVPs in acromegaly which significantly correlated with Lown scale of premature ventricular contractions		Maffei et al. [34]
48 patients with acromegaly: 16 active disease, 32 cured or 'well controlled', under treatment with sandostatin analogs, and 38 healthy volunteers	LVPs are frequently seen in active acromegaly as an early and sensitive parameter of myocardial injury		Herrmann et al. [36]

Table 1. LVP studies.

Extracardiac disorders were also associated with LVPs, especially hypertension, metabolic syndrome, obesity, eating disorders, diabetes mellitus, renal failure, chronic obstructive pulmonary disease (COPD), acromegaly, thalassemia, connective tissue diseases, epilepsy, and schizophrenia [6, 23–27]. Antiarrhythmic therapy, thrombolytic drugs, statins, steroids, and coronary interventions may influence LVPs [6].

Sudden cardiac death is higher in psychiatric patients, especially those with depression and schizophrenia than in the general population [28]. Several factors influence the relationship with cardiovascular disorders in patients with depression: social factors (poverty, social inequality, reduced access to healthcare), biological factors (endothelial dysfunction, impaired heart rate variability and platelet function, inflammation, hyperactivity of hypothalamic-pituitary-adrenal axis), higher prevalence of cardiovascular risk factors, and therapy (side effects of tricyclic, lower adherence) [29]. Both schizophrenia and depression impair the autonomic tone, ion channels, alter connexin 43 expression, and may cause drug-induced cardiac fibrosis [28].

Several factors enable ventricular arrhythmias in patients with epilepsy, such as sympathovagal imbalance, impaired cardiac repolarization, mutations of ionic channels affecting both the brain and the heart, dysfunctional cortical networks, ictal hypoxemia and hypercapnia, stress hormones, therapy, cardiorespiratory interactions, and associated cardiovascular diseases [24, 30]. Epilepsy patients more frequently displayed abnormal SAECGs with LVPs compared to healthy controls, correlated with disease duration, uncontrolled seizures, and polytherapy [23]. Svalheim et al. [31] reported no electrocardiographic changes (in standard ECG and SAECG) after antiepileptic drugs (carbamazepine and lamotrigene) in 26 epileptic patients.

COPD was associated with cardiovascular morbidity and mortality, considering negative cardiac effects of hyperinflation, exercise limitation, smoking, and hypoxemia [6]. Carjea found a higher prevalence of LVPs in patients with COPD, especially in moderate and severe cases [32]. Yildiz et al. [33] reported a significantly increased total QRS duration in patients with COPD compared to control subjects and LVPs but no significant association with premature ventricular contractions. Despite higher prevalence of LVPs, premature ventricular contractions, and complex ventricular arrhythmias in patients with COPD compared to healthy controls, SAECG had little value in stratification of ventricular arrhythmia risk in a study including 41 patients with COPD and 63 patients without any history of pulmonary disease [27].

Persistent, life-threatening ventricular arrhythmias may occur in several endocrine disorders, such as pheochromocytoma, acromegaly, primary aldosteronism, Addison disease, hypo- and hyperparathyroidism, and hypothyroidism [4]. Ventricular arrhythmias may occur due to excess or insufficient hormone activity on myocardial receptors, myocardial changes, electrolyte imbalances, or acceleration of progression of structural cardiac disorders [4]. Sudden death and increased prevalence of ventricular arrhythmias and LVPs have been described in acromegaly [34]. Ventricular arrhythmia risk in acromegaly is related to the specific cardiomyopathy associated with left ventricular hypertrophy, myocardial fibrosis, comorbidities, especially hypertension and sleep apnea, and, possibly, to the direct effects of the growth hormone and insulin growth factor 1 on myocardial cells and cardiac ion channels [34, 35]. The prevalence of LVPs was significantly higher in patients with acromegaly compared to healthy controls, related to a longer duration of the disease, premature ventricular contractions, and left ventricular hypertrophy [34]. Herrmann et al. [36] also reported LVPs in patients with active and well-controlled acromegaly, as a sensitive and early sign of myocardial injury, not related to muscle mass and body mass index, age, gender, and duration of the disease.

Thyroid hormone exerts several effects on the cardiovascular system [37]. Ventricular arrhythmia and sudden cardiac death may occur especially in hypothyroidism, probably related to prolonged QT interval [4]. LVPs have been described in hypo- and hyperthyroidism, according to a study including 278 patients with thyroid disorders even in subclinical dysfunctions [38]. A case of severe primary hypothyroidism was presented with an abnormal SAECD with LVPs, which disappeared with thyroxine therapy [37].

Future SAECD studies should also include patients with Cushing's syndrome, considering impaired cardiac function and structure due to the direct toxic effect of cortisol, increased blood pressure, central obesity, metabolic syndrome, hyperglycemia, and chronic hypokalemia [39]. Subclinical structural and functional cardiac alterations are very common but underdiagnosed [39].

3. Intra-QRS potentials

IQRSPs are low-amplitude notches (the order of microvolts), usually invisible in the standard ECG, which may occur anywhere in the signal-averaged QRS [2] and may not prolong the normal QRS duration [40]. They were described as the signals with sudden slope changes [40]. Extracting IQRSPs is challenging, considering that they are very weak signals, with abrupt changes in slope, approximation errors, and the differences among patients with ventricular arrhythmias [41]. The root mean square values were highly correlated with the parameters of the abnormal intra-QRS potentials in healthy controls but not in patients with ventricular tachycardia [40].

A combination of IQRSPs and LVPs can improve predictive accuracy for patients of high risk of ventricular arrhythmias.

4. P-wave potentials

P-wave signal-averaged electrocardiography, atrial late potentials (ALP), and abnormal intra-P-wave potentials could detect patients at risk of supraventricular arrhythmias, especially atrial fibrillation [42, 43]. ALP originates from areas of delayed and heterogenous conduction within the atrial myocardium, responsible for the occurrence of AF [44].

Prolonged filtered P-wave duration (FPD) in P-wave signal-averaged electrocardiography has been used as a noninvasive, powerful predictor of AF, the first episode and recurrences, in lone, occult or silent atrial fibrillation, in stroke, heart failure, hypertension, hypertrophic cardiomyopathy, hypothyroidism and in patients undergoing coronary artery bypass surgery [44–46]. A prolonged SAEKG P-wave duration was also mentioned in septal atrial defect, especially in patients who experienced AF, not corrected after atrial septal defect closure, and it was demonstrated that atrial conduction disturbances occur early, requiring an early intervention to prevent the development of late AF (Table 2) [47].

There is no consensus about the cut-off point for FPD, which was 121 ms in hypertensive patients Auriti et al. [48], 124 ms in patients in sinus rhythm, 136 ms in hypertensive patients with a history of atrial fibrillation, 132 ms in patients with COPD, and 155 ms in several other studies [43, 45, 46, 49], differences related to different averaging and filtering methods [45].

Study population	Results	Follow up	References
45 patients with exacerbation of COPD and 58 age-matched patients with no history of pulmonary disease in a control group	The patients with acute exacerbation of COPD have a higher incidence of supraventricular arrhythmias. P-wave SAEKG analysis has little value in the arrhythmic risk evaluation of these patients	Isolated atrial premature beats (APB) and supraventricular tachycardia (SVT)	Buzea et al. [43]
37 hypertensive patients with a first AF episode 37 age- and sex-matched hypertensive controls without AF	P-wave temporal and energy characteristics can identify hypertensive patients at risk of AF recurrence		Dakos et al. [50]
68 stroke patients in sinus rhythm, without history of AF	ALP is a novel predictor of AF in stroke patients. P-SAEKG should be considered in stroke	11±4 months	Yodogawa et al. [44]
35 patients with atrial septal defect	Prolonged P-wave duration does not change after atrial septal defect closure	8±6 months after atrial septal defect closure	Thilen et al. [47]
4 generations kindred of 27 individuals, 8 with AF on the ECG	Persons with AF and mutation carriers (on chromosome 5p15) can be identified by a prolonged P-SAEKG duration		Darbar et al. [49]
41 patients with two or more symptomatic episodes of idiopathic and persistent atrial fibrillation after successful electrical cardioversion and 25 healthy controls	Fragmented electrical activity, use of amiodarone, and positive terminal portion of the Z-lead of the P-SAEKG were independent predictors of recurrence of idiopathic and persistent atrial fibrillation	6 months, 12 months, atrial fibrillation recurrences	Barbosa et al. [42]

Study population	Results	Follow up	References
101 patients in sinus rhythm before coronary artery bypass grafting (CABG)	The risk of AF after CABG can be predicted preoperatively with P-wave SAECCG		Budeus et al. [46]
55 hypertensive patients with a history of atrial fibrillation 40 hypertensive patients without a history of atrial fibrillation.	Hypertensive patients with paroxysmal atrial fibrillation can be detected while in sinus rhythm by signal-averaged ECG P-wave duration		Aytemir et al. [45]

Table 2. Atrial late potentials (ALP) and fragmented electrical activity on the P-wave.

Besides FPD, Buzea et al. [43] also used the RMS voltages in the last 40, 30, and 20 ms of the filtered P-wave (RMS 40, RMS 30, and RMS 20), the root mean square voltage of the filtered P-wave potentials (RMS-p), and the integral of the potentials during the filtered P-wave (Integral-p), and defined ALP as FPD > 132 ms and RMS 20 < 2.3 μ V.

Fragmentations are expected to occur throughout atrial depolarization and not only in its terminal part, and inter- and intra-atrial conduction may be impaired [42]. High-frequency fragmented electrical activity on the P-wave in patients with recurrent AF is the expression of atrial electrical heterogeneity, responsible for reentry circuits in the atria [42]. Barbosa et al. [42] used spectral turbulence analysis of the P-SAECCG to detect abnormal intra-P-wave potentials, demonstrating that fragmented electrical activity is an independent predictor of early AF recurrence.

5. Limitations

Most of the reviewed studies were observational, retrospective, with a low sample size and event rate, but careful statistical analysis may compensate the mentioned limitations. LVPs were detected using various equipment, commercially available or not, using different averaging and filtering methods. On the other hand, filtered QRS duration was not measured sequentially, considering therapy in all studies, and there was a lack of uniformity of the normality criteria for the diagnosis of LVPs.

False positive LVPs were reported in patients with junctional rhythm with retrograde P-waves, atrial flutter, and incomplete bundle branch block [51–53]. Combined TD and spectral turbulence analysis of the SAECCG could improve its predictive value for fatal arrhythmias [54]. The positive predictive accuracy nearly doubled compared to TD or STA, without loss in sensitivity and specificity [54]. A high number of false positive LVPs was reported in myocardial infarction, as well, and in the early postinfarction period; in inferior myocardial infarction in time-domain analysis and anterior myocardial infarction according to STA [54, 55]. Delayed terminal conduction may increase the incidence of false positive results in SAECCG, but the incidence of false positive LVPs was significantly lower if the combination of SAECCG-QRS, LAS40, and RMS40 was used in patients with incomplete bundle branch block [53]. LVPs detected during sinus rhythm and lost after premature ventricular contractions

may be responsible for false positive LVPs, and those revealed by ventricular extrastimuli and concealed during sinus rhythm may cause false negative LVPs [56]. Sensitivity might be low in patients with ventricular tachycardia due to early activation of potential sites of ventricular tachycardia in sinus rhythm, falling within the normal QRS duration [56]. The number of false positive results may be reduced by signal-averaging during premature ventricular stimulation [56].

Larger follow-up studies are needed to confirm the significance and usefulness of LVPs in different cardiac and noncardiac disorders.

6. Conclusions

This chapter brought back into focus SAECEG, a noninvasive, low-cost, simple, and rapid method as a predictor of sudden cardiac death, using amplified ECG signals. Even though SAECEG is not a routine screening test for sudden cardiac death risk and despite its low positive predictive value for arrhythmic events, LVPs and intra-QRS potentials provide valuable information not only in cardiac but also in extracardiac disorders, including psychiatric disorders, epilepsy, chronic obstructive pulmonary disease, and endocrine disorders. P-wave signal-averaged electrocardiography predicts atrial fibrillation episodes in patients with several disorders, such as hypertension, atrial septal defect, stroke, and chronic obstructive pulmonary disease.

Author details

Ioana Mozos^{1*} and Dana Stoian²

*Address all correspondence to: ioanamosos@umft.ro

1 Department of Functional Sciences, Victor Babeş University of Medicine and Pharmacy, Timișoara, Romania

2 Department of Internal Medicine, Victor Babeş University of Medicine and Pharmacy, Timișoara, Romania

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