REVIEW ARTICLE

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Signal-averaged electrocardiography: Past, present, and future

Konstantinos A. Gatzoulis MD, PhD[1] | Petros Arsenos MD, PhD[1] |
Konstantinos Trachanas MD[2] | Polychronis Dilaveris MD, PhD[1] | Christos Antoniou MD,
PhD[1] | Dimitris Tsiachris MD, PhD[3] | Skevos Sideris MD, PhD[2] | Theofilos M. Kolettis
MD, PhD[4,5] | Dimitrios Tousoulis MD, PhD[1]

[1]Electrophysiology Laboratory and First University Department of Cardiology, Hippokration General Hospital, National and Kapodestrian University of Athens, Athens, Greece

[2]Department of Cardiology, Hippokration General Hospital, Athens, Greece

[3]Electrophysiology Laboratory Athens Medical Center, Athens, Greece

[4]Department of Cardiology, University of Ioannina, Ioannina, Greece

[5]Cardiovascular Research Institute, Ioannina, Greece

Correspondence
Konstantinos A. Gatzoulis, Hippokration General Hospital, Athens, Greece.
Email: kgatzoul@med.uoa.gr

Abstract

Signal-averaged electrocardiography records delayed depolarization of myocardial areas with slow conduction that can form the substrate for monomorphic ventricular tachycardia. This technique has been examined mostly in patients with coronary artery disease, but its use has been declined over the years. However, several lines of evidence, derived from hitherto clinical data in patients with healed myocardial infarction, indicate that signal-averaged electrocardiography remains a valuable tool in risk stratification, especially when incorporated into algorithms encompassing invasive and noninvasive indices. Such an approach can aid the more precise identification of candidates for device therapy, in the context of primary prevention of sudden cardiac death. This article reappraises the value of signal-averaged electrocardiography as a predictor of arrhythmic outcome in patients with ischemic heart disease and discusses potential future indications.

KEYWORDS
late potentials, myocardial infarction, risk stratification, syncope, ventricular tachycardia

1 | INTRODUCTION

Signal-averaged electrocardiography (SAECG) records low-amplitude electrical activity in the myocardium. Initially proposed for the noninvasive recording of His bundle potential,[1] its use shifted swiftly toward the detection of the depolarization of ventricular areas with slow conduction, manifesting as late potentials (LPs). These signals are revealed after the removal of interference, by averaging a large number of high-resolution recordings.[2] Based on the correlation of LPs with substrates for sustained ventricular tachyarrhythmias, this noninvasive tool was soon added in the armamentarium of risk assessment for sudden cardiac death (SCD) in various clinical settings. However, the initial enthusiasm weaned, following the demonstration of generally low positive predictive accuracy of SAECG on the total survival of selected patients with coronary artery disease.

As a result, the clinical use of SAECG has declined rapidly, with many centers abandoning this technique altogether. This article reviews the relevant literature, aiming at reexamining the value of SAECG as a predictor of SCD, and suggests potential applications in various cardiac diseases. These topics gain importance in the context of primary SCD prevention, in view of the increasing demand for amending current risk-stratification algorithms.[3]

2 | MAIN PRINCIPLES

Myocardial regions with excessive fibrosis are characterized by inhomogeneous electrical conduction, leading to the completion of local depolarization after the remaining ventricular myocardium. These delayed activation signals originate from slow and inhomogeneous
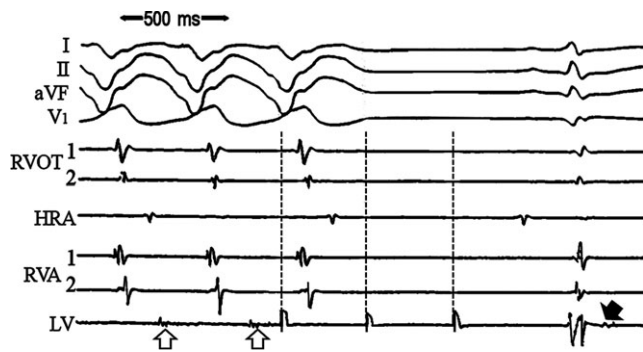
FIGURE 1 VT patient with an old anterior wall MI. From top to the bottom body surface, leads I, II, aVF, and V1, followed by endocardial electrograms from the right ventricular outflow tract (RVOT), the high right atrium (HRA), the right ventricular apex (RVA), and the left ventricular (LV) infarct zone. During the sinus rhythm, there are late fragmented and low-amplitude signals originating in the LV infarct zone (arrow). During the VT (left side), the fragmented potentials of the LV zone prolong their duration bridging the diastolic phase of the VT cardiac cycle (arrows), disappearing upon VT termination (slow pathway conduction block)

depolarization of myocardial regions of the left (LV) and right (RV) ventricles, which provide the substrate for reentrant ventricular tachycardia (VT) (Figure 1). Delayed local depolarization manifests as LPs, depicted as low-amplitude signals at the final portion of the QRS complex; these signals can be recorded in a lead obtained after mathematical combination of three separate orthogonal leads. LPs are described by the duration of the terminal portion of the QRS complex that display slow amplitude signals (less than 40 μV, LAS-40), and indirectly by the total duration of the filtered QRS complex. Their magnitude is measured by the root mean square voltage of the terminal 40 ms of the filtered QRS complex (RMS-40). Based on these definitions, the detection criteria proposed in 1991[4] include (i) filtered QRS≥114 ms, (ii) RMS-40 < 20 μV, and (iii) LAS-40 > 38 msec, with the specificity of the method depending on the number of positive criteria (Figure 2). Importantly, these measurements were validated under the strict requirement for the presence of narrow QRS complexes in a standard 12-lead ECG, thereby excluding a large proportion of patients with right or left bundle branch block, or with wide QRS complexes and nonspecific intraventricular conduction defects. To overcome this limitation, modified criteria have been suggested in such patients, encompassing longer duration and lower amplitude of LPs; specifically, (i) filtered QRS≥145 ms, (ii) RMS-40 < 17.5 μV, and (iii) LAS-40 > 50 ms can be applied in cases of wide QRS complexes[5] (Figures 3 and 4). LPs are generally considered present, when at least 2 of 3 conventional or modified criteria are satisfied.

3 | HEALED MYOCARDIAL INFARCTION

In the setting of healed myocardial infarction (MI), monomorphic VT is invariably caused by reentrant mechanisms, originating from myocardial sites located at the infarct border.[6] Accordingly, LPs are
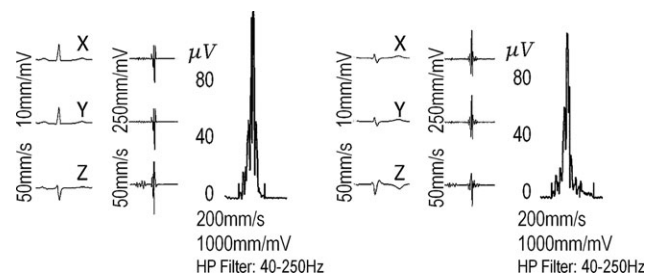

FIGURE 2 SAECG from two patients. The one (right) with a history of sustained monomorphic ventricular tachycardia and the other (left) without such a history. The RMS-40 of the filtered QRS complex is lower in the VT patient (4 vs 34 μV). The LAS-40 duration is longer in the VT patient (78 vs 29 msec). The duration of the filtered QRS complex is also longer in the VT patient (114 vs 97 msec). RMS: root mean square, LAS: low-amplitude signal

recorded in nearly 90% of post-MI patients with a history of sustained monomorphic VT, as opposed to only ~20% in its absence.[7] Moreover, SAECG is associated with high negative predictive value (>95%), with normal recordings strongly suggesting absence of a substrate for monomorphic VT; such inferences are supported by series of post-MI patients, reporting low incidence of arrhythmic events in patients with normal SAECG.[8,9] Considering the high negative predictive value, SAECG may play an important role as a screening test in post-MI patients.[10]

3.1 | The CABG-PATCH

The correlation of LPs with a substrate for VT formed the rationale for the CABG-PATCH trial, which included patients with LV dysfunction undergoing surgical revascularization.[11] This study randomized (in 1:1 fashion) 900 patients with an ejection fraction (EF) of ≤35% and abnormal SAECG to standard treatment or to implantation of a cardioverter-defibrillator (ICD). Over a mean follow-up of 32 ± 16 months, ventricular tachyarrhythmias were recorded in 19.4% of treated patients and in 14.3% of controls, but this difference failed to reach statistical significance. Of note, postoperative infections were higher in the ICD group, leading to device explantation in ~9% of patients. No survival benefit was evident after treatment, with almost identical total survival rates in both groups. However, in a subsequent analysis,[12] the 198 deaths in the trial were reexamined by an independent events committee; cumulative arrhythmic mortality at 42 months was 6.9% in the control group and 4.0% in the ICD group, this difference nearly reaching statistical significance (P = .057). By contrast, cumulative nonarrhythmic cardiac mortality at 42 months was similar, that is, 12.4% in controls and 13.0% in the ICD group. From this analysis,[12] it can be concluded that ICD therapy reduced arrhythmic death by 45% in the CABG-PATCH cohort, without affecting nonarrhythmic mortality; hence, the neutral effect on total mortality can be explained by the high prevalence of nonarrhythmic mortality, reaching 71% of deaths. Thus, careful evaluation of the data reported in the CABG-PATCH trial indicates that SAECG is of value in risk stratification of post-MI patients.
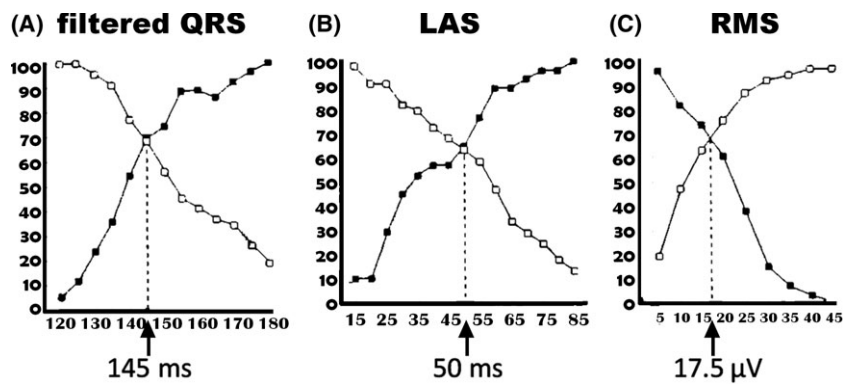
FIGURE 3 Sensitivity versus specificity plot for different LP criteria among patients with a widened QRS complex. The optimal combination of sensitivity and specificity for the sustained VT induction, despite the presence of a wide QRS (≥120 msec) complex is provided by a (A) filtered QRS and (B) LAS >145 and 50 msec, respectively, with a (C) RMS <17.5 μV Ref. (5)
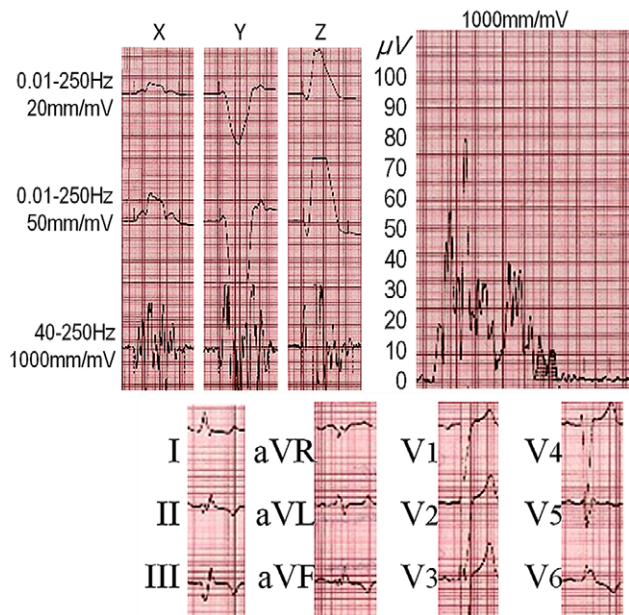
FIGURE 4 Post-MI patient with recurrent sustained VT and LBBB. Despite the presence of bundle branch block, LPs of long duration (LAS: 147 msec) and of very low amplitude (RMS: 8 μV) are revealed. Total filtered QRS duration: 203 msec

3.2 | The MUSTT trial

The value of SAECG was further corroborated by a subanalysis of the Multicenter Unsustained Tachycardia Trial (MUSTT)[13]; in this cohort of post-MI patients with LVEF≤40%, spontaneous nonsustained VT, induced sustained VT, and filtered QRS duration >114 ms on SAECG independently predicted arrhythmic death or cardiac arrest, as well as cardiac and total mortality. Abnormal SAECG and EF<30% identified a particularly high-risk subset for arrhythmic and cardiac death, with 5-year mortality rates of 36% and 44%, respectively.

3.3 | Multifactorial risk stratification

Although LPs reflect myocardial areas with slow conduction, no information is provided on their functionality; in other words, the presence of LPs cannot accurately depict those substrates that fulfill the requirements to sustain monomorphic VT by reentrant mechanisms. As a result, the positive predictive accuracy of SAECG is generally poor, as shown by a number of clinical reports.[9] Based on the poor performance of this and other noninvasive indices in the evaluation of arrhythmic outcomes, the need for multifactorial risk stratification has been put forward[14]; indeed, an improved positive predictive value for major arrhythmic events, at the range of 50%, was estimated for patients with LPs, frequent premature ventricular contractions, and decreased heart rate variability.[15] Comparable results were reported after combining SAECG with noninvasive indices describing autonomic function (such as heart rate variability, turbulence, and deceleration capacity, as well as baroreceptor sensitivity), repolarization abnormalities (such as QT prolongation, increased QT interval dispersion, or T-wave alternans), and spontaneous ventricular arrhythmias (such as ventricular couplets or nonsustained VT).[15–17] Along these lines, concurrent presence of LPs, complex ventricular tachyarrhythmias on ambulatory electrocardiography, and LV aneurysm were associated with high incidence of sustained VT during long-term follow-up of a large series of post-MI patients.[18] Moreover, the presence of LPs on the SAECG was associated with poor long-term outcome of post-MI patients with nonsustained VT and LV dysfunction, independent of the results of programmed ventricular stimulation.[13] Interestingly, in a cohort of patients with similar clinical characteristics, the detection of LPs and nonsustained VT on Holter recordings could accurately predict the inducibility of sustained VT at programmed ventricular stimulation.[19] As a result, SAECG, combined with other noninvasive variables, can be used as a screening tool in post-MI patients that are eligible for programmed ventricular stimulation,[20] thereby greatly enhancing the predictive accuracy of each individual approach.

The value of SAECG in this context was further demonstrated in a meta-analysis,[21] in which the predictive accuracy of the following additional variables was assessed: LVEF, heart rate variability, complex ventricular tachyarrhythmias on ambulatory electrocardiography, and programmed ventricular stimulation; the sensitivity for each individual variable was low, but their combination could accurately define a low-risk group, with an arrhythmia incidence of <3%, and a high-risk group, with an arrhythmia incidence of >40%.

3.4 | Limitations of current algorithms

Reperfusion strategies after acute coronary occlusion, widely practiced during the past decade, have altered the characteristics of

patients, when compared to earlier populations; indeed, prompt reperfusion decreases infarct size and transmurality, thereby ameliorating the substrate for monomorphic VT.[22] This development increases the need for more accurate identification of potential candidates for ICD therapy and supports emerging views, challenging the current use of LVEF as the main variable in primary SCD prevention.[23] Specifically, LVEF is subject to operator biases and depends on loading conditions and heart rate that limit its accuracy; additionally, it cannot discern arrhythmic mortality post-MI, which, in fact, may be relatively higher at earlier stages of heart failure.[24] The value of SAECG, incorporated in risk-stratification strategies, is further underscored by a recent study[25] in patients with preserved LV function, undergoing infarct-scar characterization by cardiac magnetic resonance; wide variation was reported in the extent of potential substrates for monomorphic VT, which correlated with noninvasive indices, including SAECG. Much information on the value of prophylactic ICD implantation in such patients is awaited from the ongoing PRESERVE-EF study,[26] which examines high-risk patients, based on complex ventricular tachyarrhythmias, presence of LPs, prolonged QTc, T-wave alternans, and abnormal autonomic function. The predictive value of such algorithms may be enhanced, if supplemented with the analysis for fragmented QRS complexes on 12-lead ECG; this promising tool constitutes another marker of depolarization abnormality, representing conduction delay caused by myocardial scar in patients with previous MI.[27]

4 | DILATED AND RIGHT VENTRICULAR CARDIOMYOPATHIES

4.1 | Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by diffuse fibrosis, contrasting the usually well-demarcated substrate surrounding an infarct scar; hence, complex ventricular tachyarrhythmias can arise with several mechanisms, with a varying incidence observed in different DCM cohorts. Resulting from this complex pathophysiology, risk stratification remains a challenge in these patients, with several concerns raised on the value of arrhythmic markers in DCM; actually, many centers often omit the electrophysiologic evaluation in DCM, opting to use LVEF as a sole criterion. However, the widespread skepticism on this practice[3] was fueled by the recent DANISH trial,[28] in which 556 patients with LVEF ≤35% were assigned to receive an ICD and 560 patients to standard care; after a median follow-up period of 67.6 months, SCD was lower after ICD, but total mortality was comparable in the two groups.

Current evidence indicates that multifactorial approaches are also pertinent among DCM patients, encompassing invasive and noninvasive indices.[3] SAECG holds a place in this respect, as shown by early clinical reports, where SAECG could discriminate those DCM patients with a history of VT from those without,[29] albeit with an inferior predictive value compared to MI patients.[30]

In keeping with these findings, one-year event-free survival was 95% in a larger cohort of DCM patients with absence of LPs, contrasting the only 39% in patients with an abnormal SAECG[31]; of note, multivariate analysis in this study demonstrated that SAECG and functional class were independent predictors of survival. In relevance with that proposed in MI patients, a cluster of noninvasive indices can guide the referral of patients for programmed ventricular stimulation,[32] an approach that merits further investigation.

4.2 | Right ventricular cardiomyopathy

LPs, reflecting fragmented and delayed electrograms in the RV, are commonly recorded in patients with RV cardiomyopathy; based on these observations, abnormal SAECG is considered a minor criterion in the relevant diagnostic algorithm.[33] In a relatively large series of 138 patients,[34] SAECG was abnormal in 57%, this percentage rising to 94.4% among those with extensive form of the disease. The sensitivity of SAECG in this cohort was 57%, with a specificity of 95%; LPs correlated also with the incidence of VT, albeit to a lesser extent. The largest duration and the lowest amplitude LPs have been described in the more ominous "Naxos disease," a form of RV dysplasia caused by plakoglobin deletion, inherited via a recessive mode[35] (Figure 5).

Regular physical exercise results in physiological cardiovascular changes, including biventricular dilatation, accompanied by ECG abnormalities resembling RV cardiomyopathy.[36] Of note, prolonged filtered QRS duration on SAECG, correlating with RV dimensions, can be detected in elite and amateur athletes participating in combined high dynamic and high static sports.[37] SAECG has an important role in differentiating the "athlete's heart" from RV cardiomyopathy, as such patients frequently exhibit markedly abnormal SAECG concerning all three parameters, as opposed to only nonspecific filtered QRS prolongation in athletes.[38]

	NAXOS DISEASE	CAD/sustained VT
filtered QRS (ms)	144	125
RMS (µV)	5	22
LAS (ms)	76	35
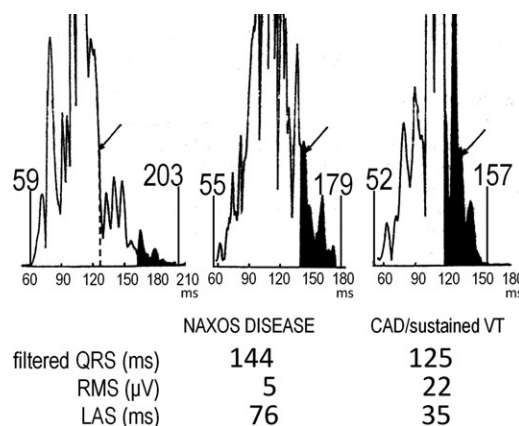
FIGURE 5 SAECG from a Naxos disease patient (left), a post-MI patient with sustained VT (center), and a healthy control (right). LPs are revealed in the two patients being of longer duration and of lower amplitude in the Naxos disease patient Ref. (60)

5 | OTHER INDICATIONS

5.1 | Tetralogy of Fallot

An increased risk of SCD is observed in adult patients with congenital heart disease, usually years after the surgical repair of the defect. Abnormal SAECG parameters are frequently detected in this setting, as shown in a series of 27 patients with Fallot tetralogy and complete right bundle branch block; in this report, abnormal SAECG was associated with nonsustained monomorphic VT on Holter recordings.[39] In another clinical study,[40] LPs correlated with the inducibility of VT during programmed ventricular stimulation and the occurrence of VT during follow-up, suggesting a role in risk stratification of asymptomatic patients with surgically repaired tetralogy of Fallot.

5.2 | Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant disorder, with prominent skeletal muscle manifestations; cardiac involvement is frequent, secondary to myocardial fatty infiltration, degeneration, and fibrosis, presenting as conduction disturbances or VT. LPs are recorded in these patients, but their prognostic significance is debated.[41] In a series of 53 patients with myotonic dystrophy, LPs correlated with complex ventricular tachyarrhythmias,[42] although these findings could not be reproduced in a recent series.[43] Nonetheless, SAECG, supplementing periodic follow-up with imaging modalities, holds a place in the evaluation of patients with myotonic dystrophy.

5.3 | Evaluation of syncope

Syncope of uncertain etiology is not uncommonly encountered in clinical practice; in the context of structural heart disease, difficult therapeutic dilemmas are often raised, on the grounds of clinical data demonstrating increased mortality during long-term observation. Such patients invariably require thorough electrophysiologic evaluation, aiming at the identification of brady- or tachyarrhythmic causes of syncope.[44] For example, in a series of 189 patients, VT was identified as the cause of unexplained syncope in 15%; the analysis of diagnostic workup revealed a 17-fold risk of VT in the presence of previous MI and abnormal SAECG.[45] Thus, SAECG can aid the identification of patients with unexplained syncope that can benefit from electrophysiologically guided approaches.

5.4 | Cardiac sarcoidosis and hypertrophic cardiomyopathy

SAECG can be useful in revealing cardiac involvement of sarcoidosis, invariably manifested as conduction abnormalities or ventricular tachyarrhythmias. In a series of 60 patients, LPs were present in 80% of patients with cardiac sarcoidosis, but also in 46% of those with pulmonary sarcoidosis without overt cardiac involvement[46]; this finding might represent latent myocardial fibrosis, alerting to closer

follow-up in such cases. Contrasting these findings, there is no evidence favoring the use of SAECG in patients with hypertrophic cardiomyopathy[47]; hence, this method does not appear to have a role in the risk stratification of such patients.

6 | POTENTIAL FUTURE APPLICATIONS

6.1 | Substrate ablation for ventricular tachycardia

Early reports on surgical treatment for VT have shown normalization of SAECG, in cases of successful substrate resection, followed by absence of VT recurrence during follow-up[48] (Figure 6). Based on these observations, the hypothesis that this tool can be utilized in ablative procedures was examined in 50 patients with post-MI VT.[49] A linear correlation was seen between endocardial scar area and filtered QRS; importantly, patients with normalized SAECG after ablation had more favorable long-term outcomes, with a hazard ratio of ~6 for VT recurrence for those with narrow QRS and persistent LPs.[49]

6.2 | Brugada syndrome

There is evidence that SAECG may be of value in the risk stratification of patients with Brugada syndrome, a difficult and much-debated issue. The role of noninvasive markers reflecting conduction or repolarization abnormalities was examined in a series of 33 such patients[50]; a history of syncope or aborted sudden death was present in 19, of whom ventricular fibrillation or polymorphic VT was
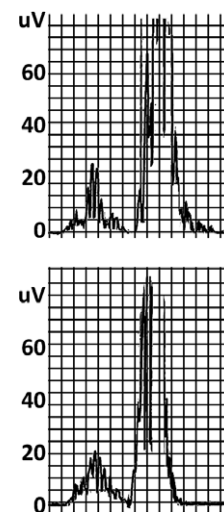
FIGURE 6 Elimination of late potentials in the signal-averaged electrocardiogram (SAECG) after aneurysmectomy. SAECG performed in a 64-year-old postmyocardial infarction patient with left ventricular aneurysm before (fQRS = 191 ms, RMS-40 = 1 μV, LAS = 104 ms) and after (fQRS = 113 ms, RMS-40 = 16 μV, LAS = 35 ms) aneurysmectomy of the left ventricle showing disappearance of the pre-existing late potentials. The presenting sustained ventricular tachycardia (VT) (both spontaneous and induced preoperatively) was not induced postoperatively Ref. (61)

induced by programmed ventricular stimulation in 15. LPs were present in 73% of the total cohort, with this variable displaying the most significant correlation with major arrhythmic events on multivariate logistic regression analysis.[50]

The pathophysiologic basis for LPs in Brugada syndrome is still under investigation.[51] Recent data derived from an ex vivo canine model challenge previous conclusions, attributing LPs to abnormal conduction or structural abnormalities in the RV epicardium; these experiments indicated that LPs in Brugada syndrome may be associated with the development of abnormal repolarization in the RV epicardium that can set the stage for concealed reentry.[52] Interestingly, circadian periodicity has been noted in the presence of LPs; this observation, derived from Holter-SAECG recordings, was characterized by increased incidence of LPs during the night, likely resulting from enhanced vagal tone.[53] Based on this finding, LPs during nighttime, along with enhanced T-wave amplitude variability, have been proposed as additional noninvasive risk-stratification tools.[54] Nonetheless, further research is needed on this subject, prior to the clinical use of SAECG in Brugada syndrome.

6.3 | Epilepsy and psychiatric disorders

Sudden death in epileptic patients has attracted considerable research interest during the past years. Although presumed arrhythmic in origin, the underlying pathophysiology remains elusive; hence, there are no established methods of identifying patients with epilepsy, at high risk of dying suddenly.[55] SAECG may prove useful in this regard, as suggested by a clinical report of 45 epileptic patients; LPs were detected in 48%, correlating with factors that have been linked also to sudden death, such as disease duration, uncontrolled seizures, and multiple antiepileptic medications.[56]

LPs have been also demonstrated in psychotic patients, mostly attributed to pharmacologic effects.[57,58] Indeed, antipsychotic drugs are well known to prolong repolarization, thus giving rise to early afterdepolarizations; in addition, these agents can also induce myocardial fibrosis, thereby affecting ventricular depolarization, and may set the stage for reentrant tachyarrhythmias.[59] However, the clinical significance of these observations remains unclear.

7 | CONCLUSIONS

The SAECG is an inexpensive, safe, and highly reproducible technique that provides information on the presence of a substrate for monomorphic VT. LPs have been mostly examined in patients with a history of MI, but its use has been declined over the years. Critical appraisal of the published clinical data indicates that SAECG remains a valuable addition to risk-stratification algorithms that may lead into more precise identification of candidates for ICD therapy. Such an approach for primary prevention of SCD can be expanded to DCM, as well as to various structural heart disease entities. Given the relative paucity of data, clinical studies are awaited, examining the prognostic value of SAECG in post-MI

patients treated with primary percutaneous coronary interventions, even in the absence of significant left ventricular dysfunction. LPs in primary electrical disorders, such as Brugada syndrome, are intriguing, but the underlying pathophysiology and clinical significance are still under investigation.

CONFLICT OF INTEREST

Authors declare no conflict of interest for this article.

ORCID

Petros Arsenos (iD) http://orcid.org/0000-0003-4426-8407

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