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Prevalence of late potentials on signal-averaged ECG in patients with psychiatric disorders

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ABSTRACT

Background: Sudden cardiac death (SCD) occurs three times more often in psychiatric patients than in the general population. QRS fragmentation (QRSfr) and signal-averaged electrocardiography (SAECG) are simple, inexpensive, readily available tools for detecting the presence of abnormal depolarization and late potentials (LPs) in these patients, a result of either the underlying disease or treatment.
Methods: Frequency of LP detection by SAECG and QRSfr was studied in 52 psychiatric patients and compared with 30 healthy (without known structural heart disease or occurrence of ventricular arrhythmia) controls. Patients were then prospectively followed up and incidence of SCD was recorded.
Results: LP prevalence was significantly higher in patients than in controls (16/52–31% vs 2/30–7%, $p = 0.012$), while QRSfr was similar between these two groups ($p = 0.09$). Of the LP presence criteria, the root mean square value at terminal 40 msec of the QRS (RMS40) was significantly lower in patients (32 μV, SD = 19 μV, vs 46 μV, SD = 32 μV, $p = 0.015$). Among patients, no differences were noted between the LP positive and negative groups regarding age, sex, number of medications, class of antipsychotics and defined daily doses. Mean follow-up was 46 months (SD = 11) and during it 3 patients suffered SCD. Although 2 SCD victims had both LPs and QRSfr concurrently present, neither of them, nor their simultaneous presence could definitely account for the events.
Conclusions: LP prevalence in psychiatric patients was significantly higher than in controls. SAECG performance was feasible in all cases and constitutes a readily available tool for assessing myocardial electrophysiological alterations in this patient group.

1. Introduction

Psychiatric disorders are a growing public health problem. Regarding schizophrenia alone, 0.3–0.7% of the general population will develop the disease during its lifetime [1]. Furthermore, depression constitutes the fourth most common cause of morbidity worldwide with a prevalence reaching 20% in CAD and 45% in post-myocardial infarction patients, increasing group mortality [2], with similar findings in heart failure [3]. SCD has been found to be approximately three times higher in both depression and schizophrenia patients [4–7], a finding driven by a multitude of underlying mechanisms [4]. These data, combined with difficulties in defining those at high SCD risk, especially in the general population [8,9], necessitate the implementation of an easily performed, readily available, screening test on these patients.

SAECG may be used to noninvasively evaluate the myocardial substrate and its arrhythmogenic potential [10–12] by detecting the presence of abnormal, slowly depolarized ventricular segments. Presence of these "late potentials" (LPs) has been found, even in the era of early revascularization, to bear prognostic significance for the occurrence of potentially malignant and malignant ventricular arrhythmias [11–14]. Given the effects that both schizophrenia and depression exert on the electrophysiological properties of the myocardial substrate, such as altering the autonomic tone [15–18], influencing the circadian rhythms [19–21] and ion channel expression [22,23] or even causing drug-induced cardiac fibrosis by certain antipsychotics used in the treatment

Abbreviations: CAD, coronary artery disease; SCD, sudden cardiac death; SAECG, signal-averaged electrocardiography; LPs, late potentials; QRSfr, QRS fragmentation; fQRS, filtered QRS; LAS, low amplitude signal; RMS40, root mean square value at terminal 40 msec of QRS; QTc, rate corrected QT; DDD, defined daily dose; EF, ejection fraction.

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of these common disorders [24,25], SAECG appears a reasonable method for the assessment of these effects.

Indeed, in two preliminary observational studies among small groups of depressed and schizophrenic patients, unfavorable SAECG parameters have been documented [26,27].

QRSfr is defined as presence of one or more "high frequency components" on the QRS complex in 12 lead electrocardiography [28]. It is thought to constitute a convenient scar marker, visualizing disorganized depolarization around myocardial tissue with abnormal electrophysiological properties [29]. Furthermore, it has been shown to bear prognostic significance in coronary artery disease patients [30].

It was thus attempted to study the prevalence of LPs, detected by means of SAECG, and QRSfr in a group of psychiatric patients under treatment, as compared with age-matched controls without organic heart disease. Furthermore, we also attempted to correlate these findings with the occurrence of SCD during long term follow-up.

2. Methods

In the present study, 52 hospitalized psychiatric patients, treated with a variety of psychotropic agents, and a control group of 30 healthy individuals (free from organic heart disease and without history of ventricular arrhythmias, unexplained syncope or psychiatric disorder, not receiving any psychotropic agents) were submitted to SAECG according to a previously described protocol [31]. Presence of LPs was diagnosed if 2 of the following 3 criteria were present:

1. fQRS duration ≥ 114 msec,
2. LAS duration ≥ 38 msec and
3. RMS40 ≤ 20 μV.

A noise level of <0.6 μV was considered acceptable.

A MAC 5000 digital electrocardiograph (GE MARQUETTE, Fairfield, CT, U.S.A.) was used for the control cases, while a CARDIOVIT AT-10 plus (SCHILLER diagnostics, Baar, Switzerland) was used for the patient cases.

QT interval was corrected for heart rate by means of the Fridericia equation. QTc was considered prolonged if >440 msec in men and >460 msec in women.

QRSfr was defined as

1. Presence of an additional R wave (R')
2. Notching in the nadir of the S wave,

in 2 contiguous leads, corresponding to a major coronary artery territory on the resting 12-lead ECG [32], in standard speed and sensitivity settings.

Cardiac function data were obtained by echocardiography, whenever available.

Antipsychotic medications were classified as typical or atypical based on their mechanism of action [33]. DDD was calculated based on the WHO Collaborating Centre for Drug Statistics Methodology index [34]. DDDs were calculated for each medication class independently (i.e. typical–atypical antipsychotics, tricyclics–selective serotonin reuptake inhibitors) as well as cumulatively, per therapeutic indication (i.e. all antipsychotics, all antidepressants and all anxiolytics).

Patients were followed-up and the occurrence of any of the following endpoints was recorded:

1. SCD (defined as death within 1 h from symptom onset, or death during sleep [10,11])
2. Non-cardiac death
3. Patient alive

Student's t-test was used for parametric, the Mann–Whitney U test for non-parametric, and Fisher's exact test for categorical variables. A p-value of ≤0.05 was considered statistically significant. SPSS 23 statistics software (IBM — Armonk, N.Y., U.S.A.) was used for all analyses.

Our study complies with the principles of the Declaration of Helsinki and informed consent was obtained from each participant or his legal guardian if indicated.

3. Results

Regarding psychiatric diagnoses, of the 52 patients: 36 suffered from schizophrenia, 5 from schizophreniform disorder, 2 from disorders due to cerebral damage, 2 from ethanol abuse-related disorders, 4 from depression, 2 from bipolar disorder, and 1 from dysthymia. All patients received psychiatric medications, as indicated. Of the 52 patients, 12 (23%) were on typical, 10 (19.2%) on atypical and 28 (53.8%) on both classes of antipsychotics. In total, 50patients were receiving antipsychotics (96.1%). Nine patients (18.3%) were on antidepressants of any class (4–7.6% on tricyclics), while 36 of 52 (69.2%) were on anxiolytics (benzodiazepines). Two patients (3.8%) had CAD, both with relatively preserved left ventricular ejection fraction (45% and 52%). Patient and control demographics are shown in Table 1, comparison of ECG and SAECG parameters between patient groups based on LP presence in Table 2 and medication data in Table 3.

Table 1
Basic demographic data, SAECG findings and QRSfr in patient and control groups.

	Patients (n = 52)	Controls (n = 30)	p for difference
Age (years)	58.9 SD = 12	56.1 SD = 7.9	0.26
Sex (male n, %)	32 (61.5%)	22 (73%)	0.34
Coronary heart disease (known) n, %	2 (3.8%)	0 (0%)	0.53
QTc duration (msec)	428 SD = 33.5	415 SD = 27	0.07
Standard (unfiltered) QRS duration (msec)	91 SD = 11	90 SD = 10	0.68
Filtered QRS duration (msec)	92 SD = 17	92 SD = 10	1
Low amplitude signals duration (msec)	35 SD = 16	30 SD = 9	0.12
Root mean square QRS size at final 40 msec (μV)	32 SD = 19	46 SD = 32	0.015
Late potential presence (n, %)	16 (31%)	2 (7%)	0.013
Fragmented QRS (n, %)	21 (40%)	6 (20%)	0.09

The measured QTc of patients was 428 msec (SD = 33.5 msec). Based on the aforementioned criteria, 10 male and 4 female patients had QTc prolongation (37%). Control QTc was 415 msec (SD = 17 msec) (p = 0.07 for difference between controls and patients).

SAECG performance was feasible in all patients. Mean number of averaged beats was 870 (SD = 238 beats) and mean noise level was 0.5 μV (SD = 0.25 μV). Twelve lead ECG and SAECG parameter comparison between patients and controls is shown in Table 1. Presence of LPs (Fig. 1) was statistically significantly higher among patients, compared with controls (16/52, 31% vs 2/30, 7% — p = 0.012). In addition, mean RMS40 was lower in the patient group (32 μV, SD = 19 μV vs 46 μV, SD = 32 μV, p = 0.015). Standard and fQRS as well as LAS duration were similar between patients and controls. QRSfr presence did not significantly differ between patients and controls (21 patients - 40% and 6–20% of healthy controls, p = 0.09).

Among patients, no differences were noted between the LP positive and negative groups regarding age, sex, presence of CAD, number of averaged QRS complexes and QRS duration. However, as expected, statistically significant differences were noted regarding fQRS, LAS duration and RMS40 value, both as dichotomous and continuous variables (Table 2). Although 7 LP positive patients also had QRSfr (44%), no statistically significant correlation was noted (p = 0.77).

The use of antipsychotic medications was not found to differ among LP groups in psychiatric patients. Class of antipsychotics taken (typical only, atypical only and both) was also similar between groups (p = 0.66). Similar findings were noted for the use of antidepressants and anxiolytics (p = 0.33 and p = 0.24 respectively). Furthermore, when using DDDs as a quantitative measure of drug consumption, no differences were noted between the LP positive and LP negative patient groups (Table 3). Echocardiography data were available in 17 (33%) patients. Mean EF was 57% (SD = 5%). Two of the three patients with mildly depressed (45 ≤ EF < 55%) EF had known CAD, 2 had LPs and all had QRSfr.

Table 2
Comparison of SAECG parameters between patient groups, based on LP presence.

Parameter	LP positive (n = 16)	LP negative (n = 36)	p for difference
fQRS msec (continuous)	108 SD = 21	85.5 SD = 8	<0.001
fQRS positive (dichotomous) n, %	5 (31.25%)	0 (0%)	0.002
RMS40 μV (continuous)	12 SD = 5.5	41 SD = 16	<0.001
RMS40 positive (dichotomous) n, %	16 (100%)	5 (14%)	<0.001
LAS msec (continuous)	52 SD = 17	27 SD = 6.5	<0.001
LAS positive (dichotomous) n, %	16 (100%)	1 (3%)	<0.001

Table 3
Medication data for patients in relation to the presence or absence of LPs.

Typical antipsychotics only				
	All	LP positive	LP negative	p
Patient number	12	3	9	0.40
Medication number per patient	1.67 SD = 0.49	1.67 SD = 0.58	1.67 SD = 0.5	1
DDD per patient	3.61 SD = 2.95	4.86 SD = 4.07	3.19 SD = 2.66	0.42
Atypical antipsychotics only				
	All	LP positive	LP negative	p
Patient number	10	2	8	0.35
Medication number per patient	1.33 SD = 0.71	1 SD = 0	1.43 SD = 0.79	0.49
DDD per patient	1.56 SD = 1.09	1.1 SD = 1.3	1.7 SD = 1.1	0.53
Both classes of antipsychotics				
	All	LP positive	LP negative	p
Patient number	28	10	18	0.42
Medication number per patient	2.61 SD = 0.69	2.80 SD = 0.92	2.50 SD = 0.51	0.28
DDD per patient	3.76 SD = 2.79	3.35 SD = 2.35	3.98 SD = 2.92	0.56
Any antipsychotic				
	All	LP positive	LP negative	p
Patient number	50	15	35	0.065
Medication number per patient	2.14 SD = 0.84	2.33 SD = 1.05	2.06 SD = 0.74	0.30
DDD per patient	3.32 SD = 2.64	3.35 SD = 2.68	3.30 SD = 2.67	0.95
Any antidepressant				
	All	LP positive	LP negative	p
Patient number	9	4	5	1
Medication number per patient	1.13 SD = 0.35	1 SD = 0	1.25 SD = 0.5	0.36
DDD per patient	0.90 SD = 0.56	0.6 SD = 0.5	1.19 SD = 0.48	0.14
Any anxiolytic				
	All	LP positive	LP negative	p
Patient number	36	13	23	0.34
Medication number per patient	1.06 SD = 0.24	1 SD = 0	1.09 SD = 0.29	0.28
DDD per patient	1.60 SD = 0.9	1.78 SD = 0.75	1.49 SD = 0.98	0.36

Due to small numbers (n = 9 for all antidepressants), a subgroup analysis was not performed. DDD: Defined daily dose.

Mean follow-up duration was 46 (SD = 11) months. During this period, 5 patients (9.6%) died, 3 suffering SCDs and 2 non-cardiac deaths. Both non-cardiac deaths were related to lung cancer complications. Two SCD patients had both positive LPs and QRSfr. However, no statistically significant differences were noted regarding SCD occurrence based on LP or QRSfr presence ($p = 0.22$ and $p = 0.56$ respectively), nor did the presence of both LPs and QRSfr significantly increase SCD risk compared to the presence of either one or none of these parameters ($p = 0.052$ and $p = 0.13$ respectively). EF data were only available for 1 SCD patient (EF = 52%, CAD, LP and QRSfr present, along with frequent ventricular ectopy) (Fig. 1).

4. Discussion

SCD has been found to occur significantly more often in psychiatric patients than in the general population [4–7]. The underlying etiology is considered multifactorial: These patients more often do not comply with their medication regimens, have limited access to healthcare services and suffer from other CAD risk factors [4]. Furthermore, increased stress leads to dysautonomia and activation of the hypothalamus–pituitary–adrenal axis that ultimately cause, apart from the autonomic imbalance, increased inflammation and altered ion channel and connexin 43 expression [22].

The effect of medication, as an in itself predisposing to SCD factor in psychiatric diseases, has also been emphasized [35]. Antidepressants, both older (tricyclic) and newer (selective serotonin/norepinephrine reuptake inhibitors), inhibit a host of ion channels (sodium, calcium and potassium channels [36]), critical for the electrophysiologic properties of the myocardium. Thus it is conceivable that, aside from the disease itself, treatment medications could also increase the risk of sudden death. Antipsychotics show anticholinergic and QTc prolongation effects, attributable in part to potassium current inhibition, with certain substances inducing myocardial fibrosis [24,25]. Studies appear conflicting as to whether the diseases per se or treatment by modern mainstream medications are responsible for the increased SCD prevalence in this population. However, concerning antidepressants, in the largest relative study so far (TILDA study — [37]), autonomic imbalance was related to medications rather than to the presence of depression. Clinically, their effects on repolarization may lead to triggered activity-related arrhythmias, including torsades, and their potential effects on fibrosis to reentrant arrhythmias [25].

LP and QRSfr presence in SAECG and the 12 lead ECG are two of the easiest to apply non-invasive substrate assessment methods. In this context, abnormal depolarization of ventricular myocardial segments, potentially promoting arrhythmogenesis, can be recorded, either during (QRSfr) or at the final QRS segment (LPs). LP acquisition, however, has the added advantage of more precise measurement, at the μV-level by depressing ambient noise through signal averaging.

Indeed, in the present study a higher prevalence of LPs was found in psychiatric patients receiving psychotropic drugs than in healthy controls (16/52 vs 2/30, $p = 0.012$). This prevalence of abnormal late potentials was lower than what was previously reported among 33 schizophrenic patients [27], being 31% in the current study as opposed to 48% in the former single available so far study. More specifically, a lower RMS40 value was found to be driving this difference (46 μV, SD = 32 μV vs 32 μV, SD = 19 μV, $p = 0.015$). Whether this points to a specific effect, nosologic and/or pharmacological, on the inferoposterior wall, known to be depolarized relatively late, or constitutes a chance finding due to sample size remains unanswered. On the contrary, no difference on QRSfr prevalence was noted in the present study between psychiatric patients and healthy controls.

Our findings suggest that the relative potency of medication regimens, as assessed both by medication number and by DDD, cannot predict its electrophysiological effects on the SAECG (Table 3 — comparison between LP patient groups). This is in accordance with the findings by Nahshoni et al. [27] who found DDD to be actually lower in LP positive psychiatric patients. This points to either nosologic effects leading to LP presence or divergent effects of medications on the brain and heart physiology. Obviously, conducting a randomized trial to answer this question would be unethical, inasmuch as it would entail using a group of untreated patients as controls.

However, it has been previously shown that the sodium channel blocking effects of antidepressant medications may unfavorably influence the SAECG parameters of 11 depressed females in a similar manner to the unfavorable effect of type IA antiarrhythmic agents [26]. Due to the small number of patients receiving antidepressant medications in our study, we did not perform a subanalysis in order to reveal a potentially detrimental effect of these agents on the SAECG.

Despite similar underlying pathophysiology, we could not detect a relationship between LP and QRSfr presence. Such a relationship has also not been noted in Brugada syndrome patients [38].

Event number during follow-up, with emphasis on SCD, was low, due to small sample size, precluding adequate power to detect potential differences and effects of LPs and/or QRSfr. However, it should be noted that two SCD patients had both LPs and QRSfr, one suffering from CAD with well-preserved EF (52%). Thus, it is conceivable that an interplay of subclinical electrophysiologic alterations caused by CAD, even in the absence of significant left ventricular dysfunction or symptomatic ischemia [39,40] with the psychotropic medications on board and the underlying psychiatric disorder present, might have created the perfect storm for malignant arrhythmogenesis (Fig. 1). Obviously, larger trials will be necessary to verify or refute this hypothesis.

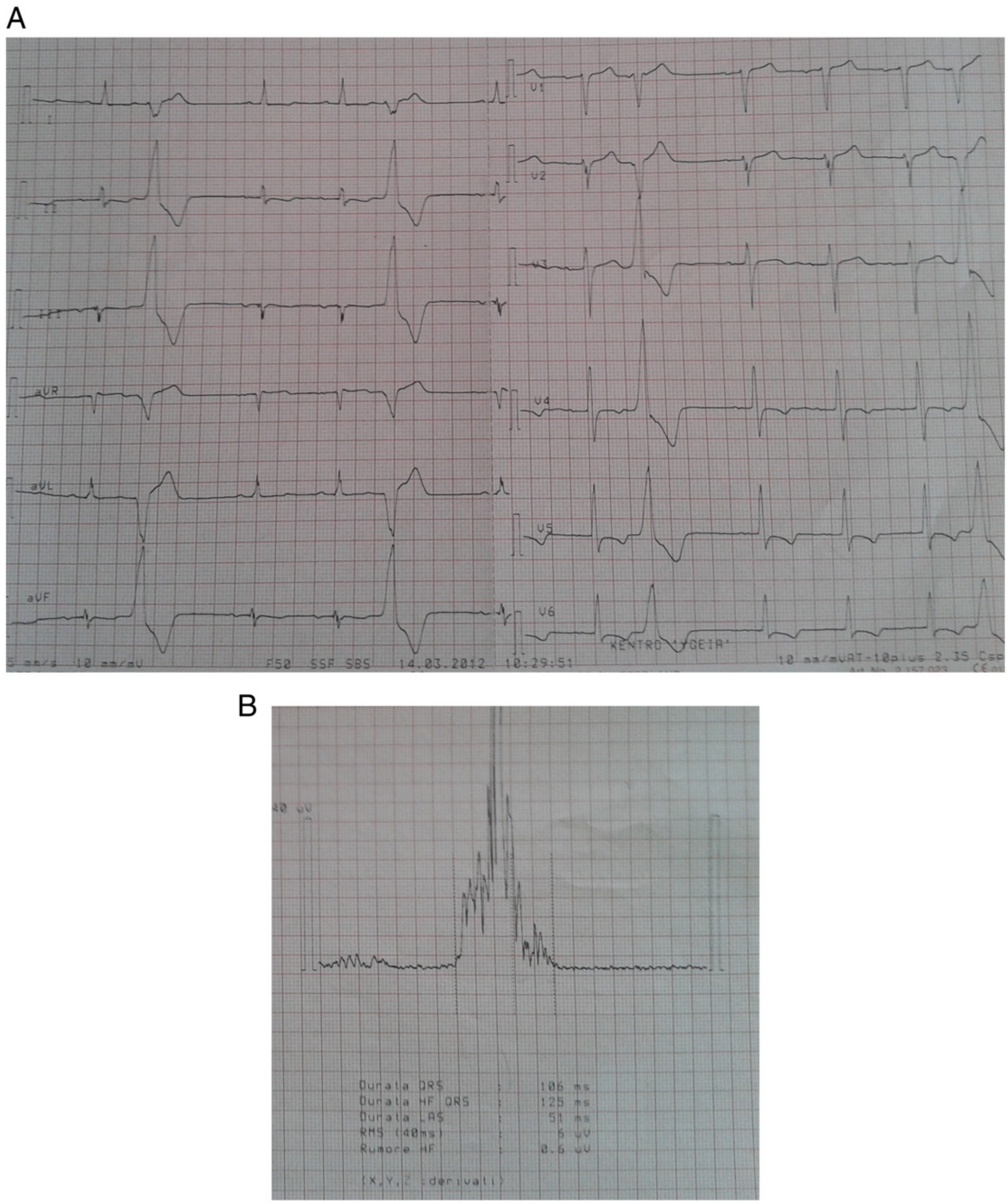

Fig. 1. A. 12 lead ECG. QRS fragmentation in the inferior wall (leads II, III, aVF) is evident in this tracing (Rsr and notched S patterns). Furthermore, significant ventricular ectopy in the form of extrasystoles is present. B. SAECG (same patient as in Fig. 1A). Late potential presence is evident in this recording as delayed depolarization following the bulk of the QRS complex. Sensitivity is 1000 mm/mV and paper speed 100 mm/s. All three parameters are abnormal (fQRS duration 125 msec, LAS duration 55 msec, and QRS40 6 mV. Both tracings come from a 60 year old organic psychosis patient, with known CAD, preserved EF (52%), on low dose of atypical antipsychotics (DDD = 0.2). Thirty-eight months post assessment he died suddenly without any preceding anginal or/and heart failure symptoms.

5. Study limitations

Our study is an observational one, with a low event rate and small sample size, thus unable to control cause and effect hypothesis. Our control group was not screened for a subclinical structural heart disease, rather a clinical evaluation and an electrocardiogram were used — however this renders it closer to the concept of the "general population". Our psychiatric patient group is heterogeneous, including patients with a variety of disorders which led to short- or long-term hospitalization and thus findings may not be applicable to the commonly encountered psychiatric population in the outpatient setting. Furthermore, many patients were taking multiple classes of medications, rendering the study of any class-specific effect difficult. Finally, we had no data on the severity of psychiatric disorders, which could, should their neurological and cardiovascular effects be parallel, allow for the detection of relevant correlations. However, our sample constitutes the largest psychiatric population to date to have been evaluated for the presence of LPs [26,27].

6. Conclusions

Hospitalized psychiatric patients that are already exhibiting abnormal intraventricular conduction and repolarization prolongation could be at higher risk for adverse arrhythmic events following initiation of therapy, warranting closer monitoring. LPs, detected by SAECG are found significantly more often in this group than in controls, as opposed to QRSfr. The precise underlying mechanism, as well as potential ramifications for long-term prognosis remain to be determined by large, prospective clinical trials. With the current small observational study, it is attempted to bring back into focus the effect of psychiatric diseases and/or psychotropic medications on depolarization, as assessed by detection of LPs in SAECG.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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