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Signal-Averaged Electrocardiogram in Physically Healthy, Chronic 3,4-Methylenedioxymethamphetamine (MDMA) Users

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Abstract

Objectives—3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) use has been associated with cardiac arrhythmias. Markers of ventricular late potentials (VLP), which may be a precursor to malignant ventricular arrhythmias, can be detected by signal-averaged electrocardiography (SA-ECG), but not by standard ECG.

Methods—We evaluated SA-ECG parameters in 21 physically healthy, recently abstinent MDMA users who also used cannabis (11 males, mean [SD] age 23.3 [4.6] years, 2.8 [2.0] years of use), 18 physically healthy cannabis users (8 males, mean [SD] age 26.6 [7.1] years, 11.2 [5.4] years of use) and 54 non-drug-using controls (21 males, mean [SD] age 28.4 [7.8] years). We analyzed three SA-ECG parameters considered markers of VLPs: duration of filtered QRS complex (fQRS), duration of low amplitude potentials during terminal 40 ms of QRS complex (LAS40), and root mean square voltage during terminal 40 ms of QRS complex (RMS40).

Results—MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in fQRS, LAS40, or RMS40 values or in the proportion of subjects with abnormal SA-ECG parameters. There were significant gender differences among controls, but not among MDMA users.

Conclusion—These findings suggest that chronic MDMA use is neither quantitatively nor qualitatively associated with a high prevalence of abnormal SA-ECG parameters indicative of VLP markers.

Keywords

MDMA; cannabis; signal-averaged ECG; ventricular late potentials

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) has cardiovascular effects similar to those of stimulants such as cocaine,^{1,2} including dose-dependent increases in heart rate and blood pressure.^{3,4} At higher doses, MDMA may produce cardiac arrhythmias such as tachycardia and ventricular fibrillation, which may lead to sudden death.^{5–8} Cannabis use also increases heart rate, but tends to lower blood pressure and is less associated with cardiac arrhythmias.^{9,10} Some experimental studies and case reports have associated cannabis use

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with premature ventricular contractions and tachyarrhythmias such as atrial fibrillation, ventricular tachycardia, and ventricular fibrillation.^{11–14}

Ventricular late potentials (VLPs) are aberrant impulses during sinus rhythm that may precede the onset of certain arrhythmias, such as ventricular tachycardia (VT). They are considered as predictors of ventricular arrhythmias and sudden cardiac death in individuals who have survived a myocardial infarction.^{15,16} VLPs are generally masked by electrical noise on the standard electrocardiogram (ECG), but can be detected by signal-averaged electrocardiography (SA-ECG). In this technique, the voltage signal from each ECG lead is averaged over multiple beats to cancel out random noise and enhance the sensitivity for detecting low amplitude signals.

Several SA-ECG parameters have been used to detect VLP markers. These include duration of the filtered QRS complex (fQRS), duration of high frequency, low amplitude signals (potentials below 40 gV) in the terminal period of ventricular activation (QRS complex) (LAS), and root mean square (RMS) voltage in the terminal 40 ms of the QRS complex (RMS).^{15–18} Abnormal values for these SA-ECG parameters are considered markers of VLPs. Published normal values for SA-ECG parameters and criteria for VLPs vary somewhat; some are gender-specific.^{15–18} SA-ECG parameters have been correlated with body surface area (BSA)¹⁸ and body mass index (BMI),¹⁹ but not with age.^{20,21} We are not aware of any literature on SA-ECG measures or VLPs in MDMA or cannabis users.

We present here data on SA-ECG results in a sample of 21 physically healthy, MDMA users, 54 healthy, non-drug-using controls, and 18 healthy cannabis users. Cannabis users were studied as a positive control for the MDMA users, all of whom also used cannabis.

METHODS

Subjects

MDMA-using subjects were non-treatment-seeking adults recruited from the community and meeting the following criteria: 18–40 years of age, history of MDMA use supported by a urine test positive for amphetamines (which also detect MDMA) or MDMA-positive hair test in the past 90 days, in good physical health based on medical history, physical examination, clinical laboratory tests, and 12-lead ECG with 3-minute rhythm strip, no family history of myocardial infarction or sudden death before age 50, and no personal history of cardiovascular disease, seizure, loss of consciousness for more than 3 minutes, or clinically significant MDMA-related adverse event.

Cannabis-using subjects were recruited from the community. They had to be at least 18 years of age, have a urine drug screen positive for cannabis and negative for all other illegal drugs, no more than three uses per month of other illegal drugs in the 3 months prior to screening, and be in good physical health based on medical history, physical examination, and 12-lead ECG with 3-minute rhythm strip. Exclusion criteria included family history of non-traumatic sudden death before the age of 50 or personal history of cardiovascular disease.

Non-drug-using control subjects were recruited from the community. They had to be at least 18 years of age, have no more than 3 self-reported lifetime uses of any illegal drug (with no use in the year prior to screening), have a negative urine drug screen, and be in good physical health based on medical history, physical examination, and 12-lead ECG with 3-minute rhythm strip. Exclusion criteria included family history of non-traumatic sudden death before the age of 50 or personal history of cardiovascular disease.

The study was approved by the Institutional Review Board of the National Institute on Drug Abuse (NIDA). All subjects gave written informed consent when not acutely intoxicated, and were paid for their study participation.

Procedures

MDMA-using subjects were admitted to the closed research ward of the NIDA Intramural Research Program on the evening prior to testing. To prevent use of unauthorized drugs, subjects and their belongings were searched for drugs on admission, no passes or visitors were allowed, all personal belongings and mail were screened by staff, and periodic urine samples were tested for drugs. SA-ECG recordings were obtained before any research drug administration. Cannabis-using subjects and non-drug using control subjects were given the SA-ECG after providing informed consent, a negative urine drug screen (except for cannabis-positive urine for the cannabis users), and negative breath alcohol test.

All SA-ECGs were obtained using a MAC[®] VU Resting ECG Analysis System with accompanying software: Hi-Res signal averaging program 002C and 002D (Marquette Electronics, Milwaukee, WI). All SA-ECGs were obtained non-fasting between 6:00 a.m. and 6:30 p.m. with subjects in the supine position. Subjects did not eat or drink 30 minutes before the testing. Subjects had normal heart rate and blood pressure around the time of the ECGs (data not shown). Bandpass digital filtering used a high-pass filter set at a Blackman-Harris window²² of 40–250 Hz. To be included in the analysis, SA-ECGs had to have a noise level < 1.0 μ V and be calculated on > 40 beats.

Detection of VLP markers was based on time-domain analysis of three standard, validated SA-ECG variables²³: fQRS, LAS40, and RMS40.

Data Analysis

Groups were compared on both quantitative values and proportion of subjects with abnormal SA-ECG parameters based on published normal values.¹⁷ Because of possible gender differences in SA-ECG parameters,^{15–18} gender-specific comparisons were also done. Current cigarette smokers were compared to non-smokers to evaluate effects of smoking status. Comparison of group characteristics used analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Potential confounding factors among subject characteristics were identified from the literature (gender, BMI, BSA) or by bivariate correlational analyses from our previous study involving cocaine and SA-ECG (age) (unpublished data). Identified quantitative confounding factors (age, BMI, BSA) were used as covariates in analyses of covariance (ANCOVA) performed with a general linear model for each SA-ECG parameter; gender was addressed by performing gender-specific analyses. The two-tailed alpha was set at 0.05. All statistical tests were performed with SPSS v.15.0 (SPSS Inc., Chicago, IL).

RESULTS

SA-ECG data were obtained from 21 MDMA users (all of whom also used cannabis), 18 cannabis users, and 54 non-drug using control subjects (Table I). There was no use of other illegal drugs, such as cocaine and heroin, by the subjects (data not shown).

MDMA users, cannabis users, and non-drug-using controls differed significantly from each other in age, race, and alcohol and cigarette use (Table I). Male MDMA users, cannabis users, and non-drug-using controls were similar in BMI (23.8 [3.7] kg/m² vs. 27.9 [6.6] kg/m² vs. 26.7 [5.1] kg/m²; $p = .19$), and BSA (1.94 [.15] m² vs. 2.02 [.24] m² vs. 2.02 [.20] m²; $p = .54$), but differed significantly in age (24.2 [5.4] years vs. 25.0 [7.4] years vs. 33.2 [7.5] years;

$p = .002$) and race (73% vs. 100% vs. 52% African-American; $p < .05$). Female MDMA users, cannabis users, and non-drug using controls were similar in age (22.4 [3.6] years vs. 27.8 [7.0] years vs. 25.4 [6.4] years; $p = .15$), race (80% vs. 100% vs. 67% African-American; $p = .10$), BMI (24.8 [6.8] kg/m² vs. 28.6 [6.7] kg/m² vs. 26.7 [6.7] kg/m²; $p = .45$), and BSA. Male non-drug-using controls differed significantly from female non-drug-using controls in age (33.2 [7.5] years vs. 25.4 [6.4] years; $p < .001$) and BSA (2.02 [0.20] m² vs. 1.81 [0.25] m²; $p = .002$), but were similar in race (52% vs. 67% African-American; $p = .39$) and BMI (26.7 [5.1] kg/m² vs. 26.7 [6.7] kg/m²; $p = .98$).

SA-ECGs used in the analyses had the following characteristics (mean [SD]): 260.1 [3.2] beats detected, 259.7 [2.7] beats averaged; 0.25 [0.06] μ V noise level. There were significant correlations between fQRS and LAS40 ($r = .51$, $p < .001$), fQRS and RMS40 ($r = -.57$, $p < .001$), and LAS40 and RMS40 ($r = -.56$, $p < .001$).

Among the 21 MDMA users or among the 18 cannabis users, quantitative SA-ECG parameters did not correlate significantly with age, BMI, BSA, or with substance use measures (data not shown).

Among the 54 non-drug using control subjects, quantitative SA-ECG parameters did not correlate significantly with age or BMI (data not shown). BSA was significantly correlated with fQRS ($r = .49$, $p < .001$) and RMS40 ($r = -.28$, $p = .04$), but not LAS40 ($r = .26$, $p = .06$).

After controlling for age, BMI, and BSA, MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in fQRS (109.2 [6.8] ms vs. 108.1 [6.6] ms vs. 108.1 [6.6] ms; $p = .81$), LAS40 (31.3 [6.7] ms vs. 29.4 [6.5] ms vs. 30.0 [6.5] ms; $p = .66$), or RMS40 (34.8 [17.9] μ V vs. 41.1 [17.4] μ V vs. 38.8 [17.5] μ V; $p = .54$). MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in the proportion of subjects with abnormal fQRS values (0% vs. 6% vs. 6%; $p = .64$), LAS40 values (5% vs. 0% vs. 6%; $p = .82$), or RMS40 values (10% vs. 6% vs. 7%; $p = 1.0$). MDMA users, cannabis users, and non-drug-using controls did not differ from each other in the proportion of subjects with at least one abnormal SA-ECG parameter (10% vs. 6% vs. 11%; $p = .89$), at least two abnormal SA-ECG parameters (5% vs. 6% vs. 4%; $p = 1.0$), or all three abnormal SA-ECG parameters (0% vs. 0% vs. 4%; $p = 1.0$).

After controlling for age, BMI, and BSA, male MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in fQRS, LAS40, or RMS40 values (Table II) or in the proportion of subjects with abnormal values (all proportions were $\leq 14\%$). The proportion of subjects with at least one abnormal value was 9%, 13%, and 19%, respectively ($p = 0.85$ for group differences). Female MDMA users, cannabis users, and non-drug-using controls also did not differ significantly from each other in quantitative values (Table II) or proportion of subjects with abnormal values (all proportions were $\leq 10\%$). The proportion of subjects with at least one abnormal value was 10%, 0%, and 6%, respectively ($p = 0.77$ for group differences). After controlling for age, BMI, and BSA, male controls users were significantly different from female controls in fQRS (111.9 [6.8] ms vs. 105.4 [6.4] ms; $p = .003$), but not in LAS40 (28.8 [7.8] ms vs. 30.7 [7.4] ms; $p = .44$) or RMS40 (32.9 [19.0] μ V vs. 42.2 [17.9] μ V; $p = .12$) values. Male controls did not differ significantly from female controls in the proportion of subjects with abnormal SA-ECG parameters (data not shown).

Male MDMA users did not differ significantly from female MDMA users in either the means or proportion of subjects with abnormal SA-ECG parameters (data not shown).

Among male controls, smokers were not significantly different than non-smokers in either the means or proportion of subjects with abnormal SA-ECG parameters (data not shown).

DISCUSSION

This study found that MDMA users, cannabis users, and non-drug-using controls did not differ significantly from each other in either quantitative parameters or in proportion of subjects with abnormal SA-ECG parameters, even after controlling for several potential confounding variables (gender, age, BMI, BSA). These findings suggest that neither MDMA nor cannabis use is associated with cardiac electrophysiological abnormalities (detectable by SA-ECG) in medically screened MDMA users with normal standard ECGs.

Among the control subjects, we found significant gender differences in fQRS values, consistent with previous reports in the literature.^{16–18} Gender differences could be due to effects of sex hormones (estrogen, testosterone) on cardiac electrophysiological parameters and arrhythmias.^{24,25} There were no gender differences in SA-ECG parameters among MDMA users, suggesting that MDMA use may blur possible gender differences.

MDMA users in this study had a similar prevalence of at least one abnormal SA-ECG parameter (10%) as does the general population with no history of myocardial infarction (6%).¹⁵ We previously found that cocaine users had a significantly higher prevalence of at least one abnormal SA-ECG parameter than the general population (27% vs. 6%) (unpublished data), suggesting a possible trend towards a higher prevalence of VLP markers among cocaine users. In contrast, MDMA users seem to show no such trend, suggesting that MDMA use may create less of a risk for VLPs than does cocaine use.

The major limitations of this study are small sample sizes and limited external validity (generalizability). MDMA users were medically screened to exclude those with clinically significant medical conditions or most risk factors for cardiovascular disease, except for cigarette smoking, and were not tested while under the acute influence of MDMA. Thus, study subjects may not be representative of the entire population of MDMA users.

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Table 1

Demographic and substance use characteristics of 54 non-drug-using controls, 18 cannabis users, and 21 MDMA users

Subject Characteristic	Non-drug using controls	Cannabis users	MDMA users	P value for Group D
Number of subjects	54	18	21	
Age (years)	28.4 (7.8)	26.6 (7.1)	23.3 (4.6)	p = .02
Sex (%)				p = .57
Male	39	44	52	
Female	61	56	48	
Race (%)				p = .002
African-American	61	100	76	
White/Other	39	0	24	
Height (inches)	66.8 (4.0)	67.1 (3.9)	67.3 (4.1)	p = .89
Weight (lbs)	169.4 (40.5)	180.4 (41.6)	156.8 (35.9)	p = .18
Body Mass Index (kg/m²)^a	26.7 (6.1)	28.3 (6.5)	24.3 (5.3)	p = .11
Body Surface Area (m²)^b	1.89 (.25)	1.95 (.24)	1.83 (.24)	p = .28
MDMA use (%)^c	0	0	100	N/A
Years of use	0	0	2.8 (2.0)	
Use in prior month (days)	0	0	7.3 (6.6)	
Alcohol Use (%)^d	81	100	100	p = .02
Years of use	8.9 (10.3)	9.8 (5.9)	7.5 (4.2)	p = .68
Use in prior month (days)	1.4 (3.0)	4.2 (5.4)	7.8 (5.4)	p < .001
Cigarette use (%)^d	19	50	85	p < .001
Cigarettes per day	9.7 (8.5)	11.2 (6.7)	12.3 (7.5)	p = .70
Cannabis use (%)^e	0	100	100	p = 1.0^f
Years of use	0	11.2 (5.4)	8.3 (3.4)	p = .06^f
Use in prior month (days)	0	24.3 (6.3)	18.0 (11.8)	p = .04^f

^a Body Mass Index (BMI) = (Weight [kg])/(Height [m])²^b Body Surface Area (BSA) = ((Height [cm]) × (Weight [kg])/(3600))^{1/2} 26^c 1 MDMA user did not report extent of MDMA use^d 7 non-drug using controls and 1 MDMA user did not report extent of alcohol use^e 1 MDMA user did not report extent of cannabis use^f P value for difference between cannabis users and MDMA users

Sex-specific quantitative comparison of signal-averaged electrocardiogram parameters among MDMA users, cannabis users, and non-drug using controls*

Table II

	fQRS (ms) ^a		LAS40 (ms) ^a		RMS40 (gV) ^a	
	AdjMean	SD	AdjMean	SD	AdjMean	SD
Male MDMA users (n = 11)	109.5	7.5	30.9	8.5	34.7	14.2
Male cannabis users (n = 8)	114.3	7.1	31.3	8.1	32.0	13.6
Male non-drug-using controls (n = 21)	113.1	7.5	30.8	8.5	31.2	14.2
P value for group difference	p = .31		p = .99		p = .82	
Female MDMA users (n = 10)	108.4	5.0	31.5	5.8	35.0	20.2
Female cannabis users (n = 10)	102.7	5.0	28.1	5.8	48.0	20.0
Female non-drug-using controls (n = 33)	105.2	4.8	29.5	5.6	43.7	19.4
P value for group difference	p = .06		p = .43		p = .35	

* Values are presented as adjusted means and standard deviations after controlling for age, BMI, and BSA

^a fQRS = duration of filtered QRS complex, LAS = duration of low amplitude (< 40 μV) signals during terminal phase of QRS complex, RMS = root mean square voltage during terminal 40 ms of QRS complex