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of first time ICD recipients were candidates for S-ICD.[1]

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ORIGINAL ARTICLE

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QT prolongation by dexamphetamine: Does experience matter?

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Abstract

Introduction: Case reports of life-threatening cardiac arrhythmias and sudden cardiac arrest (SCA) among amphetamine users have raised serious concerns about the cardiac safety of this class of drugs. This is important in light of the high prevalence of dexamphetamine (dAMPH) prescription for attention-deficit/hyperactivity disorder (ADHD), and its rising use as a recreational drug. The objective was to investigate electrocardiogram (ECG) parameters upon intravenous administration of a single dAMPH dose in habitual recreational dAMPH users (users) and healthy gender/age/ intelligence-quotient-matched controls (non-users).

Methods and results: ECG recordings were made in 18 users and 18 non-users during administration of dAMPH (0.3 mg/kg body weight). Baseline ECG was normal in both groups. dAMPH elicited increased heart rate and corrected QT time (QTc) prolongation in both groups (all $P < 0.001$, QTc = 502 in one individual). QTc prolongation was attenuated in users compared to non-users, exhibiting a significant interaction effect ($P = 0.04$).

Conclusion: SCA associated with amphetamine use may be related to its QTc prolonging effects, particularly during first-time use. These observations may provide a rationale for conducting ECG analysis immediately after the first-time use of amphetamines, as this could potentially unmask vulnerable individuals.

KEYWORDS

arrhythmia, dexamphetamine, psychostimulants, QT prolongation, sudden death

1 | INTRODUCTION

Amphetamines are stimulant drugs most commonly known for the treatment of attention-deficit hyperactivity disorder (ADHD). They are also used as recreational drugs, albeit at higher dosages. Case reports of life-threatening cardiac arrhythmias and sudden cardiac arrest (SCA) among amphetamine users have raised serious concerns about the cardiac safety of these drugs.[1,2] Accordingly, the Food and Drug Administration issued a warning in 2006 cautioning the association of stimulant drugs for ADHD treatment with serious cardiovascular events such as SCA.[3] Understanding the nature and causes of this association is clearly relevant, given that the prevalence of both ADHD[4] and recreational amphetamine use[5] is high and rising. Retrospective cohort studies have not confirmed that the incidence of SCA among ADHD patients treated with amphetamines is increased on average.[6–8] Yet, case reports indicate that there are individuals with increased susceptibility to SCA, in particular, those with first-time use of amphetamines.[1] This complexity has remained unresolved, as systematic studies on the effects of amphetamines on human cardiac electrophysiologic properties have been lacking.

We aimed to shed further light on this complexity by comparing changes in electrocardiogram (ECG) parameters upon intravenous bolus administration of a single high dose of dexamphetamine (dAMPH) between habitual recreational dAMPH users and nonusers.

2 | METHODS

2.1 | Subjects

This work was part of a study in which the role of dopamine in habitual recreational dAMPH users (users) and drug-naive controls

(non-users) was investigated.[9,10] 19 users and 22 gender/age/intelligence quotient (IQ)-matched non-users were recruited through online advertisements and flyers at local universities and colleges, as earlier described.[10] Users had consumed amphetamines on at least 30 occasions prior, whereas nonusers reported no history of amphetamine use or other drugs that interact with the dopamine system. Exclusion criteria were a history of a chronic neurological or psychiatric disorder, family history of SCA, abnormal ECG, a positive drug screen, smoking more than 15 cigarettes per day, drinking more than 30 alcoholic beverages per week, and current use of psychotropic medication. Participants were asked to abstain from nicotine, caffeine, alcohol, and cannabis for 24 hours, as well as other drugs one week prior to the study (the latter was confirmed by a urine drug screen), and signed informed consent. The study procedures were approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam and were conducted in accordance with the standards of the Declaration of Helsinki.

2.2 | Study procedures and design

Participants made two study visits, at least one week apart, once for a brain magnetic resonance imaging (MRI) scan and once for a single-photon emission computed tomography (SPECT) scan to measure dopamine receptors and dopamine released by dAMPH. The results obtained from these scans are reported elsewhere.[9,10] Participants received dAMPH on both study visits. The ECG was measured during the SPECT scan session. Participants were randomized within-group to first undergo the MRI or SPECT scan session. One dAMPH bolus (0.3 mg/kg) was injected via a cannula in an antecubital vein over 2 minutes, and flushed with 15 mL saline solution. Twelve-lead ECG data were recorded at baseline and at 2, 4, 8, 10, 12, and 20 minutes after administration of the dAMPH bolus, respectively.

2.3 | Data analysis

ECG parameters were measured by a rater blind to the group status, and included: heart rate (HR), PR interval, QRS interval, QT duration, and corrected QT time (QTc) duration (Bazett). The main effect of time as well as time*group interaction effects were analyzed using a repeated-measures analysis of variance (ANOVA) with Greenhouse–Geisser corrections in case of inequality of homogeneity of variances. Data were analyzed in SPSS version 22.0.

3 | RESULTS

3.1 | Demographics

Two non-users were excluded from the study because of abnormal ECG. For two non-users, data could not be analyzed due to technical issues. In addition, one individual from the user group was excluded due to a positive drug screen for amphetamines. Thus, in total 36 participants (N = 18 for both groups) were included in the analyses. Groups were well-matched in terms of age, IQ, and body mass index (BMI) (Table 1).

3.2 | Baseline ECG

Baseline ECG parameters did not differ significantly between groups and were normal on average (Table 1). This included QTc duration, which was <430 milliseconds for all participants (range 320.7–429.7 milliseconds).

3.3 | ECG changes upon dAMPH administration

dAMPH administration elicited no significant changes in PR and QRS duration (Table 1), but only in HR, QT duration, and QTc duration. HR increased significantly ($P < 0.001$) in both groups (Fig. 1A), but after an initial drop at 2 minutes post-dAMPH in the user group, non-users showed a higher peak HR with a faster return to baseline values (time*group interaction, $P = 0.06$). QTc duration significantly ($P < 0.001$) increased upon dAMPH administration (Fig. 1B). One non-user even reached a QTc duration of 502 milliseconds at 8 minutes after dAMPH administration (see ECG in Fig. 2). QTc prolongation was attenuated in users compared to non-users, exhibiting a significant interaction effect ($P = 0.04$). No association was found between time-since-last-dAMPH-use and QTc prolongation ($r = -0.22$, $P = 0.30$).

4 | DISCUSSION

We found that dAMPH increased HR and QTc duration, and that QTc prolongation was largest and occurred most rapidly in non-users, even leading to a potentially dangerous QTc duration (502 milliseconds)[11] in one individual from the non-user group. QT prolongation may be an important contributing factor in the occurrence of SCA, particularly in vulnerable individuals.[12] Despite the clear QTc prolonging effect of dAMPH, QTc duration at baseline was normal in users who were confirmed amphetamine free by drug screens. This suggests that QTc duration is not altered by habitual use per se (e.g., by direct changes to cardiac electrophysiology or by changes in the brain or autonomic nervous system that indirectly influence cardiac physiology), but rather by the acute effects of dAMPH on cardiac electrophysiology. This finding seems at odds with a previous study of ECG parameters in individuals with amphetamine dependence who were included in a trial to study the effects of ondansetron.[13] In that study, 27% of individuals had high-normal or prolonged QTc (>440 milliseconds) before ondansetron treatment. However, it was not reported whether they were in an amphetamine-free state (which seems unlikely given that they were included in this trial because of their amphetamine dependence) or had any other QT prolonging drugs or comorbidities at the time of ECG recording. Moreover, the participants in the present study were using predominantly dAMPH rather than methamphetamine (which is more potent because it crosses the blood–brain barrier more easily) and were not dependent on the drug, suggesting that the total exposure to amphetamines was much lower in the current study.

The pathophysiologic basis of our observations and the case reports of life-threatening cardiac arrhythmias and SCA upon use of amphetamine (derivatives) may be found in two cellular studies. The first study[14] reported that methamphetamine accelerated the

beating rate and altered intracellular Ca^{2+} oscillation patterns in cultured neonatal rat cardiomyocytes. These effects were due to direct effects on L-type Ca^{2+} channels to increase Ca^{2+} entry into the myocytes, and were independent of adrenergic signaling or Ca^{2+} handling by the sarcoplasmic reticulum. The resulting increase in depolarizing current is expected to shift the balance between depolarizing and repolarizing forces, reducing the net repolarizing forces and to result in delayed repolarization and QT prolongation. Moreover, the increase in intracellular Ca^{2+} levels and Ca^{2+} oscillations will facilitate ectopic beat formation and cardiac arrhythmia.[15] The second study reported that methamphetamine administration to neonatal rat ventricular myocytes induced electrophysiological remodeling in that it

TABLE 1 Demographics and ECG data

Parameter	Nonusers	Users	Test-Statistic	P-Value*
N	18	18		
Age (years)	21.2 ± 2.9	21.2 ± 1.7	t = 0.07	0.95
IQ	104.7 ± 7.1	104.4 ± 5.0	U = 199	0.13
BMI	23.4 ± 2.2	22.6 ± 2.8	U = 127	0.28
Study entry characteristics				
Systolic blood pressure	129 ± 13	130 ± 18	U = 100	0.08
Diastolic blood pressure	69 ± 9	63 ± 9	U = 145	0.61
HR (bpm)	69 ± 15	75 ± 16	U = 147	0.86
Baseline characteristics (0 minutes after dexamphetamine bolus)				
HR (bpm)	63 ± 8	69 ± 11	t = −1.8153	0.09
PR	169 ± 16	160 ± 22	t = 1.3836	0.19
QRS	95 ± 11	93 ± 11	t = 0.3149	0.76
QT	375 ± 32	368 ± 27	t = 0.7145	0.48
QTc	382 ± 29	391 ± 18	t = −1.0357	0.31
Peak characteristics (10 minutes after dexamphetamine bolus)				
HR (bpm)	95 ± 20	89 ± 22	t = 1.1211	0.28
QT	343 ± 38	347 ± 34	t = −0.4813	0.64
QTc	428 ± 34	416 ± 27	t = 1.0444	0.31
End-point characteristics (20 minutes after dexamphetamine bolus)				
HR (bpm)	84 ± 15	90 ± 21	t = −0.9702	0.35
PR	155 ± 19	154 ± 13	t = 0.1138	0.91
QRS	95 ± 11	93 ± 11	t = 0.3149	0.76
QT	353 ± 36	345 ± 33	t = 0.7199	0.48
QTc	412 ± 21	416 ± 23	t = −0.6028	0.55

Bpm = beats per minute; HR = heart rate. Data are expressed as mean ± standard deviation; * $P < 0.05$.

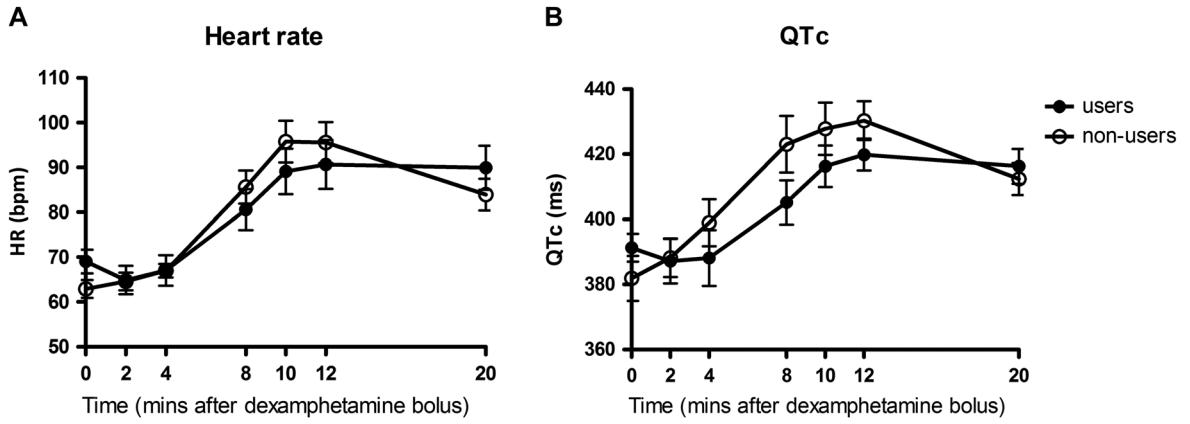

FIGURE 1 ECG results—ECG results from recordings taken at intervals between 0 and 20 minutes after the intravenous administration of a dexamphetamine bolus in drug-naive participants (nonusers, n = 18) and recreational amphetamine users (users, n = 18). (A) A significant increase in heart rate (beats per minute) was found in both groups ($P < 0.001$). (B) A significant QTc interval prolongation occurred in both groups ($P < 0.001$), but this effect was attenuated in users. Plots show mean, and error bars represent the standard error of the mean

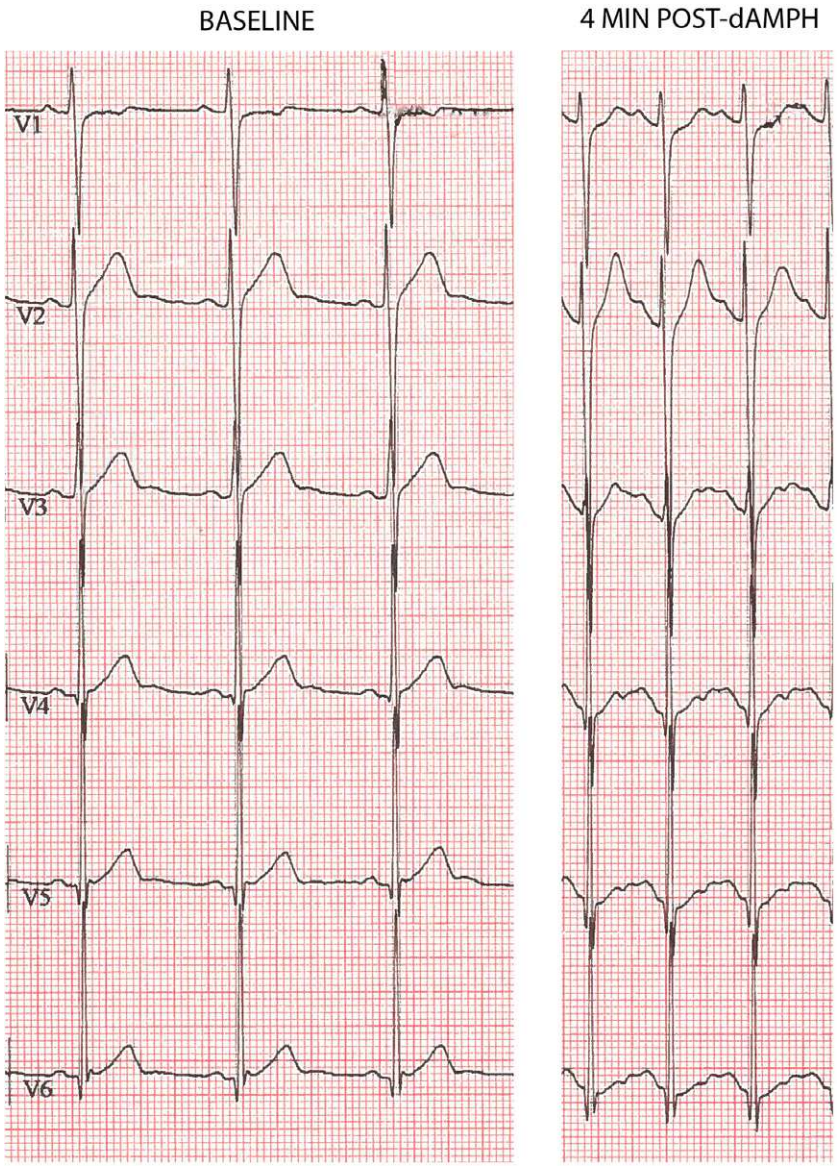

FIGURE 2 Example ECG of control subject (nonuser) before dAMPH infusion and 4 minutes after start of dAMPH infusion. QT duration upon dAMPH administration adapts too slowly to increase in heart rate. Note development of prominent U waves, most clearly in V3–V6 [Color figure can be viewed at wileyonlinelibrary.com]

reduced the expression of sarcolemmal ion channel subunits, which carry I_{to} (this current plays a key role in repolarization), I_{K1} (which stabilizes the resting membrane potential), and the L-type Ca^{2+} current $I_{Ca\text{-}L}$.[16] Downregulation of I_{to} will prolong QTc duration, while downregulation of $I_{Ca\text{-}L}$ will have the opposite effect. Of note, while all effects were reversible upon washout of methamphetamine, the reversal to baseline levels took longer for the $I_{Ca\text{-}L}$ channel subunits. These findings are consistent with our observation that users had attenuated QTc prolongation upon dAMPH administration when compared to nonusers. In users, $I_{Ca\text{-}L}$ may still be downregulated from their previous use of amphetamines, while reversal of downregulation of I_{to}, which occurs faster, was already complete. Similarly, the findings from these cellular studies may explain why case reports of SCA during amphetamine use dealt with first-time drug users, in whom there was no prior amphetamine use that could have attenuated the proarrhythmic effects of amphetamines. For instance,[1] first-time use of 3,4-methylene-dioxymethamphetamine (MDMA) elicited ventricular arrhythmia and SCA in an individual who had increased vulnerability to the increases in intracellular Ca^{2+} levels and Ca^{2+} oscillations, because he was found to carry a mutation in the *RYR2* (ryanodine receptor-encoding gene). Conversely, electrophysiological remodeling by amphetamine may also have deleterious effects, as demonstrated by another case report.[2] Here, a woman suffered extreme QTc prolongation and SCA after daily use (for a week) of methamphetamine. As daily use would have allowed insufficient time for reversal of I_{to} (and $I_{Ca\text{-}L}$) downregulation between drug applications, thereby magnifying the QTc prolonging effects of amphetamines. This was exacerbated by the fact that she turned out to have inherited Long QT syndrome, carrying a mutation in *KCNH2* (potassium voltage-gated channel subfamily H member 2), which encodes the repolarizing current I_{Kr}.

5 | CONCLUSION

Taken together, these observations may provide leads to design strategies aimed at increased safety in the use of amphetamines. Proarrhythmia of these drugs is in part mediated by QTc prolongation and occurs in individuals with increased vulnerability, e.g., because they carry genetic variants. First-time use is an excellent time to unmask increased vulnerability, because electrophysiological remodeling, which may attenuate signs of vulnerability, has not taken place. These observations may provide a rationale for conducting ECG analysis immediately after the first-time use of amphetamines.

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