

Cardiovascular Effects of 3,4-Methylenedioxymethamphetamine

A Double-Blind, Placebo-Controlled Trial

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Background: The psychoactive stimulant 3,4-methylenedioxymethamphetamine (MDMA), also known as "ecstasy," is widely used in nonmedical settings. Little is known about its cardiovascular effects.

Objective: To evaluate the acute cardiovascular effects of MDMA by using transthoracic two-dimensional and Doppler echocardiography.

Design: Four-session, ascending-dose, double-blind, placebo-controlled trial.

Setting: Urban hospital.

Patients: Eight healthy adults who self-reported MDMA use.

Intervention: Echocardiographic effects of dobutamine (5, 20, and 40 $\mu\text{g}/\text{kg}$ of body weight per minute) were measured in a preliminary session. Oral MDMA (0.5 and 1.5 mg/kg of body weight) or placebo was administered 1 hour before echocardiographic measurements in three weekly sessions.

Measurements: Heart rate and blood pressure were measured

at regular intervals before and after MDMA administration. Echocardiographic measures of stroke volume, ejection fraction, cardiac output, and meridional wall stress were obtained 1 hour after MDMA administration and during dobutamine infusions.

Results: At a dose of 1.5 mg/kg, MDMA increased mean heart rate (by 28 beats/min), systolic blood pressure (by 25 mm Hg), diastolic blood pressure (by 7 mm Hg), and cardiac output (by 2 L/min). The effects of MDMA were similar to those of dobutamine, 20 and 40 $\mu\text{g}/\text{kg}$ per minute. Inotropism, measured by using meridional wall stress corrected for ejection fraction, decreased after administration of dobutamine, 40 $\mu\text{g}/\text{kg}$ per minute, but did not change after either dose of MDMA.

Conclusions: Modest oral doses of MDMA increase heart rate, blood pressure, and myocardial oxygen consumption in a magnitude similar to dobutamine, 20 to 40 $\mu\text{g}/\text{kg}$ per minute. In contrast to dobutamine, MDMA has no measurable inotropic effects.

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3,4-Methylenedioxymethamphetamine (MDMA), also known as "ecstasy," is a psychostimulant with structural similarities to both amphetamine and the hallucinogenic phenethylamine mescaline. 3,4-Methylenedioxymethamphetamine (and its analogues) seems to produce a spectrum of pharmacologic effects distinct from such structurally similar compounds, suggesting that MDMA may represent a new class of psychotropic agents (1-4).

Use of MDMA may be increasing. Emergency department visits related to MDMA increased from 637 in 1997 to 1143 in 1998. In 1998, the estimated lifetime prevalence and annual prevalence of MDMA use, respectively, were 2.7% and 1.8% in 8th graders, 5.8% and 3.6% in 12th graders, and 7.2% and 2.9% in young adults (5). Use of MDMA has been associated with sudden death and cardiovascular collapse (6). Acute cardiovascular effects of MDMA (and its analogues) include tachycardia and hypertension (7, 8). Understanding the cardiovascular effects of MDMA may improve prediction of and intervention in cases of MDMA cardiotox-

icity. The purpose of this study was to measure the acute cardiovascular effects of oral MDMA and to compare these effects with those of a well-characterized cardiostimulant, the β -agonist dobutamine. The cardiovascular response to MDMA and dobutamine were measured by using quantitative two-dimensional echocardiography.

METHODS

The study was approved by the University of California, San Francisco, Committee on Human Research and was performed under an investigational new drug (IND) protocol approved by the U.S. Food and Drug Administration (IND 53,648). All participants provided informed consent. The eight healthy paid volunteers had used MDMA at least four times in the past 3 years. At least 1 week after dobutamine echocardiography, participants were tested in 3 weekly sessions with an ascending-dose, double-blind, placebo-controlled design using orally administered MDMA hydrochloride, 0.5 mg/kg of body weight or 1.5 mg/kg, or placebo.

Participants underwent a medical examination and laboratory screening tests to confirm good general health. Exclusion criteria were significant medical or psychiatric illness; dependence on drugs (except caffeine or nicotine), according to criteria defined by the *Diagnostic and Statistical Manual of Mental Disorder*, 4th edition; history of adverse reactions to study drugs or recent use of psychoactive drugs; cardiovascular risk factors (total cholesterol level > 6.48 mmol/L [250 mg/dL] or smoking > 2 packs of tobacco cigarettes per day); deficient cytochrome P450 2D6 activity (assessed by using dextromethorphan phenotyping); or inability to give informed consent. Women were required to have negative results on a serum pregnancy test (Unilab, San Jose, California) on admission to the study and negative results on a urine pregnancy test (TestPack Plus, Abbott Laboratories, Abbott Park, Illinois) before each MDMA session.

Participants were asked to refrain from use of illicit psychoactive drugs for at least 7 days and ethanol for at least 48 hours before testing. Nicotine and caffeine were restricted during MDMA sessions until 8 hours after drug administration and were otherwise not allowed within 30 minutes of any measure. To rule out recent psychoactive drug use, qualitative urinalysis (Unilab, San Jose, California) was performed the day before MDMA sessions and on each day that data were collected.

Dobutamine hydrochloride (Dobutrex, Lilly, Indianapolis, Indiana) was administered in ascending doses of 5, 20, and 40 $\mu\text{g}/\text{kg}$ per minute. Doses were delivered intravenously and increased every 5 minutes until the dose of 40 $\mu\text{g}/\text{kg}$ per minute was completed. Heart rate, systolic blood pressure, and diastolic blood pressure were obtained before MDMA administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after MDMA administration. The rate–pressure product (heart rate \times systolic blood pressure) was calculated. Metabolite and MDMA pharmacokinetics, neuroendocrine measures, subjective mood ratings, and structured psychiatric measurements are reported in detail elsewhere (Jones and colleagues. In preparation).

Echocardiography was performed 1 hour after MDMA administration by using a commercially available Doppler echocardiography machine (Sequoia, Acuson, Mountain View, California). End-diastolic and end-systolic volumes were calculated by using the bi-plane method of discs (9). From these measurements, standard

calculations of stroke volume, ejection fraction, and cardiac output were made. Meridional systolic wall stress was calculated by using previously defined formulas (10).

The response to MDMA (0.5 mg/kg, 1.5 mg/kg, or placebo) was compared with the response to dobutamine (5, 20, and 40 $\mu\text{g}/\text{kg}$ per minute) by using repeated-measures analysis of variance. Drug condition and observation times were considered within-participant factors. After a significant *F* test, pairwise comparisons were performed by using the least-squares means analysis. Effects were considered statistically significant at a *P* value less than or equal to 0.05. Data were adjusted for sphericity by using the Huynh–Feldt adjustment factor.

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RESULTS

The mean age (\pm SD) of the five men and three women who completed the study was 29 ± 5 years (range, 24 to 39 years). The participants had reportedly used MDMA 49 ± 65 times (range, 5 to 200 times). After completing part of the first MDMA session, one additional participant chose to withdraw from the study because of professional obligations. Data from this participant are excluded from analysis.

Peak hemodynamic effects (defined as the maximal observed value) occurred 1 to 1.5 hours after MDMA administration. Because all echocardiograms were obtained at least 1 hour after the MDMA dose and required approximately 15 minutes to complete, we used peak hemodynamic effects for comparison with echocardiographic data. Except for diastolic blood pressure, there were no significant differences between the peak hemodynamic effects and those measured 1 hour after administration of MDMA. Although diastolic blood pressure 1 hour after administration of 1.5 mg/kg of MDMA was statistically less than the peak (69 ± 5 mm Hg vs. 76 ± 10 mm Hg; $P < 0.01$), the absolute magnitude was small and does not substantially change the results. The cardiovascular effects of MDMA and dobutamine are summarized in the **Table**.

We found that MDMA, 1.5 mg/kg, and dobutamine, 20 and 40 $\mu\text{g}/\text{kg}$ per minute, increased heart rate (by 28 beats/min), systolic and diastolic blood pressures (by 25 mm Hg and 7 mm Hg, respectively), and rate–

Table. Comparative Cardiovascular Effects of MDMA and Dobutamine in Eight Participants*

Variable	Baseline Value	MDMA, 0.5 mg/kg†	MDMA, 1.5 mg/kg†	Dobutamine, 5 μ g/kg per minute	Dobutamine, 20 μ g/kg per minute	Dobutamine, 40 μ g/kg per minute
Hemodynamic measures						
Heart rate, beats/min	69 \pm 7	74 \pm 10‡§	97 \pm 12§ ¶	66 \pm 9‡§**	83 \pm 15‡§ ††	110 \pm 19‡§ ¶***††
Systolic blood pressure, mm Hg	109 \pm 14	117 \pm 12‡§**	134 \pm 10 ¶††	113 \pm 7‡§**	130 \pm 15 ¶††	140 \pm 22 ¶††
Diastolic blood pressure, mm Hg	69 \pm 5	66 \pm 3§**	76 \pm 10§ ¶***††	63 \pm 7‡	62 \pm 6‡	62 \pm 5‡
Rate–pressure product‡‡	7490 \pm 1265	8494 \pm 1298‡§**	13 451 \pm 2500§ ¶***††	7419 \pm 932‡§**	10 573 \pm 1210‡§ ***††	15 213 \pm 2922‡§ ¶***††
Echocardiographic measures						
Ejection fraction	0.68 \pm 0.06	0.71 \pm 0.04§**	0.70 \pm 0.07§***††	0.75 \pm 0.08‡§ **	0.82 \pm 0.07‡§ ¶††	0.82 \pm 0.05‡§ ¶††
Cardiac output, L/min	3.8 \pm 0.6	4.1 \pm 1‡§**	5.8 \pm 1.3§ ¶††	4.1 \pm 1‡§**	5.6 \pm 1.5§ ¶††	7.3 \pm 2.2‡§ ¶***††
Meridional wall stress, g/cm ²	21 \pm 3	21 \pm 3	23 \pm 4	21 \pm 2	22 \pm 3	22 \pm 4
Inotropic effects§§	0.31 \pm 0.05	0.30 \pm 0.06	0.33 \pm 0.09§***††	0.28 \pm 0.05‡	0.28 \pm 0.04‡	0.26 \pm 0.06‡

* Values are the mean \pm SD. Significance was defined as $P < 0.05$. MDMA = 3,4-methylenedioxyamphetamine.

† Values are peak effect for hemodynamic measures and 1 hour postdose for echocardiographic measures.

‡ Significantly different from MDMA, 1.5 mg/kg.

§ Significantly different from dobutamine, 40 μ g/kg per minute.

|| Significantly different from baseline.

¶ Significantly different from MDMA, 0.5 mg/kg.

** Significantly different from dobutamine, 20 μ g/kg per minute.

†† Significantly different from dobutamine, 5 μ g/kg per minute.

‡‡ Determined by multiplying systolic blood pressure by heart rate.

§§ Determined by dividing meridional wall stress by ejection fraction.

pressure product, whereas MDMA, 0.5 mg/kg, and dobutamine, 5 μ g/kg per minute, did not. Peak heart rate changes after administration of MDMA or dobutamine are shown in the top part of the **Figure**. The peak increases in heart rate, systolic blood pressure, and rate–pressure product after 1.5 mg/kg of MDMA were significantly greater than after 20 μ g/kg per minute of dobutamine but less than after 40 μ g/kg of dobutamine.

Changes in cardiac output after administration of MDMA or dobutamine are shown in the middle part of the **Figure**. We found that 1.5 mg/kg of MDMA and 20 and 40 μ g/kg per minute of dobutamine increased cardiac output, but 0.5 mg/kg of MDMA and 5 μ g/kg per minute of dobutamine did not. The increase of 2 L/min in cardiac output after 1.5 mg/kg of MDMA was similar to that after 20 μ g/kg per minute of dobutamine but less than that after 40 μ g/kg per minute of dobutamine. Neither dobutamine nor MDMA changed left ventricular end-diastolic volume.

Consistent with its inotropic properties, dobutamine decreased left ventricular end-systolic volume and produced dose-dependent increases in ejection fraction. In contrast, neither dose of MDMA significantly decreased end-systolic volume. Consequently, ejection fraction was unchanged after MDMA administration.

Meridional wall stress was used to compare the inotropic effects of MDMA and dobutamine by correcting

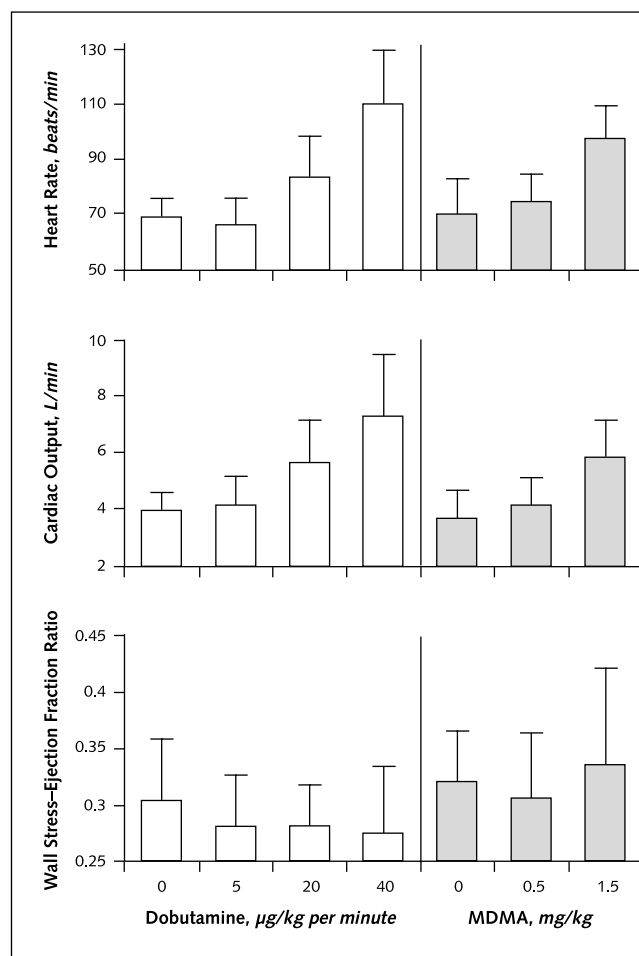
for ejection fraction. Meridional wall stress did not change significantly with any dose of either agent. Consistent with the inotropic properties of dobutamine, the ratio of meridional wall stress to ejection fraction progressively decreased with each successive dobutamine dose and was significantly reduced at a dose of 40 μ g/kg per minute. This variable was unchanged with either dose of MDMA (**Figure, bottom**).

Subjective effects of MDMA—feelings of relaxation, well-being, and improved mood—reached their maximum between 1.5 and 3 hours. Most participants felt that 0.5 mg/kg of MDMA produced “very weak” effects (although two felt that it was of “medium” strength), whereas 1.5 mg/kg was considered a “medium” to “somewhat strong” dose. Further details on the pharmacokinetic and dynamic effects of MDMA will be reported elsewhere (Mendelson and colleagues. In preparation).

DISCUSSION

We compared the effects of a well-known cardiovascular β -agonist to those of an uncharacterized illicit compound by using clinically validated outcome measures. Contrasting the effects of these compounds may help physicians better understand the cardiovascular risks associated with illicit MDMA use. Dobutamine and MDMA both produce dose-dependent increases in

Figure. Comparison of the effects of dobutamine or 3,4-methylenedioxymethamphetamine (MDMA) on peak heart rate (*top*), cardiac output (*middle*), and ratio of meridional wall stress to ejection fraction (*bottom*).



Error bars represent standard deviation.

heart rate, blood pressure, and cardiac output. Although both compounds are cardiostimulants, dobutamine has positive inotropic effects whereas MDMA has no measurable inotropic effects. In the absence of inotropism, incremental increases in afterload produce proportional increases in force or tension per unit of cross-sectional area of the ventricular wall. This increase in tension is known as wall stress and is directly related to myocardial oxygen demand. Our study shows that MDMA increases systolic and diastolic blood pressure in the absence of a significant change in cardiac contractility and end-systolic wall thickness. Therefore, MDMA may increase myocardial oxygen consumption more than is ex-

pected from the observed changes in heart rate and blood pressure.

Our participants were not dependent on MDMA or other stimulants and generally used MDMA approximately twice per month. In contrast to the single oral doses administered in our study, repeated, binge-pattern dosing may be increasing among users (11). In addition, behavioral and environmental factors accompanying illicit MDMA use may increase risk for cardiovascular complications. Sustained exercise (such as dancing), high ambient temperature and humidity, and crowded conditions are common in nightclub settings and are thought to potentiate the neurologic toxicity of MDMA and related compounds (12–14). Finally, in illicit users, preexisting cardiovascular conditions could increase cardiovascular risk compared with the carefully screened healthy volunteers in our study.

If emergency treatment is needed for MDMA-induced vascular instability, β -blockers may be an attractive choice. They block the chronotropic effects of MDMA and may antagonize the behavioral changes that the agent produces in animals (15, 16). However, the use of β -blockers alone raises the theoretical concern of the effects of unopposed α stimulation. Therefore, the combination of a β -blocker and a vasodilator (such as nitroglycerine or nitroprusside) would seem to be a reasonable treatment strategy in patients presenting with significant hypertension and tachycardia.

Our study has several limitations. We obtained only one postdose echocardiogram, and the effects of MDMA over several hours or after several doses may lead to additional cardiovascular changes not detected 1 hour after a single dose. This measurement time was chosen because it was near the reported time of peak MDMA plasma levels (17, 18). Our study does not address many factors commonly associated with illicit MDMA use that can influence cardiovascular risk, such as exercise, polydrug use, repeated MDMA use, and environmental factors (which might impair thermoregulation).

In conclusion, MDMA produces dose-related increases in myocardial oxygen demand without an increase in contractility. This combination may lead to higher risk for cardiovascular complications in users.

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