Journal of the Neurological Sciences 370 (2016) 107–111

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Impaired arterial smooth muscle cell vasodilatory function in methamphetamine users

Ghaemeh Nabaei, MD, Shahram Oveisgharan, MD, Askar Ghorbani, MD, Farzad Fatehi, MD, MSc *

Iranian Center of Neurological Research, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 10 July 2016
Received in revised form 15 September 2016
Accepted 16 September 2016
Available online 17 September 2016

Keywords:
Methamphetamine
Stroke
Carotid intima-media thickness
Flow-mediated dilatation
Nitroglycerine-mediated dilatation
Ultrasound

ABSTRACT

Objectives: Methamphetamine use is a strong risk factor for stroke. This study was designed to evaluate arterial function and structure in methamphetamine users ultrasonographically.
Methods: In a cross-sectional study, 20 methamphetamine users and 21 controls, aged between 20 and 40 years, were enrolled. Common carotid artery intima-media thickness (CCA-IMT) marker of early atherogenesis, flow-mediated dilatation (FMD) determinants of endothelium–dependent vasodilation, and nitroglycerine-mediated dilatation (NMD) independent marker of vasodilation were measured in two groups.
Results: There were no significant differences between the two groups regarding demographic and metabolic characteristics. The mean (±SD) CCA-IMT in methamphetamine users was 0.58 ± 0.09 mm, versus 0.59 ± 0.07 mm in the controls ($p = 0.84$). Likewise, FMD% was not significantly different between the two groups [7.6 ± 6.1% in methamphetamine users vs. 8.2 ± 5.1% in the controls; $p = 0.72$], nor were peak flow and shear rate after hyperemia. However, NMD% was considerably decreased in the methamphetamine users [8.5 ± 7.8% in methamphetamine users vs. 13.4 ± 6.2% in controls; $p = 0.03$].
Conclusion: According to our results, NMD is reduced among otherwise healthy methamphetamine users, which represents smooth muscle dysfunction in this group. This may contribute to the high risk of stroke among methamphetamine users.

1. Introduction

Methamphetamine, a commonly abused recreational drug, is a potent addictive psychostimulant that affects the central nervous system dramatically in many ways [1].

Dependence on the drug has risen to an epidemic level worldwide and has become a concerning public health problem [2].

Methamphetamine enhances the release and also blocks the reuptake of dopamine, producing stimulant effects such as intense euphoria that may contribute to its extensive abuse [3]. In addition, it is toxic to the system of dopaminergic neurotransmitter and has systemic hemodynamic effects [4]. The use of methamphetamine is a strong risk factor for stroke [5,6]; although the precise underlying mechanism of stroke in methamphetamine users is unknown, the proposed mechanisms are, elevated blood pressure, vasculitis, vasospasm, accelerated atherosclerosis, and cardioembolism resulting in ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, especially among young patients [6–8].

Flow-mediated dilatation (FMD), and nitroglycerin mediated dilatation (NMD) of the brachial artery are commonly used noninvasive tests to evaluate endothelial–dependent and endothelial–independent vasodilation, respectively [9]. They are measured ultrasonographically by variations in brachial artery diameter in response to arterial flow changes provoked by reactive hyperemia for FMD and nitroglycerine use for NMD [10].

Common carotid artery intima-media thickness (CCA-IMT) is a measure of subclinical vascular disease, providing valuable insights into early atherogenesis and has been related to a greater risk of cerebrovascular and cardiovascular events in the future [11–13].

To the best of our knowledge, vascular function and structure in chronic methamphetamine users has not been previously investigated. Given the uncertain pathogenesis of stroke in methamphetamine users, the study was designed to noninvasively test the premise that methamphetamine users have impaired endothelial–dependent and –independent function as well as structure compared to non-users by evaluating, brachial artery FMD, NMD and CCA-IMT in participants.

2. Methods

This cross-sectional study was conducted between August 2014 and October 2015 in Shariati Hospital, affiliated with Tehran University of Medical Sciences. Forty-one males aged between 20 and 40 years were enrolled in the study.

* Corresponding author at: Iranian Center of Neurological Research, Shariati Hospital, North Kargar Street, Tehran 14117-13135, Iran.
E-mail address: f-fatehi@tums.ac.ir (F. Fatehi).

http://dx.doi.org/10.1016/j.jns.2016.09.027
0022-510X/

In the case group (methamphetamine users), 20 otherwise healthy male subjects were recruited from organizations such as 'Congress 60' and the 'Iranian National Center for Addiction Study' (INCAS). They were cigarette-smoking inhalant methamphetamine users who met the DSM-V criteria for methamphetamine dependence. Subjects were excluded if they had a self-reported history of other illicit substance use or alcohol dependence.

For the control group, 21 age-matched healthy male cigarette smokers with no history of methamphetamine use and no illicit drug dependence were recruited from Shariati hospital staff.

We had to enroll cigarette smokers in the control group as finding non-cigarette smoking methamphetamine users was nearly impossible, and cigarette smoking is a well-known cause of arterial endothelial dysfunction. Exclusion criteria included a history of cardiovascular diseases (ischemic heart disease, atrial fibrillation, heart block, and valvular heart diseases, stroke, peripheral vascular disorders, hypertension), diabetes mellitus, hypercholesterolemia, a body mass index (BMI) >30 (kg/m^2), rheumatologic disease, thyroid disease, pituitary tumor, dependence on other illicit drugs, and alcohol. Subjects with a cumulative cigarette smoking exceeding 15 pack-years were not enrolled as Kweon et al.'s study showed cumulative cigarette smoking >20 pack-years could significantly affect CCA-IMT [14]. Light alcohol use (equivalent to 7.5 drinks per week) was not considered as an exclusion criterion.

Subjects underwent a detailed substance, cigarette and alcohol consumption interview. The lifetime use of methamphetamine was calculated as:

$$\text{Lifetime use of methamphetamine (grams)} = \text{average quantity of daily use (grams)} \times \text{duration of use (days)}.$$

The following tests were performed for all the subjects (methamphetamine users and controls): fasting lipid panel [total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride (TG) blood levels], complete blood count (CBC), fasting blood glucose (FBS), C-reactive protein (CRP) and HIV-Ab test. Plasma glucose concentration was measured using the glucose oxidase procedure. Triglycerides, total cholesterol, and high-density lipoprotein and low-density lipoprotein cholesterol were measured with spectrophotometric assays. C-reactive protein was measured with latex agglutination test, and all methods were standardized.

2.1. Flow-mediated dilatation (FMD) technique

All examinations were performed after a 15-min relaxation in the supine position at the Shariati Hospital neurosonology room which was temperature-controlled (20–23 °C), between the hours of 7:00–12:00 AM, after an overnight fast. The methamphetamine users were instructed not to use methamphetamine during the preceding 12 h to allow a half-life of elimination, to avoid the possible conflicting acute effects of the drug on vascular indices (due to its sympathomimetic role). Firstly, resting blood pressure (BP) and heart rate were measured in the upper left arm using a standard mercury sphygmomanometer. Ultrasound analysis was performed using a 5.0 to 12.0 MHz linear probe of the SonoAce ×8 Cardiovascular Ultrasound System (manufactured in Korea). All arterial pressure measurements and ultrasound assessments were performed by the same expert person in the neurosonology room who was unaware of the subjects' clinical characteristics.

Brachial artery FMD of the right side was imaged roughly 5–10 cm proximal to the antecubital fossa in the longitudinal plane. Subjects were placed supine with their right arm maintained at heart level in an 80°–90° angle from their chest. A segment with clear near and far intimal boundaries between the lumen and vessel wall was chosen. The best quality end-diastolic frames were selected, and measurements of the brachial artery diameter, from the intima of the far wall to the intima of the near wall were taken to determine average baseline diameter (B1). After baseline ultrasound imaging, Doppler readings of pre-inflation flow were performed. A 5-min inflation of a pneumatic cuff (50 mm Hg > SBP of the patient) positioned around the forearm closely below the medial epicondyle, followed by a quick deflation using a standard sphygmomanometer was accomplished to induce hyperemia and vasodilation. During cuff inflation, average brachial artery diameter was measured and upon cuff release, peak blood flow was determined within the first 20 s of reactive hyperemia. Digital images of the artery were then captured every 5 s from 20 s to 120 s to determine peak dilatation (B2) and FMD was considered as (B2 − B1) / B1. Changes in diameter caused by FMD was calculated as the percentage change compared to the rest time: FMD % = FMD × 100. Shear rate was calculated as blood velocity (cm/s) divided by vessel diameter (cm) before and after inflation.

2.2. Nitroglycerin-mediated dilatation (NMD) test

To determine endothelium-independent vasodilation, 10 min after cuff release, baseline measurements were repeated, and it was assured that the artery has returned to baseline diameter. Next, a sublingual nitroglycerin (NTG) tablet (0.4 mg) was administered 10 min after cuff release, and 4 min later brachial artery images were obtained to determine maximum nitroglycerine mediated brachial artery dilatation (B3). NMD was calculated as follows: NMD = (B3 − B1) / B1. Change in diameter caused by NMD was calculated as the percentage: NMD % = NMD × 100.

We performed three recordings for measuring baseline diameters, FMD, and NMD and averaged the measurements. All measurements were conducted by the same expert person unaware of the clinical characteristics of the subjects.

2.3. Common carotid artery intima-media thickness (CCA-IMT) measurement technique

In the supine position and the neck slightly hyperextended, allowing optimal visualization of the bilateral CCAs, carotid bulb, extracranial internal and external carotid arteries, two parallel echogenic lines detached by an anechoic space could be inspected at arterial wall levels. The distance between the two lines is a reliable index of the thickness of the intima-media.

The end-diastolic IMT of the far wall was measured in bilateral CCAs, 1 cm proximal to the bulb. Three views of the carotid bulb on each side were taken: 1 anterior, 1 lateral (at 45°), and 1 posterior and the mean of the CCA-IMTs was calculated as the mean of the CCA-IMT on the right and left CCAs in 3 projections mentioned: Mean CCA-IMT = (CCA-IMT_{right} + CCA-IMT_{left}) / 2. All IMT measurements were performed by the same expert who was blinded to the clinical characteristics of the patients.

2.4. Ethical considerations and consent forms

The study was approved by the Ethics Committee of Tehran University of Medical Sciences. All the subjects gave their informed consents before conducting the study.

2.5. Statistical analysis

We used RStudio (R version 3.1.2) to analyze the data and applied the Shapiro-Wilk test to determine the normal distribution of all the continuous variables. Since the clinical data (such as age, SBP, DBP, BMI, lipid profile and blood sugar) did not follow a normal distribution, we used non-parametrical tests (Mann-Whitney test) to compare the two groups. Accordingly, the results are presented as Median [interquartile range (IQR = 25th–75th percentiles)].

Due to the normal distribution of FMD%, NMD%, peak flow rate, shear rate and CCA-IMT, student's *t*-test was used to analyze the differences between the two groups, the results of which are presented as