Evaluation of regional myocardial perfusion in methamphetamine abusers using real-time myocardial contrast echocardiography

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Abstract

Aims: To evaluate the feasibility of assessing regional myocardial perfusion using real-time myocardial contrast echocardiography (MCE) at rest for detecting coronary microcirculation abnormalities in methamphetamine abusers. **Material and methods:** Twenty-two male methamphetamine abusers (11 without chest pain, 11 with chest pain), free of ascertained coronary artery disease, were enrolled in this study. A control group of 22 age-matched male healthy participants was studied for comparison. Standard 2D, flow and tissue Doppler echo with measurements of cardiac morphologic and functional indicators, MCE with measurements of regional myocardial perfusion were performed, respectively. **Results:** Compared to healthy participants, methamphetamine abusers had higher blood pressure, greater left ventricular mass index and more impaired diastolic function, with preserved cardiac sizes and systolic function. Methamphetamine abusers with chest pain had a faster heart rate than those without chest pain and healthy participants. MCE in methamphetamine abusers, especially with chest pain, had significant longer contrast agent arrival times, less functional capillary blood volumes, slower microvascular flow velocities and less myocardial perfusion than healthy participants ($p < 0.05$). Moreover, along with the increases of dosage and duration of use (from group A to group C, group A: 1-2 g/day, <2 years; group B: 2-3 g/day, 2-5 years; group C: >3 g/day, >5 years) the reductions in the myocardial perfusion indices were more significant ($p < 0.01$). The cutoff value with 5.1 dB²/s of the myocardial perfusion at the left ventricular apex had a sensitivity of 87.5%, specificity of 75.2% and accuracy of 81.9% for differentiating methamphetamine abusers from normal subjects. **Conclusions:** Real-time MCE can effectively detect coronary microcirculation abnormalities in methamphetamine abusers at rest and myocardial perfusion is significantly reduced in methamphetamine abusers. This finding may be involved in the occurrence and development of cardiac damage.

Keywords: methamphetamine; chest pain; myocardial perfusion; myocardial contrast echocardiography

Introduction

Myocardial ischemia is one of the common injuries of methamphetamine use. The mechanism is related to

the spasm (vasoconstriction) of the normal or atherosclerotic coronary arteries associated with increased platelet aggregation, blood pressure and heart rate [1,2]. Previous clinical research on methamphetamine-induced myocardial ischemia focused on large epicardial coronary arteries using invasive cardiac catheterization [3,4] but studies concerning the coronary microcirculation abnormalities are lacking.

Real time myocardial contrast echocardiography (MCE) is a recently developed technique that utilizes low mechanical index to minimize microbubble destruction and permits quantitative measurements of myocardial perfusion from the immediate post-destruction frame of real-time perfusion according to time vs. background-subtracted acoustic intensity plots [5,6]. This measure-

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ment enables the direct assessment of global and regional myocardial structure, the degree and adequacy of microvascular perfusion as well as the presence of wall motion abnormalities [7,8]. Therefore, MCE is regarded as an ideal tool for the detection of coronary artery stenosis, assessment of myocardial viability and correct triaging of patients to revascularization at rest or/and stress [8-10]. However, there are few data in the literature regarding the role of this technique for assessing regional myocardial perfusion in methamphetamine abusers.

We tested the hypothesis that real time MCE at rest could effectively detect the changes of myocardial perfusion in methamphetamine abusers, comparing the results with healthy participants.

Material and methods

Study population

Our study was approved by the Human Research Ethics Committee of Fangqiang Forced Quarantine and Drug Rehabilitation Center of the Jiangsu Province and free informed consent was obtained from all participants. A detailed cardiac history was collected at the recruitment from more than 2000 male adults of different methamphetamine exposure conditions (dosage: from 0.5 g to 6 g/d; duration: from 2 months to 10 years), including cardiovascular risk factors, clinical history or physical and echocardiographic exams. Exclusion criteria were: ascertained coronary artery disease and previous myocardial infarction, primary cardiomyopathies, congenital heart disease, arterial hypertension, hyperlipidemia, diabetes, previous 2D echocardiographic wall motion abnormalities, rhythm other than sinus, prosthetic valves or pacemakers, echocardiographic ejection fraction (EF) <50%, more than mild valvular stenosis or regurgitation, assumption of cardiac medications and standard echo images of inadequate quality. Finally, the study population consisted of 22 participants (19-51 years old, median age 37 years): 11 methamphetamine abusers without chest pain and 11 with chest pain. According to the dosages and durations of methamphetamine use the participants were also divided into three groups: group A, intake 1-2 g/day, <2 years (n=7); group B, intake 2-3 g/day, 2-5 years (n=7); and group C, intake > 3g/d, >5 years (n=8). A control group of 22 age-matched male healthy participants (19-50 years old, median age 26 years) was used for comparison. All methamphetamine abusers underwent coronary angiography (digital subtraction angiography or computed tomography). Meanwhile, the electrocardiographic (ECG) findings (ST-T changes, sinoatrial block, atrioventricular block, complete right or left bundle branch block, premature beat, ectopic tachycardia, low

voltage, or abnormal Q wave) and myocardial enzymes (troponin, creatine kinase, glutamate transaminase, lactate dehydrogenase, etc.) were recorded.

Standard 2D, flow and tissue Doppler echo examination

The echocardiographic study was performed in the left lateral decubitus position and with ECG recorded simultaneously. The echocardiographic data were acquired with a commercially available ultrasound system (Vivid E9, GE Healthcare, Milwaukee, WI) equipped with an M5S single-crystal matrix array transducer (1.7-3.3 MHz). Left atrial end-systolic anteroposterior diameter (LA), left ventricular end-diastolic anteroposterior diameter (LV), right atrial end-systolic transverse diameter (RA), right ventricular end-diastolic anteroposterior diameter (RV), tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF) and left ventricular mass index (LVM index) were obtained by real time 2D echo method. Flow Doppler sample was placed at the tip level of the mitral leaflets from the apical 4-chamber view. The peak early diastolic transmitral filling velocities (E) were measured. Tissue Doppler sample was placed at the septal mitral annulus from the apical 4-chamber view. The peak early diastolic septal tissue velocities (E') were measured and the ratio of E/E' were calculated.

Real time MCE

A commercially available second-generation contrast agent, SonoVue® phospholipid-shell sulfur hexafluoride microbubbles (Bracco, Milan, Italy) was used. A total of 59 mg of Sonovue® was diluted in 5 mL of saline according to the manufacturer's protocol. At the beginning 1.5 mL of this solution was administered intravenously at an infusion rate of about 0.5 mL/s in order to gain a visible ventricular opacification and myocardial enhancement, quickly followed by the administration of 1 mL at an infusion rate of about 1 mL/min to assure optimal myocardial enhancement.

MCE data were acquired with a commercially available ultrasound system (Mindray M9, Mindray Medical Systems, Shenzhen, China) equipped with a 1-5 MHz C5-1s transducer, using a multi-pulse contrast-specific imaging protocol (power modulation imaging) combined with pulse inversion power Doppler. Examination was performed from the apical four-chamber view with septum focused in the middle of the window. Gain, depth, transmit focus, and post-processing were optimized at the beginning of the study and held constant throughout. The optimal balance between myocardial contrast enhancement and attenuation in our setting was achieved at a very low mechanical index of 0.067 (acoustic power 4.8%, thermal index of soft tissue, 0.0). The replenishment of

Fig 1. The myocardial contrast echocardiography obtained from a healthy participant at various time intervals: a) -1s (1s before the destructive pulse sequence) b) destructive pulse sequence (denoted as T0) and (b to h) at 3,5,10,15,20,30 s after the destructive pulse sequence, respectively.

myocardial Sonovue® at consecutive pulsing intervals after a destructive pulse with an MI of 1.352 (acoustic power 96.6%, thermal index of soft tissue 0.3) was recorded; only end-systolic frames were used for analysis.

Image analysis was performed off-line by two experienced operators, according to established methods [6,11]. Briefly, a large region-of-interest was placed over the midventricular septum and left ventricular apex of twenty to forty consecutive end-systolic images beginning with the immediate post-destruction frame, respectively (fig 1). Time vs background-subtracted acoustic intensity plots were then generated and fit to the exponential function $y=A(1-e^{\beta t})$, where y is the acoustic intensity at a time of t , A is the plateau where acoustic intensity represents myocardial blood volume, and β represents the mean microbubble flux rate through the microcirculation (referred to as microvascular flow velocity). Data are reported as the average of at least three separate microbubble destruction-refill time vs acoustic intensity plots. Myocardial perfusion was calculated as the product of myocardial blood volume (A) and microvascular flow velocity (β). In our study, A and β were the peak intensity (PI) and ascending slope (AS) derived from microbubble destruction-refill time vs acoustic intensity plots, respectively (fig 2). In addition, the microbubble arrival times (ATs) were recorded.

Intraobserver and interobserver variability for measurements of A and β parameters were obtained by repeated, blinded analysis of 20 randomly selected patients after a minimum time interval of 2 weeks.

Statistical analysis

Results are expressed as mean±standard deviation. The differences between two groups were tested using unpaired samples t-test. A receiver operating characteristic curve (ROC) analysis of the myocardial perfusion

was used to differentiate methamphetamine abusers from normal subjects, determine the optimal cut-off points and validity parameters. Bland & Altman was used to measure the inter/intra observer variability. A value of $p<0.05$ was considered statistically significant. All statistical analysis was performed with SPSS version 16 software for Windows (SPSS Inc, Chicago, IL).

Results

Coronary angiography revealed unobstructed arteries in all methamphetamine abusers. All of them had normal blood glucose and lipid concentrations. The echocardiographic measurements were successfully completed in all subjects.

As shown in Table I, SBP, DBP, LVM index and E/E' were significantly greater in methamphetamine abusers with/without chest pain comparing with healthy participants ($p<0.05$). HR was greater in methamphetamine abusers with chest pain than in those without chest pain

Fig 2. A typical time-intensity plot obtained from a healthy participant (a) and a methamphetamine abuser (b) (exposure condition, 2g/day for 4 years). Note that the arrival time (AT) in this methamphetamine abuser appears significantly prolonged, the rate of bubble replenishment (AS) significantly reduced, and the maximum video intensity (PI) moderately reduced.

and healthy participants. ECG traces and myocardial enzymes levels were abnormal in methamphetamine abusers with chest pain and normal in those without chest pain and healthy participants. Age, LV, LA, RV, RA, LVEF and TAPSE were not significantly different among methamphetamine abusers with/without chest pain and healthy participants ($p>0.05$).

In table II are detailed the differences of MCE indices among healthy participants, methamphetamine abusers with chest pain and those without chest pain. Compared to healthy participants, methamphetamine abusers had significant longer contrast agent arrival times (ATs), less functional capillary blood volumes (PIs), slower microvascular flow velocities (ASs) and less myocardial perfusion ($PI \times AS$). Moreover, methamphetamine abusers with chest pain also had longer ATs, less functional capillary blood volumes (PIs), slower microvascular flow velocities (ASs) and less myocardial perfusion ($PI \times AS$) than those without chest pain.

Table III and figure 3 showed the changes of MCE indices under different methamphetamine exposure conditions. From group A to group C, contrast agent arrival times (ATs) extended sequentially and the functional capillary blood volume (PI), microvascular flow velocity (AS) and myocardial perfusion ($PI \times AS$) decreased successively.

The area under the curve (AUC) of the myocardial perfusion at the left ventricular apex was 0.92 (0.84-1.00) at a cutoff value with 5.1 dB²/s with sensitivity of 87.5%, specificity of 75.2% and accuracy of 81.9% for differentiating methamphetamine abusers from normal subjects. The AUC of the myocardial perfusion at midventricular septum was 0.84 (0.71-0.97) at a cutoff value with 4.3 dB²/s with sensitivity of 87.5%, specificity of 68.9% and accuracy of 77.3 % for differentiating methamphetamine abusers from normal subjects.

Interobserver and intraobserver agreement for measurement of the MCE indices (ATs, PIs and ASs) were

Table I. Characteristics of healthy participants and methamphetamine abusers (MBs) with/without chest pain

Variables	Healthy participants	MBs without chest pain (n=11)	MBs with chest pain (n=11)
Age, y	38.2±8.4	37.9±8.1	38.5±8.3
HR, beats/min	73.34±8.47	75.62±9.34	96.54±12.34*
SBP, mm Hg	112.45±11.37	126.88±19.78*	139.74±21.76*
DBP, mm Hg	63.77±16.56	74.56±18.39*	93.96±20.17*
ECG findings	Normal	Normal	Abnormal
Myocardial enzymes	Normal	Normal	Abnormal
RV, mm	18.26±2.18	18.89±3.37	19.65±3.82
RA, mm	30.66±4.78	31.65±4.90	32.76±4.86
LV, mm	40.34±4.44	41.67±4.65	42.89±4.43
LA, mm	26.78±5.29	30.67±6.43	31.62±5.10
LVEF(%)	68.56±9.13	66.54±8.59	69.67±9.43
LVM index, g/m ²	87.52±15.49	109.93±21.57*	112.78±21.66*
E/E'	4.98±1.39	6.92±1.93*	7.08±2.16*
TAPSE	18.59±6.67	17.95±7.56	17.83±7.95

* $p<0.05$; Data are expressed as mean±standard deviation. DBP – diastolic blood pressure; E/E' – ratio of peak early diastolic transmitral filling velocity (E) and peak early diastolic septal mitral annulus tissue velocity (E'); HR – heart rate; LA – left atrial end-systolic anteroposterior diameter; LV – left ventricular end-diastolic anteroposterior diameter; RA – right atrial end-systolic transverse diameter; RV – right ventricular end-diastolic anteroposterior diameter; SBP – systolic blood pressure; TAPSE – tricuspid annular plane systolic excursion.

Table II. Comparison of regional myocardial perfusion in healthy participants and methamphetamine abusers (MBs)

Variables	Healthy participants	MBs without chest pain (n=11)	MBs with chest pain (n=11)
<i>Apex</i>			
AT, s	1.66±0.87	6.82±2.59*	17.54±6.75**†
PI, dB	43.64±5.80	27.02±3.53*	17.94±1.48***†
AS, dB/s	0.83±0.22	0.25±0.17*	0.13±0.05***†
$PI \times AS$, dB ² /s	37.98±11.31	7.37±4.01*	2.33±0.94***†
<i>interventricular septum</i>			
AT, s	1.83±0.92	7.09±2.88*	19.33±7.78**†
PI, dB	39.33±6.02	23.76±5.42*	15.66±1.11***†
AS, dB/s	0.56±0.15	0.18±0.28*	0.11±0.06***†
$PI \times AS$, dB ² /s	22.17±9.85	5.22±10.53*	1.72±0.63***†

Data are expressed as mean±standard deviation. PI – peak intensity; AS – ascending slope; AT – arrival time. * $p<0.05$; ** $p<0.01$, values are different from healthy participants; † $p<0.05$; †† $p<0.01$ values are different from methamphetamine abusers without chest pain

Table III. Comparison of regional myocardial perfusion among methamphetamine abusers of different exposure conditions (A: 1-2g/day, <2 years; B: 2-3g/day, 2-5 years; C: >3g/day, >5 years)

Variables	Group A (n=7)	Group B (n=7)	Group C (n=8)
<i>Apex</i>			
AT, s	6.77±2.43	13.89±5.58*	26.33±9.27*†
PI, dB	29.34±5.66	17.02±4.29*	8.57±1.55*†
AS, dB/s	0.31±0.17	0.22±0.07*	0.13±0.06*†
PI×AS, dB2/s	9.12±2.37	3.76 ±1.22*	1.14±0.39*†
<i>interventricular septum</i>			
AT, s	7.06±2.53	15.44±7.94*	27.18±9.55*†
PI, dB	26.27±6.33	13.89±4.62*	7.43±1.81*†
AS, dB/s	0.26±0.16	0.17±0.07*	0.12±0.05*†
PI×AS, dB2/s	6.86±2.12	2.39±0.92*	0.89±0.24*†

Data are expressed as mean±standard deviation. PI – peak intensity; AS – ascending slope; AT – arrival time. *p<0.01, values are different from the group A; † p<0.01, values are different from the group B

Fig 3. The performance of the myocardial perfusion for differentiating methamphetamine abusers from normal subjects using receiver operating characteristic curve analysis. IVS – interventricular septum; LV apex – Left ventricular apex.

all very good: intraclass correlation coefficients were all >0.98 for interobserver and intraobserver variability.

Discussions

This is the first study on the feasibility of assessing regional myocardial perfusion in chronic methamphetamine addicts recruited from drug rehabilitation center using real-time MCE. This study showed that real-time MCE can effectively detect the changes of regional myocardial perfusion in methamphetamine abusers at rest and that the regional myocardial perfusion was significantly reduced in methamphetamine abusers. The technique had a good performance on differentiation of methamphetamine abusers from normal subjects. To the best of our knowledge, real-time MCE had never been used before for serial assessment in this clinical setting.

During the last few years, second generation contrast agents (e.g., SonoVue® phospholipid-shell sulfur hexafluoride microbubbles) have become commercially available in China. Meanwhile, the improved image quality in echocardiography, combined with new ultrasound technical developments (e.g., power modulation imaging and pulse inversion power Doppler) made it possible to obtain echocardiographic images of myocardial perfusion. Coronary microcirculation contains 80% of the total myocardial blood volume and regulates nutrient exchange in cardiac myocytes [12]. Using echogenic gas-filled microspheres with similar size and rheologic properties to red blood cells, the destruction-refill kinetic data permit repeated quantitative measures of microvascular flow velocity and capillary blood volume. Now, MCE is technically matured and has gained wide use in the clinical diagnosis and laboratory researches. In this study, we employed a commercially available ultrasound system, Mindray M9, equipped with a 1-5MHz C5-1s transducer, using a multi-pulse contrast-specific imaging protocol (power modulation imaging), combined with pulse inversion power Doppler, utilizing contrast agent characters with both 2nd harmonic and non-linear fundamental signal to get improved signal-to-noise ratio for better diagnostic details and longer contrast agent duration for better observation.

The main findings of our study are that methamphetamine abusers, especially ones with chest pain, had significant longer contrast agent arrival times, less functional capillary blood volumes, slower microvascular flow velocities and less myocardial perfusion than healthy participants. Moreover, along with the increase of dosage and duration of use, the reductions in these myocardial perfusion indices were more significant. These findings suggest that methamphetamine induces constriction at the level of the coronary microcirculation and the major site of methamphetamine's action is probably at the most

distal coronary microvessels and capillary networks. These findings provided direct evidence for our previous studies in which methamphetamine has been shown to decrease coronary sinus flow and myocardial function [13,14].

Our data are consistent with Gurudevan et al in an earlier MCE study [6] in 10 healthy young men, in which the authors demonstrated that low-dose cocaine challenge evokes a sizeable decrease in myocardial perfusion. However, in our study we found that the predominant effect of methamphetamine was to decrease both myocardial capillary blood volume and microvascular flow velocity, while in Gurudevan et al earlier study cocaine decreased myocardial capillary blood volume rather than microvascular flow velocity. The different findings in our study may be due to the different populations studied (chronic methamphetamine-addicted patients, not healthy young men), half of them with previous chest pain and ischemic ECG changes and different methamphetamine exposure conditions.

Our study had several limitations that should be considered. First, methamphetamine abusers had greater blood pressure and more impaired LV diastolic function than healthy participants. An increased LV pressure from diastolic dysfunction theoretically could contribute to our results by causing extravascular compression of coronary microvessels. However, we did not measure LV end-diastolic pressure. Secondly, the repeatability of measurement of ascending slope from microbubble destruction-refill time vs acoustic intensity plots was always poor. New quantitative measurements methods of myocardial perfusion are needed. Thirdly, the sample size of the study was so small that grouping based on without/with chest pain and grouping based on different exposure conditions was difficult. A series of studies based on larger populations would be more persuasive. Finally, we assessed LV regional myocardial perfusion only at rest. It would be interesting to expand this study to RV myocardial segments at rest or/and at stress.

Conclusions

Our study demonstrated that regional myocardial perfusion is significantly reduced in methamphetamine abusers, especially in those with chest pain. Although it had some limitations, as mentioned above, this study still enriches the understanding of the pathogenesis of chest pain in methamphetamine abusers and still holds considerable clinical promise for monitoring, predicting and follow-up of the myocardial ischemia and cardiac toxicity of methamphetamine as well as the effects of detoxification treatment.

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Conflict of interest: none

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