Observational Study

Imaging plaque inflammation in asymptomatic cocaine addicted individuals with simultaneous positron emission tomography/magnetic resonance imaging

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Abstract

BACKGROUND
Chronic cocaine use is associated with stroke, coronary artery disease and myocardial infarction, resulting in severe impairments or sudden mortality. In the absence of clear cardiovascular symptoms, individuals with cocaine use disorder (iCUD) seeking addiction treatment receive mostly psychotherapy and psychiatric pharmacotherapy, with no attention to vascular disease (i.e., atherosclerosis). Little is known about the pre-clinical signs of cardiovascular risk in iCUD and early signs of vascular disease are undetected in this underserved population.

AIM
To assess inflammation, plaque burden and plaque composition in iCUD aiming to detect markers of atherosclerosis and vascular disease.

METHODS
The bilateral carotid arteries were imaged with positron emission tomography/magnetic resonance imaging (PET/MRI) in iCUD asymptomatic for
INTRODUCTION

Cocaine use disorder (CUD), chronic brain disease, imparts multiple cardiovascular effects. The phenomenology of cocaine addiction involves decades of chronic cocaine and other drug use as well as an unhealthy lifestyle (e.g., poor sleep and nutrition) that affect cardiovascular health. Furthermore, cocaine’s main vasoactive metabolite benzoylmetylecgonine, a tropane alkaloid, is associated with hematological effects on the vessel and the loss of the endothelium’s protective functions[4,5]. Cocaine creates an elevated immune system inflammatory state with increased pro-inflammatory cytokines, and brain-derived neurotrophic factor levels, all contributing to vascular disease[6-7]. These effects are expressed by activation of cells in the endothelium (interior surface of blood vessels) leading to macrophage proliferation and vascular inflammation, with subsequent formation of complex plaque that manifests as structural abnormalities and progresses to atherosclerotic disease[6-9]. Atherosclerosis cardiovascular disease, healthy controls, and individuals with cardiovascular risk. PET with 18F-fluorodeoxyglucose (18F-FDG) evaluated vascular inflammation and 3-D dark-blood MRI assessed plaque burden including wall area and thickness. Drug use and severity of addiction were assessed with standardized instruments.

RESULTS

The majority of iCUD and controls had carotid FDG-PET signal greater than 1.6 but lower than 3, indicating the presence of mild to moderate inflammation. However, the MRI measure of wall structure was thicker in iCUD as compared to the controls and cardiovascular risk group, indicating greater carotid plaque burden. iCUD had larger wall area as compared to the healthy controls but not as compared to the cardiovascular risk group, indicating structural wall similarities between the non-control study groups. In iCUD, wall area correlated with greater cocaine withdrawal and craving.

CONCLUSION

These preliminary results show markers of carotid artery disease burden in cardiovascular disease-asymptomatic iCUD. Broader trials are warranted to develop protocols for early detection of cardiovascular risk and preventive intervention in iCUD.

Core tip: Despite undetected clinical signs, cocaine use increases risk of stroke, coronary artery disease and myocardial infarction. Simultaneous carotid positron emission tomography/magnetic resonance imaging can effectively evaluate vascular inflammation and plaque burden in individuals with cocaine use disorder. Cocaine users had increased wall area, comparable to individuals with cardiovascular risk and significantly higher than healthy controls. Wall area in cocaine users positively correlated with greater cocaine withdrawal and craving. Broader trials are warranted to develop protocols for early detection of cardiovascular risk and preventive intervention in individuals with cocaine use disorder.

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reflected a long-term inflammatory process, where, in medium to large arteries (e.g., the carotid arteries), it may be present even before it becomes susceptible to rupture, without overt clinical symptoms. However, once symptoms occur, the artery is severely damaged and cerebral ischemia can ensue, a common fatal outcome in CUD.

Significant advances in multi-modal imaging for early detection of atherosclerosis in asymptomatic populations who are at increased risk for vascular disease (e.g., individuals with high cholesterol, Type II diabetes mellitus) have proven efficacy for preventive treatment. Thus, characterizing the atherosclerotic cascade with magnetic resonance imaging (MRI) and positron emission tomography (PET) in asymptomatic individuals at cardiovascular risk can help delineate disease stage and inform on medication choices and follow-up. The presence of inflammation captured by PET- with 18F-fluorodeoxyglucose (18F-FDG) is an important indicator of early stage disease progression and validation that the cause of vascular pathology is indeed atherosclerosis. For the purpose of imaging vascular inflammation, FDG is internalized (but not metabolized as in brain FDG) by tissues with active anaerobic metabolism, such as inflamed areas. 18F-FDG PET can quantify inflammation in atherosclerotic plaques and has been correlated consistently with plaque macrophage content (white blood cells that increase inflammation and stimulate the immune system) in atherosclerotic rabbits and patients. An important indication of atherosclerosis overall burden is assessed using MR, an excellent modality for evaluating the blood vessel wall. The MR sequence uses black (or dark) blood techniques, in which the blood appears black and the arterial wall can be seen, accurately depicting plaque presence, size, and morphology with sub-millimeter resolution and high reproducibility, providing new indices of atherosclerotic burden that can be applied in large scale studies to varied populations.

Thus, PET with FDG can detect early disease stages and simultaneous MR is used to quantify atherosclerosis burden. Such simultaneous PET/MRI has never been used for early detection of vascular pathology in asymptomatic drug addicted individuals. Targeting this population for early detection is of urgency now that the “Crack generation” of the mid 1980s is aging. Owing to decades of cocaine and comorbid tobacco and alcohol use, these individuals with CUD (iCUD) are at particularly high risk for vascular disease and atherosclerosis. Hence, the characterization of atherosclerosis by multimodal imaging can help to detect early signs of disease and inform treatment trials with non-invasive end-points. We applied imaging protocols with PET/MRI of the bilateral carotids for measuring markers of cardiovascular risk for the first time in iCUD. We hypothesize that iCUD will have elevated inflammation and atheromatous plaque burden as compared to non-addicted controls and even as compared to non-addicted individuals with established cardiovascular risk who are a decade older.

**MATERIALS AND METHODS**

**iCUD and healthy controls**
We studied a group of iCUD ($n = 14$), a group of non-addicted healthy controls ($n = 10$), and a group of non-addicted individuals with cardiovascular risk ($n = 62$). Individuals with CUD and non-addicted healthy controls were recruited using advertisement in websites, local newspapers, bulletin boards, and by word-of-mouth with calls for imaging in individuals with cocaine problems or healthy controls. Subjects were given a complete physical examination that included electrocardiography and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid functions to ensure good physical health. Drug use was assessed with urine tests in all subjects on screening day and pregnancy was tested in women on screening as well as on imaging visits. In addition, on screening day alcohol use was measured with a breathalyzer and tobacco use was measured by levels of nicotine and cotinine in blood. An in-depth interview included the following instruments for assessing inclusion/exclusion criteria: The Structured Clinical Interview for the Diagnostic and Statistical Manual-IV of Axis I Disorders (research version) for psychiatric diagnostics. Addiction Severity Index, a semi-structured interview provided an estimate of the years of drug/alcohol and severity of use and a detailed assessment for recent and lifetime history of use of various drugs including alcohol. We supplement this interview with brief, well-validated, instruments of addiction severity to assess potential covariates: Cocaine Selective Severity Assessment Scale evaluated cocaine withdrawal symptoms occurring over the past 24 h, Cocaine Craving Questionnaire assessed cocaine craving symptoms over the past 24 h, and Severity of Dependence Scale examined the severity of addiction during the past.
Background represents the average of the SUVmean-slice values acquired from the 10
the jugular vein was chosen for background ROI placement. The SUVmean-
total of 10 measurements. The lowest fused image SUVmean-slice within each slice of
2 on both the right and left sides for a acquire five measurements of at least 10 mm
were measured for each slice.
sides. The mean and maximum standardized uptake values (SUV) of the target vessel
separately, as the bifurcation is often not at the same level when comparing the two
mark the region of interest (ROI). The right and left carotid arteries were analyzed
drawing tool, the common carotid artery was traced on the fused images. MRI signal
caudal extent up to the level of the carotid bifurcation. Using the closed polygon
common carotid artery was assessed where it was well delineated from its most
target and adjacent tissue were used as guidelines to best
differences between the target and adjacent tissue were used as guidelines to best

The technique employed has been previously described in other studies
10,32. The
neck were fused with PET images of the same region and analyzed in the axial plane.
Image analysis of PET/MRI data was performed
Analysis of inflammation by PET:
Participants were
imaging at rest in supine position 90 min after injection of 10mCi of 18-FDG[13]. MRI
sequences for PET attenuation correction were acquired while the FDG was still
imaging of the internal carotid arteries extending 3
cm below and above the carotid bifurcations using a 4-channel carotid coil was
conducted. After localization with gradient echo sequences, time-of-flight images
were acquired to delineate vessel lumen (interior of the vessel). Then, dark blood
images were obtained using 3D SPACE with multiple contrast weightings. Proton
density weighted, T1 and T2 weighted images were acquired
for PET attenuation correction were acquired while the FDG was still
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were acquired to delineate vessel lumen (interior of the vessel). Then, dark blood
images were obtained using 3D SPACE with multiple contrast weightings. Proton
density weighted, T1 and T2 weighted images were acquired
for PET attenuation correction were acquired while the FDG was still
circulating. 3-D dark-blood MRI imaging of the internal carotid arteries extending 3
cm below and above the carotid bifurcations using a 4-channel carotid coil was
conducted. After localization with gradient echo sequences, time-of-flight images
were acquired to delineate vessel lumen (interior of the vessel). Then, dark blood
images were obtained using 3D SPACE with multiple contrast weightings. Proton
density weighted, T1 and T2 weighted images were acquired
during free breathing[27-29], during free breathing[27-29], un-triggered with fat suppression,
with template based attenuation correction as previously validated[30,31]. PET data for one subject, right and left carotid
MRI data of one subject, and right carotid MRI data of a third subject were not
analyzable for iCUD.

Non-addicted individuals with cardiovascular risk
In addition to our healthy control comparison group, MRI values in iCUD were
compared with values of existing data[26] from 62 non-addicted individuals (age 64.6 ± 7.8, 83% males), with the following inclusion criteria: (1) Ability to understand and
give informed consent; (2) Men and women aged 18–75 years; (3) Previous known
coronary heart disease or at high risk of coronary heart disease (diabetes or a 10-year
risk of coronary heart disease events > 20% by Framingham Risk scoring), triglyceride
concentrations of 400 mg/dL or lower (≤ 4.5 mmol/L), and carotid or aortic arterial wall (target) to background (blood) ratio (TBR) of 1.6 or higher, as identified by 18-
FDG uptake measured by PET/CT during the screening period; and (4) Clinically
stable and receiving appropriate and stable treatment with a statin or other low-density lipoprotein (LDL)-C lowering drugs with LDL-C concentrations of 100 mg/dL or
lower (< 2.6 mmol/L) unless receiving maximum tolerated doses of therapy or
intolerant to statins. Exclusion criteria included: (1) Concomitant treatment with
fibrates or nicotinic acid; (2) Presence of uncontrolled blood pressure or diabetes
(HbA1c >10%); and (3) Recent (< 3 mo) clinically significant coronary or cerebral
vascular event, diagnosis of familial hypercholesterolaemia, or a glomerular filtration
rate lower than 30 mL/min. Other reasons for exclusion were standard for this type of
trial, as previously described[31].

Imaging
Carotid PET/MR image acquisition:18F-FDG PET was used to evaluate arterial
inflammation within the right and left carotid of the subjects[10,12,26]. Participants were
imaged at rest in supine position 90 min after injection of 10mCi of 18-FDG. MRI
sequences for PET attenuation correction were acquired while the FDG was still
circulating. 3-D dark-blood MRI imaging of the internal carotid arteries extending 3
cm below and above the carotid bifurcations using a 4-channel carotid coil was
conducted. After localization with gradient echo sequences, time-of-flight images
were acquired to delineate vessel lumen (interior of the vessel). Then, dark blood
images were obtained using 3D SPACE with multiple contrast weightings. Proton
density weighted, T1 and T2 weighted images were acquired, during free breathing[27-29], un-triggered with fat suppression, with template based attenuation correction as previously validated[30,31]. PET data for one subject, right and left carotid
MRI data of one subject, and right carotid MRI data of a third subject were not
analyzable for iCUD.

Analysis of inflammation by PET: Image analysis of PET/MRI data was performed
using OsiriX MD (Pixmeo, Geneva, Switzerland). T2 TSE MRI images of the head and
neck were fused with PET images of the same region and analyzed in the axial plane.
The technique employed has been previously described in other studies[10,32]. The
common carotid artery was assessed where it was well delineated from its most
caudal extent up to the level of the carotid bifurcation. Using the closed polygon
drawing tool, the common carotid artery was traced on the fused images. MRI signal
differences between the target and adjacent tissue were used as guidelines to best
mark the region of interest (ROI). The right and left carotid arteries were analyzed
separately, as the bifurcation is often not at the same level when comparing the two
sides. The mean and maximum standardized uptake values (SUV) of the target vessel
were measured for each slice.

Background was measured within the jugular veins using an oval drawing tool to
acquire five measurements of at least 10 mm² on both the right and left sides for a
total of 10 measurements. The lowest fused image SUVmean-slice within each slice of
the jugular vein was chosen for background ROI placement. The SUVmean-
background represents the average of the SUVmean-slice values acquired from the 10
background slices. TBR mean and maximum were then calculated by dividing respectively the target SUVmean of a slice and the target SUVmax of a slice by the SUVmean-background. The TBRmean-overall and TBRmax-overall represent the average of the metric’s values when considering all slices evaluated for each artery. The most diseased segment (MDS) is defined as the highest TBRmax-slice and that of its two adjacent slices and the TBR of the MDS (TBR-MDS) is the average of the TBRmax-slice of this three level segment. Calculations were made using Excel (Microsoft, Washington, USA).

**Analysis of atherosclerotic burden by MRI:** 3D-SPACE MRI images of the neck were obtained and reformatted into the axial plane prior to analysis. Using these reformatted ‘black blood’ MRI images, the carotid arteries were analyzed at a dedicated workstation running the software program VesselMASS, (VesselMASS, Division of Image Processing, Department of Radiology, Leiden University Medical Center, Leiden, Netherlands). The technique used has been previously described in other studies[33,34]. As with the MR/PET analysis, the common carotid artery was assessed separately and bilaterally in the slices where each vessel was well delineated, from its most caudal extent up to the level of the carotid bifurcation. The metrics acquired for each vessel included: lumen area, wall area, total vessel area, wall thickness and wall thickness SD. A normalized wall index was also calculated to account for arterial wall size differences that are found within each subject.

**Statistical analyses**
Statistical analysis was conducted in SPSS (IBM Corp., Version 23.0. Armonk, NY) to compare between the iCUD and the healthy control group on demographics and drug use by a two samples t-tests (two-tailed). Comparisons of PET/MR measurements between the iCUD and the healthy controls groups were conducted by univariate analysis of covariance (ANCOVA) while controlling for age. Comparisons of MRI measurements between the iCUD and the group of individuals with cardiovascular risk were conducted by one sample t-tests (two-tailed) using the mean values of the group of individuals with cardiovascular risk (since only mean values were available for this group). Associations between the findings that differed between the iCUD and the healthy control group and drug use measures were examined by partial correlations with age and nicotine lifetime use (which differed significantly between the groups) as covariates. A familywise correction for multiple correlations at significance level of $P = 0.05$ was applied.

**RESULTS**

**Participants**
Cocaine addicted individuals were slightly older than non-addicted healthy controls and about a decade younger than those with cardiovascular risk. The race distribution was unequal, with more African Americans in the iCUD group. There were no differences between the iCUD and non-addicted healthy controls in gender, education, body mass index, and resting heart rate. Framingham risk scores were available only for a limited number of participants (3 iCUD scored 8.7 ± 3.6 vs 6 healthy controls 2.7 ± 2.1, $P < 0.05$). iCUD were chronic users with 21.9 ± 7.9 years of cocaine use, 20.8 ± 11.8 years of alcohol use, and 9.1 ± 10.5 years of cannabis use; 64% were current smokers whereas in the healthy controls 10.0% were current and 20.0% were past smokers (groups differences on lifetime use of cocaine, cannabis, and nicotine smoking, $P < 0.001$; alcohol lifetime use did not differ between the iCUD and healthy control groups) (Table 1).

**Imaging results**
According to norms established in clinical research studies of risk detection[35,36], TBR ≥ 1.6 is indicative of inflamed plaque. The PET FDG results showed that both iCUD (85%) and the healthy controls (90%) had slightly inflamed plaque in one or both carotid arteries. There were no significant differences in plaque inflammation between the iCUD and the non-addicted healthy controls measured by maximum target-to-background ratios and measures of most diseased segment (Table 2).

The MRI measures demonstrated that the iCUD had significantly elevated carotid plaque burden as compared to the non-addicted healthy controls and the group of individuals with cardiovascular risk (Figure 1 and Figure 2, Table 2). The ANCOVA results showed that, as compared to the healthy controls, the iCUD group had significantly increased wall thickness and wall area. Notably, in one sample t-tests using the individuals with cardiovascular risk comparison group’s mean values, a similar pattern of elevated plaque in iCUD was observed as follows: iCUD had
Table 1  Sample characteristics: Demographics, cardiovascular risk, and drug use

|                          | Group 1: Cardiovascular risk ($n = 62$) | Group 2: Healthy controls ($n = 10$) | Group 3: Cocaine users ($n = 14$) |
|--------------------------|--------------------------------------|------------------------------------|----------------------------------|
| Demographics             |                                      |                                    |                                  |
| Race                     | 62 white (94%); 4 other              | 5 black (50%); 4 white; 1 other    | 13 black (93%); 1 white          |
| Gender                   | 55 men (83%)                         | 8 men (80%)                        | 10 men (71%)                     |
| Age                      | 64.6 ± 7.8                           | 46.2 ± 5.3                         | 50.8 ± 4.1                       |
| Education                | NA                                   | 15.0 ± 2.0                         | 13.6 ± 1.8                       |
| Cardiovascular risk      |                                      |                                    |                                  |
| BMI                      | NA                                   | 29.1 ± 5.0                         | 28.3 ± 3.7e                     |
| Heart rate               | NA                                   | 74.9 ± 11.9                        | 79.1 ± 10.9                      |
| Total cholesterol        | NA                                   | 182.7 ± 28.2                      | 163.3 ± 28.9f                   |
| HDL cholesterol          | NA                                   | 55.8 ± 16.1f                       | 42.3 ± 9.1e                     |
| Drug use                 |                                      |                                    |                                  |
| Alcohol lifetime         | NA                                   | 18.9 ± 13.4                        | 20.8 ± 11.8                      |
| Cocaine lifetime         | NA                                   | NA                                 | 21.9 ± 7.9                      |
| Nicotine lifetime        | 12% current                          | 10.0% current; 20.0% past; 70.0%   | 64.3% current; 28.6% past; 7.1%  |
|                           | never; 3.5 ± 8.1                     | never; 26.4 ± 10.1                 | never; 26.4 ± 10.1               |
| THC lifetime             | NA                                   | 0.5 ± 1.3                          | 9.1 ± 10.5                      |
| Cocaine withdrawal       | NA                                   | NA                                 | 18.6 ± 11.9                     |
| Cocaine craving          | NA                                   | NA                                 | 14.7 ± 14.5                     |
| Severity of drug dependence | NA                               | NA                                 | 3.2 ± 3.6                       |

1$n = 13$.  
2$n = 7$.  
3$P < 0.001$.  
4$P < 0.05$.  
5$P < 0.001$.  
6Cardiovascular risk > cocaine users:  
7Healthy controls < cocaine users:  
8Healthy controls < cocaine users:  
9$P < 0.05$.  

significantly thicker wall, whereas the cardiovascular risk group and healthy controls did not differ on this measure indicating the presence of more plaque and worse structural disease state in the carotids of iCUD than the much older symptomatic comparison sample, who has been identified for risk for cardiovascular events. Using the cardiovascular risk comparison group’s mean values for wall area, significant differences were detected when compared with healthy controls but differences did not reach significance when compared with iCUD.

Testing whether these elevated inflammation markers in iCUD correlated with addiction symptoms, we found that plaque burden (wall area) was positively associated with the degree of cocaine withdrawal and craving even after controlling for age and nicotine use and also familywise error correcting for multiple analyses. The greater the cocaine withdrawal symptoms ($r = 0.838, P_{uncorr} = 0.003, P_{corr} = 0.021$) and the greater the cocaine craving ($r = 0.787, P_{uncorr} = 0.007, P_{corr} = 0.049$) the larger the wall area in iCUD (Figure 3). No correlations with PET inflammation markers were found.

**DISCUSSION**

In this study, we conducted noninvasive vascular PET/MR imaging of the bilateral carotid arteries in iCUD and two control groups. Elevated markers of carotid artery atherosclerotic disease burden were found in iCUD as compared to non-addicted healthy controls and even as compared to older non-addicted individuals with high risk for cardiovascular disease. Specifically, the MRI measure of carotid wall structure showed higher thickness in the iCUD as compared to the healthy controls and cardiovascular risk group, indicating greater carotid plaque burden. The iCUD also had larger wall area as compared to the healthy controls (a difference that did not reach significance when compared to the cardiovascular risk group), indicating
structural wall abnormalities that reached levels of those in the cardiovascular risk group. These elevated cardiovascular disease markers were associated with elevated degree of cocaine withdrawal and craving in iCUD, indicating a relationship between the extent of substance use disorder and the development of atherosclerosis.

The carotid FDG-PET images indicating the presence of inflammation did not differ between the iCUD and non-addicted healthy controls, as most of these individuals had inflammatory presence in one side or bilaterally in the carotid arteries. This result may indicate the beginning of an atherosclerosis process in all subjects with inflammation levels (i.e., TBR) over 1.6 which cholesterol deposition, inflammation, extracellular-matrix formation and thrombosis have important roles. Thus, although many of the healthy control group  in the indices of plaque burden. Atherosclerosis and progression to cardiovascular disease are characterized by a slow and "silent" disease accumulation that occurs over decades and progress from a chronic inflammatory condition that can be converted into an acute clinical event by plaque rupture and thrombosis[6,37]. Since iCUD in this study had over 20 years of lifetime cocaine use as well as nicotine and alcohol it is possible that they passed the inflammatory disease stage and have been converted into an acute clinical event by plaque rupture and thrombosis[6,37]. Since iCUD in this study had over 20 years of lifetime cocaine use as well as nicotine and alcohol it is possible that they passed the inflammatory disease stage and have progressed into an atherosclerosis disease state with a clear vascular structural impact (i.e., the formation of plaques). Interestingly, iCUD who had increased carotid plaque burden also had greater withdrawal and craving, which have been implicated with negative outcomes of cocaine dependence[22,23].

**Caveats and future studies**

These preliminary results should be considered in light of several caveats which limit the generalizability of the findings, including small sample size, the limited number of patients with cardiovascular disease and the potential for selection bias.

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**Table 2 Positron emission tomography/magnetic resonance imaging results by group**

|                        | Group 1: Cardiovascular risk(n = 62) | Group 2: Cocaine users (n = 13) | Group 3: Healthy controls (n = 10) | Group 2 and 3 difference [Sig. (ANCOVA)] |
|-----------------------|-------------------------------------|---------------------------------|-----------------------------------|------------------------------------------|
| PET results           |                                     |                                 |                                   |                                          |
| Target-to-Background ratio (TBR max) | Left      | NA                              | 1.77 ± 0.10                      | 1.77 ± 0.07                              | F(1, 20) = 0.3, P = 0.619                |
|                       |                                     | Right                           | 1.93 ± 0.09                      | 1.76 ± 0.04                              | F(1, 20) = 1.9, P = 0.178               |
|                       |                                     | R+L                             | 1.85 ± 0.09                      | 1.76 ± 0.05                              | F(1, 20) = -0.2, P = 0.687             |
|                       |                                     |                                 |                                   |                                          |
| MR results            |                                     |                                 |                                   |                                          |
| Wall thickness (mm; mean, SE) | Left      | NA                              | 1.53 ± 0.06                      | 1.25 ± 0.04                              | F(1, 20) = 7.6, P = 0.012              |
|                       |                                     | Right                           | 1.50 ± 0.07                      | 1.20 ± 0.05                              | F(1, 19) = 8.3, P = 0.009              |
|                       |                                     | R+L                             | 1.51 ± 0.06                      | 1.22 ± 0.04                              | F(1, 20) = 100, P = 0.005              |
| Wall area (mm²)       |                                     |                                 |                                   |                                          |
| Left                  | NA                                  | 35.67 ± 2.25                    | 29.02 ± 1.54                     | F(1, 20) = 3.3, P = 0.086               |
| Right                 | NA                                  | 34.51 ± 2.06                    | 27.37 ± 1.43                     | F(1, 19) = 4.9, P = 0.039              |
| R+L                   | NA                                  | 32.28 ± 1.43                    | 28.19 ± 1.31                     | F(1, 20) = 4.9, P = 0.039              |

1n = 12.
2Cocaine users > Cardiovascular risk: P < 0.001.
3Cardiovascular disease risk and healthy controls group difference: t(9) = 1.12, P = 0.294.
4Cardiovascular risk > healthy controls: P < 0.05.
5Cocaine users and Cardiovascular risk group difference: t(12) = 1.49, P = 0.163. NA: Not available.
women, and the absence of a match on race. Race is very important for cardiovascular disease with African-American individuals showing greater progression of coronary atherosclerosis as compared to Caucasians\cite{39}. Notably, among African-American men, cocaine was the largest contributor to overdose deaths\cite{40}. Therefore, close matching on race in similar future studies could reduce potential bias in results. Despite considerable efforts, recruitment of healthy control individuals who match the iCUD group on years of nicotine smoking was also a challenge. While nicotine smoking, which is part of the phenomenology of CUD (frequently concomitant with multiple substance use), was accounted for in analyses, matching between groups on nicotine use could provide a better approximation of the vascular effects of cocaine use. Data for PET-\textsuperscript{18}FDG in the cardiovascular risk group and data for calculating Framingham Risk Scores for the full sample were not available. The cross sectional design of the study further limited tracking of disease progression as should be done in future studies. Thus, examining iCUD with less years of lifetime cocaine use and those in earlier stages of the addiction disease could provide opportunities for further stratification of the progression of atherosclerosis disease, even prior to structural narrowing of the arteries. In addition, longitudinal studies should explore whether preventive cardiovascular measures will combat disease progression and may also reduce addiction symptoms. Early detection and preventive intervention protocols will thus await the results of a broader trial.

**Conclusion**

Given the known vascular toxicity induced by cocaine\cite{1,41} and the progressing age of the crack generation, there is a public health imperative for early detection of the preclinical markers of atherosclerosis in iCUD\cite{42-44}. Once pathology is identified, and especially if identified at an early stage, timely intervention can be deployed to prevent the progression into severe impairments, emergency cardiovascular events and premature mortality.
Figure 2  Dark blood magnetic resonance imaging images. A, B: Healthy vessel in a control subject; C, D: Increased carotid wall thickness (arrows) and area in a cocaine addicted individual. A and C show longitudinal images of the left carotid bifurcation. B and D show axial images of the lateral carotid.

Figure 3  Partial correlation plot. A: Wall area associations with Cocaine withdrawal symptoms, controlled for age and nicotine; B: Wall area associations with Cocaine craving, controlled for age and nicotine.

ARTICLE HIGHLIGHTS

Research background
Cocaine is one of the most commonly illicit drugs involved in emergency department visits, amounting to a vast social and economic burden. Cocaine use disorder (CUD), a chronic relapsing condition, frequently leads to life-threatening vascular disease including stroke, coronary artery disease and myocardial infarction. Cocaine’s main vasoactive metabolite benzoylmethylecgonine, a tropane alkaloid, is associated with hematological effects on the vessel and the loss of the endothelium’s protective functions leading to elevated immune state including macrophage proliferation, atherosclerosis, and ischemic vascular disease. The life-style associated with chronic cocaine use (poor sleep and nutrition) further affects cardiovascular health.
Research motivation

Despite the known vascular toxicity associated with cocaine use, individuals with (iCUD) seeking addiction treatment receive mostly psychotherapy and psychiatric pharmacotherapy with no attention to vascular disease in the absence of clear symptoms. Little is known about the pre-clinical signs of cardiovascular risk in iCUD and early signs of vascular disease are undetected in this underserved population.

Research objectives

We aim to assess inflammation composition and plaque burden in individuals with cocaine use disorder aiming to quantify markers of atherosclerosis and vascular disease. The characterization of vascular disease in iCUD with no pre-clinical cardiovascular symptoms can inform development of future preventive and treatment protocols.

Research methods

Advancements in multi-modal imaging technologies have been efficacious in early detection of atherosclerosis in asymptomatic populations who are at heightened risk for vascular disease. Simultaneous magnetic resonance imaging (MRI) and positron emission tomography (PET) allows for the precise quantification of inflammatory composition and plaque burden during a single non-operator dependent scan.

The bilateral carotid arteries were imaged with PET/MRI in iCUD asymptomatic for cardiovascular disease, healthy controls, and MRI in individuals with cardiovascular risk. PET with 18F-fluorodeoxyglucose evaluated vascular inflammation and 3-D dark-blood MRI assessed plaque burden including wall area and thickness. Addiction questionnaires assessed drug use and severity of addiction.

Research results

The MRI measure of wall structure was thicker in iCUD as compared to the controls and even as compared with the cardiovascular risk group, indicating greater carotid plaque burden. iCUD had also statistically significant larger wall area as compared to the healthy controls but not as compared to the cardiovascular risk group (the later results did not reach significance). These findings indicate structural wall similarities between the iCUD and cardiovascular risk study groups.

The majority of iCUD and controls had carotid FDG-PET signal greater than Target-to-Background ratios (TBR max) 1.6, indicating the presence of inflammation, yet, overall the observed inflammatory levels in both groups were mild (TBR max level under 3). In iCUD, wall area correlated with greater cocaine withdrawal and craving.

Research conclusions

For the first time in cocaine addiction, this preliminary study used noninvasive simulations PET/MRI vascular imaging of the bilateral carotid arteries in cardiovascular disease-asymptomatic iCUD and two control groups, including healthy individuals and those with cardiovascular disease risk. Aligned with study hypothesis, we observed markers of elevated carotid artery plaque burden in iCUD, reaching similar (wall area) and even exceeding (wall thickness) levels of those in cardiovascular risk group. This plaque burden in iCUD was positively associated with extent of cocaine withdrawal and craving symptoms, indicative of a relationship between the severity of addiction and vascular disease state.

Several caveats limit generalizability of findings, including a small sample size, the limited number of women, and variance between groups in race and nicotine smoking. These factors were covaried in the current analyses, nonetheless, matching between groups in future studies would provide a better approximation of cardiovascular disease in iCUD.

Research perspectives

This PET/MRI investigation showed that markers of cardiovascular disease abnormalities were detected in iCUD with no presenting clinical symptoms. Expanding this line of research to examination of iCUD with fewer years of lifetime cocaine use could provide further stratification of cardiovascular disease progression in this population. Broader trials are warranted to develop protocols for early detection of cardiovascular risk and preventive intervention in individuals with cocaine use disorder.

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