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Coronary Plaque Progression and Regression in Asymptomatic African American Chronic Cocaine Users with Obstructive Coronary Stenoses: A Preliminary study

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Abstract

Objective—Although rapid progression of coronary atherosclerosis was observed in chronic cocaine users, it is unknown whether reduced cocaine use retards the progression of atherosclerosis. We investigated whether reduced cocaine use over a 12-month period was associated coronary plaque regression in cocaine users.

Methods—Fifteen African American chronic cocaine users with previously coronary CT angiography (CCTA) - confirmed >50% coronary stenosis in Baltimore, Maryland, were enrolled in a study to investigate whether reduced cocaine use is associated with changes in coronary plaque burden over a 12-month period of cash-based incentive intervention, which was implemented to systematically reinforce cocaine abstinence. In addition to previous CCTA (pre-intervention), CCTA was performed at the intervention baseline and post-intervention. Plaque analyses were performed to determine (1) the trajectory of plaque changes in the absence of intervention by comparing the pre-intervention to the intervention baseline studies, and (2) the trajectory of plaque changes associated with the intervention by comparing the intervention baseline to the post-intervention studies, and (3) whether reduced cocaine use was independently associated with changes in coronary plaque burden.

Results—During the 12-month cash-based incentive intervention period, cocaine use in participants was lower. The medians of noncalcified plaque indices were 37.8(IQR:29.3–44.0), 43.1(IQR:38.3–49.0), and 38.7(IQR:31.2–46.8) mm^2 at pre-intervention, intervention baseline and

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None.

post-intervention, respectively. Multivariable generalized estimating equation analysis showed that (1) both total plaque and noncalcified plaque indices at pre-intervention were significantly lowered as compared with intervention baseline levels, (2) both total plaque and noncalcified plaque indices after intervention were significantly lowered as compared with intervention baseline levels, and (3) reduced cocaine use was independently associated with lower total plaque volume index (P<0.0001) and noncalcified plaque volume index (P=0.010).

Conclusions—Our findings suggest that continued cocaine use may be associated with noncalcified plaque progression while reduced cocaine use may be associated with noncalcified plaque regression. Larger studies are needed to confirm these findings.

Keywords

coronary plaque regression; cocaine use; noncalcified coronary plaque volume index; contrast-enhanced coronary CT angiography; cash-based incentive intervention

Introduction

Extracted from the leaves of the *Erythroxylon coca* plant, cocaine is a psychomotor stimulant that has been used worldwide [Benzaquen et al., 2001], and one of the most commonly used illicit drugs worldwide and in the United States. It is estimated worldwide that up to 20 millions of people between the ages of 15 and 64 years used cocaine in 2009 [Degenhardt L, 2012]. Despite many efforts and initiatives to control cocaine use, the United States still faces an epidemic of its use by adolescents and young adults from all socioeconomic backgrounds. In 2013, there were 1.5 million chronic cocaine users aged 12 years or older, or 0.6 percent of the US population [Substance Abuse and Mental Health Services Administration, 2014].

Cocaine has been implicated in accelerating the development of atherosclerosis [Benzaquen et al., 2001; Dressler et al., 1990; Ebersberger et al., 2013]. Nevertheless, most studies are cross-sectional, retrospective chart reviews, or based on autopsy findings. The exact underlying mechanisms linking cocaine use with clinical and subclinical coronary atherosclerosis are not well defined. A large body of literature has demonstrated that chronic cocaine use is associated with several clinical cardiovascular complications, including angina pectoris, myocardial infarction and cardiac death [Degenhardt L, et al., 2012; Benzaquen, et al., 2001; Dressler, et al., 1990; Aquaro et al., 2011]. Despite pathological, clinical, and epidemiological evidence suggesting that chronic cocaine use is associated with the development and progression of coronary atherosclerosis, the existing evidence that cocaine induces and/or accelerates coronary atherosclerosis remains controversial because of differences in study design, study population and the statistical methods employed [Benzaquen, et al., 2001; Dressler, et al., 1990; Aquaro et al., 2011; Chang et al., 2011; Ebersberger et al., 2013].

Since 2000, we recruited and followed up approximately 1,500 African Americans (AAs) to investigate the effects of cocaine use and other factors on subclinical coronary atherosclerosis in Baltimore, Maryland. We reported that long-term cocaine use is independently associated with obstructive coronary stenosis [Lai et al., 2008] and that

duration of cocaine use is associated with levels of an endothelial dysfunction biomarker, endothelin-1 (ET-1) [Tai et al., 2012]. Endothelin-1 has pro-inflammatory properties and is associated with cardiovascular risk [Bossard et al., 2015].

We further found that cocaine use can be reduced with the use of a cash-based incentive intervention, and that reduced cocaine use is associated with reduced endothelin-1 levels [Lai et al., 2015].

These surprising results prompted us to hypothesize that reduced cocaine use potentially retards coronary plaque progression in chronic cocaine users with existing coronary plaque burden. To test this hypothesis, we enrolled 15 chronic cocaine users with coronary CT angiography (CCTA)-confirmed prior >50% coronary stenosis from AAs who participated in one of our CCTA studies, and implemented a 12-month cash-based incentive intervention to reduce cocaine use. Thus, three sets of demographic, behavioral, laboratory, and imaging data were collected: (1) pre-intervention, which is the last research visit prior to the intervention baseline, (2) intervention baseline, and (3) the 12-month post-intervention follow-up. The objectives of this preliminary study were to examine (1) whether coronary plaque burden increases over the period in which no intervention was performed (from the pre-intervention to intervention baseline period), (2) whether coronary plaque burden decreases with reduced cocaine use over the period in which cash-based incentive intervention was available (from intervention baseline to post-intervention), and (3) whether reduced cocaine use was independently associated with changes in coronary plaque burden.

Methods

Study design and participants

Between March and June, 2014, 15 African American (AA) chronic cocaine users (3 women and 12 men) were consecutively enrolled from our ongoing study into a preliminary study to explore whether a change in cocaine use is associated with a change in coronary plaque burden in chronic cocaine users with contrast-enhanced coronary CT angiography (CCTA)-confirmed >50% obstructive coronary plaque at the Johns Hopkins Hospital, Baltimore, Maryland, USA.

Inclusion criteria were (1) Participation in our ongoing longitudinal study investigating the adverse effect of cocaine use and other factors on subclinical atherosclerosis in AAs, Baltimore, Maryland with the use of contrast-enhanced CCTA, (2) Aged 25 years or older (3) The presence of at least one-vessel >50% obstructive coronary plaque, confirmed by contrast-enhanced CCTA, (4) Chronic cocaine use defined as use of cocaine by any route for at least 6 months, administered at least 4 times a month, and (5) Self-reported recent cocaine use, confirmed by a positive urine test for cocaine or benzoylecgonine during the initial screening visit, and fulfilling diagnostic criteria for cocaine dependence on a computerized version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Exclusion criteria were (1) Any evidence of clinical CAD or any symptoms believed to be related to cardiovascular disease, (2) History of serious physical disease or current physical disease, chronic obstructive pulmonary disease, seizure, head trauma or CNS tumors, or current or past histories of serious psychiatric disorder (i.e., Axis I, DSM IV), other than substance

abuse or dependence, (3) Infrequent cocaine users (fewer than 4 times a month, consecutive 6 months), (4) Pregnancy or child-bearing potential and not using effective birth control measures or the intent to become pregnant during the follow-up period, (5) Chronic kidney disease with an estimated glomerular filtration rate of < 60 ml/minute/1.73 m^2, (6) Ever on statin therapy, and (7) Contraindication to CT scans, including a history of contrast allergy.

The Committee on Human Research at the Johns Hopkins School of Medicine approved the study protocol and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines.

Procedures

Interview, medical chart review, physical and laboratory examinations—At a time prior to the current investigation (pre-intervention), baseline of the intervention and 12-month after intervention (post-intervention), the following data were acquired in all study participants at research visits:

A detailed interview to obtain information regarding sociodemographic characteristics, medical history; behaviors, including alcohol consumption, drug use, and cigarette smoking; and medications. For HIV-positive participants, detailed information regarding HIV-related risk factors, duration of known HIV infection, and medications, including ART use, was also collected. A medical chart review was used to confirm the information on medical history and medications provided by the study participants. A physical examination was performed and vital signs were recorded. Routine clinical laboratory blood chemistry tests were conducted. The following laboratory tests were also performed at each of the pre-intervention, intervention baseline and post-intervention visits: total serum cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), high-sensitivity CRP (hsCRP), and ET-1.

Anthropometry and Blood Pressure Measurement—Blood pressures were measured with a standard mercury sphygmomanometer (average of three measurements). Height and weight, as well as waist and hip circumferences were recorded.

Phlebotomy—An approximate 30 cc blood sample was drawn after a fasting interval of at least 12 hours.

ET-1 assay—Extraction of plasma, assay, and calculation of results all followed the procedures specified for ELISA kit of ET-1 (R&D Systems, Inc., Minneapolis, MN). Standards, control and the samples were assayed simultaneously in duplicate. The within run coefficient of variation was 5%.

Voucher-based Incentive Interventions—The voucher based inventive program was described previously [Lai et al., 2015]. Briefly, a voucher-based method was used to reinforce cocaine abstinence. Voucher value escalates with longer episodes of abstinence. The voucher-based incentive program employed a management procedure that systematically reinforces cocaine abstinence, with features modeled after the escalating voucher incentive program developed by Higgins and colleagues [Higgins et al., 1993].

Points (1 point= $1) were awarded for cocaine negative test results. The number of points earned increased with the duration of abstinence and therefore rewards prolonged abstinence (maximum reward $100). There is also a “reset-penalty” where, in case of a positive urine test, not only are the points not awarded, but the escalating voucher values are reset again. Specifically, should drug use be detected via submission of a cocaine positive urine sample, the participant will need to re-start the incentive program at the week 1 level and proceed again through the weekly steps. Not only does avoidance of the reset serve as a motivator for continued abstinence, but the return to more intensive monitoring is a clinically indicated response to evidence of drug relapse.

The frequency of urine tests decreases over time once a stable period of abstinence has been established. Specifically, in the first 4 weeks, participants will be asked to provide urine tests twice a week, and will earn $10 if two urine tests are both negative. In weeks 2 and 3, the participant will earn $20 for two negative urine tests, and will earn $30 for two negative urine tests in week 4. In weeks 5–8, only one urine test per week is required and potential earnings increase from $30 to $40 per week. After week 8, when a stable period of abstinence has been established, frequency of urine collection continues to decline with biweekly testing in weeks 8–16, and then once monthly testing after week 16. To counteract the decreased frequency of reinforcement with longer time between testing, value of the potential earnings increases to $80 with bi-weekly testing in weeks 10–16 and $100 with once-monthly testing in weeks 20–52. Earned money will be distributed immediately after each negative urine test in the form of a check. Doing so provides immediate acknowledgement and reinforcement for the negative test. After money is earned, it belongs to the participant and is never taken back irrespective of subsequent drug use or other adverse behaviors.

Urine Benzoylecgonine Test—Urine tests were scheduled in advance. Urine samples were collected under observation of a same-sex research assistant, and the temperature of the sample examined to confirm its validity. Cocaine metabolite quantitation were conducted using an immunochromatography rapid drug test (DOA 1 Panel Dip Card – COC, MP Biomedicals, Solon, OH). This was used as a preliminary test result for the voucher based intervention. Samples were also stored for quantitative urine analysis [Preston et al., 1997]. Missing samples were considered positive.

Reduction in cocaine use—According to questionnaire data, all the study participants used cocaine daily (the mean times of cocaine use per day was 2.9±2.0 times/day, ranged from 1 time/day to 7 times/day) at intervention baseline. Thus, reduction in cocaine use at post-intervention was defined as 365 days – cumulative urine positive days during the 12-month intervention period according to urine tests.

Days of cocaine use are calculated as follows: in the first 4 weeks, participants will be asked to provide urine tests twice a week, and a positive urine result was calculated as 3.5 days of cocaine use. In weeks 5–8, only one urine test per week is required and a positive urine result was calculated as 7 days of cocaine use. In weeks 9–16, frequency of urine collection continues to decline with biweekly testing and a positive urine result was calculated as 14

days of cocaine use. After week 16, one urine test per month is required and a positive urine result was calculated as 30 days of cocaine use.

Contrast-enhanced CCTA—Cardiac CT scans were performed at pre-intervention, intervention baseline and at the 12-month follow-up on a Siemens second-generation, 128-slice, dual-source CT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). No premedication was used. After a test bolus application to optimize the acquisition timing for the participant (10 cc bolus of contrast), CT angiography was performed. The scan parameters were 100–120 kVp (depending on the patient's size), Care Dose quality reference standard of 320 mAs (Care Dose 4D was used to minimize radiation dose), rotation time was 0.28 seconds, collimation was 128 x 0.6 mm, and average acquisition time was under 5 seconds (heart rate dependent). Scan data were reconstructed with .75 mm thickness at .5 mm reconstruction spacing using a B26ASA and B30f reconstruction kernel with iterative reconstruction. The scan protocol used 80 ml–100 ml of an iso-osmolar contrast agent (Vispaque-320, GE Medical Systems) injected at 5–6 cc/sec. Images for calcium scoring were obtained pre-contrast (120 kVp, 3 mm slice thickness)

All images were interpreted by a radiologist with board certification in cardiac CT interpretation.

CCTA volumetric plaque analysis—Plaque analysis was performed independently in the Department of Radiology and Imaging Sciences, National Institutes of Health Clinical Center with the use of the QAngioCT software (Research Edition, version 2.0.5; Medis Medical Imaging Systems, Leiden, the Netherlands) (Figure 3A). The software has been validated against IVUS [Park et al., 2015], and was used extensively in clinical studies [Rodriguez et al., 2015; Papadopoulou et al., 2012; Ferencik et al., 2015; Auscher et al., 2015].

The image analysts were blinded to participants' characteristics. The coronary tree was automatically extracted, and each of the major vessels (i.e. the left anterior descending artery, the left circumflex artery, and the right coronary artery) was individually analyzed from the ostium to the point at which the internal vessel caliber decreased to < 2.0 mm, exclusive of focal stenosis. Segmentation was performed according to AHA nomenclature [Cerqueira et al., 2002]. Segments with image artifacts or stents were excluded. Automated longitudinal contouring of the inner lumen and outer wall was performed and results were manually adjusted when clear deviations were noted. Results of automated contouring of the inner lumen and outer wall were also reviewed on transverse reconstructed cross-sections of the artery on a section-by-section basis at 0.5-mm increments [Rodriguez et al., 2015]. Lumen attenuation was adaptively corrected on an individual-scan basis by using gradient filters in combination with the intensity values in the arteries, allowing for comparison between data sets [Park et al., 2015]. Total plaque volume (calcified plus noncalcified plaque volume) was calculated by subtracting the lumen volume from the outer wall volume. The plaque burden per unit length was calculated as segmental plaque volume (in mm^3) / length (in mm) of the corresponding segment, yielding the total plaque volume index (in mm^2); noncalcified plaque volume index was calculated as the total volume index minus the calcified plaque volume index (in mm^2) [Rodriguez et al., 2015].

Statistical analysis—Statistical analysis was performed with SAS 9.4 (SAS Institute, Cary NC). All continuous parameters were summarized by medians and interquartile ranges (IQRs), and all categorical parameters were summarized as proportions. To compare differences between intervention baseline and post-intervention for demographic and clinical characteristics, laboratory parameters, and other factors, the non-parametric Wilcoxon two-sample test was used for continuous variables and the Fisher's exact test was employed for categorical variables.

Data from three visits (pre-intervention, intervention baseline and post-intervention) were used to perform longitudinal analysis. To examine (1) whether coronary plaque burden increased over the period in which no intervention was performed (from the pre-intervention to intervention baseline period), and (2) whether coronary plaque burden decreased with reduced cocaine use over the period in which cash-based incentive intervention was available (from intervention baseline to post-intervention), a generalized estimating equation (GEE) model with the time variable as covariate of interest was used [Liang et al., 1986]. Two indicator variables, pre-intervention visit vs. otherwise, and post-intervention vs. otherwise, were created (intervention baseline visit as the reference). Univariable GEE analysis was performed to explore crude association between change in coronary plaque burden (total plaque volume index, calcified plaque volume index, and noncalcified plaque volume index) and time. A multivariable GEE model was used to adjust for potential confound factors, including pre-intervention plaque burden, the 2013 ACC/AHA cardiovascular risk score [Goff et al., 2014], and CRP levels. To examine whether reduced cocaine use was independently associated with changes in coronary plaque burden, a variable, reduction in cocaine use, defined as 365 days – cumulative urine positive days during the 12-month period, was included in the GEE models. Univariable GEE analysis was performed to explore crude association between change in coronary plaque burden (total plaque volume index, calcified plaque volume index, and noncalcified plaque volume index) and reduction in cocaine use. A multivariable GEE model was used to adjust for potential confound factors, including the above-mentioned time variable, pre-intervention plaque burden, the 2013 ACC/AHA cardiovascular risk score, and CRP levels. The p-values reported are two-sided. A p-value <0.05 indicated statistical significance.

Results

General characteristics

The demographics and clinical characteristics of the 15 study participants are presented in Table 1. The median age was 49 years and 20% were women. Among the 15 participants, 12 were HIV infected. The median duration of cocaine use was 20 (IQR: 7–30) years. The median time interval between pre-intervention and intervention baseline was 3.99 (IQR: 2.41–7.11) years, while the median time interval between intervention baseline and post-intervention was 1.04 (IQR: 0.78–1.04) years.

Reduction in cocaine use, CRP and endothelin-1

According self-report data from questionnaires, all the study participants used cocaine daily at intervention baseline. During the 12-month intervention, the mean cumulative days of

cocaine use was 50 (SD: 95) days, and median was 7 (interquartile range: 0 – 35) days. The reduction in cocaine use during the intervention period was statistically significant (P<0.0001, Figure 1). CRP and endothelin-1 over time are presented in Figure 1 and Table 1.

The median ET-1 levels were 1.43 (IQR: 1.11,1.94) pg/mL, 1.53 (IQR: 1.35,2.25) pg/mL, and 1.26 (IQR: 0.97,1.52) pg/mL for the pre-intervention, intervention baseline and post-intervention, respectively. The ET-1 at post-intervention was significantly lower than that at intervention baseline (p=0.003). The median CRP levels were 1.5 mg/dL (IQR: 0.7–3.7), 1.8 mg/dL (IQR: 0.6,4.5) pg/mL, and 1.6 mg/dL (IQR: 0.1,7.5) pg/mL for the pre-intervention, intervention baseline and post-intervention, respectively. The CRP at post-intervention was not significantly lower than that at intervention baseline (p=0.24). Thus, the upward trajectories of the ET-1 and CRP levels, i.e. between the pre-intervention and intervention baseline periods, were interrupted during the 12-month intervention period of reduced cocaine use.

Coronary plaque burden over time

The medians with IQRs of coronary plaque burden over time are presented in Table 1 and Figure 2. Total coronary plaque volume index, calcified plaque volume index, and noncalcified plaque volume index appeared to increase from pre-intervention to intervention baseline, and noncalcified plaque volume index seemed to decrease from intervention baseline to post-intervention. However, none of these differences was statistically significant.

Changes in coronary plaque burden over time

Total plaque volume—By univariable GEE analysis, total plaque volume index at intervention baseline was significantly higher as compared with pre-intervention level (p=0.026, Table 2). After controlling for pre-intervention total plaque volume index, the 2013 ACC/AHA defined cardiovascular risk, and CRP, total coronary plaque volume index at intervention baseline remained higher as compared with pre-intervention level (p-value = 0.048, Table 2). Similarly, in multivariable analysis, total plaque volume index after intervention was significantly lowered as compared with intervention baseline level (p = 0.013, Table 2).

Calcified plaque—By univariable GEE analysis, calcified plaque volume index at intervention baseline was significantly higher as compared with pre-intervention level (p=0.014, Table 2); this relationship was maintained in multivariable models (p=0.048, Table 2). However, after intervention, calcified plaque volume was not significantly higher as compared with intervention baseline level in the multivariable analysis (p=0.20, Table 2).

Noncalcified plaque—By univariable GEE analysis, noncalcified plaque volume index at intervention baseline was not significantly higher as compared with pre-intervention level (p=0.057, Table 2). In multivariable analysis adjusting for pre-intervention plaque burden, the 2013 ACC/AHA defined cardiovascular risk, and CRP, the difference in noncalcified plaque volume index from pre-intervention to intervention baseline was not significant (p=0.11, Table 2). However, after further adjustment for reduction in cocaine use,

noncalcified plaque volume index at pre-intervention was significantly lowered as compared with intervention baseline level in the multivariable model (P=0.008, Table 3). Multivariable GEE analyses suggested that noncalcified plaque volume index at post-intervention was significantly lowered as compared with intervention baseline level in the multivariable model (P=0.005, Table 2, and P=0.003, Table 3).

Changes in coronary plaque burden and changes in cocaine use over time

Total plaque volume—By univariable GEE analysis, changes in total plaque volume index was not significantly associated with reduction in cocaine use (p=0.11, Table 3). However, multivariable GEE analysis shows that after controlling for time variable, pre-intervention total plaque volume index, the 2013 ACC/AHA defined cardiovascular risk, and CRP, reduction in cocaine use was significantly associated with a lower total plaque volume (p=0.019, Table 3).

Calcified plaque—By univariable GEE analysis, changes in total calcified plaque volume index was not significantly associated with reduction in cocaine use (p=0.09, Table 3). Multivariable GEE analysis shows that after controlling for time variable, pre-intervention total calcified plaque volume index, the 2013 ACC/AHA defined cardiovascular risk, and CRP, reduction in cocaine use was not significantly associated with a lower total plaque volume index (p=0.54, Table 3).

Noncalcified plaque—By univariable GEE analysis, changes in total noncalcified plaque volume index was not significantly associated with reduction in cocaine use (p=0.24, Table 3). However, multivariable GEE analysis shows that after controlling for time variable, pre-intervention noncalcified plaque volume index, the 2013 ACC/AHA defined cardiovascular risk, and CRP, reduction in cocaine use was significantly associated with a lower noncalcified plaque volume index (p=0.010, Table 3).

Case study

A case study demonstrating plaque regression from intervention baseline to post-intervention is shown in Figure 3B. According to self-report data from questionnaires, the participant had used cocaine daily prior to intervention. He underwent first contrast-enhanced coronary CTA in November, 2005, >50% coronary stenosis was confirmed at the Johns Hopkins Hospital (total plaque volume index: 43.8 mm^2, calcified plaque volume index: 0.9 mm^2, and noncalcified plaque volume index: 42.9 mm^2). Then, he participated in this study and had two consecutive CCTAs in September, 2014 (intervention baseline, total plaque volume index: 48.4 mm^2, calcified plaque volume index: 5.1 mm^2, and noncalcified plaque volume index: 43.3 mm^2), and September 2015 (after 12 months of intervention, total plaque volume index: 35.8 mm^2, calcified plaque volume index: 4.6 mm^2, and noncalcified plaque volume index: 31.2 mm^2). During the 12 months of intervention, he used cocaine 77 days according to urine tests. The images show curved multiplanar reconstructions of the left anterior descending artery (LAD). Plaque in the arterial wall is defined by the outer vessel boundary (adventitia) and lumen boundary.

Discussion

The key findings of this investigation suggest that, while prior to intervention, coronary plaque burden, as measured by total coronary plaque volume index and noncalcified plaque volume index significantly increased over approximately 4 years (from pre-intervention to intervention baseline), coronary plaque burden significantly decreased from the intervention baseline to post-intervention after 12-month intervention in chronic cocaine users with obstructive coronary stenosis who never received any statin therapy. Furthermore, this study also suggests that reduced cocaine use may be significantly associated with lower total plaque volume index and noncalcified plaque volume index.

CAD usually begins with subclinical asymptomatic coronary atherosclerotic plaques accumulating in the vessel wall. Following positive remodeling, these plaques may gradually compromise the coronary lumen, leading to luminal stenosis [Sakakura et al., 2013; Schoenhagen et al., 2015; Dalager et al., 2015]. The presence and extent of CAD on CCTA are strong, independent predictors of cardiovascular events [Bamberg et al., 2011]. Studies have demonstrated that probably owing to their biophysical properties, noncalcified plaques are considered more vulnerable and prone to rupture than are calcified plaques, which are viewed as more stable [26–29]. The data summarized in meta-analyses of studies with patients who underwent CCTA demonstrate that the extent of coronary plaque and stenosis, especially obstructive (>50% in diameter) coronary stenoses are strong independent predictors of future cardiovascular events [25,30]. A meta-analysis (N=7,335 patients) demonstrated that compared to the absence of obstructive (>50%) coronary stenosis, the presence of obstructive coronary stenosis was associated with a 10-fold higher risk for all cardiovascular events (cardiovascular death, nonfatal myocardial infarction (MI), unstable angina requiring hospitalization, and revascularization) and a 6-fold risk for death, MI, and unstable angina requiring hospitalization independent of the presence of coronary artery calcification [Bamberg et al., 2011].

Coronary plaque progression

The results of this study demonstrate that after controlling for potential confounding factors, including pre-intervention plaque burden, cardiovascular risk defined by the 2013 ACC/AHA guidelines [Goff et al., 2014], CRP and reduction in cocaine use, total coronary plaque volume index and noncalcified plaque volume index at intervention baseline were significantly higher as compared with pre-intervention levels.

Since all the participants were not on any statin therapy, changes in coronary plaque burden in this time period could be regarded as the natural history of disease progression in asymptomatic chronic cocaine users with obstructive coronary stenosis. Despite the fact that the natural history of coronary atherosclerosis by CCTA in patients with clinical CAD is documented [Papadopoulou et al., 2012; Nicholls et al., 2010], coronary plaque progression in those without cardiovascular symptoms has not been reported. Although our data revealed cardiovascular risk defined by the 2013 ACC/AHA guidelines increased from pre-intervention to intervention baseline, it was not significant in GEE models, suggesting that conventional cardiovascular risk may not play an independent role in promoting plaque burden in this study population, The GEE analysis showed that CRP was independently

associated with total plaque index and noncalcified plaque index, suggesting that CRP may play a significant role in disease progression.

While several cross-sectional analyses observed a higher prevalence of atherosclerosis in cocaine users [Ebersberger et al., 2013; Patrizi et al., 2006], data on longitudinal coronary changes are scarce. In a previous study, the authors followed 57 asymptomatic cocaine users with coronary plaque using contrast-enhanced CTA, and found that the incidence of coronary plaque progression, defined as the development of obstructive (>50%) coronary stenosis was 15.1/100 person-years [Lai et al., 2015]. It should be noted that the degree of coronary stenosis is not comparable with plaque volume as they represent different properties of the disease.

Coronary plaque regression

This study also shows that after controlling for potential confounding factors, including pre-intervention plaque burden, cardiovascular risk defined by the 2013 ACC/AHA guidelines, CRP and reduction in cocaine use, total plaque volumes index, and noncalcified plaque volume index at post-intervention were significantly lower compared with those at the intervention baseline, suggesting total plaque and noncalcified plaque regression during the 12-month intervention period. Furthermore, this study demonstrates that that reduced cocaine use may be significantly associated with lower total plaque volume index and noncalcified plaque volume index. These findings have not been reported in literature previously.

The exact mechanisms by which reduced cocaine use is associated with regression or arrest of progression of coronary plaque are not known, but inflammation appears to be a significant link. Inflammation has been associated with plaque progression [Puri et al., 2013] and the pathophysiology of atherosclerosis with accumulation of inflammatory cells in the arterial wall has characteristics of an inflammatory process [Pant et al., 2014]. In this study, CRP levels were significantly reduced after the 12-month intervention (Figure 1, Table 1). Therefore, it appears plausible that lower levels of inflammation and endothelial damage, achieved by a reduction in cocaine use are responsible for this favorable effect. Although several studies demonstrate that statin therapy reduces coronary plaque volume [Nicholls et al., 2011], the participants in the present study never received statin therapy, further suggesting that reduced cocaine use may have reduced inflammation and endothelial damage, leading to stabilization or regression of coronary plaque.

It is worth nothing that according to the GEE analyses presented in Table 3, CRP is not only a factor that was independently associated with both total plaque volume and noncalcified plaque volume, but also a negative confounding factor for the association of reduction in cocaine use with both total plaque volume and noncalcified plaque volume: in the univariable GEE analyses, reduction in cocaine use was not significant, however, the addition of CRP as a covariate in the multivariable GEE models resulted in significant regression coefficients for ‘reduction in cocaine use.

Statin adherence may be very poor in AA chronic cocaine users. It has been reported that the odds of non-adherence are 53% greater in non-white than in white patients [Lewey, et al.,

2013; Kopjar et al., 2003], that statin adherence is also low in those with substance abuse [Kopjar et al., 2003], and that outcomes in those with very low adherence to statin are worse than in those who never used statins [Phan et al., 2014; De Vera, et al., 2014].

Further studies are needed to explore the mechanisms underlying the association between reductions in cocaine use and changes in coronary plaque.

The findings of this investigation may have important implications for coronary artery disease prevention among cocaine users, especially for cocaine users with HIV infection. Cocaine use may not only promote coronary plaque progression, but also triggers/exacerbates adverse cardiovascular comorbidities induced by antiretroviral therapy (ART) [Lai et al., 2016].

To the best of our knowledge, this study is the first non-pharmaceutical investigation to explore whether abstinence from, or reduced, cocaine use yields beneficial cardiovascular effects, in particular a reduction in coronary plaque burden in AA cocaine users with subclinical atherosclerosis.

Our study has several strengths that should be mentioned: (1) Progression of coronary plaque burden prior to intervention in the participants is known because of prior studies in those participants, allowing those data to more effectively assess the impact of the intervention, and (2) Coronary plaque analysis was used to quantify changes in coronary plaque burden. In previous analyses, all the CCTA outcome variables were based on coronary luminal stenosis quantification, not on coronary plaque quantification. Coronary stenosis quantification analysis provides useful information about 2-D diameter stenosis, however, this analysis does not quantify and characterize coronary plaque progression/regression.

Limitations

This study has several limitations that must be acknowledged. First, this is a preliminary study with a small sample size and short follow-up time. Thus, we cannot exclude the possibility that our findings may be influenced by sample-specific distributions. Second, the study participants were not a random community sample. Thus, the study findings may have limited generalizability. Third, since the urine testing was scheduled in advance, and since the urine testing was not random, but scheduled in advance, some participant could have timed their cocaine use so as to avoid detection. Fourth, the study may have missed cocaine use episodes given the short half-life of cocaine (approximately 0.8 ± 0.2 hours) and benzoylecgonine (approx. 6 hours) and the fact urine was tested, at most, twice a week (e.g., negative on Monday, used Tuesday, negative Thursday, used Friday/Saturday, negative on Monday, etc.). Fifth, since 13 of the 15 participants were HIV-infected, the impact of HIV infection on coronary plaque burden could not be investigated. Sixth, we did not collect dietary data so that we could not exclude the possibility that dietary factor played some role. However, based on our previous dietary data collected based on 24- hour recall, there was little variation in dietary factors in this population. Seventh, since the urine testing was only used to determine whether participants had “recently” used cocaine, estimating reduction in

cocaine use was based on an assumption that all the study participant had used cocaine daily prior to the intervention. Although questionnaire data suggested the study participants may have used cocaine daily, recall bias and other biases may occur. Eighth, reduction in cocaine use was defined as as subtracted difference from 365 days of "cumulative urine positive days during the 12-month intervention period according to urine tests". The 365 days of cocaine use are based on self-report, but the days of cocaine use during the 12-month intervention period are based on urine result. Lastly, as this study is not a randomized clinical trial, no causal inference can be drawn from these data.

Conclusions

These limitations notwithstanding, the findings of this study demonstrated a provocative association between reduced cocaine use and coronary plaque regression, and may have important implications for the prevention of cocaine-induced coronary artery disease. Also, since a large proportion of cocaine users have been infected with HIV, reducing cocaine use may retard HIV/ART-associated coronary artery disease. Further studies, especially randomized clinical trials should be conducted to verify these findings.

In conclusion, reduced cocaine use, achieved during a 12-month intervention program was associated with a significant reduction of non-calcified plaque volume index in AA chronic cocaine users. This preliminary study demonstrates potentially beneficial effects of cocaine abstinence/reduction on inflammation and coronary plaque phenotype.

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References

Aquaro GD, Gabutti A, Meini M, Prontera C, Pasanisi E, Passino C, Emdin M, Lombardi M. Silent myocardial damage in cocaine addicts. Heart. 2011 Dec; 97(24):2056–62. [PubMed: 21690608]

Auscher S, Heinsen L, Nieman K, et al. Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: Assessment with serial coronary CT angiography. Atherosclerosis. 2015; 241(2):579–587. [PubMed: 26115069]

Bamberg F, Sommer WH, Hoffmann V, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011; 57:2426–2436. [PubMed: 21658564]

Bauer RW, Thilo C, Chiaramida SA, et al. Noncalcified atherosclerotic plaque burden at coronary CT angiography: a better predictor of ischemia at stress myocardial perfusion imaging than calcium score and stenosis severity. AJR Am J Roentgenol. 2009 Aug; 193(2):410–8. [PubMed: 19620437]

Benzaquen BS, Cohen V, Eisenberg MJ. Effects of cocaine on the coronary arteries. Am Heart J. 2001; 142(3):402–10. [PubMed: 11526352]

Bossard M, Pumpol K, van der Lely S, et al. Plasma endothelin-1 and cardiovascular risk among young and healthy adults. Atherosclerosis. 2015; 239(1):186–91. [PubMed: 25617859]

Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from

the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002 Jan 29; 105(4):539–42. [PubMed: 11815441]

Chang AM, Walsh KM, Shofer FS, et al. Relationship between cocaine use and coronary artery disease in patients with symptoms consistent with an acute coronary syndrome. Acad Emerg Med. 2011; 18:1–9. [PubMed: 21182565]

Dalager MG, Bøttcher M, Thygesen J, et al. Different Plaque Composition and Progression in Patients with Stable and Unstable Coronary Syndromes Evaluated by Cardiac CT. Biomed Res Int. 2015; 2015:401357. [PubMed: 26339610]

Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet. 2012; 379(9810):55–70. [PubMed: 22225671]

De Vera MA, Bhole V, Burns LC, et al. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol. 2014; 78(4):684–98. [PubMed: 25364801]

Dressler FA, Malekzadeh S, Roberts WC. Quantitative analysis of amounts of coronary arterial narrowing in cocaine addicts. Am J Cardiol. 1990; 65(5):303–8. [PubMed: 2301258]

Ebersberger U, Sudarski S, Schoepf UJ, et al. Atherosclerotic plaque burden in cocaine users with acute chest pain: analysis by coronary computed tomography angiography. Atherosclerosis. 2013 Aug; 229(2):443–8. [PubMed: 23880201]

Ferencik M, Mayrhofer T, Puchner SB, et al. Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain - Results from the ROMICAT II trial. J Cardiovasc Comput Tomogr. 2015; 9(6):538–45. [PubMed: 26229036]

Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 63:2935–59. [PubMed: 24239921]

Huang H, Virmani R, Younis H, et al. The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation. 2001; 103:1051–1056. [PubMed: 11222465]

Higgins ST, Budney AJ, Bickel WK, et al. Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry. 1993; 150(5):763–9. [PubMed: 8480823]

Hulten EA, Carbonaro S, Petrillo SP, et al. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol. 2011; 57:1237–1247. [PubMed: 21145688]

Kopjar B, Sales AE, Piñeros SL, et al. Adherence with statin therapy in secondary prevention of coronary heart disease in veterans administration male population. Am J Cardiol. 2003; 92(9): 1106–8. [PubMed: 14583366]

Lai H, Stitzer M, Treisman G, et al. Cocaine abstinence and reduced use associated with lowered marker of endothelial dysfunction in African Americans: a preliminary Study. J Addict Med. 2015; 9(4):331–9. [PubMed: 26164164]

Lai S, Fishman EK, Lai H, et al. Long-term cocaine use and antiretroviral therapy are associated with silent coronary artery disease in African Americans with HIV infection who have no cardiovascular symptoms. Clin Infect Dis. 2008 Feb 15; 46(4):600–10. [PubMed: 19641630]

Lai H, Moore R, Celentano DD, et al. HIV infection itself may not be associated with subclinical coronary artery disease among African Americans without cardiovascular symptoms. J Am Heart Assoc. 2016 Mar 24.4(3):e002529.

Lewey J, Shrank WH, Bowry AD, et al. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J. 2013; 165(5):665–78. e1. [PubMed: 23622903]

Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986; 73:13–22.

Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol. 2010; 55(21):2399–407. [PubMed: 20488313]

Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. N Engl J Med. 2011; 365(22):2078–2087. [PubMed: 22085316]

Pant S, Deshmukh A, Gurumurthy GS, et al. Inflammation and atherosclerosis--revisited. J Cardiovasc Pharmacol Ther. 2014; 19(2):170–8. [PubMed: 24177335]

Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, et al. Natural history of coronary atherosclerosis by multislice computed tomography. JACC Cardiovasc Imaging. 2012 Mar; 5(3 Suppl):S28–37. [PubMed: 22421228]

Park HB, Lee BK, Shin S, et al. Clinical Feasibility of 3D Automated Coronary Atherosclerotic Plaque Quantification Algorithm on Coronary Computed Tomography Angiography: Comparison with Intravascular Ultrasound. Eur Radiol. 2015; 25(10):3073–83. [PubMed: 25994190]

Pasterkamp G, Falk E, Woutman H, et al. Techniques characterizing the coronary atherosclerotic plaque: influence on clinical decision making? Am J Cardiol. 2000; 36:13–21.

Patrizi R, Pasceri V, Sciahbasi A, et al. Evidence of cocaine-related coronary atherosclerosis in young patients with myocardial infarction. J Am Coll Cardiol. 2006; 47(10):2120–2. [PubMed: 16697335]

Phan K, Gomez YH, Elbaz L, et al. Statin treatment non-adherence and discontinuation: clinical implications and potential solutions. Curr Pharm Des. 2014; 20(40):6314–24. [PubMed: 24953391]

Preston KL, Silverman K, Schuster CR, et al. Assessment of cocaine use with quantitative urinalysis and estimation of new uses. Addiction. 1997; 92(6):717–27. [PubMed: 9246799]

Puri R, Nissen SE, Libby P, et al. C-reactive protein, but not low-density lipoprotein cholesterol levels, associate with coronary atheroma regression and cardiovascular events after maximally intensive statin therapy. Circulation. 2013; 128(22):2395–403. [PubMed: 24043299]

Rodriguez K, Kwan AC, Lai S, et al. Coronary Plaque Burden at Coronary CT Angiography in Asymptomatic Men and Women. Radiology. 2015; 277(1):73–80. [PubMed: 26035436]

Sakakura K, Nakano M, Otsuka F, et al. Pathophysiology of atherosclerosis plaque progression. Heart Lung Circ. 2013 Jun; 22(6):399–411. [PubMed: 23541627]

Schoenhagen P, Yan F. Progression of coronary artery disease. Experience with computed tomography. Herz. 2015 Sep; 40(6):869–74. [PubMed: 26259733]

Scott J. Pathophysiology and biochemistry of cardiovascular disease. Curr Opin Genet Dev. 2004; 14:271–279. [PubMed: 15172670]

Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014.

Tai H, Lai H, Jani J, et al. HIV infection and cocaine use induce endothelial damage and dysfunction in African Americans. Int J Cardiol. 2012 Nov 15; 161(2):83–7. [PubMed: 21600668]

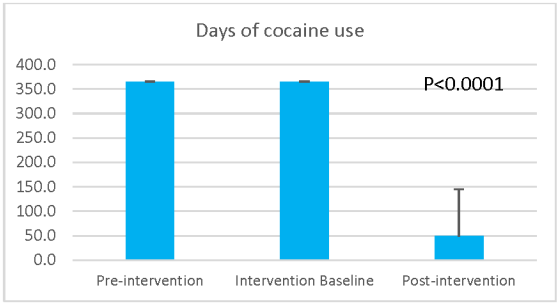

Figure 1A

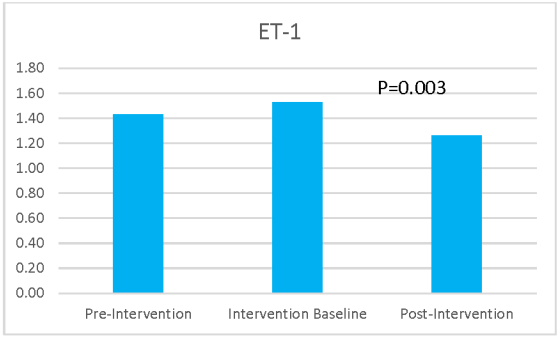

Figure 1B

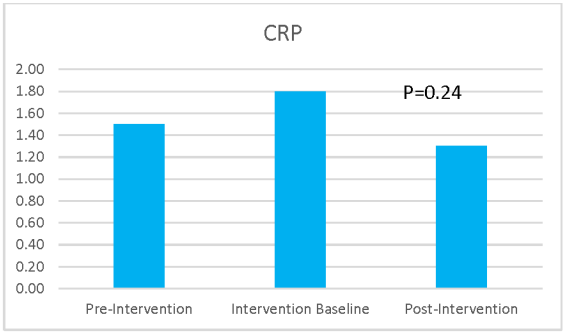

Figure 1C

Figure 1. Mean cumulative days of cocaine use, median CRP and median endothelin-1 over time

Figure 1.A. At pre-intervention and intervention baseline, we assumed that all participants used cocaine 365 days a year (mean ± SD = 365±0). At post-intervention, the mean cumulative days of cocaine use was 50.4±95.3 days, which was significantly reduced compared to that at intervention baseline (365±0 days) (P<0.0001, paired t-test). **Figure 1.B**. The median CRP levels were 1.5 (IQR: 0.7,3.7) mg/dL for pre-intervention, 1.8 (IQR: 0.6,4.5) mg/dL for intervention baseline, and 1.6 (IQWR: 0.1,7.5) mg/dL, respectively. There was no statistical difference in CRP between intervention baseline and post-intervention (P=0.24, Wilcoxon signed-rank test). **Figure 1.C**. The median endothelin-1 levels were 1.43 (IQR:1.11,1.94) pg/mL for pre-intervention, 1.53 (IQR:1.35,2.25) pg/mL for intervention baseline, and 1.26 (IQR: 0.96,1.52) pg/mL for post-intervention, respectively. There was statistical difference in endothelin-1 between intervention baseline and post-intervention (P=0.003, Wilcoxon signed-rank test).

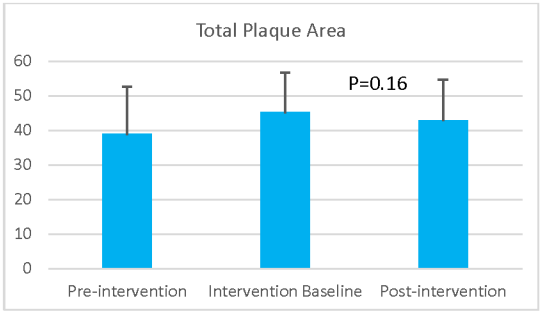

Figure 2A

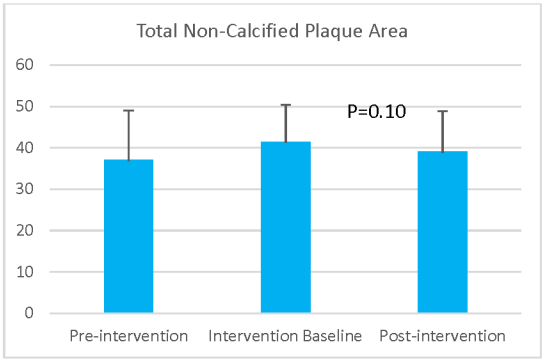

Figure 2B

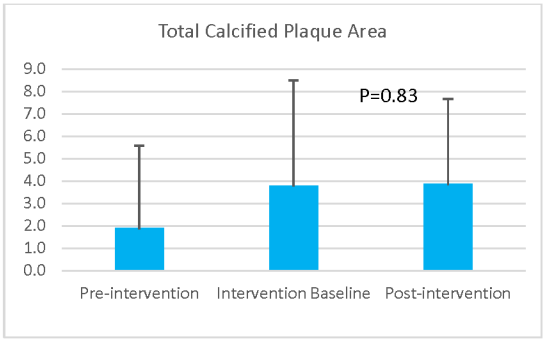

Figure 2C

Figure 2. Total coronary plaque volume index, calcified plaque volume index and noncalcified plaque volume index over time

Figure 2.A. The mean total plaque volume indices were 39.0 (±SD:13.6) mm^2 for pre-intervention, 45.3 (±SD:11.4) mm^2 for intervention baseline, and 43.0 (±SD:11.7) mm^2 for post-intervention, respectively. The difference between intervention baseline and post-intervention was not significant (P=0.16, paired t-test). **Figure 2.B**. The mean calcified plaque volume indies were 1.9 (±SD:3.7) mm^2 for pre-intervention, 3.8 (±SD:4.7) mm^2 for intervention baseline, and 3.9 (±SD:3.8) mm^2 for post-intervention, respectively. The difference between intervention baseline and post-intervention was not significant (P=0.83, paired t-test). **Figure 2.C**. The mean noncalcified plaque volume indies were 37.1 (±SD: 11.9) mm^2 for pre-intervention, 41.5 (±SD:9.0) mm^2 for intervention baseline, and 39.1 (±SD:9.8) mm^2 for post-intervention, respectively. The difference between intervention baseline and post-intervention was not significant (P=0.10, paired t-test).

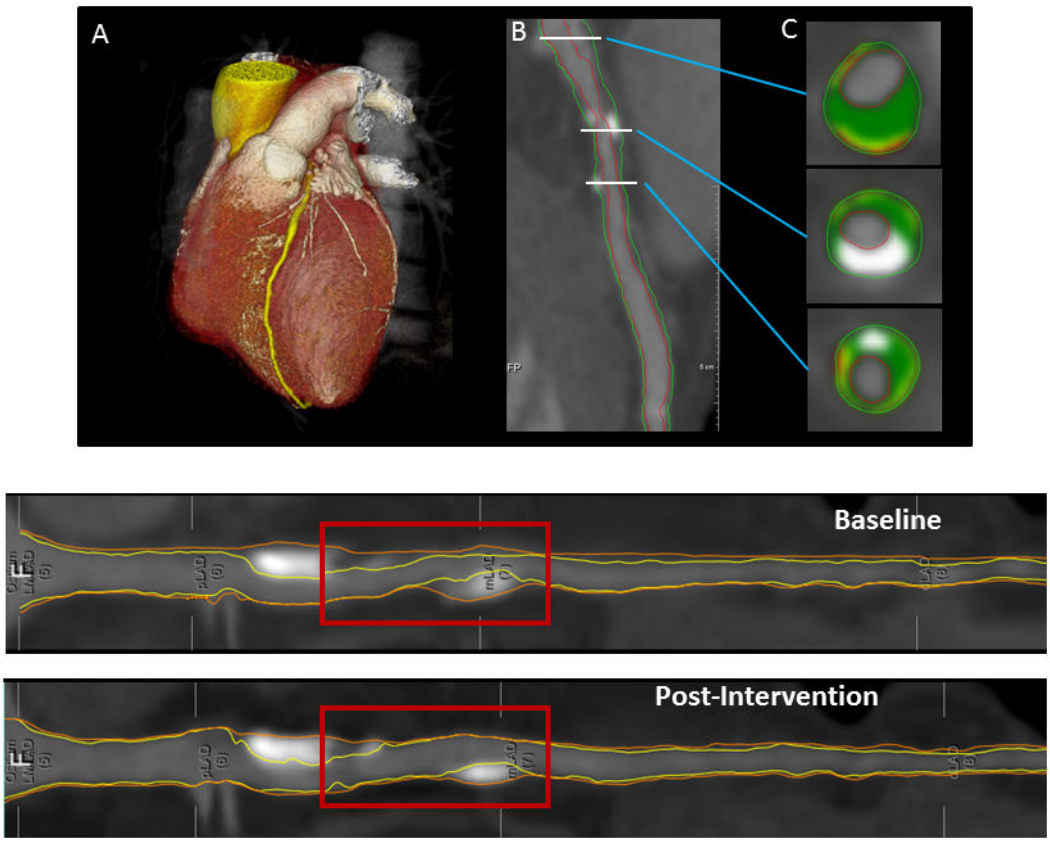

Figure 3. Coronary CT angiography: Volumetric plaque analysis

Figure 3A. A: Volumetric reconstruction of the heart. The left anterior descending artery (LAD) is marked in yellow. B: Longitudinal reconstruction of the LAD. The lumen border and the outer vessel borders are marked green and red respectively. C: Cross sections are shown at various levels showing non-calcified plaque (marked green in upper image) and partially calcified plaques (calcium marked white in middle and lower image). **Figure 3B**. Coronary plaque regression detected by consecutive coronary CTA in the 58-year-old male cocaine user. According to self-report data from questionnaires, this participant had used cocaine daily prior to intervention. He underwent a contrast-enhanced coronary CTA on November 22, 2005, >50% coronary stenosis was confirmed at the Johns Hopkins Hospital (total plaque volume index: 43.8 mm^2, calcified plaque volume index: 0.9 mm^2, and noncalcified plaque volume index: 42.9 mm^2) Then, he participated in this study and had two consecutive CCTAs on September 17, 2014 (intervention baseline, total plaque volume index: 48.4 mm^2, calcified plaque volume index: 5.1 mm^2, and noncalcified plaque volume index: 43.3 mm^2), and September 24, 2015 (after 12 months of intervention, total plaque volume index: 35.8 mm^2, calcified plaque volume index: 4.6 mm^2, and noncalcified plaque volume index: 31.2 mm^2). During the 12 months of intervention, he used cocaine 77 days according to urine tests. The images show curved multiplanar reconstructions the left anterior descending artery (LAD). Plaque in the arterial wall is defined by the outer vessel boundary (adventitia) and lumen boundary.

On CCTA images the coronary tree was analyzed using the software QAngioCT (Medis, Leiden). A centerline is defined for each major vessel and vessel contours are defined using

a semiautomatic method. CT: Siemens Flash, 120 kVp. Software: QAngio CT, Medis, Leiden, NL. Curved multiplanar reconstructions of the LAD in intervention baseline and 12-month follow up exam with lumen/wall boundary (yellow line) and outer wall boundary (orange line) as detected by QAngioCT. Two mixed plaques in the proximal LAD are seen. A reduction of plaque volume from intervention baseline to post-intervention is noted using plaque quantification. The red box indicates an area where plaque regression is seen on visual assessment.

Table 1

Characteristics of 15 African American chronic cocaine users with obstructive coronary plaques*

Characteristic	Pre-Intervention	Intervention Baseline	Post-Intervention	p-value**
Age (year)	49 (46–54)	54 (52–58)	55(53–59)	<0.0001
Male sex (%)	80.0	80.0	80.0	
Family history of CAD (%)	33.3	33.3	33.3	
Cigarette smoking (%)	93.3	93.3	93.3	
HIV infection (%)	80.0	86.7	86.7	
Cocaine positive days in 12 months			7 (0–35)	
Alcohol use (%)	100.0	100.0	100.0	
Hypertension (%)	13.3	20.0	26.6	
Diabetes (%)	0.0	0.0	0.0	
BMI (kg/m^2)	26.5 (22.3–31.1)	26.9 (22.9–30.7)	24.6(23.8–29.9)	0.81
Systolic BP (mm Hg)	122 (111–131)	123 (119–131)	125(116–141)	0.73
Diastolic BP (mm Hg)	78 (63–81)	72 (59–79)	77(68–81)	0.35
CRP (mg/dL)	1.5 (0.7–3.7)	1.8 (0.6–4.5)	1.3(0.1–7.5)	0.24
hsCRP≥2 mg/mL (%)	40.0	46.7	46.7	1.00
Glucose (mg/dL)	77 (73–88)	85 (76–92)	83(80–89)	0.89
Total cholesterol (mg/dL)	174 (157–210)	174 (144–186)	167(150–193)	0.90
LDL-C (mg/dL)	81 (70–110)	84 (64–97)	81(68–99)	0.86
HDL-C (mg/dL)	56 (45–68)	63 (53–66)	62(60–78)	0.27
Triglycerides (mg/dL)	117 (67–208)	103 (81–148)	107(63–137)	0.17
Endothelin-1 (pg/mL)	1.43(1.11–1.94)	1.53(1.35–2.25)	1.26(0.96–1.52)	0.003
vWF antigen (%)	195(158–256)	187(138–301)	172(139–274)	0.47
Coronary calcium score	78(22–155)	165(61–390)	192(93–474)	0.29
The 2013 risk (%)	7.1 (4.0–13.6)	8.9 (5.7–17.3)	10.8(6.4–19.4)	0.89
Low 2013 risk (%)	53.3	26.7	33.3	0.32
Total coronary plaque volume (mm^3)	331.4(197.5–368.3)	395.4(197.0–646.7)	360.2(188.6–502.7)	0.95
Total calcified plaque volume (mm^3)	16.4(6.4–31.8)	44.1(12.8–85.0)	45.1(17.2–97.9)	0.71
Total noncalcified plaque volume (mm^3)	275.6(175.2–336.5)	326.0(180.1–419.7)	286.5(171.7–393.5)	0.79
Total coronary plaque volume index (mm^2)	38.9(30.5–44.3)	44.9(39.9–52.7)	43.6(35.8–50.7)	0.23
Calcified plaque volume index (mm^2)	1.0(0.3–1.7)	3.1(1.1–4.5)	3.4(1.0–4.6)	0.21
Noncalcified plaque volume index (mm^2)	37.8(29.3–44.0)	43.1(38.3–49.0)	38.7(31.2–46.8)	0.14

*Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

Abbreviations: BMI, body mass index (kg/m^2); hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; glucose, fasting glucose; eGFR, estimated glomerular filtration rate; the 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [22]; low 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk≤7.5% [22].

**p-values are for the comparisons between intervention baseline and post-baseline (12 months after the intervention baseline) based on the Wilcoxon rank test.

Table 2

Changes in coronary plaque burden over time (the time variables covariate of interest, coded as pre-intervention vs. intervention baseline, and pose-intervention vs. intervention baseline), GEE analysis

	Unadjusted		Adjusted for pre-intervention plaque burden*		Adjusted for pre-intervention plaque burden*, and the 2013 lowrisk†		Adjusted for pre-intervention plaque burden*, the 2013 low risk†, and CRP‡	
	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value
Outcome variable: total plaque volume index								
Pre- intervention visit	−0.1995(−0.3747,−0.0244)	0.026	−0.1999(−0.3703,−0.0294)	0.022	−0.2838(−0.4860,−0.0816)	0.006	−0.1825(−0.3639,−0.0012)	0.048
Post- intervention visit	−0.0590(−0.1295,0.0115)	0.10	−0.0580(−0.1295, 0.0115)	0.10	−0.0669(−0.1373, 0.0034)	0.06	−0.1039(−0.1861,−0.0217)	0.013
Pre-baseline total plaque volume index			0.0191(0.0152,0.0229)	<0.0001	0.0399(−0.0703,0.1501)	0.48	0.0143(0.0100,0.0186)	<0.0001
The 2013 low risk					0.1189(0.0131,0.2247)	0.028	−0.0097((−0.2070,0.1875)	0.92
CRP							0.0182((0.0106,0.0250)	<0.0001
Outcome variable: calcified plaque volume index								
Pre- intervention visit	−0.8385(−1.5045,−0.1724)	0.014	−0.8393(−1.4728,−0.2058)	0.009	−0.8741(−1.6346,−0.1136)	0.024	−0.7665(−1.5270,−0.0060)	0.048
Post- intervention visit	0.20151(−0.0126,0.4228)	0.065	0.2051 (−0.0126,0.4428)	0.064	0.1997(−0.0294,0.4289)	0.088	0.1722(−0.0887,0.4331)	0.20
Pre-baseline calcified plaque volume index			0.3805(−0.5141,1.2751)	0.40	0.04161(−0.3285,0.41169)	0.83	−0.3854(−1.3157,0.6144)	0.45
The 2013 low risk					0.0806(−0.7325,0.8936)	0.85	−0.1827(−1.3157,0.9503)	0.75
CRP							0.0180(−0.0208,0.0568)	0.36
Outcome variable: noncalcified plaque volume index								
Pre- intervention visit	−0.1625(−0.3295,0.0045)	0.057	−0.1712(−0.3354,−0.0070)	0.041	−0.2161(−0.3958,−0.0363)	0.019	−0.1387(−0.3122,0.0348)	0.11
Post- intervention visit	−0.0674(−0.1361,0.0013)	0.055	−0.0674(−0.1361,0.0013)	0.055	−0.0783(−0.1504,−0.0063)	0.033	−0.1097(−0.1862,−0.0331)	0.005
Pre-baseline noncalcified l plaque volume index			0.0189(0.0132,0.0246)	<0.0001	0.0916(−0.0302,0.2134)	0.14	0.0158(0.0107,0.0210)	<0.0001
The 2013 low risk					0.1649(0.0662,0.2618)	0.001	−0.0251(−0.281,0.1680)	0.79

	Unadjusted		Adjusted for pre-intervention plaque burden*		Adjusted for pre-intervention plaque burden*, and the 2013 lowrisk†		Adjusted for pre-intervention plaque burden*, the 2013 low risk†, and CRP‡	
	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value	Regression coefficient (95%CI)	p-value
CRP							0.0175(0.0092,0.0259)	<0.0001

*pre-intervention plaque burdens are pre-intervention total coronary plaque volume index, noncalcified plaque volume index, or calcified plaque volume index (log-transformed).

†The 2013 low risk, cardiovascular risk<0.075%, defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [21].

‡CRP, high-sensitivity C-reactive protein.

Table 3

Changes in coronary plaque burden and reductions in in cocaine use, GEE analysis

	Unadjusted		Adjusted for pre-intervention plaque burden*		Adjusted for time variable§, pre-intervention plaque burden*, and the 2013 low risk†		Adjusted for time variable§, pre-intervention plaque burden*, the 2013 low risk†, and CRP‡	
	Regression coefficient (95%CI)	**p-value**	**Regression coefficient (95%CI)**	**p-value**	**Regression coefficient (95%CI)**	**p-value**	**Regression coefficient (95%CI)**	**p-value**
Outcome variable: total plaque volume index								
Pre- intervention visit					−0.4578(−0.9087, −0.0070)	0.047	−0.5997(−1.0463,−0.1531)	0.009
Post- intervention visit					−0.0883(−0.9087,−0.0070)	0.028	−0.1115(−0.0436,−0.1969)	0.011
Pre-baseline total plaque volume index			−0.0018(−0.0592,0.0556)	0.95	0.1662(−0.0092, 0.3416)	0.06	0.0144(0.0112,0.0177)	<0.0001
The 2013 low risk					0.4395(0.1493, 0.7296)	0.003	0.0117(−0.1852,0.2087)	0.91
CRP							0.0206(0.0132,0.0281)	<0.0001
Reduction in cocaine use (days)§	0.0004(−0.0001,0.0010)	0.11	0.0036(−0.0004,0.0076)	0.08	−0.0004(−0.0020, 0.0011)	0.58	−0.0013(−0.0024, −0.0002)	0.019
Outcome variable: calcified plaque volume index								
Pre- intervention visit					2.8818(−7.5876,13.3512)	0.59	−0.2813(−1.2949,0.7322)	0.59
Post- intervention visit					0.1841(−0.0444, 0.4127)	0.11	0.2541(0.0100,0.4983)	0.041
Pre-baseline calcified plaque volume index			−1.2192(−2.5063,0.0679)	0.06	−0.0247(−0.4703, 0.4209)	0.21	0.1925(0.1244,0.2605)	<0.0001
The 2013 low risk							−0.7145(−1.6641,0.2351)	0.14
CRP			0.0025(−0.0010,0.0060)	0.16	0.0121(−0.218, 0.0461)	0.48	−0.0006(−0.0496,0.0485)	0.98
Reduction in cocaine use (days)§	0.0021(−0.0004,0.0046)	0.09					0.0012(−0.0030,0.0054)	0.54
Outcome variable: noncalcified plaque volume index								
Pre- intervention visit					−0.3969(−0.7121, −0.0817)	0.014	−0.5734(−0.9941,0.1526)	0.008

	Unadjusted		Adjusted for pre-intervention plaque burden*		Adjusted for time variable§, pre-intervention plaque burden*, and the 2013 low risk†		Adjusted for time variable§, pre-intervention plaque burden*, the 2013 low risk†, and CRP‡	
	Regression coefficient (95%CI)	**p-value**	**Regression coefficient (95%CI)**	**p-value**	**Regression coefficient (95%CI)**	**p-value**	**Regression coefficient (95%CI)**	**p-value**
Post- intervention visit					−0.0829(−0.1570, −0.0089)	0.028	−0.1187(−0.1976,−0.0397)	0.003
Pre-baseline noncalcified l plaque volume index			0.0230(0.0201,0.0260)	<0.0001	0.0204(0.0127, 0.0281)	<0.0001	0.0161(0.0123,0.0283)	<0.0001
The 2013 low risk					0.02331(−0.0432, 0.5093)	0.098	0.0064(−0.1833,0.1961)	0.95
CRP							0.0203(0.0123,0.0283)	<0.0001
Reduction in cocaine use (days)§	0.0003(−0.0002,0.0008)	0.24	−0.0009(−0.0016,−0.0002)	0.013	−0.0005(−0.0018, 0.0008)	0.44	−0.0013(−0.0024, −0.0003)	0.010

*Pre-intervention plaque burdens are pre-intervention total coronary plaque volume index, noncalcified plaque volume index, or calcified plaque volume index (log-transformed).

§time variable, coded as pre-intervention vs. intervention baseline (reference), and post-intervention vs. intervention baseline (reference).

†The 2013 low risk, cardiovascular risk<0.075%, defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [21].

‡CRP, high-sensitivity C-reactive protein.

§Reduction in cocaine use (days) is defined as 365 – days of cocaine use.