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Cocaine use is associated with a higher prevalence of elevated ST2 concentrations

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Abstract

Background—Cocaine is a well-known risk factor for acute cardiac events, but the effects in users outside of acute events are less clear. We investigated a possible association between cocaine use and the concentration of a novel biomarker for cardiac stress and heart failure, ST2.

Methods—A case-control study was conducted to compare ST2 concentrations by the presence of cocaine in patients presenting for care, but not cardiac care, at an urban safety net hospital.

Results—In samples taken from 100 cocaine-positive and 100 cocaine-negative patients, the presence of cocaine was associated with ST2 concentrations > 35 ng/mL. Serum concentrations of benzoylecgonine, a major cocaine metabolite, were significantly correlated with ST2 concentrations.

Conclusions—Cocaine use is associated with subclinical cardiac stress and damage outside of acute cardiac events. This information could add to better stratification of cocaine users with elevated ST2 concentrations who may be at higher risk for developing heart failure and other cardiac complications.

Keywords

cocaine; benzoylecgonine; ST2; drugs of abuse; cardiac stress

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Introduction

An estimated half million visits to the emergency department in the United States in 2011 involved cocaine use [1]. In this respect, chest pain is the most common presentation [2]. As cocaine increases myocardial oxygen demand by increasing heart rate, blood pressure, and myocardial contractility, and simultaneously decreases myocardial oxygen supply by coronary vasoconstriction, ischemia and myocardial infarction (MI)[1] may ensue [2]. It has been estimated that cocaine use contributes to one in every four MIs in people of 18–45 years of age [2]. In a sample of safety net hospital patients who were not currently seeking cardiac care, we recently reported a higher prevalence of detectable cardiac troponin (cTn) I concentrations in those who used cocaine compared to those who did not use cocaine, suggesting potential subclinical cardiac injury [3].

As cocaine, in addition to increasing the risk of MI, increases the risk of heart failure (HF), cardiomyopathy, and arrhythmias [2], we hypothesized that cocaine users may have a higher prevalence of elevated (soluble) ST2 concentrations, a novel biomarker for cardiac stress and HF. The ST2 gene encodes both soluble ST2 and a transmembrane receptor form of ST2, ST2 ligand (ST2L), which are generated by alternative splicing [4]. IL33 is an interleukin secreted by stretched fibroblasts and has anti-hypertrophic and anti-fibrotic effects via ST2L signaling [4]. The expression of soluble ST2, a truncated soluble receptor, is mechanically induced in stretched cardiomyocytes [4]. It is considered as a ‘decoy’ receptor by binding IL-33 and making it unavailable for cardioprotective signaling [4]. ST2 concentrations are increased in both acute and chronic HF [5, 6], but also in severe pulmonary disease and sepsis [7]. Therefore, ST2 is used as a prognostic tool for risk-stratification and is less valuable for diagnosis. A ST2 concentration greater than the clinical cut point of 35 ng/mL is associated with worse prognosis in HF [8]. Elevated ST2 concentrations in the general population are associated with a higher risk for the development of HF, major cardiovascular events, and death [9].

Cocaine’s main metabolites are benzoylecgonine and ecgonine methyl ester. Approximately half of the absorbed dose metabolizes to benzoylecgonine, and one-third to one-half metabolizes to ecgonine methyl ester [10]. Benzoylecgonine has vasoconstrictive properties, whereas ecgonine methyl ester has thought to have little pharmacological activity [10]. To test the hypothesis that cocaine use is associated with a higher prevalence of elevated (> 35 ng/mL) ST2 concentrations, we analyzed serum ST2, cocaine, and benzoylecgonine concentrations in a previously conducted case-control study in which the effect of cocaine exposure was assessed in patients who were not currently seeking cardiac care [3].

Materials and Methods

The study and experimental design of this case-control study have been described previously [3]. In short, remnant specimens came from patients receiving lab services in health care units throughout Zuckerberg San Francisco General, with the exception of Cardiology.

[1]Abbreviations: ACS, acute coronary syndrome; cTn, cardiac troponin; HF, heart failure; LC, liquid chromatography; MI, myocardial infarction; ST2L, ST2 ligand

During two six-week periods, occurring 6/1/15–7/9/15 and 12/14/15–1/25/16, specimens were sequentially obtained among patients for whom urine drug testing was ordered by a health care provider and was accompanied by a serum sample. Urine drug testing was performed using standard competitive immunoassays. To isolate the effect of cocaine, samples were restricted to those negative for amphetamines. The first 100 specimens positive for cocaine/benzoylecgonine (the immunoassay recognizes both), and negative for amphetamines, were considered cases; the first 100 specimens negative for cocaine/benzoylecgonine and amphetamines were considered controls. Samples were de-identified and linked to patient age, race and gender. Based on medical chart review, patients receiving care for cardiac complications were excluded. The study was considered to have minimal risk to human subjects as data were limited to de-identified retrospective medical records and testing of existing biological specimens. The study protocol was approved by the Institutional Review Board at the University of California, San Francisco, USA, who deemed that patient consent was not required.

Serum ST2 analysis was performed by Critical Diagnostics (San Diego, CA) using the Presage® ST2 ELISA Assay kit as described [11]. Serum cocaine and benzoylecgonine concentrations were measured using a clinically validated liquid chromatography (LC) tandem mass spectrometry method. Sample preparation consisted of acetonitrile protein precipitation, nitrogen-drying of supernatant, and reconstitution in starting LC conditions. LC conditions and mass spectrometry instrumentation were as described [12]. Linear range for both analytes was 1–5000 ng/mL.

The Chi-square test was used to evaluate the association of drug exposure, as assessed from the urine drug screen results, with the prevalence of ST2 concentrations >35 ng/mL. Natural log-transformation was used to account for skewed data when comparing serum cocaine, benzoylecgonine, and ST2 concentrations as continuous variables. Comparisons were performed with Kruskal-Wallis tests and analyses were conducted in Stata Version 14.1 (Stata Corp, College Station, TX).

Results and Discussion

The characteristics of the 200 patients included in this sample have been reported previously [3]. The median patient age was 51 years (interquartile range, IQR, 37 – 59), and this was not significantly different between cases (median: 52, IQR 40 – 57) and controls (median: 51, IQR 33 – 60); p = 0.82. A total of 71 patients were female (cases: 36, controls: 35; p = 1.00). The race/ethnicity characteristics were as follows: 51 patients were Caucasian (cases: 13, controls: 38), 9 were Asian/Pacific Islander (cases: 3, controls: 6), 90 were African American (cases: 62, controls: 28), 47 were Latino/a (cases: 19, controls: 28), and 3 were of other race/ethnicity (cases: 3, controls: 0). Cases were more likely to be African American and less likely to be Caucasian compared to Asian/Pacific Islander, Latino/a or “other” race/ethnicity categories (chi-square test: p<0.001).

Table 1 shows the association of drug exposure by urine toxicology results with serum ST2 concentrations. A positive result for cocaine/benzoylecgonine was significantly associated with a ST2 concentration > 35 ng/mL. There were no statistically significant associations for

the other tested drug classes. In addition, case samples were analyzed for serum cocaine and serum benzoylecgonine concentrations, and the log-transformed concentrations were plotted against log-transformed ST2 concentrations (Figure 1). Serum benzoylecgonine concentrations were significantly correlated with ST2 concentrations (Figure 1a). This was not the case for cocaine (Figure 1b), possibly due to the shorter half-life of cocaine (~0.7–1.5 hours) compared to benzoylecgonine (~5–6 hours).

Among safety net hospital patients who were not presenting for an acute cardiac event nor general cardiac care, these results suggest that cocaine use is associated with subclinical cardiac stress. This is in agreement with our previous results suggesting that cocaine use is associated with subclinical cardiac injury [3] and an earlier study regarding silent cardiac damage in which cocaine users were evaluated by cardiovascular magnetic resonance [13]. In the latter study, fibrosis was found in 73% of the subjects and focal edema was found in 47% [13]. This demonstrates that cocaine produces both long-term effects, *i.e.* gradual remodeling through fibrosis, and short-term effects, *i.e.* edema secondary to relatively recent exposure [13]. The elevated ST2 concentrations in this study may reflect the long-term effects of cocaine use and we suggest that ST2 monitoring of chronic cocaine users on an outpatient basis could add to the traditional serum biomarkers of cardiovascular disease risk.

Since cocaine use is associated with an increased prevalence of detectable cTnI [3] and an increased prevalence of elevated ST2 concentrations (this study), a multimarker approach for risk-stratification may be considered. Although cTn is commonly increased in HF, routine cTn measurements are currently not recommended unless there is suspicion of underlying acute coronary syndrome (ACS) [14]. Therefore, and as ST2 concentrations are not increased in ACS [15], a multimarker approach including ST2 may overcome limitations related to cTn as single biomarker for risk-stratification, *i.e.* interpretation of elevated cTn levels. In a multimarker risk-stratification model in MI patients, only ST2, cTn, and myeloperoxidase were complementary predictors of cardiovascular death or HF [16].

Several limitations have to be considered. Specimens were from patients for whom drug testing was ordered, suggesting a concern of drug abuse. This may have overrepresented higher-risk patients, possibly explaining the high proportion of elevated ST2 levels in our population. Other explanations are: 1) patients presented to a hospital for care, indicating a poorer health status; and 2) this is a safety net hospital caring for low-income individuals, which are known to be in worse health. Because information was obtained from medical records, there is no consistent data on the amount and frequency of cocaine use or on other cardiac risk factors. While these data were used in our prior study regarding associations between cocaine use and cTnI [3], we did not adjust analyses reported here for multiple comparisons. This was because there are very few studies regarding associations between cocaine and subclinical cardiac complications, and adjustment for multiple comparisons is not advised in new research areas and exploratory research [17].

In conclusion, our results indicate significant associations between cocaine use and ST2 concentrations. This information could add to better future stratification of cocaine users with elevated ST2 concentrations, who may be at high-risk for developing HF and other cardiac complications.

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Highlights

- Cocaine use is associated with ST2 concentrations > 35 ng/mL
- Serum cocaine metabolite concentrations correlate with ST2 concentrations
- Cocaine use may result in significant subclinical cardiac stress

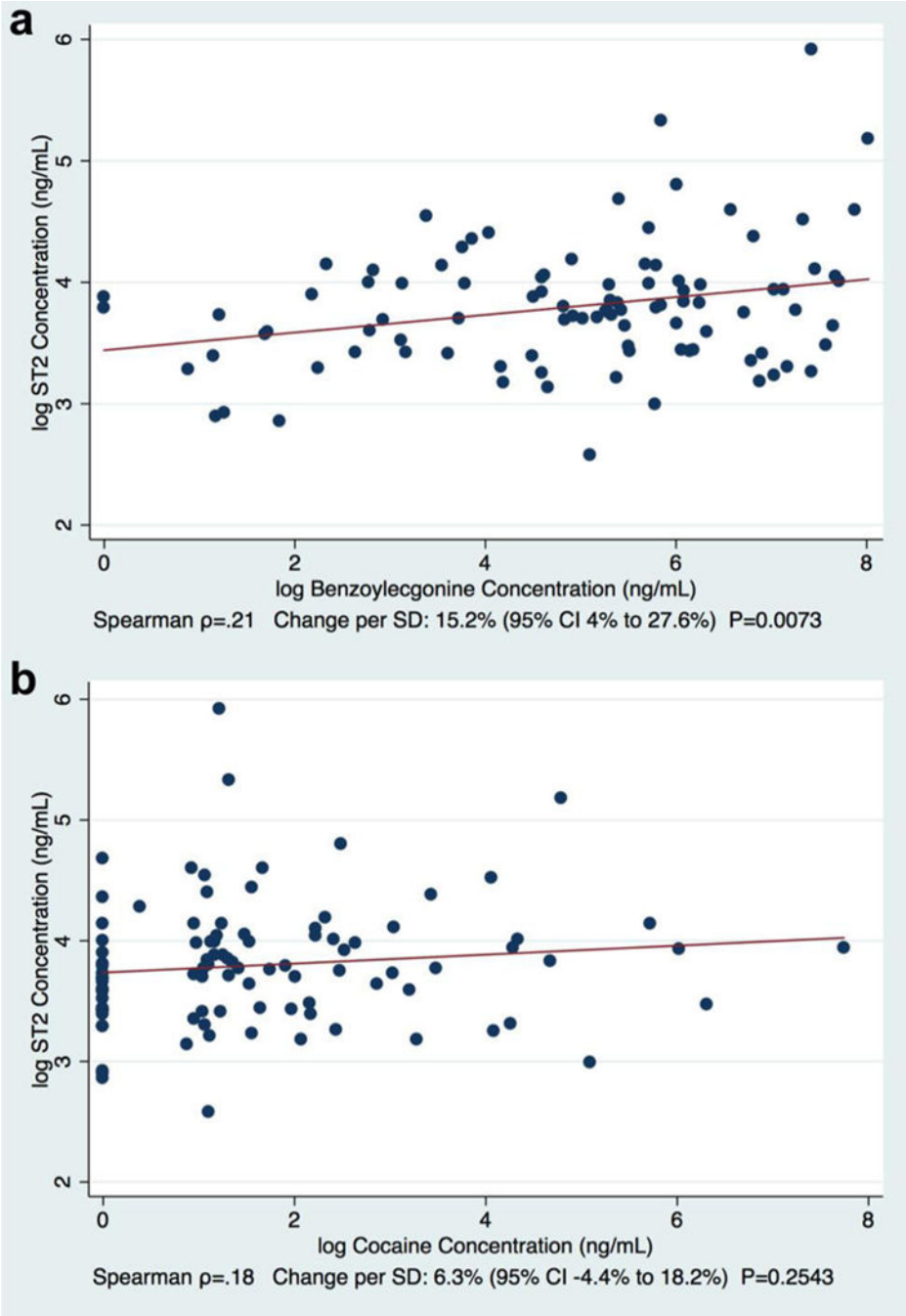

Figure 1.

Correlation between natural log-transformed concentrations of ST2 and natural log-transformed concentrations of (**a**) benzoylecgonine and (**b**) cocaine among patients in a non-cardiology urban safety net hospital between 6/1/15–7/9/15 and 12/14/15–1/25/16 (N=100).

Table 1

Association of serum ST2 concentration (≤ 35 or > 35 ng/mL) with the presence of different drug types by urine toxicology among patients in a non-cardiology urban safety net hospital between 6/1/15–7/9/15 and 12/14/15–1/25/16 (N=200).

	ST2 concentration (ng/mL)		p-value
	≤ 35 n (row%)	**>35 n (row%)**	
Cocaine/Benzoylecgonine (+)	32 (32)	68 (68)	0.03 *
(−)	47 (47)	53 (53)	
Benzodiazepine (+)	17 (34)	33 (66)	0.36
(−)	62 (41)	88 (59)	
Methadone (+)	6 (25)	18 (75)	0.12
(−)	73 (41)	103 (59)	
Opiates (+)	22 (38)	36 (62)	0.77
(−)	57 (40)	85 (60)	
Oxycodone (+)	10 (34)	19 (66)	0.55
(−)	69 (40)	102 (60)	

* $p<0.05$