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Cocaine Use and Pulmonary Hypertension

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Abstract

Evidence linking cocaine to the risk of pulmonary hypertension (PH) is limited and inconsistent. We examined whether cocaine use, in the absence of other known causes of PH, was associated with elevated systolic pulmonary artery pressure (sPAP) and increased probability of PH. We compared patients with documented cocaine use to a randomly selected age, sex, and race-matched control group without history of cocaine use. All participants had no known causes of PH and underwent echocardiography for noninvasive estimation of sPAP. We used routinely reported echocardiographic parameters and contemporary guidelines to grade the probability of PH. In 88 patients with documented cocaine use (mean age $\pm$ standard deviation 51.7 ± 9.5 years), 33% were women and 89% were of Black race. The commonest route of cocaine use was smoking (74%). Cocaine users compared with the control group had significantly higher sPAP (mean $\pm$ standard deviation, 30.1 ± 13.1 vs 22.0 ± 9.8 mm Hg, $p < 0.001$) and greater likelihood of PH (25% vs 10%, $p = 0.012$). In multivariable analyses adjusted for potential confounders including left ventricular diastolic dysfunction, cocaine use conferred a fivefold greater odds of echocardiographic PH ($p = 0.006$). Additionally, a stepwise increase in the likelihood of PH was noted across cocaine users with negative or no drug screen on the day of echocardiography to cocaine users with a positive drug screen (multivariable p for trend = 0.008). In conclusion, cocaine use was associated with a higher sPAP and an increased likelihood of echocardiographic PH with a probable acute-on-chronic effect.

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DISCLOSURES

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SUPPLEMENTARY MATERIALS

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INTRODUCTION

Cocaine abuse is a public health problem in the United States. About 5.5 million Americans (2.0% of the United States population) >12 years of age reported using cocaine in the past year.¹ Cocaine use in the United States accounts for around 36% of global consumption.² Drugs and toxins are categorized as “definite” or “possible” causes of pulmonary hypertension (PH) in the 6th world symposium on PH.³ Although cocaine is considered as a possible risk factor for PH,³ the published evidence is limited to a case report,⁴ few case series,^{5,6} and small interventional studies,^{7,8} with overall inconclusive results.^{9,10} Invasive right heart catheterization is needed to confirm the diagnosis of PH, defined as an increased mean pulmonary artery pressure (PAP) >20 mm Hg at rest;³ however, transthoracic echocardiography is an accepted noninvasive tool for screening and monitoring of PH in clinical practice and population-based studies.^{11,12} Therefore, we sought to evaluate the association between cocaine use and echocardiographic evidence of PH in a hospital-based sample.

METHODS

We conducted a retrospective cohort study of patients with documented cocaine use compared with a proportionate number of control patients with no evidence of cocaine use at the University of Arkansas for Medical Sciences Medical Center, Little Rock, Arkansas. We received approval for the study from the Institutional Review Board (reference number 206174).

To identify cocaine users, we queried our institutional enterprise data warehouse and compiled a list of all patients with relevant International Classification of Diseases, ninth revision (ICD-9), codes for cocaine use or positive urine toxicology screen for cocaine in outpatient or inpatient settings between January 2014 and March 2017. Thereafter, we manually reviewed the medical records and excluded patients without documentation of cocaine use or an echocardiogram during the study period. Subsequently, we extracted information on demographics, route of cocaine use, history of other substance use, co-morbidities, and relevant echocardiographic data and further excluded patients with known causes for PH such as heart failure, reduced left ventricular ejection fraction (<35%), chronic obstructive pulmonary disease, obstructive sleep apnea, other chronic lung diseases, liver cirrhosis, portal hypertension, history of human immunodeficiency virus infection, connective tissue disease, amphetamine use, pulmonary embolism, and sickle cell disease.³ Lastly, we randomly selected age, sex, and race-matched control group of patients with no history of cocaine use, no known causes for PH and underwent echocardiography during the same time period and extracted information on clinical covariates and echocardiographic data.

We calculated body-mass index as weight in kilograms divided by height in meters squared. We used systolic and diastolic blood pressure measurements recorded on the day of the echocardiogram. We calculated mean systemic arterial blood pressure as 1/3 the systolic plus 2/3 the diastolic blood pressure. We defined coronary artery disease as presence of

myocardial infarction, percutaneous coronary artery intervention or coronary artery bypass graft surgery.

We quantified cardiac chamber sizes and determined left ventricular diastolic dysfunction (LVDD) according to existing guidelines from the American Society of Echocardiography.^{13–16} We estimated right atrial pressure based on the diameter of inferior vena cava (IVC) and its respiratory variation.^{12,17} We derived systolic pulmonary artery pressure (sPAP) from the tricuspid regurgitation (TR) peak velocity obtained by Doppler echocardiography using the modified Bernoulli equation ($sPAP = 4 \times [TR \text{ peak velocity}]^2 + \text{right atrial pressure}$).¹⁷ We graded the probability of PH as a 3-category variable (low, intermediate, and high) and a 2-category variable (unlikely and likely) using routinely reported echocardiographic parameters and the European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of PH (Table 1).¹² We also defined PH as a sPAP >40 mm Hg to compare with reported prevalence in the general population.¹¹

We used echocardiographic parameters as reported by cardiologists certified by the National Board of Echocardiography. We validated TR peak velocity measurements in a random sample of 20 echocardiograms (10 each from cocaine and control groups) by manual review of echocardiograms and measurement of TR peak velocity blinded to the original echocardiogram report, and assessed the correlation between the 2 sets of readings.

We summarized the distribution of covariates as percentages for categorical variables, and means $\pm$ 1 standard deviation for continuous variables. We randomly selected age, sex, and race matched control group using a margin of 3 years for age to obtain a cocaine-user to control-group ratio of 1:1. We compared differences between groups using independent sample t test for continuous variables and Chi-square test (or Fisher's exact test as appropriate) for categorical variables. We examined Pearson product moment correlation coefficient to assess reproducibility of TR peak velocity measurement between readers. We constructed histograms with superimposed normal Gaussian and Kernel probability density curves, and Box-and-Whiskers plots to depict the distribution of estimated sPAP and pie charts to display the probability of PH in 3 categories – low, intermediate, and high. We used linear regression analyses to evaluate the association between cocaine use and estimated sPAP and logistic regression analyses to examine the association between cocaine use and various categories of PH. In multivariable models, we adjusted for demographic and clinical variables associated with cocaine use with a univariate p value of <0.10 and Doppler indices consistent with LVDD. To elucidate the influence of acute effects of cocaine on estimated sPAP and the likelihood of PH, we subclassified cocaine users in to individuals with “negative urine toxicology or had no drug screen” and those with “positive urine toxicology screen” on the day of echocardiography for the estimation of sPAP and performed multivariable regression analyses. We considered a 2-sided p value of <0.05 as statistically significant. We conducted all statistical analyses using SAS software, version 9.4.

RESULTS

Our initial database query based on ICD-9 codes and results of toxicology screen revealed 342 patients with possible cocaine use over the study period. During chart review, we

excluded 40 patients (12%) due to lack of documented evidence of cocaine use, 80 patients (23%) due to lack of echocardiograms, and another 134 patients (39%) due to known causes of PH (Supplementary Table 1). The final study sample of cocaine users included 88 patients (26%). Of these, 82 patients (93%) had evidence of active cocaine use in the year before the echocardiogram. The self-reported duration of cocaine use ranged from at least 1 year to about 40 years. Forty seven patients (53%) had a positive toxicology screen on the day of echocardiography.

Among 54 patients with documented route of cocaine use, 40 patients (74%) smoked cocaine, 11 (20%) injected cocaine intravenously, 7 (13%) sniffed cocaine in powder-form, and 1 (2%) ingested cocaine through oral route (Figure 1). Four patients reported both snorting and smoking cocaine and 1 patient reported snorting and ingesting cocaine.

Cocaine users were generally middle-aged, predominantly men (67%) and of Black ancestry (89%) (Table 2). By design, the cocaine and control groups were matched by age, sex, and race. The numerical difference in age between the 2 groups was likely due to the ± 3 -year age margin required to assemble a cohort with cocaine-to-control group ratio of 1:1. Cocaine users had lower body-mass index ($p = 0.002$) but similar systemic blood pressure ($p > 0.10$). A greater proportion of cocaine users smoked cigarettes ($p = 0.005$) and marijuana ($p = 0.012$) and had a higher prevalence of coronary artery disease ($p = 0.003$). Slightly higher proportion of alcohol intake in cocaine users was not statistically significant ($p = 0.17$). None of the 88 cocaine users had documented evidence of methamphetamine use.

Both groups had similar left ventricular ejection fraction ($p = 0.51$; Table 2). The association between cocaine use and LVDD or left atrial dilation was borderline (p value between 0.07 and 0.09). Right ventricular chamber dimensions and prevalence of valvular heart disease including moderate or severe pulmonary regurgitation were similar in the 2 groups. The TR peak velocity as reported by board-certified echocardiographers was highly correlated with our blinded read and measurement (Pearson correlation co-efficient = 0.95). Enlargement of right atrium and IVC, and, consequently, higher right atrial filling pressure was more evident in cocaine users ($p < 0.04$). Interventricular septal flattening was noted in 2 individuals, 1 each from cocaine and control groups, and estimated sPAP in both was > 60 mm Hg.

In participants with data on estimated sPAP (58 cocaine users and 57 control participants), cocaine users had higher sPAP compared with control group (mean $\pm$ SD, 30.1 ± 13.1 vs 22.0 ± 9.8 , $p < 0.001$) (Figures 1 and 2). In multivariable analyses adjusting for age, body-mass index, current or past cigarette smoking, current or past marijuana use, LVDD, atrial fibrillation, and coronary artery disease, the association between cocaine use and elevated sPAP remained highly statistically significant ($p < 0.001$). Using PH definition of sPAP > 40 mm Hg, prevalence was 3.4% in the control group and 12.5% in the cocaine group.

In all participants with data on PH likelihood categories (88 cocaine users and 88 control participants), a greater proportion of cocaine users were noted to have a higher likelihood of PH compared with matched controls (25% vs 10%, $p = 0.012$) (Figure 1 and Table 3). In multivariable analyses adjusted for additional potential confounders including LVDD, a fivefold greater odds of PH was evident ($p = 0.006$). In multivariable models evaluating PH

likelihood as a 3-category variable, a threefold increase in the odds of intermediate probability PH in cocaine users did not reach statistical significance ($p = 0.15$) but a statistically significant 10-fold greater odds of high probability PH ($p = 0.008$) was noted, albeit with wide 95% confidence intervals likely due to small sample size. In addition, a progressively higher prevalence of cocaine use across increasing categories of PH likelihood was evident (multivariable-adjusted p for linear trend = 0.003). Of note, exclusion of IVC size and its respiratory variation from the definition of PH (Table 1) did not alter the number of individuals classified into low, intermediate, and high PH likelihood categories.

In secondary analyses, in participants with data on sPAP, the estimated sPAP progressively increased from the “control group” to “cocaine users with toxicology negative or not performed on the day of echocardiography” to “cocaine users with toxicology positive on the day of echocardiography” (multivariable-adjusted p for trend <0.001) (Table 4). A 2.2-fold greater odds in the likelihood of PH was noted across these 3 groups (multivariable-adjusted p for trend = 0.008). Substitution of sPAP with TR peak velocity showed similar results (data not shown).

DISCUSSION

Chronic cocaine use was associated with an elevated sPAP and an increased likelihood of PH in a hospital-based cohort of cocaine users without known causes of PH compared with age, sex, and race-matched controls with additional adjustment for potential confounders. Cocaine use conferred a fivefold greater odds of PH. The effect of cocaine on sPAP and the likelihood of PH were more pronounced in patients with a positive toxicology screen for cocaine on the day of echocardiography suggesting that cocaine may have an acute-on-chronic effect on increased sPAP.

Some previous case reports and case series have linked cocaine use to PH. Acute severe PH occurred in a 24-year-old woman after intravenous cocaine use and the elevation in sPAP subsided after 2 days.⁴ Intimal and medial hypertrophy of muscular pulmonary arteries was demonstrated in lung biopsies of 4 women with chronic crack use and borderline-to-severe PH.⁵ Echocardiographic sPAP >30 mm Hg was noted in 8 of 13 asymptomatic intravenous cocaine users.⁶ Contrary to these reports, intranasal administration of cocaine in 10 patients referred for cardiac catheterization to evaluate chest pain demonstrated no change in mean PAP.⁷ However, all participants in this study did not previously use cocaine, and the dose of cocaine was lower than what is usually used by illicit drug users. Another single blinded crossover study in 10 healthy habitual crack smokers (9 men and 1 woman) with no previous history of PH who received intravenous saline (placebo) followed by intravenous cocaine showed no significant change in the estimated mean PAP.⁸ In this study too, the subjects received moderate dose of cocaine, which could be less than the recreational dose used by the patients in our study. Further, pulmonary acceleration time/ejection time was used to estimate mean PAP compared with TR Doppler profile used in our study to estimate sPAP.

Cocaine use may augment pulmonary vascular tone by blocking reuptake of sympathetic neurotransmitters such as norepinephrine in synaptic junctions and releasing vasoconstrictor peptides such as endothelin-1 from endothelial cells.^{18,19} Cocaine may promote proliferation

of pulmonary smooth muscles and worsening of endothelial dysfunction.²⁰ Smoking and sniffing cocaine may cause parenchymal and airway lung diseases such as pulmonary hemorrhage, crack lung, eosinophilic lung disease, emphysema, and bronchiolitis obliterans²¹ that can contribute to the development of PH. Cocaine use potentiates coronary vasospasm and thrombosis²² and worsens left ventricular systolic and diastolic dysfunction²³ that may, in turn, passively elevate pulmonary pressures. Intravenous cocaine use may cause embolization of foreign particles such as talc resulting in reduction of the pulmonary vascular bed by chronic inflammation and granuloma formation.²⁴ Cocaine may induce pulmonary artery medial hypertrophy even in the absence of foreign particle embolization.²⁵ Lastly, Levamisole, the most common illicit adulterant of cocaine,²⁶ metabolizes to aminorex, which has been linked to PH.²⁷

To our knowledge, this is the largest study in published literature to evaluate the impact of cocaine use on estimated sPAP and probability of PH.^{4-10,28} The key strengths of our study include examination of consecutive patients over a 3-year period who had documented cocaine use and an echocardiographic estimate of sPAP or PH, exclusion of patients with known causes of PH, and adjustment for additional potential confounders in multivariable analyses. Ascertainment of drug screen status on the day of the echocardiogram provided a hint into the possible acute effect of cocaine use on PAP.

We acknowledge several limitations. First, our study was based on retrospective chart review, which is contingent on adequacy of documentation in medical records. Although we meticulously reviewed every mention of the word “cocaine” in the medical records, the frequency, exact duration, and route of cocaine use could not be determined in all eligible patients. Second, our study sample of cocaine users was predominantly men and of Black ancestry; hence, generalizability of our findings to women or other races/ethnicities may be limited. Third, invasive right heart catheterization, the gold standard for estimation of PAP, was unavailable. Fourth, sPAP could not be ascertained in about a third of participants due to insufficient TR Doppler profile and/or inadequate visualization of IVC. However, the extent of missing information on sPAP was similar in the cocaine and control groups (34% vs 35%) and is commensurate with published literature.^{29,30} For this reason and because TR peak velocity, and, in turn, sPAP may be underestimated in patients with severe TR,¹² we included other echocardiographic variables such as right ventricular dilation, right ventricular hypertrophy, right atrial enlargement, moderate or severe pulmonary regurgitation, and flattening of interventricular septum in the definition of PH. Fifth, data on pulmonary function tests were not available for most patients; however, we excluded patients with evidence of chronic lung diseases by careful review of medical records. Lastly, although we noticed a possible acute-on-chronic effect of cocaine on sPAP, we did not have serial echocardiograms to examine the resolution of elevated sPAP after dissipation of acute effects of cocaine.

In summary, our study found a significant association between cocaine use and elevated sPAP and likelihood of PH based on echocardiography. There may be an acute-on-chronic effect of cocaine on rise in sPAP. This is the largest published study to examine the association between cocaine use and PH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cocaine use and pulmonary hypertension. The diagram shows routes of cocaine use (smoking, snorting, ingesting, and intravenous) using proportional Venn diagram, distribution of systolic pulmonary artery pressure using histogram, normal Gaussian curve and Kernel density curve, and probability of pulmonary hypertension (low, intermediate, and high) using pie chart in the control group (*upper panel*) and the cocaine group (*lower panel*). N denotes number of participants.

Figure 2.

Distribution of systolic pulmonary artery pressure among cocaine users and control group participants. The diagram shows mean (*diamond-shaped marker inside the box*), median (*line inside the box*), interquartile range (*bottom and top edges of the box*), 1.5 times interquartile range (*whiskers extending from each box*), and outliers (*circle-shaped markers outside the box*). N denotes number of participants. *Adjusted p value was derived using multivariable linear regression analyses adjusted for age, body-mass index, current or past cigarette smoking, current or past marijuana use, left ventricular diastolic dysfunction, atrial fibrillation, and coronary artery disease.

Table 1

Classification of pulmonary hypertension *

Peak TR velocity, m/s (sPAP, mm Hg)	Echocardiographic signs of PH [†]	PH likelihood	
		3-categories	2-categories
2.8 (35) or not measurable	No	Low	Unlikely
2.8 (35) or not measurable	Yes	Intermediate	Likely
2.9-3.4 (36-50)	No		
2.9-3.4 (36-50)	Yes	High	
>3.4 (>50)	Not required		

TR = tricuspid regurgitation; sPAP = systolic pulmonary artery pressure; PH = pulmonary hypertension.

* Based on routinely ascertained echocardiographic parameters and guidelines from the European Society of Cardiology and the European Respiratory Society for the diagnosis and treatment of pulmonary hypertension.¹²

[†] Echocardiographic signs of PH included right ventricular dilation, right ventricular hypertrophy, right atrial enlargement, moderate or severe pulmonary regurgitation, and flattening of interventricular septum (D-shaped left ventricle) in systole.

Table 2

Baseline demographics, clinical characteristics and echocardiographic features of cocaine users compared with the control group

Variable	Cocaine users (N = 88)	Control group (N = 88)	p value
Age, years (mean $\pm$ SD)	51.7 $\pm$ 9.5	48.9 $\pm$ 10.3	0.06
Women	33%	33%	1
Black	89%	89%	1
Body mass index (kg/m ² $\pm$ SD)	27.6 $\pm$ 6.1	31.4 $\pm$ 9.5	0.002
Blood pressure (mm Hg $\pm$ SD)			
Systolic	130.1 $\pm$ 18.1	131.0 $\pm$ 16.9	0.38
Diastolic	81.5 $\pm$ 12.0	79.0 $\pm$ 14.1	0.11
Mean	97.7 $\pm$ 13.0	96.4 $\pm$ 13.4	0.49
Cigarette smoker	81%	61%	0.005
Alcohol drinker	48%	38%	0.17
Marijuana	31%	15%	0.012
Prescription opioids	25%	35%	0.14
Benzodiazepines	9%	8%	0.84
Heroin	3%	0%	0.25
Phencyclidine	3%	0%	0.25
Barbiturates	1%	0%	1
Systemic hypertension	73%	73%	1
Atrial fibrillation	5%	11%	0.095
Coronary artery disease	17%	3%	0.003
Echocardiographic Features			
LV ejection fraction (mean $\pm$ SD)	57.2 $\pm$ 7.9	57.8 $\pm$ 5.6	0.51
LV diastolic dysfunction (grade) *			0.09
I	29%	21%	
II	8%	5%	
III	1%	0%	
Right ventricular enlargement	11%	7%	0.31
Right ventricular hypertrophy	5%	0%	0.12
Left atrial enlargement	17%	8%	0.073
Right atrial enlargement	14%	5%	0.038
Valvular heart disease	10%	10%	0.98
Moderate or severe PR	1%	2%	1
Inferior vena caval dilation [†]	18%	6%	0.016
with normal respiratory variation	12%	5%	
with blunted respiratory variation	6%	1%	
Right atrial pressure (mm Hg $\pm$ SD) [†]	4.3 $\pm$ 3.2	3.4 $\pm$ 1.7	0.017
TR peak velocity(m/s $\pm$ SD) [‡]	2.5 $\pm$ 0.6	2.1 $\pm$ 0.5	<0.001
Ventricular septal flattening	1%	1%	1

N = number of participants; SD = standard deviation; LV = left ventricle; PR = pulmonary regurgitation; TR = tricuspid regurgitation.

* Doppler indices of LV diastolic function was available among 83 in the cocaine group and 77 in the control group.

[†] Data on inferior vena caval diameter and its respiratory variation and estimated right atrial pressure was available among 84 in the cocaine group and 85 in the control group.

[‡] TR peak velocity could not be ascertained in 34.7% of participants (31 participants in the cocaine group and 30 participants in the control group) due to inadequate TR Doppler profile.

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Table 3

Results of logistic regression analyses evaluating the association between cocaine use and pulmonary hypertension *

Pulmonary hypertension	Cocaine (N=88)	Control (N=88)	Odds ratio (95% Confidence Interval), p value	
			Unadjusted	Multivariable-adjusted [†]
As dichotomous variable				
Unlikely	66 (75.0%)	79 (89.8%)	1.00 (referent)	1.00 (referent)
Likely	22 (25.0%)	9 (10.2%)	2.93 (1.26-6.79), 0.012	4.97 (1.59-15.50), 0.006
As 3-category variable				
Low probability	66 (75.0%)	79 (89.8%)	1.00 (referent)	1.00 (referent)
Intermediate probability	11 (12.5%)	6 (6.8%)	2.19 (0.77-6.25), 0.14	2.96 (0.69-12.77), 0.15
High probability	11 (12.5%)	3 (3.4%)	4.39 (1.18-16.39), 0.028	10.66 (1.85-61.35), 0.008
Trend across categories			2.12 (1.19-3.78), 0.011	3.19 (1.48-6.89), 0.003

N = number of participants

* Study sample excluded participants with known causes of pulmonary hypertension. The cocaine and control groups were matched by age, sex, and race.

[†] Adjusted for age, body-mass index, current or past cigarette smoking, current or past marijuana use, left ventricular diastolic dysfunction, atrial fibrillation, and coronary artery disease.

Table 4

Results of regression analyses evaluating the association between cocaine use and systolic pulmonary artery pressure and likelihood of pulmonary hypertension in relation to results of toxicology screen on the day of echocardiographic estimation of systolic pulmonary artery pressure *

	Linear regression analyses				Logistic regression analyses		
	N	sPAP, mm Hg, mean $\pm$ SD	Multivariable- adjusted [†] p value	N	PH likely, Events (%)	Multivariable- adjusted [†] Odds ratio (95% CI, p value)	
Control group	57	22.0 $\pm$ 9.8	1.00 (referent)	88	9 (10.2%)	1.00 (referent)	
Cocaine users							
Toxicology screen – or not performed	25	28.8 $\pm$ 12.6	0.003	41	9 (22.0%)	4.51 (1.26-16.15), 0.021	
Toxicology screen +	33	31.0 $\pm$ 13.6	<0.001	47	13 (27.7%)	5.43 (1.55-19.00), 0.008	
Trend across categories			<0.001			2.21 (1.23-3.99), 0.008	

N = number of participants; sPAP = systolic pulmonary artery pressure; PH = pulmonary hypertension; CI = confidence interval.

* Study sample excluded participants with known causes of pulmonary hypertension. The cocaine and control groups were matched by age, sex, and race.

[†] Adjusted for age, body-mass index, current or past cigarette smoking, current or past marijuana use, left ventricular diastolic dysfunction, atrial fibrillation, and coronary artery disease.