Quantitative Comparison of Coronary Artery Flow and Myocardial Perfusion in Patients with Acute Myocardial Infarction in the Presence and Absence of Recent Cocaine Use

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Abstract. Background: Numerous factors have been implicated in the pathogenesis of cocaine associated myocardial infarction (CAMI). However, the relative contributions each of these mechanisms provide to the pathogenesis of CAMI have not been well defined. We hypothesized that significant angiographic differences exist between CAMI patients vs thrombotic AMI patients (TAMI) and normal controls.

Methods: The TIMI Flow Grade, corrected TIMI Frame Count (CTFC), TIMI Myocardial Perfusion Grade (TMPG), presence of triple-vessel disease, stenosis severity, and presence of angiographically apparent thrombus were compared in patients who sustained CAMI to TAMI patients and normal controls.

Results: 2,495 angiograms were analyzed (CAMI = 57, TAMI = 2,403, Controls = 35). Impairment in both epicardial and microvascular flow in patients with CAMI was intermediate between TAMI and controls. Compared to TAMI patients, CAMI patients were less likely to have 3 vessel disease (8.9% vs. 19.1%; $p < 0.05$), epicardial stenosis was less severe (14.9+/−30.2 vs. 72.6+/−18.6; $p < 0.0001$), less thrombus was present (6.5% vs. 33.1%; $p < 0.001$) and TIMI grade 3 flow was observed more frequently (76% vs. 59%). Normal TMPG 3 perfusion was significantly impaired in both CAMI and TAMI patients when compared to controls without AMI (TMPG 3 was 40% and 26.6% vs. 100% respectively; $p < 0.001$ for both). The majority of patients in both AMI groups had diminished or absent tissue level perfusion (TMPG 0 flow, CAMI 53.9 vs. TAMI 56.8%).

Conclusions: Both epicardial and microvascular flow is impaired in CAMI. While epicardial flow among CAMI patients is slightly better than TAMI patients, the incidence of little or severely impaired tissue level perfusion is nearly identical.

Key Words. TIMI myocardial perfusion grade, TIMI flow grade, TIMI frame count, cocaine, myocardial infarction

Abbreviations. TIMI: Thrombolysis in Myocardial Infarction; CTFC: Corrected Thrombolysis in Myocardial Infarction Frame Count; TMPG: TIMI Myocardial Perfusion Grade; DSA: Digital subtraction angiography; AMI: Acute myocardial infarction; rt-PA: Recombinant tissue plasminogen activator; CAMI: Cocaine Associated Myocardial Infarction.

Introduction

*C*hest pain is the most frequently reported cardiac consequence of cocaine abuse [1]. Numerous factors have been implicated in the pathophysiology of cocaine associated myocardial ischemia, including coronary artery vasoconstriction [2], platelet aggregation [3–6], *in situ* thrombus formation [7–10], and premature atherosclerosis [4,9,11,12]. However, the relative contributions of each of these pathophysiologic mechanisms have not been widely investigated and are poorly understood.

Initial case reports of CAMI have documented myocardial infarction in young individuals with angiographically normal coronary arteries [13–15]. However, no study consistently demonstrated cocaine-induced epicardial vasoconstriction sufficient to cause symptoms or electrocardiographic changes

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Condensed abstract. Compared to TAMI patients, CAMI patients were less likely to have 3 vessel disease, stenosis, and thrombus. The majority of patients in both AMI groups had diminished or absent tissue level perfusion. While epicardial flow among CAMI patients is slightly better than TAMI patients, the incidence

consistent with myocardial ischemia raising a question regarding the primacy of epicardial coronary vasoconstriction in the pathophysiology of CAMI [16]. Autopsy and case series have confirmed that cocaine use is associated with atherosclerosis, and many patients with CAMI have underlying coronary artery disease [4,9,11,17].

To gain a better understanding of the pathophysiology of CAMI, we evaluated epicardial and microvascular flow in patients who sustained CAMI, and compared these indexes to the findings in normal subjects and in patients with acute myocardial infarction unrelated to cocaine. We hypothesized that both epicardial and microvascular perfusion would be impaired in CAMI.

Methods

A total of 2,563 patients were available for analysis. CAMI was present in 60 patients with acute myocardial infarction as defined by World Health Organization (WHO) criteria [18], and a urine toxicology analysis was positive for cocaine or cocaine metabolites. These patients were cared for at Hurley Medical Center (Flint, Michigan) between January 1, 1997 and January 1, 2001. This study was approved by the Hurley Medical Center Institutional Review Board.

Normal CTFC data were obtained from a control group of 78 patients without myocardial infarction and without obstructive coronary artery disease who presented to the West Roxbury Veterans Administration Hospital. Myocardial perfusion data were retrospectively obtained from 36 patients who were found to have no significant obstructive coronary artery disease and normal epicardial and tissue level perfusion who had undergone cardiac catheterization at University of California San Francisco Medical Center.

A total of 2,428 TIMI patients from the TIMI 4, 10A, 10B, and 14 trials had angiographic data available for analysis [19–22], and are referred to as thrombotic AMI (TAMI). The TIMI 4 trial was a randomized, double blind comparison of 3 thrombolytic regimens in 416 patients: anistreplase (Eminase or APSAC, 30 U IV), front-loaded recombinant tissue plasminogen activator (rtPA) (Activase or alteplase), or combination therapy [19]. The TIMI 10A trial was a non-randomized, open label study of 8 ascending doses of tenecteplase (TNK) (5, 7.5, 10, 15, 20, 30, 40, and 50 mg IV over 5 seconds in 113 patients [20]. TIMI 10B was a randomized comparison of TNK (30, 40, and 50 mg) and 90 minute infusion of rtPA (Activase or alteplase) in 854 patients [21]. The TIMI 14 trial compared full dose thrombolytic therapy with abciximab and a low dose thrombolytic in 1187 patients [22].

Visual assessment of coronary blood flow

The TIMI Flow Grade and 90 minute Corrected TIMI Frame Count (CTFC) were assessed by a single observer (CMG), who was blinded to treatment assignment and clinical outcome. TIMI flow grade was assessed at an angiographic core laboratory as previously defined [23]. The CTFC was also assessed as previously defined [24]. In brief, the CTFC is the number of cine frames required for contrast to first reach standardized distal coronary landmarks in the culprit artery and is measured with a frame counter on a cine viewer. A frame count of 100, a value that is the 99th percentile of patent vessels, was imputed to an occluded vessel. CTFC is a measure of time, and data were converted when necessary to be based upon the most common filming speed in the U.S. of 30 frames/second. TIMI Myocardial Perfusion Grades (TMPG) were also assessed as previously defined [25]. In brief, in TIMI myocardial perfusion grade 0, there is minimal or no myocardial blush; in TIMI myocardial perfusion grade 1, dye stains the myocardium and this stain persists on the next injection; in TIMI myocardial perfusion grade 2 dye enters the myocardium but washed out slowly so that dye is strongly persistent at the end of the injection; and in TIMI myocardial perfusion grade 3 there is normal entrance and exit of dye in the myocardium so that dye is mildly persistent at the end of the injection.

Assessment of stenosis, thrombosis, and 3 vessel disease

Stenosis was defined by the percent coronary artery diameter obstruction. Average values were recorded for the left anterior descending, right coronary artery, and left circumflex coronary artery. Zero was imputed for arteries with no lesion; a value of 100 was imputed for occluded coronary arteries. Angiographically evident thrombus was classified using the TIMI Thrombus Grade classification scheme, assessed visually using the following grading system: Grade 0: No cineangiographic characteristics of thrombus present. Grade 1: Possible thrombus present. Angiography demonstrates characteristics such as reduced contrast density, haziness, irregular lesion contour or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus. Grade 2: Thrombus present-small size: Definite thrombus with greatest dimensions less than or equal to $\frac{1}{2}$ vessel diameter. Grade 3: Thrombus present—moderate size: Definite thrombus but with greatest linear dimension greater than $\frac{1}{2}$ but less than 2 vessel diameters. Grade 4: Thrombus present—large size: As in Grade 3 but with the largest dimension greater than or equal to 2 vessel diameters. Grade 5: Total occlusion. Triple vessel disease was defined as the presence of a >50% lesion in the left anterior descending, circumflex and right coronary arteries.

Digital subtraction angiography in the assessment of myocardial perfusion

Digital subtraction angiography (DSA) has validated that TMPG 3 is associated with normal kinetics of myocardial perfusion, and was therefore utilized to quantify myocardial "blush" when considering CAMI vs. control patients [25,26]. DSA techniques were not developed until after the completion of the TIMI trials. Therefore, comparisons of DSA blush scores between CAMI vs. thrombotic AMI patients were unavailable. DSA was performed at end diastole by aligning cineframes images before dye filled the myocardium with those at the peak of myocardial filling to subtract spine, ribs, diaphragm and the epicardial artery. A representative region of the myocardium was sampled that was free of overlap by epicardial arterial branches to determine the increase in the Gray scale brightness of the myocardium when it first reached its peak intensity. The number of frames required for the myocardium to first reach its peak brightness was converted into time (sec) by dividing the frame count by 30. In this way, the rate of rise in brightness (Gray/sec) could be calculated.

Statistical analysis

All analyses were performed using Stata version 6.0. All continuous variable values were reported as the mean $\pm$ standard deviation unless otherwise specified. The Chi-Square or Fisher's exact test was used to analyze categorical variables. The non-parametric two-sample Wilcoxon Rank-Sum test (Mann-Whitney test) was utilized when the data were not normally distributed or when values were imputed for an occluded artery. Multivariate linear and logistic regression analysis was used to adjust for differences in baseline characteristics (included if $p < 0.1$).

Results

Comparison of infarct characteristics and time to treatment

Infarct characteristics of TAMI patients are reported elsewhere [19–22]. There were 60 patients who presented with CAMI during the study period; 31 had ST-elevation AMI. Only 2 patients with CAMI received thrombolytic agents. Angiographic data were available for 58 patients. One subject was excluded because the quality of the angiogram prohibited accurate analysis. Therefore, 57 patients with CAMI were included in the analysis. Time of symptom onset to treatment was significantly longer in CAMI vs. TAMI patients (2883.5+/−2129 vs. 216+/−159.7 min; $p < 0.0001$).

Comparison of baseline demographic characteristics

Baseline characteristics are shown in Table 1. Compared to TAMI patients, CAMI patients were significantly younger (43.5 $\pm$ 8.4 vs. 58.5 $\pm$ 11.0 yrs; $p < 0.001$), more likely of African-American origin (84.2 vs. 5.7%; $p < 0.001$), cigarette smokers (82.5 vs. 48.8%; $p < 0.001$) with a history of hypertension (45.6 vs. 33.4%; $p = 0.05$).

Comparison of patients with CAMI vs. normal controls

When compared to patients without coronary artery disease, the CTFC was significantly higher (slower epicardial flow) in the CAMI cohort (21.0 $\pm$ 3.1 vs. 33.6 $\pm$ 16.6; $p < 0.0001$) (Table 2). Although the majority of CAMI patients (75.7%) quantitatively achieved TIMI Flow Grade 3, they did so less frequently than did normal controls ($p < 0.001$). Only 44.7% of CAMI patients had CTFCs <28, a CTFC which in the past has been used to define the 95th percentile of the upper limit of normal flow. Thus,

Table 1. *Baseline Characteristics in Cocaine MI, TIMI AMI, and Normal Control Patients*

	Cocaine MI pts	TIMI AMI pts	Normal pts	*p*-value (CAMI vs. normal)	*p*-value (CAMI vs. AMI)
Age (years)	43.4 $\pm$ 8.4, $n = 57$	58.5 $\pm$ 11.0, $n = 2403$	53.7 $\pm$ 14.0, $n = 35$	<0.001	<0.001
Gender (% male)	75.4% 43/57	76.8% 1855/2416	61.1% 22/36	0.14	0.85
Race (% black)	84.2% 48/57	5.8% 141/2416	5.5% 2/36	<0.001	<0.001
Smoking (%)	82.4% 47/57	48.7% 1174/2410	N/A	N/A	<0.001
Hx diabetes (%)	8.7% 5/57	13.3% 321/2409	22.2% 8/36	0.068	0.31
Hx hypertension (%)	45.6% 26/57	33.5% 804/2401	33.3% 12/36	0.24	0.053
Family hx CAD (%)	35.1% 20/57	37.3% 853/2287	N/A	N/A	0.73

Table 2. Angiographic Data in Cocaine MI Patients vs. Normal Patients

	Cocaine MI	Normals	p-value
CTFC (frames)	33.6 ± 16.6, $n = 143$	21.0 ± 3.1, $n = 78^*$	<0.0001
TIMI flow grade			
TFG 3	75.7%, 128/169	100%, 91/91	<0.001
TFG 2	20.1%, 34/169		
TFG 1	0.6%, 1/169		
TFG 0	3.6%, 6/169		
3 vessel disease	8.9%, 5/56	0%, 0/91	0.007
Thrombus present (Grades 2–5)	6.5%, 11/170	0%, 0/91	0.01
TIMI myocardial perfusion grade			
TMPG 3	40.0%, 66/165	100%, 91/91	<0.001
TMPG 2	4.2%, 7/165		
TMPG 1	1.8%, 3/165		
TMPG 0	53.9%, 89/165		
DSA blush brightness	5.6 ± 5.6, $n = 136$	10.9 ± 5.7, $n = 65$	<0.0001
Frames to first blush	70.3 ± 36.9, $n = 109$	50.8 ± 20.3, $n = 83$	<0.0001

even though the majority of CAMI patients had TIMI grade 3-epicardial perfusion, the minority had truly quantitatively normal flow.

Compared to the normal controls, CAMI patients had considerably less TMPG 3 flow (Only 40% vs. 100%; $p < 0.001$). The majority of CAMI patients (53.9%) studied had little or no tissue level perfusion (TMPG 0 flow). Quantitation of the TIMI Myocardial Blush Grades using DSA revealed that CAMI patients had significantly lower microvascular perfusion when compared to patients without coronary artery disease (Table 2). In particular, there was a reduction in peak Gray (brightness) ($p < 0.0001$) and a delay in the number of frames required to achieve

first blush ($p < 0.0001$). Even after adjusting for differences in baseline characteristics between patients in the CAMI cohort and the cohort of patients without coronary artery disease (age, race, history of diabetes), CAMI patients had significant reduction in peak brightness ($p < 0.001$) and a delay in the number of frames required to achieve first blush ($p < 0.001$).

Comparison of patients with CAMI vs. TAMI
In patients with TAMI, the CTFC was significantly higher (reflecting slower flow) than for patients with CAMI ($49.4 +/- 32.8$ vs. $36.7 +/- 21.5$ frames; $p < 0.0001$) (Table 3). Even after adjusting for age, race,

Table 3. Angiographic Data in Cocaine MI Patients vs. TIMI 4, 10A, 10B and 14 Acute MI Patients

	Cocaine MI	TIMI AMI	p-value
CTFC (frames)—patent arteries only	33.6 ± 16.6, $n = 143$	35.9 ± 22.4, $n = 1818$	0.23
CTFC (frames)—patent and occluded arteries	36.7 ± 21.5, $n = 150$	49.4 ± 32.8, $n = 2304$	0.0001
TIMI flow grade			<0.001*
TFG 3	75.7%, 128/169	58.6%, 1422/2428	
TFG 2	20.1%, 34/169	21.4%, 520/2428	
TFG 1	0.6%, 1/169	4.7%, 113/2428	
TFG 0	3.6%, 6/169	15.4%, 373/2428	
TIMI myocardial perfusion grade			0.001†
TMPG 3	40.0%, 66/165	26.6%, 206/775	
TMPG 2	4.2%, 7/165	6.2%, 48/775	
TMPG 1	1.8%, 3/165	10.5%, 81/775	
TMPG 0	53.9%, 89/165	56.8%, 440/775	
Stenosis	14.9 ± 30.2, $n = 169$	72.6 ± 18.6, $n = 2382$	<0.0001
Ejection fraction	60.8 ± 15.9, $n = 53$	58.4 ± 14.6, $n = 1154$	0.25
3 vessel disease	8.9%, 5/56	19.1%, 482/2524	0.057
Mitral regurg (2+)	7.4%, 4/54	2.46%, 29/1179	0.052
Thrombus present (Grades 2–5)	6.5%, 11/170	33.1%, 802/2424	<0.001‡
Thrombus present—patent arteries only	2.5%, 4/162	18.8%, 362/1923	<0.001‡
Pulsatile flow	10.1%, 17/169	9.2%,173/1888	0.7

*Comparing grade 3 in cocaine patients vs. TIMI AMI patients.

†TMPG data from TIMI 10B only.

‡$p < 0.001$ even after adjusting for artery location in multivariate model.

Table 4. *Regression Models for Angiographic Data in Cocaine MI Patients vs. TIMI 4, 10A, 10B and 14 Acute MI Patients Adjusting for Age, Race, Smoking, History of Hypertension and Time to Treatment*

Logistic regression	O.R.		*p*-value
TIMI Flow Grade 3	2.18		0.013
TIMI Myocardial Perfusion Grade 3 (blush grade)	1.13		NS
Thrombus present (Grades 2–5)	0.11		<0.001
Thrombus present—patent arteries only	0.13		0.006
Linear regression	Coef.	*R*-value	*p*-value
CTFC (frames)–patent and occluded arteries	−14.36	−0.093	0.003
Stenosis	−57.7	−0.59	<0.001

smoking, history of hypertension, and time to treatment, the CTFC was significantly higher (slower epicardial flow) in TAMI patients ($p < 0.003$). Correspondingly, TIMI Flow Grade 3 was achieved more frequently in CAMI versus TAMI patients (75.7% vs. 58.6%; $p < 0.001$) (Table 3). Using multivariate analysis, the odds of TIMI Flow Grade 3 was twice as great in CAMI patients versus those with TAMI ($p = 0.013$) (Table 4). The incidence of 3 vessel disease also tended to be lower in CAMI than TAMI patients (8.9 vs. 19.1%), although this difference was not significant ($p = 0.3$). Thus, the impairment in epicardial flow in patients with TAMI was greater than in patients with CAMI. In addition, the degree of stenosis was significantly greater in TAMI vs. CAMI patients ($p < 0.001$). The odds of having coronary thrombus was 9 times greater in TAMI compared to CAMI patients (O.R. 0.11; $p < 0.001$, 95% C.I. = 0.06, 0.22). TMPG grade 3 flow was achieved less frequently in TAMI than CAMI patients (26.6 vs. 40.0%; $p < 0.001$) (Table 3). However, when adjusting for differences in demographic variables and time to treatment, this difference was not significant (O.R. 1.13, 95% C.I. = 0.97, 3.2, $p = $ NS). No difference in left ventricular ejection fraction was noted between groups ($p = 0.4$).

Discussion

The risk of AMI is increased 24 fold in the hour after cocaine use [27], and up to 6% of patients who present to the ED with cocaine-induced chest pain sustain AMI [28,29]. The pathogenesis of cocaine associated myocardial infarction is multifactorial. We explored the relative contributions of previously reported pathogenic mechanisms using coronary arteriography.

Although initial reports of cocaine associated myocardial ischemia focused on the lack of coronary artery disease [1], subsequent investigations have suggested that many patients with CAMI do in fact have atherosclerotic coronary artery disease [30]. Autopsy series have found atherosclerosis in 50% to 63% of young patients who died cocaine related deaths [4,9,11], and clinical series have found that up to 67 percent of patients with cocaine associated myocardial infarction have atherosclerotic coronary artery disease [30]. There is growing evidence that the early development of coronary artery disease in young patients with CAMI may reflect an association between cocaine and premature atherosclerosis, which has been demonstrated in animal models [31].

The impairment in both epicardial and microvascular flow in patients with CAMI appears to be intermediate between TAMI patients and patients with normal coronary arteries. The fact that these patients have angiographic findings that are intermediate between normal patients and those with thrombotic ST elevation MI may explain in part the lower risk of complications among CAMI patients [12,17]. Compared to the matched cohort with normal coronary arteries, the patients with CAMI had significantly poorer epicardial and microvascular perfusion, as assessed by the CTFC, TIMI myocardial perfusion grade, DSA blush brightness and frames to first blush. Although TMPG 3 flow was achieved more frequently in CAMI relative to TAMI patients (40.0 vs. 26.6%; $p < 0.001$), this difference was not significant after adjusting for demographics and time to treatment. Furthermore, the majority of patients in both groups had similar frequencies of TMPG 0 flow (53.9 vs. 56.8%). Our data supports the hypothesis that patients with cocaine associated myocardial infarction have impairment of both epicardial and microvascular flow compared to normal patients.

Cocaine-induced thrombosis may be an important mechanism in the development of AMI. Numerous autopsy studies have demonstrated the presence of platelet rich thrombi in coronary arteries [3,4]. However, little is known about the *in vivo* effects of cocaine on platelet function. In the present study, the odds of coronary thrombus formation were 9 fold higher in TAMI patients than CAMI patients. However, because the time to catheterization was significantly longer in CAMI patients, conclusions regarding cohort comparisons in this regard may be unreliable. The finding that the average vessel stenosis for CAMI patients was only 14.9%, yet greater than 50% of such patients presented with ST-elevation AMI, suggests that thrombosis may have played an important pathogenic role. In addition, it should be noted that the angiogram may not be that sensitive in detecting thrombus when compared to direct visualization of the artery using angioscopy [32]. Consensus guidelines and evidence based recommendations have suggested that treatment of cocaine associated ST-segment elevation AMI with percutaneous intervention is preferred over fibrinolytic therapy due to the low mortality of CAMI patients, and the potential

increased risk of these agents in this cohort. Future angiographic studies performed within 90 minutes of presentation with CAMI patients may further clarify these recommendations.

Several limitations are noteworthy. It is possible that a small number of TAMI patients actually had CAMI. However, it is unlikely that this would have influenced the overall results. In addition, we cannot exclude the possibility that the results may have been influenced by selection bias, since the CAMI cohort is small. Because of the delay in door to catheterization time in the CAMI cohort, the contributory effect of coronary vasospasm cannot be ascertained from this study. Last, adjusting for differences in demographics and time to treatment did not alter the results. However, we cannot entirely exclude the possibility that this intervention delay did not have a confounding effect, particularly with regard to epicardial stenosis and thrombus burden. Thus, these results are preliminary, and require prospective validation. Future studies will require uniformity in treatment regimens and angiographic technique, as well as the use of Doppler wire to improve the accuracy of coronary flow.

Acknowledgment

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