Recreational drug use among young, hospitalized patients with acute coronary syndrome: A retrospective study

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ABSTRACT

Background: Cocaine use is a well-established risk factor for acute coronary syndrome (ACS) although other recreational drugs (RD), are increasingly considered as potential cardiac risk factors. Compared to ACS without RD use, worse outcomes have been described for RD-associated ACS.

Objective: The aim of this study was to explore the use of RD in a contemporary cohort of young ACS patients.

Methods: Between June 2016 and October 2019, ACS patients aged 18–50 years, admitted to OLVG Hospital in Amsterdam, were retrospectively analysed. Medical chart review was performed to obtain patient and clinical characteristics, RD use, cardiac risk factors, outcome and follow up.

Results: A total of 229 patients were included in the study. Recreational drug use prior to ACS was present in 24.9% of all patients, with cannabis (16.2%), cocaine (4.8%), or both (2.6%) most commonly observed. RD users were predominantly young men (87.7%) and had a significantly higher tobacco use compared to non-RD users (89.5% vs. 62.8%, P < 0.001), also after adjusting for age and sex. RD use was associated with larger myocardial infarctions with significantly higher CK-MB levels (104 ± 66 U/L vs 62 ± 50 U/L, P = 0.001) and poorer left ventricular function measured by echocardiography as compared to non-users (P = 0.007).

Conclusion: Recreational drug use was present in almost 25% of all young ACS patients evaluated for drug use and was associated with larger myocardial infarction resulting in poorer left ventricular function as compared to non-users. Additionally, RD-users were younger and were more often tobacco users, compared to non-users.

1. Background

Acute coronary syndrome (ACS) is a well-known cause of morbidity and mortality with well-established risk factors in the literature [1,2]. One less common acknowledged risk factor for ACS is recreational drug (RD) use. Since RD use is increasing worldwide, especially among young adults, a higher number of patients will present to the emergency department with RD related complications [3]. The mechanisms underlying RD-associated ACS are diverse and include activation of the sympathetic nervous system leading to an increased cardiac oxygen demand, a decreased cardiac oxygen delivery due to coronary vasospasm [4-6], in addition to the direct prothrombotic effects [7,8]. Cocaine is the most extensively studied RD with regard to cardiovascular complications [7,9,10], increasing ACS risk five-fold [11]. Also, 6% of...
cannabis-associated chest pain patients in the emergency department are diagnosed with acute myocardial infarction [10,12]. Additionally, patients < 50 years old with cocaine-induced myocardial infarction (CIMI) suffer larger myocardial infarctions and have an increased hospital mortality as compared with non-cocaine associated ACS patients [9].

Since sympathomimetic activation, coronary vasospasm and pro-thrombotic effects are also caused by RD other than cocaine, it is expected that these other RD will increase the risk of ACS in a similar way. Several studies have described cannabis, cathinones, amphetamine, methamphetamine and 3,4-methylenedioxymethamphetamine in relation to ACS [4,8,13–18]. However, the prevalence of RD-associated ACS is unknown.

The aim of this study was to explore the use of RD in a contemporary cohort of relatively young ACS patients. An additional aim was to compare RD using to non-RD using ACS patients in terms of patient and clinical characteristics, cardiac risk factors and outcome.

2. Methods

This retrospective observational study was performed between June 2016 and October 2019 at the coronary care units of two hospital sites in Amsterdam. All patients diagnosed with ACS aged 18–50 years old were included. Exclusion criteria were the absence of a RD history (positive or negative) reported by the treating physician in the electronic patient record and absence of a urine toxicology screening (TST-U) result. According to local guidelines, RD history and TST-U was standard practice.

Patients were identified through medical chart review of all patients with an ACS diagnosis in the electronic patient record. Medical chart review to obtain demographic data, current tobacco use, cardiovascular risk factors as defined by the European society of cardiology, the GRACE risk stratification score, vital signs, type of ACS as defined by the European Society of Cardiology guidelines [1,2], peak high-sensitive cardiac Troponin-T (hs-cTnT), peak creatine kinase-myoglobin binding (CK-MB) levels, left ventricular function measured by echocardiography, coronary angiography results and major adverse cardiac events (MACE), was performed. MACE was defined as the occurrence of any of the following events: recurrent acute myocardial infarction, unplanned revascularization, or death within 6 weeks after hospital discharge. The study population consisted of two groups, 1; the RD user group, and 2; the non-RD user group. The RD user group consisted of patients with either a positive TST-U result for RD and/or self-reported RD user patients. The nonuser group consisted of all patients with a negative TST-U results and/or negative drug history. The TST-U was performed using a point of care immunoassay test (Triage TOX Drug Screen®, Alere, San Diego, Inc.9975, USA) able to detect amphetamine, methamphetamine, benzodiazepine, methadone, cocaine and cannabis. The sensitivity and specificity of the TST-U test for all RD is 96% or higher, except for methadone for which it reports a sensitivity of 80% [19]. The time interval for detecting RD exposure is up to two days for amphetamines, methamphetamines and cocaine, one to five days for methadone, and days to months for cannabis [20].

The main outcome of the study was the presence and type of RD found in young ACS patients. Other variables of interest were relevant clinical characteristics, the extent of myocardial injury (measured by peak levels of hs-cTnI and CK-MB), and left ventricular function, and the occurrence of MACE.

All variables retrieved were stored anonymously in Castor EDC (www.castoredc.com). Three predefined separate statistical analyses were performed. Firstly, the RD user group was compared to the non-RD user group, secondly and thirdly the cannabis and cocaine users were compared to non-RD users respectively. Because there were only a few cases of other RDs, these and poly-drug users were not included in these sub analyses. All categorical variables and the occurrence of RD in combination with ACS were derived using descriptive statistics expressed as numbers, and frequencies expressed as percentages. To compare these frequencies, the Chi-square and Fisher’s exact tests were used. Continuous variables were expressed either as mean ± standard deviation, or as median (interquartile range), depending on normality. Means between two groups were compared using the independent samples T-test. When assumptions concerning normal distribution were not met, a 10 log transformation was performed. If this did not transform the data into normally distributed data, the Mann-Whitney U test was performed. Univariate logistic regression analysis was performed to identify patient characteristics associated with RD use. When P < 0.1, predefined variables were entered in multivariable logistic regression to obtain adjusted odds ratios. P-values < 0.05 were considered statistically significant. Ethical approval was granted by the OLVG Hospital local ethics committee.

3. Results

Over the three-year study period, 478 patients between 18 and 50 years old were diagnosed with ACS. Of those, 229 (47.9%) had information on drug use reported and were included in the analyses (Fig. 1). Fifty-seven of the included patients (24.9%) reported RD use, most commonly cannabis (n = 37; 16.2%), cocaine (n = 11; 4.8%) or both (n = 6; 2.6%). Only three patients with other types of RD were identified, namely one with methamphetamine and amphetamine co-intoxication, one with methamphetamine intoxication, and one with a self-reported cannabis oil intoxication.

Included patients were mostly male (RD vs. non-RD users: 87.7% vs. 76.7%; P = 0.081) and patients in the RD user group were younger (42.7 ± 19.3 years; P = 0.003) (Table 1). Furthermore, the only cardiac risk factor that significantly differed between the two groups was tobacco use (RD vs. non-RD users: 89.5% vs 59.1%; P < 0.001). Three patients (5.3%) had never smoked, and three patients (5.3%) had quit smoking for more than three months. Five of these six non-smoking patients had at least one other cardiac risk factor. The patient that developed ACS after ingesting cannabis oil had no other risk factors. The extent of the myocardial infarction was larger in the RD user group compared to the non-RD user group with a higher peak hs-cTnT (35.5 ng/L ± 213.8 ng/L vs. 17.8 ng/L ± 162.1 ng/L; P = 0.063) and a significantly higher CK-MB (37 U/L ± 197 U/L) vs. 16 U/L (IQR 4–71 U/L; P = 0.041), respectively. A significantly lower left ventricular function was found in the user group compared to the non-user group (P = 0.007).

In the sub analysis comparing CIMI and cannabis associated myocardial infarction (CAMI) patients, all CIMI patients (n = 11) were male, as were 81.1% (30 out of 37) of CAMI patients. CAMI and CIMI patients were significantly younger (45.3 ± 5.5 vs 42.8 ± 5.3; P = 0.014 and 41.1 ± 6.3; P = 0.016 respectively) compared to non-RD user ACS patients. In addition, tobacco use was higher among CAMI (89.2%; P = 0.028) and CIMI patients (100%; P < 0.001) compared to non-RD users (i.e., 59.1%). There were no significant differences in other cardiovascular risk factors. Also, no significant differences in heart rate, blood pressure, type of ACS and number of coronary arteries involved were observed. Nevertheless, CAMI patients had significantly

![Fig. 1. Flowchart of the inclusion process.](image-url)
higher peak hs-cTnT (30.9 ± 55.0 ng/L vs 17.8 ± 162.2 ng/L; P = 0.044) (Fig. 2) and peak CK-MB (114 ± 118 U/L vs 62 ± 96 U/L; P = 0.021) compared to non-RD users (Fig. 3). Atherosclerotic coronary artery disease was the most common cause of ACS in all groups. For two CAMI patients, one CMI patient and one patient with a co-intoxication of cannabis and cocaine, coronary spasm was the mechanism of the ACS, while no spasms were reported for non-users.

4. Discussion

Recreational drug use was present in approximately 25% of young (<50 years), predominantly male, ACS patients. Cannabis (16.2%) and cocaine (4.8%) or both (2.6%) accounted for the majority of RD used and compared to non-RD users, the cardiac risk profiles of these patients were similarly high. ACS patients reporting or testing positive for RD use were younger at hospital admission compared to non-RD users (42.7 years vs 45.3 years, P < 0.001), suggesting early clinically relevant cardiovascular toxicity caused by RD use. Many of the young ACS patients had cardiovascular risk factors, which is consistent with current evidence [21]. Previous studies found that RD users have a similar risk profile compared to non-users after correction for substance abuse [22, 23], even though CAMI has often been reported in healthy young men.
with low cardiac risk profiles [4,8,13].

However, it is known that RD users smoke more frequently than non-RD users [6], and when compared to a large American retrospective study among ACS patients (< 50 years), the prevalence of smoking (89.5% vs 70.3%) and hypercholesterolemia (75.4% vs 45.7%) among RD users in our population was very high, suggesting a proatherogenic urban lifestyle [23]. Of note, hypercholesterolemia was also high among our non-RD users (68.8%). On the other hand, cocaine may have a direct effect on cholesterol itself. In a study by Escobar et al. cocaine users had low levels of high density lipoprotein cholesterol and high levels of triglycerides, LDL cholesterol, and total cholesterol [24]. Another study on cocaine dependent patients, showed that females had significantly higher triglyceride levels and lower HDL cholesterol, and males had higher triglyceride levels compared to controls [25]. Regarding cannabis effects on cholesterol, a review by Lazarte et al. concluded that high-quality evidence regarding the effect of cannabis on lipoproteins remains sparse and inconsistent [26]. Although the review by Ravi et al. concluded that cannabis users have a higher high-density lipoprotein cholesterol concentrations compared to non-users [27].

Furthermore, the frequency of RD use was nearly 2.5 times higher compared to the previously mentioned American cohort, mostly due to the high prevalence of CAMI (16.1% vs 6.0%) [23]. The prevalence of cocaine use was 5%, which is in concordance with the American cohort [23], but much lower than reported previously in ACS patients in our hospital (i.e., 13.5%) [28], and a national health survey reporting 25% CIMI among ACS patients (<46 years) [29]. This difference might be due to selection bias in either of the studies, as they were all retrospective studies relying on physicians questioning and patients reporting drug use.

In contrast to what is expected after cocaine use, the blood pressure and heart rate were similar regardless RD use. This suggests that the patients were not experiencing excess sympathomimetic stimulation at the time of presentation. At coronary angiography all CIMI patient were diagnosed with coronary artery disease. Even the patients with suspected coronary vasospasm did have some degree of coronary artery disease. However, a previous study found normal coronary arteries in 48% of CIMI patients, suggesting a high incidence of coronary vasospasm [5]. On the other hand, 20% of CAMI patients were not diagnosed with coronary artery disease and 2 of these patients (5.2%) were diagnosed with vasospasm. Several other studies have demonstrated coronary vasospasm on coronary angiography in CIMI patients [4,6].

Compared to non-users, RD-users demonstrated significantly higher

![Fig. 2. High sensitive cardiac troponin (hs-cTn) results among recreational drug (RD) users and non-users (log-transformed).](image-url)
levels of myocardial necrosis biomarkers. When combined with the poorer left ventricular function observed, this suggests that RD users suffered more extensive myocardial injury, resulting in worse cardiovascular outcome [1,2]. DeFilippis et al. also observed higher normalized Troponin values in their CIMI patients but did not report left ventricular function [23].

Due to a high loss to follow-up, and few MACE reported, our study could not demonstrate reliable long-term outcomes for RD users. However, earlier studies reported worse prognosis for RD users including a 5-fold risk of death and a 4-fold risk of MACE for CIMI patients [23]. By contrast, Gupta et al. did not find a significant mortality difference between cocaine users and non-RD users [22].

In addition to cocaine and cannabis, two ST-elevation myocardial infarction patients tested positive for methamphetamine and for amphetamine combined with methamphetamine. Both had hypercholesterolemia, combined with a positive family history for cardiovascular diseases or tobacco use. One study found a small but significant association between amphetamine abuse and an increased ACS risk (OR 1.61; P = 0.0004) [15]. For ACS related to methamphetamine, only a few case reports and case-series have been described to date [18].

Despite a standard protocol to subject ACS patients < 46 years old to a TST-U and extensive attention for recreational drug history taking in our hospital, 52% of patients did not have a RD history recorded and/or TST-U performed. This suggests that physicians often do not appreciate RD use as an important risk factor for ACS. A previously undertaken national Dutch survey among emergency physicians and cardiologists confirms this [30]. Therefore, it is important to increase awareness of the necessity of a thorough drug history and toxicological screening in order to better identify patients at risk. This has the potential to improve risk stratification, management and follow-up, including adequate drug counselling for these patients. This is especially important since drug use is not included in cardiac risk stratification scores and there is ongoing debate whether RD-related ACS should be treated with beta-blockers [31].

5. Limitations

The cross-sectional and retrospective nature of this study is a limitation and although it is expected that missing data regarding RD use were random. In addition, the majority of RD use was identified through self-report. However, when patients do report RD use, this is expected to be reliable [32]. Given that the time of RD use before onset of symptoms

Fig. 3. Creatine kinase-MB results among recreational drug (RD) users and non-users (log-transformed).
was not reported and the time interval for detecting RD exposure is much longer for cannabis (days to months) compared to other RD. Overestimation of cannabis associated ACS is possible. Furthermore, clinical characteristics were not reported in a standard manner and therefore heterogeneity in the collected data occurred. Since OLVG hospital is a cardiac intervention referral center, follow up for many patients (i.e., 40%) was at another hospital resulting in missing data. Therefore, the occurrence of MACE at follow up must be judged carefully. Consent to collect data from the other follow up centers was not granted. Unfortunately, a causal relationship between RD use and ACS cannot be determined based on these data. It has been suggested that cardiac risk factors and increased risk behavior might have influenced the well-established association between cocaine use and ACS [33]. To establish the possible existence of a causal relationship between RD use and ACS, the focus for future studies should be on high quality longitudinal observational studies.

6. Conclusion

Recreational drug use was present in almost 25% of young ACS patients that were evaluated for recreational drug use and was associated with larger myocardial infarctions resulting in poorer left ventricular function as compared to non-users. Additionally, recreational drug users were younger and more often smoked tobacco, compared to non-users. Therefore, increased awareness for recreational drug related ACS and adjusted workup and treatment is important.

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CRediT authorship contribution statement

FG, MK and RR conceived the study, and designed the trial. FG, MK, MK and RR supervised the conduct of the trial and data collection. Medical chart review was performed by MH. FG and MH managed the manuscript, and all authors contributed substantially to its revision. FG drafted the revised manuscript, and all authors contributed substantially to its revision. FG takes responsibility for the paper as a whole.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that has been used is confidential.

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