Cocaine-related sudden death: a prospective investigation in south-west Spain

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Aims
With an estimated 12 million consumers in Europe, cocaine (COC) is the illicit drug leading to the most emergency department visits. The aim of this study was to examine a consecutive series of sudden deaths (SDs) to focus on the prevalence, the toxicological characteristics, and the causes of death in COC-related fatalities.

Methods and results
Prospective case–control study of forensic autopsies was carried out in the time interval November 2003 to June 2006 at the Institute of Legal Medicine, Seville, south-west Spain, with a reference population of 1 875 462 inhabitants. Toxicology included blood ethanol analysis and blood and urine investigation for drugs of abuse and medical drugs. Autopsy was performed according to the European standardized protocol. Ten age- and sex-matched patients who died of violent causes with no antecedents of COC consumption and negative toxicology served as controls. During the study period, 2477 forensic autopsies were performed, including 1114 natural deaths. Among the latter, 668 fulfilled the criteria of SD and 21 (all males, mean age 34.6 ± 7.3 years) resulted to be COC-related (3.1%). Cocaine was detected in 67.1% of the blood (median 0.17 mg/L, interquartile range 0.08–0.42) and in 83.0% of the urine samples (median 1.15 mg/L, interquartile range 0.37–17.34). A concomitant use of ethanol was found in 76.0% and cigarette smoking in 81.0%. Causes of SD were cardiovascular in 62.0%, cerebrovascular in 14.0%, excited delirium in 14.0%, respiratory and metabolic in 5.0% each. Left ventricular hypertrophy was observed in 57.0%, small vessels disease in 42.9%, severe atherosclerotic coronary artery disease in 28.6%, and coronary thrombosis in 14.3%.

Conclusion
Systematic toxicology investigation indicates that 3.1% of SDs are COC-related and are mainly due to cardio-cerebrovascular causes. Left ventricular hypertrophy, small vessel disease, and premature coronary artery atherosclerosis, with or without lumen thrombosis, are frequent findings that may account for myocardial ischaemia at risk of cardiac arrest in COC addicts.

Keywords
Cocaine • Death sudden • Epidemiology • Pathology • Toxicology

Introduction
Cocaine (COC) has a long history of use and abuse, which has increased considerably in the last 20 years overcoming other classical abuse drugs such as heroin. Nowadays, COC is the illicit drug that leads to the most emergency department visits in the USA1 and is also one of the most frequent causes of drug-related death reported by forensic pathologists.2 In Europe, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), COC is a growing public health issue being the second most commonly used illicit substance among the general European population after cannabis. The estimated number of COC consumers is about 12 million Europeans with an overall prevalence of 3.7% of the total adult population (15–64 years). Ever in lifetime experience of COC is reported by more than 5% of the total adult European population in three countries: UK (7.7%), Spain (7.0%), and Italy (6.6%). The prevalence of use of COC is higher among young adults (15–34 years), with around

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Cocaine and sudden death

7.5 million young Europeans (5.4% on average) estimated as having used it at least once in their lifetime. In the year 2007, an estimated 3.5 million (2.4%) Europeans young adults have used COC, with the highest prevalence levels, of over 3%, being found in Spain, Italy, and the UK. 2–4

Cocaine has been linked to a high incidence of cardiac arrhythmias and sudden death (SD) due to cardiovascular or cerebrovascular complications related to its sympathomimetic effects that result in an increase of heart rate, myocardial oxygen demand, temperature, and blood pressure. 5–7

From a pathological viewpoint, acute and chronic abuse of COC has been associated with coronary and myocardium abnormalities. 8 The latter include myocardial infarction, myocarditis, cardiac hypertrophy, and dilated cardiomyopathy. 9–17 As far as vascular involvement is concerned, repeated COC administration may accelerate the development of atherosclerosis in humans and animals. 14,18–20 Moreover, myocardial ischaemia in COC users can be due to vasoconstriction in the setting of normal coronary arteries. 21 Cocaine use has been also associated with intravascular thrombosis due to platelets aggregation and release of thrombogenic substances from the endothelium. 5,12,13,16,19,22–25

Overall, the aetiology of COC-induced myocardial infarction is likely to be multi-factorial, being the result of coronary artery vasoconstriction, accelerated atherosclerosis, and thrombosis. 13

The objective of this study is to assess the prevalence of COC-related fatalities in a consecutive series of SD cases, focusing on their toxicological and pathological characteristics, with special reference to cardiovascular abnormalities associated with COC abuse.

Methods

According to the Spanish Legislation, all cases of violent or suspicious (sudden unexpected) deaths must undergo a medicolegal investigation with the aim of establishing the cause and the manner of death. We carried out a prospective case–control study of all forensic autopsies performed at the Forensic Pathology Service (Institute of Legal Medicine, Seville). The Forensic Pathology Service covers the town of Seville and province, located at the south-west of Spain, with 14,036 km² of extension and a reference population of 1,875,462 inhabitants according to the 2008 census (954,206 women and 921,256 men). The study was performed during a period of 32 months, from 1 November 2003 to 30 June 2006. The cases included in the study were those of SD in which COC compounds were detected by toxicological analysis.

The autopsies were performed, with a post-mortem delay of less than 18 h, according to the Recommendations on the Harmonization of Medicolegal Autopsy Rules produced by the Committee of Ministers of the Council of Europe 26 and the guidelines for the autopsy investigation of cardiac SD from the Association for European Cardiovascular Pathology. 27 Specifically, a protocol was followed which included: clinical antecedents of the case, death scene investigation, body height and weight, waist circumference (WC), and complete macroscopic autopsy with weight and examination of all organs. Histological studies of all organs were performed at the INT-CF in Seville, Spain.

According to the World Health Organization criteria for body mass index (BMI), a person was defined overweight when 25–29.9 kg/m² and obese when ≥30 kg/m². Central obesity, according to WC, was defined if ≥94 cm for men. However, central obesity was considered of high cardiovascular risk if ≥102 cm in men.

Excited delirium (ED) is defined as a syndrome characterized by psychosis or delirium accompanied by agitation and hyperthermia. 28,29

Personal history, cardiovascular risk factors and antecedents of drug abuse and smoke were obtained by interview with the family and from the Provincial Centre for Drug Addictions of Seville (CPD).

Toxicology protocol

At autopsy, blood (obtained from peripheral veins adding potassium oxalate and sodium fluoride as preservatives) and urine were collected for toxicological analyses that were carried out at the National Institute of Toxicology and Forensic Sciences (INT-CF) in Seville. Blood ethanol analysis was performed according to the standardized method of the INT-CF, which consists of head-space gas chromatography with a flame ionization detector. For the analysis of drugs of abuse and medical drugs, a cloned-enzyme donor immunoassay was first performed in blood and urine. Then, independently of the result obtained in the immunoassay, all samples were submitted to a broad toxicological analysis (including medical drugs, like anti-depressives, hypnotics, benzodiazepines, etc., and drugs of abuse, such as COC, opiates, cannabis, and amphetamine-related compounds). The methodology consists of solid-phase extraction with Bond-Elut Certify columns and identification, confirmation and quantification by gas chromatography with nitrogen-phosphorous detector, liquid chromatography with diode-array detector, and gas chromatography–mass spectrometry (GC–MS) in the electronic ionization mode. It must be pointed out that all cases were confirmed by GC–MS. Cocaine consumption was established by the presence of COC itself (limit of detection, LOD, 0.006 mg/L) and/or its major metabolites, benzoylecgonine (BE) (LOD, 0.105 mg/L) and ecgonine methyl ester (EME) (LOD, 0.006 mg/L). Simultaneous consumption of COC and ethanol was determined by the presence of ethylbenzylecgonine (cocaethylene, CE) (LOD, 0.006 mg/L).

Cardiovascular pathology investigation

Heart weights were compared with expected heart weights in relation to body weights according to Kitzman et al. 30 Hearts were examined according to standardized protocol. 27 Myocardial hypertrophy was assessed on the basis of heart weight and left ventricular (LV) wall thickness.

A detailed histological study of the heart was performed at the INT-CF in Seville and at the Institute of Pathological Anatomy, University of Padua Medical School, Italy and included myocardial samples of the ventricles (anterior, lateral and posterior walls of LV, septum, and anterior and posterior walls of right ventricle) and samples of the major epicardial coronary arteries at the proximal, medium, and distal levels as well as of grossly visible stenotic lesions. All sections were stained with haematoxylin and eosin, Masson trichrome, Azan trichrome, and elastic van Gieson. Coronary atherosclerosis was classified by luminal stenosis degree into mild (10–50%), moderate (51–75%), and severe (>75%). Small intramyocardial vessel disease due to medial hypertrophy, intimal thickening, and periadventitial fibrosis was semiquantitatively scored, according to the degree of cross-sectional luminal narrowing, as mild (1–3+), moderate (2–4+), and severe (3+). Myocardial sections were independently reviewed by two pathologists who were blinded as to the source of the specimen. Presence of myocarditis, acute myocardial ischemic damage, myocardial fibrosis, and interstitial oedema were also assessed.

Ten hearts from patients, age and sex-matched, who died from violent causes (seven traffic accidents and three suicides by hanging)
with no antecedents of COC consumption and negative toxicological results, served as controls.

The cause of death was classified according to the results of medicolegal investigation on the basis of clinical antecedents, circumstances of the death, autopsy findings, and toxicology.

**Statistical analysis**

Quantitative parameters are shown as mean ± standard deviation or as median and interquartile range (P25 and P75) for non-Gaussian distributed data. This methodology was performed on the global data and according to case—control groups. The means of quantitative variables from both groups were compared by the Student t-test or the non-parametric U test from Mann—Whitney in case of not normal distributions. When obtaining significant differences, 95% confidence intervals were calculated for means differences. Finally, to analyse the relations between qualitative variables, the χ² test was applied or alternatively the non-asymptotic Monte-Carlo methods for small samples and the Fisher’s exact test. A two-sided value of P < 0.05 was considered significant. Statistical analysis of the data was performed using SPSS for Windows version 15.0.

**Results**

In the study period, 2477 forensic autopsies were performed, including 1363 (55.0%) corresponding to violent deaths (homicides, suicides, or accidents) and 1114 (45.0%) to natural deaths. Among the latter, 668 (60.0%) fulfilled the criteria of SD, 534 (80.0%) being of cardiovascular origin. There were 21 cases of COC-associated SDs, representing 0.8% of total deaths, 1.8% of natural deaths, and 3.1% of SDs, with an annual incidence rate of 1.2 SD/year.

**Demographics and anthropometric data**

Age, personal antecedents, circumstances of the death, and anthropometric data of COC-related SDs are summarized in Table 1.

<table>
<thead>
<tr>
<th>Age, Personal Antecedents, Circumstances of the Death, and Anthropometric Data</th>
<th>COC-Related SDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 21 cases were male, mean age 34.6 ± 7.3 years (range 21–45 years). Ten cases (47.6%) were found dead (eight at home, one in a toilets bar, and one in a parking lot) and 11 (52.4%) presented sudden cardio-respiratory arrest (nine at home, one in the street, and one in the workplace). In these last cases, eight were declared dead on arrival and only three were admitted to hospital in comatose state but presented hypoxic-ischaemic encephalopathy dying some hours later (one cerebral haemorrhage, one ED, and one cardiac death with left ventricular hypertrophy, LVH). In 10 cases (47.6%), death occurred on weekends. Antecedents of drug consumption were present in nine cases (42.8%), absent in 11 (52.4%), whereas no information was obtained in one case. There were antecedents of active smoking in 17 cases (81.0%, heavy smokers in six cases), and ex-smoking in one case, two cases were non-smokers, and in one case no information was obtained. Cardiovascular risk-factors, other than smoking and obesity, were observed in six cases (28.5%), i.e. hypertension, diabetes, and alcoholism, two cases each (9.5%). Mean BMI was 29.90 ± 5.9 kg/m². Obesity was present in 11 (52.3%) cases. The average WC was 98.1 ± 16.2 cm. Central obesity was present in 12 (57.1%) cases.</td>
<td>21 cases of COC-associated SDs, representing 0.8% of total deaths, 1.8% of natural deaths, and 3.1% of SDs, with an annual incidence rate of 1.2 SD/year.</td>
</tr>
</tbody>
</table>

All control subjects were male, mean age 33.5 ± 7.1 years, with the following mean values BMI = 27.5 ± 3.2 kg/m², WC 94 ± 9.1 cm, heart weight 393.6 ± 54.8 g, and LV wall thickness 14.4 ± 2.5 mm.

**Toxicology**

Quantitative toxicological results are presented in Tables 2—4 summarized the results of COC and its metabolites in the blood and urine, respectively.

Ethanol was reported if blood concentration was at or above 0.1 g/L. It was detected in 13 (61.9%) cases and the median concentration was 0.17 g/L, (interquartile range 0.12–0.30 g/L). Ethanol and CE in blood and CE in urine were detected in 16 cases (76.2%). In two of the three cases with ED toxicological analysis gave positive results for ethanol in blood and CE in blood and urine.

Other drugs detected were morphine in three (14.3%), cannabis in two (9.5%), and methylenedioxy-metamphetamine/methylenedioxy-amphetamine in one (4.8%) cases. Benzodiazepines were detected in two (9.5%) cases.

**Pathology**

Causes of death are reported in Table 1. Cardiac causes were found in 13 cases (61.9%), six of whom with severe coronary atherosclerosis (plus luminal thrombosis in three), four with severe LVH, and three without structural abnormalities, being considered arrhythmic SD; cerebral haemorrhage in three cases (14.3%), ED in three cases (14.3%), and pulmonary haemorrhage and metabolic cause (diabetic ketoacidosis) one each.

**Cardiovascular findings**

Main cardiovascular findings are summarized in Table 5.

Mean heart weight was 423.7 ± 73.6 g (range 300–590 g) and mean LV wall was 16.7 ± 2.5 mm. Mean expected heart weight according to Kitzman et al. was 364.3 ± 41.9 g (range 297–460 g) (P < 0.001; confidence interval 25.9–92.3). Mean LV wall thickness in the 10 controls was 14.40 ± 2.6 mm (P = 0.02; confidence interval 0.3–4.3). In nine (42.9%) cases, the heart weight was >450 g. Left ventricular hypertrophy was observed in 12 cases (57.0%), being in four cases (19.0%) the unique relevant cardiac finding.

Acute myocardial infarction was diagnosed in five (23.8%) and a healed myocardial infarction in two cases (9.5%) (Figure 1). Areas of replacement-type myocardial fibrosis were noted in eight cases (38.1%).

Coronary atherosclerosis was observed in 16 cases (76.2%), and in six of them was the main cause of death. Coronary atherosclerosis was severe in six (28.6%, all multivessel), moderate in three (14.3%, two single vessel and one multivessel), and mild in seven (33.3%, four multivessel and three single vessel) (Figure 2). Acute occlusive thrombosis was observed in three cases (14.3%) (Figure 3), one of which showed also a previous re-vascularized organized thrombosis. Thrombosis was precipitated by plaque erosion in three coronary segments and by cap rupture in one segment.

Small vessels disease was observed in 15 cases (71.4%), being moderate/severe in 9 (42.9%) (Figure 4). Similar lesions were not found in the small vessels of the other organs, such as the brain.
Table 1  Demographics, circumstances, and autopsy causes of death in 21 cocaine-related sudden death cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, sex</th>
<th>Personal antecedents</th>
<th>Circumstances of death</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
<th>WP (cm)</th>
<th>Cause of death/ main autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21, M</td>
<td>Smoker (dose unknown)</td>
<td>SCRA after argument in street. Admitted to hospital with brain death dying 12 h later</td>
<td>81</td>
<td>174</td>
<td>26.9</td>
<td>85</td>
<td>Cerebral, subarachnoid haemorrhage</td>
</tr>
<tr>
<td>2</td>
<td>45, M</td>
<td>Schizophrenia, smoker (dose unknown)</td>
<td>Found dead at home</td>
<td>65</td>
<td>168</td>
<td>23.2</td>
<td>78</td>
<td>Cardiac, LVH</td>
</tr>
<tr>
<td>3</td>
<td>43, M</td>
<td>Alcoholic and drug addict, smoker (30 cig/day)</td>
<td>Reduced by police after menacing neighbours, presented SCRA, admitted to hospital with brain death dying 12 h later</td>
<td>105</td>
<td>167</td>
<td>37.7</td>
<td>110</td>
<td>Excited delirium</td>
</tr>
<tr>
<td>4</td>
<td>36, M</td>
<td>Smoker (dose unknown)</td>
<td>Admitted to hospital in comatose state dying 4 h later</td>
<td>96</td>
<td>168</td>
<td>34</td>
<td>107</td>
<td>Cardiac, LVH</td>
</tr>
<tr>
<td>5</td>
<td>34, M</td>
<td>Smoker (dose unknown)</td>
<td>Found dead in a parking lot</td>
<td>79</td>
<td>168</td>
<td>28</td>
<td>94</td>
<td>Cardiac, no cardiac structural findings</td>
</tr>
<tr>
<td>6</td>
<td>39, M</td>
<td>Alcoholic, smoker (dose unknown)</td>
<td>Reduced by the police in agitated state presented SCRA, dead after CPR</td>
<td>97</td>
<td>170</td>
<td>33.5</td>
<td>103</td>
<td>Excited delirium</td>
</tr>
<tr>
<td>7</td>
<td>36, M</td>
<td>Drug addict, smoker (dose unknown)</td>
<td>Found dead at friends home</td>
<td>102</td>
<td>176</td>
<td>32.9</td>
<td>107</td>
<td>Cardiac, LVH</td>
</tr>
<tr>
<td>8</td>
<td>30, M</td>
<td>Cocaine consumer</td>
<td>SCRA after seizure, dead on arrival</td>
<td>74</td>
<td>167</td>
<td>26.6</td>
<td>92</td>
<td>Cardiac, no cardiac structural findings</td>
</tr>
<tr>
<td>9</td>
<td>28, M</td>
<td>Smoker (20 cig/day)</td>
<td>SCRA after chest pain, dead on arrival</td>
<td>59</td>
<td>166</td>
<td>21.4</td>
<td>73</td>
<td>Cardiac, coronary atherosclerosis, acute occlusive thrombosis, acute myocardial infarction</td>
</tr>
<tr>
<td>10</td>
<td>35, M</td>
<td>Hypertension, smoker (dose unknown)</td>
<td>Found dead at home</td>
<td>105</td>
<td>164</td>
<td>39.1</td>
<td>112</td>
<td>Cerebral, subarachnoid haemorrhage, ruptured berry aneurysm of the right medial cerebral artery</td>
</tr>
<tr>
<td>11</td>
<td>45, M</td>
<td>Drug addict, smoker (40 cig/day)</td>
<td>Found dead in a toilets bar with paraphernalia of recent drugs consumption</td>
<td>80</td>
<td>171</td>
<td>27.4</td>
<td>91</td>
<td>Cardiac, no cardiac structural findings</td>
</tr>
<tr>
<td>12</td>
<td>37, M</td>
<td>Smoker (40 cig/day)</td>
<td>SCRA at home, dead after CPR</td>
<td>80</td>
<td>180</td>
<td>24.7</td>
<td>77</td>
<td>Cardiac, coronary atherosclerosis, acute myocardial infarction</td>
</tr>
<tr>
<td>13</td>
<td>26, M</td>
<td>Cocaine consumer, smoker (40–60 cig/day)</td>
<td>Found dead at home</td>
<td>85</td>
<td>169</td>
<td>29.7</td>
<td>101</td>
<td>Pulmonary haemorrhage</td>
</tr>
<tr>
<td>14</td>
<td>28, M</td>
<td>Diabetes Type I, smoker (dose unknown)</td>
<td>SCRA just after smoking cocaine free-base cigarette, dead after CPR</td>
<td>84</td>
<td>166</td>
<td>30.5</td>
<td>102</td>
<td>Cardiac, coronary atherosclerosis, acute myocardial infarction</td>
</tr>
<tr>
<td>15</td>
<td>32, M</td>
<td>Diabetes, schizophrenia, Cocaine and ecstasy consumer, smoker (dose unknown)</td>
<td>Found dead in friends house</td>
<td>64</td>
<td>174</td>
<td>20.8</td>
<td>81</td>
<td>Metabolic death, diabetic keto-acidosis</td>
</tr>
<tr>
<td>16</td>
<td>37, M</td>
<td>Ex-drug addict, Virus B Hepatitis +, smoker (dose unknown)</td>
<td>SCRA at home. Dead after CPR</td>
<td>57</td>
<td>169</td>
<td>20</td>
<td>75</td>
<td>Cardiac, coronary atherosclerosis, acute occlusive thrombosis, acute myocardial infarction</td>
</tr>
<tr>
<td>17</td>
<td>26, M</td>
<td>Anxiety disorder</td>
<td>Reduced by the police in agitated state in the street presented SCRA, dead on arrival</td>
<td>121</td>
<td>177</td>
<td>38.6</td>
<td>124</td>
<td>Excited delirium</td>
</tr>
<tr>
<td>18</td>
<td>25, M</td>
<td>Smoker (15 cig/day)</td>
<td>Found dead at home</td>
<td>103</td>
<td>175</td>
<td>33.6</td>
<td>102</td>
<td>Cardiac, LVH</td>
</tr>
<tr>
<td>19</td>
<td>34, M</td>
<td>Sleep apnoea syndrome, smoker 40–60 cig/day</td>
<td>Found dead while sleeping</td>
<td>138</td>
<td>181</td>
<td>39.1</td>
<td>133</td>
<td>Cardiac, coronary atherosclerosis</td>
</tr>
</tbody>
</table>
lungs, liver, and kidneys. We did not observe any relationship between the degree of epicardial coronary artery atherosclerosis and the small intramyocardial vessels disease. Myocarditis, according to Dallas criteria, was observed only in one case (4.7%), who presented an inflammatory infiltrate consisting mainly of eosinophils and some lymphocytes.

**Controls**

Histological study showed a moderate atherosclerosis only in one case (10%), mild atherosclerosis in five (50.0%), and normal coronary arteries in four (40.0%). Only mild and patchy interstitial fibrosis was observed in seven controls (70%). A mild and localized medial hypertrophy of small intramyocardial vessels was observed only in three cases (30.0%) (Monte-Carlo method \( P = 0.038 \)). Acute and chronic ischaemia and myocarditis were never observed.

**Discussion**

Cocaine-associated deaths are not-so-rarely events, since they represent 0.8% of the total forensic autopsies and 3.1% of SD autopsies prospectively carried out in south-west Spain. Although cerebrovascular, respiratory and metabolic causes can be involved, COC-related SDs are mainly due to cardiovascular complications. In fact, cardiac hypertrophy, obstructive small vessel disease, and severe premature coronary artery atherosclerosis, with or without thrombosis, are frequent findings, which may account for myocardial ischaemia and cardiac arrest associated with the use of COC. These data underline the need to use a complete uniform protocol, always including toxicology investigation of the blood and urine for drugs of abuse, when performing SD autopsies.

Our data are consistent with the previous studies on COC-associated deaths, reporting a male predominance, an average age in the mid-thirties, employed users, death at home and mainly on weekends, \(^{1,7,32,33}\) and are in contrast with heroin-related deaths, where there is no weekend peak, reflecting the high proportions of unemployed users in this population. \(^{34}\) Previous studies have reported that in cases of cardiac arrest associated with the use of COC, patients are more likely to survive hospitalization with complete neurological recovery. \(^{35}\) Once hospitalized, COC abusers who present with myocardial infarction are prone to better outcome when compared with age-matched controls. \(^{36}\) However, in our study, only three cases (14.3%) were hospitalized but presented hypoxic-ischaemic encephalopathy dying some hours later.

**Cocaine concentrations**

Wide variations in COC and metabolites are observed, as previously reported both in living patients and in autopsy cases. \(^{14,33,34,37,38}\) In the absence of ethanol consumption, BE and EME are the main COC metabolites in the blood and urine. The half-lives of both metabolites are much longer than the half-life of parent drug. Ecgonine methyl ester has a half-life of about 4 h, whereas the half-life of BE is about 6 h and can be detected 24 h after COC use. \(^{10}\)

In our study, blood analysis gave positive results for COC in 67.0% of cases, with a median concentration of 0.17 mg/L, which is higher than that reported by Darke et al. \(^{33}\) in COC-related deaths (0.10 mg/L), but lower than those reported by Jenkins et al. \(^{37}\) in COC-associated deaths (0.3 mg/L) and by Blaho et al. \(^{38}\) in patients attended in an emergency department. Benzoylecgonine was found in 71.0% of blood samples, with a median concentration of 3.7 mg/L, much higher than those reported by Darke et al. \(^{33}\) (0.40 mg/L) and by Jenkins et al. \(^{37}\) (2.5 mg/L). Something similar occurs with EME, which was detected in 67.0% of the cases with a median concentration of 4.1 mg/L, value that is considerably higher than 0.21 mg/L reported by Blaho et al. \(^{38}\) These variations are explained by the pharmacokinetic of the drug that depends on multiple factors, which may be related to the drug (post-mortem interval, route of administration, post-mortem stability, redistributitive process in different organs, concomitant use of other substances), or to the individual (BMI, acute or chronic use, underline health, age, sex). Our data are in agreement with the previous studies, indicating that COC concentrations should be always interpreted cautiously. Any amount of the drug can be considered to have the potential for toxicity due to the fact that some patients have poor outcomes with relatively low blood concentrations, whereas others tolerate large quantities without consequences. \(^{30,38–40}\)

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**Table 1 Continued**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, sex</th>
<th>Personal antecedents</th>
<th>Circumstances of death</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
<th>WP (cm)</th>
<th>Cause of death/ main autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>45, M</td>
<td>Hypertension. Ex-smoker</td>
<td>SCRA arrest after witness a familiar argument in the workplace. Dead after CPR</td>
<td>78</td>
<td>157</td>
<td>31.7</td>
<td>113</td>
<td>Cardiac, coronary atherosclerosis, recanalized thrombosis and acute occlusive thrombosis, acute and healed myocardial infarction</td>
</tr>
<tr>
<td>21</td>
<td>45, M</td>
<td>Ex-drug addict. Liver cirrhosis</td>
<td>Found dead at home</td>
<td>85.4</td>
<td>168</td>
<td>30.3</td>
<td>101</td>
<td>Cerebral, intraventricular haemorrhage</td>
</tr>
</tbody>
</table>

BMI, body mass index; CPR, cardio pulmonary resuscitation; cig, cigarette; LVH, left ventricular hypertrophy; M, male; SCRA, sudden cardio-respiratory arrest; WP, waist perimeter.

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J. Lucena et al.
Concomitant cocaine–ethanol abuse

Up to 75.0% of COC users simultaneously drink ethanol because it prolongs and enhances the euphoric effects of the drug. Concomitant COC and ethanol consumption determines the production of an active metabolite, CE, which is more toxic than COC or ethanol alone and has been associated with a 25-fold increase in SD. In our study, ethanol and/or CE were detected in 76.0% of COC-related SDs, indicating a simultaneous COC and ethanol abuse in the majority of cases.

However, other authors support the hypothesis that COC-using decedents are more likely to test positive for morphine than ethanol. In our series, other drugs of abuse were detected in a...
of patients with COC-related intracerebral haemorrhage have an underlying vascular abnormality, as confirmed by our case with a ruptured berry aneurysm.

Two main cardiac structural abnormalities have been observed in our series of COC addicts, i.e. cardiac hypertrophy and atherosclerotic coronary artery disease.

Chronic COC use has been associated with the development of cardiac hypertrophy in humans. In our series, LVH was observed in 57.0% of cases, being in 19.0% the unique relevant cardiac finding. Different hypothesis have been postulated to explain LVH in COC abusers, such as the transient elevation of systolic blood pressure after COC use or the direct stimulation of myocardial α-adrenergic receptors. Henning et al. in experiments with rats, suggested that COC can cause cardiac hypertrophy by protein kinase C- and calcium/calmodulin kinase II-dependent mechanisms, which lead to increase adult cardiomyocyte protein expression.

Some controversy does exist about the heart weight in COC addicts. However, increased heart weight is a recognized consequence of ‘chronic’ COC use and this may provide a predisposing substrate for myocardial ischaemia. Virmani et al. reported an increased heart weight in only 20.0% of COC-associated deaths. However, the young age (mean 29 ± 6 years) and the sex differences (29 males and 11 females) could explain the discrepancies with our results. On the other hand, Dressler et al. found that 50.0% of COC addicts, with a mean age of 32 years (range 15–50; 17 males and 5 females), have heart weights ≥450 g. Karch et al. also described a highly significantly increased in heart weight in 48 males COC-related deaths when compared with 51 age and sex-matched controls (mean 426 vs. 369 g, P = 0.009). In our series, the heart weight was >450 g in 42.9% of cases, and the mean heart weight was significantly increased when compared with controls.

A greater frequency of severe coronary atherosclerosis in COC-associated SDs than that expected for a population with a mean age of 34 years was also found, being observed in nearly one-third of cases, all with a multivessel distribution. Signs of acute ischaemia were detected in 24.0% of cases and healed myocardial infarction in 9.0%. Dressler et al. found a 36.0% of severe coronary atherosclerosis in autopsy cases of COC addicts and Mittelman and Wettl a 62.0% of prevalence in COC addicts who died suddenly. In vitro studies support the role of COC in increasing endothelial cell permeability, a factor that may explain the accelerated atherosclerosis observed in some COC abusers. In this study, the toxicity of CE was found to be equipotent to COC, whereas BE and EME had little or no effect on endothelial cell membrane permeability. Our results support this hypothesis, because half of the cases with severe atherosclerosis gave positive results for CE in the blood and/or urine. Noteworthy, the coronary plaques of young COC-related SD victims have the features of the so-called ‘accelerated atherosclerosis’, i.e. an exuberant fibrointimal proliferation of smooth muscle cells, with scarce or absent lipid core. Repeated COC administration could lead to endothelial damage, possibly mediated by vasoconstriction, thus promoting the development of premature coronary atherosclerosis both in humans and in animals.

Several studies have documented myocardial ischaemia associated with COC use, even in the setting of normal coronary

### Table 3 Toxicological results of cocaine and metabolites in the blood in 21 cocaine-related sudden death cases

<table>
<thead>
<tr>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/21</td>
<td>66.7</td>
<td>0.08</td>
<td>0.17</td>
<td>0.42</td>
<td></td>
<td>15/21</td>
<td>71.4</td>
<td>0.90</td>
<td>3.70</td>
<td>7.98</td>
<td></td>
</tr>
<tr>
<td>4/21</td>
<td>19.0</td>
<td>0.02</td>
<td>0.06</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COC, cocaine; BE, benzoylecgonine; EME, ecgonine methyl ester; CE, cocaethylene.

### Table 4 Toxicological results of cocaine and metabolites in urine in 18 cocaine-related sudden death cases

<table>
<thead>
<tr>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
<th>Cocaine</th>
<th>Benzoylecgonine</th>
<th>Ecgonine methyl ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/18</td>
<td>83.3</td>
<td>0.37</td>
<td>1.15</td>
<td>17.34</td>
<td></td>
<td>18/18</td>
<td>100</td>
<td>8.41</td>
<td>94.18</td>
<td>128.40</td>
<td></td>
</tr>
<tr>
<td>14/18</td>
<td>66.7</td>
<td>0.11</td>
<td>4.10</td>
<td>14.48</td>
<td></td>
<td>11/18</td>
<td>61.1</td>
<td>0.16</td>
<td>0.44</td>
<td>4.63</td>
<td></td>
</tr>
</tbody>
</table>

COC, cocaine; BE, benzoylecgonine; EME, ecgonine methyl ester; CE, cocaethylene.

minor proportion, being cannabis the most frequent (24.0% of cases), whereas opiates were found in 14.0%. On the basis of morphine/codeine ratios, we can consider that these persons consumed heroin.

### Cocaine acute mechanisms

Locally, COC acts as anaesthetic because of its ability to inhibit membrane permeability to sodium channel, thereby reducing or blocking the initiation and transmission of electrical signals. In the myocardium, this action determines an electrocardiographic pattern similar to that observed in the Brugada syndrome. Moreover, in the range of concentrations achieved in humans, COC suppresses the cardiac human ether-à-go-go related gene potassium channel thus providing an additional mechanism for COC-induced arrhythmias and SD. Cocaine inhibits the pre-synaptic reuptake of noradrenalin, dopamine, and serotonin. Alterations related to dopamine and serotonin are mainly responsible for the psychological and behavioural manifestations.

### Cerebrovascular and cardiovascular abnormalities in cocaine-related sudden deaths

They represent the most relevant findings in our series of COC-related SD. Ischaemic and haemorrhagic stroke associated with COC abuse have been extensively reported in the medical literature. Noteworthy, previous studies indicate that 78.0% of patients with COC-related subarachnoid haemorrhage and 48.0%
arteries, and intravascular thrombosis in both coronary and peripheral arteries has been reported. Evidence suggests that COC activates platelets aggregation and stimulates the release of thrombogenic substances from the endothelium.\footnote{\textsuperscript{5,12,13,18,19,22–25,56}} In cases with no or minimal fibrointimal proliferation, the thrombosis is usually attributed to coronary artery spasm causing focal endothelial injury and platelet aggregation.\footnote{\textsuperscript{21}} However, in our series, acute occlusive thrombosis was always found in the setting of an atherosclerotic plaque, mostly complicated by a mechanism of endothelial erosion.

Noteworthy, 81.0\% of COC addicts have antecedents of concomitant cigarette smoking, 29.0\% being heavy smokers. Cigarette smoking has long been associated with coronary artery disease secondary to both endothelial dysfunction and platelet aggregation.\footnote{\textsuperscript{27}} Furthermore, oxygen demand increases much more with the combination of COC ingestion and cigarette smoking than with either one alone.\footnote{\textsuperscript{28}} Thus, the association of COC and cigarette smoking may be considered as a ‘lethal cocktail’ that promotes the development of premature accelerated coronary atherosclerosis.

An additional interesting observation is the high prevalence in our series of small vessel disease, consisting of media hypertrophy, intimal proliferation, and periadventitial fibrosis,\footnote{\textsuperscript{59}} accounting for narrowed lumen in 42.9\% of the cases. An endomyocardial biopsy study in patients with COC-induced chest pain already demonstrated marked thickening of small coronary vessels, suggestive of previous arterial injury as a result of repetitive vasoconstriction.\footnote{\textsuperscript{60}} Cocaine-induced vasospasm in normal and atherosclerotic coronary artery has been reported in several animal and human studies.\footnote{\textsuperscript{2,10,21,61,62}} However, in our cases, we did not observe any correlation between the degree of atherosclerosis and that of small vessel disease.

Finally, myocarditis has been reported to occur as an adverse reaction to various drugs including COC. In our series, it was detected only once, a patient who presented signs of eosinophilic myocarditis, most probably as a hypersensitivity reaction to COC or to its metabolites.\footnote{\textsuperscript{10,14}}

\textbf{Study limitations}

Like previous studies, the one herein reported is based on COC-related SDs and this may result in a bias on the frequency

<table>
<thead>
<tr>
<th>Case</th>
<th>Heart weight (g)</th>
<th>LVW thickness (mm)</th>
<th>LVH</th>
<th>CAD stenosis / extent</th>
<th>Type of plaque</th>
<th>Coronary thrombosis</th>
<th>Myocardial infarction</th>
<th>Small vessel disease</th>
<th>Fibrosis</th>
</tr>
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<tbody>
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<td>1</td>
<td>375</td>
<td>17</td>
<td>+</td>
<td>10%, SV</td>
<td>Fibrocellular</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>495</td>
<td>18</td>
<td>+</td>
<td>30%, SV</td>
<td>Fibrocellular</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>455</td>
<td>17</td>
<td>+</td>
<td>60%, MV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>460</td>
<td>23</td>
<td>+</td>
<td>50%, MV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>360</td>
<td>14</td>
<td>0</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>405</td>
<td>15</td>
<td>0</td>
<td>60%, SV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>458</td>
<td>17</td>
<td>+</td>
<td>30%, MV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>370</td>
<td>15</td>
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<td>20%, MV</td>
<td>Fibrocellular</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>300</td>
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<td>60%, MV</td>
<td>Fibrocellular</td>
<td>Acute occlusive thrombosis (LAD)</td>
<td>Acute myocardial infarction</td>
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<td>–</td>
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<tr>
<td>10</td>
<td>380</td>
<td>20</td>
<td>+</td>
<td>40%, MV</td>
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<td>–</td>
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<td>–</td>
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<tr>
<td>11</td>
<td>360</td>
<td>15</td>
<td>0</td>
<td>10%, SV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>12</td>
<td>370</td>
<td>16</td>
<td>+</td>
<td>80%, MV</td>
<td>Fibro-atheromasic calcified</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
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<tr>
<td>13</td>
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<tr>
<td>14</td>
<td>420</td>
<td>16</td>
<td>+</td>
<td>80%, MV</td>
<td>Fibrocellular</td>
<td>–</td>
<td>Acute myocardial infarction</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>395</td>
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<td>0</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>335</td>
<td>15</td>
<td>0</td>
<td>80%, MV</td>
<td>Fibro-atheromasic</td>
<td>Acute occlusive thrombosis (RCA)</td>
<td>Acute myocardial infarction</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>470</td>
<td>20</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>460</td>
<td>17</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>540</td>
<td>14</td>
<td>0</td>
<td>75%, MV</td>
<td>Fibro-atheromasic calcified</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>525</td>
<td>19</td>
<td>+</td>
<td>95%, MV</td>
<td>Fibro-atheromasic calcified</td>
<td>Re-canalized old thrombosis (RCA), acute thrombosis (LAD)</td>
<td>Acute and healed myocardial infarction</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>21</td>
<td>590</td>
<td>20</td>
<td>+</td>
<td>90%, MV</td>
<td>Fibro-atheromasic</td>
<td>–</td>
<td>Healed myocardial infarction</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; LAD, left anterior descending coronary artery; LVH, left ventricle hypertrophy; LVW, left ventricular wall; SV, single vessel; MV, multivessel; RCA, right coronary artery; –, negative; +, mild; ++, moderate; ++++, severe.
and amount of coronary artery disease among all COC users. On the other hand, a great percentage of the cases were also heavy cigarette smokers and obese. Furthermore, some cases presented other cardiovascular risk factors such as hypertension, diabetes, and alcoholism. For this reason, we cannot exclude that coronary disease may be the final result of the concomitant effects of COC use and other risk factors.

**Figure 1** Myocardial infarction in cocaine addicts. (A) Acute transmural antero-septal myocardial infarction, about 10 days old, visible on gross examination, precipitated by occlusive coronary thrombosis (Case 9, 28 years old); (B) histology showing myocyte lysis (Case 14, 28 years old) (haematoxylin–eosin); (C) histology showing healed myocardial infarction with replacement-type fibrosis (Case 20, 45 years old) (haematoxylin–eosin).

**Figure 2** Atherosclerotic plaques of the coronary arteries without luminal thrombosis in cocaine addicts. (A) Fibro-atheromasic plaque with calcification and cholesterol clefts in LAD and first diagonal branch determining an 80% reduction in arterial lumen (Case 12, 37 years old) (trichrome stain); (B) Fibro-atheromasic plaque in LAD determining an 80% reduction in arterial lumen (Case 14, 28 years old) (haematoxylin-eosin); (C) Fibro-atheromasic calcified plaque in LAD determining a 95% reduction in arterial lumen (Case 20, 45 years old) (haematoxylin-eosin).
Conclusions

Cocaine is a commonly used illicit drug that not-so-rarely leads to SD, being found in 3.1% of consecutive SDs autopsies. As it is pointed out by the EMCDDA, COC abuse represents a growing public health issue in Europe and our findings underline the need to use a uniform protocol when performing SD autopsies, always including toxicology investigation of the blood and urine for illicit drugs. The cause of death in COC addicts is cardio-cerebrovascular in the majority of cases. Cardiac hypertrophy, obstructive small vessel disease, and premature coronary artery atherosclerosis, with or without lumen thrombosis, are the main

**Figure 3** Coronary lumen thrombosis in cocaine addicts. (A) Acute thrombosis of the RCA due to endothelial erosion upon an eccentric fibro-atheromasic plaque with thick fibrous cap (Case 16, 37 years old) (trichrome stain); (B) Close-up of the previous showing fibrin deposition on the intimal surface of atherosclerotic plaque (haematoxylin–eosin); (C) Same case of (A and B) showing thromboembolism in distal branches (haematoxylin–eosin); (D) Acute thrombosis of the LAD due to endothelial erosion of an eccentric non-critical fibro-atheromasic plaque (Case 9, 28 years old) (trichrome stain); (E) acute thrombosis due to fibrous cap rupture of a fibro-atheromasic plaque in the LAD (Case 20, 45 years old) (trichrome stain); (F) recanalized old thrombosis of the RCA [Case 20, same of (E), 45 years old] (haematoxylin–eosin).
structural abnormalities which may account for myocardial ischaemia and arrhythmic cardiac arrest.

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References


