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The relationship between polysubstance abuse and myocardial histopathological lesions

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ABSTRACT

Background: Substance abuse can affect most organs of the body, with the cardiovascular system being a primary target. Objective: This study aims to investigate the association between myocardial lesions and polysubstance use status. Subjects and Methods: Subjects and Methods: A total of fifty-five deceased individuals were examined at the Ho Chi Minh City Forensic Medicine Center, all of whom tested positive for substance abuse through blood tests. Myocardial injuries were assessed using Hematoxylin and Eosin (HE) and Trichrome Masson histopathology specimens. Results: The study found that all cases (100%) involved morphine use, with 65.5% involving the concurrent use of two substances and 7.3% involving the concurrent use of three substances. The most common myocardial lesions observed were fibrotic proliferation (72.7%) and ischemia-related lesions (34.5%). Conclusion: The study demonstrates a significant association between polysubstance abuse and the risk of fibrogenesis and fat infiltration in the myocardium. These findings underscore the importance of addressing polysubstance abuse in cardiovascular health interventions.

Keywords: *Polysubstance use, substance abuse, myocardial lesion*

1. INTRODUCTION

Substance abuse (SA) is a significant public health concern worldwide, characterized by the use of substances that alter normal physiological functions and can lead to dependence and addiction [1]. In 2015, approximately 450,000 individuals worldwide died due to drug use, with 167,750 cases directly attributable to drug consumption[1,2]. SA affects various organ systems, particularly the cardiovascular system, where it can cause serious complications [1 - 2]. Up to 32% of heroin users exhibit cardiac abnormalities [2]. Chronic abuse of illicit drugs, particularly opioids, poses a prolonged risk of cardiac dysfunction [3]. Previous studies have identified a range of cardiac abnormalities associated with substance abuse, including ventricular hypertrophy, myocardial fibrosis, cardiomyocyte hypertrophy, necrosis, perivascular hemorrhage, anemia and inflammatory cell infiltration [4 - 8]. While much research has focused on the rela tionship between specific substances and cardiovascular diseases, findings have been inconsistent. Previous studies employing conventional histology did not show significant differences between drug addicts and control groups. However, there are reports indicating that although heart abnormalities such as myocarditis and focal myocardial fibrosis are common, these conditions do not correlate with morphine or 6-MAM blood concentrations [5].

Previous research primarily focused on the relationship between opiates or opioids and cardiovascular diseases. For instance, Milroy et al. (2011) and Dettmayer et al. (2009) reported that stimulant abuse (e.g., cocaine and amphetamines) is associated with increased myocardial fibrosis, whereas intravenous opioid abuse is linked to long-term anatomical changes in the myocardium [4 - 5]. Chronic intravenous opioid users often display abnormal cardiac anatomy, which is a major cause of sudden death. Numerous studies have established a correlation between polysubstance use, overdose, and an elevated risk of other cardiac injuries, such as myocardial fibrosis and fat infiltration, which

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increase the risk of sudden death [6 - 8].

Despite extensive research on substance abuse and cardiovascular health, there is a lack of studies examining the histological changes of the myocardium in substance abusers, particularly in Vietnam. Understanding these changes is crucial for developing effective interventions and reducing the risk of sudden cardiac death in substance users. This study aims to investigate the morphological changes in myocardial tissue and the long-term effects of polysubstance abuse on the myocardium. By conducting post-mortem examinations of individuals with confirmed substance abuse, we seek to analyze the relationship between pathological cardiac injuries and polysubstance use status.

2. SUBJECTS AND RESEARCH METHODS

2.1. Study Subjects

The study was conducted from March 2019 to December 2019, included cases of death within the jurisdiction of Ho Chi Minh City, which underwent organ autopsy at the Forensic Medicine Center, and tested positive for substance abuse during toxicological examination.

Inclusion Criteria:

Cases of death involving drug use, as determined by the Forensic Medicine Center, with a decision to undergo heart autopsy.

Exclusion Criteria:

Cases were excluded if they lacked administrative information, had degraded samples, or if the samples and tissue blocks were of insufficient quality for diagnosis.

2.2. Study Design and Methodology

The study design was a cross-sectional study, aiming to assess the relationship between myocardial lesions and polysubstance use status. The entire population of 55 cases within the jurisdiction of Ho Chi Minh City, who underwent organ autopsy at the Forensic Medicine Center and tested positive for substance abuse during toxicological examination, was included in the study. Information on age, gender, and toxicological examination results was obtained from forensic records. Heart samples were dissected according to the guidelines of the European Society of Cardiovascular Pathology (2017). Selected sections included areas with lesions observed macroscopically and tissue samples representing four myocardial regions (left ventricle, right ventricle, atrioventricular node, interventricular septum). If lesions could not be observed macroscopically, representative samples from the four regions were taken. Histopathological samples were collected using Hematoxylin & Eosin (HE) staining and Trichrome Masson staining, and the results were interpreted. The collected data were analyzed using SPSS 20.0 statistical software. A p-value of < 0.05 was considered statistically significant.

3. RESULTS

3.1. General Characteristics of Study Participantss

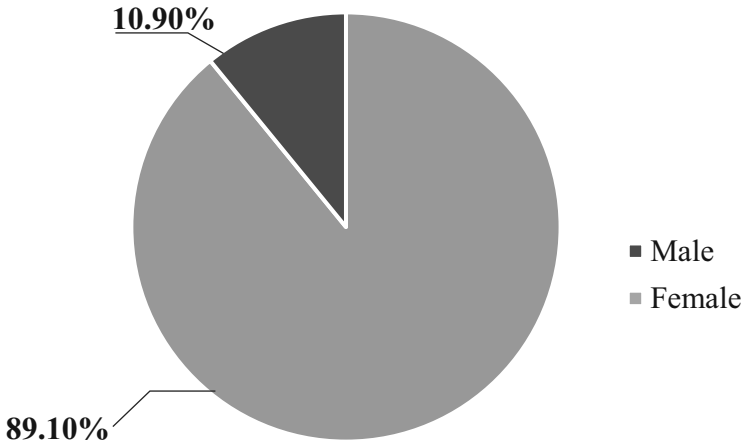


Figure 1. Gender distribution of study participants

Comment: Figure 1 illustrates a predominant male representation, accounting for 49 out of 55 participants (89.1%), with a male-to-female ratio of approximately 9:1

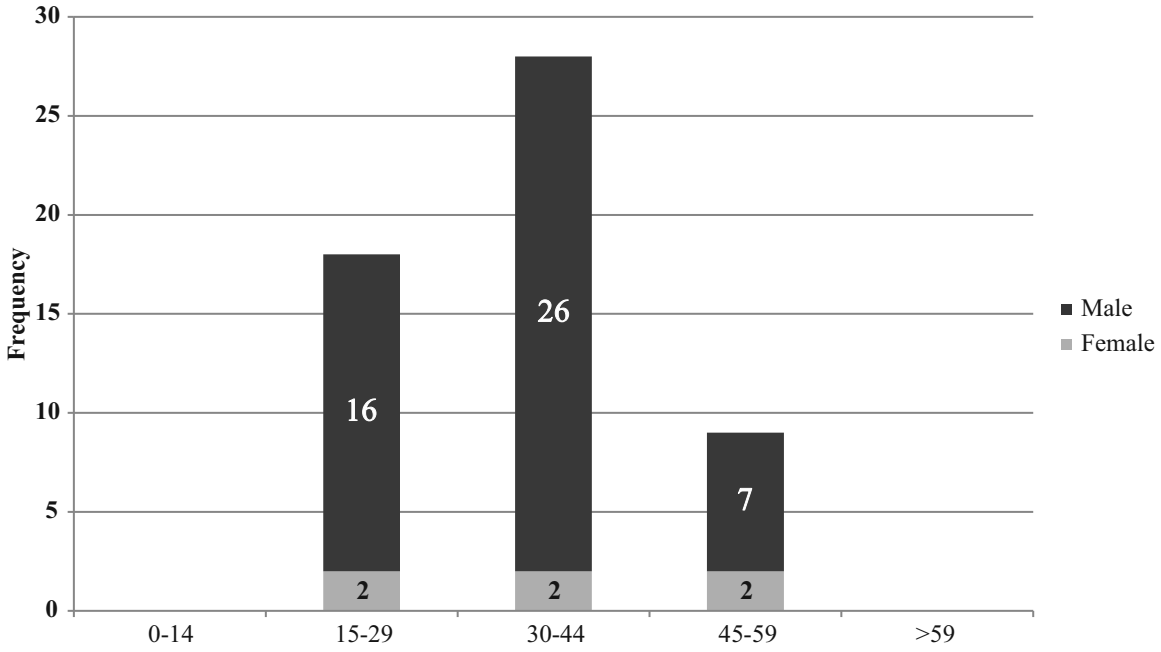


Figure 2. Frequency of victims by age group

Comment: The most common age group is 30 - 44 (28 cases; 50.9%), followed by the age group 15 - 29 with 18 cases (32.7%). The least encountered age group is 45 - 59 with 8 cases (16.4%). There were no recorded cases in the age groups 1 - 14 and 60 years and older.

3.2. Substance profile

3.2.1. Substances Detected in Victims' Blood

Table 1. Substances Detected in Victims' Blood

Substance	N	%
Morphine	55	100
Codein	39	70.9
Methamphetamine	4	7.3
MDMA	1	1.8

Comment: All 55 surveyed cases were found to have used morphine (100%). Codeine was detected in the blood of 39 cases (70.9%), while methamphetamine was found in the blood of 4 cases, accounting for 7.3%. One case (1.8%) tested positive for MDMA.

3.2.2. Number of Substances detected in blood

Table 2. Number of Substances detected in blood

Number of Substances	N	%
1	15	27.3
2	36 (35cod+1meth)	65.5
3	4 (4cod+ 3meth+1 MDMA)	7.3
Total	55	100

Comment: There were 15 cases (27.3%) where only one drug (morphine) was used. Thirty-six cases (65.5%) involved the use of two drugs; among them, 35 cases used morphine and codeine, and 1 case used morphine combined with methamphetamine. Four cases (7.3%) involved the use of three drugs; among them, 3 cases used morphine, codeine, and methamphetamine, and 1 case used morphine, codeine, and MDMA.

3.3. Histopathological Diagnosis

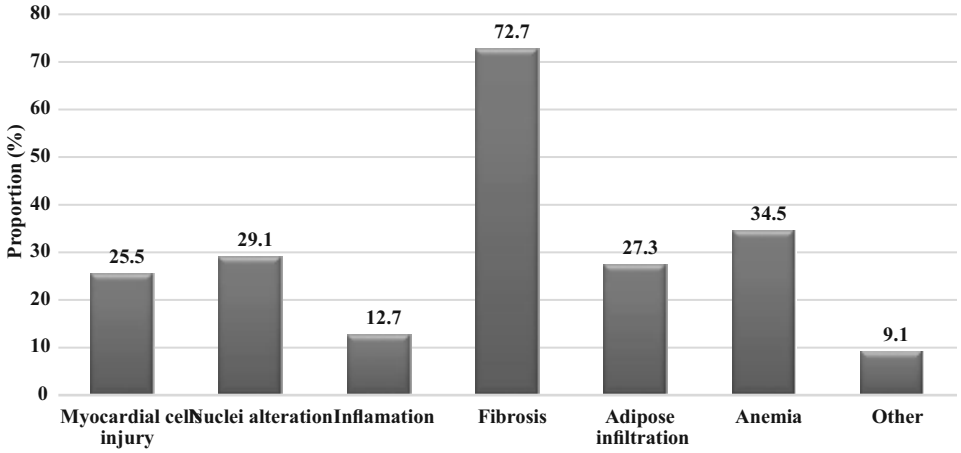


Figure 3. Cardiac muscle injury groups on anatomical pathology

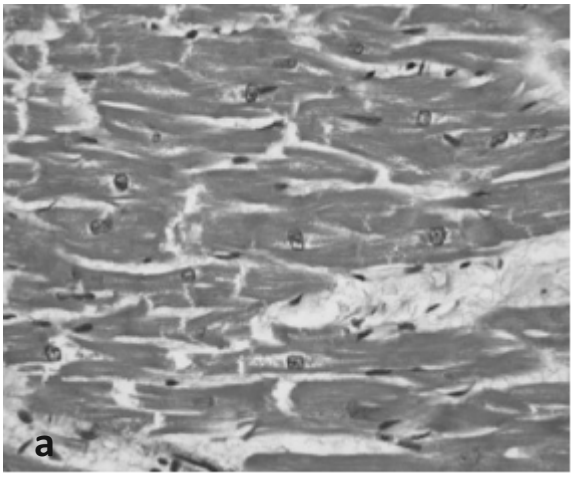
Comment: Our study observed that the most common injury is hypertrophic fibrosis, present in 40 out of 55 cases (72.7%). Among them, simple fibrosis around the vessels accounts for 25 out of 55 cases (45.5%), with fibrosis between the fibers of the heart usually being subtle. Nineteen cases showed injuries associated with ischemia. Only one case (1.8%) exhibited intramyocardial bleeding (associated with MDMA use).

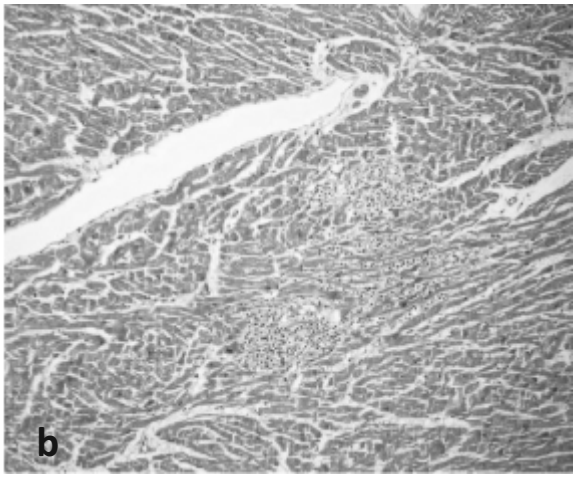
3.4. Correlations between polysubstance use and cardiac muscle injury

Table 3. Correlations between polysubstance use and cardiac muscle injury

		Morphin use only	Polysubstance use	p_value	CI95%
Myocardical hypertrophy	No	14	27	0.081 (Fisher Exact)	0.798 - 56.945
	Yes	1	13		
Inflamation	No	5	2	0.013 (Fisher Exact)	0.018 - 0.625
	Yes	10	38		
Fibrosis	No	8	7	0.015 (Fisher Exact)	1.466 - 9.801
	Yes	7	33		
Fat infiltration	No	14	26	0.045 (Fisher Exact)	1.896 - 63.451
	Yes	1	14		
Anemia	No	10	26	0.908 (Chi Square)	0.307 - 3.777
	Yes	5	14		

Comment: There is a statistically significant association between polysubstance use and inflammatory lesions, fibroproliferation and fatty infiltration in myocardial tissue (p-value <0.05).





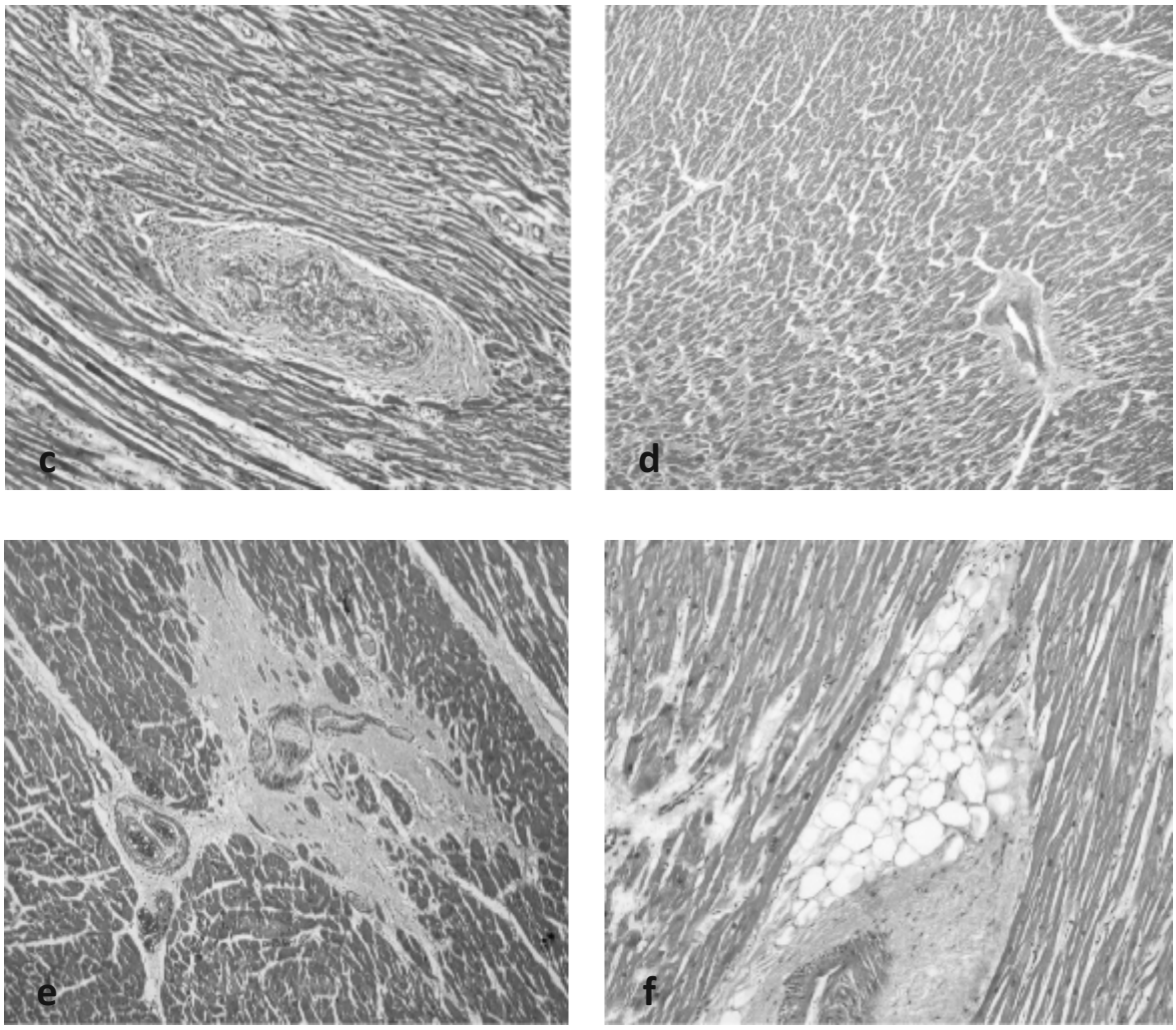


Figure 4. a) Nuclear alterations (H&E, x200).
b) Infiltration of granulomatous inflammation in myocardial tissue (H&E, x100).
c) Diffuse myocarditis (H&E, x200).
d) Fibrosis around vessels and in interstitial tissue (H&E, x200).
e) Fibrosis around typical vessels (Trichrome-Masson, x200).
f) Fibrosis and adipose infiltration around vessels (H&E, x200).

4. DISCUSSION

4.1. Drugs Detected in the Victims' Blood

In our study, all 55 cases tested positive for morphine, with 39 cases (70.9%) also positive for codeine, 4 cases (7.3%) for methamphetamine, and 1 case (1.8%) for MDMA.

The simultaneous use of multiple addictive substances is a well-documented cause of overdose deaths. A study of 329 heroin users in Sydney, Australia, reported that 68% experienced frequent overdoses and 62% combined heroin with other depressants. Another survey found that 52% of heroin users co-administered heroin with central nervous system depressants, primarily benzodiazepines (33%) and alcohol (22%)[2].

Toxicological analyses of 87 drug-related deaths among newly released prisoners in Scotland revealed that 71% had evidence of multiple drug use. A study involving 1,018 injecting drug users in Scotland indicated that 27% had overdosed and required hospitalization at least once within a year, with 19% overdosing on a single drug and 40% on six or more drugs. Among 124 young injecting drug users in San Francisco, 48% reported a history of overdose, and those who injected speedball (a combination of cocaine and heroin) had a 2.6 times higher risk of

overdose. Additionally, a study of 55 cases where in-dividuals witnessed fatal drug overdoses found that 58% of the deceased had been using multiple substances simultaneously[2-7].

In the majority of cases, fatalities due to drug use result from the synergistic effects of multiple toxic substances. Polydrug toxicity is commonly observed in studies of drug-related mortality, underscoring the prevalence of polypharmacy among individuals with substance use disorders. Research on methamphetamine and codeine-related fatalities indicates that opiates are frequently present in the majority of subjects [8]. Opiate toxicity is a prominent feature in stimulant-related deaths, suggesting an in-creased risk of fatal overdose when stimulants are combined with opiates. Codeine is often co-administered with morphine. In a 2010 study by Darke et al., the co-administration rate was 77.9%, which aligns with Seltenhammer (2013) and Kaye (2008), reporting rates of 76.3% and 72.2%, respectively, for subjects using codeine. Previous studies have demonstrated that combining methamphetamine with alcohol, cocaine, or opiates significantly increases the risk of toxicity [2-5].

Our study's results align with previous findings, showing that polysubstance use is common among drug users. Only 27.3% of cases involved the use of a single drug, morphine, while 65.5% involved the concurrent use of two drugs, primarily morphine and codeine. Additionally, 4 cases (7.3%) involved the simultaneous use of three substances.

However, some authors have reported higher rates of polysubstance use. For example, Kaye et al. (2008) found that 89% of cases involved the use of two or more drugs, while Seltenhammer et al. (2013) reported a rate of 83%. Previous studies have demonstrated that codeine is commonly used in combination with morphine. Darke et al. (2010) found a rate of 77.9%, which is consistent with Seltenhammer's (2013) study (76.3%) and Kaye's (2008) study (72.2%) [5-9]. The rate of codeine use in our study was 70.9%, showing no significant difference (Chi Square).

These findings underscore the significant risk associated with polysubstance use and emphasize the importance of understanding the combined effects of multiple drugs on the cardiovascular system and overall mortality in substance abusers [9]. Drug-related deaths are frequently attributed to the interactive effects of multiple intoxicants. Drug interaction is a common phenomenon observed in studies of drug-related deaths [9-14]. Specifically, studies on methamphetamine- and codeine-related deaths indicate that opiates are present in the majority of these cases. Opiate intoxication is a prevalent feature in stimulant-related deaths, suggesting an increased risk of overdose when central nervous system stimulants are combined with opiates. Previous research has shown that the combination of methamphetamine with alcohol, cocaine, or opiates significantly heigh-tens the risk of overdose [10, 11].

From these results, it can be concluded that drug users tend to combine multiple substances to enhance their effects. It is important to note that impure drugs sold on the black market may cause local inflammation or myocardial damage in intravenous drug users, further complicating the clinical and forensic assessment of drug-related cardiac injuries.

4.2. Associations between Multiple Drug Use and Cardiac Pathological Lesions

The majority of subjects in our study used more than one addictive substance. Previous studies have found correlations between polysubstance use, overdose, and an increased risk of cardiac injuries such as myocardial fibrosis, myocardial fatty infiltration, and sudden death.

Fibrosis

Our study identified fibrosis in cardiac muscle tissue in 7 out of 15 cases (46.7%) involving only morphine use. Among the 40 cases using more than two types of drugs, fibrosis was observed in 33 cases (82.5%) various forms, primarily around vessels and interstitial tissue. The remaining 7 cases of polysubstance user did not exhibit fibrosis (17.5%). These results suggest that the incidence of fibrosis in cardiac muscle tissue is proportional to the number of drugs used. This difference is statistically significant (Fisher Exact test, $p = 0.015$). With a 95% confidence interval (CI95%) of 1.466-19.801,

individuals using two or more drugs are more likely to develop fibrosis in cardiac muscle tissue compared to those using only morphine. This finding aligns with other studies indicating that heroin users who combine it with other substances (especially alcohol and stimulants) often exhibit fibrosis.

Cardiac tissue fibrosis is characterized by the proliferation of collagen fibers and extracellular matrix proteins, culminating in impaired cardiac function, affecting both diastolic and systolic phases. Activated fibroblasts emerge as the primary cellular actors orchestrating the fibrotic process within cardiac tissue, assuming a pivotal role in cardiac remodeling subsequent to injury induced by drug abuse or myocardial infarction [12]. The direct association between chronic heroin and other opiate abuse and myocardial fibrotic damage remains ambiguous. Presently, a prevailing trend among drug abusers is the concurrent usage of narcotics and stimulants, suggesting that myocardial fibrosis in opiate users may predominantly stem from the toxic effects of stimulants [12, 13].

Fatty Infiltration

Our study also found that among the group using only one drug, only 1 case had fatty infiltration in cardiac tissue (6.57%), compared to 35% in the group using multiple drugs. Statistical analysis showed an correlation between polydrug use and fatty infiltration (p-value = 0.045) and a CI 95% of 1.896-63.451.

Substitution of adipose tissue and fibrosis in the interstitial myocardial tissue are common features observed in drug addicts. In a study involving 50 male heroin addicts, replacement of sinus node tissue by adipose and/or fibrous tissue was observed in 21 cases (42%). Perinodal infiltration was found in 15 cases (30%). Disorganization of muscle fibers in the branches of the sinus node artery was detected in 8 cases (16%) [11]. These histological changes in the sinus node region and perinodal area provide insights into the potential mechanisms underlying arrhythmias and sudden death in drug addicts.

Inflamation

Some studies suggest that intravenous drug use may increase the incidence of myocarditis and other inflammatory conditions of the heart. Alongside right ventricular dilation, myocardial cell necrosis, and endomyocardial fibrosis, infective endocarditis serves as an example linked to intravenous drug abuse, providing compelling evidence that any form of inflammation significantly influences the development of fibrous connective tissue, particularly within the myocardium [2]. During myocardial remodeling following direct or indirect drug-induced injury, damaged myocardial cells release cytokines and other chemical mediators that not only harm healthy myocardial cells but also elicit chemotactic signals to attract inflammatory cells to the injured site. If the inflammatory condition persists, abscess formation may ensue. Additionally, trauma and injection-related infections, as well as HIV infection, contribute to heightened systemic inflammatory cell counts within myocardial tissue [2,11]. Dettmeyer's 2009 study, utilizing quantitative immuno-histochemical staining, revealed a statistically significant increase in the number of in-flammatory cells in the myocardial tissue of intravenous drug users compared to the control group[5].

Our study yielded results consistent with previous research. In the group using only morphine, 10 out of 15 cases (66.7%) exhibited inflammatory lesions in myocardial tissue. In the group using multiple drugs, 38 out of 40 cases (95%) showed such lesions. Statistical analysis revealed a significant association between polydrug use and the presence of inflammatory lesions in myocardial histopathology, with a p-value of 0.013 and a CI95% of 0.018-0.625.

Myocardical hypertrophy

Chronic abusers of stimulant drugs, including cocaine, methamphetamine, or MDMA (ecstasy), frequently present with cardiac hypertrophy, a result of prolonged catecholamine surplus. Some reports suggest that cocaine directly stimulates calmodulin kinase II, contributing to the prevalent occurrence of hypertrophic cardiomyopathy among cocaine users or abusers. This phenomenon is recognized

as stimulant-induced cardiomyopathy, a condition contingent not on dosage but on the duration of stimulant use [2,11]. Cardiac hypertrophy often coincides with myocardial fibrosis. Initially, hypertrophy serves as an adaptive mechanism, compensating for damaged myocardial tissue due to various factors such as ischemia, hypoxia, or drug toxicity [14]. However, when cell death surpasses reparative capabilities, the reparative process becomes deleterious, resulting in an elevation in collagen deposition within the myocardium, diminished cardiac function, and myocardial fibrosis [2]. The results from our study did not demonstrate a statistically significant association between poly-drug abuse and myocardial hypertrophy.

Anemia

Intoxication with morphine or opioid compounds frequently induces central respiratory depression in the brainstem, diminishing respiratory activity and subsequently reducing oxygen delivery to the body as a whole, including the heart. The decrease in oxygen supply to the myocardium can result in myocardial damage through mechanisms akin to those observed in myocardial ischemia [2, 11]. The results from our study did not demonstrate a statistically significant association between poly-drug abuse and ischemic lesions.

In addition to long-term cocaine and/or amphetamine abuse causing fibrotic remodeling in the heart, as demonstrated by Milroy & Parai (2011), prolonged opioid use also harms cardiac tissue similarly, potentially leading to functional disturbances or decreased cardiac electro-physiological activity and various arrhythmias, such as prolonged QT interval and torsades de pointes, as described by Stringer et al. (2009) [15]. The hypothesized pathway to cardiac fibrosis after chronic opioid abuse involves repeated opioid use, especially intravenous heroin injection, leading to respiratory depression due to decreased sensitivity of respiratory center neurons in the brainstem. Respiratory depression causes tissue hypoxia, including in cardiac muscle, reducing oxygen exchange processes. Decreased oxygen levels in cardiac muscle lead to programmed cell death, similar to myocardial infarction, culminating in a phase of cardiac tissue remo-deling that results in fibrosis [12, 13]. The presence of fibrosis and cardiac hypertrophy are common cardiac injuries resulting from prolonged drug use. One influencing factor is the duration of drug use [2, 4]. However, we were unable to assess the relationship between cardiac pathological lesions and the duration of drug use due to the lack of this data.

5. CONCLUSION

The results from our study reveal an association between polysubstance abuse and the risk of myocardial lesions on histopathology, encompassing inflammatory lesions, fibrosis, and adipose infiltration in myocardial tissue. Understanding these changes is crucial for developing effective interventions and reducing the risk of sudden cardiac death in substance users.

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Mối liên quan giữa tình trạng lạm dụng đa chất và tổn thương mô bệnh học cơ tim

Đỗ Thị Thương Thương

TÓM TẮT

Đặt vấn đề: Chất ma túy (CMT) tác động lên hầu hết các cơ quan, bộ phận trong cơ thể trong đó hệ tim mạch có thể được coi là cơ quan đích. Mục tiêu nghiên cứu: Xác định mối liên quan giữa các tổn thương cơ tim trên giải phẫu bệnh với tình trạng sử dụng đa chất ma túy. Đối tượng và phương pháp nghiên cứu: 55 trường hợp tử vong được giám định tử thi tại Trung tâm Pháp Y Thành phố Hồ Chí Minh, có xét nghiệm máu dương tính với CMT. Quan sát tổn thương cơ tim trên tiêu bản mô bệnh học nhuộm HE và Trichrom Masson. Kết quả: 100% các trường hợp đều có sử dụng morphine; 65.5% trường hợp sử dụng cùng lúc hai loại và 7.3% sử dụng cùng lúc ba loại. Tình trạng tổn thương tim thường gặp nhất là tăng sinh xơ và tổn thương liên quan đến tình trạng thiếu máu, tỉ lệ ghi nhận lần lượt là 72.7% và 34.5%. Các tổn thương cơ tim phổ biến nhất được quan sát là sự tăng sinh xơ (72.7%) và tổn thương liên quan đến thiếu máu cục bộ (34.5%). Kết luận: Nghiên cứu cho thấy có mối liên hệ đáng kể giữa lạm dụng đa chất và nguy cơ sinh xơ và thâm nhiễm mỡ trong cơ tim. Những

phát hiện này nhấn mạnh tầm quan trọng của việc giải quyết lạm dụng đa chất trong các can thiệp sức khỏe tim mạch.

Từ khóa: *lạm dụng thuốc, lạm dụng đa chất, tổn thương cơ tim*

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