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Aortic dissection and opioid use: Two autopsy cases and potential pathological implications

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ABSTRACT

Acute aortic syndrome (AAS) is a life-threatening condition that includes acute aortic dissection (AAD), intramural hematoma (IMH), and symptomatic penetrating aortic ulcer. While hypertension is the primary risk factor, substance abuse—especially cocaine—has been linked to AAS. However, the role of opioids remains unclear.

This study presents two autopsy cases of opioid users who died from cardiac tamponade due to aortic dissection. The first case involved a 55-year-old male undergoing methadone treatment, with biologically active methadone detected at death. The second case was a 58-year-old male with no known substance abuse history but with postmortem findings of morphine and methadone, indicating recent opioid use. Histological examination in both cases revealed vascular damage consistent with aortic dissection.

While no direct causal link has been established, chronic opioid exposure may contribute to vascular degradation through hypoxia-inducible factor-1alpha (HIF-1α)-mediated inflammation. The overlap between opioid use and AAS in these cases suggests a potential association, warranting further investigation into the vascular effects of opioids and their clinical implications.

Introduction

The term acute aortic syndrome (AAS) is a contemporary classification that encompasses acute aortic dissection (AAD), intramural hematoma (IMH), and symptomatic penetrating aortic ulcer. Typically, AAD occurs when the inner layer of the aorta (intima) weakens and tears [1,2].

Available data indicates that the occurrence of AAD ranges from 2.6 to 7.2 cases per 100,000 person-years, with most statistics derived from studies conducted on subjects from Western populations. Approximately 65 % of affected individuals are male, with the highest frequency of cases observed in individuals in their 70 s [3].

Pathophysiologically, aortic dissection arises from structural failure of the aortic wall, characterized by medial degeneration—a process marked by elastic fiber fragmentation, smooth muscle cell loss, and mucoid extracellular matrix accumulation [4]. These degenerative changes impair the aorta's ability to withstand hemodynamic stress, particularly at high-shear regions such as the ascending aorta and ligamentum arteriosum [5,6].

Hypertension is the primary risk factor for acute aortic syndromes. Additional risk factors include Marfan syndrome (MFS), bicuspid aortic valve, familial aortic dissection, and iatrogenic complications [1,2,7].

Besides cigarette smoking, cocaine and crack are the only other types of substance abuse that have a well-documented association with aortic dissection. This relationship is primarily mediated through the acute hypertensive effects induced by the drug, which significantly lowers the average age of onset compared to typical cases of aortic dissection [1, 8–10].

While cocaine is strongly linked to acute coronary syndrome (ACS) due to its vasoconstrictive and hypertensive effects, no such correlation has been established for heroin.

Can et al. (2018) explored the link between heroin use and saccular intracranial aneurysm rupture (sIA), identifying a significant association with current heroin use and stressing the importance of cessation in patients with unruptured aneurysms [11].

Wu and Lin (2018) extended this perspective, suggesting that heroin

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could also impact larger arteries, including the aorta. They documented cases of AAD in heroin users, indicating that vascular damage may persist weeks after cessation [12].

This study describes two autopsy cases of aortic dissection in individuals who had taken opioids and died from cardiac tamponade. Toxicological analyses confirmed the presence of opioids at the time of rupture, prompting examiners to consider a possible correlation between opioid use and aortic dissection. However, this remains a speculative consideration.

Case report

Case 1

A deceased male individual, estimated to be in his 50 s, was discovered inside his residence. He was known to be under treatment at the city's addiction service due to a previous history of substance abuse. From a medical history perspective, the only relevant information available was his habitual methadone use, documented by the local addiction treatment service. In forensic cases, medical records are obtained through the judicial authority, which provides access to primary care and hospital documentation. No additional chronic conditions or long-term treatments were reported in the material received.

External examination

A male cadaver, weighing 83 kg and measuring 176 cm in length, was examined. Cadaveric rigidity had developed in all joint regions; body temperature was in equilibrium with the ambient temperature; and livor mortis appeared reddish, abundant in dependent areas, and fixed.

External examination revealed two puncture wounds on the volar surface of the distal third of the right forearm. Additionally, two puncture wounds covered by a scab were observed on the posterolateral surface of the upper third of the right arm. Multiple yellowish bruises on the right arm were noted.

Autopsy

The autopsy was performed 26 h after the body was found, following the mandatory 24-hour observation period, as required by local law.

Upon opening the pericardial sac, approximately 300 cc of partially coagulated blood. The aortic dissection originated in the ascending aorta, approximately 2 cm above the aortic valve within the intrapericardial segment. A primary intimal tear, measuring 1.8 cm in length with jagged, fish-mouth edges, was identified on the anterior wall of the ascending aorta. From this site, the dissection propagated distally in a spiral fashion, coursing through the aortic arch and descending thoracic aorta before terminating 2 cm distal to the left renal artery in the suprarenal abdominal aorta.

The dissection plane extended to involve the ostium of the left renal artery, resulting in focal stenosis, though the superior mesenteric and right renal arteries remained unaffected. Adjacent to the dissection, a calcified atherosclerotic plaque measuring 4 mm in thickness was adherent to the posterior wall of the infrarenal aorta, distinct from the dissection pathology.

A full-thickness rupture, measuring 0.5 cm in diameter, was documented in the right lateral wall of the ascending aorta. (Fig. 1)

The heart exhibited right chamber enlargement, measuring 16 × 13 × 3 cm and weighing 520 g. Coronary artery analysis revealed mild atherosclerosis without significant stenosis. The atrioventricular valves were competent under hydrostatic testing, and the semilunar valves showed no abnormalities. The cardiac chambers and myocardium displayed no macroscopic pathological findings.

Examination of the head revealed no significant abnormalities. The brain appeared edematous but of normal size, weighing 1600 g, with no evident pathological alterations.

Examination of other regions and organs revealed no significant abnormalities.

Histological examination

Histological examinations were performed on organ fragments collected during the autopsy and fixed in 10 % buffered formalin at pH 7. After being washed in tap water, the samples were embedded in paraffin using an automated system. Microsections, 6–8 microns thick, were obtained from the paraffin blocks using a microtome. Following deparaffinization in xylene, the sections underwent standard hematoxylin-eosin staining procedures.

Among the most relevant findings, the myocardium exhibited diffuse fibrosis consistent with myocardial sclerosis. The lungs showed microvascular congestion. Hepatic steatosis was also observed.

A hemorrhagic dissection plane between the tunica media and adventitia was demonstrated by histologic examination of the aortic wall at the dissection site, characterized by extravasated erythrocytes and disruption of the medial architecture. Focal areas of acute hemorrhage within the vascular wall were identified, marked by interstitial erythrocyte infiltration.

Toxicological analysis

Toxicological analyses were conducted at the Forensic Medicine and

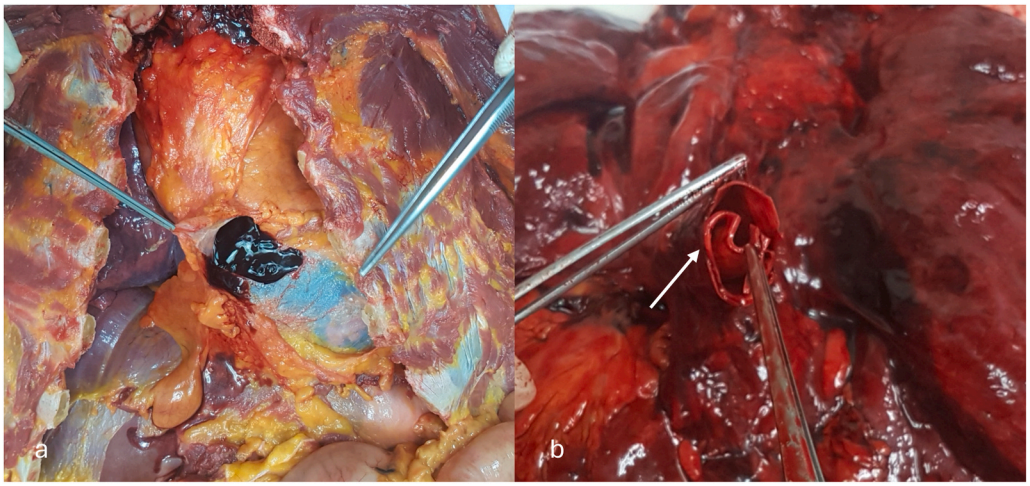

Fig. 1. ardiac tamponade and aortic dissection. (a) Hemopericardium with clotted blood (*black arrows*) within the opened pericardial sac, compressing the heart. (b) Cross-sectional view of the aortic arch showing an intimal flap (*white arrowheads*) separating the true lumen from the false lumen, characteristic of aortic dissection.

Laboratory of the University of Macerata on biological samples collected during the autopsy, including blood, urine, bile, and nails. GC-MS and LC-MS analyses identified methadone and its metabolite EDDP in all matrices. Methadone concentrations were 427 ng/mL in blood and 3412 ng/mL in bile. Ethanol was detected at 0.13 g/L. Caffeine was found in blood, urine, and bile. No opiates, cocaine, amphetamines, benzodiazepines, barbiturates, cannabinoids, or other drugs of abuse were detected. Screening for amlodipine, ramipril, enalapril, losartan, valsartan, and carvedilol via Orbitrap HPLC yielded negative findings. The results of the toxicological investigations, including screening for psychotropic and illicit substances, are summarized in Table 1.

Case 2

A male individual in his 50 s was found deceased inside his residence. His past medical history did not indicate any known substance abuse; however, it emerged that late in the evening (around 11 p.m.), the man had contacted the emergency services requesting help, stating that he was feeling unwell, had injected substances, and was experiencing an overdose. He had left the door of his residence open, presumably to allow the emergency responders to enter.

Upon arrival at the scene, the medical personnel found the man deceased, lying supine in the bedroom of his apartment.

External examination

A male cadaver, weighing 101 kg and measuring 183 cm in length, was examined. Cadaveric rigidity was diffusely evident, to a moderate extent in the upper body regions, and more pronounced in the lower extremities. The body temperature was in equilibrium with the ambient temperature. Livor mortis was abundant in dependent areas, exhibited a violet hue, and was fixed.

External examination revealed two puncture wounds on the dorsum of the right hand, a third wound at the left elbow crease, and an additional wound on the dorsum of the left hand.

Autopsy

The autopsy was performed 35 h after the discovery of the body, following a 24-hour observation period at room temperature, as required by local law. The body was then stored in a refrigerated chamber until the autopsy.

After opening the thoracic cavity, no significant abnormalities were observed in the pleural cavities. The pericardial sac contained 450 cc of blood. Aortic dissection arose from a 2.0 cm transverse intimal tear on the right lateral wall of the ascending aorta, positioned 3 cm distal to the sinotubular junction and outside the intrapericardial segment. The dissection propagated distally in a longitudinal, traversing the aortic arch and descending thoracic aorta before terminating 5 cm proximal to the aortic bifurcation in the infrarenal abdominal aorta.

The false lumen displayed partial thrombosis in the abdominal segment, with fresh hemorrhage noted at the tear site. A 7 mm ulcerated atherosclerotic plaque with overlying thrombus was identified on the anterior wall of the descending thoracic aorta, unrelated to the dissection.

A focal intimal flap was noted in the aortic arch, but no secondary tears or re-entry sites were identified. The infrarenal aorta demonstrated diffuse, non-calcified atherosclerotic thickening (up to 3 mm) distinct from the dissection pathology.

The rupture was located in the lateral wall of the ascending aorta within the intrapericardial portion.

The heart was slightly enlarged and weighed 540 g. Stenosis was found in the branches of both the left and right coronary arteries, with a maximum luminal occlusion of 30 %. No other pathological alterations were identified.

Examination of the head did not reveal any notable abnormalities. The brain exhibited signs of edema but maintained a normal size, weighing 1420 g, with no evident pathological changes. No significant abnormalities were observed in the examination of other regions and organs.

Histological examination

Histological examinations were performed on organ samples fixed in 10 % buffered formalin (pH 7), embedded in paraffin, and sectioned (6–8 μm) using a microtome. After deparaffinization in xylene, the sections were stained with hematoxylin-eosin. Among the most relevant findings, the myocardium exhibited diffuse interstitial and perivascular fibrosis.

Microscopic evaluation of the aortic wall at the dissection site reveals a striking disruption of the medial architecture, characterized by a well-defined hemorrhagic cleft dissecting through the mid-to-outer third of the tunica media. This plane of separation is marked by abundant extravasated erythrocytes. (Fig. 2)

Toxicological analysis

Toxicological analyses were conducted at the Forensic Medicine and Laboratory of the University of Macerata on blood, urine, bile, hair, and nails. Morphine was detected in blood (472 ng/mL), bile (>5000 ng/mL), urine, hair, and nails. Codeine was present in blood, urine, and bile. Methadone was identified in blood (752 ng/mL), bile (2043 ng/mL), urine, hair, and nails, together with its metabolite EDDP. No ethanol or other volatile organic compounds were detected. Screening for cocaine, amphetamines, benzodiazepines, barbiturates, cannabinoids, and other drugs of abuse yielded negative results. Orbitrap HPLC analysis for amlodipine, ramipril, enalapril, losartan, valsartan, and carvedilol yielded negative findings. Full results are summarized in Table 1.

Table 1
Summary Table of Toxicological Analysis Results. The term "Detected" indicates the presence of the substance; however, its concentration is below the minimum quantifiable limit of the analytical method. Conversely, "Not Detected" means that the substance was not found in the analyzed sample or that its concentration is below the detection limit of the instrumentation used.

Case 1				
Substance	Blood (ng/mL)	Bile (ng/mL)	Urine	Hair/Nails
Methadone	427	3412	Detected	Detected
EDDP (Methadone Metabolite)	Detected	Detected	Detected	Detected
Ethanol	0.13 g/L	Not Detected	Not Detected	Not Detected
Caffeine	Detected	Detected	Detected	Not Detected
Case 2				
Morphine	472	> 5000	Detected	Detected
Codeine	Detected	Detected	Detected	Detected
Methadone	752	2043	Detected	Detected
EDDP (Methadone Metabolite)	Detected	Detected	Detected	Detected
Ethanol	Not Detected	Not Detected	Not Detected	Not Detected

Discussion

In both of the cases described, death was attributed to hemopericardium with consequent cardiac tamponade due to aortic dissection. A notable aspect shared by both cases is the presence of opioids at the time of death, confirmed through toxicological analyses performed on major biological fluids and keratinous matrices. In the second case, the morphine concentration in blood was within a range that can be fatal in opioid-naïve individuals, but the autopsy findings clearly demonstrated cardiac tamponade as the actual cause [13].

Both individuals were obese and of advanced age, conditions that increase the likelihood of hypertension [1,2]. Although no opioid-related chronic vascular injury was identified, the wall changes observed were compatible with hypertension-associated atherosclerosis.

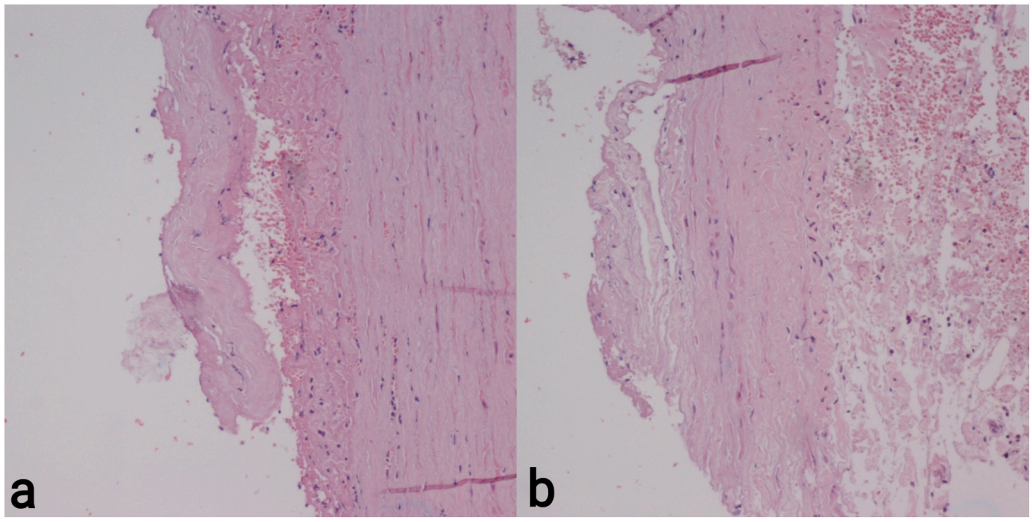

Fig. 2. Histopathology of aortic dissection (Case 2): (a) Dissection plane between intima and media with hemorrhage and fibrin deposition (H&E, 10x). (b) Diffuse hemorrhage of the tunica media with focal areas of fibrin.10x).

While the literature describes a complex, bidirectional relationship between opioids and blood pressure, our data do not support an opioid-induced hypertensive surge as the trigger for dissection [14–16]. The coexistence of active opioid exposure and acute aortic dissection therefore remains an unusual finding, warranting further study but not allowing causal inference.

Given the injection history in both cases, a further consideration concerns the potential for infectious vascular lesions in individuals who use injectable drugs. The literature describes mycotic pseudoaneurysms, endarteritis, and parietal damage associated with contaminated injections, characterized by vascular wall necrosis and an increased risk of hemorrhagic rupture [17,18]. In our two cases, however, neither the macroscopic nor the histological findings showed evidence of vascular infection (inflammatory infiltrates, septic necrosis, microabscesses, or pseudoaneurysms).

In the absence of chronic inflammatory or degenerative alterations in the aortic wall, and lacking any mechanism supported by the present cases, only theoretical models from related vascular literature can be considered for contextualization. Tsai et al. (2016) [19], for example, hypothesized a role for hypoxia-inducible factor-1α (HIF-1α) in the development of abdominal aortic aneurysms, acting through the upregulation of matrix metalloproteinases (MMP-2 and MMP-9) and consequent degradation of the aortic wall [19]. Although these data pertain to aneurysmal disease rather than dissection, they offer a conceptual model illustrating how chronic opioid-induced hypoxia might hypothetically contribute to vascular weakening.

It is important to clarify that the reference to HIF-1α is not intended to suggest that this mechanism was operative in the present cases. In our subjects, the only objective findings were acute aortic dissection and concurrent opioid intoxication. Histological examination did not reveal inflammatory infiltrates, cystic medial degeneration, or other chronic wall alterations compatible with HIF-1α–mediated changes. Instead, the morphological features were characteristic of an acute dissection, with a haemorrhagic cleavage plane and disruption of the medial architecture.

Overall, the available findings do not allow the identification of a specific mechanism linking opioid exposure to aortic wall failure. Nonetheless, the unusual coexistence of acute dissection and active opioid intoxication in both cases underscores the need to further investigate whether acute or chronic opioid exposure may influence aortic wall stability.

Conclusion

To date, no clear correlation has been established between acute or chronic opioid use and acute aortic syndrome, although some indications can be found in the literature. The cases highlight an unusual coexistence of high-level opioid exposure and acute thoracic aortic dissection. Further studies in this field could be valuable in confirming or definitively excluding this relationship and, if confirmed, in elucidating the underlying pathological mechanisms.

Ethics Approval

The publication of the cases was approved by the Ethics Committee of the University of Macerata, Protocol No. 130847, dated November 14, 2024.

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CRediT authorship contribution statement

Roberto Scendoni: Writing – review & editing, Conceptualization. **Luca Tomassini:** Writing – original draft, Formal analysis, Data curation. **Erika Buratti:** Writing – original draft. **Rino Froldi:** Formal analysis.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used OpenAI in order to organize the text and make the presentation of the contents smoother. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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.

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Code Availability

N/A

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LT, EB and RF. LT, RF and RS provided the medico-legal reports and clinical charts the case. RS coordinated the drafting of the article. All authors read and approved the final version of the manuscript.

Consent To Participate

N/A

Consent For Publication

N/A

Availability Of Data And Material

N/A

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