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Case reports in coronary artery disease 2022

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Case reports in coronary artery disease: 2022

Topic editor
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Case report: Spontaneous coronary artery rupture presenting with acute coronary syndrome: A rare diagnosis of common disease

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Acute coronary syndrome (ACS), myocardial infarction, and sudden death have all been linked to spontaneous coronary artery rapture (SCAR). Patients primarily afflicted by SCAR are those with or without cardiovascular risk factors, notably men, implying a mechanism distinct from the more prevalent atherosclerosis. Both medical and interventional treatment should consider the diverse causes of ACS as well as the patient's clinical stability. I herein report an unusual case of a 33 years old male who presented with acute chest pain to the emergency department. His physical exam was normal. The electrocardiogram showed non-specific ST segment changes in anterior leads, and the echocardiogram revealed mild anterior wall hypokinesia with no evidence of pericardial effusion. He underwent coronary angiography which revealed a contained rupture in the anterior descending coronary artery. The patient underwent uneventful lifesaving coronary artery perforation repair. It concluded that, though rare, SCAR should be considered as a differential diagnosis in patients with ACS, even in the absence of pericardial effusion in adult patients of all ages.

KEYWORDS

coronary disease, acute coronary syndrome, spontaneous coronary rupture, surgery, pericardial effusion

Introduction

A coronary artery spontaneous rupture is a rare pathology that can manifest in different ways. In this sense, it can range from simple acute coronary syndrome (ACS) to cardiogenic shock secondary to large precordial effusion. Early detection and proper management can save the patient's life. Few case reports have been published that indicate its different presentations and variety of management approaches.

Case presentation

A 33-year-old male teacher with a history of smoking presented to the emergency department complaining of retrosternal chest pain for 2 days. It was a dull ache that radiated to his back. The pain was aggravated by minimal physical activity with no relieving factors. It was associated with mild fatigue. He had no fever, dyspnea, orthopnea, or syncope, and he did not exhibit any palpitation. He had no joints pain, rash or mouth ulcers, and no history of any chest trauma. The blood pressure (BP) was 125/65 mmHg, heart rate (HR) was 78 bpm, and saturation was 98% on room air. Cardiovascular examination was within normal standards, and no abnormal findings were recorded upon chest examination. His ECG demonstrated normal sinus rhythm with non-specific ST changes in anterior leads (Figure 1). Cardiac enzyme troponin I was 6.4 ng/mL (normal range < 0.04 ng/mL). Low-density lipoprotein (LDL) measured 133 mg/dl (0–140 mg/dl), and total cholesterol was 215 mg/dL (0–239 mg/ dL). ESR 13 mm/h (normal 1–20 mm/h), C-reactive protein 2.9 mg/L (normal <10 mg/L). ANA, rheumatoid factors and ANCA were negative. Complete blood count (CBC) and renal function tests were within normal ranges. Additionally, the chest X-ray was normal.

The patient was admitted to our coronary care unit as a case of ACS and was started on an ACS management protocol that includes aspirin, clopidogrel, statin, and subcutaneous heparin (enoxaparin 1 mg/kg twice daily). A transthoracic echocardiogram revealed a low normal ejection fraction (EF 50%) with mild anterior wall hypokinesia and no pericardial effusion; otherwise, no abnormality was detected (Figure 2). The patient was stabilized overnight and taken to the coronary catheterization laboratory for a coronary angiogram. The

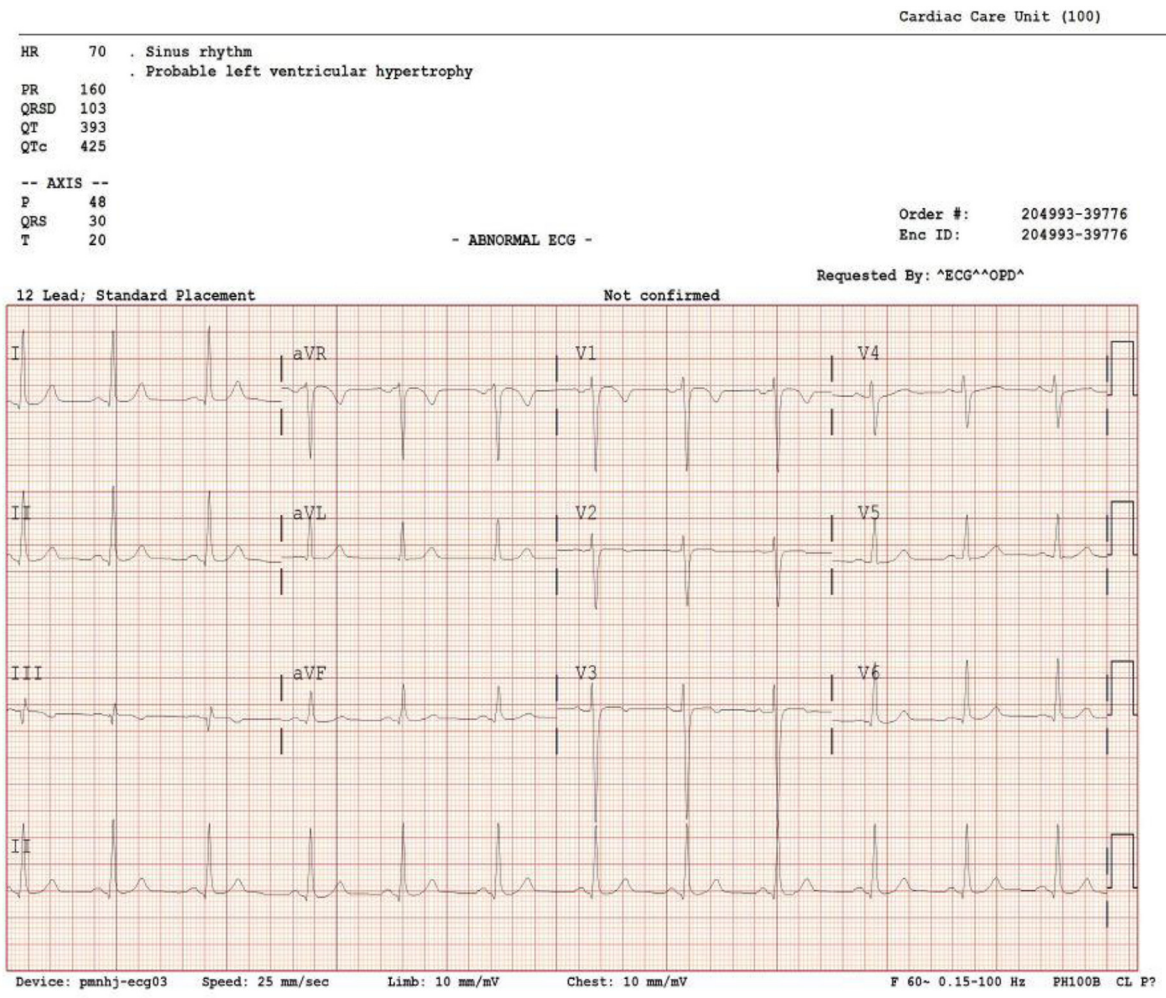

FIGURE 1
A 12-lead electrocardiogram shows non-specific ST-segment changes in anterior leads.

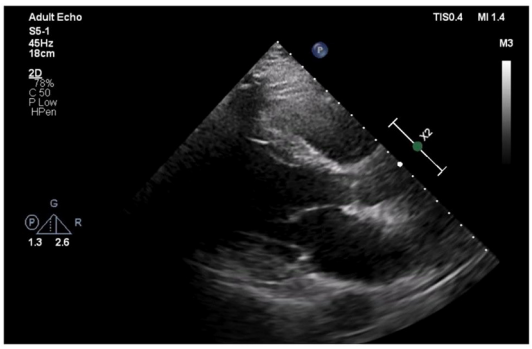

FIGURE 2
Echocardiogram of Left parasternal axis view shows no pericardial effusion.

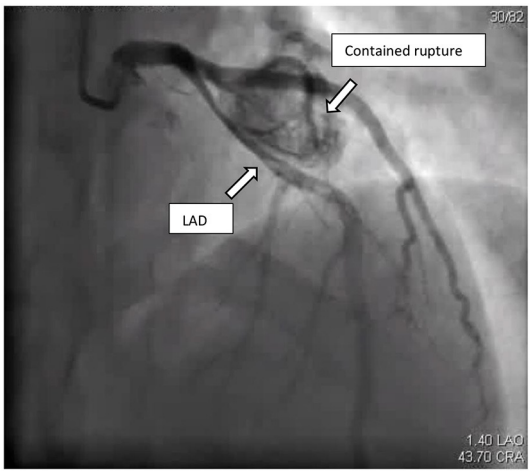

FIGURE 3
Coronary angiogram: cranial view, showed LAD with large contained rupture in proximal segment causing pressure effect on the LAD.

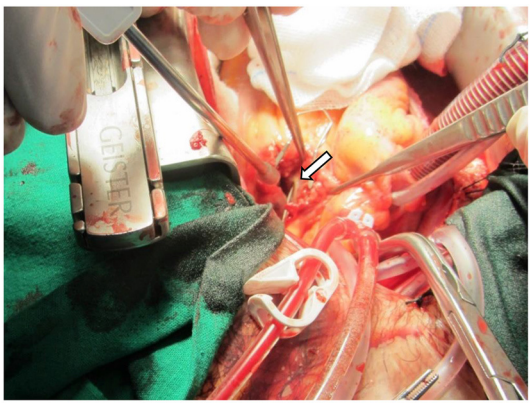

FIGURE 4
Intraoperative photo showing the LAD spontaneous rupture with probe inside the opening (arrow).

coronary angiogram showed normal left main (LM) artery, and the left anterior descending artery (LAD) exhibited a large pseudoaneurysm in proximal segment with contrast squirted in it and TIMI II-III flow in the distal LAD (Figure 3). The left circumflex artery (LCX) and the right coronary artery (RCA) were observed to be normal. The procedure was stopped, and the patient was urgently referred for a cardiac surgery consultation. Three hours later, he developed acute hypotension with a BP of 75/55 mmHg and HR of 133 bpm. Bolus IV fluid was given, and emergency bedside pericardiocentesis was performed in addition to the removal of 50 cc of fresh blood. The patient's BP stabilized, and he was taken as a lifesaving case to the operating room. Cardiopulmonary bypass (CPB) was established through the cannulation of the femoral vessels. A median sternotomy was performed, and 100 cc of fresh and clotted blood was removed from the pericardial sac. Then, careful examination of the pseudoaneurysm showed spontaneous rupture with contained bleeding. The opening of spontaneous rupture in the LAD was identified as shown in Figure 4, and it was closed with a 3–0 polypropylene continuous suture. Postoperatively, the patient did well. He did not show any signs of either myocardial infarction or left ventricle pump failure. Thus, he was discharged 6 days later in a stable condition.

Discussion

Spontaneous coronary artery rupture (SCAR) is a rare condition that might present in different ways, some of which can mimic ACS. Given its potentially fatal consequences, it requires proper and emergency identification and management.

In a literature review, Longobardi et al. identified 8 case reports on SCAR (1). ACS was the most common presentation; however, some patients presented with hemodynamic instability due to large pericardial effusion. The majority of the cases reported involved middle-aged patients (50–70 years), except for 1 case that occurred in a patient younger than 40 years (37 years old) (1). Furthermore, the literature suggests that men are more likely to have this disease compared to women. In the reported cases, only one patient was female, and her age was 65 years (2). On another note, spontaneous coronary artery ruptures can happen at any major coronary artery and are rarely reported in the side branch (3, 4). Moreover, cardiogenic shock and tamponade complicate SCAR more often when it originates from RCA (5, 6).

Many conditions can be associated with arterial diseases that may lead to SCAR (such as atherosclerosis, Kawasaki disease, localized atheromatous plaque, aneurysm, blunt chest trauma, and very rarely, infection) (6–8). Of note, Kawasaki disease

usually associated with giant calcified coronary aneurysms which might be complicated by perforation (9).

Coronary segment dilatation of more than 1.5% of the adjacent normal coronary segment is considered aneurysmal. Moreover, the prevalence of this pathology is from 0.3 to 5.3% according to early angiographic studies, the majority due to atherosclerosis (9). Common differential diagnoses of contained coronary perforation are true or pseudoaneurysm. A monolayer or double layer outwardly bulging within the coronary artery that lacks all 3 layers (intima, media, and adventitia) of the arterial wall is defined as pseudoaneurysm. This vessel wall integrity loss gives it more highly rupture-prone adventitia and perivascular tissue than true aneurysms. Pseudoaneurysm is commonly caused by traumatic dissection and perforation due to percutaneous coronary intervention (10). Differentiating true from pseudoaneurysm by plan coronary angiography is extremely difficult. However, using intravascular ultrasound (IVUS) imaging might help to delineate the aneurysm wall structure (11).

The site and size of SCAR in addition to the patient's condition can drive the management approach. Graft stenting through percutaneous coronary intervention is a reasonable option if the patient is stable and the anatomical location is appropriate (12). However, surgical intervention with pericardial evacuation must be performed when the patient is unstable or the anatomical location is not optimal (3).

My patient is unique because he was very young at 33 years of age. His only cardiac risk factor was smoking; he had no signs of inflammatory disease and no history of chronic disease or atherosclerosis, and no abnormality was detected by plain coronary angiogram a part from the perforation. Moreover, because there was no clear stenosis, atherosclerosis or aneurysm other than the perforation identified during the operation, the cardiac surgeon decided to repaired the perforation site only with no indications for bypass graft to LAD. Since I found no causative pathology, I suggested that this rupture was spontaneous.

Conclusion

Spontaneous coronary artery perforation is a rare condition that could be underreported due to its lethal presentation. A high index of suspicion should be considered when a patient presents with acute coronary artery syndrome and pericardial effusion. Early diagnosis will lead to surgical or non-surgical intervention in a way that prevents its devastating complications.

Learning points

- SCAR should be considered as a differential diagnosis in patients with acute chest pain, even in the absence of pericardial effusion.
- We should consider contained SCAR as one of the differential diagnoses when we observe large coronary pseudoaneurysm by coronary angiogram.
- In patients presenting with pericardial effusion, SCAR is a possible diagnosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Spontaneous coronary artery dissection in a man with Ehlers–Danlos syndrome

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Background: Spontaneous coronary artery dissection (SCAD), as a medical emergency, represents one of the non-atherosclerotic causes of an acute coronary syndrome (ACS). It often occurs in young and middle-aged females and is a rarity among male patients. Yet, it is easily misdiagnosed or missed even though it has one of the highest in-hospital mortality rates.

Case summary: Here, we present a young male patient admitted to the emergency department of our hospital due to a complaint of acute chest pain. During his hospitalization, we utilized several tools, including imaging modalities, genetic analyses, and clinical strategies, to ensure a proper diagnosis and management of the patient. The results indicated that the patient suffered from SCAD, as well as vascular Ehlers–Danlos syndrome (vEDS). Unfortunately, the patient died of SCAD-related sudden cardiac death (SCD) on the ninth day before the DNA analysis results were obtained. Despite a global effort and huge progress in the clinical characterization of SCAD, as well as patients' assessments, its pathophysiology remains poorly understood, with a significant recurrence risk and no specific disease-modifying therapy.

Conclusion: Vascular Ehlers–Danlos syndrome, as an inherited connective tissue disorder characterized by congenital connective tissue dysplasia, is a rare and particularly challenging monogenetic disease. It can cause life-threatening changes, including arterial dissections and ruptures, and lead to early death due to COL3A1 pathogenic variants. It is also a rare cause of SCAD. Currently, the gold standard for SCAD diagnosis is coronary angiography (CAG).

KEYWORDS

spontaneous coronary artery dissection, acute coronary syndrome, Ehlers–Danlos syndrome, imaging, percutaneous coronary revascularization

Introduction

Spontaneous coronary artery dissection (SCAD) is an important, rare, and sometimes fatal cause of acute coronary syndrome (ACS) (1), accounting for 1–4% of all the ACS cases. It often occurs in young and middle-aged female patients and is responsible for 25% of ACS in women younger than 50 years (2). Male patients with SCAD are rare and only represent approximately 10% of all the SCAD cases (1). Here, we report a 37-year-old male patient suffering from severe SCAD. The diagnosis was made using a combination of coronary angiography (CAG) and intravascular ultrasound (IVUS). He was also diagnosed with vascular Ehlers–Danlos syndrome (vEDS) type IV according to his clinical features and the identification of a mutation in *COL3A1* through genetic examinations.

Case presentation

A 37-year-old male was admitted to our hospital due to a complaint of "a sudden chest pain for 2 h." The ECG test indicated an acute anterior ST-segment elevation myocardial infarction (STEMI) (**Figure 1**). Meanwhile, the myocardial injury marker assessments showed elevated troponin T [9,925 ng/l; reference range (RR): 0–14 ng/l], creatine kinase-MB (191.8 ng/ml; RR: < 4.94 ng/ml), and myoglobin (306.6 ng/ml; RR: < 72 ng/ml). We proceeded to perform a transthoracic echocardiography (TTE) test. The results revealed regional wall motion abnormalities within the middle, and lower segments of the ventricular septum and the left ventricular apex, a moderate pericardial effusion, and a 62% left ventricular ejection fraction (LVEF). The differential diagnosis included evolving ACS, acute pulmonary embolism (PE), myocarditis, and pericardial diseases.

The patient had a previous medical history of chronic headaches of unclear origin for more than 20 years. He intermittently took a combination of paracetamol, caffeine, and aspirin in powder form to relieve his symptoms and denied any history of drug abuse. He underwent splenectomy and partial intestinal resection due to a fall-related ruptured spleen and intestine 20 years ago. He also underwent partial liver resection 4 years before the current events due to ruptured liver from another fall injury and was noted to be prone to skin abrasions and subcutaneous ecchymosis.

The physical examination showed that the patient had slightly protruding eyes, thin skin, increased skin elasticity, obviously exposed chest and forearm subcutaneous veins, visible subcutaneous ecchymosis on the forearm and lower limbs (**Figures 2A–C**), and an abnormally increased mobility of the little bilateral finger metacarpophalangeal (MCP) joints (**Figures 2D,E**). A heterozygous mutation of c.1347 + 1G > A in the *COL3A1* gene was also discovered and verified using PCR and Sanger sequencing, which indicated a protein sequence splicing mutation (**Figure 2F**). He was then clinically diagnosed with vEDS based on the synthesis of imaging techniques, medical history, clinical manifestations, and DNA sequence analyses.

The mentioned findings prompted an emergency selective CAG *via* the right radial artery, which indicated a dissection located between the proximal and middle segments of the left anterior descending (LAD) branch (**Figures 3A,B**). The results indicated a progression of the coronary artery dissection involving the left main (LM) trunk and the left circumflex branch (LCX), which caused an LCX occlusion of the proximal segment (type 4 dissection of the LCX) (**Figure 3C**) with the Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 during CAG. Accordingly, the patient developed hemodynamic instability and immediately underwent percutaneous coronary intervention (PCI). Intravascular ultrasound (IVUS) further confirmed the coronary artery dissection and guided the revascularization process. It showed a massive intramural hematoma (IMH) from the media external to the LAD stent, with the true vascular lumen of the median LCX segment being severely deformed by the dissection and the massive media layer hematoma (**Figures 3E,F**). During the procedure, three drug-eluting stents (DESs) were placed from the LAD to the LM (the stents were Promus PREMIER^{TM} 2.5 mm × 38 mm, 3.5 mm × 32 mm, and 4.0 mm × 24 mm, from Boston Scientific Corporation, United States, respectively). These stents were overlapped after revascularization with another stent at the LCX (the stent was Promus PREMIER^{TM} 2.75 mm × 20 mm, Boston Scientific Corporation, United States) and inflated (12–16 atm inflation pressure) for deployment. Finally, the results indicated that hemodynamic stability was successfully achieved, and the LCX improved to the TIMI flow grade 3 (**Figure 3D**). The patient was transferred to the cardiac care unit for treatment following the procedure. Dual antiplatelet therapy with 100 mg of aspirin and 75 mg of clopidogrel was administered once daily since the subject underwent a DES implantation.

To further clarify and eliminate potential non-coronary artery disease-related problems, we proceeded to perform a postoperative chest, abdominal, and pelvic enhanced CT examination. The chest CT revealed a stent in the left anterior descending coronary artery and hemopericardium (**Figures 3G,H**). Meanwhile, the abdominal and pelvic CT showed intestinal wall swelling, hematocele, retroperitoneal hematocele, and an iliac vascular dissection (**Figures 3I,J**). Unfortunately, the patient suffered from a sudden cardiac arrest, and all the resuscitation attempts failed. He, unfortunately, died of sudden cardiac death (SCD) on the ninth day of the index SCAD event, before the DNA analysis results were obtained. Additionally, the bedside echocardiography showed a large amount of pericardial effusion. According to the description of the doctor on duty at that time, the patient suffered from chest tightness and hypovolemic shock, and the patient died

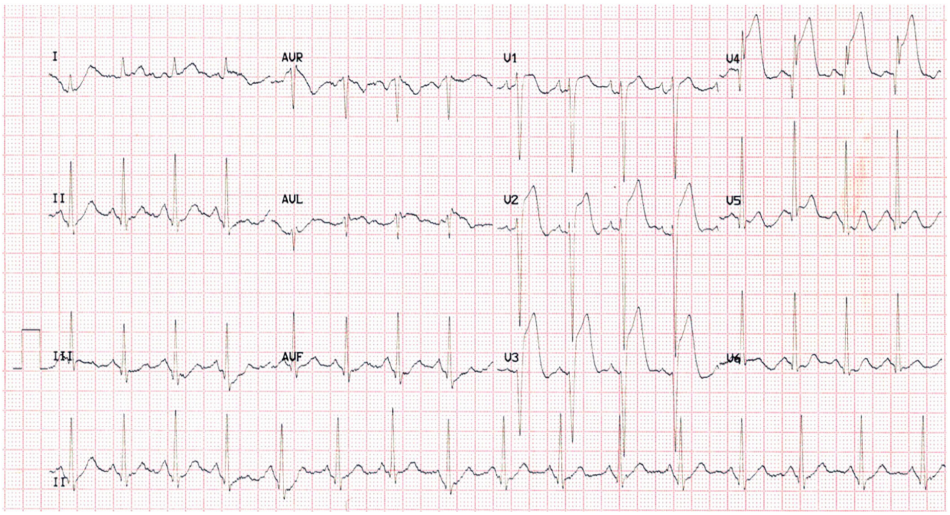

FIGURE 1
Patient's ECG on admission.

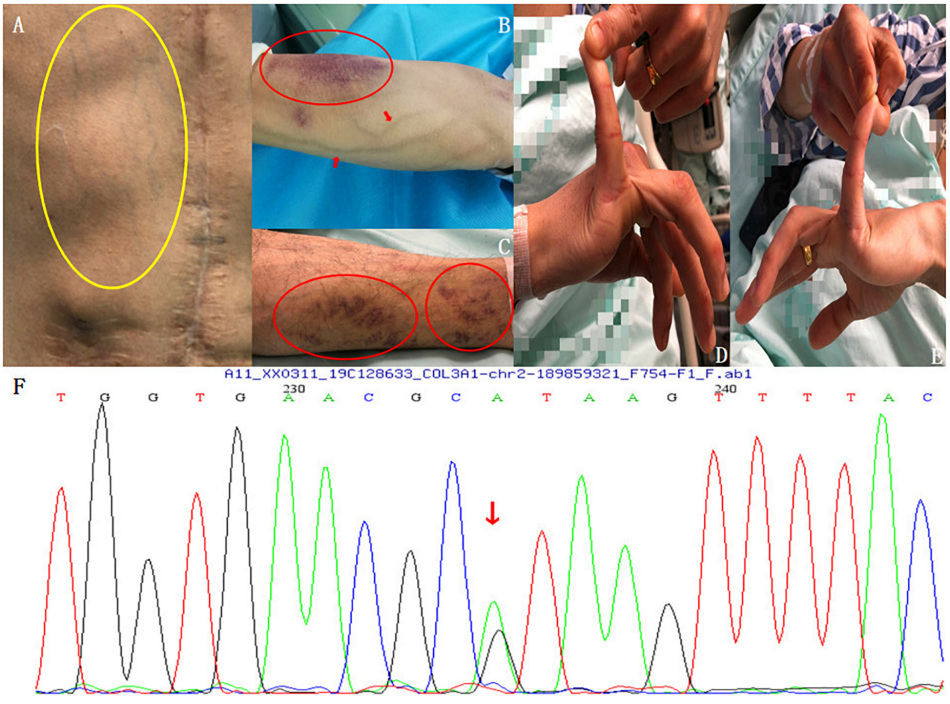

FIGURE 2
Physical examination findings. **(A)** Thin skin, increased skin elasticity, and obviously exposed subcutaneous veins of the chest wall (yellow circle). **(B)** Visible veins and subcutaneous ecchymosis (red circle) on the forearm. **(C)** Visible subcutaneous ecchymosis on the lower limbs (red circles). **(D,E)** Abnormally increased mobility of the bilateral little finger MCP joints. **(F)** Genetic testing: A heterozygous mutation of c.1347 + 1G > A in the *COL3A1* gene was found and verified using PCR and Sanger sequencing, which led to a protein sequence splicing mutation.

before pericardiocentesis. We speculated that possible causes of death included left ventricular rupture or coronary artery perforation after myocardial infarction (MI), as well as SCAD, accompanied by rupture and bleeding. Because in China, an autopsy is not accepted by the majority of people, because people hope that they will be able to have a complete body after death. The same as the cases reported in our article, in which the family refused autopsy. Interestingly, there have been

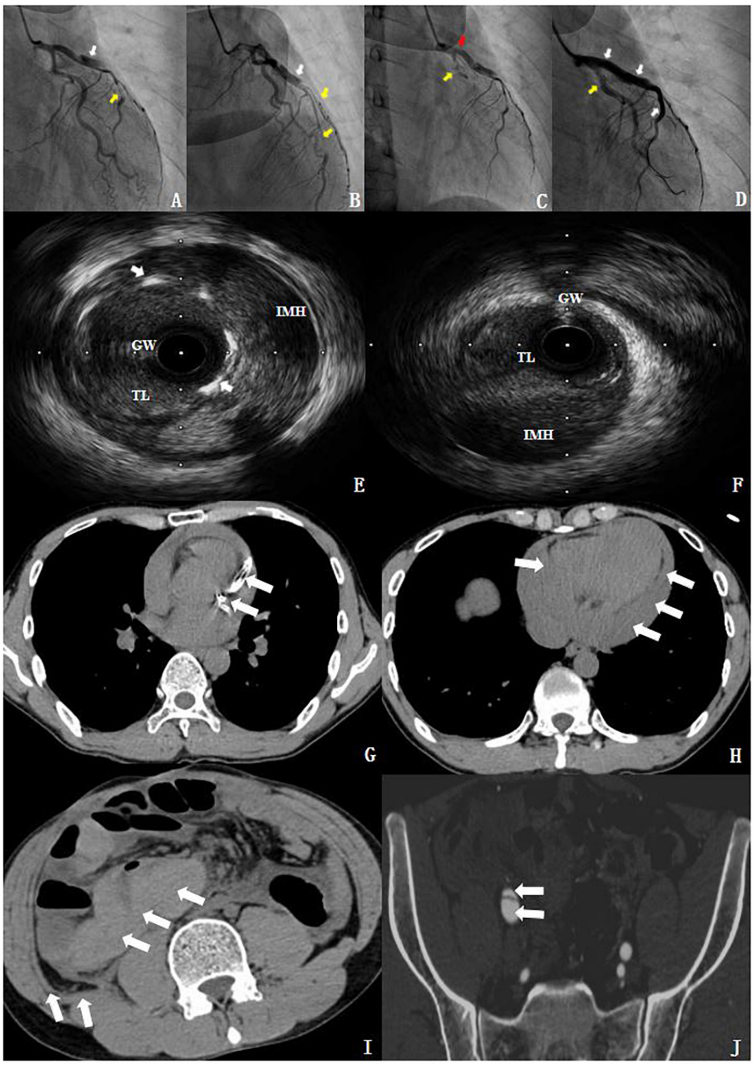

FIGURE 3
Imaging findings. **(A,B)** Coronary angiography (CAG). The white arrow shows a type 1 dissection at the proximal segments of LAD. The yellow arrow indicated a type 2 dissection at the middle segments of the LAD and the diagonal branch. **(C)** The patient showed progression of coronary artery dissection during the CAG. The red arrow demonstrates that the dissection involved the LM and the yellow arrow indicates a type 4 dissection of the LCX. **(D)** After revascularization. The white arrow shows the TIMI flow grade 3 at the LM and LAD. The yellow arrow indicates the TIMI flow grade 3 at the LCX. **(E)** IVUS showed a massive IMH from the media external to the LAD stent; the white arrow indicated the stent struts. **(F)** The true lumen (TL) of the median LCX segment was severely deformed by the dissection and the massive media layer hematoma. GW, guidewire. **(G,H)** The chest CT revealed a stent in the left anterior descending coronary artery and hemopericardium. **(I,J)** The abdominal and pelvic CT showed intestinal wall swelling, hematocele, retroperitoneal hematocele, and an iliac vascular dissection (see section "**Supplementary material**").

few reports of deaths imputed to a fatal vEDS complication (3, 4). Further probing showed that the patient had an unremarkable family history.

Discussion

SCAD often forms a continuously growing false lumen outside of the media layer of the coronary artery wall. Yet, the mechanism of SCAD occurrence is unclear. CAG is the gold standard for the diagnosis of SCAD, and optical coherence tomography (OCT), as well as intravascular ultrasound (IVUS) as essential tools for its confirmation (5) even though extra caution, is needed when imaging patients with such a condition. The cause of SCAD is unknown, but probably includes factors related to gender, especially in perinatal women (6) (the mechanism of effect is unknown), as well as fibromuscular dysplasia, systemic inflammatory condition, and hormone therapies.

Ehlers–Danlos syndrome (EDS) is an inherited connective tissue disorder characterized by congenital connective tissue

TABLE 1 Spontaneous coronary artery dissection (SCAD).

Etiology of non-atherosclerotic SCAD

Predisposing arteriopathy
A. Fibromuscular dysplasia
B. Connective tissue disorder: Marfan's syndrome, Ehlers–Danlos syndrome, Cystic medial necrosis
C. Systemic inflammation: Systemic lupus erythematosus, Crohn's disease, Sarcoidosis
D. Pregnancy
E. Coronary artery spasm
F. Idiopathic
G. Hormonal therapy
Precipitating stress events
A. Intense emotional stress
B. Intense exercise
C. Intense Valsalva-type activities
D. Labor and delivery
E. Cocaine, amphetamines, met-amphetamines, β-HCG

Angiographic classification for SCAD

Type	Characteristics
Type 1	Dissection with visible linear "flap" or dual lumen often associated with contrast hold-up
Type 2	Type 2a dissection with no visible "flap" and distal reconstitution of normal vessel architecture Type 2b dissection with no visible "flap" and no distal reconstitution
Type 3	Focal or tubular stenosis (length typically < 20 mm)that mimics atherosclerosis
Type 4	With a total, usually of a distal vessel, vessel occlusion and no cardiac embolic source and there is subsequent evidence of complete vessel healing in keeping with the natural history of SCAD

dysplasia. Primarily occurring in young and middle-aged women, SCAD is an important, rare, and fatal cause of ACS, with none to few conventional cardiovascular risk factors (7). Contrarily, male patients with SCAD are extremely rare (7, 8), and notably, they more often cite a physical stressor as the cause of the disease instead of anxiety or depression. As one of the predisposing conditions for SCAD, vEDS is a rare and particularly challenging monogenetic disease caused by a mutation in the *COL3A1* gene coding for type III procollagen. Patients with vEDS are at risk of vascular, intestinal, and uterine ruptures (9). SCAD is not common among males, and vEDS is rarer among this group.

The prevalence of vEDS is approximately 1 out of 25,000 people (10), and its primary diagnostic criteria include easy bruising, transparent skin, characteristic facial features, as well as arterial, intestinal, or uterine rupture. The mechanism of SCAD initiation remains unclear since only 1–2% of SCAD has been related to inherited connective tissue disorders (7) (**Table 1**). But, there are currently two potential theories. The first theory involves the "outside-in" mechanism, stipulating that microvascular ruptures lead to the formation of intramural hematoma on the coronary artery wall. Meanwhile, the second theory supports the "inside-out" mechanism, stating that a disrupted continuity or rupture of the endothelium and intima leads to blood penetration through the internal elastic lamina and accumulation in the media (11) (**Tables 1**, **2**). Non-invasive imaging, such as CT coronary angiography (CTCA) and MR angiography, is preferred since invasive angiographies in patients with SCAD have been associated with an increased risk of iatrogenic dissections (1).

As one of the predisposing conditions for SCAD, EDS is an inherited connective tissue disorder, manifesting as congenital connective tissue dysplasia. EDS is classified into six subtypes. Type IV, as the vascular type, also known as vEDS, is an extremely rare autosomal dominant genetic disorder characterized by changes in the vascular structure due to a mutation in the *COL3A1* gene coding for type III procollagen. It leads to increased brittleness of the connective tissue and fatal complications (for example, vascular ruptures, organ ruptures, and fistulae formation) (12). Sadly, vEDS prognosis is the worst among all the types of EDS due to previously mentioned complications (13). SCAD is not common among males, and it is even extremely rare for them to be diagnosed with vEDS. Additionally, a clinical diagnosis of vEDS is often difficult without genetic testing for *COL3A1* mutations.

SCAD treatment during the acute is determined according to the patient's clinical conditions and the TIMI flow grade as shown by CAG. According to present guidelines,

TABLE 2 Intracoronary imaging of spontaneous coronary artery dissection (SCAD) by IVUS/OCT/CT/CMR and management.

Multimodality imaging	Axial resolution (um)	Advantage	Disadvantage or limitation
Intravascular ultrasound (IVUS)	150	A. Blood clearance is not required B. IVUS has greater depth penetration	Poor spatial resolution
Optical coherence tomography (OCT)	10–20(15)	A. Higher spatial resolution B. Provides a finer depiction of vessel's wall characteristic images of SCAD	A. Necessitates blood clearance requiring a high pressure contrast injection B. Depth penetration
Computed tomography coronary angiography (CTCA)		Non-invasive	A. Lower spatial resolution and temporal resolution B. Affected by breathing and heart rate
Cardiac magnetic resonance (CMR)		Non-invasive, safe and non-radiating	A. High price is not easy to popularize B. Affected by breathing and heart rate

Management

A. Conservative management

B. Percutaneous coronary intervention (PCI)

C. Coronary artery bypass grafting (CABG)

D. Adjunctive supportive devices and transplant

E. Medical management (Decide whether to use according to individual's situation)

a. Thrombolysis: Thrombolysis is contraindicated for the acute management of SCAD

b. Antiplatelet therapies: The use of antiplatelet therapies and the duration of treatment remains an area of controversy and divergent practice in SCAD

c. Anticoagulant therapies: Limited to acute phase during revascularization procedures while chronic use should be restricted to situations where there is an unequivocal clinical indication (such as left ventricular thrombus or thromboembolism)

d. Angiotensin converting enzyme inhibitors/angiotensin receptor antagonists: SCAD patients with significant impairment of left ventricular systolic function should follow current guidelines

e. Mineralocorticoid receptor antagonists: SCAD patients with significant impairment of left ventricular systolic function should follow current guidelines

f. Beta-blockers: SCAD patients with significant impairment of left ventricular systolic function should follow current guidelines

g. Vasodilator therapies: Reserved for the empirical treatment of chest pain during the acute phase and recurrent chest pain following the index event

h. Statins: Reserved for patients with conventional indications for treatment independent of their SCAD event

i. Contraception and hormone replacement therapy: A reasonable strategy may be to avoid hormonal contraception where possible. In patients with recurrent cyclical chest pain following SCAD, low dose local hormone delivery intrauterine contraceptive devices have been anecdotally reported to be helpful

F. Cardiac rehabilitation

conservative therapy is the first-line recommended treatment for patients with SCAD. Additionally, a cutting balloon (CB) angioplasty might be an alternative option for SCAD revascularization since it permits the fenestration of the false lumen to allow communication and back-bleed of the intramural hematoma into the true lumen (14). Based on our experience, the distal position of the vascular dissection should be determined under the guidance of IVUS. In this case, the distal and proximal vessels were cut. Experience has shown that it can be cut at multiple positions, and the relatively safe ratio of cutting balloon to vessel diameter is 0.7:1.

Of course, SCAD patients' coronary revascularization is extremely challenging due to coronary arterial fragility in these patients and the tendency for dissections. That is why, conservative medical management strategies are preferred in clinically stable patients with a maintained coronary flow. No prospective randomized data are available to guide medical management and whether the standard ACS pharmacological treatment is beneficial in SCAD is unclear. Thus, these patients, based on national guidelines, are often treated empirically with medicines, such as β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and antiplatelet drugs (7). Of the mentioned drugs, celiprolol is a third-generation cardioselective β1 blocker with a β2 agonist vasodilatory effect. Its preventive effects on arterial mortality and morbidity have been evidenced in one clinical trial [the Beta-Blockers in Ehlers–Danlos Syndrome Treatment (BBEST)]. However, the study had certain limitations. Furthermore, a theoretical risk of vasospasm exacerbation exists with β-blocker treatments (15).

The decision to proceed with PCI or coronary artery bypass surgery (CABG) depends on the patient's acute presentation and technical considerations, which widely differ among clinicians. PCI with stents is recommended in cases where a major coronary artery is involved or if the patient is unstable. Meticulous angiographic techniques should be practiced in patients with SCAD. However, deep catheter intubations should be avoided, with special care given to pressure dampening and coronary injections. CABG in SCAD is generally only used as a bailout strategy and is reserved for failed PCI with ongoing

ischemia or infarction of a significant at-risk myocardial territory (for example, LM dissections with ongoing ischemia/infarction) (7).

Conclusion

In summary, clinicians need to be aware of vEDS as a potential SCAD cause and its various presentations. Additionally, cardiovascular genetic testing and targeted management should be considered for patients with SCAD, especially in younger subjects.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedical Research Ethics Committee, West China Hospital. The patients/participants provided their written informed consent to participate in this case study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QL and MM participated in the design, collected the data, and drafted the manuscript. YH helped to revise the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript.

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Transit time flow measurement guiding the surgical treatment for anomalous origin of the right coronary artery: A case report

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Anomalous origin of a coronary artery from the opposite sinus of Valsalva (ACAOS) in symptomatic patients is a rare but serious finding whose treatment consists of a surgical correction. The surgical treatment has a level of complexity that could vary from unroofing and ostioplasty to coronary artery bypass grafting. We present our management of a 59-year-old woman presenting with chest pain and dyspnea for right ACAOS with an interarterial route. The right coronary artery (RCA) was bypassed with the right internal thoracic artery. An intraoperative transit time flowmetry (TTFM) showed a competitive flow from the native RCA. RCA proximal ligation site was identified intraoperatively, considering the best mean graft flow (MGF) and the absence of ischemic events. The patient was discharged after a week without adverse events. The 1-year follow-up was uneventful. The intraoperative use of TTFM could guide the surgeon's hand making straightforward the surgical treatment for ACAOS.

KEYWORDS

coronary artery, anomalous coronary artery anatomy, ACAOS, transit time flowmetry (TTFM), case report

Background

Anomalous origin of the coronary artery from the opposite sinus of Valsalva (ACAOS) with an interarterial course could lead to fatal outcomes (1). The recommended guideline for symptomatic patients with ACAOS is a surgical approach (2, 3). Several surgical procedures of different technical complexity have been proposed to treat ACAOS (1). New intraoperative technologies could set in in order to help the cardiac surgeon simplifying the operation. Herein, we report a case in which the use of transit time flow measurement (TTFM) simplified the surgical operation of

a young woman with symptomatic right ACAOS and intramural and interarterial course (R-ACAOS-IM).

Case presentation

A 59-year-old white woman presented with chest pain and dyspnoea while sitting and watching a dramatic movie on TV. She had no preceding symptoms, and her past medical history was unremarkable. After admission to the emergency department, the symptoms resolved spontaneously. The myocardial necrosis markers (Troponin I and CK-MB) were not suggestive of myocardial infarction. The ECG revealed a normal sinus rhythm with no ischemic changes. She was transferred to the ward. Physical examination showed normal vital signs, regular heart rate and rhythm, and no extra sounds or murmurs. Transthoracic echocardiogram (TTE) showed preserved left ventricle ejection fraction (LVEF), normal wall motion, and no valvular diseases. The patient had a new onset chest pain while at rest. ECG showed new onset ST depression and T wave inversion in II, III, aVF, and V1-V3. She was quickly treated with sublingual nitroglycerine, and symptoms and ECG changes resolved. Repeat serial troponins resulted negative. She was scheduled for urgent cardiac catheterization with the diagnostic suspect of Prinzmetal angina. Coronary angiography showed unobstructed coronary arteries. After an acetylcholine test, coronary spasms were ruled out. Surprisingly, an R-ACAOS was also found (**Figure 1**). A CT coronary angiogram confirmed the origin of the right coronary artery (RCA) from the left sinus of Valsalva, with an intramural course and a malignant path between the aorta and the pulmonary artery (**Figure 2**). Despite being frightened, the patient consented to surgical correction of the coronary anomaly, which was performed by coronary artery bypass grafting. After a full sternotomy approach, the right internal mammary artery (RIMA) was harvested. Before cutting it distally, the TTFM was used to measure the RIMA flow, which was 22 mL/min. After dissecting the vessel distally, we noticed a nice flow with no sign of RIMA spasm. The RCA was isolated at its mid tract, and an off-pump coronary artery bypass grafting (OPCAB) has been performed with RIMA using a coronary shunt of 1.75 mm. After completing the anastomosis, transit time flowmetry (TTFM) showed a poor graft flow (6 mL/min with a pulsatility index (PI) of 2.0), indicating a competitive flow with the native RCA (**Figure 3**). Therefore, the RCA was proximally isolated and temporary occluded for 10 min in order to evaluate the best graft flow without ischemic drawbacks. At a graft flow of 20 mL/min with a PI of 0.7, the RCA was proximally ligated (**Figure 3**). The patient recovered uneventfully and was discharged 5 days after the operation. The patient was relieved that everything went nicely. One year after surgery, the follow-up evaluation of the patient confirmed the continuous absence of chest pain, dyspnoea, and a negative functional test with exercise stress echocardiography.

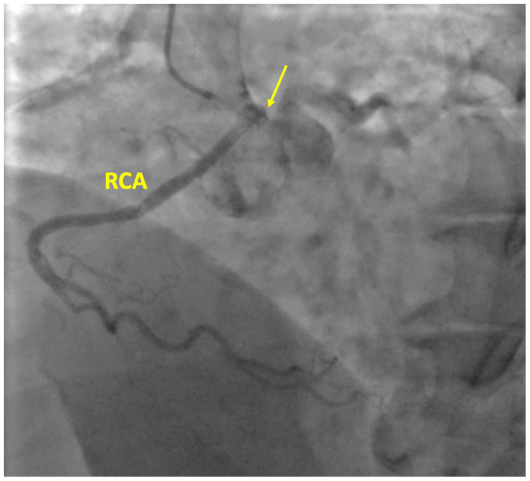

FIGURE 1
Coronary angiography of the right coronary artery (RCA). The yellow arrow is pointing the right coronary ostium originating from the left coronary sinus.

Discussion

To our knowledge, this is the first report to highlight the intraoperative use of TTFM guiding the surgical correction of malignant R-ACAOS-IM.

Despite being founded just on retrospective single-center case series and registry data, Nord American and European guidelines recommend surgery for symptomatic patients (2, 3). However, several surgical procedures are available whose complexity ranges greatly (1, 4).

Unroofing is the procedure of choice for young patients (1). The operation consists of relocating and enlarging the functional orifice to the appropriate sinus and resecting the inner wall of the intramural segment (1). Possible drawbacks of the unroofing procedure are: (1) a post-procedure aortic insufficiency due to the damage or distortion of the intercoronary commissure; (2) possible aortic dissection with coronary occlusion due to the exposure of the layers of the aortic wall to the arterial pressure; (3) aortic or coronary incision after aggressive unroofing (1).

The pulmonary translocation has the goal of decompressing the interarterial course of the anomalous coronary artery

Abbreviations: ACAOS, anomalous origin of the coronary artery from the opposite sinus of Valsalva; OPCAB, off-pump coronary artery bypass grafting; PI, pulsatility index; R-ACAOS, right ACAOS; RCA, right coronary artery; RIMA, right internal mammary artery; TTE, transthoracic echocardiogram; TTFM, transit time flow measurement.

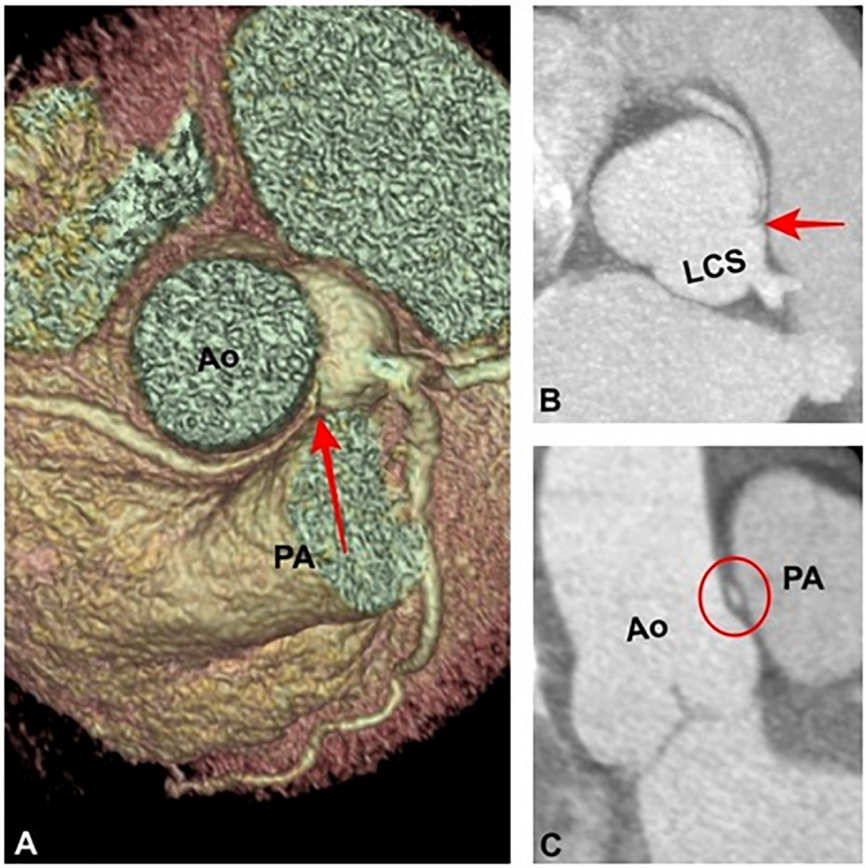

FIGURE 2
(A) Volume rendering and **(B)** maximum intensity projection reformations demonstrating an anomalous origin of the right coronary artery from the left coronary sinus and an its intramural and interarterial course (red arrows). **(C)** Coronal oblique image shows an "elliptic shape" (red circle) of the interarterial course of the right coronary artery (high-risk feature). Ao, Aorta. PA, Pulmonary Artery.

by moving the pulmonary artery confluence away from the anomalous artery either laterally or anteriorly (1). It has a remarkable difficulty level.

Ostial reimplantation or reconstruction could be performed when there is little or no intramural component. It is technically challenging because it requires full mobilization of the coronary artery, avoiding its kinking (1).

Alternatively, a new ostium could be created through an incision in the proper aortic sinus and a pericardial patch. It requires a meticulous reconstruction of the coronary artery itself (1). This is probably the most technically challenging of all of the surgical options.

Acute coronary occlusion, scarring stenosis, or pseudo-aneurysms are early and late reported complications of ostioplasty and ostial reconstruction (1).

An indirect and straightforward way to treat R-ACAOS-IM is coronary bypass grafting. This strategy prevents the risks of the unroofing procedure, and the manipulation of the aorta, and could be performed off-pump, avoiding cardiopulmonary bypass. However, the flow from the anomalous RCA could become competitive, as the flow is unobstructed at rest (5). It could impair the patency of the graft and cause graft failure (5). However, some authors considered the RIMA-RCA graft inadequate to provide a sufficient blood supply and to cover the whole RCA myocardial territory (5). Usually, it requires a proximal ligation of the coronary artery to be successful, sacrificing the blood supply of the very proximal vessels originating from the RCA. In the present case, the TTFM proved to be an easy, safe and quick tool to evaluate the feasibility of proximal RCA ligation. As mentioned in the 2018 ESC/EACTS Guidelines on Myocardial Revascularization, through intraoperative assessment of coronary graft function, TTFM enables quality control in coronary artery bypass grafting (6). Two ultrasonic transducers fixed to a single flow probe are used in transit time ultrasound technology. One sensor sends out an ultrasonic signal that will travel through a pipe packed with fluid. The signal will be reflected by the opposite fixed reflector, which will be picked up by a second sensor. The flow

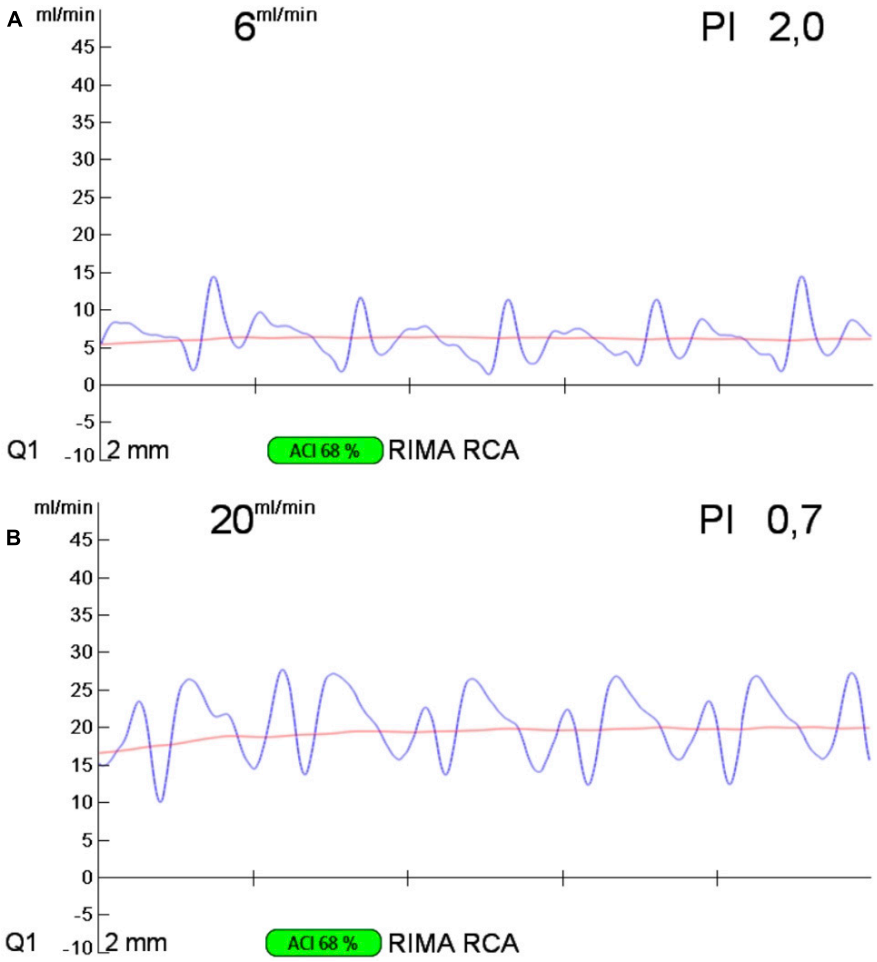

FIGURE 3
Transit time flow measurement of the RIMA-RCA bypass graft before **(A)** and after **(B)** proximal right coronary artery ligation. RIMA, right internal mammary artery; RCA, right coronary artery.

velocity in the pipe will affect the transit time of the signal, which is the difference between the upstream and downstream transit times of the ultrasound beam. The blood flow volume is inversely proportional to the transit time difference. The quality of the target vessel, the distal run-off of the bypass, and the graft quality and diameter will all affect the mean graft flow (MGF). The "PI" calculates the resistance in the graft and the distal target vascular run-off, respectively. The difference between the peak systolic flow and the peak diastolic flow is subtracted from the median flow to get its value (PI). Indicative values of a MGF of 20 mL/min and a pulsatility index (PI) of 5 were suggested in an expert opinion statement (7). A PI of > 5 and an MGF of 20 ml/min may suggest "technically unacceptable grafts." Once it was established, TTFM helped to identify a good site for the RCA ligation. By the use of TTFM, excellent MGF was ensured and ischemic events were prevented.

Conclusion

The intraoperative use of TTFM could be set in guiding the surgeon's hand making safe, easy and quick the surgical treatment for ACAOS with OPCAB.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

and institutional requirements. The patients/participants provided their written informed consent to participate in this study and for the publication of this case report. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FJ and AL drafted the manuscript and designed the study. FG, ML, CB, and VA were responsible for the collection of data and analysis. FJ, GS, and PM revised the manuscript for significant intellectual content. All authors contributed to editorial changes in the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Concurrent acute myocardial infarction and acute ischemic stroke: Case reports and literature review

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Acute myocardial infarction (AMI) and acute ischemic stroke (AIS) are the main causes of disability and mortality worldwide. Although reperfusion therapy is the most effective treatment for the two diseases, it is still a great challenge for treating the two diseases at the same time. Here we share 2 cases: one patient was hospitalized for AMI, developed AIS after receiving percutaneous coronary intervention (PCI), and suffered from cardiac rupture after alteplase thrombolytic therapy. The other patient was admitted for AIS, who had sudden chest pain during the thrombolytic process of alteplase. Considering AMI, emergency PCI was performed, and he was finally discharged.

KEYWORDS

myocardial infarction, acute ischemic stroke, intravenous thrombolysis, percutaneous coronary intervention, electrocardiogram (ECG)

Introduction

Cardiovascular and cerebrovascular diseases remain the leading cause of morbidity and mortality worldwide (1). Acute ischemic stroke (AIS) and acute myocardial infarction (AMI) are mutual risk factors, and both diseases should be timely diagnosed and treated. Sometimes we encounter patients with simultaneous AMI and AIS. As early as 2010, Omar et al. proposed the concept of cardiocerebral infarction (2). The incidence of acute cardiocerebral infarction is as low as 0.009% (3). AMI and AIS can occur at the same time or not (one disease precedes the other) (4). When the two diseases coexist, the condition worsens rapidly. Due to the different order of onset of the two diseases

Abbreviations: AMI, acute myocardial infarction; AIS, acute ischemic stroke; AF, atrial fibrillation; BP, blood pressure; CTA, computed tomography angiography; CAG, coronary angiography; CABG, coronary artery bypass grafting; ECG, electrocardiograph; LAD, left anterior descending artery; LCX, left circumflex artery; NIHSS, national institutes of health stroke scale; NOAC, novel oral anticoagulants; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

(simultaneous cardiocerebral infarction, AMI after AIS, AIS after AMI), different types of AMI and the length of onset time (within or beyond reperfusion time window), the optimal treatment plan and reperfusion method are still uncertain. Therefore, it brings great challenge and pressure to clinicians. We shared two cases to provide relevant evidence for clinical treatment decision-making.

Case 1

A 75-year-old male patient had a history of hypertension, diabetes, stroke and atrial fibrillation (AF), without oral anticoagulants. The patient was admitted to our emergency department due to chest pain for 12 h with heart rate of 90 beats/min and blood pressure (BP) of 120/70 mmHg. Emergency ECG showed AF, significant ST-T abnormality (**Figure 1A**). Transthoracic echocardiography showed left atrial enlargement, LVEF 48%, and minimal mitral regurgitation. AMI was diagnosed, and emergency coronary angiography (CAG) was performed to show diffuse plaque formation of right coronary artery (RCA), with 70% proximal stenosis, 90% middle stenosis, normal left main artery, 80% stenosis in the middle of left anterior descending artery (LAD), and 100% occlusion in the middle of left circumflex artery (LCX) (**Figure 1B**). LCX was considered as the culprit vessel, and finally a drug-eluting stent was implanted for LCX with Thrombolysis in myocardial infarction (TIMI) grade flow of 3 (**Figure 1C**). After percutaneous coronary intervention (PCI), the medicines of aspirin, clopidogrel, rivaroxaban, atorvastatin, metoprolol and irbesartan were used. Re-examination of the echocardiography showed reduced segmental movement of the left ventricular wall, LVEF 55%, no pericardial effusion, and no ventricular thrombosis. 10 days later, the patient had a sudden weakness of right limb and slurred speech. On physical examination, the right nasolabial fold became shallow, and the muscle strength of the right limb was grade 3. Emergency computed tomography angiography (CTA) of cerebral artery showed no obvious large vessel stenosis, no intracerebral hemorrhage (**Figure 1D**). AIS was considered after consultation by a neurologist. As the onset time was less than 4.5 h, intravenous recombinant tissue plasminogen activator (rt-PA) (0.9 mg/kg, total dose 70 mg, time 60 min) was performed. 40 min later, the patient suffered from a sudden drop in BP, unconsciousness, cardiac and respiratory arrest. Cardiopulmonary resuscitation was carried out immediately. Cardiac ultrasound showed a large amount of pericardial effusion. We did a pericardiocentesis and extracted 100 mL of blood fluid. But there were still no vital signs after active rescue. At last, the cause of death was considered to be cardiac rupture.

Case 2

An 84-year-old male patient with a history of cerebral infarction and hypertension was admitted to our emergency department on October 23, 2021. Before admission, the patient took aspirin, atorvastatin calcium tablets, and nifedipine controlled-release tablets orally. She suffered a slurred speech accompanied by right limb weakness for 1 h. Neurological examination indicated that the strength of right muscle was grade 0. And the National Institutes of Health Stroke Scale (NIHSS) score was 14. Cranial vascular CTA showed weak imaging of bilateral anterior cerebral arteries (**Figure 2A**). Diagnosis from the neurologist of AIS was made. Since CTA did not show arterial thrombosis, thrombectomy was temporarily not feasible, and intravenous thrombolysis was selected (rt-PA, 0.9 mg/kg). Forty five minutes later, electrocardiograph monitor showed heart rate of 40 beats/min, BP 70/40 mmHg and ECG showed ST segment elevation of inferior wall leads (**Figure 2B**). Meanwhile the patient felt obvious chest pain. Finally, cardiologists considered acute inferior wall myocardial infarction, and emergency PCI was performed. CAG showed 70% stenosis in the proximal segment of LAD, 80% stenosis in the proximal segment of LCX, 40% stenosis in the proximal segment of RCA, and 95% stenosis in the distal segment of RCA showing thrombus shadow (**Figure 2C**). Considering the culprit vessel was the RCA, thrombus aspiration was performed, and a drug-eluting stent was implanted, with TIMI grade flow of 3 (**Figure 2D**). Oral aspirin, clopidogrel and rosuvastatin were used. 48 h later, head CT showed no bleeding, but with left frontotemporal parietal lobe and left paraventricular infarction. Echocardiography showed minimal tricuspid regurgitation but no thrombus. The patient was actually monitored for AF but this was not detected. The maximum values of cTnI and NT-proBNP was 75 ng/mL and 3,520 pg/mL, respectively. After 2 weeks of treatment, the patient was discharged without chest pain or arrhythmia, but with mixed aphasia and right limbs muscle strength grade 2 (NIHSS 8).

Discussion

Studies have shown that AIS increases the risk of AMI and vice versa. In a retrospective study from 2000 to 2017, among 11,622,528 patients admitted to hospital for AMI, 1.6% (183,896) developed AIS within 24 h. Compared with non-AIS patients, patients with AMI-AIS underwent CAG less frequently (46.9 vs. 63.8%) and PCI was similar (22.7 vs. 41.8%) (5). In another retrospective study from 2003 to 2014, among 864,043 patients admitted to hospital with AIS, 1.6% (66,977) had AMI (79.5% NSTEMI and 20.5% STEMI) within 24 h. The in-hospital mortality of stroke patients with AMI was

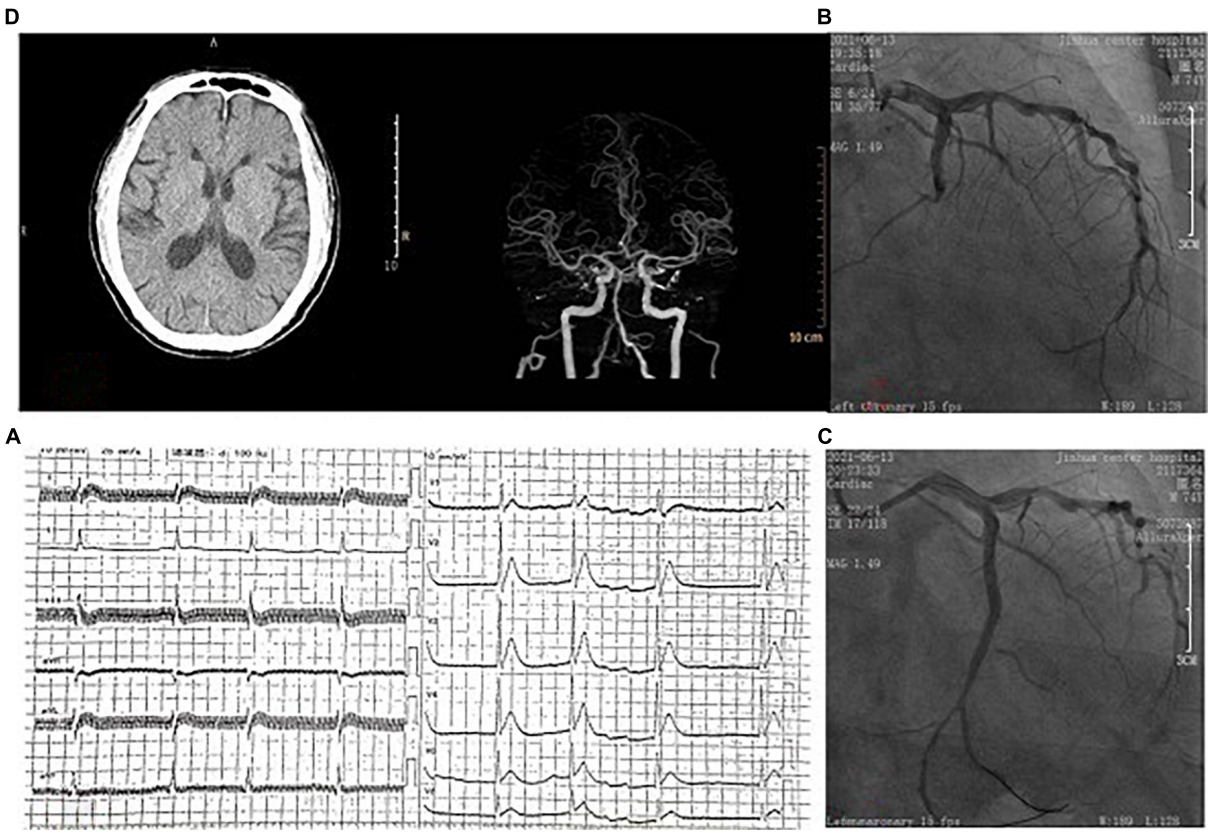

FIGURE 1
(A) On admission, ECG showed atrial fibrillation and ST-segment elevation in the anterior wall leads. **(B)** Coronary angiography showed occlusion of the left circumflex artery. **(C)** Blood flow was restored after coronary stent implantation. **(D)** Brain computed tomography showed no hemorrhage before intravenous thrombolytic therapy.

higher (21.4 vs. 7.1%), and the length of hospital stay and treatment cost increased. Although CAG and PCI can reduce the mortality of patients with AMI-AIS, only 7.5 and 2% of patients received the above treatment, respectively (6). The main reason is that clinicians are concerned about related bleeding complications after interventional therapy, especially for patients with AIS after thrombolytic therapy. Meanwhile, clinical data and relevant guidelines are lacking. Ischemic stroke is one of the serious complications after AMI. The first month after AMI is considered to be the high-risk period of ischemic stroke (7). The 1-year mortality of AMI patients with stroke (51.5%) was 15% higher than that of AMI patients without stroke (37.1%) (8). Independent risk factors for AIS in AMI patients include age, female, history of stroke, diabetes, AF, heart failure, STEMI, CABG, etc. (9). At present, ventricular thrombosis is considered to be the main cause of stroke after AMI, and the local movement disorder of ventricular wall after AMI, blood stasis, inflammation and hypercoagulability are the main cause of ventricular thrombosis (10). However, it is unclear that how to prevent ventricular thrombosis in AMI patients without AF. According to U.S. guidelines, anticoagulation therapy for 3 months may be considered in STMI patients with reduced anterior wall movement or dyskinesia (11). In a Meta-analysis, the addition of oral anticoagulants to antiplatelet agents reduced the risk of cardiovascular death, myocardial reinfarction, and stroke in STEMI patients. But the benefit was not significant in NSTEMI patients (12). As is known, AF is an independent risk factor for stroke. For patients with AF complicated with AMI, triple antithrombotic therapy is currently recommended to reduce the incidence of stroke, and the specific duration of antithrombotic therapy is determined by ischemia-hemorrhage score (13). Interestingly, although PCI can reduce the incidence of AIS in patients with AMI (9), another rare cause of AIS in patients with AMI is PCI or CABG, with an incidence of 0.38%, which generally occurs in the perioperative period and is most common within 24 h after surgery. It is related to the plaque rupture of subclavian artery, aortic arch, carotid artery and other main arteries, and the thrombosis of guide wire and catheter tip (5, 14). The occurrence time of AIS in Case 1 was 10 days after PCI, but it would be difficult to say that the AIS in Case 1 was not related to PCI after 10 days, because previous studies have shown that

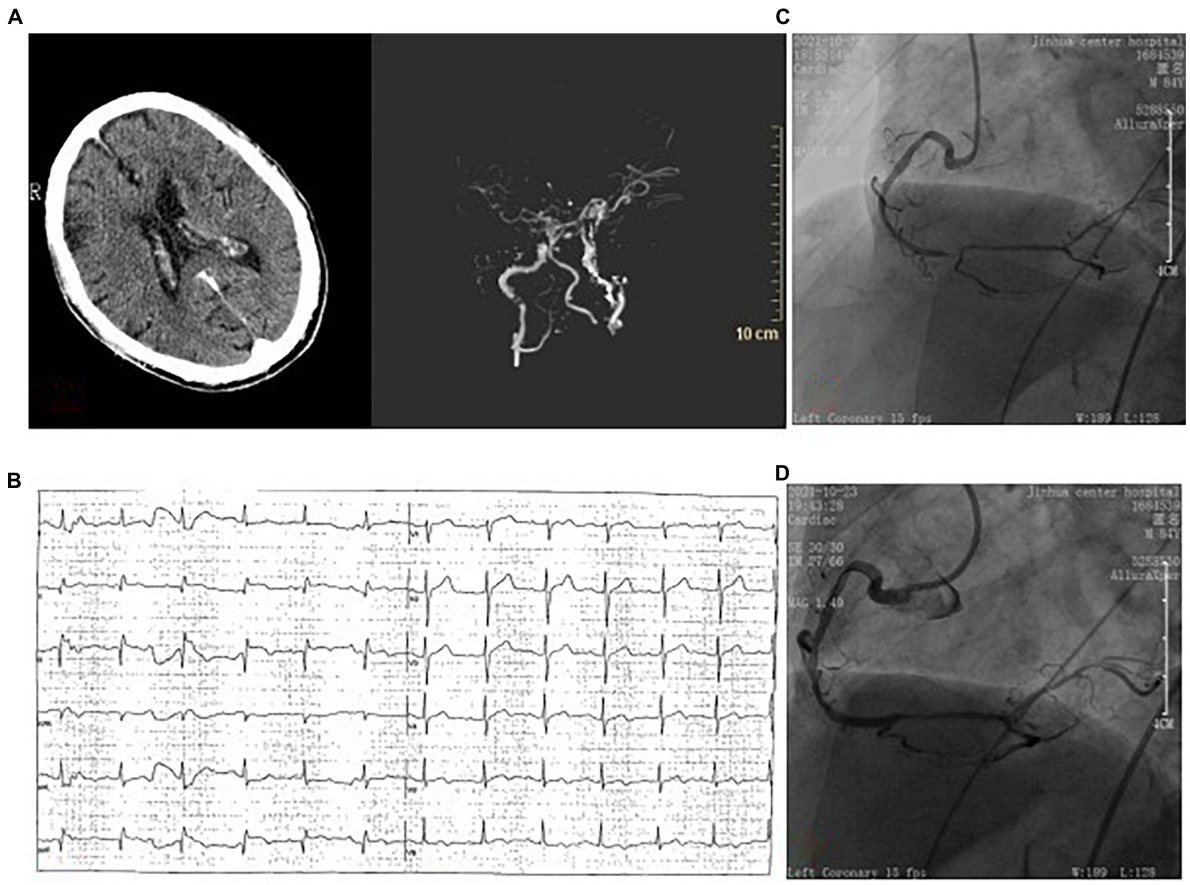

FIGURE 2
(A) Brain computed tomography angiography showed no hemorrhage before intravenous thrombolytic therapy, and showed weak imaging of bilateral anterior cerebral arteries. **(B)** ECG showed ST-segment elevation in the lower wall lead. **(C)** Coronary angiography showed 95% stenosis of the distal right coronary with thrombosis. **(D)** One drug-eluting stent was implanted in the right coronary artery.

there is a heightened risk of stroke even up to several months after PCI (15). Since the patient had AF, it is also possible that the stroke may be caused by shedding of thrombosis in the heart. The pathophysiological mechanism of AMI in AIS patients has been found to be higher prevalence of coronary heart disease and more cardiovascular risk factors. After stroke, autonomic nerve dysfunction and increased catecholamine hormone secretion lead to potential aggravation of coronary artery disease or stress myocardial injury (16). It was previously reported that a 41-year-old female patient was hospitalized for AIS with chest pain before thrombolytic therapy, which was considered to be complicated with acute anterior STMI. Thrombolytic therapy with alteplase was applied, but the patient suffered repeated chest pain, and emergency PCI was performed before she was eventually discharged (17).

The simultaneous occurrence of AMI and stroke is uncommon. Clinically, there are generally three types: the first is when AIS and AMI occur at the same time, the second is when AIS occurs after subacute myocardial infarction, and the third is that AMI occurs at the early stage of systemic thrombolysis in AIS (18). For heterochrony AMI and AIS, there is no doubt that dealing with the disease happened first, but at the same time, it will also bring some difficulty and relative contraindications to the treatment of subsequent diseases, such as ischemic stroke in the nearly past 3 months (excluding stroke within 4.5 h) is regarded as thrombolysis contraindications for AMI patients (19). AMI in the last 3 months is considered as a contraindication for thrombolytic therapy in AIS (20). Cardiac rupture and cardiac tamponade are the most serious complications of thrombolysis in AMI patients, with an incidence of 1–8% (21). Mannino et al. reported a case of acute anterior wall myocardial infarction after thrombolytic therapy in AIS patient, and finally suffered cardiac rupture and death. Meanwhile, the paper summarized 11 previously published cases of AMI after thrombolytic therapy in AIS patients, with a mortality rate as high as 64% (22). In this paper, stroke occurred after AMI in Case 1, and thrombolytic therapy was applied, resulting in complications of cardiac rupture and pericardial tamponade. The main cause of cardiac rupture is the dissolution of fibrin clots in the necrotic myocardial wall (18).

There may have deficiencies in the management of Case 1. For patients with AIS of < 4.5 h duration, who used a NOAC during the last 48 h before stroke onset, intravenous thrombolysis is not suggested (23). We were unable to test for anti-Xa activity, and Andexanet alfa was not easily got. CTA showed no large vessel occlusion, so mechanical thrombectomy was not appropriate. Given the patient's low dose of rivaroxaban, 2.5 mg twice a day, we speculated that the NOAC drug levels were low. The patient's ischemic symptoms worsened. Finally, intravenous thrombolysis was performed. In Case 2, AMI occurred during thrombolytic period of stroke, and emergency PCI was executed due to hemodynamic instability and arrhythmia. Therefore, for patients with AMI during thrombolytic period of stroke, emergency PCI may bring benefits under the condition of hemodynamic instability.

For patients with concurrent or near concurrent AMI and stroke, there is still a lack of consensus on corresponding guidelines and treatment is very difficult. The mechanisms of simultaneous occurrence of cardiocerebral infarction are as follows (3, 24, 25). (1) Simultaneous thrombosis of coronary and cerebral arteries, such as AF, type I aortic dissection involving coronary artery and common carotid artery, electrical injury resulting in coronary and cerebral artery spasm, etc. (2) Stroke caused by heart disease, such as intraventricular thrombosis, patent foramina ovale (complicated with right heart infarction), and cardiac shock after AMI. (3) Cerebral-cardiac axis disorder or cerebral infarction lead to myocardial injury. The insular cortex plays an important role in the regulation of central autonomic nervous system. Pathological changes of insular cortex are related to AF, activation of cardiac sympathetic nerve, myocardial injury and interruption of the circadian rhythms of BP.

Previous published articles have shown that ST segment elevation of inferior wall lead is the most common ECG in patients with AMI-AIS, and the treatment and clinical prognosis vary from case to case. The case 2 also had inferior wall AMI, but due to the lack of large sample data, the correlation between inferior wall AMI and stroke cannot be explained at present (24). In the acute stage of stroke, troponin in some patients increases and ST-T changes occur in ECG (26), which brings difficulties to the diagnosis of AMI-AIS. Therefore, some scholars suggested that combined intravascular therapy could improve the diagnosis and success rate of AMI-AIS (3). Intravenous rt-PA thrombolytic therapy is a first-line therapy for stroke patients with onset less than 4.5 h (19). PCI is the first-line treatment for AMI, but for hospitals without PCI capability and STEMI within 12 h of onset, thrombolytic therapy is an alternative, while NSTEMI is not suitable for thrombolytic therapy (20). Kijpaisalratana et al. proposed a management method based on hemodynamic state, and named "hyperacaute simultaneous cardiocerebral infarction" for the patients with onset less than 4.5 h. For patients with cardiocerebral infarction with hemodynamic instability, emergency PCI was performed first, followed by intravascular treatment for AIS with large vascular occlusion. For patients with stable hemodynamics, rt-PA thrombolytic therapy was selected according to the standard dose of stroke, followed by vascular therapy for AIS and PCI for AMI according to the situation (24). The 2013 AHA/ASA guidelines recommended that thrombolytic therapy may be beneficial for patients with AMI-AIS within 3–4.5 h, and rt-PA is the only one recommended for stroke (27). However, the dose and duration of rt-PA are still controversial. Some scholars suggested that for patients with AMI-AIS within 4.5 h of onset, especially for patients of anterior wall AMI with reduced LVEF, rt-PA can be given according to the doses of STEMI thrombolysis, followed by PCI (28). The 2018/AHA/ASA recommended that patients with concurrent cardiocerebral infarction within 4.5 h should be given rt-PA at stroke dose, followed by PCI (Class IIa; C) (29). 2021/ESO guidelines suggested that in the uncommon case scenario of an AIS complicating an AMI (< 6 h), alteplase may be administered if there are no other contraindications to intravenous thrombolysis. Mechanical thrombectomy may be an effective therapy in patients with large vessel occlusion and recent myocardial infarction (23). Moreover, successful thrombolytic case of Tenecteplase (TNK) have also been reported (30).

Conclusion

For patients with AMI-AIS, the clinical manifestations are diverse and complex. There is a lack of studies with large clinical sample data. The treatment includes but is not limited to intravascular thrombectomy, thrombolysis and coronary intervention. Ultimately, individualized plans need to be formulated under multi-disciplinary cooperation. At the same time, clinicians also need to consider the worst clinical outcome before making decisions, and strengthen communication with patients' families to avoid unnecessary doctor-patient disputes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

C-HB and Y-BP contributed significantly to analysis and manuscript preparation. CZ and X-MW performed in clinical data collection. C-HB and CZ wrote the manuscript. Y-BP checked and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Refractory cardiac arrest supported with veno-arterial-venous extracorporeal membrane oxygenation and left-ventricular Impella CP®–Physiological insights and pitfalls of ECMELLA

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Introduction: To the best of our knowledge, this is the first case report which provides insights into patient-specific hemodynamics during veno-arterio-venous-extracorporeal membrane oxygenation (VAV ECMO) combined with a left-ventricular (LV) Impella® micro-axial pump for therapy-refractory cardiac arrest due to acute myocardial infarction, complicated by acute lung injury (ALI).

Patient presentation: A 54-year-old male patient presented with ST-segment elevation acute coronary syndrome complicated by out-of-hospital cardiac arrest with ventricular fibrillation upon arrival of the emergency medical service. As cardiac arrest was refractory to advanced cardiac life support, the patient was transferred to the Cardiac Arrest Center for immediate initiation of extracorporeal cardiopulmonary resuscitation (ECPR) with peripheral VA ECMO and emergency percutaneous coronary intervention using drug eluting stents in the right coronary artery. Due to LV distension and persistent asystole after coronary revascularization, an Impella® pump was inserted for LV unloading and additional hemodynamic support (i.e., "ECMELLA"). Despite successful unloading by ECMELLA, post-cardiac arrest treatment was further complicated by sudden differential hypoxemia of the upper body. This so called "Harlequin phenomenon" was explained by a new onset of ALI, necessitating escalation of VA ECMO to VAV ECMO, while maintaining Impella® support. Comprehensive monitoring as derived from

the Impella® console allowed to illustrate patient-specific hemodynamics of cardiac unloading. Ultimately, the patient recovered and was discharged from the hospital 28 days after admission. 12 months after the index event the patient was enrolled in the *ECPR Outpatient Care Program* which revealed good recovery of neurologic functions while physical exercise capacities were impaired.

Conclusion: A combined mechanical circulatory support strategy may successfully be deployed in complex cases of severe cardio-circulatory and respiratory failure as occasionally encountered in clinical practice. While appreciating potential clinical benefits, it seems of utmost importance to closely monitor the physiological effects and related complications of such a multimodal approach to reach the most favorable outcome as illustrated in this case.

KEYWORDS

cardiac arrest, Impella®, acute coronary syndrome, extracorporeal cardiopulmonary resuscitation, ECMELLA, extracorporeal membrane oxygenation, unloading

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is the initiation of veno-arterial extracorporeal membrane oxygenation (VA ECMO) during refractory cardiac arrest, that is failure to obtain return of spontaneous circulation (ROSC) after prolonged conventional resuscitation attempts (1, 2). The use of VA ECMO enables clinicians to establish a "bridge to therapy" (such as emergency coronary angiography/intervention), "bridge to decision" or "bridge to recovery" while enabling proper organ perfusion. ECPR has been recently shown to have the potential to improve survival and/or neurological outcome compared to conventional CPR (3, 4). Given its relative ease of implantation and immediate provision of full circulatory support, ECPR with VA ECMO has gained wider application in carefully selected patients, with a 10-fold increase in use between 2003 and 2014. ECPR has been advocated in recent international guidelines (5–8). Very recently, adjunct left-ventricular (LV) unloading with an Impella® micro-axial flow pump (Abiomed, Danvers, USA) as an adjunct to VA ECMO (so called "ECMELLA" or "ECPELLA") has been proposed during ECPR. ECMELLA has been shown to be associated with improved survival after therapy-refractory cardiac arrest, possibly by mitigating inherent shortcomings of VA ECMO, such as hemodynamic overload of the left ventricle (9–11).

To our best knowledge, this is the first case report to comprehensively illustrate critical insights into hemodynamic monitoring as readily accessible after ECPR and immediate LV unloading by Impella®. The integration of all vital monitoring information sets the stage for optimal, patient-specific tailoring of mechanical circulatory support (MCS) at the bedside throughout the course of critical care management. This is also reflected by a successful escalation of MCS to Impella® and veno-arterial-venous ECMO (VAV ECMO) to control the complication of sudden differential hypoxemia of the upper body due to acute lung injury (ALI). As "physiology on display" this case illustrates the complex hemodynamic principles of combined MCS and informs the clinician on the adequacy of the conceived clinical management at the bedside. Close monitoring allows for timely detection of suboptimal MCS, related complications and eventually the initiation of additional interventions, all being critical elements for a successful deployment of ECPR.

Case description

A 54-year-old male patient presented with acute onset of chest pain, severe dyspnea, sweating, anxiety and arterial hypotension at his home. ST-segment elevations in leads II, III, and aVF were detected on the first electrocardiogram (ECG) by the emergency medical service (EMS). Apart from smoking (equivalent to 24 pack years), the patient's history did not reveal additional cardiovascular risk factors and his family history was unremarkable.

In the presence of the EMS, the patient collapsed due to ventricular fibrillation. Immediate CPR was commenced on scene (i.e., no no-flow time) in accordance with current guidelines on advanced cardiac life support (ACLS). Mechanical ventilation was provided with synchronized intermittent mechanical ventilation (SIMV). After 15 min of refractory CPR, the EMS decided to transport the patient to the Cardiac

Arrest Center by utilizing a mechanical resuscitation device (CorPulse®, GS Elektromedizinische Geräte G. Stemple GmbH) as a potential candidate for ECPR since all ECPR criteria were fulfilled (7, 12). Upon arrival in the cardiac catheterization laboratory, the patient's initial pH was 6.67, serum lactate level 88 mg/dL, partial pressure of CO_2 71 mmHg and end-tidal CO_2 13 mmHg. According to current guidelines, 10 electrical defibrillations, 7 mg epinephrine and 450 mg amiodarone were administered in total. Upon discretion of the ECPR team, VA ECMO support was initiated after 32 min of total low-flow time (**Figures 1**, **2A**). The cardiac rhythm deteriorated from persistent ventricular fibrillation to asystole upon VA ECMO cannulation.

Emergent coronary angiography under VA ECMO revealed a proximal occlusion of the right coronary artery, which was successfully revascularized with two drug eluting stents. Echocardiographic LV distension was detected in the asystolic patient, wherefore a LV micro-axial pump (Impella CP®) was inserted transfemorally to ensure LV unloading and increase cardiac output (**Figures 1**, **2B**) (ECMELLA). Upon addition of Impella® support, the estimated mean intracavitary left-ventricular pressure (LVP) decreased from 78 to 9 mmHg within 20 seconds (**Figure 3A**). Despite coronary revascularization, the patient remained in asystole while ECMELLA provided adequate systemic hemodynamic support, i.e., aortic pressure of approximately 70mmHg, while assuring optimal LV loading conditions at a level comparable to physiological diastolic LVPs (**Figure 3B**).

The patient was then admitted to the cardiac intensive care unit (ICU) for post-resuscitation care (13) including targeted temperature management, circulatory and respiratory management (e.g., norepinephrine infusion), as well as renal replacement therapy due to acute kidney injury. ROSC (sinus rhythm with pulsatile LVPs) was ultimately observed approximately two hours after ECMELLA initiation (**Figure 3C**).

On ICU day two, near-infrared spectroscopy (NIRS) indicated a decline in cerebral oxygen saturation during appropriate LV unloading. A chest X-ray showed bilateral pulmonary infiltrates compatible with ALI, most likely caused by a combination of aspiration pneumonia, severe transient pulmonary congestion and ischemia-reperfusion-related pulmonary inflammation. Standardized management was initiated in accordance with current ALI/ARDS and ECPR guidelines, including broad spectrum antibiotics and lung-protective mechanical ventilation (pressure-controlled ventilation mode) during ECMO treatment with low tidal volumes (6-8 ml/kg ideal body weight) and minute ventilation (i.e., avoidance of barotrauma) and with high positive end-expiratory pressures (PEEP) of at least 12 mmHg (i.e., maintenance of alveolar inflation) (7, 14). Prone positioning was not performed due to combined MCS. NIRS readings and right radial arterial blood oxygen saturation remained impaired, indicating hypoxemia of the upper body compatible with differential hypoxemia (**Figures 4A–C**). Optimization of ventilator settings were not sufficient, wherefore – according to guidelines by the Extracorporeal Life Support Organization (ELSO) guidelines – VA ECMO was converted to VAV ECMO via the right jugular vein, while continuing concomitant Impella® support (**Figure 2C**) (7).

As a result, NIRS readings and right radial oxygen saturations normalized (**Figure 4D**). The initiation of VAV ECMO resulted in a reduction of extracorporeal support flow into the arterial part of the systemic circulation, as the total flow of arterialized extracorporeal blood was divided into a venous and arterial limb of the VAV ECMO circuit. This resulted in reduced LV afterload and increased Impella® pump flow (**Figure 3D**). Finally, the patient recovered clinically and hemodynamically including increasing LVPs, aortic valve re-opening and improved LV ejection fraction (LVEF) (**Figure 3E**), allowing for stepwise weaning from VAV ECMO and Impella®.

Metabolic homeostasis, i.e., pH and lactate levels, was reached within days, while kidney function recovered and infection, i.e., leukocytes and C-reactive protein levels, diminished after antibiotic treatment (**Supplementary Figure 1** in **Supplementary material**). The patient was discharged from the hospital with a good neurologic outcome (classified as a Cerebral Performance Category [CPC] scale of 1) on day 28. Follow-up in the *ECPR Outpatient Care Program* of the Cardiac Arrest Center after 12 months following the index event showed good neurological recovery but impaired exercise capacities (see "Patient Perspective") (15).

Discussion

Although ECPR has recently gained wider attention with increasing application rates, patient selection, duration of cannulation, as well as survival and neurologic outcomes vary widely across institutions (1). Careful patient selection is crucial for successful outcomes but remains challenging in emergency settings with remarkable time constraints and lack of information on patient history. Based on international guidelines, ECPR should be considered in carefully selected patients based on generally available parameters, such as patient age ≤70 years, witnessed cardiac arrest, low-flow time ≤60 min, no-flow time ≤5 min and exclusion of asystole on the initial ECG, active bleeding or terminal illness (7, 12).

In the presence of specific EMS infrastructures and adequate adherence to aforementioned selection criteria, ECPR has great potential to significantly improve patient survival in dedicated centers. However, MCS remains a complex and demanding technique requiring solid logistics and multidisciplinary expertise. To provide a successful ECPR program including critical care management, it is of pivotal importance to gather and maintain profound

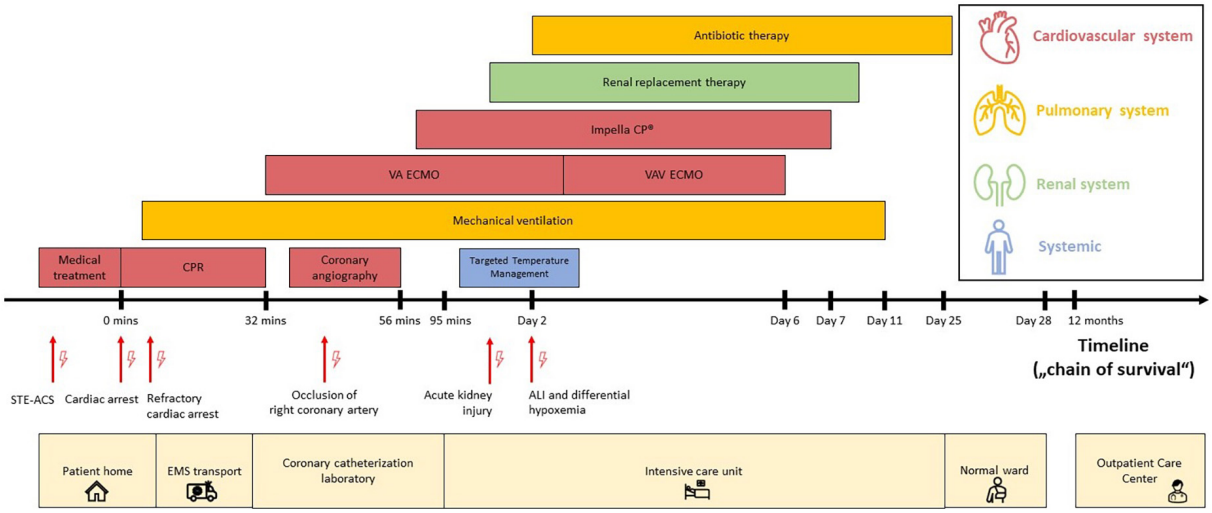

FIGURE 1
Timeline ("chain of survival") with data on the episodes of care. The timeline ("chain of survival") reflects the pre-, intra- and post-hospital course of the cardiac arrest patient, which includes the period from onset of patient symptoms for suspected STE-ACS to hospital discharge and follow-up assessment in the *ECPR Outpatient Care Program* of the Cardiac Arrest Center. Each location is displayed at the bottom (light yellow color). Each critical clinical diagnosis is highlighted with red arrows (and lightning symbols) at the timeline. The provided medical procedures are colorized by organ system: cardiovascular system (red), pulmonary system (dark yellow), renal system (green) and non-specific (blue). The image scaling does not correlate with the actual time. Abbreviations: acute lung injury (ALI); cardiopulmonary resuscitation (CPR); emergency medical service (EMS); left ventricle (LV); ST-segment elevation acute coronary syndrome (STE-ACS); veno-arterial extracorporeal membrane oxygenation (VA ECMO); veno-arterio-venous ECMO (VAV ECMO).

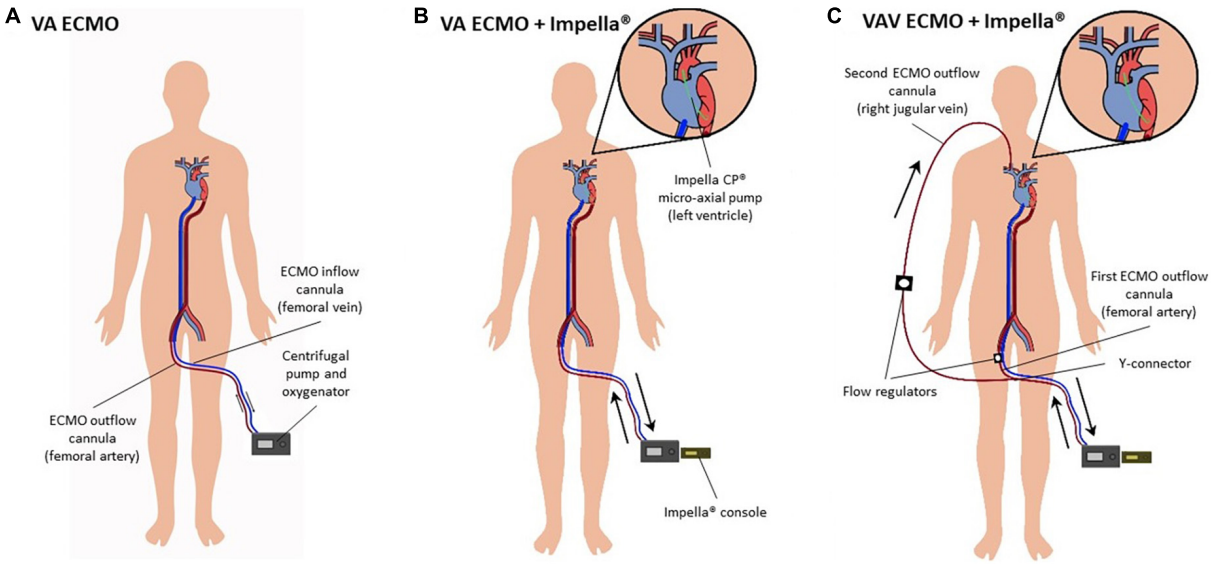

FIGURE 2
(A–C) Diagram on configurations of percutaneous mechanical circulatory support devices. **(A)** Peripheral VA ECMO. Poorly oxygenated blood is drawn from the femoral vein, oxygenated in a membrane oxygenator and returned by a centrifugal pump via the common femoral artery. **(B)** VA ECMO and Impella® pump ("ECMELLA"). The Impella® pump is placed across the aortic valve to provide continuous blood flow from the LV into the proximal ascending aorta. **(C)** VAV ECMO and Impella®. VAV ECMO is a triple cannulation technique by "upgrading" the VA ECMO configuration. A third cannula is inserted into the jugular or subclavian vein. The ECMO outflow with oxygenated blood is diverted into two cannulas by a Y-connector, one cannula toward the aorta via the common femoral artery and one toward the right atrium via the jugular or subclavian vein. Flow regulators control blood flow into the arterial and venous circuit, respectively. Abbreviations: left ventricle (LV); veno-arterial extracorporeal membrane oxygenation (VA ECMO); veno-arterio-venous ECMO (VAV ECMO).

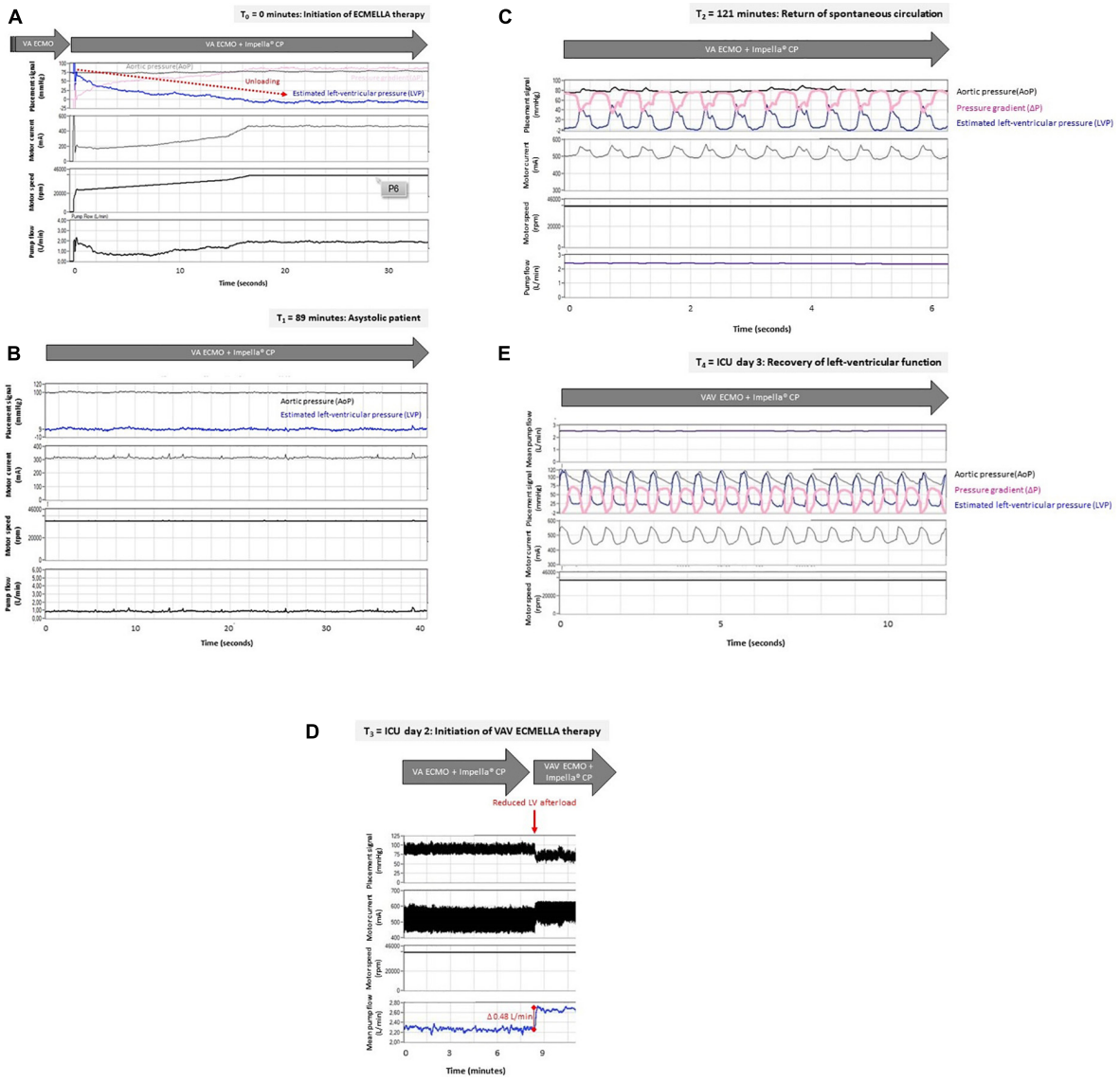

FIGURE 3
(A–E) Left-ventricular unloading in a patient with out-of-hospital cardiac arrest treated with VAV ECMO and Impella® pump. Raw data were retrospectively retrieved from the Impella CP® console (Abiomed, Danvers, USA). For each given time point after initiation of ECMELLA therapy (T0) the estimated left-ventricular pressure (LVP in mmHg), aortic pressure (AoP in mmHg, derived from Impella® pressure sensor) or mean arterial pressure (MAP in mmHg), as well as Impella® motor current (milliampere, mA), Impella® motor speed (rotations per minute, rpm) and Impella® pump flow (liters per minute, L/min) are displayed. LVP was estimated based on AoP and pressure gradient (ΔP in mmHg, derived from Impella® motor current) as follows: LVP = AoP − ΔP. **(A)** Impella CP® was inserted transfemorally in an asystolic patient with pre-existing VA ECMO. Displayed are the first 34 s after start of Impella CP® indicated by increasing motor current and motor speed. Depending on the Impella CP® flow (up to 2 L/min), the estimated LVP decreased to 9 mmHg (i.e., LV unloading indicated by red arrow). Therefore, despite asystole, the patient exhibited physiologic AoP (i.e., 75 mmHg) provided by VA ECMO flow of 4 L/min with sufficient unloading of the LV (physiologic LVP – LVEDP of 9 mmHg). **(B)** The patient remained in asystole without ROSC for approximately two hours after initiation of ECMELLA therapy indicated by static AoP and estimated LVP (no pulsatility). In this case, an Impella® pump flow of 1 L/min was sufficient to unload the LV (estimated LVP, i.e., LVEDP under asystole of 9mmHg) while a VA ECMO flow of 4 L/min provided a sufficient hemodynamic support (i.e., MAP 100 mmHg). **(C)** ROSC with sinus rhythm was achieved after approximately two hours following initiation of ECMELLA therapy as being indicated by undulating estimated LVP (pulsatility indicating cardiac contractions). Flat AoP (greater than estimated LVP) indicates lack of aortic valve opening. Of note, Impella® pump flow was set to 2.5 L/min which reduced LV preload. VA ECMO flow was set to 4 L/min. **(D)** Two days after ICU admission, VA ECMO therapy was advanced to VAV ECMO therapy while the Impella® pump remained inserted. Induction of VAV ECMO therapy (i.e., reduction of ECMO outflow to the aorta and therefore reduction in LV afterload) was associated with increased mean Impella® pump flow (increase in Impella® pump flow of 0,48 L/min, indicated by red line) with given constant pump settings (Impella® motor current). Impella pump flow was 2.7 L/min, VA ECMO flow was 2.5 L/min and VAV ECMO flow was 1.5 L/min. **(E)** Differential hypoxemia was successfully reversed by VAV-ECMELLA. LV function fully recovered over the next days. Estimated LVP was now greater than AoP resulting in opening of aortic valve and pulsatile aortic pressures (MAP 75 mmHg) despite unloading (Impella® pump flow 2 L/min). ECMO flow was 1.5 L/min. Abbreviations: ECMELLA (VA ECMO plus Impella CP®); intensive care unit (ICU); left-ventricular (LV); return of spontaneous circulation (ROSC); veno-arterial extracorporeal membrane oxygenation (VA ECMO); VAV-ECMELLA (VAV ECMO plus Impella CP®).

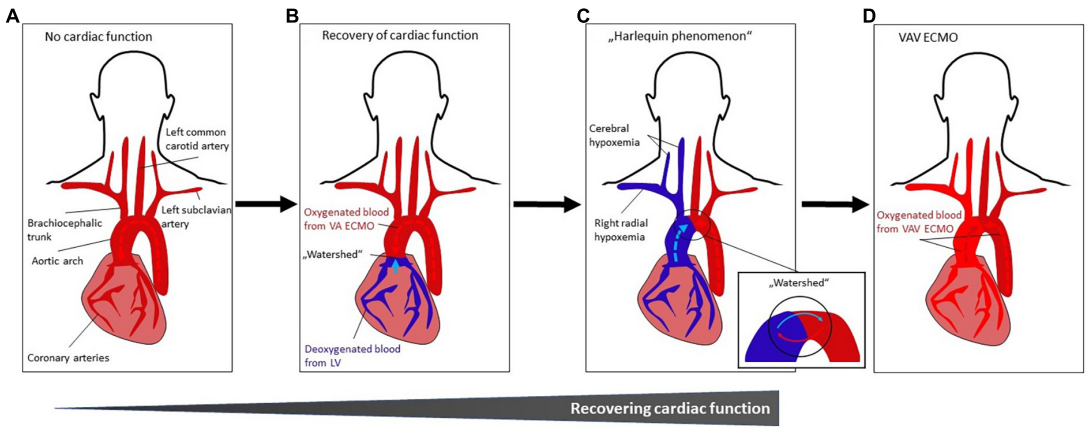

FIGURE 4
(A–D) Occurrence and treatment of differential hypoxemia during VA ECMO treatment. **(A)** *No cardiac function.* Systemic perfusion with oxygenated blood (indicated by dark red color) is solely dependent from VA ECMO flow which is infused retrogradely toward the heart. **(B)** Recovery of cardiac function with impaired pulmonary gas exchange. The LV starts ejecting poorly oxygenated blood from the pulmonary circulation (indicated by blue color) that mixes with oxygenated blood from the VA ECMO ("watershed" or "mixing cloud"). The location of the "watershed" depends on the LV function and the VA ECMO flow. With severe myocardial dysfunction (e.g., due to cardiac arrest), the watershed is close to or at (if asystolic patient) the aortic valve. **(C)** *Harlequin phenomenon.* With improving LV function, the "watershed" may move more distally in the aortic arch. As a result, given impaired pulmonary function, poorly oxygenated blood from the LV is ejected into the aortic arch, coronary and cerebral arteries, resulting in ischemia and cyanosis of the upper body (in this case, right upper body), while the lower body is sufficiently oxygenated by the VA ECMO circuit. This phenomenon is known as *differential hypoxemia*, *watershed phenomenon*, *two-circulation syndrome* or *Harlequin phenomenon*. **(D)** *VAV ECMO.* The Harlequin phenomenon (**Figure 3C**) can be treated by converting VA ECMO to VAV ECMO. Thus, ECMO-oxygenated blood (indicated by lighter red color) is infused from a third ECMO cannula via the jugular or subclavian vein through and the pulmonary circulation into the LV and upper body (see **Figure 1C**). Abbreviations: left ventricle (LV); veno-arterial extracorporeal membrane oxygenation (VA ECMO); veno-arterio-venous ECMO (VAV ECMO).

knowledge on the physiology and peculiarities of different MCS modalities including combined support strategies among healthcare providers involved in patients' daily management. This case comprehensively illustrates the spectrum of critical hemodynamic and related critical care challenges of VA ECMO and VAV ECMO support and adjunct use of Impella®.

Veno-arterial extracorporeal membrane oxygenation

In this clinical case, cardiac arrest was refractory to conventional resuscitation attempts requiring ECPR with VA ECMO prior to coronary revascularization.

Technique

There are two VA ECMO cannulation principles - peripheral and central (16).

Peripheral cannulation

Peripheral VA ECMO is the preferred strategy for ECPR due to its relative ease and rapidity of cannulation. Through a venous cannula (femoral vein, multistage cannula in superior/inferior vena cava and right atrium), blood is drained from the venous system by an extracorporeal centrifugal pump, oxygenated in a membrane oxygenator and returned to the arterial circulation via a cannula in the common femoral artery (**Figure 2A**). Notably, VA ECMO blood flow into the femoral artery and aorta is continuous and directed retrogradely as compared to physiological conditions, both potentially contributing to an increased cardiac afterload. VA ECMO allows for systemic circulation with oxygenated blood to adequately perfuse all end-organs after cardiac arrest, commonly striving for 4 L/min in adults. Due to the lack of palpable femoral pulsatility during cardiac arrest, ultrasound- or fluoroscopic-guided cannulation or surgical cut-down should be considered to facilitate cannulation, which is well possible in peripheral VA ECMO under conditions of on-going CPR.

Central cannulation

In central VA ECMO, at least one of the cannulas (venous or arterial) is placed directly in a cardiac chamber or central vessel (i.e., vena cava, pulmonary artery or aorta). Central VA ECMO necessitates open cardiac surgery and allows to obtain higher VA ECMO flows due to shorter and larger bore cannulas and is generally considered in the context of cardiac surgery or if peripheral cannulation is deemed impossible.

Relevant physiological considerations

Given the continuous and retrograde nature of aortic perfusion in peripheral VA ECMO, an increased LV afterload and related stresses on the myocardium may commonly occur.

Hence, the LV pressure-volume loop is shifted upwards and rightwards (**Supplementary Figure 2**) (17). In more detail, higher LV end-diastolic volumes (LVEDV) and pressures (LVEDP) can be observed, as being described in our clinical case (**Figure 3A**). This may formally be translated into increased stroke work and enhanced myocardial oxygen demand, especially when considering that increased myocardial stresses may also compromise myocardial perfusion and further reduce myocardial oxygen delivery. LV hemodynamic overload might result in increased left atrial and pulmonary capillary wedge pressures (PCWP) that, in turn, promote unwanted pulmonary congestion and impaired pulmonary oxygen exchange. This creates a vicious circle, where LV contractility may potentially further be impaired cumulating into a progressive inability to eject blood against an increased LV afterload. In case of severe LV dysfunction, as commonly encountered following cardiac arrest, a condition of severe hemodynamic LV overload may occur. Without urgent correction, this may deteriorate toward life-threatening conditions such as aortic valve standstill, impending LV cavity thrombosis. Furthermore, hydrostatic pulmonary edema as well as ALI may ensue, the latter further complicating adequate pulmonary gas exchange and tissue perfusion, which in combination with ventricular arrhythmias and overload-induced irreversible myocardial damage or hampered recovery may jeopardize a good clinical outcome (1).

On the other hand, if cardiac function starts recovering while the pulmonary gas exchange remains impaired due to a complex multi-mechanistic ALI, the LV will potentially eject poorly oxygenated blood into the aorta that will mix with the properly oxygenated ECMO-derived blood. The retrogradely infused blood arising from the VA ECMO circuit and entering the aorta toward the heart meets the blood that is (poorly) oxygenated in the lungs and ejected by the native heart ("watershed" or "mixing cloud") (**Figures 4A–C**). The location of the "watershed" depends on the delicate balance between the native LV function and the degree of VA ECMO flow. With severe myocardial dysfunction (as being observed after cardiac arrest), the watershed is close to or at the aortic valve (e.g., in an asystolic patient). With improving LV function the watershed may move more distally within the aortic arch. If patients on VA ECMO develop severe pneumonia, pulmonary edema or ALI, oxygenation of blood in the pulmonary circulation is often severely impaired. As a result, poorly oxygenated blood is ejected from the LV into the aortic arch, coronary and cerebral arteries, resulting in hypoxemia of the upper body, while the lower body is sufficiently oxygenated through the VA ECMO circuit. This phenomenon is known as *differential hypoxemia*, *watershed phenomenon*, *two-circulation syndrome* or *Harlequin syndrome* and has important clinical implications. Conversion of VA ECMO to VAV ECMO needs to be considered in this setting (**Figure 4D**).

Clinical considerations

Signs of LV overload should be monitored based on serial non-invasive and invasive methods, including clinical examination (increased ventilation efforts, tracheal secretions, bloody or watery sputum), vital signs (hypoxemia), transthoracic echocardiography (increased LV end-diastolic dimensions, decreased LVEF, mitral valve regurgitation or impaired aortic valve opening), chest radiography (pulmonary congestion) and pulmonary artery catheter measurements (pulmonary artery pressure, increased PCWP and mean right atrial pressure). Recovery of cardiac function is indicated by increasing pulse pressure and MAP, whereas deterioration of cardiac function is indicated by the opposite combined with increasing LVEDP and PCWP (18).

Of note, VA ECMO support requires systemic anticoagulation wherefore clinicians should closely monitor signs of bleeding. On the other hand, the large cannulas may increase the risk of limb ischemia and venous thrombosis. VA ECMO is (relatively) contraindicated in patients with aortic valve insufficiency, aortic dissection and high bleeding risk. Perfusion of the extremities and the brain should be carefully monitored (for example by NIRS) to detect differential hypoxemia. An antegrade cannula should be inserted distally to the insertion point of the arterial ECMO cannula to provide antegrade limb perfusion.

Left-ventricular unloading with Impella®

In this clinical case, potent LV unloading during VA ECMO was successfully performed by concomitant use of Impella CP®.

Technique

In patients with LV overload, timely mechanical LV unloading should be considered. There are multiple strategies for percutaneous or surgical unloading (2, 19). LV unloading with an Impella® micro-axial flow pump is considered to be one of the most potent and widely accepted strategies when deploying percutaneous MCS devices. The Impella® pump is placed across the aortic valve to provide continuous blood flow from the LV into the proximal ascending aorta and, thus, allows to decrease LV volume and pressure (**Figure 2B**). The correct positioning of the Impella® pump can be easily confirmed with bedside echocardiography or fluoroscopy. Different types of Impella® pumps are available, providing different levels of hemodynamic support: Impella 2.5 (maximum flow rate 2.5 L/min); Impella CP (3.0-4.0 L/min); Impella 5.0 (5.0 L/min; surgical insertion) and Impella 5.5 (up to 6.0 L/min; surgical insertion).

Relevant physiological considerations

The direct hemodynamic effects of ECMELLA are the loss of isovolumetric periods due to continuous Impella® blood flow from the LV into the aorta throughout the cardiac cycle. Hence, the pressure-volume loop is shifted to the left (LV unloading) and its shape is changed from trapezoid to triangular (**Supplementary Figure 2**) (17). In principle, the Impella® pump causes three main effects:

Increase in cardiac power output

Given the pump's support level (P level) and the pressure gradient between the aorta and LV (generated against an increased LV afterload in the setting of VA ECMO support), the Impella® provides an active increase in forward flow, as demonstrated in this case (**Figure 3A**).

Increase in oxygen supply

The blood flow in the coronary arteries is determined by the pressure gradient across the coronary arterial system and its related vascular resistance. Assuming that the venous pressure and the resistance of the primary arterial vascular bed is fixed under ischemic conditions of an altered autoregulation, the coronary artery flow will largely depend on the aortic pressure. While Impella® augments pressure in the ascending aorta, it promotes LV unloading by reducing LVEDP and LVEDV, which also reduces stresses imposed on the myocardium, generally dictated by Laplace's Law. Therefore, hemodynamic support with Impella® has the potential to favorably alter the myocardial oxygen supply. Moreover, it should be noted that a reduction of LVEDP and PCWP will likely contribute to an improved pulmonary oxygen exchange, breaking the vicious circle.

Decrease in oxygen demand

The Impella® reduces LVEDP and LVEDV leading to reduced myocardial mechanical loading conditions. The reduction of preload will reduce contractility based on the Frank-Starling mechanism, leading to reduced mechanical work and lowered myocardial oxygen demand. Taken together, the delicate balance between myocardial oxygen demand and supply is likely to be favorably altered in an individual patient when deploying Impella® as an adjunct to VA ECMO and when comprehensive bedside monitoring allows individualized tailoring of MCS as based on mechanistic insights.

Clinical considerations

While the use of ECMELLA has been extensively shown to be a practically very feasible and effective strategy in cardiogenic shock in humans and in animal models (20–23) research in the field of ECPR is urgently required. There are presently no established recommendations for LV unloading during therapy-refractory cardiac arrest, although multiple centers have been utilizing this strategy in the setting of ECPR (9–11). Currently, the decision for Impella® unloading is left to the discretion and experience of the ECPR team based on clinical, hemodynamic, radiographic and echocardiographic parameters.

Limited hemodynamic support, contraindications (such as aortic stenosis, prosthetic aortic valve, LV thrombus or ventricular septal defect) and higher treatment costs should be considered when performing LV unloading with Impella®. Clinicians should also carefully monitor signs and markers of hemolysis which might be due to increased levels of shear stress in the Impella® micro-axial pump. An antegrade perfusion cannula at the Impella® insertion site is rarely needed due to the small size of the Impella® access.

Veno-arterial-venous extracorporeal membrane oxygenation

In this clinical case, the patient developed ALI while cardiac function was recovering. Deterioration of pulmonary gas exchange resulted in diminished NIRS readings and right radial hypoxemia. Therefore, treatment was converted from VA ECMO to VAV ECMO.

Technique

VAV ECMO is a triple cannulation technique utilized for patients who either develop differential hypoxemia (e.g., due to severe lung failure) on VA ECMO for heart failure support or, vice versa, who develop heart failure on VV ECMO for lung failure support. In this case, VAV ECMO was an "upgrade" from VA ECMO by insertion of a third cannula into the right jugular vein (**Figure 2C**). The venous drainage cannula in the femoral vein drains blood from the inferior caval vein, while the ECMO outflow with oxygenated blood is diverted into two cannulas by a Y-connector, with one leading toward the aorta through the femoral artery and one toward the right atrium through the jugular or subclavian vein. Consequently, VAV ECMO additionally provides oxygenated blood (from the arterial limb of the ECMO circuit) to the pulmonary, coronary and cerebral circulations.

Relevant physiological considerations

Since ECMO outflow is diverted to the aorta and the jugular vein, the total amount of retrograde aortic flow to the heart is reduced accordingly, wherefore LV afterload tends to be reduced. As a consequence, LVP decreased and Impella® pump flow increased after conversion to VAV ECMO therapy (**Figure 3D**).

Clinical considerations

In this clinical case, VAV ECMO aided to counteract differential hypoxemia in the patient's upper body since ECMO-oxygenated blood was ejected from the LV (**Figure 4D**). The diversion of the ECMO outflow cannulas has to be monitored

with flow sensors on the circuit limbs and balanced with adjustable clamps since important changes in flow balance may affect oxygen saturation, preload, afterload and the position of the watershed. Serial echocardiographic monitoring as well as oxygenation monitoring of the upper (NIRS and right radial artery) and lower body (in case of impaired function of the membrane oxygenator) are crucial to assess right and left ventricular function, as well as adequate tissue oxygenation.

Current trends in cardiopulmonary resuscitation

Apart from ECPR, recent international guidelines propose a centralized care of cardiac arrest patients in specialized Cardiac Arrest Centers (24). Hence, ECPR programs have been designed in metropolitan areas to facilitate ECPR in selected patients, such as the "Minnesota Mobile Resuscitation Consortium" (25). Importantly, in order to further improve the chain of survival, recent international guidelines propose the raise of CPR awareness and involvement of communities, such as community responders and telephone-guided CPR (24).

The time period between cardiac arrest and onset of ECPR is a crucial determinant for patient survival (26, 27). The ideal therapeutic window for ECPR has been propagated to be within 60 minutes after patient collapse (28). Low-flow times in out-of-hospital cardiac arrest (OHCA) are generally longer than in in-hospital cardiac arrest (IHCA) due to the time required to provide conventional advanced life support on scene, transport time to the ECPR center and duration of VA ECMO implantation (3, 4, 29, 30). In order to shorten low-flow times, multiple pre-hospital ECPR programs have been established to increase ECMO accessibility for patients with OHCA distant to ECPR centers. For example, a vehicle-based and helicopter-borne ECPR program were introduced in the Paris area with an average low-flow time of 57 minutes and 110 minutes, respectively (31, 32). Additionally, multiple case reports and series on pre-hospital ECPR have been published (33–35) in addition to several forthcoming (pre-hospital) ECPR trials (36–38).

Of note, low-flow time in this case was considerably low due to geographic proximity to the Cardiac Arrest Center, pre-hospital alert of the ECPR team with timely protocol-based preparations (including immediate ECMO priming), in-hospital availability of a senior interventional cardiologist with extensive ECPR case volumes and an uncomplicated percutaneous femoral access with ultrasound and fluoroscopic guidance in a rather young, non-obese patient.

Despite the current trends, data on ECPR selection criteria are still lacking. Selection criteria for ECPR with highest survival probability have been proposed by international societies (7, 12), such as witnessed cardiac arrest, no-flow time of less than 5 min, low-flow time of less than 60 min, high-quality CPR and reversible underlying cause of cardiac arrest (such as ACS). ECPR is not recommended for example when pH is <6.8 or lactate >180 mg/dL, as well as when patients are older than 70 years or have life-limiting comorbidities. The low pH level in this case presentation (pH 6.67) was in part due to hypercapnia (pCO_2 71 mmHg) with a lactate of 88 mg/dL in the first blood gas analysis indicating temporary hypoventilation rather than very low flow, while all other ECPR criteria were fulfilled wherefore ECPR was considered to be suitable for this young patient.

Patient's perspective

The patient was followed-up in the *ECPR Outpatient Care Program* after 12 months (**Figure 1**). He showed good recovery of neurological function while physical exercise capacity was still limited. Moreover, the patient reported depressive symptoms and mild impairment of memorizing new information. He required help to plan his daily life and has not yet been able to return to work as a machinist. Yet, significant impairments in performance of activities of daily living (Barthel Index: 100/100 points; modified Rankin Scale: 1/6 points) and cognitive function (Mini–Mental State Examination: 26/30 points; CPC scale: 1/5 points) could not objectively be quantified using generally accepted measuring tools.

Additionally, the patient reported dyspnea on exertion. While the vital parameters were unremarkable at rest, the bicycle ergometry was terminated prematurely after approximately 3.5 minutes at 75 Watts (38% of target value). The "six-minute walk test" and the "timed up and go test" showed impaired results with 229 meters of total walking distance and 18 s of total time period, respectively. The LVEF was preserved with 56% and echocardiographic myocardial strain analysis was unremarkable.

Conclusion

This clinical case exemplifies that alongside relevant clinical and physiological bedside observations, a patient-specific, combined MCS strategy may successfully be deployed in complex scenarios of severe cardio-circulatory and respiratory failure that may arise during and after cardiac arrest. It is of utmost importance to closely integrate all clinical monitoring information that is gathered in the catheterization laboratory and the critical care unit to allow for timely detection of physiological pitfalls and related clinical complications of such multimodal approach to achieve the best patient outcomes after ECPR.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

TT, LF, and CS: conception and design. TT, LF, DD, CN, TW, WK, GG, AA, and CS: data collection and interpretation of data. TT, LF, DD, TW, WK, GG, AA, UL, and CS: drafting of the manuscript or revising it critically for important intellectual content. TT, LF, DD, CN, TW, GG, AA, UL, and CS: final approval of the manuscript submitted.

Conflict of interest

Author CN was employed by Abiomed Europe GmbH.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1045601/full#supplementary-material

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Case report: Treatment of a patient with STEMI and cardiogenic shock caused by RCA originating from LAD

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The right coronary artery (RCA) originating from the left anterior descending artery (LAD) is a very rare variation of coronary artery anomaly. This kind of anomaly is usually considered to be clinically benign. Here, we present an acute myocardial infarction patient with a single coronary artery (SCA), in whom the LAD and RCA are both occlusive at the same time. He suffered from ventricular fibrillation, cardiogenic shock, and severe bradyarrhythmias many times. Fortunately, this patient survived from death through our effective medical procedures.

KEYWORDS

AMI, percutaneous coronary intervention (PCI), anomaly, drug-coated balloon (DCB), ventricular fibrillation (VF)

Introduction

Coronary artery anomalies are present at birth, and they are relatively uncommon findings in coronary angiography. Rarely, only one coronary artery originates from the aortic trunk supplying the entire heart; as a rare variation, a single coronary artery (SCA) arises from the left sinus of Valsalva, and the right coronary artery (RCA) originates from the left anterior descending artery (LAD) (1, 2). This kind of anomaly is usually considered to be clinically benign (1). Here, we report the case of a patient with acute myocardial infarction and a SCA in whom the LAD and RCA were both occluded at the same time. This report is the first such an anomaly associated with a variety of serious complications. The patient underwent percutaneous coronary intervention two times to the LAD/RCA bifurcated lesion and finally completed revascularization half a year after symptom onset.

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Case report

The patient was a 76-year-old man with a history of cerebral infarction. He was admitted to the emergency room because of sudden and severe chest pain over the previous 3 h. The first electrocardiography showed obvious ST elevation in V2–V4 (**Figure 1**), and his troponin I level was > 80 pg/ml, which exceeded the laboratory's testing limit. The first blood pressure was 67/40 mmHg, and a high dose of dopamine and noradrenaline is used to maintain adequate blood pressure. Then, the patient suffered from sudden cardiac arrest and ventricular fibrillation several times, and chest compressions and electric defibrillation were performed urgently over the course of diagnosis and treatment. We decided to perform emergency coronary angiography. During coronary angiography, the left coronary ostium was located normally. Selective left coronary angiography demonstrated a normal left main coronary artery, ostial LAD occlusion, and 40% ostial left circumflex artery (LCX) lesions (**Figure 2A**). Multiple attempts to cannulate the right coronary ostium were unsuccessful. As the blood pressure could not be maintained merely depending on the use of vasopressor drugs, intra-aortic balloon pump (IABP) was performed to hold the blood pressure and prevent ischemia-reperfusion injury.

With the aid of IABP, a guide wire was used to cross the occluding lesion of the LAD, and TIMI grade 3 blood flow was achieved after balloon angioplasty. We found that the left circumflex is the dominant artery and RCA originated from the middle of the LAD (**Figures 2B, C**). As the ECG monitor showed a ventricular rate of 36 and iii° AV block occurred, we performed a temporary pacemaker. Due to massive thrombosis in the coronary arteries and unstable vital signs, we decided to stop the operation and initiate intensive antithrombotic therapy. After 2 weeks of therapy, the patient's vital signs stabilized, his chest pain disappeared, and his heart failure improved. We gradually removed the IABP, temporary pacemaker, and vasopressors. Then, coronary artery bypass surgery (CABG) or re-percutaneous coronary intervention (PCI) was recommended for the patient, but he and his family rejected this recommendation.

Four months after discharge, the patient was advised again to undergo coronary angiography, and the results showed complex and severe triple bifurcated lesions, with 90% ostial LAD lesions, 80% ostial D1 lesions, and 70% ostial RCA lesions (**Figure 2D**). Following coronary angiography, we discussed the revascularization strategy. Two Sion blue wires were passed down the LAD, D1, and anomalous RCA, and two 2.5 × 20 mm drug-coated balloons were deployed in the D1 and RCA

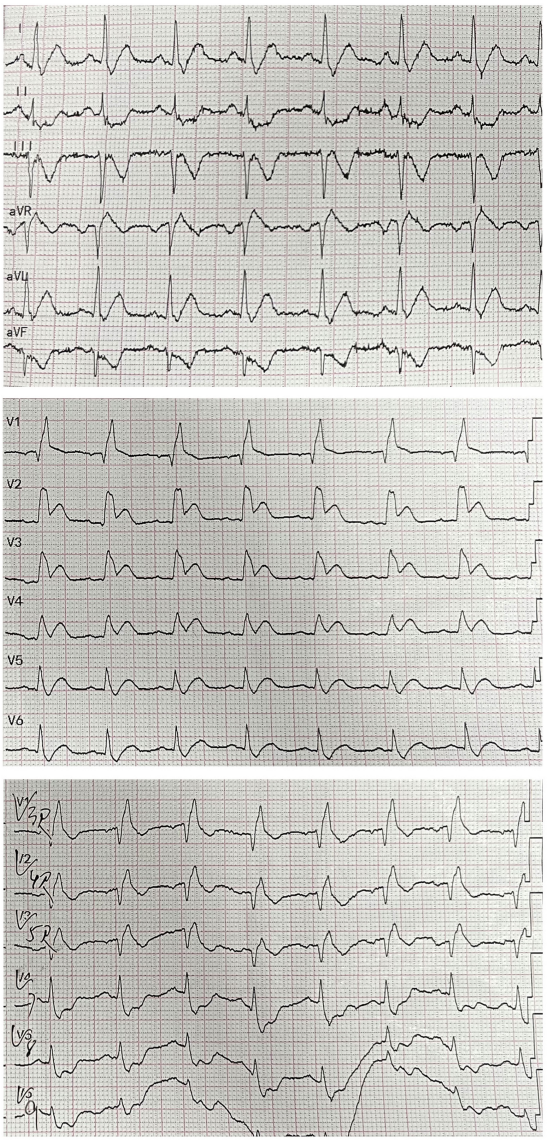

FIGURE 1
A 18-lead electrocardiogram of the patient showing ST elevation in V2–V4 leads with widespread inverted T-waves in inferior, posterior, and right ventricular leads.

(**Figures 2E, F**). Then, the LAD/RCA/D1 bifurcation was treated with a 3.0 × 36 mm (10 atm) drug-eluting stent (DES) placed in the LAD and two Maverick 2.0 × 20 mm (6 atm) balloons placed in the D1 and RCA (**Figure 2G**), which were dilated simultaneously for kissing balloon inflation. Then, a proximal optimization technique (POT) was performed with a Quantum Maverick 3.0 × 15 mm high-pressure balloon placed in the LAD. With no symptoms of discomfort, PCI was completed, and the outcomes were satisfactory (**Figure 2H**). After 3 days, the patient was discharged home on aspirin, ticagrelor, and rosuvastatin. After a

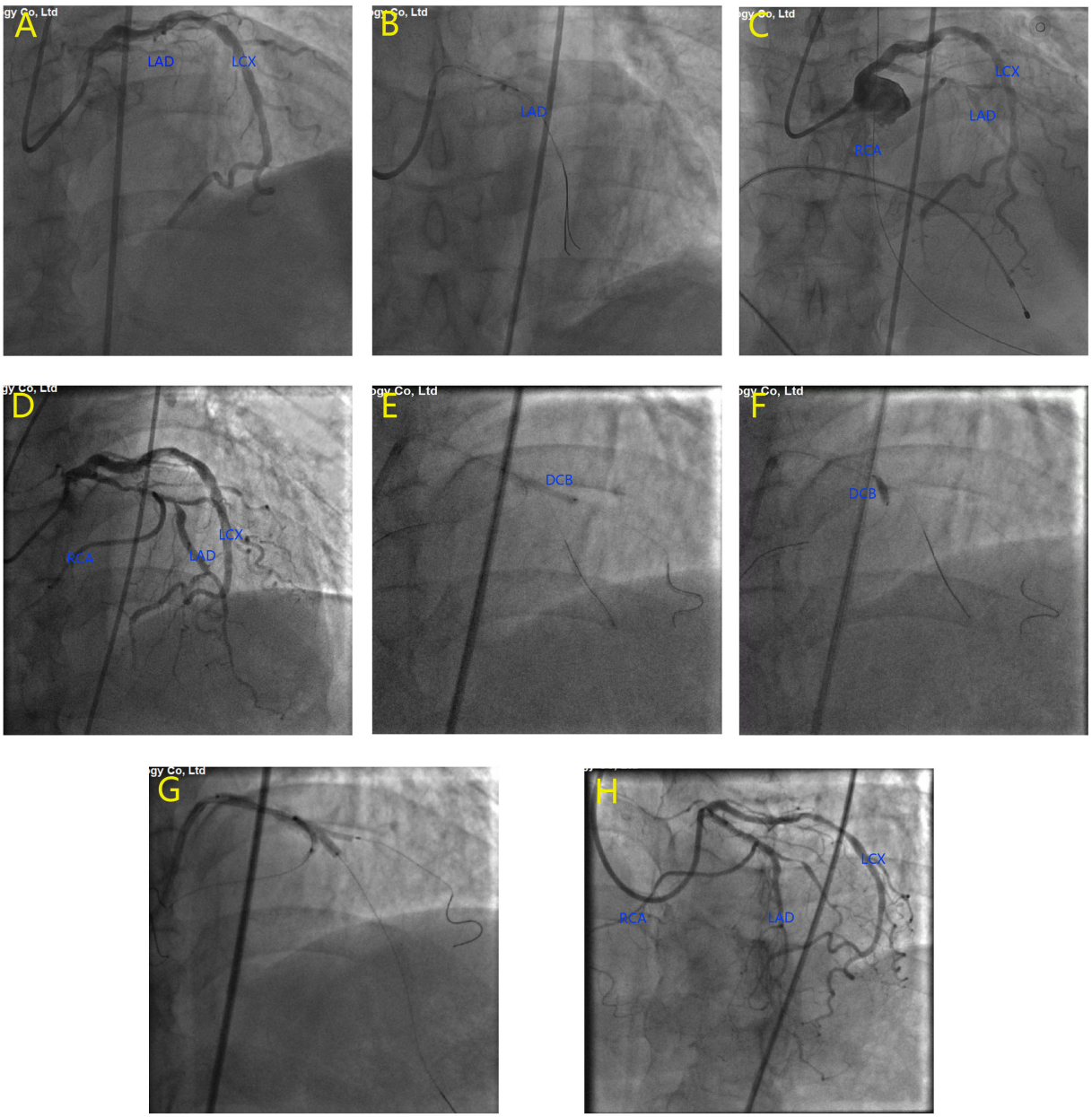

FIGURE 2
Emergency coronary angiography at the onset of acute myocardial infarction. The results showed that the proximal left anterior descending artery (LAD) was completely occluded **(A)**. Balloon dilatation was performed on the occlusive site **(B)**. TIMI grade 3 flow was restored in LAD and right coronary artery (RCA) **(C)**. The second coronary angiography at 4 months after myocardial infarction. The results showed high-grade lesion at the proximal LAD, as well as at LAD/RCA bifurcation and LAD/diagonal bifurcation **(D)**. Drug-eluting balloons were used to dilate the diagonal branch **(E)** and the RCA **(F)**. A drug-eluting stent in LAD and 2 balloons in D1 and RCA were dilated simultaneously for kissing balloon inflation **(G)**. Final imaging results after procedure **(H)**.

1-month follow-up, we performed computed tomography angiography (CTA) of the coronary artery. Through CTA, we confirmed that the anomalous RCA originated from the middle of the LAD (**Figure 3**). It passed between the aorta and pulmonary artery in the group of L-II variants (1).

Discussion

In previous studies, we learned that approximately 1.3% of the population has coronary artery anomalies (1), and these anomalies are found in 0.2 to 1.3% of patients undergoing coronary angiography and 0.3% of autopsy

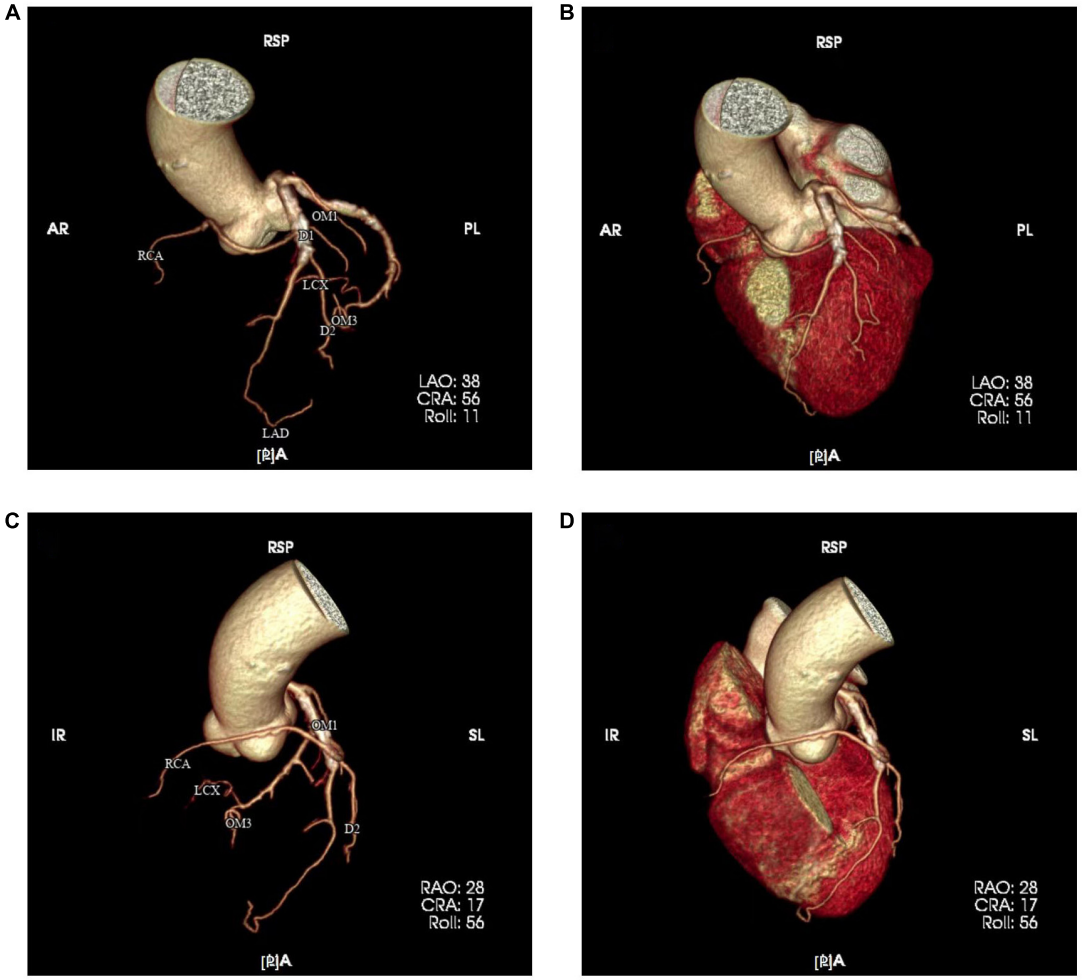

FIGURE 3
Coronary computed tomography angiography (CTA) was re-examined one month after PCI and resulting images **(A–D)** confirmed the anomalous origin of the right coronary artery.

series (3). Coronary artery anomalies are considered to be the second most common cause of sudden cardiac death among young athletes. While an SCA, first defined by Hyrtl in (4), is a rare congenital anomaly, it occurs in approximately 0.024 to 0.066% of individuals (5). The first antemortem diagnosis was made by means of coronary angiography in 1967 (6).

To date, an increasing number of associated cases of an SCA have been reported, including an SCA arising from the LSV or RSV. Most of the published SCA case reports describe an RCA originating from the proximal or middle segment of the LAD, and this kind of anomaly was well-recognized as being clinically benign (1). Besides that, when the anomalous coronary artery courses between the aorta and pulmonary trunk, it is considered a malignant course and may cause sudden death (7). Here, we present a symptomatic case associated with the RCA originating from the LAD, and we did not find a similar case by searching PubMed. In such patients, LAD stenosis will also influence blood flow in the RCA. In the worst-case scenario, LAD stenosis can instantly cause simultaneous occlusion of both the LAD and RCA, resulting in a high risk of death and a poor prognosis. This 76-year-old man suffered from ventricular fibrillation, cardiogenic shock, and severe bradyarrhythmia many times throughout the diagnostic and treatment process; thus, this patient experienced all serious adverse events associated with LAD stenosis. Fortunately, this patient survived with the use of IABP, a temporary cardiac pacemaker, and an emergency operation. Many people survive such a complicated lesion. Selective revascularization was performed with DES and DCB 4 months later, and the patient was discharged from the hospital. We will continue to pay attention to the patient's prognosis in the future.

Once a coronary artery anomaly is found in a patient, it is recommended that early preventive or even early treatment measures must be taken if there are lesions with a common origin, as seen in this patient. As the common origin is equivalent to LM, in the case of occlusion, the consequences would be severe and possibly fatal.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: A rare manifestation of vasospasm induced myocardial infarction with ST-segment elevation in a young male patient

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Background: Minority of acute myocardial infarctions (MI) are caused by a non-atherosclerotic occlusion of the coronary artery. We present a case report, where MI with ST-segment elevation was provoked by a vasospasm, which is a rare aetiological finding.

Case presentation: 27-year-old male patient presented to the emergency department because of a sudden onset chest pain radiating to the left arm. The patient underwent percutaneous coronary intervention (PCI) to the right coronary artery (RCA) 3 months ago due to inferior wall MI, however, chest pain episodes kept on recurring at night throughout the whole period after the intervention. During current admission, initial electrocardiogram (ECG) demonstrated ST-segment elevation in leads II, III and aVF. Coronary angiogram revealed diffuse severe narrowing of the right coronary artery, which was relieved with intracoronary administration of nitrates and verapamil. After coronary angiogram patient was given oral long-acting nitrates and verapamil, however, during the following days nocturnal chest pain episodes reoccurred. It was decided to swap verapamil to diltiazem, which led to complete cessation of angina episodes. The patient was discharged in stable condition and symptom free. It was suspected that the first MI was of vasospastic origin, which likely led to unnecessary stenting.

Conclusions: This clinical case has demonstrated the challenges clinician could face in order to correctly diagnose vasospasm-induced MI because of its rare occurrence and highly variable presentation. We strongly suggest using intracoronary nitroglycerine during coronary angiography as a standard

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practice to avoid a potential diagnostic error and unnecessary stenting. Although, in some cases the reason behind coronary artery spasm (CAS) remains unclear, medical treatment can be very effective for CAS prevention.

KEYWORDS

STEMI, vasospasm, young patient, CAS, case report

Introduction

Myocardial infarction with ST-segment elevation (STEMI) is an event during which myocardial ischemia results in myocardial injury or necrosis (1). The dominant cause for this emergency condition is acute atherosclerotic plaque rupture followed by a total coronary artery occlusion (2). However, it is estimated that in 3–25% of all acute MI cases the cause is of non-atherosclerotic occlusion origin, one of which is vasospasm (3–5). Women have 5-times higher chance of presenting with MI without a ruptured atherosclerotic plaque than men; the incidence is also higher in non-Caucasian patient group (6). In this case report we present a young Caucasian male patient who had inferior wall STEMI caused by profound vasospasm in the right coronary artery (RCA).

Case description

27-year-old male patient presented to the emergency room because of a sudden onset severe chest pain (8-9 points on visual analog scale) radiating to the left arm and neck. Three months ago he was admitted to a different percutaneous coronary intervention (PCI) center due to inferior wall STEMI and two drug-eluting stents were implanted: one in the proximal part of the RCA, the other in the right posterolateral (rPL) branch (Figure 1). During the one-month period after procedure the patient complained of recurrent episodes of chest pain at rest, not related to exertion, similar to those experienced during the heart attack but less intense. In the same PCI center a repeat coronary angiogram was performed due to a suspicion of unstable angina but no visual stenoses were identified, coronary artery flow was not impaired (Figure 2, Table 1). Patient was advised to continue dual antiplatelet therapy and atorvastatin. A week prior to current admission, almost every night he had episodes of chest pain lasting 15–30 min and ceasing spontaneously. Past medical history included hypertension, dyslipidemia, smoking, excessive alcohol consumption prior to the first episode of STEMI and COVID-19 infection 9 months ago with no residual symptoms. He was not suffering from any other chronic disease.

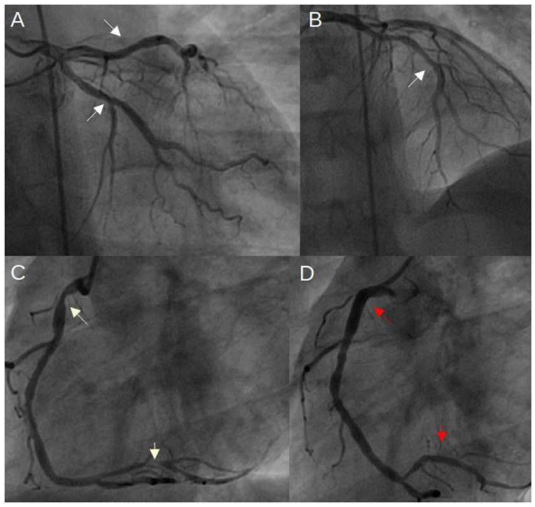

FIGURE 1
Coronary angiogram 3 months ago, when inferior wall MI occurred. **(A, B)** mild coronary artery narrowings in both LCx and LAD (white arrows); **(C)** severe narrowings in the RCA (white arrows); **(D)** RCA after stents implantation (red arrows indicate both implanted stents) (LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; RCA, right coronary artery).

Diagnostic assessment

During the current hospital admission, an initial electrocardiogram (ECG) showed ST-segment elevation in leads II, III and aVF with reciprocal ST-segment depression in leads I and aVL (Figure 3). Based on patient's complaints and ECG findings, inferior wall ST-elevation myocardial infarction (STEMI) was suspected and the patient was taken for an urgent coronary angiogram. It revealed a diffuse severe narrowing of the right coronary artery (RCA) and mild to moderate stenoses in both left anterior descending (LAD) and left circumflex (LCx) arteries (Figure 4). Suspecting vasospasm, the right coronary artery was injected intracoronarily with 300 mcg of nitroglycerine, which only partially relieved the spasm. Therefore additional 100 mcg of nitroglycerine and 2.5 mg of verapamil were administered and the luminal patency was successfully restored. The same drug combination was

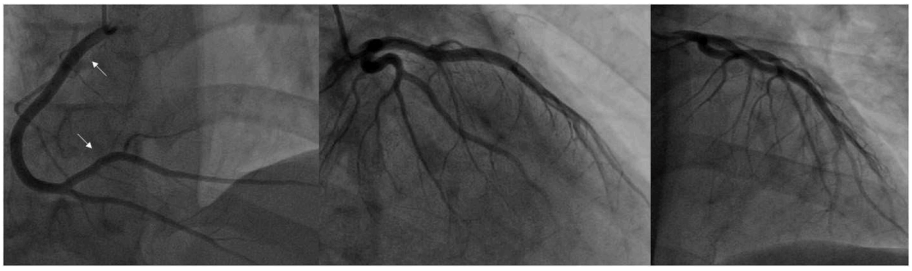

FIGURE 2
Coronary angiogram when recurrent chest pain episodes occurred after PCI. Both left and right coronary arteries are patent, their filling is unimpaired. No narrowings in the mid RCA, LAD and LCx, which were observed during the initial coronary angiogram, are present. White arrows indicate stents implanted in the RCA (LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery).

TABLE 1 Timeline of the clinical case.

Date	Event
Three months prior to current admission	Inferior wall STEMI, two drug-eluting stents placed.
Two months prior to current admission	Due to recurring chest pain episodes repeat coronary angiogram was performed, no stenoses identified.
One week prior to current admission	Every night patient experienced chest pain episodes, which ceased spontaneously.
Day of admission (day 1)	Patient presented to ER because of a sudden onset severe chest pain radiating to the left arm and neck. ECG showed ST elevations in inferior wall leads, patient was taken for an urgent coronary angiogram. It revealed diffuse severe and mild narrowings of coronary arteries which were successfully treated with intracoronary injections of nitroglycerine and verapamil. Chest pain stopped.
Day 3	During the night, patient complained of chest pain which subdued after taking nitroglycerine.
Day 6	Nocturnal chest pain episodes persisted despite increasing verapamil dosage–medication was switched to diltiazem.
Day 13	After changing medication, no more chest pain episodes occurred. Patient was discharged in stable condition.

ECG, electrocardiogram; ER, emergency room; STEMI, ST-elevation myocardial infarction.

then injected into the left coronary artery (LCA) relieving its spasms as well. After intracoronary injections of medications chest pain stopped. It was confirmed that the inferior STEMI was secondary to a vasospasm in RCA. Post-procedural ECG showed the return of ST-segment to the baseline (Figure 5A). The patient was given ticagrelor 90 mg bd, aspirin 100 mg od, atorvastatin 80 mg od, omeprasol 20 mg od, amplodipine 5 mg bd, and verapamil 80 mg od. After 24 h, with no recurrent chest pain and in stable condition, patient was transferred out from the CCU to the regular cardiology ward.

Detailed medical examination and various tests were done to detect potential cause of vasospasm. The patient was consulted by a rheumatologist. However, no symptoms in patient's history related to vasculites or collagenoses were found and physical examination showed no abnormalities. Electrolyte panel, markers of inflammation, thyroid function tests, level of eosinophils in blood, markers of autoimmune diseases were within normal limits, drug abuse screening test came back negative as well (Table 2). Temporal artery duplex ultrasonography did not reveal any pathological findings either. Transthoracic echocardiogram was unremarkable with preserved left and right ventricle ejection fraction.

During the night of the third hospitalization day patient complained of chest pain, which subdued after taking nitroglycerine. The ECG recorded during the pain episode did not reveal any new electrocardiographic signs of myocardial ischemia (Figure 5B). Verapamil dosage was increased to 80 mg bd and isosorbide dinitrate (ISDN) 20 mg od was given as well. Whereas chest pain episodes persisted even after further increasing verapamil dosage to 80 mg tds, it was decided to switch verapamil to diltiazem. The optimal effect was achieved with a total daily dose of 360 mg diltiazem. No more chest pain episodes as well as potentially lethal rhythm disturbances were recorded.

The patient was discharged in stable condition without chest pain on the 13 day after arriving to the emergency room. He was prescribed ticagrelor for the next 10 months, aspirin, esomeprasol, statin, ISDN and diltiazem.

Discussion

The reported case demonstrates a young male patient who had a vasospasm-induced inferior wall STEMI and had two stents implanted because previous MI was thought to be caused by a ruptured atherosclerotic plaque. Despite the treatment, chest pain episodes continued and only the third coronary angiogram led to the discovery that these angina attacks were

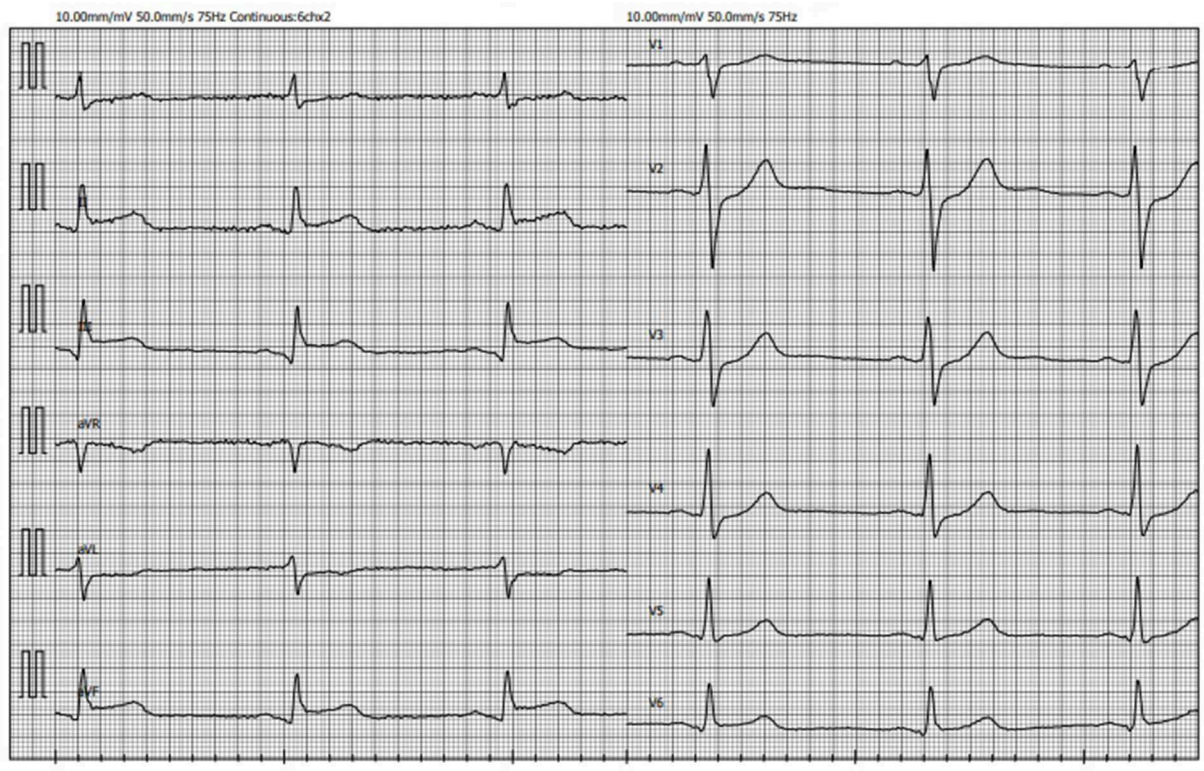

FIGURE 3
ECG recorded on admission demonstrating ST-segment elevation in leads II, III, aVF with reciprocal ST-segment depression in leads I and aVL (ECG, electrocardiogram).

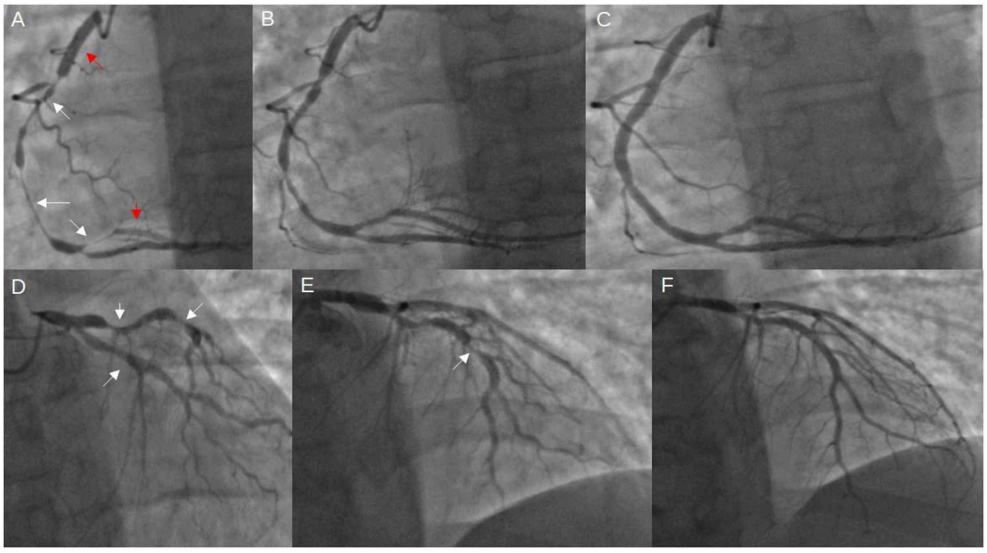

FIGURE 4
Coronary angiogram from the current stay. **(A)** severe diffuse RCA spasm (indicated by the white arrows), previously implanted stents (red arrows); **(B)** improved RCA spasm after intracoronary injection of 300 mcg nitroglycerine; **(C)** further resolution of vasospasm after administering additional 100 mcg nitroglycerine and 2.5 mg verapamil; **(D, E)** visible vasospasms in both LCx and LAD; **(F)** vasospasm resolution after 100 mcg nitroglycerine and 2,5 mg verapamil intracoronarily (LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery).

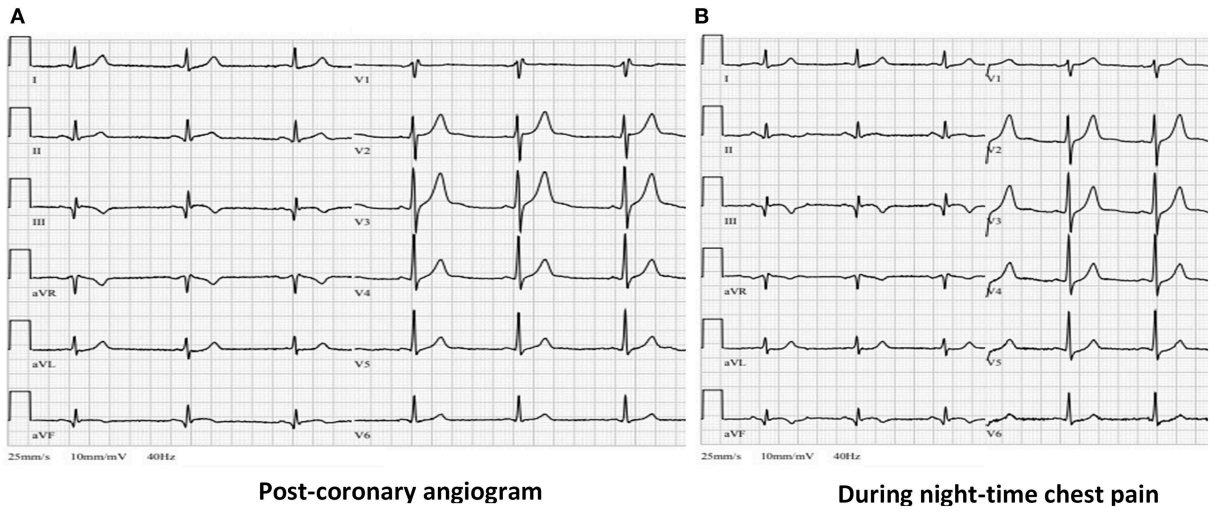

FIGURE 5
(A) Post-procedural ECG from ICU showing resolution of ST-segment elevation in leads II, III and aVF with formation of negative "reperfusion" T waves in III and aVF leads. **(B)** ECG during the night chest pain episode showing no significant changes compared with **(A)** (ECG, electrocardiogram, ICU, intense care unit).

of vasospastic origin. As seen in the angiographic images above, the spasms presented both as local and diffuse narrowings, which made it easy to be mistaken and be treated by implanting stents. The main cause of observed vasospasms remained unclear in this case.

Development of coronary artery spasm (CAS) depends on a wide range of risk and precipitating factors. Hung et al. listed older age, smoking and higher blood levels of C-reactive protein (CRP) as risk factors associated with increased susceptibility to developing CAS. In our case the patient was young and had normal CRP blood levels, however, he was a smoker. Smoking is associated with endothelial damage due to increased amount of reactive oxygen species (7). We can suppose that smoking could have been a contributing factor for spasms to occur. Furthermore, in the same article by Hung et al., mental/physical stress, parasympatho- and sympathomimetics, central nervous system (CNS) stimulants and cold pressor as a sympathetic activator were referred to as precipitating factors potentially contributing to the onset of CAS (8). The presented patient denied feeling stressed out mentally or physically. The patient denied the abuse of CNS stimulants or narcotics as well and it was confirmed with a negative drug abuse screening test.

CAS usually occurs to postmenopausal women and middle- or old-aged men. It is very uncommon for young men to develop CAS. Therefore, a genetic predisposition plays an important role in the pathogenesis of a coronary spasm. Genetic epidemiological studies have reported that several genetic variants of the genes for angiotensin-converting enzyme, angiotensin II receptor type, endothelial nitric oxide synthase (e-NOS) and paraoxonase are associated with the higher risk for coronary artery spasm (9–11). For example, several studies have discovered the polymorphisms of Glu298Asp in the exon 7 and T−786C in the 5′-flanking region of the e-NOS gene and have shown that these polymorphisms increase the risk of CAS (12, 13). However, genetic testing was not performed to the reported patient.

Triptans used to treat migraine are also known as triggers of coronary artery spasm through an action at 5-HT1B-receptors, which can be found in the coronary arteries (14–16). Because of vasoconstrictive activity triptans are contraindicated in cases of uncontrolled arterial hypertension or coronary artery disease (17). In our reported case the patient denied suffering from migraine and the use of triptans as well. Circadian variation was proposed in a work by Yasue et al. as another possible spasmogenic risk factor along the other ones which have already been mentioned. This risk factor may be relevant to our patient, since he complained of chest pain episodes during night rest, which is usual time for CAS to occur due to yet unelucidated pathological pathway (18). Moreover, Lee et al. demonstrated that subclinical hypothyroidism could be associated with coronary spasms (19). However, the thyroid function of our patient was unimpaired. In some rare cases eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss Syndrome, may also cause coronary spasms, which are believed to be mediated by vasoactive compounds produced by eosinophils (20). Considering this risk factor, the patient was consulted by the rheumatologist and various markers for auto-immune diseases were tested but they all came back negative. Rarely vasospasms could also be induced in the setting of an allergic or anaphylactic reaction–such condition

TABLE 2 Laboratory tests.

Laboratory test	Initial values	Repeated values	Reference values*
Inflammation markers (CRP, mg/l)	11.9	–	≤5
Electrolyte panel (mmol/l): • Potassium (K) • Sodium (Na) • Chloride (Cl)	K −4.2	K −4.4	K 3.8 −5.3
	Na −141	Na −138	Na −134-145
	Cl −106	Cl −104	Cl −98-107
Thyroid function test (TSH, mU/l; FT4, pmol/l; ATPO kU/l; T3 nmol/l)	TSH −1.323;	–	TSH −0.4-4,0
	FT4 −14.62;		FT4 −9.0-19.0
	ATPO−0.6		ATPO < 5.61
	T3 −1.52		T3 −0.89 −2.44
Drug abuse screening test (from urine)	Negative ()	–	Negative
Auto-immune disease markers	- Jo-1: Negative, - anti-beta2-GP1 Ig GAM: Negative, - DFS70: Negative, - dsDNR: Negative, - CENP-B: Negative, - AMA-M2: Negative, - SS-A: Negative, - Sm: Negative, - PM-Scl: Negative, ENA: - nRNP/Sm Negative, - PCNA: Negative, - Scl-70: Negative, - rib. P.-protein: Negative, - Ro-52: Negative, - nucleosomes: Negative, - SS-B: Negative, - histones: Negative.	–	Negative
Level of eosinophils in blood (*10^9/l)	0.8	0.6; 0,7	0–0.7
Troponin I (ng/l)	10716	1047	≤35
Lipid panel (mmol/l)	Total cholesterol −2,21	–	Total cholesterol-<5,2
	Triglycerides −0,87		Triglycerides–≤1,8
	HDL-cholesterol −0,90		HDL-cholesterol->0,91
	LDL-cholesterol – 0,91		LDL-cholesterol-≤3,0
Liver enzymes (U/L)	AST −329		AST–≤40
	ALT −66		ALT-≤40

*Reference values adapted from the laboratory of medical center patient was currently treated in.
ATPO, anti-thyroid proxidase; CRP, C-reactive protein; FT4, free thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase.

is known as the Kounis Syndrome (KS). It describes an acute coronary syndrome, which is associated with mast cell and platelet activation during allergic reaction (21). The presented patient, however, had no symptoms of allergic reaction and blood level of eosinophils was normal every time it was checked during this hospital stay, thus KS as a possible cause of spasms was ruled out.

During CAS, various electrocardiographic findings can be present: ECG may be normal at the beginning of an attack or when the attack is mild, or ST-segment elevation/ depression may be visible. Furthermore, patients experiencing coronary spasms may present with or without symptoms, thus the diagnosis of CAS rarely can be made by symptoms or ECG findings alone (22). The reported patient had typical clinical and electrocardiographic presentation of STEMI with chest pain and ST-segment elevation on the ECG as well.

Provocation testing adjunctive to coronary angiography is considered to be the most reliable method for diagnosing CAS

in cases when spasms are suspected to be the cause of angina episodes and need to be confirmed (23). Most commonly, intracoronary injection of ergonovine or acetylcholine are used to provoke coronary spasm (22). After the first episode of STEMI our patient had repeat angina attacks at rest, strongly suggestive of vasospastic angina. Therefore, second coronary angiogram was performed at the same hospital, which demonstrated completely normal coronary arteries. However, provocation testing for CAS was not done at that time, likely due to not enough experience in such testing. We could speculate that should the CAS provocation test was performed, the correct diagnosis could have been established earlier and with adequate medical treatment, the second MI could have been prevented. Thus, provocation testing or at least a trial of medical therapy should be encouraged when there is a high clinical suspicion of vasospastic angina. The third coronary angiogram, which was performed in a different (our) hospital, demonstrated various levels of coronary narrowings, which were relieved by the intracoronary injection of nitroglycerine and verapamil, confirming the spasm as a cause of angina.

The patient received long acting nitrates with verapamil at first, which was later changed to diltiazem due to recurring chest pain episodes. Both these medications are calcium channel blockers (CCB), which are effective for the prevention of vasospasms and angina attacks (18). As for the acute angina attacks due to CAS, sublingual nitrate remains the main treatment (23).

During the previous hospital stay our patient had stents implanted suspecting STEMI to be of atherosclerotic plaque rupture rather than of vasospastic origin. Intravascular imaging, such as intravascular ultrasound or optical coherence tomography, was not performed. We believe, that intravascular imaging should be strongly considered in clinical cases like this–when there are factors, associated with a high probability of a non-atherosclerotic MI, such as very young patient's age. In the study conducted by Katoh et al., it was discovered that in both infarct-related and unrelated arteries coronary spasms could be provoked by high frequency and that spasms after stenting were more likely to occur distally from the implanted stent (24). Similarly, diffuse coronary spasm was observed distal to the proximal stent in our patient. The authors recommend using CCB for suppressing further coronary spasms.

This clinical case has demonstrated the challenges one could face in order to correctly diagnose vasospasm-induced MI because of its rare occurrence and highly variable presentation. Though ACS caused by vasospasm is relatively rare, we strongly suggest using intracoronary nitroglycerine during coronary angiography as a standard practice to avoid a potential diagnostic error and unnecessary stenting. The recommended treatment for further CAS prevention is CCB, however, as seen in this case, it is also crucial to select the correct medication. Although, in some cases the reason behind CAS remains unclear, medical treatment can be very effective for CAS prevention as it was showed in this clinical case presentation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LD and GR: conception and drafting of the work, acquisition, and interpretation of data. GD and AB: conception of and revising the work. PB: conception and drafting of the work and revising the work. All authors read and approved the final manuscript, as well as have agreed both to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case report: Polyarteritis nodosa as a substrate for a massive myocardial infarction

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This report describes a rare case of a global myocardial infarction caused by severe vasospasm of the coronary arteries secondary to the administration of pyridostigmine in a patient with polyarteritis nodosa (PAN). Details about the clinical presentation, the typical electrocardiographic pattern of multivessel disease, the differential diagnoses suspected in the multi-imaging approach, and the treatment of cardiogenic shock are described. The definitive diagnosis of infarction and the histopathological findings compatible with polyarteritis nodosa were made by autopsy.

KEYWORDS

STEMI, vasculitis, polyarteritis nodosa, myocardial infarction, vasospasm (VS)

Introduction

Polyarteritis nodosa (PAN) is a systemic vasculitis that typically affects medium-sized vessels (1). Coronary arteries are less frequently affected, and symptoms of myocardial ischemia and infarction are rare (2).

We present the case of a 53-year-old female patient referred to the emergency department for suspected acute coronary syndrome. While her coronary angiography was normal, she rapidly developed refractory cardiogenic shock and died. Autopsy revealed a massive global myocardial infarction and findings consistent with polyarteritis nodosa. To our knowledge, this is the first case of acute global myocardial infarction in a patient with polyarteritis nodosa. The catastrophic presentation of this case is the result of the combination of an underlying disease and precipitant factors.

Case description

A 53-year-old female patient with no comorbidities or previous clinical history began 6 months before her admission to the emergency department (ED) with weakness of lower extremities. She consulted a neurologist who, suspecting myasthenia gravis, prescribed pyridostigmine and prednisone, however, no improvement was observed. A few days after the initiation of pyridostigmine, the patient suffered sudden onset of chest pain and presented to the ED. Vital signs were: 110/80 mmHg, heart rate 86 beats per minute, respiratory rate 18 breaths per minute and physical examination was normal on admission. An electrocardiogram demonstrated ST-segment elevations in aVR and V1, in addition to ST-segment depressions from V3 to V6, DI and aVL (**Figure 1**). High-sensitivity cardiac troponin T level were 9164 ng/l (0–8 ng/l). Thus, non-ST segment elevation myocardial infarction (NSTEMI) was diagnosed.

Diagnostic assessment

Since a non-ST segment elevation myocardial infarction was the first suspected diagnosis, the patient was taken to the cardiac catheterization laboratory, where the coronary angiogram revealed no significant lesions (**Figure 2**).

According to the diagnostic approach for MINOCA, additional coronary angiography review by several experts was performed to ensure the absence of obstructive coronary artery disease, and to rule out intracoronary emboli/thrombi and spontaneous coronary artery dissection (3). Intracoronary imaging and intracoronary physiological tests were not incorporated in the approach since no obstructive coronary lesions were found in the context of acute coronary syndrome.

Transthoracic echocardiogram demonstrated global wall-motion abnormalities; global thickening of the left ventricle and severe systolic dysfunction (LVEF 20%); findings suggestive of differential diagnoses such as Takotsubo cardiomyopathy or other cardiomyopathies were excluded. Cardiac magnetic resonance imaging (MRI) showed late enhancement with gadolinium distributed globally and heterogeneously throughout the left ventricle (**Figure 3**).

Intramuscular electromyography exhibited prolonged latencies, reduced amplitudes, absence of F waves and absence of H reflex were observed, findings consistent with polyradiculoneuropathy.

Therapeutic interventions

Shortly after hospital admission, the patient showed hemodynamic deterioration. Blood pressure dropped to 70/50 mmHg and cold extremities, profuse sweating, and dyspnea were noted. Due to the fact that the hemodynamic evaluation showed a low cardiac index, high pulmonary artery

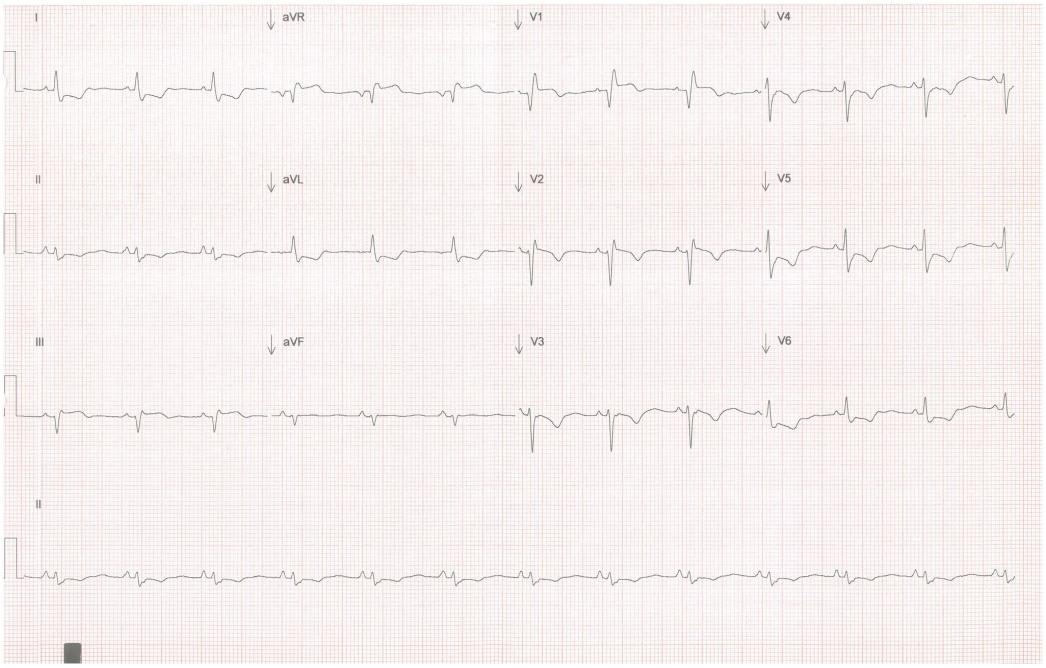

FIGURE 1
Twelve-lead EKG showing high-risk ischemic features. ST-segment elevation is observed in aVR and V1, as well as ST-segment depression in six different leads (V3, V4, V5, V6, DI, aVL).

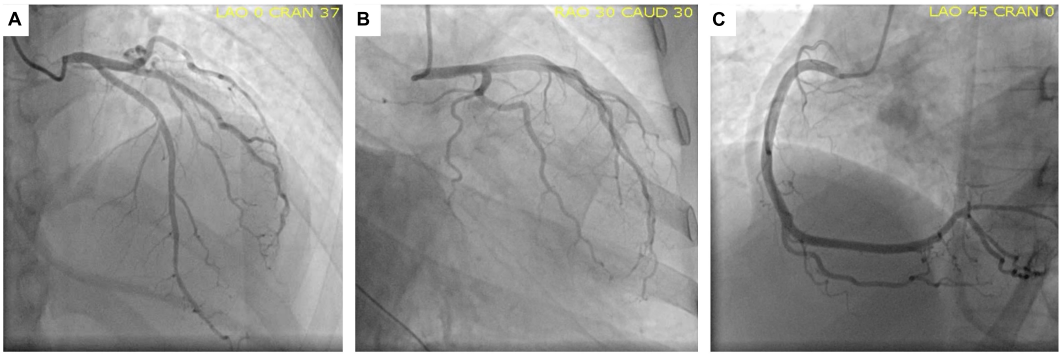

FIGURE 2
Normal coronary angiography. Anterior-posterior cranial view **(A)**, Caudal left-anterior-oblique view **(B)** and Left-anterior-oblique view **(C)** showing the circumflex artery, left anterior descending artery, and right coronary artery, respectively, without lesions.

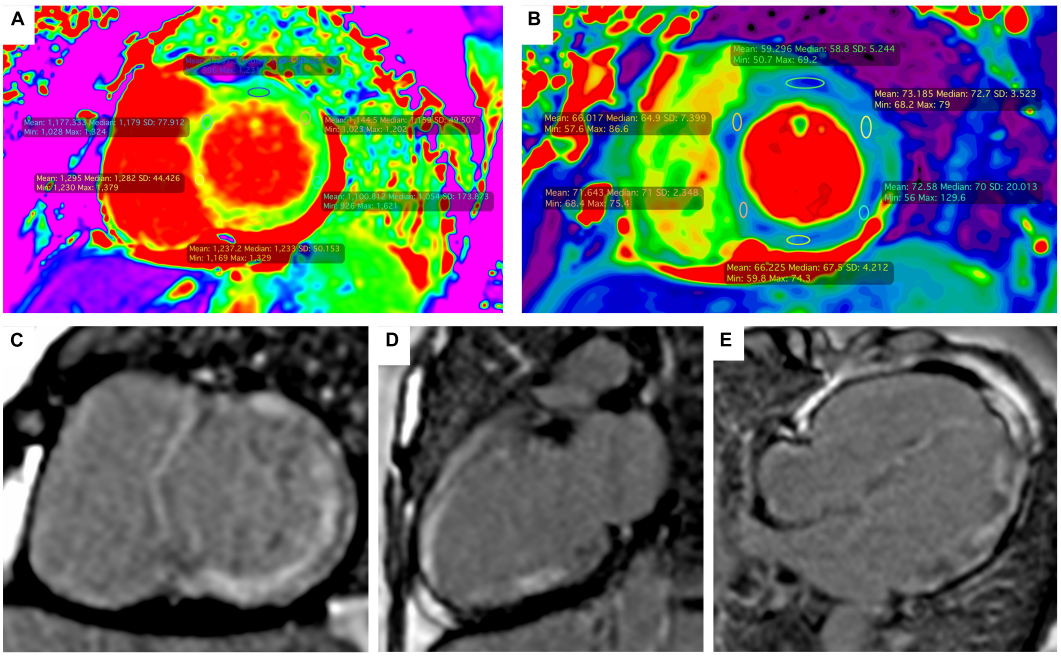

FIGURE 3
Magnetic resonance imaging. Short-axis ShMOLLI color maps showing diffuse high native values T1 **(A)** and T2 **(B)** which is compatible with myocardial edema and fibrosis. Late gadolinium enhancement with intramyocardial and transmural pattern was observed in the short axis view **(C)**, two chambers view **(D)** and four chambers view **(E)**.

wedge pressure and high peripheral vascular resistance, the diagnosis of cardiogenic shock was made. Norepinephrine and dobutamine infusions were started to maintain peripheral perfusion.

Based on the significant yet inconclusive MRI findings, endomyocardial biopsy was conducted in order to more accurately distinguish between myocarditis and myocardial infarction. Unfortunately, the biopsy was inconclusive, demonstrating non-specific inflammation. In the subsequent hours, hypotension and low cardiac index persisted. Levosimendan drip was started, elective endotracheal intubation was performed, and an intra-aortic balloon pump was placed as bridge to bridge treatment.

Follow up and outcomes

Despite hemodynamic support, and while waiting for ECMO cannulation, the patient developed refractory cardiac arrest. After 30 min of resuscitation, the medical team together with the patient's family decided to stop CPR due to poor prognosis.

An autopsy was performed to identify the underlying cause of the cardiogenic shock and consequently the cause of death. An infarct of variable thickness (transmural and non-transmural) was found throughout the entire left ventricle, in addition to intimal thickening in the coronary arteries. These findings were also found in kidney and intestine arteries, which in conjunction with the muscle weakness secondary to polyneuritis led to the diagnosis of Polyarteritis nodosa (**Figure 4**).

Discussion

In contrast to the myocardial infarction in patients with atherosclerotic disease, most of the infarction events reported in patients with PAN are related to the disease pathology itself: up to 13% of patients may have coronary lesions such as stenosis, aneurysms, spontaneous coronary dissection or ectasia (4). These characteristic coronary dilations produce a vascular bed where blood flow may be slow or turbulent which in turn may facilitate the formation of thrombi, occlusion and subsequent infarction (5).

Previously, only one case of myocardial infarction in a patient with PAN and normal coronary arteries has been previously reported; however, features of such case included a well-located myocardial territory and a mild clinical presentation (6) which differ from the present report.

In our case, the diagnosis of probable PAN was based on the Japanese diagnostic criteria, revised in 2005 (7), meeting 2 clinical criteria (myocardial infarction and polyneuritis), angiographic findings (occlusion of the bowel arteries). Although no fibrinoid necrosis was found in the biopsies, the involvement of medium and small caliber arteries was confirmed, without involvement of arterioles, venules or capillaries, which is typical in PAN (8). Historical findings suggest that the arteries were in a chronic phase of the

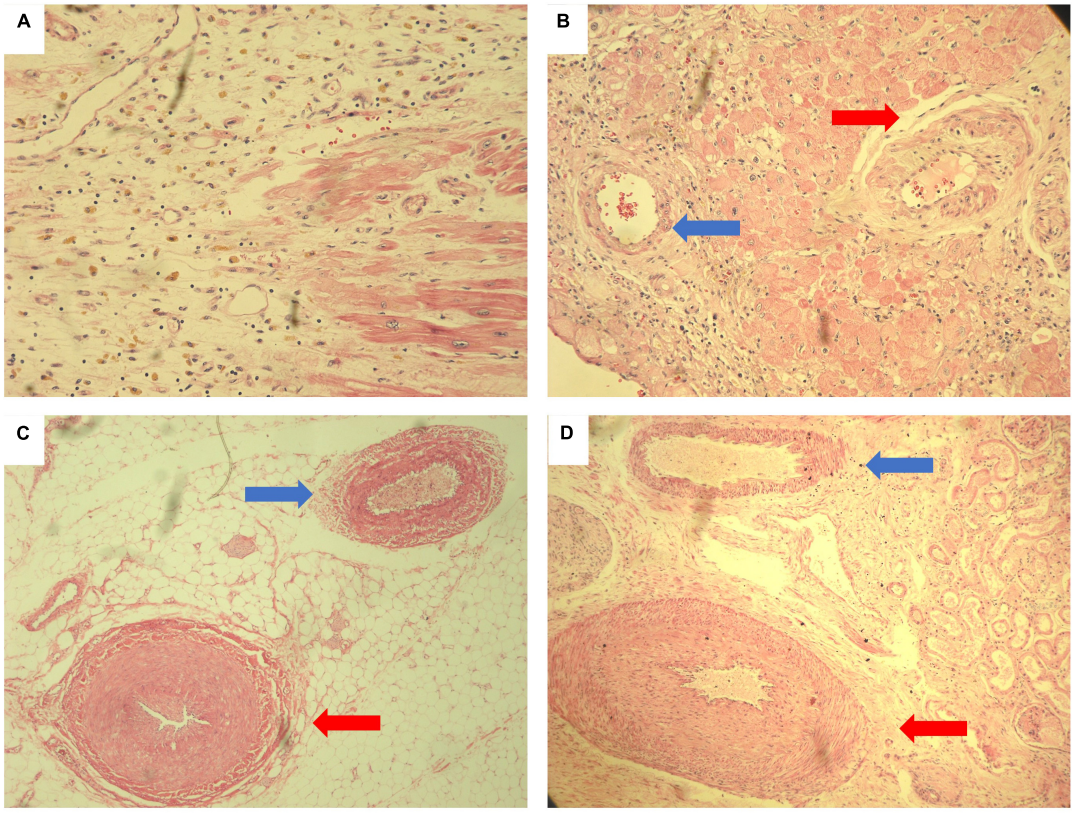

FIGURE 4
Histological autopsy samples stained with hematoxylin and eosin. Myocardial necrosis with reparative granulation tissue formed by fibroblasts with initial deposits of collagen fibers. Numerous pigmented macrophages (whose cytoplasm is reddish) and abundant new vessels. Findings compatible with acute myocardial infarction of 10 to 14 days of evolution. **(A)** Intramyocardial coronary artery with marked thickening of the wall and reduced lumen (red arrow). There are spindle cells with the appearance of reparative fibroblasts that cause a disorganized appearance for comparison. On the left (blue arrow), an artery with normal characteristics is observed. **(B)** Medium caliber mesenteric artery (red arrow) with marked thickening of the wall that reduces the lumen to a cleft. In comparison, a mesenteric artery with normal characteristics is observed (blue arrow). **(C)** Medium caliber renal artery with marked thickening of the wall due to intimal hyperplasia that significantly reduces the lumen of the vessel (red arrow). Above (blue arrow) a renal artery with normal characteristics **(D)**.

disease where fibrinoid necrosis is replaced by marked intimal thickening with apparent obliteration of the lumen with minimal or no cellular swelling around the walls of the arteries (9).

Beyond the alterations described in the arteries, the definitive diagnosis of infarction was confirmed at autopsy. This was key for the description of the pathophysiology of cardiac involvement and in order to differentiate other entities, such as myocarditis, given the cardiac magnetic resonance findings.

Although the definitive diagnosis of myocarditis remains histopathological, it is true that cardiac magnetic resonance findings may be sufficient to establish a strong suspicion of this disease (10). However, there are multiple entities such as myocarditis, myocardial infarction, amyloidosis, focal or diffuse fibrosis whose characteristics overlap in cardiac magnetic resonance findings (11). In fact, large studies comparing the characteristics of acute myocardial infarction and myocarditis on cardiac magnetic resonance base the differences on the pattern of late enhancement (transmural, subepicardial, and subendocardial) and whether the distribution corresponds to a vascular territory (12). In our case, the affected regions of the myocardium did not correspond to a single vascular territory, so the suspicion of an infarction practically vanished at that time.

It was not until the autopsy that the diagnosis of myocarditis was ruled out. Multiple histological sections were made and none of them met the Dallas diagnosis criteria for myocarditis (13). Instead, an infiltrate characterized by neutrophils, granulation tissue with the formation of new blood vessels and collagen deposition was observed. Typical of acute myocardial infarction with an evolution of 10 to 14 days (14). Same time of evolution of the clinical picture of the patient.

Although the distribution of the infarct does not obey a specific vascular territory, non-transmural multifocal diffuse infarcts have been described as a well-established cause of MINOCA, especially under pathophysiological substrates such as diffuse vasospasm (15).

The authors hypothesized a vasospastic component for the present case. According to Lanza et al., two factors are required for this hypothesis to be true: a susceptible vessel and a triggering stimulus. Susceptibility to vasospasm is related to microstructural changes caused by chronic inflammation, fibromuscular hyperplasia and adventitial abnormalities, presents in PAN, which cause vessel hyperreactivity (16). While the triggering stimuli of vasospasm seem to be related to sympathetic and parasympathetic activity (17). In this particular case, we suspect that the stimulus that could trigger spasm in all the coronary arteries could have been the pyridostigmine that he received before the onset of his clinical presentation (18). Under normal conditions, acetylcholine causes vasodilation through the secretion of nitric oxide in the parasympathetic nerves. However, in high doses, it can induce direct stimulation of muscarinic receptors and cause vasoconstriction.

It is possible that the greatest limitation in this approach is not having any imaging test that demonstrates coronary vasospasm. Nevertheless, it is possible to postulate the association since the patient had the substrate to develop vasospasm (alterations in the coronary arteries due to vasculitis) and she received a stimulus that has already been reported as a cause of vasospasm (pyridostigmine) (18). The timing of the onset of symptoms also supports the suspicion, since it was not until the patient received pyridostigmine that she began with chest pain and later cardiogenic shock. Finally, histopathology gave the definitive diagnosis of myocardial infarction and did not show occlusions or thrombi in the coronary arteries.

This case constitutes another type of coronary artery disease manifestation described so far in patients with PAN. It strengthens the theory that the ischemic substrate can be caused by coronary vasospasm and exemplifies that in such patients, myocardial infarctions not limited to a vascular territory can also occur and cause serious hemodynamic consequences.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ER-M, JL-L, FV-S, CC-G, AG-O, EA-C, and JV-E wrote the clinical case. FS-J, DG, RG-N, AA-M, JB, and DM wrote the discussion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case Report: A balloon-based technique to remove a pearl-like embolus out of the coronary artery

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Coronary embolism is considered a rare non-atherosclerotic etiology of acute myocardial infarction, whereas atrial fibrillation is the main etiology of coronary embolism. We report a rare case of a patient with coronary embolism with a specific pearl-like embolus attributed to atrial fibrillation. For this patient, we used a balloon-based technique to successfully remove the embolus from the coronary artery.

KEYWORDS

acute myocardial infarction, coronary embolism, atrial fibrillation, embolus, aspiration thrombectomy

Introduction

A 78-year-old male patient was transferred to the emergency department with a complaint of syncope during defecation. He was reported to have fallen on the floor 4 h before his transfer and to have awakened after a few minutes without chest pain, speech impairment, or limb movement disorder. On admission, his vital signs were as follows: pulse rate, 42 beats/min; blood pressure, 84/44 mmHg; and respiratory rate, 16 breaths/min. A physical examination revealed no neurological signs and grade V/V muscle strength. An electrocardiogram showed atrial fibrillation (AF), complete heart block, junctional escape rhythm, and ST-segment elevation in leads II, III, aVF, and V3R-V5R (**Figure 1**). Laboratory tests showed an initial troponin T of 6,938 ng/L; total cholesterol, 142 mg/dl; low-density lipoprotein cholesterol, 82 mg/dl; high-density lipoprotein cholesterol, 43 mg/dl; and triglycerides, 36 mg/dl. Transthoracic echocardiography revealed a mild hypokinesis in the inferoposterior wall, moderate mitral regurgitation, and no intracardiac or left atrial thrombus (left ventricular ejection fraction of 49%). The patient had a previous medical history of atrial fibrillation for more than 30 years but was not taking any anticoagulant drugs. He had no history of smoking, hypertension, or diabetes mellitus.

A diagnosis of acute inferior and right ventricular ST-segment elevation myocardial infarction was made. Aspirin (300 mg) and ticagrelor (180 mg) were given. A temporary pacemaker (frequency 60 bpm, voltage 5 mv) was implanted to maintain a normal heart rate through the right femoral vein.

Unfractionated heparin was given by loading 6,000 IU intravenously and infusing with 1,000 IU per hour during the procedure to maintain the activated coagulation time greater than 300 s. An emergency coronary angiogram showed a total occlusion of the proximal right coronary artery (RCA) with a globular filling defect without any collateral vessels from the left coronary system (**Figure 2**). A 6 Fr JR 4.0 guiding catheter (Teruma, Japan) was

Abbreviations
AF, atrial fibrillation; AMI, acute myocardial infarction; CE, coronary embolism; LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

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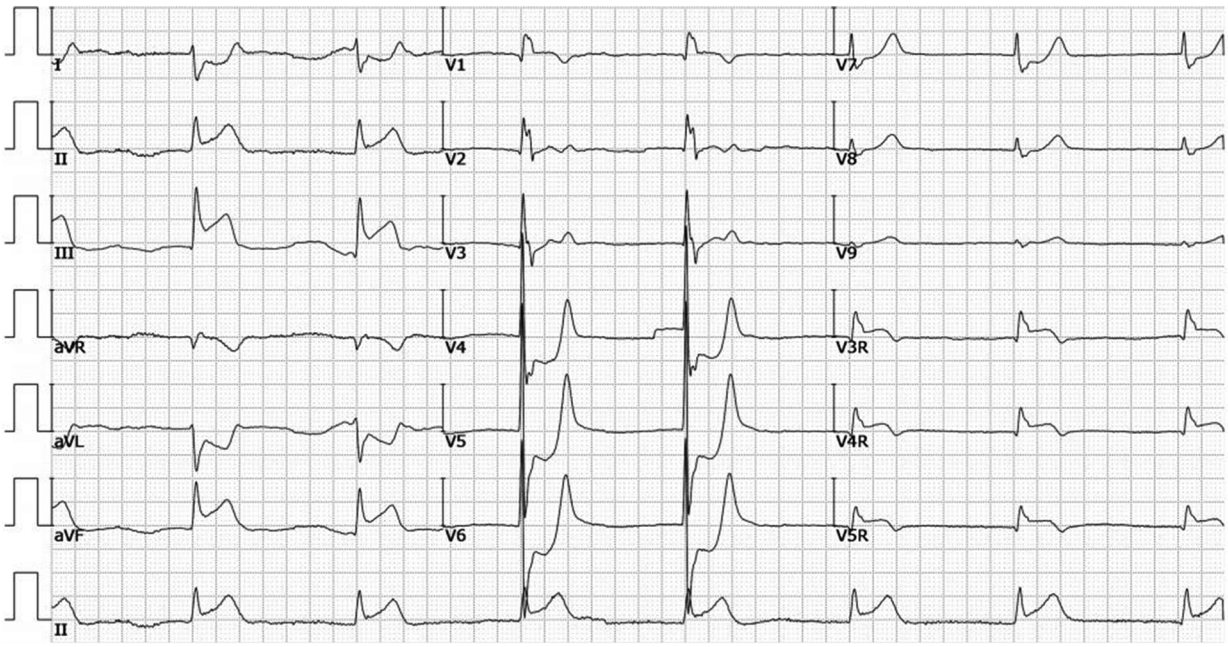

FIGURE 1
ECG in the ER before the coronary angiogram. ECG showing AF, complete heart block, junctional escape rhythm, and ST-segment elevation in leads II, III, aVF, and V3R-V5R.

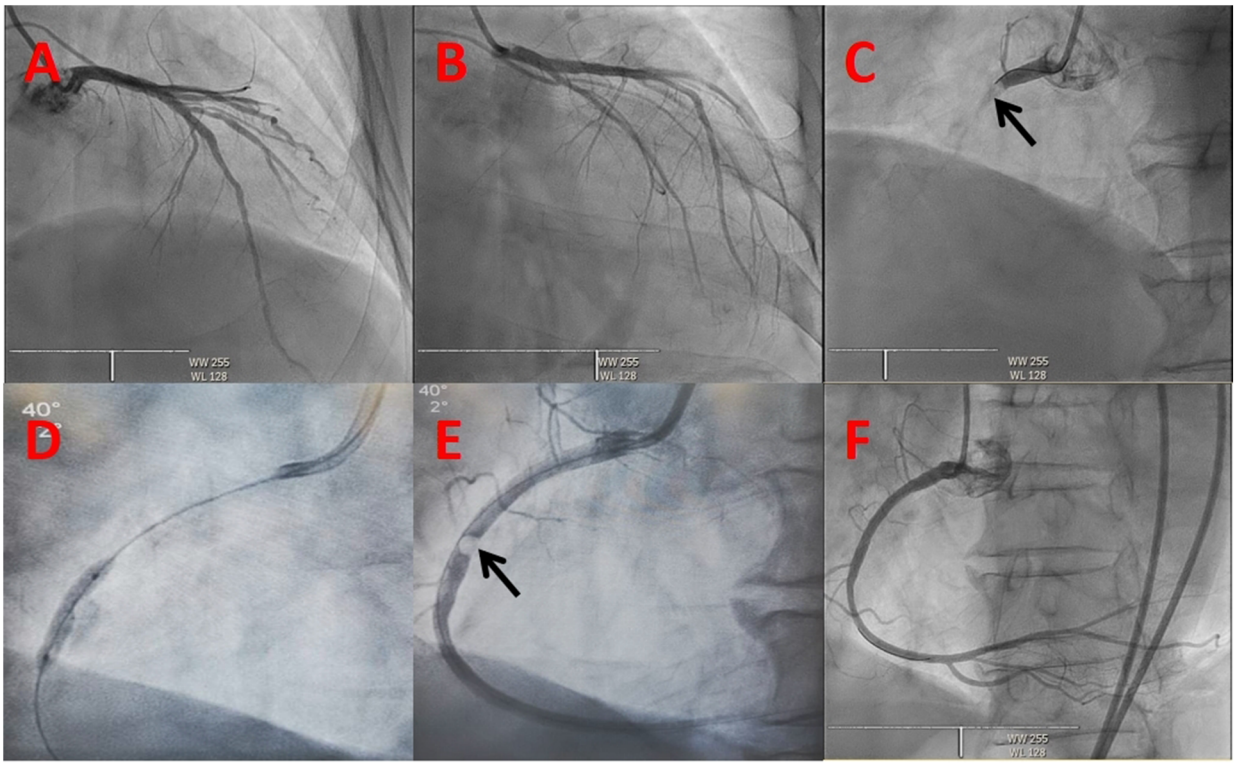

FIGURE 2
Coronary angiogram. The initial view of the coronary angiogram in (**A**–**C**) revealing a normal left coronary system and an embolism in the proximal right coronary artery (dark arrow): (**A**) Cranial 30, (**B**) RAO 30 + Caudal 30, (**C**) LAO 40. (**D**) Hourglass sign of balloon angioplasty. (**E**) Embolus in the proximal right coronary artery (dark arrow). (**F**) Right coronary angiogram showing TIMI 3 blood flow after the intervention.

engaged in the RCA. Run-through wire (Teruma, Japan) and Sion wire (ASAHI, Japan) failed to pass through the lesion. We considered that the occlusion was not a common thrombotic lesion and attempted to open the lesion using Fielder XT (Abbott, USA) wire under the Finecross microcatheter (Teruma, Japan). With careful manipulation, the wire was advanced to the distal end of the RCA through the occlusion. A 1.5 × 15 mm Maverick balloon (Boston Scientific, USA) was successfully passed through the lesion and was inflated to 6 atm, but the coronary angiogram showed no blood flow in the RCA. The balloon was converted to a 2.0 × 20 mm Maverick balloon and inflated to 6 atm, but again, it did not yield the desired results. We then performed aspiration thrombectomy using Rebirth (Goodman, Japan). But no thrombus was aspirated. Then, we used a Sprinter balloon of different sizes (2.0 × 20 mm and 2.5 × 15 mm) (Medtronic, USA), which successively dilated the lesion, and an hourglass sign was revealed (Figure 2). The blood flow recovered to TIMI 1 and the embolus ran deeper into the RCA (Figure 2). To make the characteristics of the embolus clear, we decided to perform intravenous ultrasound (IVUS) (Boston Scientific, USA). IVUS showed calcification and posterior echo attenuation in the mid-RCA (Figure 3). We realized that the embolus was hard and calcified, and the usual methods would not work. The option of emergency coronary artery bypass grafting was considered. But the patient's hemodynamics were still unstable, and he suffered ventricular fibrillation several times during the procedure. The cardiac surgeon reasoned that the mobility of the embolus in the RCA rendered it difficult to be detected accurately and that the surgical risk was too high. The patient's family also did not favor surgery. After a detailed discussion, we decided to use a balloon-based technique to extract the embolus from the coronary artery. First, we would use a balloon to pass through the embolus to the distal portion of the RCA. Second, the balloon would be inflated to low pressure and then be pulled backward to bring the embolus together out of the coronary artery. Finally, we would perform selective organ angiography to locate the escaped culprit embolus and prevent embolization to the major related organs, i.e., brain, intestines, and kidneys.

An 8-Fr short dilator was inserted through both femoral arteries, and Angioguard (6 mm) umbrellas (Cordis, USA) were inserted in both carotid arteries through an 8-Fr MPA catheter (Cordis, USA)

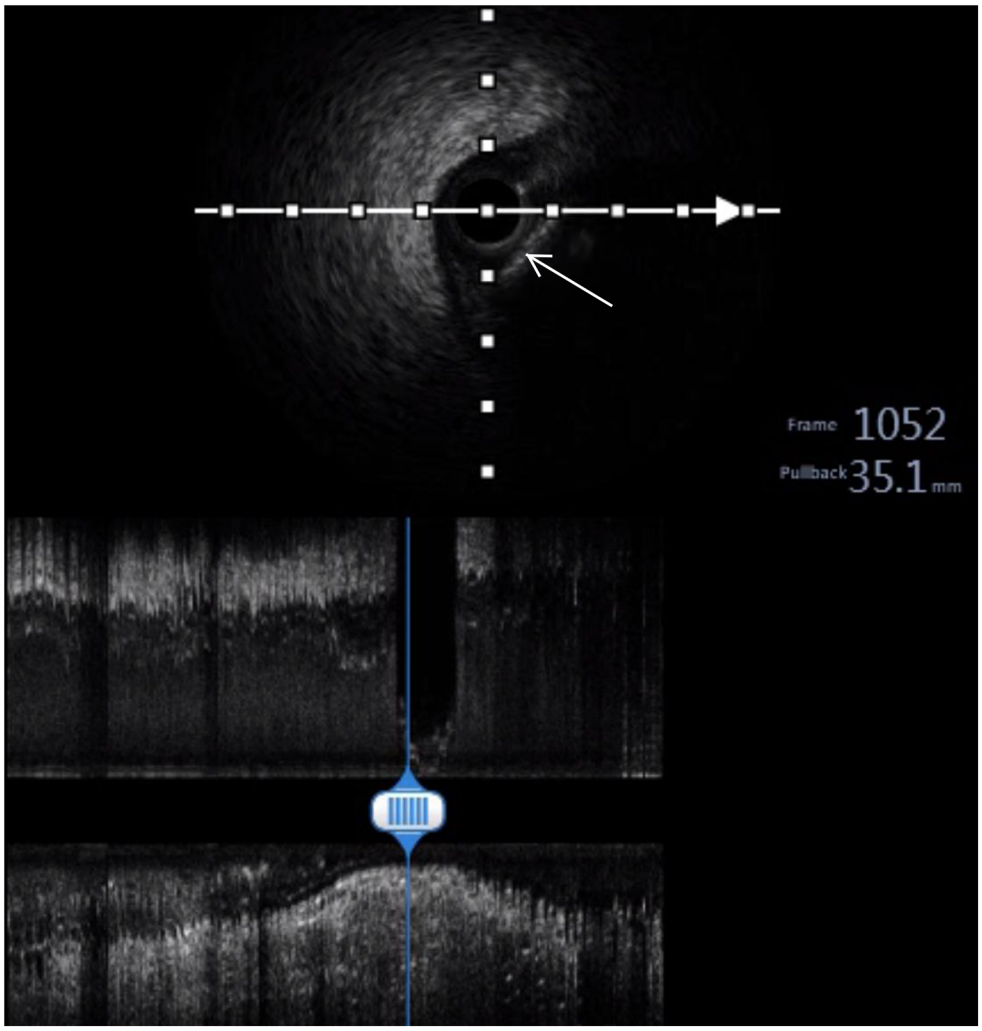

FIGURE 3
Intravenous ultrasound (IVUS). IVUS showing calcification and posterior echo attenuation in the middle RCA (white arrow).

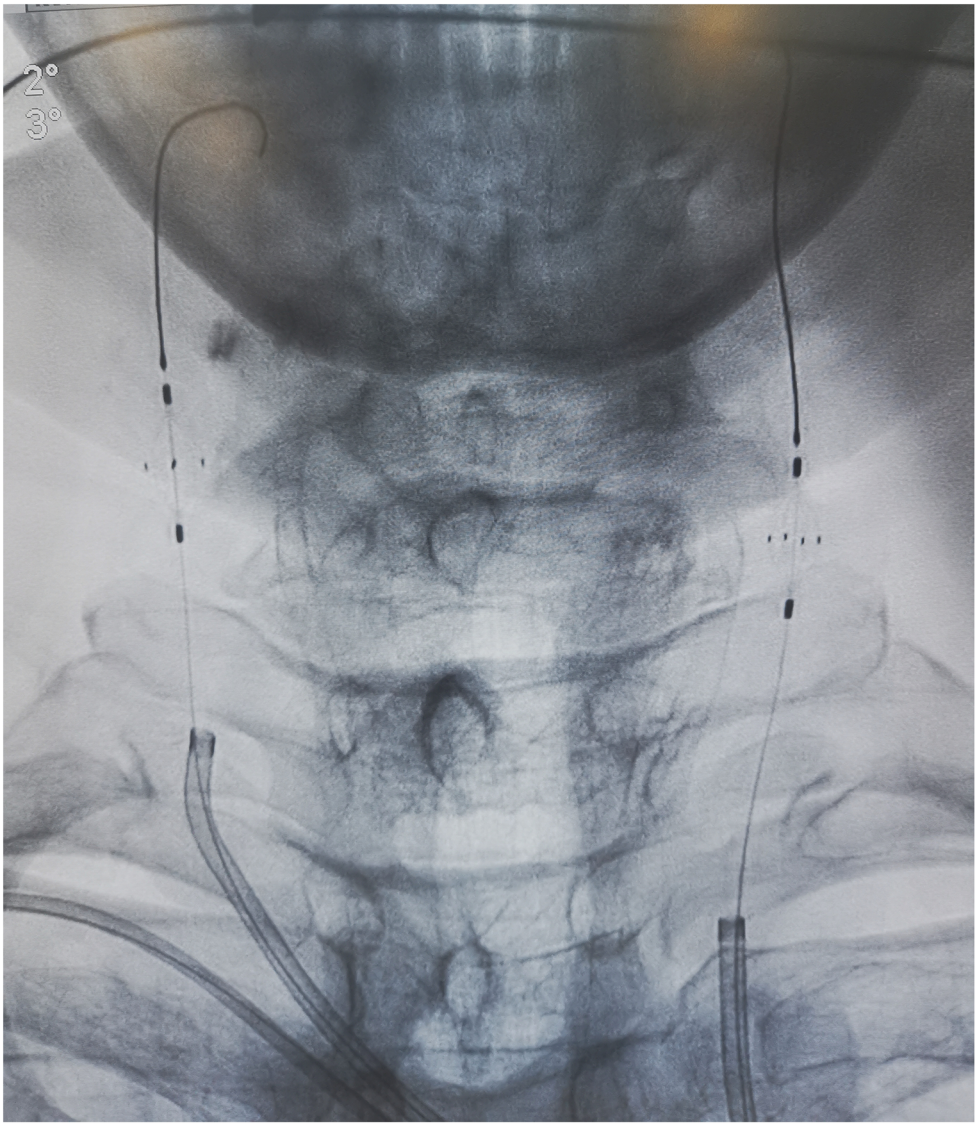

FIGURE 4
Angioguard umbrellas in both carotid arteries.

(Figure 4). A 2.5 × 15 mm Sprinter balloon was successfully passed through the lesion and was inflated to 4 atm. Then, we dragged the balloon and the embolus together out of the coronary artery carefully and slowly. A subsequent coronary angiogram in the RCA showed that blood flow had recovered to TIMI 3. Further, we performed a cerebral artery, superior mesenteric artery, and lower limb artery angiogram to confirm the escape site of this embolus after the removal procedure with vital organ protection. Fortunately, we found that the embolus was brought to the right peroneal artery (Figure 5). The patient did not feel any lower limb pain, and the pulse of the dorsalis pedis artery was palpable. Finally, we completed this tough coronary procedure, and the total time consumed was 4 h and 53 min. The patient was then safely transferred to the intensive care unit. An electrocardiogram after the procedure revealed that the ST segment had returned to baseline and no significant Q wave was detected in the inferior leads (Figure 6).

The next day, we decided to remove the embolus from the body with the help of a vascular surgeon in order to avoid the risk of the patient contracting lower limb ischemia. We used the same method to drag the embolus from the right peroneal artery to the right femoral artery and then pulled it out of the body by incising the femoral artery. The culprit turned out to be a hard gray pearl-like embolus. Further histopathological examination revealed the organized and calcified nature of the embolus. Fibrinoid necrosis developed at the center of the embolus with a few mixed red blood cells, and surrounding it was a thick layer of fibrotic tissue with hyaline degeneration and peripheral calcification (Figure 7).

After the procedure, the patient did not experience recurrent myocardial infarction, but he suffered congestive heart failure and gastrointestinal bleeding (melena) in the hospital. With guideline-directed medical treatment, he showed recovery and was discharged one month later with an antithrombotic therapy of rivaroxaban 15 mg qd + clopidogrel 75 mg qd. He recovered well afterward and remained in NYHA class I at month 3 of follow-up.

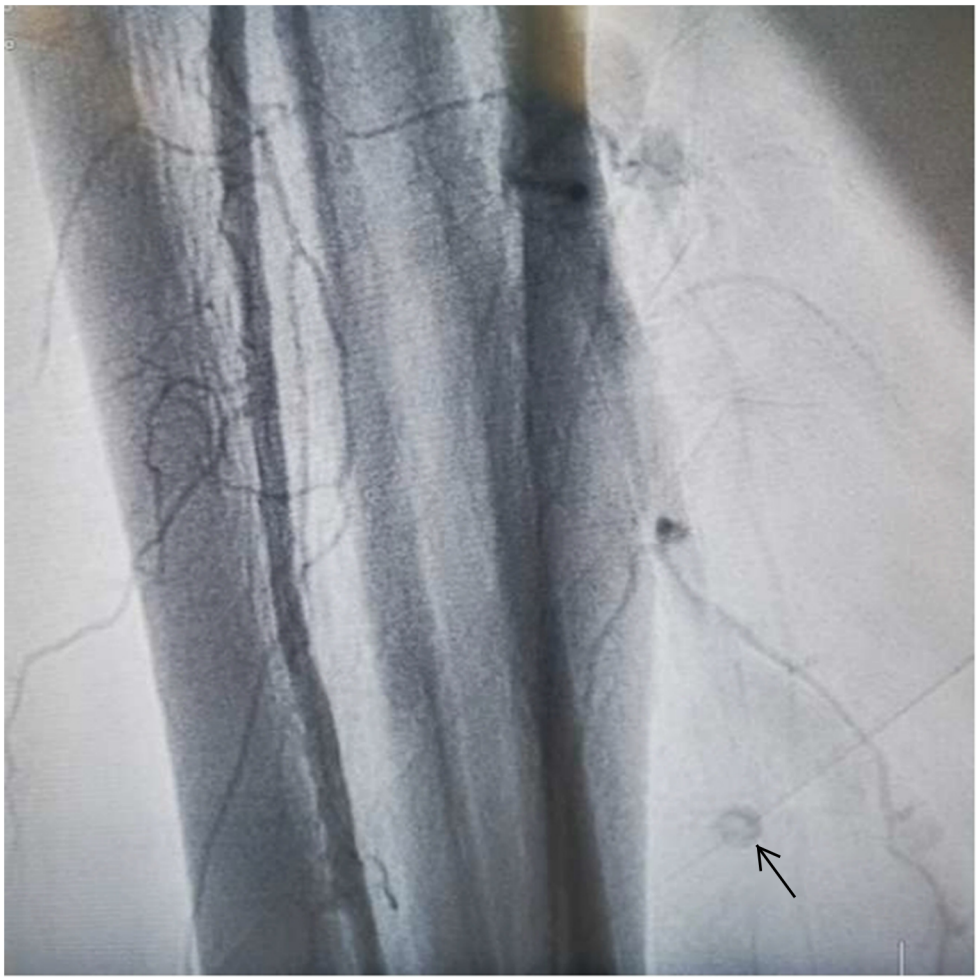

FIGURE 5
Lower limb artery angiography showing a filling defect (dark arrow) in the right peroneal artery.

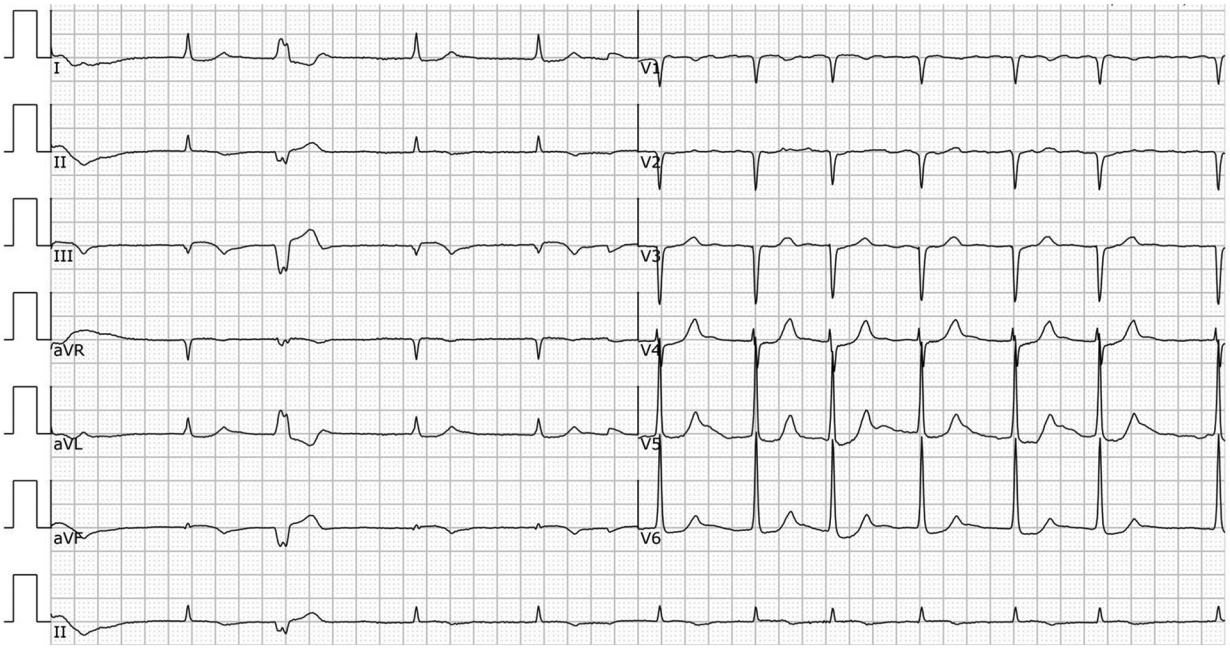

FIGURE 6
ECG after the procedure. ECG showing AF, and premature ventricular beats.

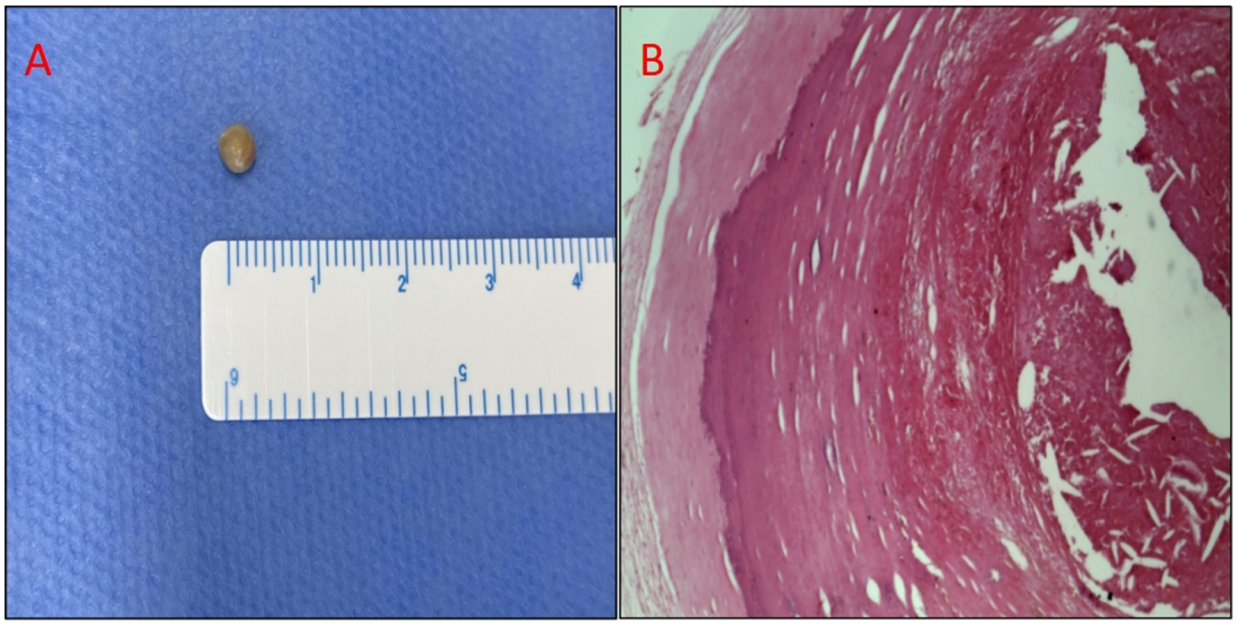

FIGURE 7
(A) Photograph of the retrieved embolus: gray globular tissue with a diameter of 4 mm. (B) Photomicrograph of the embolus. Hematoxylin and eosin staining. At the center of the embolus is fibrinoid necrosis with a few mixed red blood cells, and the surrounding is a thick layer of fibrotic tissue with hyaline degeneration and peripheral calcification.

Coronary embolism is an under-recognized etiology of AMI with the potential to yield significant morbidity and mortality rates. A retrospective study found that the prevalence rate of coronary embolism in patients with AMI was 2.9% and that AF was the most important cause (1). Aspiration thrombectomy remains the mainstay of treatment for coronary embolism (2, 3). However, in the case of a more organized and calcified embolus, as in this case, aspiration thrombectomy may not be effective, and other unconventional techniques may be needed to be used. IVUS is very important because it can help us clearly define the characteristics of the embolus. In this case, the technique of dragging the embolus out of the coronary artery using a balloon inflated with low pressure may be an effective choice. However, it should be noted that the protection of the brain and other major related organs is very important because it will be catastrophic if the embolus causes a stroke or other systematic embolisms.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

KW is responsible for writing this case report. XC, LD and BW participated in the treatment. BW revised the case report. All authors have contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1086483/full#supplementary-material.

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A case report and literature review of myocardial infarction with nonobstructive coronary arteries (MINOCA) possibly due to acute coronary vasospasm induced by misoprostol

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Coronary artery vasospasm (CVS), an uncommon cause of acute chest pain, can be provoked by vasoconstriction-induced medications. Misoprostol, a prostaglandin analog, is a safe medication to terminate a pregnancy. However, misoprostol can cause coronary artery vasospasm due to vasoconstrictor properties, leading to acute myocardial infarction with nonobstructive coronary arteries (MINOCA), especially in patients with a high risk for cardiovascular disease. We report a case of a 42-year-old female with a past medical history of hypertension who presented with ST-elevation myocardial infarction following the administration of a high-dose Misoprostol. The fact that coronary angiogram and intravascular ultrasound revealed normal coronary arteries suggested transient coronary vasospasm. CVS is a severe but rare cardiac adverse effect associated with high-dose misoprostol. This medication should be prescribed with caution and close monitoring, especially in those with pre-existing heart disease or cardiovascular risk factors. Our case raises awareness of severe cardiovascular complications that can be related to using misoprostol in high-risk patients.

KEYWORDS

MINOCA, myocardial infarction in the absence of obstructive coronary artery disease, acute myocardial infarction, prostaglandin e1 analogue, coronary vasospasm.

Background

Coronary arteries disease without significant flow-limiting lesions or severe coronary vasospasm can result in an acute imbalance between oxygen demand and supply, causing acute myocardial infarction with non-obstructive coronary disease (MINOCA) (1). In 2019, the American Heart Association's practical guidelines and algorithm were

established to provide clinical guidance for the diagnosis and treatment of MINOCA (2). Misoprostol, a prostaglandin E1 analog, is currently used under the recommendation of the National Institute For Health and Care Excellence 2019 and the American College of Obstetricians and Gynecologists 2020 for the termination of pregnancy (3, 4). However, misoprostol uncommonly can induce acute coronary vasoconstriction when used with a high dose (5). Herein, we report a case of a 42-year-old female suffering from acute STEMI due to severe coronary vasospasm following the administration of high-dose misoprostol (400–1200 mcg within 24–48 h) for abortion induction.

Case presentation

A 42-year-old Vietnamese female (gravida 5 para 3) with a past medical history of hypertension reported taking Mifepristone 200 mg to induce the termination of her 5-week pregnancy one day before admission. The patient continued to take misoprostol 600 mcg sublingually one hour before hospitalization. She then experienced acute severe left-sided chest pain, dyspnea, and nausea prompted her to go to the hospital. Upon arrival, the patient noted bradycardia with a heart rate of 55 beats per minute and hypotension with a blood pressure of 70/40 mmHg. The other vital signs were stable, with a respiratory rate of 20 breaths per minute and saturation at 99% on room air. ECG showed 2 mm ST elevations in II, III, aVF, V1, V3R, and V4R with reciprocal depressions in I, aVL, and V6 (**Figure 1**). Laboratory findings were remarkable for markedly elevated hs-troponin T (103 ng/l). Since the presentation suggested acute ST-elevation myocardial infarction (Killip I) of the inferior and right ventricle, the patient was started on loading dual anti-platelet therapy and statin. Thirty minutes later, she reported that her chest pain had improved. Repeat ECG showed normal sinus rhythm with a heart rate of 70 beats per minute and complete resolution of ST-elevation. The subsequent coronary angiography revealed normal coronary without flow-limiting lesions (**Figure 2**). IVUS of RCA showed no evidence of significant stenotic lesions, thrombus, or dissections (**Figure 3**). Transthoracic echocardiography revealed a preserved ejection fraction of 68% without wall motion abnormalities or other structural heart

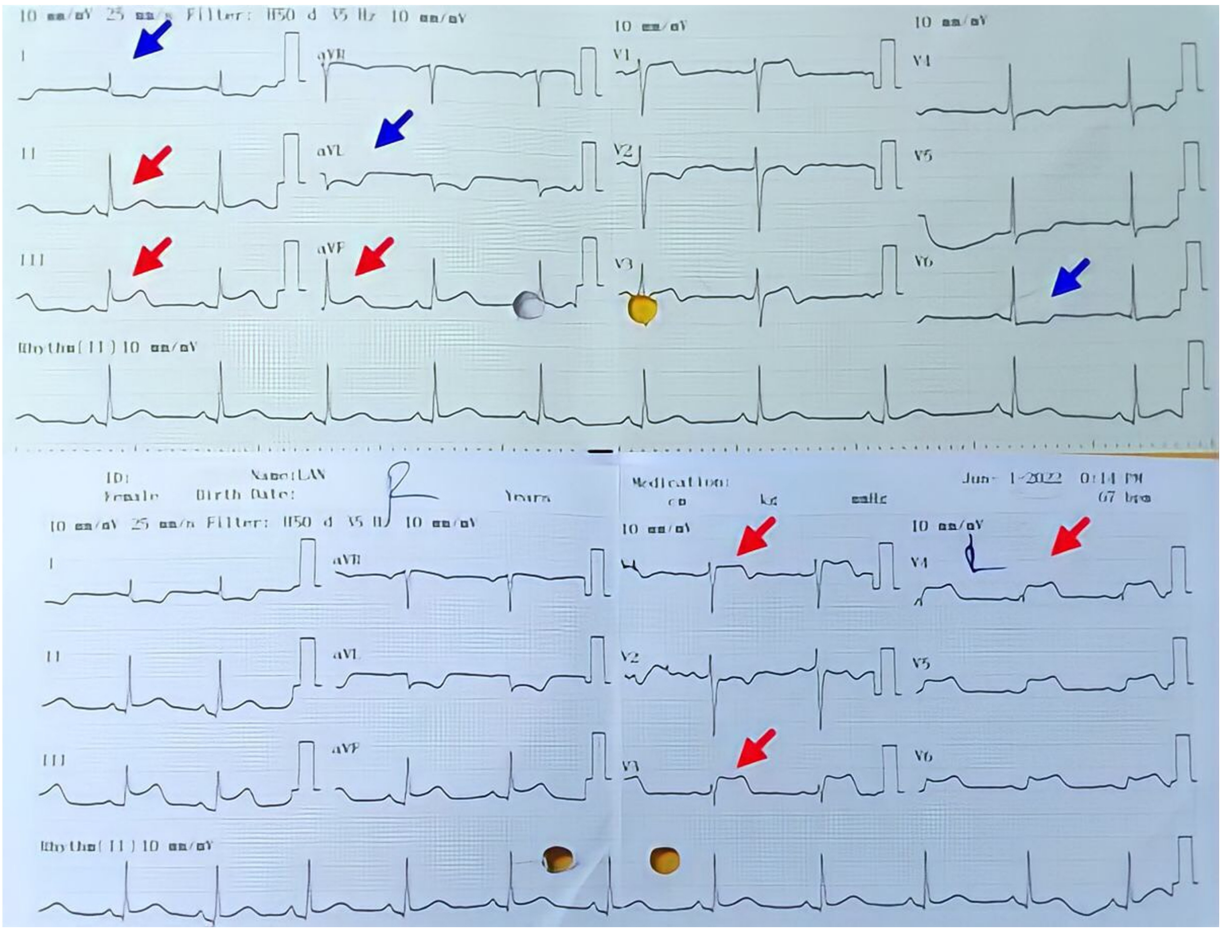

FIGURE 1
The upper ECG shows a 2 mm ST elevation (red arrow) at leads DII, DIII, aVF, V1, with reciprocal depression (blue arrow) in DI, aVL, and V6. This ECG suggests an inferior myocardial infarction with ST elevation. The lower ECG with right-side lead indicates a 2 mm ST elevation (red arrow) at lead V3R, and V4R which suggests a right ventricular myocardial infarction. RCA was suspected as culprit lesion.

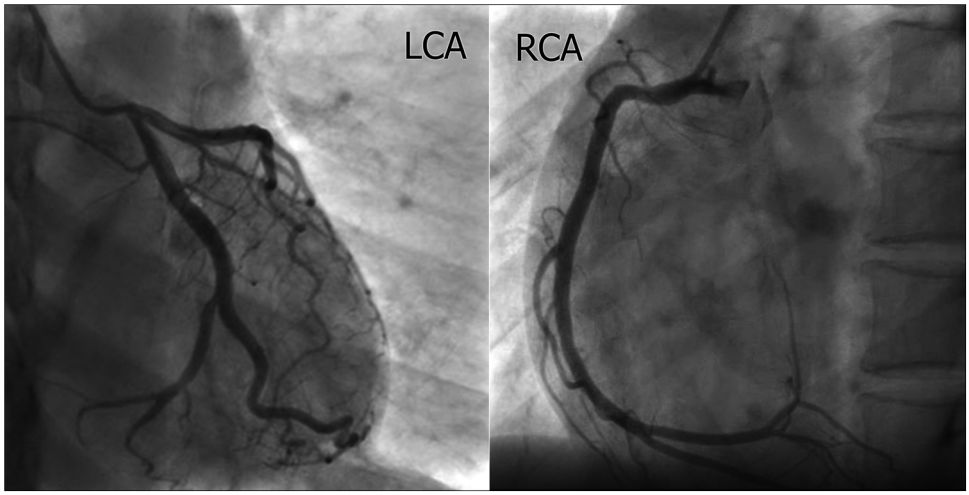

FIGURE 2
Coronary angiography revealed patent coronaries including LCA (left) and RCA (right) without significant flow-limiting lesions.

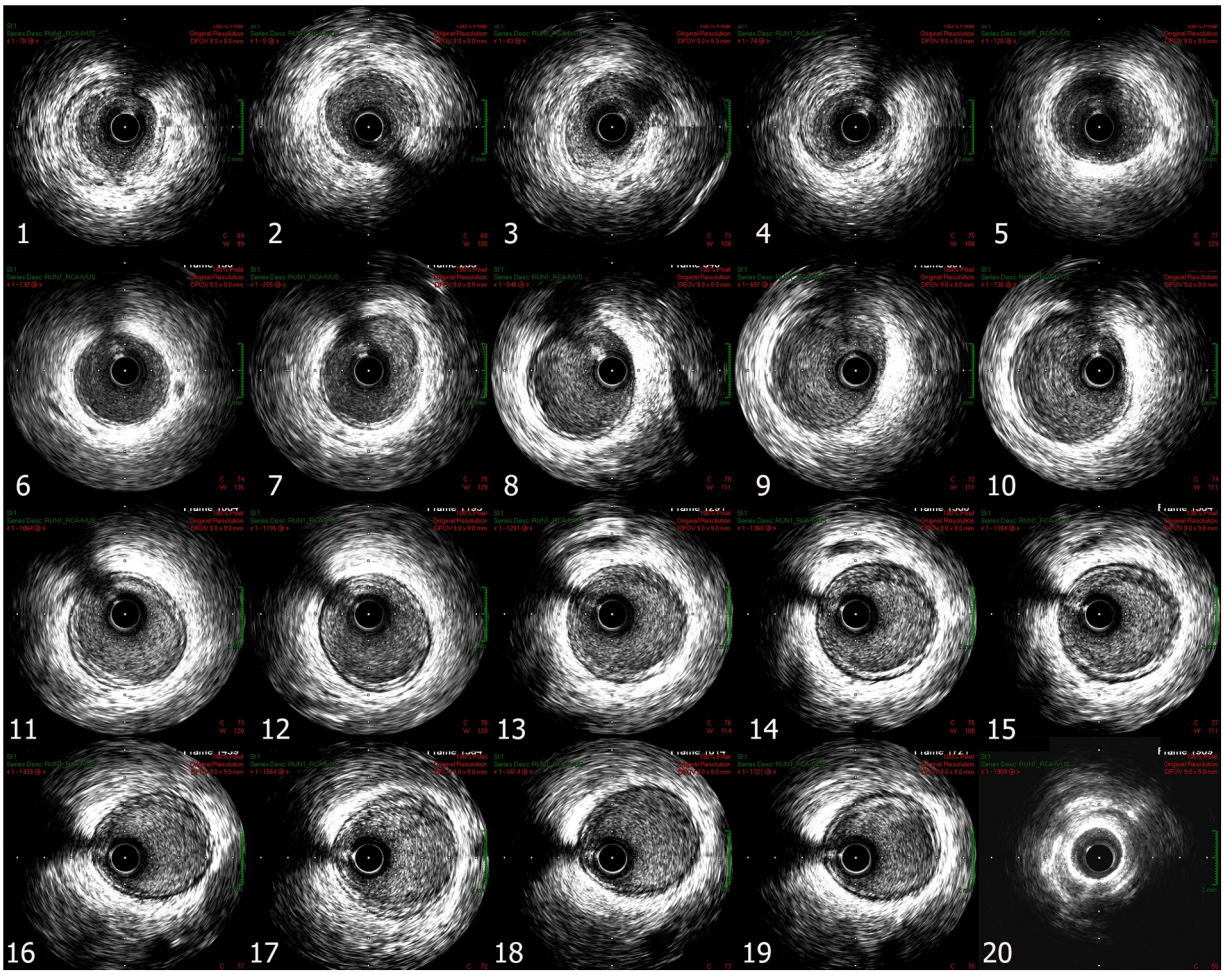

FIGURE 3
Right coronary artery IVUS showed no significant stenotic lesion, no thrombus, and no dissection in proximal RCA (image 1 to 5), mid RCA (image 6 to 10), and distal RCA (image 11 to 20).

diseases. Troponin level also decreased to 74 ng/L after 3 h of hospitalization and normalized after six days. The patient satisfied the criteria of MINOCA following the Fourth Universal Definition of Acute Myocardial Infarction with the elevated dynamic change of cardiac biomarker, ST elevation on ECG, and the result of coronary angiography without significant obstructing lesion (6). Due to the correspondence between the pharmacologic characteristics of Misoprostol and the clinical manifestation of patient, we assume the MINOCA is possibly caused by coronary vasospasm induced by misoprostol (6). She was eventually discharged with calcium channel blocker, beta-blocker, and statin. The patient remained asymptomatic and hemodynamically stable during her follow-ups in 30 days, 3 months, 6 months, and 12 months after discharge.

Discussion

About 6% of patient with acute myocardial infarction is diagnosed with nonobstructive coronary arteries by coronary angiography (7). Myocardial infarction with nonobstructive coronary arteries (MINOCA) is considerably confirmed when there is no evidence of other etiologies at the time of coronary angiography. A definite diagnosis usually requires extensive workup for various pathologies. Montone et al. reported 46% of patients with MINOCA responded to provocation testing, confirming coronary vasospasm (8). Coronary vasospasm is defined as an intense constriction of coronary arteries resulting in a significant imbalance between oxygen demand and supply. This phenomenon can provoke severe myocardial ischemia, acute myocardial infarction, or sudden cardiac death (1). The incidence of this disease varies significantly among races and between countries such as Japanese (24.3%), Taiwanese (19.3%) and Caucasian populations (7.5%) (9). Dr. Myron Prinzmetal first described this condition in 1959 and reported 32 cases of vasospastic angina (non-exertional chest pain) (1). The classic diagnostic criteria require a normal coronary angiography with spasm response to a provocative test (10). Various pathologic mechanisms were proposed, including the direct effect of catecholamines, inflammation, dysfunction of endothelial cells, smooth muscle cell hypercontractility, or increased oxidative stress (10). Compared to classic angina due to atherosclerotic artery disease, vasospastic angina induced by coronary vasospasm frequently happens in young female patients without significant cardiovascular risk factors (11). Moreover, typical precipitating factors for this condition include cold exposure, mental stress, stimulants, and medications, such as sympathomimetics and vasoconstrictor agents (10, 11). The cardiovascular events or adverse effects of misoprostol were summarized in **Table 1** (5, 12–21).

Prostaglandin E (PGE) analogs have both vasoconstrictor and vasodilator properties (**Supplementary Image S1**). This medication has a long history of adverse cardiovascular effects. PGE2 analog, such as Sulprostone, has been reported to have severe cardiovascular complications such as acute myocardial infarction, cerebral ischemic stroke, and severe hypotension (18, 22, 23). Among the PGE1 analog, misoprostol in combination with mifepristone was approved by the European Medicines Agency for treating incomplete abortion and miscarriage, while Gemeprost was used with caution due to the risk of severe adverse cardiac events (5). The cornerstone mechanism of these complications was the various effect of Prostaglandin E receptors (EP), including EP 1, 2, 3 and 4. While EP 1 and EP 3 induce vasoconstrictors, EP 2 and EP 4 have substantial vasodilator properties. PGE2 analog stimulates all 4 four receptors, while the PGE1 analog activates only EP 2, 3 and 4 (18).

The selective activation of PGE1 explains these agents' less frequent and severe cardiovascular complications. According to the prevailing hypothesis, it is widely believed that misoprostol exhibits a dose-dependent effect on the elevation of Norepinephrine (NE) levels. Consequently, the increased NE levels are thought to induce pronounced vasoconstriction and contribute to the occurrence of cardiovascular adverse events (24). In patients with medical history or high risk of cardiac disease, misoprostol was recommended to be used at a very low dose of 25 mcg every 4 h in combination with prior Mifepristone 200 mg to limit cardiovascular complications for induction labor (26).

Despite being commonly used in obstetrics and gynecology practice for labor induction and considered generally safe, misoprostol still carries a potential risk of cardiac adverse effects. In this particular patient, the Naranjo Score yields a score of 7 out of 13 points, suggesting a moderate likelihood of misoprostol being responsible for the observed cardiac adverse events (5, 22, 23). On the other hand, misoprostol at higher doses is typically used for terminating a pregnancy, yet evidence of its safety is still unclear. WHO recommends that a single dose of misoprostol 400 mcg should be given orally within 24–48 h after taking mifepristone to induce medical abortion for less than 7-week pregnancy. Additionally, besides the dose, the route of administration can impact the process of absorption, bioavailability, and the concentration of active compounds in the bloodstream (27). Misoprostol is usually administered by several pathways, including buccal, sublingual, vaginal, oral, or rectal. Among various routes, a sublingual pathway has the highest peak of plasma drug concentration while the vaginal with water has the most prolonged time of adequate drug concentration (25). So theoretically, the risk of adverse events is highest in these two administration pathways.

Thus far, there are no definitive criteria to diagnose Misoprostol-induced coronary spasm. In our case, the patient with risk factors for coronary artery disease exposed to Misoprostol 15–20 minutes before the onset of chest pain suggested a probability of association. Additionally, the plasma concentration of Misoprostol peaks at about 30 min and declines rapidly by 120 min if used orally (25). This pharmacokinetic can explain the resolution of chest pain and normalization of ST-T changes on ECG shortly after hospitalization. Moreover, the diagnosis is more consistent

TABLE 1 Literature review of previous studies.

Author	Age (year)	Background	Current medications	Indication	Dosage and route	Time	Events	Angiogram
Sung/ Korea/2009 (12)	44	Hypertension, hemodialysis	Carvedilol nifedipine valsartan	Abortion	Misoprostol vaginal 1,000 m cg in total in 20 h then IV sulprostone 42 mcg/h	8 hours after sulprostone	Myocardial infarction	RCA narrow responsive to NTG 400 mcg
Miriam/ Spain/2010 (13)	32	Primigravida active smoking obesity (BMI 32 kg/m^2)	No	Termination of pregnancy (17 weeks)	200 mg mifepristone follow with 800 mcg misoprostol vaginally after 48 hours	2 hours	Hypotension, anteroseptal MI	–
Ray/India/ 2011 (13)	32	Pregnancy-induced hypertension	Methyldopa 250 mg twice daily	Postoperative vaginal bleeding	Misoprostol 800 mcg vaginally	20 minutes	Pulmonary edema	–
Owusu/ USA/2015 (15)	42	Hypertension	Norethindrone 0,35 mg daily	Facilitate hysteroscopy	Misoprostol 200 mcg sublingual	–	VF, Inferior and lateral MI, cardiac arrest	Normal left main coronary artery, 60% LAD stenosis 70% RCA stenosis
Prashanth[a]/ India/2016 (16)	32	BMI 28 kg/m^2	–	Facilitate hysteroscopy	Misoprostol vaginally 200 mcg 30 minutes prior to procedure and Misoprostol 600 mcg rectally during the procedure due to blood loss (800 ml)	1 hour	Hypertensive crisis	–
Prashanth[b]/ India/2016 (16)	24	Primigravida	–	postpartum hemorrhage	Misoprostol rectally 600 mcg then 250 mcg prostaglandin F2 alpha + and 0,2 mg IV methylergometrine	1 hour 15 min	Hypertensive crisis	–
Matthesen/ Denmark/ 2017 (17)	41	G3P2 One spontaneous abortion One vaginal delivery	–	Termination of pregnancy	Misoprostol (dosage not listed)	Not listed	Cardiac arrest	Coronary angiography revealed coronary artery spasm, which responded to NTG
Mazhar/ Saudi Arabia /2018 (5)	39	G3P2 One spontaneous abortion	No	Incomplete abortion (6w4d)	Misoprostol 400mcg every 12 h (800 mcg in total)	45 minutes after the second dose	MI	Perform on the fifth day did not yield abnormalities
Munoz-Franco 2019 (18)	10	G6P2 Three miscarriages, active smoking, hyperlipidemia	No	Incomplete abortion	Misoprostol 400 mcg vaginally	20 minutes	Lateral and anterior MI	Severe stenosis in the middle segment of LAD, which responded to NTG
Sugito 2020 (19)	39	Depression	Recent amphetamine use	Termination of pregnancy	Misoprostol (dosage not listed)	1 hour	VF, MI, cardiac arrest	Diffuse multi-vessel coronary spasm, which improved with intracoronary NTG
Lokhande 2021 (20)	57	COVID-19 infection		Uterine bleeding	Misoprostol (dosage not listed)	Not listed	ST elevation in inferior leads	70% stenosis of RCA, which resolved entirely with intracoronary NTG

IV, intravenous, RCA, right coronary artery, NTG, nitroglycerin, MI, myocardial infarction, LAD, left anterior descending, VF, ventricular fibrillation.
Note: a, b: Prashanth et al. reported 2 cases in this paper.

with coronary vasospasm when the following angiogram and IVUS exclude occluded coronary arteries. The dynamic changes of cardiac biomarkers, ECG and clinical symptoms of the patient suggest the diagnosis of MINOCA possibly due to coronary vasospasm induced by misoprostol. New imaging modalities such as optical coherence tomography and cardiac magnetic resonance (CMR) can be used to clarify the underlying pathologic mechanism. CMR plays a crucial role in the diagnostic evaluation of patients with MINOCA, as it is recommended for excluding non-ischemic cardiac causes including cardiomyopathies, myocarditis, pericarditis, and Takotsubo syndrome. CMR has been found to be useful in confirming the diagnosis in up to 74% of cases (6). However, further investigation of this case is challenging due to our limited facilities.

Conclusion

Myocardial infarction with nonobstructive coronary arteries due to acute coronary vasospasm is a severe condition precipitated by medications with vasoconstricting properties, such as misoprostol, as a PGE1 analog. Notwithstanding isolated case reports describing notable cardiovascular events linked to misoprostol administration, it is considered a safe and appropriate choice as the initial treatment option for medical abortion, aligning with the recommendations outlined in the current practice guidelines.

Our case proposes a precaution in using misoprostol in patients with a high risk for cardiovascular disease, who should be closely monitored for any emerging severe complications.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NVH and LTKH contributed to conception and design of the study. LTKH and LHNM organized the database. LHNM and TT wrote the first draft of the manuscript. LHNM and NQKL revised and approved the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1115358/full#supplementary-material.

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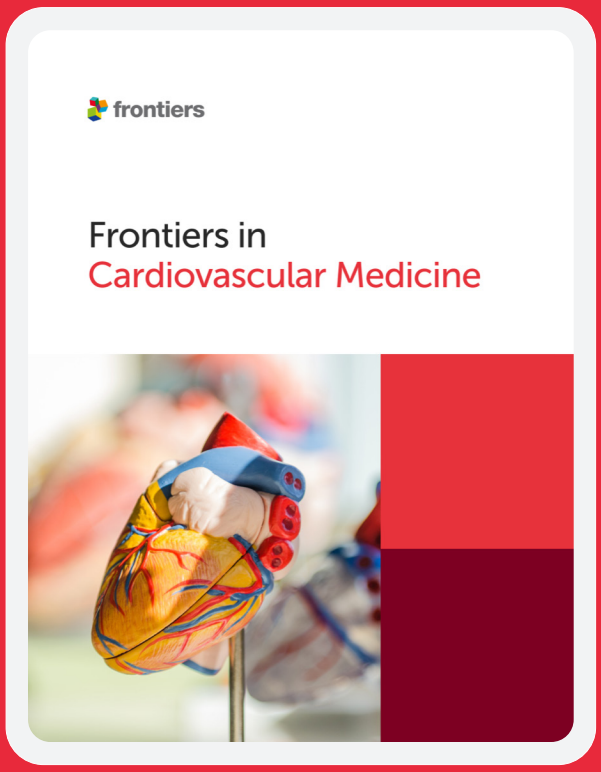

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