

TERLIPRESSIN-RELATED ACUTE MYOCARDIAL INFARCTION: A CASE REPORT AND LITERATURE REVIEW

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Acute ST-segment elevation myocardial infarction after the administration of terlipressin in patients with hemorrhagic esophageal varices is a rare but life-threatening complication. We report the case of a 73-year-old female patient with esophageal variceal bleeding complicated with acute ST-segment elevation myocardial infarction after intravenous injection of terlipressin. We discuss the underlying mechanisms of terlipressin-related acute myocardial infarction and review the literature.

Key Words: terlipressin, acute myocardial infarction
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Terlipressin (Glypressin[®], Ferring Pharmaceuticals A/S, Copenhagen, Denmark), a synthetic analog of triglycyl lysine vasopressin, is effective in controlling hemorrhagic esophageal varices in patients with liver cirrhosis and portal hypertension [1–3]. The possible side effects of terlipressin include abdominal cramping, headache, pallid face, and arterial blood pressure elevation [2]. However, less attention has been paid to the use of terlipressin in patients who are at high risk for cardiovascular events. We present a rare but crucial case demonstrating persistent ST-segment elevation myocardial infarction (STEMI) after a therapeutic dose of terlipressin for esophageal variceal bleeding. The ST segment returned to baseline after discontinuation of terlipressin treatment. Unfortunately, the patient developed cardiogenic shock with multiple organ failure and expired despite aggressive medical treatment. The relevant literature was reviewed to explore the possible pathogenic mechanism.

CASE PRESENTATION

A 73-year-old female with hepatic cirrhosis and esophageal varices documented for 6 months visited the emergency department for two episodes of vomiting with fresh blood and drowsiness during the past 24 hours. She had risk factors for coronary artery disease, including diabetes and raised serum cholesterol (256 mg/dL) and triglyceride levels (302 mg/dL), but no definite prior ischemic cardiac event. Emergency endoscopy revealed active bleeding from tortuously protuberant esophageal varices. Initial management included endoscopic ligation of the esophageal varices, blood transfusion, and saline infusion. Terlipressin was administered for active bleeding, as an intravenous (IV) bolus of 2 mg injected over 1 minute, followed by a maintenance dose of 2 mg IV bolus 8 hours later.

The patient was admitted for further management. Unfortunately, she complained of cold sweating, dyspnea, and abdominal cramping 4 hours after the second dose of terlipressin. Physical examination showed blood pressure of 135/70 mmHg, heart rate of 78 beats/minute, and respiratory rate of 21 breaths/minute. Moist rales over bilateral lung fields and S3 gallop over the apex of the heart were noted. She was intubated immediately for airway patency owing to impending respiratory failure; 12-lead surface electrocardiography (ECG) revealed diffuse ST-

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segment elevation up to 4–5 mm in the precordial leads V2 to V5 (Figure 1). Acute STEMI was diagnosed according to the clinical symptoms and ECG changes. Sublingual nitroglycerin (0.6 mg) was given to relieve the symptom but little effect was obtained. Primary percutaneous transluminal coronary angioplasty (PTCA) was considered for urgent reperfusion of the infarct-related coronary artery (IRA) within the 12 hours of golden time.

Emergency coronary angiography revealed discrete and calcified narrowing with 90% luminal diameter stenosis in the bifurcation of the left anterior descending (LAD) artery-diagonal 1 (D1) branch without obvious intracoronary thrombus but thrombolysis in myocardial infarction (TIMI) grade 2 flow in the LAD artery. No critical stenosis was found in the left circumflex and right coronary arteries. Coronary intervention was not performed because of the preserved coronary blood flow in the IRA (Figure 2). Intra-aortic balloon counterpulsation was used to augment perfusion of the coronary vasculature with significant stenosis in the LAD artery. Persistent ST-segment elevation with wide QRS complexes (current-of-injury pattern) in leads V2 to V6, I and aVL on the surface ECG were noted at the serial follow-up (Figure 3) and did not return to baseline (Figure 4) until terlipressin (given IV at an interval of 8 hours with a total dose of 14 mg within 48 hours) was discontinued. Cardiac enzymes were elevated: creatine phosphokinase (CK) was 812 IU/L and CK-MB was 25.1 IU/L. Cardiac troponin-I was also raised to a peak of 46.36 ng/mL 40 hours after the onset of symptoms. Transthoracic echocardiography revealed hypokinesia in the anterior and apicoseptal segments of the left ventricle. Unfortunately, the patient progressed to cardiogenic shock and multiple organ failure despite aggressive medical treatment. She died on the 10th day after coronary care unit admission.

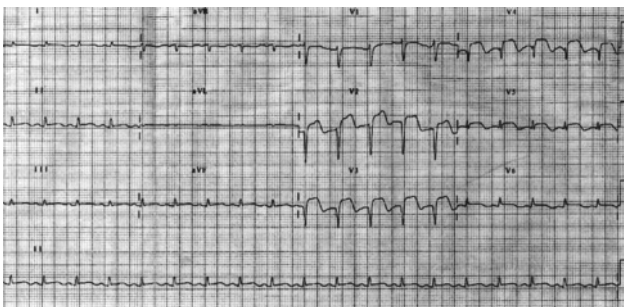


Figure 1. Marked ST-segment elevation in leads V2 to V5 after injection of terlipressin. Q waves are also present in leads V2 to V4.

DISCUSSION

Portal hypertensive bleeding is a common and serious complication of liver cirrhosis. All patients with liver cirrhosis should undergo endoscopic examination to evaluate possible causes of current or future portal hypertensive bleeding [1–3]. In cases of acute esophageal variceal bleeding, early treatment with vasoactive drugs, such as terlipressin, somatostatin, or octreotide, can save lives when skilled endoscopists are not immediately available [2]. The efficacy and mechanisms of action of terlipressin in arresting portal hypertensive hemorrhage and improving the disturbed cardiovascular status of cirrhotic patients, including those with hepatorenal syndrome, are well documented. Due to its vasoconstrictive effects on dilated splanchnic blood vessels, terlipressin can reduce blood flow into the portal vein, and thus reduce portal venous pressure and blood flow through porto-systemic shunts [2].

Acute myocardial infarction generally occurs in the presence of known risk factors and pre-existent coronary artery disease [4]. Atypical presentations due to therapeutic and illicit drug use are also documented, and lead to the consideration of alternative pathophysiologic rationales for myocardial infarction. There are many causes of myocardial infarction without coronary atherosclerosis [4]. These include coronary arteritis; metabolic disease or intimal proliferative disease causing coronary mural thickening; vasospasm of coronary arteries; dissection of the aorta involving coronary arteries; infective endocarditis; mural thrombus from the left atrium, left ventricle, or pulmonary veins; coronary artery aneurysms; hematologic hypercoagulability; cocaine abuse [5,6]; and desmopressin, which might elicit coronary artery thrombosis in hemophilic patients receiving infusions of factor VIII concentrate [7] or paradoxical coronary vasospasm resulting in acute myocardial infarction in blood donors [8].

Cardiac events after terlipressin injection are uncommon. To our knowledge, our case is the second report of terlipressin-related acute myocardial infarction; the first was reported by Rosario et al in 1996 [9]. They described a 46-year-old cirrhotic patient without previous cardiovascular disease who had an episode of sustained ventricular tachycardia (VT) several minutes after injection of 2 mg terlipressin for hemorrhagic esophageal varices. After the VT ended, surface ECG showed ST-segment elevation in the precordial leads and echocardiography revealed hypokinesia over the anteroapical segment of the left ventricle. Coronary arteriography revealed normal

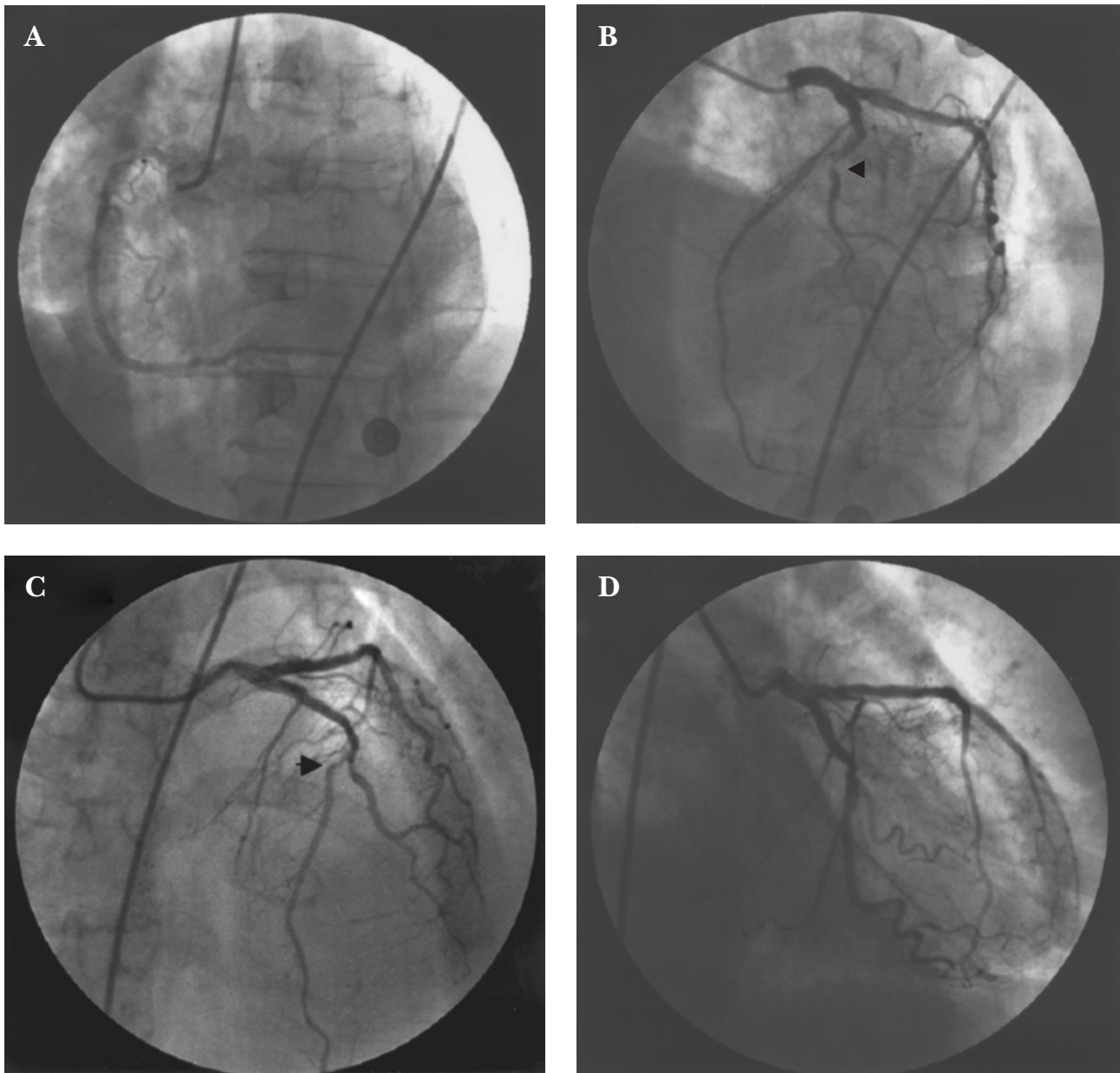


Figure 2. (A) Right coronary angiogram reveals irregular narrowing over the proximal portion of the right coronary artery. (B, C, D) Left coronary angiogram demonstrates a bifurcated stenotic lesion of 90% of the luminal diameter of the mid-left anterior descending artery and D1 branch (arrowheads).

coronary arteries in the corresponding territories and relatively normal coronary blood flow, which made the authors propose that the underlying mechanism of the terlipressin-associated myocardial infarction was coronary vasospasm caused by the vasoconstrictive effect of the drug.

In our case, ST-segment elevation in the precordial leads accompanied by symptoms of acute coronary syndrome occurred 12 hours after initiation of terlipressin

treatment. The ST-T change returned to baseline with pathologic Q waves in leads V1 to V4 after terlipressin was discontinued. Coronary angiography was performed during terlipressin treatment. Although there was significant stenosis in the bifurcation of the LAD-D1 branch, no obvious thrombus could be demonstrated and TIMI grade 2 flow in the LAD artery was preserved at emergency coronary angiography. The time sequence of the events and serial ECG changes suggested terlipressin as the cause of this

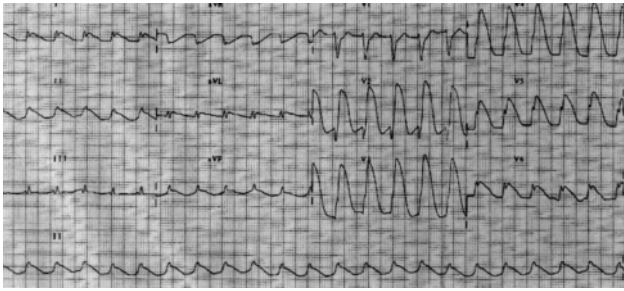


Figure 3. Prominent ST-segment elevation with tall T waves referred to as a monophasic "current-of-injury" pattern in leads V2 through V6, I and aVL 24 hours after the onset of dyspnea.

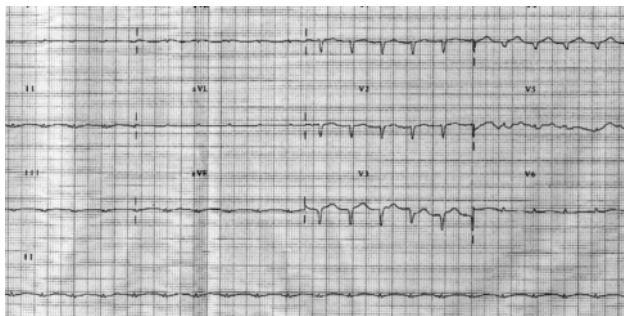


Figure 4. ST segments return to baseline in the precordial leads and Q waves in leads V1 to V4.

cardiac event. Therefore, coronary vasoconstriction induced by terlipressin was considered the most likely mechanism of inducing severe myocardial damage manifested by the "current-of-injury" pattern of ECG changes during the course of terlipressin treatment.

The pathogenesis of terlipressin-related myocardial ischemia and infarction includes one or more of the following elements: an increased myocardial oxygen demand in the face of a limited or fixed supply; marked vasoconstriction of the coronary arteries; and enhanced platelet aggregation and thrombus formation. Vasopressin induces an increase in three major determinants of the myocardial oxygen demand: heart rate, systemic arterial pressure and left ventricular contractility [10,11]. In addition to increasing the myocardial oxygen demand, administration of even small amounts of vasopressin may cause inappropriate vasoconstriction of the epicardial coronary arteries, which may decrease the myocardial oxygen supply and cause

significant ischemic burden. Although vasoconstriction induced by vasopressin can occur both in normal and diseased segments of the coronary arteries, the diseased segments are affected more. Therefore, during vasopressin treatment, patients with established atherosclerotic coronary artery disease are probably at higher risk for an ischemic cardiac event.

In conclusion, intravenous terlipressin is an effective treatment for patients with esophageal variceal bleeding, but in rare cases, especially in older patients and those with risk factors for atherosclerosis, chronic myocardial ischemia, and pre-existing coronary artery disease, cardiac complications may ensue. In our case, the patient presented with chest discomfort, dyspnea, and impending respiratory failure after terlipressin injection. The clinical symptoms and ST-segment elevations on surface ECG made physicians pay more attention to the adverse side effects of terlipressin, which were considered the most likely cause of the serious cardiac event.

REFERENCES

1. Ferguson JW, Tripathi D, Hayes PC. Review article: the management of acute variceal bleeding. *Aliment Pharmacol Ther* 2003;18:253-62.
2. Strump DL, Hardin TC. The use of vasopressin in the treatment of upper gastrointestinal hemorrhage. *Drugs* 1990;39:38-53.
3. Fiaccadori F, Pedretti G, Biraghi M, et al. Terlipressin and endoscopic sclerotherapy control variceal bleeding and prevent early rebleeding in cirrhotic patients. *Curr Ther Res* 1993;54:519-28.
4. Cheitlin M, McAllister HA, de Castro CM. Myocardial infarction without atherosclerosis. *JAMA* 1975;231:951-9.
5. Lange RA, Hillis RD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001;345:351-8.
6. Williams MJ, Stewart RA. Serial angiography in cocaine-induced myocardial infarction. *Chest* 1997;111:822-4.
7. Bond L, Bevan D. Myocardial infarction in a patient with hemophilia treated with DDAVP. *N Engl J Med* 1988;318:121.
8. McLeod BC. Myocardial infarction in a blood donor after administration of desmopressin. *Lancet* 1990;336:1137-8.
9. Rosario R, Lalanne B, Lebre P, et al. Myocardial infarction after injection of terlipressin for digestive hemorrhage. *Gastroenterol Clin Biol* 1996;20:712-3.
10. Goldsmith SR. Vasopressin as vasopressor. *Am J Med* 1987;82:1213-20.
11. Bergstrom DL, Keller C. Drug-induced myocardial ischemia and acute myocardial infarction. *Crit Care Nurs Clin North Am* 1992;4:273-8.

Terlipressin 引起之急性心肌梗塞 — 一病例報告及文獻回顧

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血管加壓素對於因為肝硬化和門脈高壓所併發的食道靜脈瘤出血有相當不錯的療效，但是在很少的情形下，特別是有心臟血管疾病危險因子的病人，有可能導致急性心肌梗塞及心因性休克。我們報告一例因為要治療食道靜脈瘤出血而靜脈注射一種血管加壓素 – terlipressin，患者於注射十二小時後引發心電圖上呈現 ST 上昇之急性心肌梗塞，之後又合併心因性休克及多重器官衰竭而死亡的病例。我們回顧相關文獻並且探討其可能的致病機轉。

關鍵詞：血管加壓素，急性心肌梗塞
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