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Case Report

Instant subacute stent thrombosis after maximum-load cardiopulmonary exercise test in a clopidogrel poor metabolizer with acute coronary syndrome

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ABSTRACT

A 63-year-old man with a hobby of full marathon and triathlon fainted while commuting on a 25-km one-way bicycle trip and was admitted to the hospital after return of spontaneous circulation. The patient was diagnosed with acute coronary syndrome, and contrast-enhanced computed tomography for trauma diagnosis indicated suspicion of liver injury. Although coronary angiography revealed a severe stenotic lesion in the left anterior descending artery, percutaneous coronary intervention (PCI) was deferred because of thrombolysis in myocardial infarction grade 3 flow. Following neurological recovery, the patient was started on dual antiplatelet therapy (aspirin and clopidogrel). On day 11, a 3.0/34-mm Resolute Onyx stent (Medtronic, Dublin, Ireland) was deployed following rotablation. As a pre-discharge evaluation, a maximum-load cardiopulmonary exercise test was performed 8 days after PCI. However, the patient developed stent thrombosis after 2 h. Subsequently, the patient was diagnosed as a clopidogrel poor metabolizer using a blood test.

Learning objective: Existing guidelines recommend a cardiopulmonary exercise test (CPET) before or immediately after the discharge of patients with acute coronary syndrome (ACS). However, the safety of the maximum-load CPET has not been established, especially in clopidogrel poor metabolizers with ACS. Acute maximal exercise induces platelet aggregation; therefore, further discussion is needed regarding the timing of CPET, exercise load level, and patient observation post-CPET in ACS patients after stent placement.

Introduction

Pre-discharge or early post-discharge cardiopulmonary exercise test (CPET) for patients with acute coronary syndrome (ACS) is a Class I indication in the Japanese Circulation Society (JCS) [1] and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines [2]. Moderate exercise in patients after elective percutaneous coronary intervention (PCI) did not increase the risk of major adverse cardiovascular events (MACE), including stent thrombosis [3]. However, there are few reports on the safety of acute-phase maximum-load CPET in patients with ACS. Herein, we report a case of subacute stent thrombosis that occurred immediately after a maximum-load CPET in a clopidogrel poor metabolizer (PM) with ACS.

Case report

A 63-year-old man with a hobby of full marathon and triathlon fainted while commuting on a 25 km one-way bicycle ride and received cardiopulmonary resuscitation from a bystander. The patient returned to spontaneous circulation after four attempts of resuscitation with an automated external defibrillator and was admitted to the hospital 5 min later. The Glasgow Coma Scale on arrival was E1V1M1 and the patient was intubated. Electrocardiogram (ECG) showed ST elevation in leads aVR and ST depression in other leads (Fig. 1A). Contrast-enhanced computed tomography (CT) showed suspected liver injury that likely resulted from chest compression or the fall during a bicycle ride (Fig. 1B). Coronary angiography (CAG; Fig. 1C, Online Movie 1) revealed a severe stenotic lesion with severe calcification in the left anterior descending artery, and the right coronary artery was non-dominant and intact (Fig. 1D). However, PCI was deferred because of thrombolysis in myocardial infarction (TIMI) grade 3 flow, possibility of hypoxic encephalopathy, and liver injury, as well as the risk of stent underexpansion if the calcification was not debulked. The maximum creatine

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phosphokinase (CK) level was 347 U/L. Aspirin (100 mg/day) and heparin were administered from the day of admission. After post-cardiac arrest care, including target temperature management, the patient recovered without neurological disturbance, and 75 mg/day clopidogrel was administered from day 6. No progression of anemia or elevation of liver enzymes was observed. On day 11, a Resolute Onyx stent (3.0/34 mm, Medtronic, Dublin, Ireland) was deployed following rotablation (Fig. 1E). Intravascular ultrasound showed good stent expansion (Fig. 1F, a–c and Online Movie 2). The patient underwent a maximum-load CPET (94 % maximal oxygen uptake; R value, 1.17; Borg scale, 15/18; Fig. 2A) 8 days after PCI to facilitate his post-discharge marathon and triathlon participation. Although no significant ECG changes were observed during the CPET (Fig. 2B), the patient complained of chest pain after 2 h, with ST elevation in ECG leads aVL and V1–V3 (Fig. 2C). Emergent CAG and optical coherence tomography (OCT) revealed stent thrombosis (Fig. 3A, B and a–c), which was treated using excimer laser-facilitated balloon angioplasty (Fig. 3C). OCT showed disappearance of thrombi in the stent (Fig. 3D, and d–f). The maximum CK level was 2270 U/L. Antiplatelet therapy was switched from aspirin (100 mg/day) and clopidogrel (75 mg/day) to aspirin (200 mg/day) and ticagrelor (180 mg/day). No cardiovascular events occurred, and the patient was discharged on day 19. A blood test revealed the patient to be a clopidogrel PM (*2/*2).

Discussion

We report a case of instant subacute stent thrombosis after a maximum-load CPET in a clopidogrel PM with ACS. The metabolism and effectiveness of clopidogrel are affected by CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) gene polymorphisms; at present, the Pharmacogene Variation Consortium has defined over 35 star (*) allele haplotypes [4]. CYP2C19 PMs are characterized by the presence of two non-functioning alleles (e.g. CYP2C19 *2/*3). The frequency of the minor allele of this single-nucleotide polymorphism varies with ethnicity; it is the most prevalent among South Asians (32.5 %), East Asians (31 %), and Africans (18 %) [5]. Clopidogrel PMs have been reported to have an increased risk of MACE, including stent thrombosis. However, there is a lack of clinical evidence demonstrating that a change in antiplatelet therapy based on the CYP2C19 genotype is associated with a in change patient outcomes; therefore, routine clinical use of genotyping for CYP2C19 in patients who undergo PCI is not recommended. Common genetic variation in CYP2C19 does not seem to affect prasugrel or ticagrelor drug action. In the TRITON-TIMI 38 trial, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis; however, it was associated with an increased risk of major bleeding, including fatal bleeding [6]. Considering the efficacy, bleeding risk, and price of these antiplatelet drugs, clopidogrel and prasugrel are Class I indications for patients with ACS in the JCS and ACC/AHA guidelines. However, according to the European Society of Cardiology guidelines, clopidogrel, instead of prasugrel, should be considered for patients with high bleeding risk [7]. In the PRASFIT-ACS Study, prasugrel (20 mg loading dose and a 3.75 mg maintenance dose) was associated with a low incidence of ischemic events and a low risk of clinically serious bleeding in Japanese patients with ACS. In the present case, CT at admission showed the possibility of a liver injury; as a result, aspirin and heparin were administered in the acute phase, and clopidogrel was added later. However, the patient was a clopidogrel PM and developed stent thrombosis. As prasugrel has shown efficacy and safety in Japanese patients, the selection of prasugrel should have been considered in the patient. In the

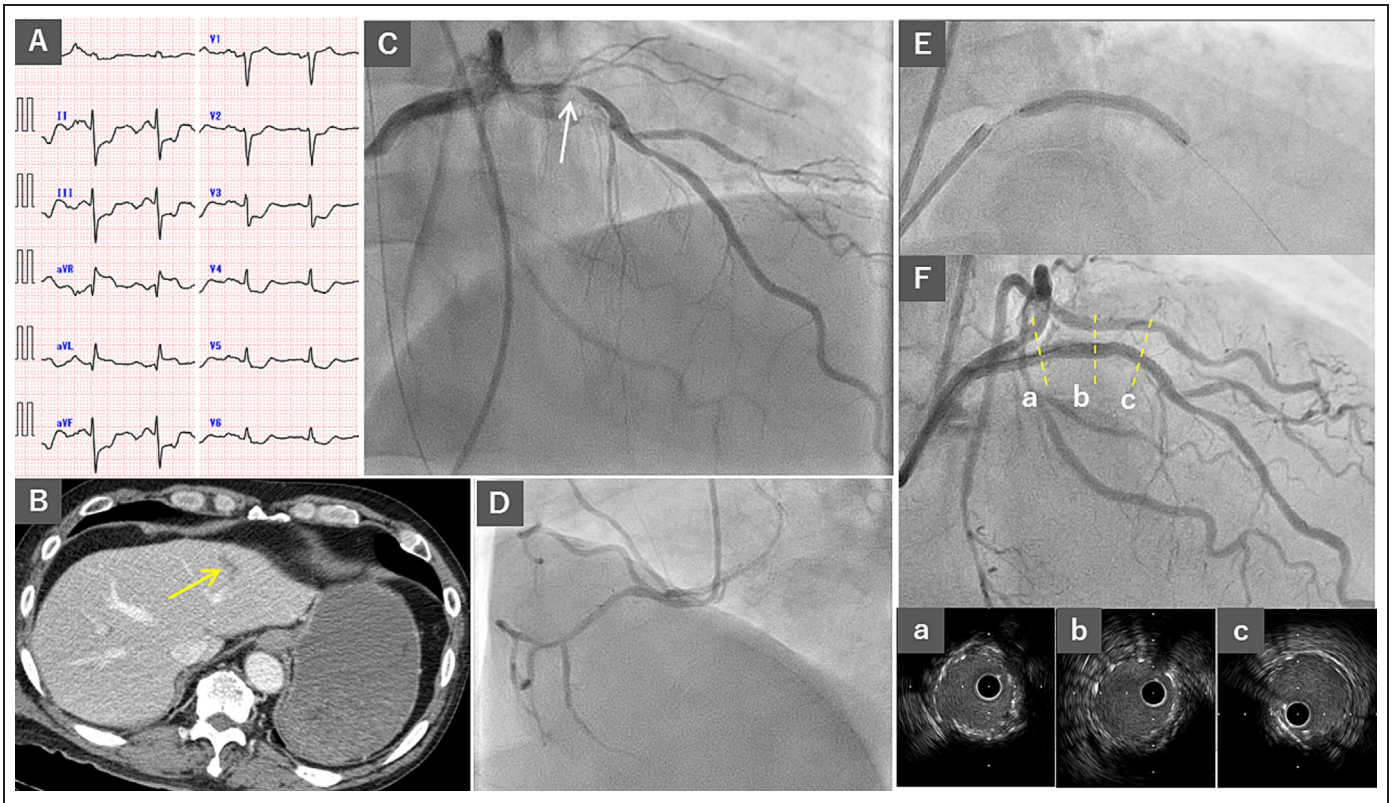
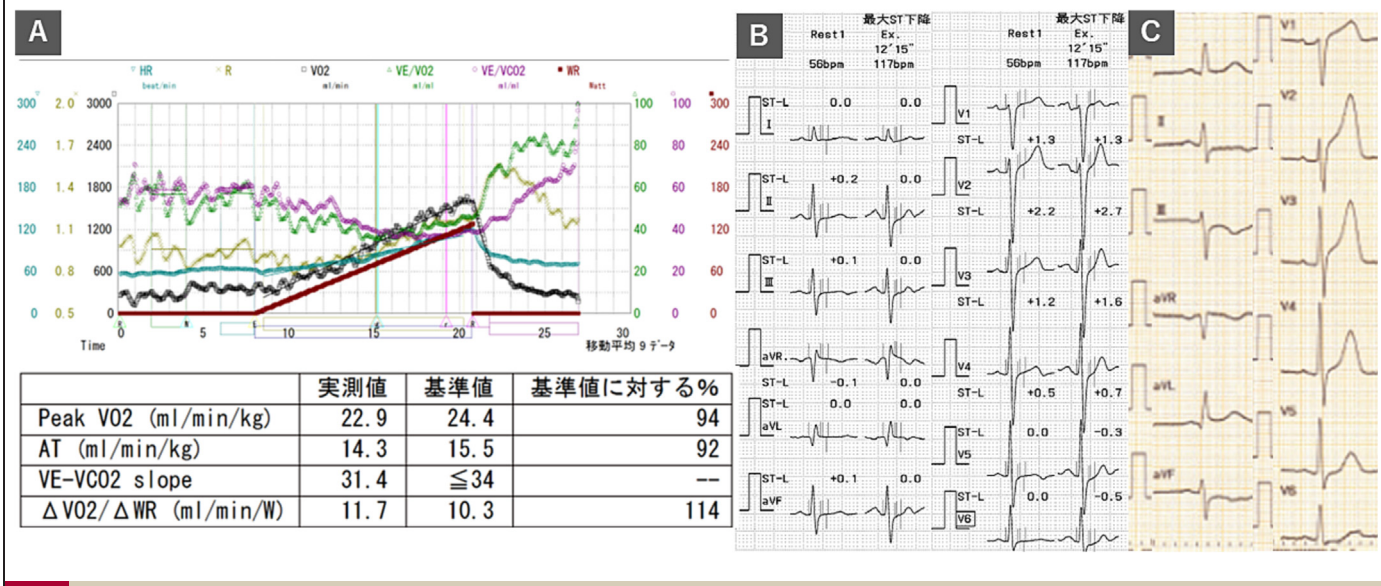


Fig. 1. Examination findings on admission and first percutaneous coronary intervention on day 11. (A) Electrocardiogram showing ST elevation in leads aVR and ST depression in other leads. (B) Computed tomography showing suspected liver injury (yellow arrow). (C) Coronary angiography revealing a severe stenotic lesion with severe calcification in the left anterior descending artery (white arrow). (D) The right coronary artery is non-dominant and intact. (E) Deployment of a Resolute Onyx stent (3.0/34 mm, Medtronic, Dublin, Ireland). (F) Post-treatment angiography. (a)–(c) Intravascular ultrasound showing good stent expansion.



	実測値	基準値	基準値に対する%
Peak VO2 (ml/min/kg)	22.9	24.4	94
AT (ml/min/kg)	14.3	15.5	92
VE-VCO2 slope	31.4	≦34	--
ΔVO2/ΔWR (ml/min/W)	11.7	10.3	114

Fig. 2. Stent thrombosis immediately after cardiopulmonary exercise test (CPET). (A) Summary of CPET results. (B) Electrocardiogram (ECG) at rest and maximum load. (C) ECG 2 h after CPET.

present case, 180 mg of ticagrelor was administered at the time of stent thrombosis, followed by a maintenance dose of 180 mg/day. By choosing ticagrelor to be taken twice daily, we considered minimizing the time of diminished blood level of the drug. Patients with severe ACS are often at high risk of bleeding. Thus, it is necessary to determine the antiplatelet therapy regimen for each patient by considering the risks and benefits.

Pre-discharge or early post-discharge CPET for patients with ACS is a Class I indication. Acute strenuous exercise increases platelet count and platelet-derived microparticles, leading to platelet aggregation and subsequent sudden cardiac death and MACE [8]. Previous studies reported that platelet thrombus formation on collagen increased at an average of 20 % after 30 min at 70 % maximal oxygen uptake [9]. Although habitual moderate exercise has an inhibitory effect on platelet aggregation, the effect disappears 2 weeks after the end of training [10]. Furthermore, patients with coronary artery disease may lack healthy vascular endothelial function (e.g. production of nitric oxide), which is supposed to counteract platelet aggregation. In the present case, the patient probably developed stent thrombosis mainly due to being a clopidogrel PM; however, other factors, such as decreased vascular endothelial function, post-hospital detraining, and acute maximum-load CPET, may have been involved. As no significant ECG changes were observed during

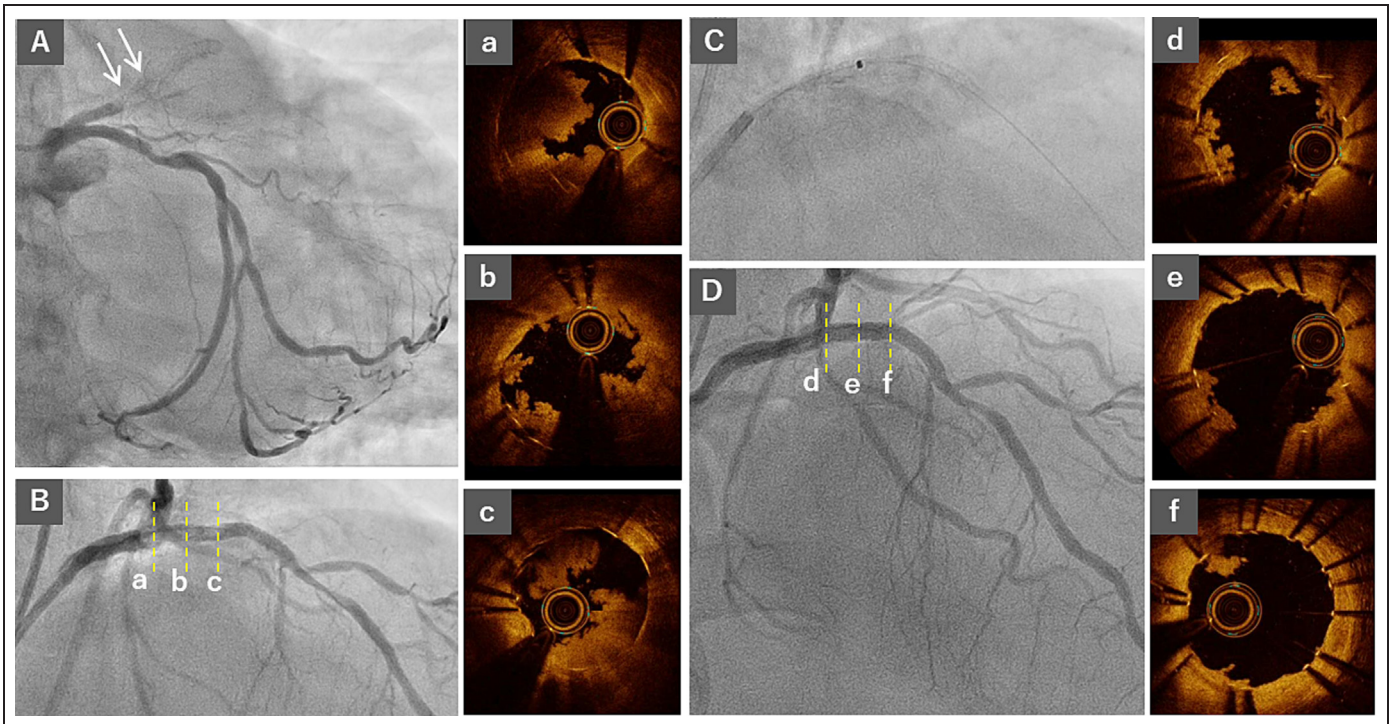


Fig. 3. Percutaneous coronary intervention (PCI) for stent thrombosis. (A) Emergent coronary angiography revealing stent thrombosis (white arrows). (B) Angiography after balloon dilatation. (a)–(c) Optical coherence tomography (OCT) images after balloon dilatation. (C) Excimer laser procedure. (D) Final angiography after dilatation with a 3.0-mm balloon. (d)–(f) OCT images after PCI.

the CPET, stent thrombosis likely developed owing to rapid platelet aggregation after CPET. CPET is necessary for post-discharge exercise recommendations in most patients with ACS. However, in patients with ACS with high thrombotic risk, such as clopidogrel PM or with long or multiple stents, acute maximum-load CPET may be risky, and submaximal CPET may be considered. In addition, patients should be carefully observed for some time after CPET.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jccase.2023.08.011.

Patient permission/consent statement

Written informed consent was obtained from the patient.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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