Spontaneous Coronary Artery Bead-like Spasm: A Case Report and Literature Review

Che-Ming Chang[1,2,3], Ren-Chung Lee[1], Kou-Gi Shyu[1]

[1]*Division of Cardiology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital*
[2]*School of Medicine, Taipei Medical University*
[3]*School of Medicine, Fu-Jen Catholic University*

Abstract

Coronary artery spasm refers to a sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near total occlusion. In this article, we report on a 67-year-old male admitted because of intermittent chest tightness/pain with positive Tl-201 myocardial perfusion scan. His electrocardiogram showed atrial fibrillation, a heart rate of 56 bpm, poor R-wave progression and nonspecific T-wave abnormalities. The Tl-201 myocardial perfusion scan was done under dipyridamole stress and showed apical and basal-inferior wall ischemia. Because frequent chest tightness/pain bothered him despite medication therapy, he was admitted for coronary angiography examination. The angiography revealed bead-like lesions in the middle to distal region of the left anterior descending artery. After intracoronary nitroglycerin injection, angiography of the left anterior descending coronary artery showed patency. Intravascular ultrasound examination found no obvious intravascular stenosis. After cardiac catheterization examination, he was prescribed Ranolazine 500 mg bid, oral, and was discharged. Cigarette smoking was prohibited. His chest pain/tightness symptoms improved after medication adjustment and follow-up by the outpatient department.

Keywords: coronary artery bead-like spasm

Introduction

Coronary artery spasm (CAS) refers to a sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near total occlusion. If the spasm lasts long enough, patients can have chest pain (angina) and even a heart attack. Unlike typical angina, which usually occurs with physical activity, CAS often occurs at rest, typically between midnight and early morning.

Other names for CAS are Prinzmetal's angina, vasospastic angina or variant angina. Bead-like spasm of the coronary artery is a variant form of CAS, and its occurrence is quite low.[2] It manifests as multiple tandem concentric stenotic lesions in the coronary artery, and may occur in a single vessel, multiple vessels, at the site of a stenosis (either minor or severe) or in angiographically normal coronary

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Address for correspondence: Dr. Kou-Gi Shyu, MD
Division of Cardiology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital; No.95, Wen-Chang Rd., Shih-Lin, Taipei, Taiwan
Tel: +886-2-28332211; Fax: +886-2-28123397; E-mail: cmchang1@yahoo.com

arteries.[1] Depending on the clinical picture, the pathophysiology of coronary bead-like spasm may involve a series of arterial segments. In the following discussion, we will focus on CAS, which causes a type of angina classified as variant angina, first described in 1959 by Prinzmetal et al.[3] Because the angina of CAS occurs in the absence of myocardial oxygen demand, unlike the common form of effort angina, the authors hypothesized that it was caused by an increased vessel tonus, resulting in transient coronary artery stenosis. Some years later, coronary angiography was performed during spontaneous variant angina, which showed CAS could occur at the site of a stenosis or in angiographically normal coronary arteries. However, CAS may involve two or more segments of the same (multifocal spasm) or of different (multivessel spasm) epicardial coronary arteries. Coronary angiography also showed that CAS could occur at the site of a stenosis (either minor or severe) or in angiographically normal coronary arteries, usually at a localized segment of an epicardial artery (focal spasm).[4] The causes and mechanisms underlying CAS are still poorly understood, and research in this field has been limited by many factors. We will discuss some possible mechanisms in the following description.

Case presentation

A 67-year-old male was transferred by family doctor to the CV-OPD (cardiovascular outpatient department) due to intermittent "sudden chest tightness or pain" lasting minutes to hours, especially in the early morning, since years. Electrocardiography was performed and showed atrial fibrillation, a heart rate of 56 bpm, poor R-wave progression and nonspecific T-wave abnormalities (Figure 1). We performed a transthoracic echocardiography (TTE) examination, which revealed bi-atrial enlargement, no regional wall motion abnormalities with fair ejection fraction (EF) of 62%, mild mitral regurgitation, moderate tricuspid regurgitation with moderate pulmonary hypertension (TR-PG = 52 mmHg), and mild PR. Tl-201 myocardial perfusion scan was done under dipyridamole stress. It showed apical and basal-inferior wall ischemia (Figure 2).

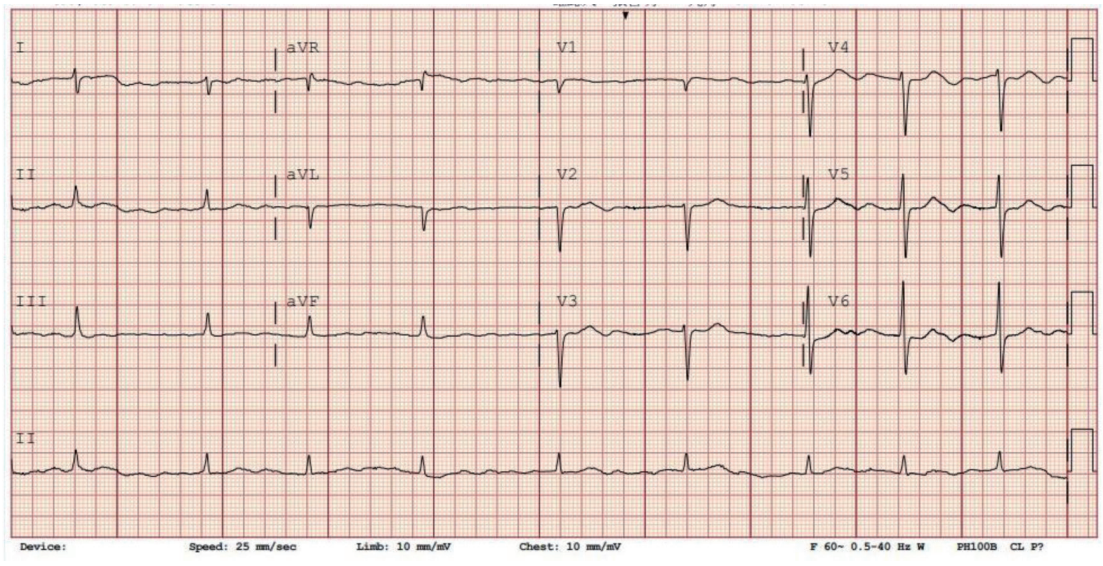

Figure 1. Electrocardiogram.
A 12-lead electrocardiogram shows atrial fibrillation, heart rate around 56 bpm, poor R-wave progression and nonspecific T-wave abnormalities.

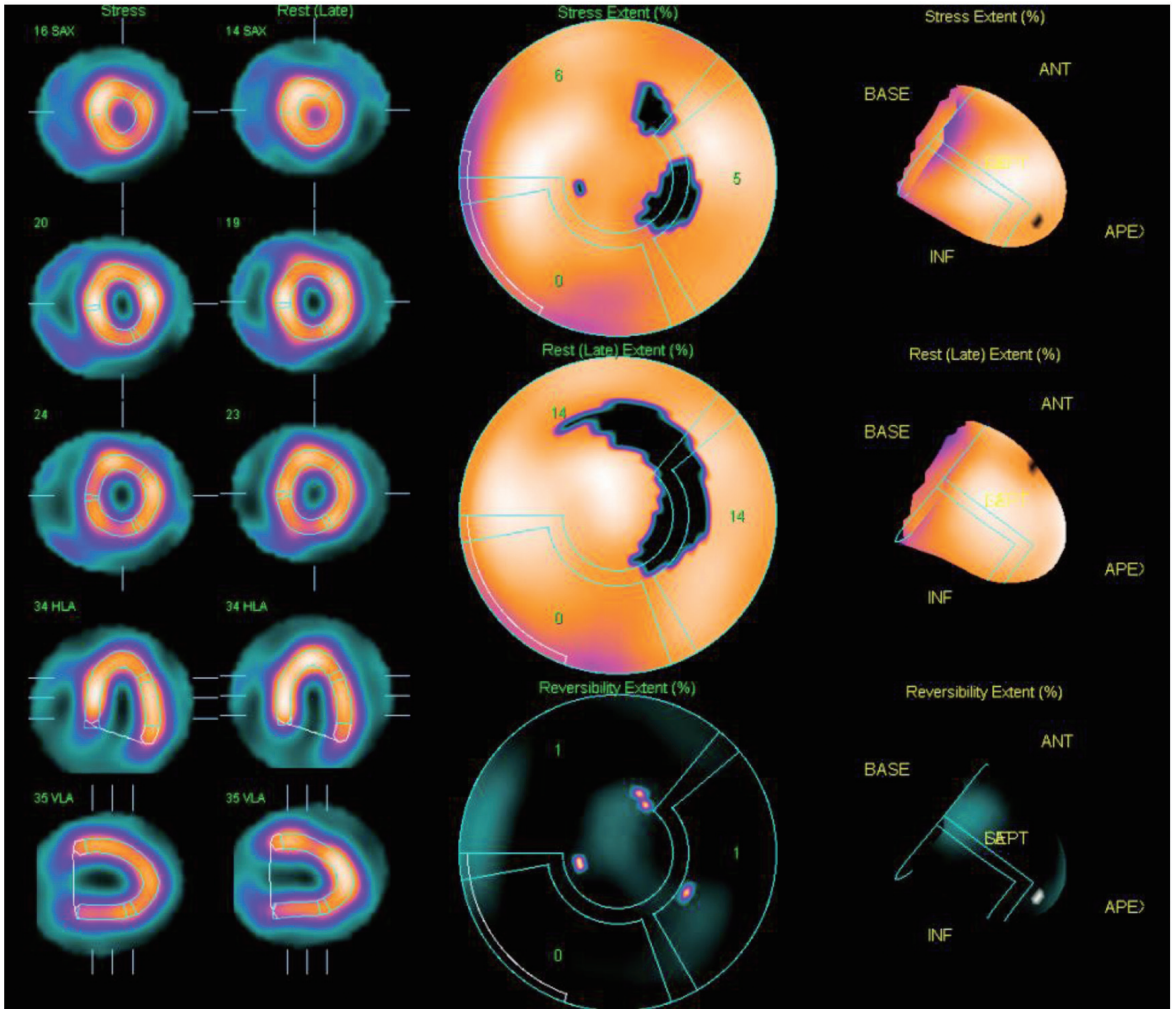

Figure 2. TI-201 Myocardial perfusion scan.
TI-201 Myocardial perfusion scan shows apical-basal-inferior wall mild ischemia.

Past admission history included frequent cellulitis and extremities thrombosis episodes with three admissions in the past 8 years, including one-time coronary angioplasty about 16 years prior. He smoked cigarettes for over 30 years (more than one pack per day). Because the frequent chest tightness/pain bothered him despite medication therapy, he was admitted for coronary angiography examination.

The coronary angiography showed bead-like lesions in the middle to distal region of the left anterior descending coronary artery (Figure 3). After intracoronary nitroglycerin injection, angiography of the left anterior descending artery showed patency (Figures 3-A, B). Intravascular ultrasound (IVUS) examination showed no obvious intravascular stenosis (Figures 3-C, D). Serum magnesium level was later found to be within normal range. He was prescribed Ranolazine 500 mg bid, oral, and discharged after cardiac catheterization examination. Further cigarette smoking was explicitly prohibited. After Ranolazine use and during follow-up at our CV-OPD, his chest pain/tightness symptoms were found to have improved.

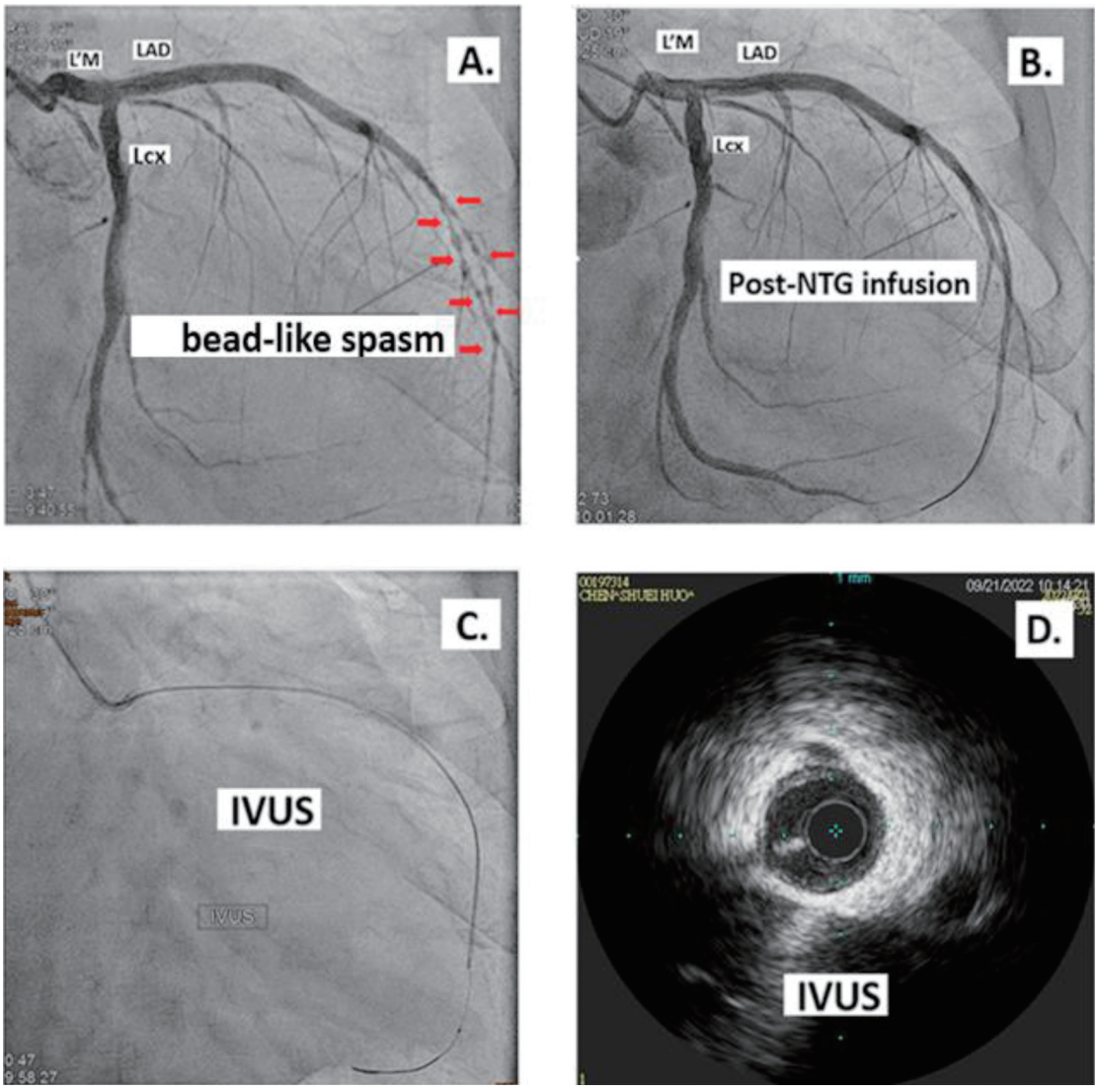

Figure 3. Coronary angiography.
(A) The angiography shows bead-like lesions over the LAD (middle to distal part) and diagonal branch. (B) After intracoronary injection of isosorbide dinitrate, these lesions disappeared. C) IVUS (Volcano Refinity) was implemented. D) No significant stenosis was noted in the IVUS examination.

Discussion

CAS is a reversible phenomenon caused by spontaneous excessive vascular smooth muscle contractility and vascular wall hypertonicity, resulting in partial or complete closure of the lumen of normal or atherosclerotic coronary arteries. The clinical characteristics of CAS include chest discomfort that is similar in quality to that of stable effort angina. The occurrence of CAS varies across populations. Among Japanese it is 24.3%, followed by Taiwanese with 19.3% and Caucasians with 7.5%.[5] Among patients aged 40 to 70 years, CAS is more common in men than in women,[6] however, it is mostly a disease of middle-aged and older men, and post-menopausal women.[7]

Notably, the occurrence of CAS has tended

to decrease with increasing use of medicines such as calcium channel blockers, angiotensin converting enzyme inhibitors and statins, the control and management of atherosclerotic risk factors, and the decreased proclivity to execute functional reactivity tests in highly effective cardiac catheterization centers. Angina pectoris is a clinical syndrome basically caused by transient myocardial ischemia induced by an imbalance between myocardial oxygen demand and supply. Mechanisms underlying the development of CAS remain unclear, but it is certainly a multifactorial disease. Multiple mechanisms such as the autonomic nervous system, endothelial dysfunction, chronic inflammation, oxidative stress and smooth muscle hypercontractility are involved. CAS may be induced by tobacco use, exposure to cold, extreme emotional stress and use of illegal stimulant drugs, such as amphetamines and cocaine.

Pathogenetic substrate of CAS

CAS is caused by the interaction of two components: (1) a usually localized, but sometimes diffuse, abnormality of a coronary artery that makes it hyperreactive to vasoconstrictor stimuli, and (2) a vasoconstrictor stimulus able to induce the spasm at the level of the hyperreactive coronary segment. Vasoconstrictor stimulus agents include catecholamines, acetylcholine (ACh), histamine, serotonin, vasopressin, thromboxane A2, endotheline-1, thrombin, alkalosis and others.[8]

Possible causes of a coronary artery spasm.

Autonomic nervous system:

Among the potential triggers of CAS, the autonomic nervous system has received a great deal of attention. The correlation between the autonomic nervous system and CAS, however, is rather complicated, because both an increase in sympathetic tone and an increase in parasympathetic tone are able to induce CAS.

1) Sympathetic activity

Noradrenaline, the neurotransmitter of efferent sympathetic fibers, can trigger vasoconstriction in vascular smooth muscle cells (VSMCs) through stimulation of α-adrenergic receptors. Clinical studies have recognized that CAS can be induced by catecholamines[9] or by external stimuli (e.g., exercise, cold pressor test)[10,11] that increase sympathetic output. In addition, the induction of CAS by some chemical substances (eg, cocaine, amphetamines) has been suggested to be related to sympathetic activation and/or VSMC sensitization to catecholamines.[12] Furthermore, it is known that β-blockers may exacerbate angina attacks in patients with variant angina, probably because of the blocking of vasodilatory coronary β2 receptors, which leaves vasoconstricting α-adrenergic receptors unopposed.[13] However, it has been discovered that an increase in coronary levels of catecholamines may follow, rather than precede, spontaneous ischemic episodes of CAS.[14] Moreover, α-blockade has often been shown ineffective in controlling symptoms in variant angina patients.[15,16]

2) Parasympathetic activity

Under physiological conditions, ACh, the neurotransmitter of parasympathetic nerve fibers, causes vasodilation via the endothelial release of nitric oxide (NO), whereas at high doses it may induce vasoconstriction through direct stimulation of VSMC muscarinic receptors. Thus, in cases of VSMC hyper-reactivity, even small concentrations of ACh might induce CAS. Some findings from clinical settings suggest a role for vagal activity as a trigger of spasm. In patients with variant angina, attacks usually happen during the night, when vagal tone is higher,[17,18] and the intracoronary administration of acetylcholine is known to induce CAS.[19]

However, the correlation between ACh-induced CAS and the role of vagal activation in inducing spontaneous spasm in patients remains uncertain. Indeed, the occurrence of ischemic

episodes predominantly during the night does not necessarily imply that CAS is triggered by vagal activation. In fact, the evaluation of cardiac autonomic changes associated with spontaneous episodes of ST-segment elevation has shown that ischemic episodes are often preceded by a reduction, rather than by an increment, in vagal activity.[20] In agreement with these data, the occurrence of vasospastic angina attacks at night is more frequent during the rapid eye movement phases of sleep, when vagal withdrawal occurs in association with an increase in adrenergic activity.[21]

Endothelial cells:

In some people with CAS, the cells do not release enough NO. This may lead to vascular spasm. The endothelium plays a significant role in the physiological regulation of coronary vascular tone, mainly through the release of several vasodilators, the most important of which is NO. Therefore, any obvious endothelial damage might impair vasodilation, thus favoring CAS in response to vasoconstrictor stimuli.[22]

It is important to observe that various vasoactive stimuli (eg, ACh, serotonin, histamine) cause vasodilation by inducing NO release by the endothelium, but, simultaneously, they may cause vasoconstriction through direct stimulation of VSMCs. Thus, in the presence of endothelial dysfunction, their release in the vessel wall can lead to vasoconstriction or CAS.[23]

Oxidative stress:

An increased generation of oxygen-reactive substances may occur under several conditions,[24-26] and has an unfavorable effect on the vessel wall, causing both endothelial dysfunction and inflammation, but also increasing the constrictor response of VSMCs.[26] This can cause inflammation, damage to endothelial cells and shrinking of vascular walls. Smoking is one root cause of oxidative stress. Cigarette smoke is the origin of a large number of free radicals causing the degradation of NO.[27]

In patients with variant angina, a possible pathogenetic route has been suggested following the documentation of low serum levels of vitamin E during the hot phases of the disease[28] and of an increased cardiac consumption of vitamin E, associated with an increased transcardiac release of lipoperoxides.[29]

Smooth muscle function:

The heart is constituted of smooth muscle. Differences in how this muscle functions may lead to CAS. The activity of vascular smooth muscle, i.e., contraction and relaxation, is regulated by the phosphorylation and dephosphorylation of the myosin light chain (MLC). Physiologically, phosphorylation is induced by an increase in the intracellular concentration of calcium ions, which, being in a complex with calmodulin, activate myosin light chain kinase leading to phosphorylation of MLC. In CAS, excessive contraction of the smooth muscles of the coronary vessels occurs in conjunction with an increase in intracellular Ca^{2+} influx.[7] Elevated expression of L-type Ca^{2+} channels and an increase in Ca^{2+} entry into VSMCs through the channels may also initiate the spasm.[30] Moreover, a Ca^{2+} influx through the α1H Ca^{2+} system is important to coronary arteries' relaxation. A deficiency of α1HT-type calcium channels inhibits the relaxing effect of ACh,[31] which may contribute to the pathogenesis of CAS. Rho-kinase (ROK) and Ras homolog family member A (RhoA), being VSMC contractility regulators, are involved in the pathogenesis of CAS. Normally, the ROK metabolic pathway modulates the level of MLC phosphorylation by the inhibition of myosin phosphatase.

The hyperreactivity of ROK in smooth muscle cells facilitates their contraction by sensitizing the myosin light chain to calcium ions, as well as indirectly increasing the phosphorylation of this chain, promoting vasoconstriction. An animal model study showed that hydroxyfasudil, the ROK inhibitor, prevented dose-dependent excessive coronary contractions, supporting the role of ROK in the pathogenesis of

CAS.[32,33]

Genetics:

Several genetic mutations have been described as potentially involved in the tendency of patients with variant angina to develop CAS. They mainly concern the gene encoding for NO synthase,[24] but polymorphisms have also been described for other proteins able to modulate vascular tone, like adrenergic and serotoninergic receptors,[34,35] or antioxidant enzymes, angiotensin-converting enzyme and inflammatory cytokines.[34-38]

Inflammation:

The possibility of inflammation in the pathogenesis of CAS was suggested by the detection, in postmortem studies, of inflammatory cells, in particular mast cells, in coronary vasospastic segments, as previously discussed.[39,40] Cigarette smoking, an important risk factor for CAS, is related to low-grade inflammation and an increased hs-CRP level.[41,42] This confirms that even minor elevations of the hs-CRP level in serum are essentially and independently associated with coronary spasms. Furthermore, a recent study suggested that coronary spasms are associated with inflammation of coronary adventitia and perivascular adipose tissue.[43] It also indicated that insulin resistance is associated with CAS, although this may not directly cause the condition.

Magnesium deficiency :

Magnesium is recognized to be an endogenous calcium antagonist, and infusion of magnesium inhibits hyperventilation-induced attacks in patients with CAS.[44] Magnesium deficiency can be observed in 45% of patients with variant angina, and magnesium deficiency may be related to the genesis of CAS in some patients.[45,46] Obsessive alcohol consumption can also lead to angina attacks following a magnesium-dependent mechanism, on account of magnesium deficiency caused by excessive urinary excretion of magnesium.[47]

Medication management:

The foundation of CAS management is lifestyle changes and the removal of risk factors.[6,48,49] It is recommended to quit smoking, consuming alcohol,[6,7] and using substances such as cocaine.[6,49]

Another part of conservative treatment is pharmacotherapy, with calcium channel blockers (CCBs) being the first-line treatment.[47,48] Both dihydropyridine and non-dihydropyridine CCBs have been shown to be effective in reducing the recurrence of CAS.[49] Nitroglycerin or isosorbide dinitrate (ISDN) is converted to NO in vivo. The effectiveness of nitrates is explained by the high sensitivity of the contracted coronary arteries to nitrates and the deficiency of endogenous NO.[7,48] Long-acting nitrates are other drugs used to reduce the risk of angina,[49] and can be used both as monotherapy and as an adjunct to treatment with CCBs.[49] The effect of nitrates varies with the dose. Small doses cause a reduction in venous return and preload. By contrast, high-dose nitrates, similarly to CCBs, result in a decrease in afterload and thus a decrease in the heart's oxygen demand, while improving oxygen supply to the myocardium.[51] Statins are a group of medications that cause CAS reduction and improve overall clinical status. The effect of statins is possible due to their property of inhibiting the RhoA/ROCK pathway and an increase in NO activity,[7] and hence they are an important adjunct to CAS pharmacotherapy.[49] Inhibitors of the RhoA/ROK pathway, such as fasudil, a Rho-kinase inhibitor, may prove beneficial in the treatment of CAS because of the contraction-reducing properties of VSMCs. Another drug with positive effects in CAS patients is Nicorandil. This medication causes coronary artery dilatation as a result of its nitrate-and potassium-channel-activating properties.[7,48,51,52] Nicorandil is recommended for patients with refractory CAS.[49] Ranolazine is an antianginal drug that inhibits the late sodium current in cardiomyocytes under ischemic conditions.[5] It reduces the intracellular sodium and calcium overload, which in turn improves

myocardial relaxation and diastolic function.

Drugs contraindicated in CAS include beta-blockers[49,52,54] but also, among others, catecholamines, parasympathetic stimulants and ergot alkaloids.[48,49] They have vasoconstrictive effects and cause coronary vasospasms.[48,52,54]

Conclusions

After cardiac catheterization examination, this 67-year-old male was definitively diagnosed with spontaneous coronary artery bead-like spasm. His other vascular related events were arterial embolism and thrombosis of the lower extremities, s/p thrombolytic therapy and necrotizing fasciitis of the left leg and foot with s/p debridement and flap repair about 8 years prior. After an uneventful recovery, he was discharged with medication for coronary vasospasm including calcium channel antagonist, nitrate, anti-hypertensive agent, NOAC, statin and ranolazine. Further studies are required to elucidate the pathogenesis of this interesting disease (CAS) and develop more effective, disease-modifying medication for its treatment.

Abbreviations

ACh	acetylcholine
CAS	Coronary artery spasm
CCBs	Calcium channel blockers
EF	Ejection fraction
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
Lcx	Left circumflex artery
LM	Left main coronary artery
MLC	myosin light chain
NO	Nitric oxide
NOAC	Novel oral anti-coagulant
RhoA	Ras homolog family member A
ROK	Rho-kinase
Tl-201	Thallium 201
TTE	Transthoracic echocardiography
VSMCs	Vascular smooth muscular cells

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