REVIEW ARTICLE

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Coronary Artery Spasm: Risk Factors and Pathophysiological Mechanisms

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Abstract

Coronary artery spasm (CAS) is a common complication associated with transradial access (TRA) for coronary interventions, particularly affecting elderly patients. Coronary artery spasm (CAS), an intense vasoconstriction of coronary arteries that causes total or subtotal vessel occlusion, plays an important role in myocardial ischemic syndromes including stable and unstable angina, acute myocardial infarction, and sudden cardiac death. Coronary angiography and provocative testing usually are required to establish a definitive diagnosis. While the mechanisms underlying the development of CAS are still poorly understood, risk factors include sex, age, smoking, hypertension, and diabetes. Physical and/or mental stress, alcohol consumption and administration of pharmacological agents are precipitation factors. Moreover, polymorphisms in genes encoding for ALDH2, endothelial NO synthase, paraoxonase 1, NADH/NADPH oxidase, and interleukin-6 are linked with occurrence of CAS. Accordingly, oxidative stress, endothelial dysfunction, and low-grade chronic inflammation play an important role in the pathogenesis of CAS, leading to increased coronary smooth muscle Ca^{2+} sensitivity through RhoA/ROCK activation and hypercontraction.

Keywords: Coronary artery spasm, pathophysiology, paraoxanase, nitric oxide.

1. Introduction

Coronary artery spasm (CAS) is marked by sudden, severe constriction of a coronary artery, potentially leading to vessel blockage. It's a key factor in cardiovascular issues like variant angina and heart attacks. CAS can happen in both healthy and diseased arteries, disrupting blood flow to the heart **(Zhao et al., 2018; Maguire et al., 2019)**. Coronary artery spasm, characterized by reversible vasoconstriction driven by spontaneous hypercontractility of vascular smooth muscle, has gained recognition under the term myocardial infarction with nonobstructive coronary arteries (MINOCA). This phenomenon narrows the lumen of both normal and atherosclerotic coronary arteries, compromising myocardial blood flow. Recent research suggests that myocardial ischemia in these cases occurs despite unchanged myocardial oxygen demand, likely due to increased vascular tonus at the level of coronary stenosis **(Mohammed et al., 2023)**.

The documentation of coronary spasm via coronary

angiography in the early 1970s, particularly during variant angina attacks, established its role in the condition. The advent and widespread use of ambulatory ECG monitoring for myocardial ischemia, particularly in Japan, have led to the reporting of numerous cases of variant angina **(Hung et al., 2020) (Figure 1)**.

2. Clinical Features

Coronary artery spasm (CAS) can manifest with or without obstructive epicardial coronary artery disease (CAD), but it is particularly linked to angina and ischemia in patients with unobstructed coronary arteries **(Ong et al., 2012)**.

CAS involves exaggerated vasoconstriction of the coronary arteries, leading to myocardial ischemia and angina **(Lanza et al., 2011)**. Diagnosis of CAS may occur during a spontaneous chest pain attack while the patient is in the catheter laboratory, although more frequently, it's established through intracoronary provocative spasm testing using agents like acetylcholine (ACh) or ergonovine **(Montone et al., 2021)**. Despite being described over 50 years ago and highlighted in current guidelines **(Knuuti et al., 2020)**, a significant portion of the cardiology community remains unfamiliar with this condition. Nonetheless, CAS holds clinical significance as it is associated with considerable morbidity due to impaired quality of life and an increased risk of non-fatal cardiovascular events **(Seitz et al., 2022)**.

3. Diagnosis

The diagnosis of coronary spasm is not necessarily easy and cannot be directly established based on symptoms. Coronary artery spasm may present with or without symptoms **(Yasue and Kugiyama, 1997)** and can exhibit either normal electrocardiographic findings at the beginning of an attack or when the attack is mild, or ST-segment elevation or depression during the attack. The attack is transient, often lasts only a few seconds, and is unpredictable. Thus, ambulatory monitoring of ECG is extremely important to detect the attack **(Yasue et al., 2008)**.

Coronary angiography with provocation testing is considered the most convincing and reliable test for diagnosing vasospastic angina (VSA) **(Matta et al., 2020)**. However, provocation testing is justified when we suspect VSA in a patient, but our suspicions have not been definitively confirmed **(Franczyk et al., 2022)**. The provocation test involves an intracoronary injection of vasoconstricting agents, among which ergonovine and acetylcholine are the most commonly used **(Matta et al., 2020)**. The test assesses the percentage of vessel lumen reduction, which can be 50%, 70%, 75%, or 90% **(Swarup et al., 2022)**.

4. Precipitating Factors and Risk factors

Precipitating factors for coronary artery spasm (CAS) include physical or mental stress **(Yeung et al., 1991)**, magnesium deficiency **(Teragawa et al., 2000)**, alcohol consumption (**Fernandez et al., 1973)**, cold exposure, hyperventilation, and certain medications (e.g., cocaine, beta-blockers, ergot alkaloids) **(Yasue et al., 1983)**. Activated platelets release vasoconstrictors like thromboxane and serotonin, contribute to CAS **(Hung et al., 2013) (Figure 2)**.

Other risk factors include age, smoking, hypertension, LDL cholesterol, diabetes, and high-sensitivity C-reactive protein (hs-CRP) **(Libby et al., 2016)**. These factors often coexist and interact, with smoking having a stronger effect on younger individuals, especially men **(Hung et al., 2013)**. While a high percentage of CAS patients smoke, some do not, indicating other contributing factors **(Takagi et al., 2013)**. In men with low hs-CRP, diabetes contributes to CAS, while in women with high hs-CRP, diabetes and hypertension negatively affect CAS **(Hung et al., 2013)**.

5. Coronary Vascular Tone Autoregulation and Pathogenesis of CAS

Coronary artery spasm occurs due to a failure in the autoregulation of coronary vascular tone. The myocardium's high oxygen extraction at rest means an increase in oxygen demand requires an equivalent rise in coronary blood flow, regulated by mechanisms involving nitric oxide (NO), acetylcholine, adenosine, and mechanical stimuli like shear stress **(Hubert et al., 2020)**.

The exact mechanisms behind CAS remain unclear, but it is a multifactorial condition with the following key contributors **(Figure 3)**:

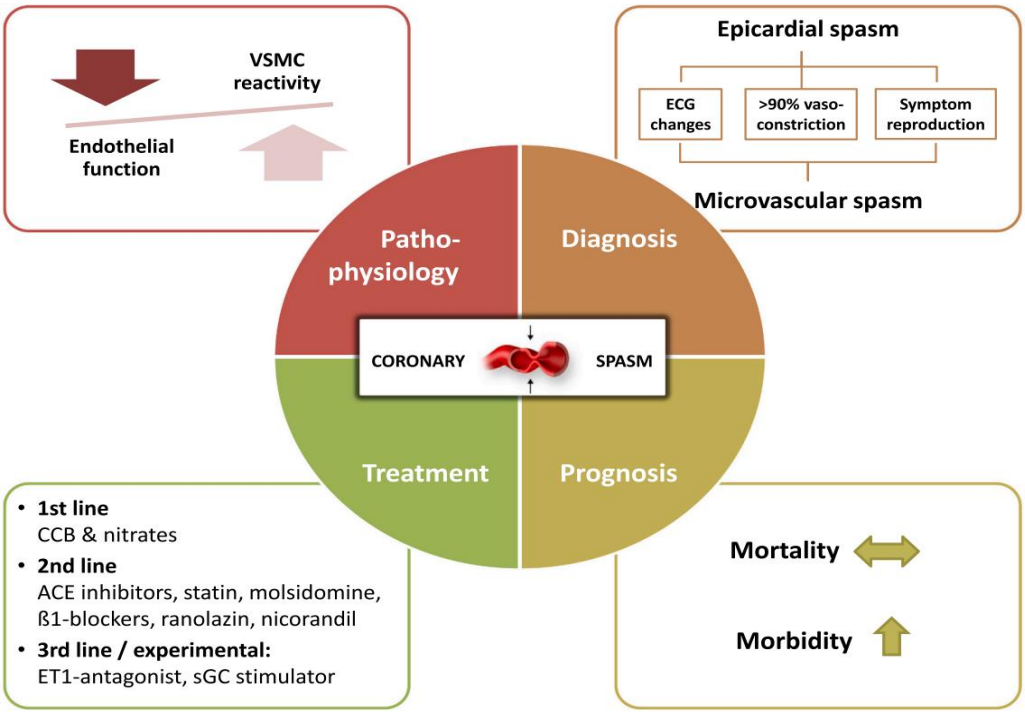

Figure 1: Central illustration. Update on coronary artery spasm 2022 – A narrative review **(Seitz et al., 2022)**.

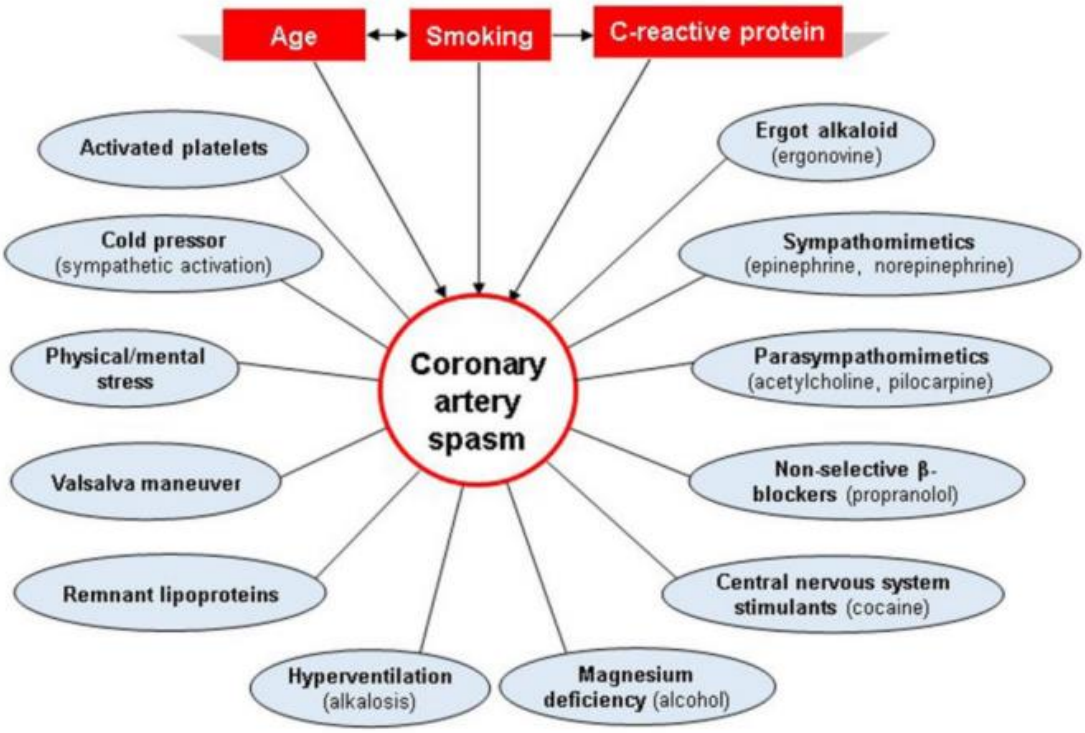

Figure 2: Risk factors and precipitating factors for the development of coronary artery spasm (CAS). While risk factors, which often coexist and interact with one another, increase a person's susceptibility to developing CAS, precipitating factors may contribute to the onset of CAS and act in the same patient to cause angina in different conditions. The risk factors and precipitating factors are represented by rectangles and circles, respectively **(Hung et al., 2014)**.

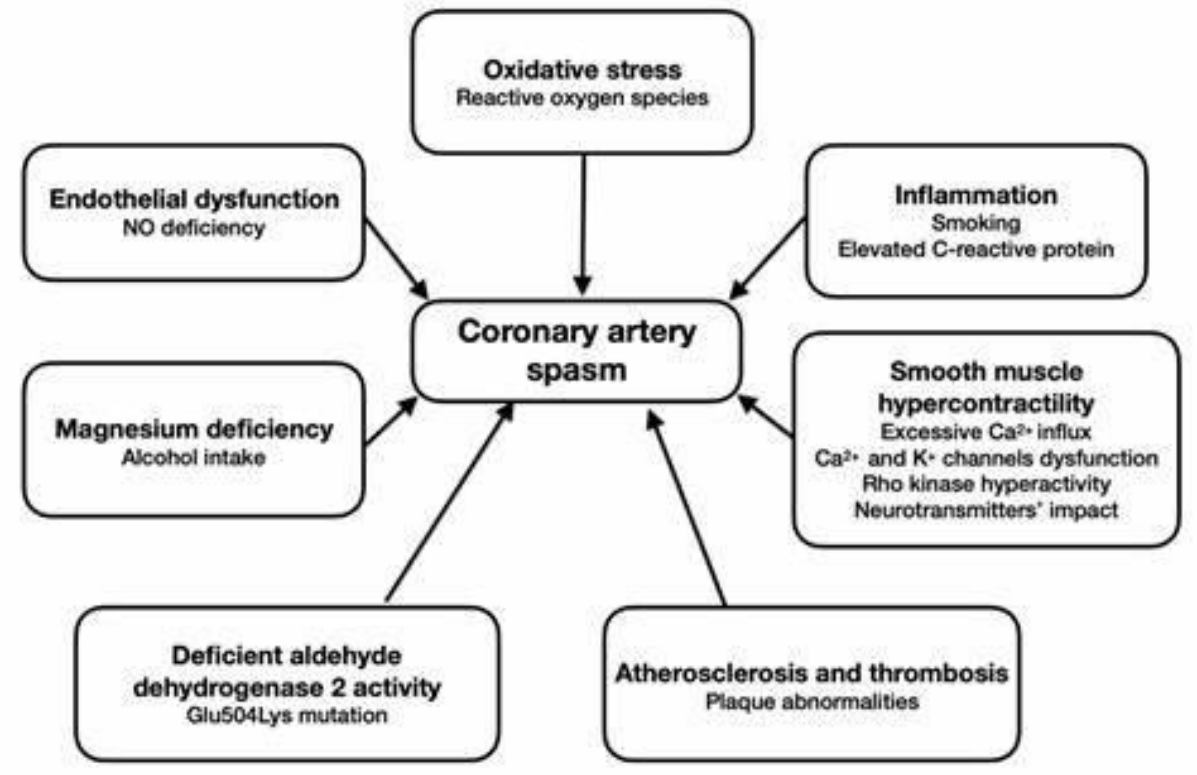

Figure 3: Cellular Mechanisms of Coronary Artery Spasm **(Franczyk et al., 2022)**.

I. Autonomic Nervous System Dysfunction:

Coronary artery spasm is linked to both sympathetic and parasympathetic nervous systems. It frequently occurs at rest, during high vagal activity. Increased catecholamines and adrenergic activity play a role, with selective beta-blockers like atenolol being more effective than non-selective ones such as propranolol **(Matta et al., 2020)**.

II. Endothelial Dysfunction:

Nitric oxide produced by the endothelium enhances vasodilation, but its deficiency leads to vasoconstriction **(Nakayama et al., 1999)**. Treatments with vitamin E and statins improve endothelial function and reduce CAS symptoms **(Motoyama et al., 1998)**.

III. Chronic Inflammation:

Coronary artery spasm is associated with inflammation, as seen in elevated hs-CRP levels and inflammatory markers like IL-6 **(Hubert et al., 2020)**. This inflammation can reduce NO activity **(Itoh et al., 2007)**, with chronic tobacco smoking further exacerbating the condition **(Yasue et al., 2006)**.

IV. Oxidative Stress:

An imbalance in reactive oxygen species (ROS) and antioxidants leads to oxidative damage, contributing to endothelial dysfunction and vasoconstriction **(Hayyan et al., 2016)**. Smoking is a major factor, and antioxidants like vitamin C can help reduce the effects of oxidative stress in smokers **(Franczyk et al., 2022)**. CAS is also strongly linked to gene polymorphisms associated with antioxidant effects, including ALDH2 **(Mizuno et al., 2015)**, paraoxonase 1 **(Itoh et al., 2002)**, NADH/NADPH oxidase $p22^{phox}$, stromelysin-1, interleukin-6 **(Murase et al., 2004)**, and phospholipase C (PLC)-δ1 **(Nakano et al., 2002)**. Additionally, thioredoxin, a marker of oxidative stress, is elevated in CAS patients **(Miyamoto et al., 2004)**.

V. Smooth Muscle Hypercontractility:

Coronary artery spasm is linked to hypercontraction of coronary smooth muscle caused by increased intracellular calcium (Ca^{2+}) levels. Phosphorylation of myosin light chain (MLC) is key in this process, which is regulated by calcium and calmodulin **(Maseri et al., 2009)**. Calcium-channel blockers are effective in reducing CAS by inhibiting Ca^{2+} entry. Additionally, the

Rho-associated kinase (ROCK) pathway plays a significant role by inhibiting myosin light chain phosphatase (MLCP), enhancing muscle contraction **(Uehata et al., 1997)**. Statins can also block the RhoA/ROCK pathway, improving CAS by increasing endothelial nitric oxide (NO) levels **(Yasue et al., 2008)**.

VI. Atherosclerosis and Thrombosis:

Atherosclerosis, marked by cholesterol-rich plaque accumulation, often coexists with CAS **(Xu et al., 2021)**. Though CAS can occur in normal vessels, it is more common in arteries with atherosclerotic plaques **(Pellegrini et al., 2022)**. The two conditions share common risk factors like smoking and elevated hs-CRP **(Libby et al., 2016)**. CAS can trigger the rupture of stable plaques, leading to coronary thrombosis and myocardial infarction (MI). Prolonged CAS promotes platelet activation and thrombus formation, contributing to acute coronary syndromes **(Etsuda et al., 1993)**.

VII. Magnesium Deficiency:

Magnesium levels in the body may be related to the occurrence of CAS. Its deficiency is one of the factors causing coronary vasospasms **(Matta et al. 2020)**. Magnesium deficiency, present in 45% of CAS patients, contributes to coronary vasospasm by increasing intracellular calcium sensitivity and promoting smooth muscle contraction. Magnesium acts as a natural calcium antagonist, blocking calcium channels, which helps prevent muscle contraction **(Yasue et al., 2019)**. Supplementation may reduce CAS episodes, especially in those triggered by hyperventilation.

VIII. Deficient Aldehyde Dehydrogenase 2 (ALDH2) Activity:

ALDH2 plays a protective role against oxidative damage by eliminating harmful aldehydes produced during lipid peroxidation **(Singh et al., 2013)**. CAS patients often have higher levels of reactive oxygen species (ROS), leading to increased risk of MI. Deficient ALDH2 activity exacerbates oxidative stress and contributes to CAS development **(Yasue et al., 2019)**.

IX. Genetics:

Cardiovascular diseases, including myocardial infarction (MI), coronary artery disease (CAD), and stroke, are leading causes of mortality worldwide **(Zhao et al., 2018)**. Genetic factors significantly contribute to CAD, with studies suggesting that hereditary influences account for 30–60% of interpersonal differences in CAD risk. Variations in certain genes can increase the likelihood of developing CAD by 1.1 to 1.3 times **(Balcerzyk-Matić et al., 2022)**. CAS is traditionally more prevalent in Asians, with genetic variants in aldehyde dehydrogenase 2 (ALDH2) and Rho-associated kinase 2 (ROCK2) being associated with CAS in these populations. Genetic polymorphisms related to endothelial NO synthase and the endothelin-1 pathway have been identified in both Asian and Caucasian CAS patients **(Ford et al., 2020)**. Studies of genetic mutations or polymorphisms in the pathogenesis of CAS have been inconsistent **(Miwa et al., 2005)**. Mutations or polymorphisms of the endothelial NO synthase gene **(Kaneda et al., 2006)** and polymorphisms of paraoxonase 1 gene **(Ito et al., 2002)** play a role in the pathogenesis of CAS. However, NO gene polymorphisms are found in only one-third of patients **(Yasue et al., 2008)**. Polymorphisms in genes coding for other proteins that have been described in CAS include adrenergic and serotoninergic receptors **(Kaumann and Levy, 2006)**, angiotensin-converting enzyme **(Oike et al., 1995)**, and inflammatory cytokines **(Nakano et al., 2002)**.

In a Japanese cohort study, the NADH/NADPH oxidase gene is a susceptibility locus in men, while stromelysin-1 and interleukin-6 genes are susceptibility loci in women **(Murase et al., 2004)**. ALDH2 deficiency, most common in the East Asian population, is strongly associated with CAS **(Chen et al., 2014)**, with an increased effect due to the coexistence of smoking and/or alcohol **(Mizuno et al., 2016)**. However, family history is not a risk factor for CAS.

Furthermore, CAS activity has fluctuations, with circadian variations in the short term and active and inactive phases in the long term **(Lanza et al., 2011)**. Thus, gene-environment interactions may exist in the development of CAS **(Murase et al., 2004)**.

6. Conclusions

Awareness of possible silent and fatal cases of CAS by clinicians is crucial. CAS is a multifactorial condition, involving atherosclerosis, thrombosis, endothelial dysfunction, oxidative stress, chronic inflammation, genetic predisposition, and many other factors. More

research is needed to understand the pathophysiology of this disease and develop potent, medications and treatments. Knowing the underlying processes of CAD and CAS and how they are influenced by genetics might help develop personalised preventative and treatment plans that take into account each patient's unique genetic profiles.

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