Relationship between Inflammation and Vasospastic Angina

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Coronary artery spasm (CAS) is a dynamic coronary stenosis causing vasospastic angina (VSA). However, VSA is a potentially lethal medical condition with multiple presentations, including sudden cardiac death. Mounting evidence supports the relation of local or systemic inflammation to VSA.

angina vasospasm inflammation coronary artery disease

1. History of Coronary Artery Spasm (CAS)

Prinzmetal and colleagues observed an atypical angina occurring at rest associated with an elevated ST segment on electrocardiograms transiently in patients with atherosclerotic coronary artery disease (CAD) [1]. The angina would have been due to a transient decrease in coronary blood flow, since, at rest, cardiac work is not increased. Subsequently, the term “variant angina” was suggested by Prinzmetal et al. in 1959, and they suggested that CAS was the cause because it was relieved immediately after administrating nitroglycerin. In the 1970s, variant angina was found to be caused by CAS, which was confirmed by coronary angiography. CAS can potentially occur at the site of atherosclerotic CAD [2] or diffuse spastic changes in angiographically normal coronary arteries. As a result, the investigators termed it a “variant of the variant” [3] or “vasospastic angina (VSA)” [4]. The majority of CAS cases are accompanied by ST-segment depression or T-wave changes instead of ST-segment elevation [5][6][7]. Therefore, the term “VSA” is a broader term to represent CAS-induced angina, irrespective of electrocardiographic manifestations. The term “variant angina” is usually expressed as CAS-induced angina associated with concurrent ST-segment elevation transiently on electrocardiogram. Recently, a Japanese guideline development by the Japanese Circulation Society has suggested that variant angina is a type of VSA [4]. The CAS experts in the Joint Working Groups in Japan [4] proposed using the term “VSA” to represent coronary vasomotor-disorder-related angina and this concept has been widely accepted [8].

VSA differs from typical angina in its pathogenesis, although the exact pathophysiology of VSA is not clear at present. VSA usually occurs during resting status, especially in the night and early morning, but it found that some patients may have angina with ST-segment deviations during exercise [9]. It suggested that the spastic coronary arteries are abnormal, as the dilator response to exercise is not adequate as it would be in normal coronary arteries. There are variations in the occurrence of VSA, i.e., daily, weekly, monthly, and circadian [10]. Many cardiologists have found that CAS can cause stable angina, acute coronary syndrome, syncope, heart failure, cardiac arrhythmias, and even sudden cardiac death [4][11]. Therefore, it is crucial to identify CAS as the underlying cause of a cardiovascular event because the treatment options will be different according to the diagnosis, i.e.,

pharmacological treatment first for CAS-induced and pharmacological treatment plus coronary intervention for atherosclerotic coronary artery stenoses. As a matter of fact, a correct diagnosis leads to correct treatments, and this logic of causality is the core value of clinical medicine. Recently, guidelines developed by the European Society of Cardiology for the management of survivors of sudden cardiac death have suggested that the diagnosis of CAS-induced sudden cardiac death may be considered [12].

2. Relation of Local and Systemic Inflammation to VSA

No single mechanism can be held responsible for the development of CAS. Some mechanisms have been proven to play a role in CAS causing VSA, i.e., allergy [13], oxidative stress [14], endothelial dysfunction [15], deficient aldehyde dehydrogenase 2 activities [16], chronic low-grade inflammation [17], magnesium deficiency [18], and hypercontraction of coronary artery smooth muscle [19]. Furthermore, age, cigarette smoking, and high-sensitivity C-reactive protein (hs-CRP) are risk factors for VSA [20]. Other factors act as inducers for VSA occurrence [11], such as physical and/or mental stress, alcohol consumption, Valsalva maneuver, hyperventilation, and other pharmacological agents, such as propranolol, ergot alkaloids, sympathomimetics and parasympathomimetics, and cocaine. Chronic low-grade inflammatory conditions seem to play the central role, interacting with each of the above-mentioned mechanisms. Although different pathophysiologies exist in VSA, the final pathway is contraction of coronary artery smooth muscle, clinically causing VSA [21].

In 1978, Lewis and colleagues [22] described a patient who was deceased due to cardiogenic shock because of inferior wall ST-segment elevation associated with localized pericarditis. These investigators initially suggested an interaction between chronic inflammation and CAS. Subsequently, Forman et al. [23] found a VSA patient who presented with sudden death, in whom infiltrating mast cells were found at the adventitia of a spastic coronary artery. In 1988, Ferguson et al. [24] reported a 17-year-old boy who had developed two episodes of VSA following assumed acute viral myocarditis. In 1991, Iwasaki et al. [25] reported CAS in a 59-year-old male with biopsy-proven acute myocarditis. In 2008, Yilmaz et al. [26] found that CAS without CAD occurs in 70% of endomyocardial biopsy-proven PVB19 myocarditis and suggested that CAS plays an important role in the occurrence of angina pectoris in these patients. Other studies have also found intimal injury and neointimal hyperplasia with infiltrating inflammatory cells in coronary plaques or arteries in patients with VSA [27][28]. Despite a lack of angiographical evidence of coronary artery narrowing, diffuse intimal thickening in spastic arteries has been demonstrated by intracoronary ultrasound [29]. Using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, inflammatory changes in coronary adventitia and perivascular adipose tissue were found to be associated with CAS in VSA patients [30]. Coronary perivascular ^{18}F-fluorodeoxyglucose uptake decreased after prescription of a calcium antagonist in patients with VSA. Furthermore, adventitial vasa vasorum significantly increased in VSA patients, as confirmed by optical coherence tomography analysis. All the above findings suggest that local coronary inflammatory changes play a role in the early anatomical changes in the coronary arteries in CAS, which was also suggested by Marzilli and colleagues [31]. These early anatomical changes in the coronary arteries in CAS might induce subsequent functional changes in these arteries, which might be the basis of future characteristics of spastic coronary arteries.

Increased levels of soluble intercellular adhesion molecule-1 or secretory type II phospholipase A2 have been noted in patients with VSA [32][33]. A prior serum inflammatory biomarker studies also found increased levels of hs-CRP, interleukin-6, monocyte chemoattractant protein-1, soluble intercellular adhesion molecule-1, and soluble vascular adhesion molecule-1 in patients with VSA [17][34], indicating that systemic inflammatory changes associated with subsequent endothelial dysfunction are present in spastic coronary arteries. Endothelial dysfunction is the earliest process of atherosclerotic lesion formation [35]. Furthermore, atherosclerosis impairs the coronary arterial vasodilator function, which is an important function of endothelium [36]. Recently, scholars also found elevated peripheral leukocyte Rho-associated coiled-coil-containing protein kinase activity in patients with VSA [37]. Rho-associated coiled-coil-containing protein kinase activity was decreased in the VSA group after treatment with antispastic agents for 3 months. Rho-associated coiled-coil-containing protein kinase activity was independently associated with diagnosis of VSA and was found to be correlated with VSA activity. Rho-associated coiled-coil-containing protein kinase activation has been noted in association with attenuated endothelial nitric oxide synthase expression [38], increased vascular smooth muscle cell DNA synthesis and migration [39], and increased monocyte adhesion and spreading [40]. Some molecular studies in the porcine model with interleukin-1 beta showed that the expressions of Rho-kinase mRNA and RhoA mRNA were increased in the spastic coronary segment as compared with the control coronary segment [41]. Using a Rho-kinase inhibitor, Y-27632, not only inhibited serotonin-induced vascular smooth muscle hypercontraction but also accentuated myosin binding subunit phosphorylation [42]. The above molecular studies indicate that Rho-kinase is upregulated at the spastic site and causes vascular smooth muscle hypercontraction. Therefore, the pathogenesis of VSA could be a combination and interplay of endothelial dysfunction, systemic inflammation, and smooth muscle hypercontraction.

In 1991, Kounis et al. [13] postulated a concept of allergic angina based on observing an acute allergic condition associated with acute coronary syndromes. They then suggested that histamine, the main amine during allergy, could induce CAS manifested as VSA or acute myocardial infarction. Subsequently, they modified their understanding of the Kounis syndrome towards mast cell activation [43], further making an argument for allergic inflammatory-response-induced CAS.1 There are three variants of the Kounis syndrome [43], i.e., Type I: allergic VSA due to endothelial dysfunction in patients without underlying CAD, Type II: an allergic reaction causing CAS or plaque erosion in patients with underlying asymptomatic CAD, and Type III: an allergic CAS in the setting of coronary thrombosis, including stent thrombosis. A prior case report demonstrated that type I Kounis syndrome occurred in a 45-year-old sigmoid cancer patient who had drug-allergic VSA with the chemotherapy agent oxaliplatin [44]. Because treatment strategies for Kounis syndrome and asthma are not exactly the same as for pure VSA, knowledge of individual hypersensitivity is required.

Using the National Health Insurance Research Database, it also noticed that asthma is independently associated with new-onset VSA (odds ration = 1.85) [45], providing further evidence of the interplay between allergic reaction and CAS. The risk of new-onset VSA was higher in prior steroid users irrespective of the oral (odds ratio = 1.22) or inhaled route (odds ratio = 1.89). Further analysis showed that the prevalence of asthma in VSA patients (4.4%) was the highest, followed by patients who had VSA associated with atherosclerotic coronary artery disease (2.6%) and atherosclerotic coronary artery disease treated by coronary intervention (1.8%). These results further indicate that an interplay exists between the bronchial spasm of asthma and the CAS of VSA. Inflammation can contribute

to the occurrence of asthma [46]. As a result, the inflammatory process plays an important role in the occurrence of bronchial spasm and CAS.

Smoking is an important association factor for VSA [47]. A investigation [48] reported an odds ratio of 2.58, similar to a prior CAS investigation's 2.41 [43]. A synergistic interaction between smoking and hs-CRP was further identified in the study [48]. Among smokers, the interaction was linear and monotonic. In non-smokers, a threshold effect of hs-CRP was observed on VSA. After adjusting for hs-CRP as a confounder in analyzing the impact of smoking on VSA development, a decreased odds ratio was found, suggesting hs-CRP as an important covariate of VSA. Furthermore, it found that the relation of hs-CRP to VSA is different between genders [20]. A non-threshold model for male patients and a threshold model for female patients can be interpreted as more male smokers (lifestyle) and older smokers (induction time) contributing to the natural history of VSA development. Interestingly, hypertension was found to be negatively associated with VSA [49], suggesting that VSA is different from coronary atherosclerosis in terms of pathogenesis. Recently, a cellular study [50] also noted that elevated levels of monocytic interleukin-6 and α7 nicotinic acetylcholine receptor mRNA expression and protein production are related to the interaction between nicotine and C-reactive protein. This effect is positive on the occurrence of CAS. Another big data analysis using the National Health Insurance Research Database found that anxiety and depression diagnosis are risk factors for VSA [51]. Patients with anxiety and depression have a higher risk of new-onset CAS compared with new-onset atherosclerotic coronary artery disease (odds ratios = 2.29 and 1.34, respectively). Further analysis found that a stronger risk association is noted when comparing CAS with a control group without atherosclerotic coronary artery disease or CAS (odds ratios = 5.20 and 1.98, respectively). In the study, there was no gender difference in the association of anxiety and depression with CAS. An elevated inflammatory condition in patients with depression and anxiety with potential causality has been documented in United Kingdom Biobank and Netherlands Study of Depression and Anxiety cohorts [52]. Using the National Health Insurance Research Database, it noted that CAS is associated with incident diabetes irrespective of gender, indicating a link between the inflammation of VSA and the insulin resistance of incident diabetes [53].

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