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Predisposing Factors for Coronary Vasospasm in Prinzmetal Angina – A Literature Review

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ABSTRACT

Introduction and Purpose: Prinzmetal angina or vasospastic angina (VSA) is cardiac ischemia caused by spasm of the coronary arteries. It is characterized by chest pain at rest and ST-segment elevation on electrocardiographic (ECG). Vasospasm can be focal or diffuse, but VSA often remains undiagnosed. The purpose of this study is to present risk factors for coronary vasospasm in Prinzmetal angina based on the available literature.

Materials and Methods: A literature review was conducted from the PubMed database, covering studies from 2015-2025. Meta-analyses and randomized controlled trials were analyzed. Key phrases such as “Prinzmetal angina,” “risk factors” and “angina pectoris” were used. Selected papers were evaluated for results and conclusions.

Description of the State of Knowledge: Symptoms of VSA include recurrent chest pain, relieved by nitrates. They occur at rest, mainly at night. VSA can be asymptomatic, leading to

arrhythmias or sudden cardiac death. Diagnosis requires criteria, including confirmation of coronary artery spasm with more than 90% stenosis, observed during provocative testing.
Conclusions: VSA is associated with genetic and environmental factors, such as smoking, hyperthyroidism and chronic inflammation. Despite its coexistence with coronary artery disease, its presence does not always negatively affect prognosis. Further research may contribute to better diagnosis and personalization of therapy.
Keywords: Prinzmetal angina, angina pectoris, risk factors for angina pectoris

1. INTRODUCTION AND PURPOSE

Prinzmetal angina, also known as vasospastic angina (VSA), is one of the clinical manifestations of myocardial ischemia resulting from dynamic narrowing of the coronary arteries. The condition is typified by its occurrence during periods of rest and its manifestation as transient ST-segment elevation in electrocardiographic recordings. The nature of coronary spasms can be categorized as either focal or diffuse. VSA can accompany various clinical conditions, such as stable angina, sudden cardiac death, acute coronary syndrome, cardiac arrhythmias, or syncope. However, it often remains unrecognized. The true prevalence of coronary spasm remains uncertain and is contingent upon the demographic characteristics of the study population.

The precise mechanisms underlying coronary artery spasm remain to be fully elucidated. Possible etiological factors include vascular smooth muscle hyperreactivity, endothelial dysfunction, magnesium deficiency, chronic low-grade inflammation, autonomic nervous system dysregulation, and oxidative stress. Furthermore, genetic factors may also influence the onset of this condition [1].

The present review aims to present the risk factors for coronary spasm in Prinzmetal angina that have been identified in the modern literature.

2. MATHERIALS AND METHODS

A review of the literature available in the PubMed database was conducted to assess the risk factors associated with Prinzmetal angina. The database was searched for publications from 2015 to 2025. The analysis focused primarily on studies involving human subjects, encompassing meta-analyses of observational studies and randomized controlled trials. The search strategy employed key phrases such as "Prinzmetal angina," "vasospasm-induced angina," and "risk factors." The selected papers were evaluated in terms of the results and conclusions presented.

3. DESCRIPTION OF A STATE OF KNOWLEDGE

3.1 Symptoms

Prinzmetal's angina is characterized by recurrent episodes of chest pain, which are typically alleviated by the administration of nitrates. The distinctive characteristics of VSA differentiate it from classic angina. The attacks do not occur as a result of physical exertion or emotional stress; rather, they manifest at rest, typically during nocturnal or morning hours. The duration of these pain episodes typically ranges from five to fifteen minutes, with a swift resolution following the administration of sublingual nitroglycerin.

It is noteworthy that the manifestations of VSA can exhibit significant variability. In some patients, the condition remains asymptomatic; in others, it manifests as angina. In more severe cases, VSA can lead to serious cardiac incidents, including arrhythmias, myocardial infarction, or cardiac arrest. In extreme cases, coronary vasospasm may occur without overt symptoms, potentially leading to sudden death [2].

3.2 Diagnosis

The Coronary Vasomotion Disorders International Study (COVADIS) group developed international standard diagnostic criteria. To establish a definitive diagnosis of VSA, the fulfillment of the following conditions is requisite:

1.The presence of nitrate-responsive angina symptoms must be observed, accompanied by at least one of the following:

a) the occurrence of angina at rest,

b) variability of symptoms throughout the day,

c) the induction of angina by hyperventilation, or

d) the relief of symptoms after the administration of calcium channel blockers (CCBs).

2.The presence of transient ischemic changes on ECG, occurring during spontaneous pain episodes.

3.Documented coronary artery spasm, leading to a narrowing of the vessel lumen by more than 90%, observed spontaneously or in response to provocative tests (with concomitant pain and ischemic changes on the ECG).

If only two of these criteria are met, the patient is diagnosed with "suspected VSA" [3].

Coronary artery spasm frequently coexists with epicardial coronary artery disease (CAD) and coronary endothelial dysfunction. Consequently, it is recommended that a comprehensive assessment of coronary vascular function be performed using a single procedure, namely coronary angiography with invasive analysis of physiological parameters, which is currently the preferred diagnostic method [4].

3.3 Provocative Tests

The most reliable method for assessing coronary vasospasm is angiography combined with pharmacological stimulation, using substances such as acetylcholine (ACh) or ergonovine. This approach constitutes a pivotal element in the diagnosis of VSA, as it exhibits high sensitivity and specificity in detecting epicardial vasospasm. The efficacy of other provocative agents, such as serotonin and histamine, has also been documented.

It is imperative to emphasize that the administration of provocative tests should be entrusted exclusively to experienced medical teams. A transient occlusion of a coronary artery, resulting in a stenosis of greater than 90%, accompanied by symptoms of myocardial ischemia, such as angina and ST-segment changes, is considered a positive result. Selective pharmacologic provocative testing has been shown to have a lower risk of complications when compared with diagnostic coronary angiography [5].

3.4 Treatment

The therapeutic approach for Prinzmetal angina encompasses drug therapy, lifestyle modification, and the avoidance of substances that can induce coronary vasospasm. Examples of such substances include beta-blockers and triptans.

Calcium channel blockers are regarded as the preferred initial treatment, particularly in patients with comorbidities such as hypertension, atrial fibrillation, or heart failure with preserved ejection fraction. The utilization of long-acting nitrates has been demonstrated to reduce ST-segment changes and alleviate symptoms of vasospastic angina. The combination of these medications with calcium channel blockers has been shown to enhance therapeutic efficacy. The efficacy of incorporating α1-adrenergic receptor antagonists and statins into standard treatment regimens remains uncertain.

The selection of appropriate pharmaceutical agents should take into account the individual needs of the patient, taking into account the patient's body tolerance, the risk of side effects, and potential drug interactions. Non-selective beta-blockers have the potential to exacerbate VSA due to their ability to inhibit vasodilation through the blockade of β2-adrenergic receptors. Sumatriptan, a serotonin receptor agonist, is contraindicated due to its potential for directly inducing coronary vasospasm. Additionally, the use of high-dose aspirin has been observed to exacerbate VSA symptoms [6].

4. DISCUSSION

4.1 Genetic Factors

The present study sought to analyze the risk of vasospastic angina (VSA) among siblings of those diagnosed with the condition, as well as among those without a diagnosis. To this end, a nationwide family cohort in Sweden was utilized. The study's primary hypothesis was that individuals with a family history of VSA are at an elevated risk of developing the disease, independent of shared environmental factors. The study population comprised sibling pairs born in Sweden between 1932 and 2018, and it employed incidence rate ratios (IRRs) and adjusted hazard ratios (HRs) to evaluate the relative risk among relatives of individuals with VSA compared to those without the condition. The study encompassed a total of 5,764,770 individuals, of whom 3,461 (0.06%) were diagnosed with VSA (median age of diagnosis: 59 years, interquartile range [IQR]: 63-76). The majority of the patients were female (2,236, 64.61%). The incidence rate of VSA among individuals with affected siblings was 0.31 per 1,000 person-years (95% CI: 0.24-0.42), and among those without affected siblings was 0.04 per 1,000 person-years (95% CI: 0.04-0.04), resulting in an IRR of 7.58 (95% CI: 5.71-10.07). The adjusted model demonstrated that the risk of disease among siblings of individuals with VSA was considerably elevated (HR: 2.56; 95% CI: 1.73-3.79). The study's findings underscore a familial predisposition to VSA, independent of common environmental factors, thereby emphasizing the necessity for additional research investigating the influence of both genetic and non-genetic factors on the development of the disease [7].

A study was conducted to identify genetic factors associated with Prinzmetal angina. The genome-wide association study included patients who had undergone genotyping. The analysis encompassed 5,720 cases of VSA (mean [SD] age: 67 years; 64.2% male) and 153,864 control subjects (mean [SD] age: 62 years; 50.3% male), which were divided into three distinct data sets. The strongest association with VSA was identified for variants in the RNF213 region (odds ratio [OR]: 2.34; 95% confidence interval [CI]: 1.99-2.74; $P = 4.4 \times 10^{-25}$). The rs112735431

variant was identified as the most probable causative factor. Homozygous rs112735431 carriers exhibited a significantly elevated risk of VSA (odds ratio [OR]: 18.34; 95% confidence interval [CI]: 5.15-65.22; P = 7.0 × 10-6), and this association differed from the additive model (OR: 4.35; 95% CI: 1.18-16.05; P = 0.03). The analysis revealed a stronger association of rs112735431 with VSA among male subjects ($\chi^2 = 7.24$; P = 0.007) and in younger age groups (OR: 3.06; 95% CI: 2.24-4.19). Furthermore, individuals who carried the rs112735431 risk allele yet did not have coronary artery disease exhibited a higher mortality rate from acute myocardial infarction (risk ratio: 2.71; 95% CI: 1.57-4.65; P = 3.3 × 10-4). The study's findings suggest a potential link between variations in vascular cell function within the RNF213 region and the development of coronary vasospasm. The presence of the risk allele could serve as a prognostic factor [8].

Another study sought to elucidate the function of the RNF213 p.R4810K variant, a gene linked to moyamoya disease susceptibility (MMD), in coronary vasospasm (VSA). A case-control study was conducted using a database comprising 8,175 participants, 1,011 healthy controls, 1,088 patients with CAD, and 6,076 other controls without CAD (excluding 42 patients with MMD). The identification of 66 cases of VSA was conducted in accordance with established diagnostic criteria. The results indicated that the RNF213 variant was not significantly associated with CAD after comparing 1,088 CAD cases (median age 65 years [IQR: 55-73]; 18.7% women) with 1,011 healthy control subjects (median age 67 years [IQR: 56-74]; 42.8% women). When 66 VSA patients (median age 62 [IQR: 50-71]; 18.2% women) were compared with healthy control subjects, the variant was more common in the VSA group (10.6% vs. 2.1%; P = 0.001), and the association remained significant after adjustment (OR: 6.03 [95% CI: 2.12-17.15]; P < 0.001). The association was more pronounced among women and those with dyslipidemia [9].

4.2 Smoking

Smoking has been identified as a significant risk factor and trigger for coronary vasospasm (VSA). A comprehensive review of the extant literature on the subject reveals a clear and consistent association between smoking and an increase in cardiac sympathetic activity. The increased release of norepinephrine from sympathetic nerves innervating the coronary vessels can lead to epicardial vasoconstriction through activation of α1-adrenergic receptors. Furthermore, chronic smoking has been demonstrated to contribute to endothelial dysfunction in coronary arteries, manifesting as impaired vasodilatory capacity (FMD40) or vasoconstriction in response to acetylcholine. Moreover, smoking cessation has been observed

to reduce coronary vasoconstriction during acetylcholine provocation tests in patients following a recent myocardial infarction. Furthermore, studies have indicated that smoking may reduce endothelium-independent vasodilatation capacity, as demonstrated using sublingual nitroglycerin in the brachial artery. Furthermore, smoking has been observed to reduce the sensitivity of vascular smooth muscle (VSMC) to nitric oxide (NO). Nicotine has been observed to exacerbate vasoconstriction through the action of norepinephrine in the skin and to augment the contractile response to endothelin-1 in coronary vessels in rats. Furthermore, smoking has been shown to contribute to oxidative stress in endothelial cells, potentially leading to NO deficiency and the exacerbation of angina in individuals carrying pathogenic variants in the eNOS, CYBA, or ALDH2 genes. This phenomenon is associated with the functions of CYBA (p22-phox) and ALDH2, which play a role in the production of reactive oxygen species and the metabolism of harmful aldehydes present in cigarette smoke, respectively [10].

4.3 Hyperthyroidism

The present study sought to analyze the relationship between hyperthyroidism and the development of Prinzmetal angina. The data for this study were obtained from a multicenter registry of patients with symptoms that suggested the presence of VSA. All participants underwent coronary angiography and an ergonovine provocation test, and were divided into two groups: a group with known VSA and a control group. The study population included 1,239 patients (629 men and 610 women) who underwent provocative testing, of which 831 patients (67.1%) were diagnosed with VSA, while the remaining patients did not meet the diagnostic criteria for VSA. A statistically significant difference was observed between the VSA and control groups with respect to the prevalence of hyperthyroidism, with an occurrence of 10.0% in the VSA group compared to 3.7% in the control group ($p < 0.001$). Among the male population, 485 individuals (77.1%) were diagnosed with VSA, while this diagnosis was made in 346 women (56.7%). Patients with VSA exhibited significantly lower TSH values ($p = 0.013$) and higher free thyroxine (T4) levels ($p < 0.001$), while triiodothyronine (T3) levels, which were available for 820 patients (66.1%), did not differ significantly between the two groups (2.0 vs. 2.3 ng/dL, $p = 0.631$). After adjusting for confounding factors, hyperthyroidism was shown to be associated with a 3.27-fold increased risk of VSA. This association was particularly evident among female patients, where the risk was found to be 4.38 times higher. The analysis of mortality rates revealed that the presence of hyperthyroidism did not affect the overall mortality of patients with VSA. The findings of this study suggest that hyperthyroidism is an independent risk factor for VSA, particularly in the female population [11].

4.4 Inflammation

The utilization of positron emission tomography combined with computed tomography (PET/CT) employing 18F-fluorodeoxyglucose has demonstrated that inflammatory processes within the coronary vascular bed and perivascular adipose tissue are associated with the manifestation of coronary artery spasm in patients afflicted with Prinzmetal angina. It was observed that coronary perivascular 18F-fluorodeoxyglucose uptake in these patients decreased after calcium antagonists. Furthermore, analysis of serum inflammatory biomarkers revealed elevated levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular adhesion molecule-1 (sVCAM-1) in patients with VSA. This finding suggests the presence of systemic inflammation, leading to endothelial dysfunction, in patients with spastic coronary arteries.

Furthermore, the study revealed that asthma serves as an independent risk factor for VSA, with an odds ratio of 1.85, thereby substantiating a correlation between allergic reactions and VSA. Furthermore, prior steroid use has been demonstrated to elevate the risk of coronary vasospasm, irrespective of the route of administration, including both oral (odds ratio = 1.22) and inhaled (odds ratio = 1.89). A comparative analysis revealed that asthma was most prevalent in patients with VSA (4.4%), followed by patients with VSA coexisting with atherosclerotic coronary artery disease (2.6%) and those with atherosclerotic coronary artery disease treated with coronary intervention (1.8%). The findings suggest a correlation between bronchospasm in asthma and VSA, implying that inflammation may play a pivotal role in the mechanisms leading to VSA [12].

The present study sought to analyze the relationship between white blood cell (WBC) count and long-term clinical outcomes in patients diagnosed with Prinzmetal angina. The study population comprised 823 patients diagnosed with VSA who underwent coronary angiography with ergonovine provocation test and lacked significant coronary lesions. The patients were stratified into two groups based on their WBC count at the time of diagnosis: The first group (n = 546, <7490/ml) included patients with lower WBC counts, while the second group (n = 277, ≥7490/ml) consisted of patients with higher WBC counts. The primary endpoint of the study was the occurrence of major cardiovascular events. The median follow-up period was 4.3 years. The incidence of cardiovascular events did not differ significantly between the two groups (14.7% vs. 20.2%, HR 1.29, CI 0.90-1.83, P = 0.162). Conversely, Group II exhibited a significantly higher incidence of cardiac death and myocardial infarction (1.5% vs. 4.3%, HR 2.86, CI 1.14-7.17, P = 0.025). Multivariate analysis employing a Cox regression model

revealed that an elevated WBC count at diagnosis was an independent risk factor for myocardial infarction (HR 3.43, CI 1.02-11.59, P = 0.047). These findings suggest that an elevated white blood cell count may serve as a significant predictor of incident cardiac risk in patients with VSA [13].

4.5 Lipid Disorders

The potential relationship between endothelial dysfunction and oxidative stress, while not fully elucidated, is a subject of ongoing research. One particular area of investigation focuses on the association between vasospastic angina (VSA) and the oxidative stress marker malondialdehyde-modified low-density lipoprotein (MDA-LDL). The present study analyzed serum MDA-LDL levels in patients who were hospitalized for episodes of resting chest pain. The participants were divided into three groups: those with confirmed VSA, suspected VSA, and unlikely VSA. Among the subjects, 40 had a certain diagnosis of VSA, 35 were in the group of suspected VSA, and nine patients were considered unlikely to have the disease. The mean age of the participants was 60.2 years, and 61% were male. Serum MDA-LDL levels were significantly higher in patients with clinical VSA (126.3 ± 38.0 U/L) compared to those with unlikely VSA (98.7 ± 31.1 U/L). Serum MDA-LDL levels were identified as a significant predictor of a clinical diagnosis of VSA, with an odds ratio of 1.064 (95% confidence interval: 1.014-1.145; P = 0.008). In the group of patients with abnormal or borderline ECG results, the acetylcholine challenge test was significantly higher among those with elevated MDA-LDL levels than in the group with lower levels (81% vs. 37%, P = 0.032). Serum MDA-LDL has been identified as a promising biomarker for VSA, with the potential to enhance diagnostic precision [14].

4.6 Family History (FH)

A familial history of coronary artery disease (FH-CAD) is a well-known risk factor for atherosclerotic CAD; however, its frequency in patients with Prinzmetal angina and its impact on the course of VSA are not fully understood. The present study sought to ascertain the prevalence of FH-CAD in patients with atherosclerotic CAD and VSA, and to examine the clinical and prognostic characteristics of patients with VSA who have FH-CAD. To this end, coronary angiography and provocative tests were performed to assess coronary pain. Patients were divided into three groups: those with atherosclerotic CAD (362 cases), those with VSA (221 cases), and those without VSA (73 cases). The results of the study indicated that FH-CAD was less prevalent in the atherosclerotic CAD group (12%, p = 0.029) compared to the VSA (19%) and non-VSA (19%) groups. In the VSA and non-VSA groups, FH-CAD was observed

more frequently in women than in patients with atherosclerotic CAD ($p < 0.001$). While the impact of FH-CAD on vascular function in patients with VSA remains to be elucidated, it did not demonstrate a substantial influence on disease severity or prognosis. The diagnosis of FH-CAD has the potential to serve as a valuable diagnostic tool, particularly in assessing the risk of coronary artery disease in women [15].

The present study sought to elucidate the relationship between HDL cholesterol levels and VSA, with a particular focus on the differential expression of HDL cholesterol between men and women. The present study analyzed data from 797 patients (427 men and 370 women) who underwent an acetylcholine (ACh) challenge test to assess VSA. The test was considered positive if there was vasoconstriction visible on angiography, accompanied by chest pain or ischemic changes on ECG. The ACh test yielded a positive result in 414 individuals (51.9%), indicating a difference in the prevalence of VSA between the sexes. A statistically significant difference was observed between men and women in terms of the prevalence of positive test results, with a higher proportion of men exhibiting positive results (56.9%) compared to women (46.2%), yielding a statistically significant difference of $p = 0.003$. In both genders, lower HDL levels were found to be associated with an elevated risk of a positive ACh test result. The analysis revealed that among individuals suspected of having VSA, males were more likely to have a positive ACh test compared to females. Furthermore, the analysis revealed that low HDL levels emerged as a pivotal factor associated with VSA in both sexes, suggesting a significant role for this parameter in the pathophysiology of the disease [16].

4.7 Air Pollution

The present study evaluated the effects of long-term exposure to air pollution (AP) on coronary endothelial function and the occurrence of significant coronary artery spasm (CAS) using an acetylcholine (ACh) challenge test. The study population comprised 6,430 patients with chest pain who underwent intracoronary ACh testing. The air pollutants were categorized into two primary types: particulate matter ≤10 μm (PM10) and gases such as nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone. The findings indicated a positive correlation between CAS and PM10 exposure, while the effect of the other gaseous pollutants was deemed non-significant. As PM10 levels increased, the frequency of CAS and transient ST-segment elevation increased concomitantly. Furthermore, a higher frequency of spontaneous vasoconstriction was observed at elevated PM10 levels. The mean exposure to PM10 was determined to be 51.3 ± 25.4 μg/m³, and the results of the Cox regression analysis indicated a 4% increase in CAS risk with a 20 μg/m³ increase in PM10. The study thus confirms the strong

association between PM10 exposure and CAS incidence. These findings suggest an important role for environmental factors in the pathogenesis of angina pectoris [17].

The sympathetic nervous system (SNS) has been postulated to play a role in the development of vasospastic angina (VSA). The objective of this study was to evaluate SNS activity in patients with VSA using microneurography. The study's participants included 15 patients diagnosed with VSA, as confirmed by a positive ergonovine challenge test, and 15 individuals serving as negative controls. The analysis revealed that under baseline conditions, SNS activity was significantly higher in patients with VSA compared to the control group (56.8 ± 5 vs. 49.3 ± 6.3 burst/min; $p < 0.001$). In the presence of psychological stress, SNS activity increased only in patients with VSA, who continued to exhibit higher values compared to the control subjects (66.1 ± 7.2 vs. 53.6 ± 8.7 burst/min; $p < 0.001$). Furthermore, only patients with VSA demonstrated significant hemodynamic changes, including an increase in mean arterial pressure (96.2 ± 13.4 vs. 86.6 ± 9.6 mmHg; $p < 0.05$). These findings provide the first direct evidence of chronically elevated SNS activity in patients with VSA, which increases under psychological stress. This finding suggests that the sympathetic nervous system (SNS) may play a pivotal role in the pathogenesis of VSA by increasing coronary vascular tone [18].

4.8 Risk Factors Without Significant Influence

The use of computed tomographic angiography (CTA) of the coronary vessels facilitates the evaluation of perivascular adipose tissue (PVAT), encompassing its volume and perivascular attenuation index (FAI). Elevated PVAT and FAI values have been observed in patients with vasospastic angina (VSA). The objective of this study was to examine the correlation between coronary vasospasm and PVAT and FAI parameters at the single vessel level. The study population comprised 51 patients who underwent ACh and CTA over a six-month period, with a total of 125 vessels being evaluated. Vasospasm after ACh occurred in 40 vessels (32.0%), and obstructive coronary artery disease in 12 (9.6%). Subsequent analysis revealed no statistically significant disparities in PVAT volume or FAI between vessels with and without vasospasm post-ACh, nor between patients with positive and negative test results. However, a notable distinction emerged in the analysis of FAI, which exhibited a marked increase in vessels diagnosed with obstructive coronary artery disease. The findings suggest that vasospasm subsequent to ACh does not correlate with PVAT volume or FAI; however, higher FAI may be associated with obstructive coronary artery disease [19].

The relationship between vasospastic angina (VSA) and cancer, as well as the treatment thereof, remains to be elucidated. This study evaluated 786 patients undergoing an acetylcholine (ACh)

provocation test for the diagnosis of VSA. A positive test result was defined as the presence of angiographic coronary artery spasm accompanied by chest pain and/or electrocardiographic changes. Patients were divided into three groups: those with active cancer, a history of cancer, and no history of cancer. The impact of cancer type, chemotherapy, and radiotherapy on VSA was then subjected to thorough analysis. The study population included 38 subjects (4.8%) with active cancer, 84 (10.7%) with a history of cancer, and 401 (51.0%) with a diagnosis of VSA. The frequency of a positive ACh test did not differ significantly between the groups (39.5% vs. 57.1% vs. 50.9%, $p = 0.20$). The study found no association between cancer type or treatment modalities and ACh test outcomes. The present study found no association between cancer, its treatment, and VSA [20].

5. CONCLUSIONS

In consideration of the findings herein presented, several salient conclusions may be drawn regarding the risk factors associated with the occurrence of vasospastic angina (VSA). Primarily, the impact of genetic elements on the progression of the condition was substantiated. The occurrence of VSA in siblings was associated with a significantly higher risk of the disease, regardless of shared environmental factors. Furthermore, genetic studies have identified a strong association of the rs112735431 variant in the RNF213 gene with VSA, particularly in men and younger individuals, suggesting the involvement of this gene in the pathogenesis of coronary vasospasm. Furthermore, additional risk factors for VSA have been identified. Specifically, smoking has been demonstrated to exert a substantial influence by means of increasing sympathetic nervous system activity, endothelial dysfunction, and decreasing the sensitivity of vascular smooth muscle to nitric oxide. In addition, hyperthyroidism has been identified as an independent risk factor, particularly among the female population, as evidenced by the abnormal thyroid hormone levels observed in patients with VSA. Inflammation has emerged as another critical component in the pathogenesis of the disease. Elevated levels of inflammatory markers and comorbidities, such as asthma, indicate a link between chronic inflammation and coronary hyperresponsiveness. Furthermore, elevated leukocyte levels at the time of diagnosis may serve as a predictor of an increased risk of myocardial infarction and cardiac death in VSA. Conversely, lipid abnormalities, including low HDL levels and elevated MDA-LDL levels, may suggest the involvement of oxidative stress and impaired endothelial function in the development of the disease. While a family history of coronary heart disease (FH-CAD) did not have a significant impact on the severity of VSA, its higher prevalence among women with VSA may serve as a useful diagnostic element. Furthermore, exposure to

particulate matter (PM10) demonstrated a significant association with an increase in the frequency of coronary vasospasm, underscoring the importance of environmental external factors in the development of the disease. Furthermore, sympathetic nervous system activity was found to be significantly elevated in patients with VSA compared to healthy subjects, both under resting conditions and in response to mental stress. This finding suggests a potential role for this system in the mechanisms causing the disease. Furthermore, the study observed that sympathetic nervous system activity was significantly higher in patients with VSA compared to healthy subjects, both under resting conditions and in response to mental stress. This finding indicates a potential role for this system in the mechanisms causing the disease. However, certain factors, including perivascular adipose tissue volume (PVAT) and attenuation index (FAI), did not demonstrate significant differences between VSA patients and controls, suggesting that their diagnostic utility in the context of VSA may be limited. Additionally, the association between malignancy and the incidence of vasospasm remains uncertain and requires further investigation.

In summary, VSA is a multifaceted disease with a complex etiology, in which genetic, hormonal, inflammatory, environmental, and factors related to nervous and lipid system function play a significant role. A more profound comprehension of these interrelationships may facilitate more efficacious diagnosis, prevention, and treatment of this form of angina.

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Author's contributions

Conceptualization: PZ, KM;

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Formal analysis: PZ, MP;

Investigation: PZ, KM, MP, ŁK, MK, AJ;

Resources: PZ;

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References:

1. Picard F, Sayah N, Spagnoli V, Adjedj J, Varenne O. Vasospastic angina: A literature review of current evidence. Arch Cardiovasc Dis. 2019 Jan;112(1):44-55. doi: 10.1016/j.acvd.2018.08.002. Epub 2018 Sep 7. PMID: 30197243.
2. He Z, Xu X, Zhao Q, Ding H, Wang DW. Vasospastic angina: Past, present, and future. *Pharmacol Ther*. 2023;249:108500. doi:10.1016/j.pharmthera.2023.108500
3. Jenkins K, Pompei G, Ganzorig N, Brown S, Beltrame J, Kunadian V. Vasospastic angina: a review on diagnostic approach and management. *Ther Adv Cardiovasc Dis*. 2024;18:17539447241230400. doi:10.1177/17539447241230400

4. Sinha A, Rahman H, Perera D. Vasospastic Angina: A Contemporary Review of its Pathophysiology, Diagnosis and Management. *Heart Int*. 2022;16(2):99-104. Published 2022 Jul 26. doi:10.17925/HI.2022.16.2.99
5. Sheth MA, Widmer RJ, Dandapantula HK. Pathobiology and evolving therapies of coronary artery vasospasm. *Proc (Bayl Univ Med Cent)*. 2021;34(3):352-360. Published 2021 Apr 21. doi:10.1080/08998280.2021.1898907
6. Harris JR, Hale GM, Dasari TW, Schwier NC. Pharmacotherapy of Vasospastic Angina. *J Cardiovasc Pharmacol Ther*. 2016;21(5):439-451. doi:10.1177/1074248416640161
7. Ricci F, Banihashemi B, Pirouzifard M, et al. Familial risk of vasospastic angina: a nationwide family study in Sweden. *Open Heart*. 2023;10(2):e002504. Published 2023 Dec 6. doi:10.1136/openhrt-2023-002504
8. Hikino K, Koyama S, Ito K, et al. RNF213 Variants, Vasospastic Angina, and Risk of Fatal Myocardial Infarction. *JAMA Cardiol*. 2024;9(8):723-731. doi:10.1001/jamacardio.2024.1483
9. Ishiyama H, Tanaka T, Yoshimoto T, et al. *RNF213* p.R4810K Variant Increases the Risk of Vasospastic Angina. *JACC Asia*. 2023;3(5):821-823. Published 2023 Jun 27. doi:10.1016/j.jacasi.2023.05.002
10. Tran MV, Marceau E, Lee PY, Chandy M, Chen IY. The Smoking Paradox: A Twist in the Tale of Vasospastic Angina. *J Vasc Med Surg*. 2021;9(7):438.
11. Kim HJ, Jo SH, Lee MH, Seo WW, Baek SH. Hyperthyroidism Is Associated with the Development of Vasospastic Angina, but Not with Cardiovascular Outcomes. *J Clin Med*. 2020;9(9):3020. Published 2020 Sep 19. doi:10.3390/jcm9093020
12. Hung MY, Hung MJ. Relationship between Inflammation and Vasospastic Angina. *Medicina (Kaunas)*. 2023;59(2):318. Published 2023 Feb 9. doi:10.3390/medicina59020318
13. Kim DY, Kim SE, Park TK, et al. Elevated white blood cell count and long-term clinical outcomes of patients with vasospastic angina. *Coron Artery Dis*. 2024;35(5):382-388. doi:10.1097/MCA.0000000000001359
14. Oumi T, Nozato T, Sakakibara A, et al. Malondialdehyde-Modified Low Density Lipoprotein as Oxidative-Stress Marker in Vasospastic Angina Patients. *Int Heart J*. 2017;58(3):335-343. doi:10.1536/ihj.16-455
15. Teragawa H, Uchimura Y, Oshita C, Hashimoto Y, Nomura S. Frequency and Clinical Impact of Family History of Coronary Artery Disease in Patients with Vasospastic

Angina. *J Cardiovasc Dev Dis*. 2023;10(6):249. Published 2023 Jun 8. doi:10.3390/jcdd10060249

16. Saito Y, Saito Y, Kato K, Kobayashi Y. Gender differences in factors associated with vasospastic angina. *Int J Cardiol*. 2022;349:7-11. doi:10.1016/j.ijcard.2021.11.047
17. Choi BG, Lee J, Kim SW, et al. The association of chronic air pollutants with coronary artery spasm, vasospastic angina, and endothelial dysfunction. *Coron Artery Dis*. 2018;29(4):336-343. doi:10.1097/MCA.0000000000000603
18. Boudou N, Despas F, Rothem JV, et al. Direct evidence of sympathetic hyperactivity in patients with vasospastic angina. *Am J Cardiovasc Dis*. 2017;7(3):83-88. Published 2017 Jun 15.
19. Asada K, Saito Y, Takaoka H, Kitahara H, Kobayashi Y. Relation of Perivascular Adipose Tissues on Computed Tomography to Coronary Vasospasm. *Rev Cardiovasc Med*. 2025;26(2):26327. Published 2025 Feb 18. doi:10.31083/RCM26327
20. Matsumoto T, Saito Y, Saito K, et al. Relation Between Cancer and Vasospastic Angina. *Adv Ther*. 2021;38(8):4344-4353. doi:10.1007/s12325-021-01854-z