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THERAPEUTIC MANAGEMENT OF VASOSPASTIC ANGINA: STABILIZATION STRATEGIES AND ANTITHROMBOTIC THERAPY

MANEJO TERAPÊUTICO DA ANGINA VASOESPÁSTICA: ESTRATÉGIAS DE ESTABILIZAÇÃO E TERAPIA ANTITROMBÓTICA

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ABSTRACT

Vasospastic angina (VSA) is a clinically relevant entity within the spectrum of ischemic syndromes with non-obstructive coronary arteries, characterized by transient vasoconstriction of the epicardial and/or microvascular coronary bed, with variable ischemic repercussions. Although often associated with chest pain at rest and transient electrocardiographic changes, its presentation may mimic acute coronary syndromes and culminate in malignant arrhythmias, myocardial infarction, and sudden death. Diagnosis remains challenging, particularly when coronary angiography does not reveal significant lesions, requiring high clinical suspicion and, in selected centers, provocative testing with acetylcholine and/or ergonovine. In treatment, calcium channel blockers constitute the therapeutic cornerstone, with nitrates as adjunctive agents. Controversies persist regarding the role of antithrombotic therapies in VSA without obstructive atherosclerosis, especially concerning the routine use of aspirin. Recent evidence reinforces the importance of a guided approach incorporating assessment of vasomotor dysfunction and inflammatory biomarkers, as well as potential genetic implications. This narrative review synthesizes contemporary evidence on diagnosis, first-line therapies, the rationale and limitations of antithrombotic use, and the impact of inflammation on pathophysiology, pointing to future perspectives for more precise and individualized management.

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Keywords: Vasospastic Angina. Coronary Vasoconstriction. Calcium Channel Blockers. Antithrombotic Therapy. Provocative Testing. Inflammation.

RESUMO
A angina vasoespástica (AVE) é uma entidade clínica relevante dentro do espectro das síndromes isquêmicas com artérias coronárias não obstrutivas, caracterizada por vasoconstrição transitória do leito coronariano epicárdico e/ou microvascular, com repercussão isquêmica variável. Apesar de frequentemente associada a dor torácica em repouso e alterações eletrocardiográficas transitórias, sua apresentação pode mimetizar síndromes coronarianas agudas e culminar em arritmias malignas, infarto e morte súbita. O diagnóstico permanece desafiador, sobretudo quando a cinecoronariografia não evidencia lesões significativas, exigindo alta suspeição clínica e, em centros selecionados, testes provocativos com acetilcolina e/ou ergonovina. No tratamento, bloqueadores de canais de cálcio constituem a base terapêutica, com nitratos como adjuvantes. Persistem controvérsias quanto ao papel de terapias antitrombóticas na AVE sem aterosclerose obstrutiva, especialmente em relação ao uso rotineiro de aspirina. Evidências recentes reforçam a importância da abordagem orientada, incorporando avaliação de disfunção vasomotora e biomarcadores de inflamação, além de potenciais implicações genéticas. Esta revisão narrativa sintetiza evidências contemporâneas sobre diagnóstico, terapias de primeira linha, racionalidade e limites do uso antitrombótico e o impacto da inflamação na fisiopatologia, apontando perspectivas futuras para um manejo mais preciso e individualizado.

Palavras-chave: Angina Vasoespástica. Vasoconstrição Coronariana. Bloqueadores de Canais de Cálcio. Terapia Antitrombótica. Teste Provocativo. Inflamação.

RESUMEN
La angina vasoespástica (AVE) es una entidad clínica relevante dentro del espectro de los síndromes isquémicos con arterias coronarias no obstructivas, caracterizada por vasoconstricción transitoria del lecho coronario epicárdico y/o microvascular, con repercusión isquémica variable. Aunque frecuentemente se asocia a dolor torácico en reposo y alteraciones electrocardiográficas transitorias, su presentación puede simular síndromes coronarios agudos y culminar en arritmias malignas, infarto de miocardio y muerte súbita. El diagnóstico continúa siendo desafiante, especialmente cuando la coronariografía no evidencia lesiones significativas, requiriendo alta sospecha clínica y, en centros seleccionados, pruebas provocativas con acetilcolina y/o ergonovina. En el tratamiento, los bloqueadores de los canales de calcio constituyen la base terapéutica, con nitratos como agentes adyuvantes. Persisten controversias respecto al papel de las terapias antitrombóticas en la AVE sin aterosclerosis obstructiva, especialmente en relación con el uso rutinario de aspirina. Evidencias recientes refuerzan la importancia de un enfoque orientado que incorpore la evaluación de la disfunción vasomotora y biomarcadores inflamatorios, además de posibles implicaciones genéticas. Esta revisión narrativa sintetiza evidencias contemporáneas sobre diagnóstico, terapias de primera línea, la racionalidad y los límites del uso antitrombótico y el impacto de la inflamación en la fisiopatología, señalando perspectivas futuras para un manejo más preciso e individualizado.

Palabras clave: Angina Vasoespástica. Vasoconstricción Coronaria. Bloqueadores de Canales de Calcio. Terapia Antitrombótica. Prueba Provocativa. Inflamación.

1 INTRODUCTION

Vasospastic angina (CVA) is a relevant and often underdiagnosed cause of myocardial ischemia, characterized by transient vasoconstriction of the coronary arteries, which may occur in the absence of significant obstructive coronary disease. Recent evidence shows that stroke has wide clinical heterogeneity, ranging from episodes of angina at rest to malignant arrhythmias and sudden death, and is associated with endothelial dysfunction, vascular smooth muscle hypercontractility, and local and systemic inflammatory processes (Rehan et al., 2022; He et al., 2023; Jenkins et al., 2024). In addition, contemporary guidelines emphasize the importance of the correct pathophysiological identification of stroke in the context of ischemia with non-obstructive coronary arteries, aiming at accurate diagnosis and more effective therapeutic strategies (Hokimoto et al., 2023).

A consistent challenge of this pathology is related to the difficult clinical management due to complications in conventional treatments, which are used in chronic therapy. Thus, the conduct often employed in these cases is the administration of nitrates, which, in addition to not causing immediate relief, when used chronically and in the long term, are responsible for inflammatory responses that increase cardiovascular risks. In addition, for refractory patients, the use of these drugs does not exclude mortality from fatal arrhythmias during ischemic attacks (He et al., 2023).

In this context, studies more focused on the pathophysiology of vasospastic angina have shown that the inflammation that occurs in the perivascular tissue and myocardium would be the trigger for the spasms, demonstrating that these inflammations would be responsible for this activation in immune-oriented therapies. (He et al., 2023) Thus, this issue is extremely important, since recent discoveries have helped to understand the management of vascular pathophysiology and the possible improvement in stabilization and antithrombotic therapies in patients.

Therefore, this inflammatory process has been pointed out as an important modulator of Rhokinase activity, contributing to the contractile sensitization of vascular smooth muscle, and also to the perpetuation of coronary spasms. Concomitantly, endothelial dysfunction, characterized by reduced release of vasodilatory substances such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, may aggravate the imbalance between vasodilation and vasoconstriction, even though it is not considered the primary factor of the disease alone.

Vasospastic angina (ASV), historically known as Prinzmetal's or variant angina, represents a clinical manifestation of myocardial ischemia resulting from the sudden and transient spasm of epicardial coronary arteries. Unlike conventional stable angina, ASV is characterized by episodes of chest pain that occur predominantly at rest, especially during the early morning or early morning, and is often associated with transient electrocardiographic changes, such as ST-segment elevation (Jenkins et al., 2024; Rehan et al., 2022). Although it can occur in coronary arteries without significant obstructions, the presence of underlying atherosclerosis does not exclude the diagnosis and may even act as a local trigger for vascular hyperreactivity (Hokimoto et al., 2023).

The pathophysiology of ASV is multifactorial, involving endothelial dysfunction, vascular smooth muscle cell hyperreactivity, and autonomic nervous system imbalance (He et al., 2023). Recently, the role of chronic inflammation, both local and systemic, has gained prominence as a central component in the pathogenesis and recurrence of spasm episodes (Hung and Hung, 2023). The importance of accurate diagnosis and appropriate therapeutic management lies in the increased risk of serious complications, including acute myocardial infarction, lethal ventricular arrhythmias, and sudden cardiac death (Yao et al., 2023; Rehan et al., 2022). The present study aims to discuss current clinical stabilization strategies and controversies regarding antithrombotic therapy in this group of patients.

Stroke, also known as vasospastic angina, is part of the set of coronary vasomotor disorders and can manifest both in structurally normal coronary arteries and in the presence of non-obstructive atherosclerosis. From a clinical point of view, stroke represents an important cause of angina in patients with "normal" coronary angiography and also contributes to ischemia and infarction in the absence of evident culprit injury. The relevance of the topic stems from the potentially severe prognostic impact, the recurrence of symptoms, and the risk of arrhythmic events, especially when the spasm is extensive, multivetal, or associated with microvascular dysfunction (Hokimoto et al., 2023a; Jenkins et al., 2024).

The recognition and proper characterization of stroke have advanced as recent guidelines and revisions consolidate diagnostic criteria and reinforce the value of invasive provocative testing in high-suspicion scenarios. However, there is still global underdiagnosis, partly due to access limitations, fears about safety, and heterogeneity of protocols. In parallel, the therapeutic field continues to evolve: calcium channel blockers

and nitrates remain central, but there is growing interest in complementary mechanism-driven strategies, including inflammatory modulation, endothelial therapy, and a critical reassessment of routine antiplatelet use in the absence of atherothrombosis (Rehan et al., 2022; Hung & Hung, 2023; He et al., 2023).

2 METHODOLOGY

This study is a narrative review of the literature, structured with the aim of examining and compiling the main scientific evidence regarding the diagnosis and treatment of vasospastic angina. Bibliographic research was conducted using the PubMed database, using the selected descriptors: "Vasospastic angina", "Treatment" and "Diagnosis". These terms were articulated by means of Boolean operators (AND, OR) in accordance with the structured vocabulary of MeSH. The search strategy delimited the inclusion of academic productions published in the last five years, prioritizing studies with full access and written in English or Portuguese. The selection process prioritized articles that raise evidence in direct relation to the therapeutic management and the diagnostic nuances of the pathology. Duplicate publications, brief communications without scientific rigor, and texts that did not address the central theme of the research were disregarded. Data analysis was carried out qualitatively, allowing a descriptive synthesis of the information extracted from the selected journals.

This study is a narrative review of the literature, structured with the aim of examining and compiling the main scientific evidence regarding the diagnosis and treatment of vasospastic angina. Bibliographic research was conducted using the PubMed database, using the selected descriptors: "Vasospastic angina", "Treatment" and "Diagnosis". These terms were articulated by means of Boolean operators (AND, OR) in accordance with the structured vocabulary of MeSH. The search strategy delimited the inclusion of academic productions published in the last five years, prioritizing studies with full access and written in English or Portuguese. The selection process prioritized articles that raise evidence in direct relation to the therapeutic management and the diagnostic nuances of the pathology. Duplicate publications, brief communications without scientific rigor, and texts that did not address the central theme of the research were disregarded. Data analysis was carried out qualitatively, allowing a descriptive synthesis of the information extracted from the selected journals.

As a methodological complement, contemporary guidelines and consensuses of clinical practice were also included, addressing vasomotor disorders and angina with non-obstructive arteries, when pertinent to the diagnosis, stratification and treatment of stroke, respecting the time frame of five years. The narrative nature of this review implies a risk of selection bias and makes meta-analysis impossible, but allows for clinical integration of heterogeneous evidence and critical discussion of current controversies.

3 RESULTS AND DISCUSSION

3.1 DIAGNOSTIC APPROACH AND IDENTIFICATION OF SPASM

The definitive diagnosis of VA is based on three pillars. The first is the presence of anginal symptoms that respond to the use of nitrates, associated with at least one of the following characteristics: occurrence at rest, diurnal variation of the condition, triggering by hyperventilation, or improvement with the use of calcium channel blockers (CCBs). The second pillar corresponds to transient ischemic changes in the electrocardiogram during spontaneous episodes of pain. Finally, coronary artery spasm is necessary, defined as constriction greater than 90%, occurring spontaneously or after provocative tests, accompanied by pain and ischemic changes on the ECG. When only two of these three criteria are present, the diagnosis is considered to be suspected VA (Jenkins et al., 2024).

The diagnosis of ASV remains challenging, since conventional coronary angiography may not reveal fixed obstructions that justify the symptomatology. The gold standard for diagnostic confirmation involves pharmacological challenge testing using acetylcholine or ergonovine during cardiac catheterization. These agents act on different receptors of vascular smooth muscle cells, which results in distinct spasm patterns: acetylcholine tends to induce more diffuse and distal constrictions, while ergonovine, by stimulating serotonergic and alpha-adrenergic receptors, is more associated with focal and proximal spasms. Initially, ergonovine was used intravenously, demonstrating the ability to reproduce episodes similar to spontaneous ones in patients with variant angina; However, reports of serious adverse events with high doses have motivated the preferential adoption of the intracoronary route, in smaller and more selective doses, which is considered safer and equally effective. Based on the consolidation of clinical data, especially in Asian centers, the provocative test with ergonovine began to be

recognized as a valid pharmacological method for inducing coronary spasm, in a manner comparable to the test with acetylcholine. (Hokimoto et al., 2023; Jenkins et al., 2024).

According to the guidelines of the European Society of Cardiology, the provocative test with acetylcholine is recommended for the investigation of VSA, presenting high sensitivity and diagnostic specificity (Jenkins et al., 2024). The test is considered positive when there is reproduction of usual angina, the appearance of ischemic alterations on the electrocardiogram — such as ST segment elevation or depression ≥ 0.1 mV, or the appearance of new negative U waves in at least two contiguous leads — associated with coronary vasoconstriction greater than 90%. In contrast, microvascular spasm is characterized by luminal reduction of less than 90%, usually accompanied by symptoms and electrocardiographic changes triggered by lower doses of acetylcholine. Despite the wide use of these methods, there is still no universally standardized protocol for the administration of acetylcholine, with relevant variations between different centers according to local experience (Rehan et al., 2022; Jenkins et al., 2024).

In addition to invasive methods, 24-hour ambulatory electrocardiographic monitoring by Holter plays a relevant complementary role in the diagnostic approach and therapeutic management of vasospastic angina. This method allows the detection of transient ischemic episodes, often asymptomatic, characterized by ST-segment elevation or depression, as well as the identification of arrhythmias associated with coronary vasospasm. Considering the episodic, unpredictable, and often nocturnal nature of ASV, Holter monitoring enables a continuous evaluation of ischemic load and electrical instability under physiological conditions, providing information that would be difficult to capture by punctual examinations. (Yao et al., 2023; Jenkins et al., 2024)

In the context of therapeutic management, the identification of silent ischemic episodes by Holter may indicate suboptimal control of coronary vasospasm, even in the absence of evident clinical symptoms. Thus, ambulatory monitoring contributes to the objective evaluation of the response to pharmacological treatment, helping in risk stratification and in the identification of patients with a greater propensity to potentially lethal arrhythmic or ischemic events. Thus, although it does not replace invasive provocative tests, the 24-hour Holter monitor monitor is a valuable tool in the integration between functional diagnosis, therapeutic follow-up, and clinical stabilization strategies for ASV. (Rehan et al., 2022; Yao et al., 2023; He et al., 2023)

The contemporary diagnostic approach to stroke is based on the recognition that the absence of obstructive stenosis on angiography does not exclude significant myocardial ischemia. In many patients, stroke presents as angina at rest, often nocturnal or morning, with response to nitrates, and may course with transient ST elevation or infra. However, the presentation may be indistinguishable from unstable angina and even infarction, requiring systematic investigation, especially in MINOCA and ANOCA/INOCA scenarios (Jenkins et al., 2024; Hokimoto et al., 2023a).

Recent Japanese studies reinforce diagnostic criteria based on demonstration of significant vasoconstriction associated with symptoms and/or ischemic changes on the ECG, distinguishing epicardial spasm and microvascular phenotype. In this logic, the invasive provocative test with acetylcholine (or ergonovine, according to protocol) assumes the role of the standard for confirmation, especially when the clinical history and context (e.g., symptoms at rest, triggers, nitrate response, recurrence) strongly suggest vasomotor disorder (Hokimoto et al., 2023a; Hokimoto et al., 2023b).

Regarding safety, contemporary studies and protocol analyses indicate low rates of major complications when performed in experienced centers, with adequate monitoring and availability of nitrates, temporary pacemakers, and advanced support. More recent evidence broadens the discussion on the application of the test to include in selected populations with a heart attack without evident culprit injury, suggesting feasibility and acceptable safety profile, in addition to potential prognostic utility (Takahashi et al., 2022; Nishi et al., 2025; Kinoshita et al., 2024).

The current trend is to integrate the diagnosis of spasm into a broader functional assessment (vasomotor endotypes), reducing the risk of nonspecific labels and preventing unnecessary interventions. Illustratively, recent discussions warn of the risk of percutaneous procedures in moderate lesions when the dominant mechanism is vasospastic, as the persistence of symptoms after stenting may reflect unrecognized spasm, and not mechanical "failure" of revascularization (Yao et al., 2023).

3.2 FIRST-LINE THERAPEUTIC STRATEGIES

The management of vasospastic angina should prioritize a patient-centered approach, considering their individual characteristics, symptoms, and risk factors. A multidisciplinary approach should be considered necessary to ensure better disease control and quality of life. The treatment of vasospastic angina is based on three main

fronts: lifestyle modifications, adequate control of risk factors, and pharmacological treatment (Jenkins et al., 2024).

(MARIA CLARA CANDEIRA CARDOSO) The mainstay of pharmacological treatment of vasospastic angina is based on the use of calcium channel blockers (CCB), which act directly on the coronary vascular smooth muscle, reducing vasomotor hyperreactivity responsible for vasospasm. Drugs such as diltiazem, amlodipine and nifedipine demonstrate high efficacy in preventing transient arterial constriction and reducing the frequency and intensity of anginal crises, and are considered first-line therapies in VSA. In patients with incomplete clinical control, the association of different classes of CCB can be employed with the objective of enhancing the vasodilator effect and more effectively suppressing episodes of coronary spasm. (Hokimoto et al., 2023; Yao et al., 2023; Jenkins et al., 2024)

Long-acting nitrates are frequently used as an adjuvant therapy to CCBs in the management of vasospastic angina, contributing to the relaxation of vascular smooth muscle and reducing the recurrence of ischemic episodes. However, its use alone is not recommended in ASV, since it does not act on the central pathophysiological mechanism of the disease and may be limited by the development of pharmacological tolerance. Thus, the association with CCB remains the preferred strategy, especially in patients with persistent symptoms or evidence of transient ischemia documented by electrocardiographic monitoring. (Jenkins et al., 2024; He et al., 2023)

Despite the efficacy of this approach in most patients with ASV, a portion may experience recurrent vasospasm or silent ischemic episodes, even under optimized treatment. In these cases, the identification of transient electrocardiographic changes or arrhythmias associated with vasospasm, particularly by means of 24-hour Holter monitoring, may indicate suboptimal control of the disease. The integration of these functional findings into clinical follow-up allows early adjustments in the therapeutic strategy, contributing to the stabilization of the condition and to the reduction of the risk of adverse events related to coronary vasospasm. (Yao et al., 2023; Jenkins et al., 2024; He et al., 2023)

Importantly, the use of beta-blockers, particularly non-selective beta-blockers, is contraindicated in the management of vasospastic angina. Drugs such as propranolol block both beta-1 and beta-2 receptors, and inhibition of beta-2 receptors, responsible for vasodilation mediated by the adrenergic system, can result in unopposed alpha-

adrenergic activity. This imbalance favors the contraction of vascular smooth muscle and can precipitate or aggravate episodes of coronary vasospasm, exacerbating myocardial ischemia in these patients. (Hokimoto et al., 2023; Rehan et al., 2022)

In addition to the direct impact on coronary vascular tone, the use of beta-blockers in ASV may mask early symptoms of ischemia without preventing the underlying pathophysiological mechanism of the disease. Unlike atherosclerosis-related angina, in which the reduction of myocardial oxygen demand plays a central role, VSA is predominantly characterized by coronary vasomotor dysfunction. Thus, the use of beta-blockers not only lacks proven benefit in this context, but can also negatively interfere with the clinical control of vasospasm. (He et al., 2023; Jenkins et al., 2024)

Even cardioselective beta-blockers should be employed with caution in patients with ASV, since selectivity for beta-1 receptors is not absolute, especially at higher doses. In these scenarios, there may be a loss of pharmacological selectivity and consequent inhibition of beta-2 receptors, partially reproducing the deleterious effects observed with non-selective beta-blockers. For this reason, contemporary guidelines and reviews do not recommend the routine use of this drug class as a first-line therapeutic strategy in vasospastic angina. (Hokimoto et al., 2023; Jenkins et al., 2024)

In specific clinical situations, such as the coexistence of other cardiovascular conditions that would traditionally indicate the use of beta-blockers, their prescription should be carefully considered and individualized. In these cases, the therapeutic decision should consider the balance between potential benefits and the risk of exacerbation of coronary vasospasm, and close clinical and electrocardiographic monitoring is essential. Even so, calcium channel blockers remain the mainstay of the pharmacological treatment of ASV, reinforcing the central role of this class in the prevention and stabilization of vasospasm episodes. (Rehan et al., 2022; Hokimoto et al., 2023)

Thus, the exclusion of beta-blockers from the first-line therapeutic arsenal in vasospastic angina is based on solid pathophysiological bases and consistent clinical evidence. The prioritization of drugs with direct action on the coronary vascular smooth muscle, such as calcium channel blockers, associated with the judicious use of nitrates, is the most effective strategy for controlling vasospasm and reducing the risk of adverse events in this population. (He et al., 2023; Jenkins et al., 2024)

In summary, the first-line pharmacological management of vasospastic angina should be guided primarily by interventions that act directly on the central pathophysiological mechanism of the disease, characterized by hyperreactivity and coronary vasomotor dysfunction. In this context, calcium channel blockers play a central role by promoting vascular smooth muscle relaxation and effectively suppressing vasospasm episodes. Nitrates, in turn, play a relevant adjuvant role by potentiating coronary vasodilation and contributing to symptomatic control, although they should not be used in isolation due to the limitation imposed by pharmacological tolerance. In contrast, beta-blockers, especially non-selective beta-blockers, not only lack benefit in ASV, but may exacerbate coronary vasospasm by favoring unopposed alpha-adrenergic activity, which is why they are not part of first-line therapeutic strategies. Thus, the therapeutic choice in vasospastic angina should favor drugs with a direct effect on coronary vascular tone, reinforcing the need for a pathophysiologically oriented approach to clinical stabilization and reduction of the risk of adverse events. (Rehan et al., 2022; Hokimoto et al., 2023; He et al., 2023; Jenkins et al., 2024; Yao et al., 2023) The treatment of stroke aims at two central objectives: symptomatic control and prevention of ischemic/arrhythmic events associated with spasm. The most consistent evidence supports calcium channel blockers (CCB) as a first-line therapy, as it reduces vascular smooth muscle hyperreactivity and recurrence of seizures. Recent Japanese guidelines maintain this position and guide dose escalation and, when necessary, association of different BCC classes (Hokimoto et al., 2023a; Hokimoto et al., 2023b).

Nitrates remain as a reliever treatment and as an adjunct in symptomatic patients despite CCB, although their chronic use requires attention to nitrate tolerance and "free window" when applicable. In refractory cases, contemporary reviews discuss additional strategies, including BCC optimization, vasodilator alternatives (such as nicorandil where available), correction of triggers, and strict control of smoking and other risk factors. Recent literature also reinforces that beta-blockers can worsen symptoms in some patients with spasm, and should be avoided when the dominant mechanism is vasospastic, unless clearly indicated with concomitant protection by BCC (Lanza et al., 2023; Jenkins et al., 2024).

One point of practical evolution is the transition from "label processing" to "mechanism processing". This implies recognizing coexistence of epicardial and microvascular spasm, as well as variation of endotypes over time. In this sense, studies

with acetylcholine rechallenge and therapeutic personalization strategies suggest that functional reassessment can guide therapy adjustments and explain apparent failures of standard treatment, especially when multiple vasomotor endotypes coexist (Seitz et al., 2022).

3.3 ANTITHROMBOTIC THERAPY: INDICATIONS AND CONTROVERSIES

The use of acetylsalicylic acid (ASA) in ASV is a topic of clinical debate. In patients with coexisting obstructive coronary artery disease, ASA is indicated for the secondary prevention of atherothrombotic events (Jenkins et al., 2024). However, in cases of pure spasm without significant atherosclerosis, the use of high doses of aspirin can be harmful, as it inhibits the synthesis of prostacyclin (a potent endogenous vasodilator), and may theoretically aggravate the tendency to spasm (Hokimoto et al., 2023). It is therefore recommended that if used, aspirin be administered in low doses.

The use of low-dose ASA (< 100mg/day) predominantly inhibits cyclooxygenase-1 (COX-1) in platelets, blocking the production of thromboxane A2 (TXA2), a vasoconstructor and platelet activator, this effect, in theory, has been shown to be beneficial in ASV. However, the use of high-dose ASA (> 325mg/day) also inhibits the synthesis of prostacyclin (PGI2), a potent vasodilator and platelet aggregation inhibitor, this vasoconstrictor/vasodilator imbalance caused can increase the tendency to spasm in patients with endothelial dysfunction (Jenkins et al., 2024; Hokimoto et al., 2023).

Thus, ASA is well indicated, as long as it is in the appropriate dose, in patients with ASV and significant stenosis (> 50%) or for those with a history of infarction/revascularization, as a form of secondary prevention. Patients with post-Acute Coronary Syndrome (ACS) with identified vulnerable plaque, history of thromboembolism or atherothrombotic comorbidities may also be indicated, but it should be understood that in all these cases, ASA would be associated not to directly treat the vasospasm that generated the condition, but rather for associated factors and to prevent new episodes (Jenkins et al., 2024; Hokimoto et al., 2023; Rehan et al., 2022).

Statins, in turn, have demonstrated benefits that transcend lipid reduction. Due to their pleiotropic effects, statins help improve endothelial function and reduce oxidative stress and vascular inflammation, factors that contribute to the stabilization of coronary tone (Hung and Hung, 2023; He et al., 2023).

The improvement in endothelial function is due to the increased bioavailability of nitric oxide (NO) and its vasodilator effect, as well as the suppression of the RhoA/Rho-kinase pathway that reduces vascular smooth muscle hypercontractility, anti-inflammatory action by reducing markers such as hsCRP and IL-6, and reducing oxidative stress by decreasing reactive oxygen species (Jenkins et al., 2024; Rehan et al., 2022).

Thus, the potential of this drug class to reduce the frequency of angina and ischemic events in patients with ASV, including those without significant atherosclerosis, is highlighted (Rehan et al., 2022). In addition, there is also evidence demonstrating its potential to reduce the incidence of infarction in patients with ASV when associated with calcium channel blocker (CCB) therapy (Jenkins et al., 2024).

Antithrombotic therapy in stroke is one of the most controversial points of management, especially when there is no obstructive atherosclerotic disease or history of acute atherothrombotic coronary syndrome. The classical reasoning of the use of antiplatelets in coronary disease does not automatically apply to "pure" stroke, because the primary mechanism is vasomotor and not necessarily thrombotic. In addition, there is biological plausibility for the prospasmogenic effect of aspirin in some scenarios by inhibition of endothelial prostacyclin, although the clinical relevance of this mechanism varies and is not uniform (Lanza et al., 2023; Jenkins et al., 2024).

Recent meta-analyses focused on stroke generally suggest the absence of consistent benefit of aspirin on clinical outcomes when used routinely in stroke patients without significant stenosis, reinforcing that its prescription should be individualized and based on other indications (e.g., established atherosclerotic disease, previous stenting, secondary prevention by another mechanism) (Lin et al., 2021).

In practice, this leads to a pragmatic recommendation: not to prescribe antiplatelets "by default" only for the diagnosis of stroke, but to consider antithrombotics when there are comorbidities and independent indications. This approach is consistent with recent reviews and broad guidelines for chronic coronary disease, which reinforce the indication of antiplatelets according to atherothrombotic risk and clinical history, and not simply due to the presence of ischemic chest pain in a non-obstructive context (Virani et al., 2023).

3.4 THE ROLE OF INFLAMMATION AND FUTURE PROSPECTS

There have been significant advances in the understanding of the pathophysiology of vasospastic angina, with emphasis on the growing interest in the role of inflammation in its pathogenesis. Despite this, important gaps remain. From a clinical point of view, many therapeutic challenges have not yet been overcome, such as the persistence and recurrence of anginal episodes in some patients. In addition, current treatment strategies focus primarily on symptomatic relief, without offering a definitive curative approach. In parallel, although there is evidence suggesting the participation of inflammatory processes in ASV, the underlying mechanisms that connect inflammation and coronary vasospasm are not yet fully elucidated (He et al., 2023).

Recent evidence suggests that ASV can be considered a chronic inflammatory condition of the vascular system. Elevated levels of C-reactive protein (CRP) and proinflammatory interleukins are correlated with disease activity (Hung and Hung, 2023). Exploratory studies indicate that immunomodulatory therapies and the use of magnesium (which acts as a natural calcium channel blocker) may offer additional benefits in patients refractory to conventional treatment (He et al., 2023).

For patients who survive episodes of sudden death or have documented severe ventricular arrhythmias during the spasm, implantation of an implantable cardiodihydribrator (ICD) should be considered, in addition to aggressive medical therapy (Hokimoto et al., 2023; Jenkins et al., 2024).

In this context, future research should prioritize the characterization of systemic and myocardial immunoinflammatory alterations associated with ASV, as well as the identification of the main molecular mechanisms involved in its genesis. From a therapeutic point of view, the development of drugs aimed at modulating the inflammatory response is relevant, in addition to the reevaluation of existing drugs with potential benefit in this condition, supported by experimental evidence and clinical trials. Finally, the investigation of the etiological factors predisposing to coronary spasm, including the possible association with specific viral agents, represents a promising line of research for better understanding and management of the disease (He et al., 2023).

The current understanding of stroke goes beyond smooth muscle "isolated hypercontractility" and incorporates endothelial dysfunction, oxidative stress, activation of inflammatory pathways, and interactions with metabolic and genetic factors. Recent reviews highlight that inflammatory markers and immune imbalance may contribute to

vasomotor instability and clinical phenotype severity, suggesting that inflammation is more than epiphenomenon and may be a causal component in subgroups (Hung & Hung, 2023; He et al., 2023).

This perspective helps to interpret why "pure vasodilator" strategies do not always fully control the disease and why pleiotropic therapies may play a relevant role. In this context, statins stand out not only for lipid control, but for possible endothelial and anti-inflammatory effects. Contemporary real-world evidence suggests an association between statin use and reduced cardiovascular outcomes in patients with coronary spasm, particularly in subgroups without severe stenosis, although limitations inherent in observational studies persist (Lee et al., 2024; Lanza et al., 2023).

On the horizon of precision medicine, genetic studies are also gaining ground. Recent findings have associated specific variants (as in the RNF213 locus) with a higher risk of stroke and severe outcomes, pointing to subgroups with defined biological predisposition and potential future utility of risk stratification, even if routine clinical implementation remains distant (Hikino et al., 2024).

Finally, risk stratification and the prevention of sudden death are critical issues. Patients with a history of aborted cardiac arrest or spasm-associated ventricular arrhythmias constitute a very high-risk subgroup. Recent studies describe the use of implantable cardioverter-defibrillator after resuscitation in selected stroke, reinforcing that, although most patients have a good prognosis with optimized therapy, there is a fraction in which secondary arrhythmia prevention strategies should be discussed in conjunction with strict spasm control (Tateishi et al., 2022).

4 CONCLUSION

It is inferred, therefore, that ASV is a relevant and potentially serious clinical entity, whose management depends on pathophysiological knowledge focused on coronary vasomotor dysfunction and vascular smooth muscle hyperreactivity. Therefore, the present review shows that the diagnosis remains challenging, requiring an association between invasive methods, such as pharmacological provocative testing during catheterization, and complementary strategies, such as outpatient electrocardiographic monitoring.

With regard to therapies, calcium channel blockers (CCBs) are consolidated as the basis of pharmacological treatment, as they act on the central mechanism of vasospasm,

i.e., on the coronary vascular smooth muscle, while nitrates play an adjuvant role in symptomatic control, as they do not act on the central pathophysiology and are more effective in association with CCBs. In addition, the use of beta-blockers is considered, since they do not present scientifically proven benefit, with the possibility of worsening the clinical condition linked to unwanted muscle contraction. As for antithrombotic therapy, it should be individualized for the patient, and the use of ASA is justified especially in the presence of concomitant atherosclerotic disease or in secondary prevention scenarios, as statins have demonstrated additional benefits related to the improvement of endothelial function and inflammatory modulation.

Thus, the future therapeutic perspectives of the anginal patient discussed are expanded, as new evidence of the role of inflammation in the pathogenesis of ASV grows, pointing to approaches that transcend symptomatic relief and act on the underlying molecular mechanisms. Thus, the effective management of vasospastic angina requires a pathophysiologically integrated and individualized approach, competent in reducing the recurrence of episodes, minimizing complications, and improving the patient's prognosis, while, at the same time, the fulcrity of new studies for the future development of more effective stabilizing strategies is highlighted.

Vasospastic angina remains an underdiagnosed and clinically relevant condition, especially in the setting of angina and infarction with non-obstructive coronary arteries. The most important conceptual advance in recent years is the consolidation of an approach centered on vasomotor endotypes, in which the invasive provocative test, when available and safe, allows for a more accurate diagnosis and more rational therapeutic direction. Calcium channel blockers remain a mainstay of treatment, with nitrates as adjuncts, while routine use of antithrombotic therapies, particularly aspirin, is not consistently sustained when there is no independent atherothrombotic indication. Incorporating inflammation and genetic factors into the understanding of the disease paves the way for more personalized future interventions, including pleiotropic strategies and risk stratification models. Thus, the ideal management of stroke requires integration between clinical suspicion, functional diagnosis, and individualized therapy, with special attention to the subgroups of higher arrhythmic risk and to scenarios of etiological uncertainty in MINOCA/ANOCA/INOCA.

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