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INVASIVE THERAPIES FOR REFRACTORY ANGINA: CURRENT PERSPECTIVES

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Abstract: Refractory angina (RA) is a debilitating condition that is difficult to manage clinically, characterized by persistent chest pain associated with myocardial ischemia, even after optimized pharmacological therapy and exhaustion of revascularization options. With a growing prevalence, driven by population aging and an increase in chronic diseases, RA represents a significant challenge, especially in cases with microvascular dysfunction. This paper reviews the main emerging invasive therapies for the treatment of RA, with a focus on the Coronary Sinus Reducer (CSR), which redistributes blood flow to ischemic subendocardial regions. Data from the COSIRA study and multicenter registries demonstrate functional improvement and safety of the CSR, although there is still a need for large-scale validation. Other approaches analyzed include percutaneous coronary intervention (PCI) for chronic total occlusion (CTO), with increasing success rates in specialized centers, and transmyocardial laser revascularization (TMR), whose use has been limited by conflicting results. Neuromodulation and extracorporeal shockwave therapy (ESWT) are also showing promise, especially in patients who are not eligible for conventional therapies, with evidence of improved function and quality of life. We conclude that, given the limitations of traditional therapies and the growth of the RA population, there is an urgent need to expand access to and research into invasive and minimally invasive strategies, promoting an individualized and multidisciplinary approach to the management of this complex condition.

INTRODUCTION

Refractory angina (RA) is a complex clinical condition characterized by persistent and debilitating chest pain associated with myocardial ischemia, which persists despite optimized antianginal therapy and the exclusion of surgical or percutaneous revascularization, according to current clinical guidelines. This is a difficult-to-manage scenario, often referred to as "no therapeutic option", in which patients have severe functional limitations and a significant reduction in quality of life, with high consumption of health resources (LANTZ et al., 2022; RAKHIMOV; GORI, 2020).

The definition of RA has been expanded by cardiological societies to also include patients with ischemia without obstructive CAD (INOCA), reflecting the phenotypic diversity of the condition, such as microvascular angina, diffuse CAD and end-stage disease, broadening the diagnostic and therapeutic challenge for these patients (LANTZ et al., 2022).

The prevalence of RA is likely to increase in the coming decades, driven by population aging, the greater number of survivors after acute ischemic events and the growing number of patients with advanced coronary artery disease (CAD) and multiple comorbidities. (DAMMAN; PIEK, 2021; RAKHIMOV; GORI, 2020) It is estimated that up to 10% of individuals with chronic CAD have symptoms refractory to revascularization and intensive pharmacological treatment, with a direct impact on morbidity, the number of hospitalizations and healthcare costs. (DAMMAN; PIEK, 2021)

The pathophysiology of RA is multifactorial, ranging from complex epicardial obstructions to impaired coronary microvascular function. In many cases, microvascular dysfunction, alone or in combination with epicardial stenosis, contributes significantly to the perpetuation of symptoms. However, most of the available therapeutic approaches have been directed predominantly at obstructive CAD, lacking robust evidence in subgroups with isolated microvascular impairment (RAKHIMOV; GORI, 2020).

Recent studies highlight microvascular dysfunction as a factor present in up to 75% of cases of ischemia without epicardial obstruction, with a relevant prognostic impact and an association with higher cardiovascular mortality (LANTZ et al., 2022).

According to analyses of the REACH (Reduction of Atherothrombosis for Continued Health) registry, patients with RA are elderly with a mean age of 68.5 ± 8.7 years, have comorbidities such as diabetes mellitus (42% versus 29% in patients with non-refractory angina, $p<0.001$) and peripheral arterial disease (27% versus 11%, $p<0.001$), as well as a more frequent history of previous revascularizations (CHEN et al., 2021). In addition, the frequency of the disease by gender differs from the classic pattern of CAD, with a higher incidence in women (approximately 40%), many of whom have microvascular dysfunction as the predominant mechanism (GALLONE et al., 2020).

Coronary microvascular dysfunction (CMD) is an important feature in approximately 60-70% of RA patients, especially those with ischemia without obstructive coronary artery disease (INOCA). CMD is characterized by structural and functional changes in the coronary microcirculation, including hypertrophic arteriolar remodeling, capillary rarefaction and endothelial dysfunction (FORD et al., 2020). At the molecular level, there is a reduction in the bioavailability of nitric oxide (NO), an increase in the production of reactive oxygen species (ROS) and an increase in inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which compromise endothelium-dependent vasodilation (KUNADIAN et al., 2021).

In recent decades, therapeutic alternatives have emerged with the aim of restoring myocardial perfusion or modulating anginal pain mechanisms, especially in individuals ineligible for conventional revascularization. These therapies include interventions such as external counterpulsation, extracorporeal shock wave therapy, neuromodulation, autologous cell therapy and coronary sinus constriction, the latter performed using a device known as the Coronary Sinus Reduction System (CSRS) (DAMMAN; PIEK, 2021).

The recognition of new minimally invasive approaches has broadened the spectrum of options for patients with "angina without options", with promising results in clinical studies and multicenter registries, although still limited by a lack of standardization and unequal access (RAKHIMOV; GORI, 2020).

The CSRS acts by promoting an increase in coronary venous pressure, generating a hemodynamic gradient that favors the redistribution of blood flow to more ischemic subendocardial areas. Although the physiological mechanism has not been fully elucidated, it is believed that partial occlusion of the coronary sinus promotes this perfusion redistribution, with consequent symptomatic relief in patients with RA (DAMMAN; PIEK, 2021).

Data from the COSIRA study showed improvement of ≥2 functional classes of angina in 35% of patients undergoing CSRS, compared to 15% in the placebo group ($p = 0.024$). In addition, real-world registries show a clinical response rate of over 70% and high safety of the procedure (DAMMAN; PIEK, 2021; RAKHIMOV; GORI, 2020).

In addition to the COSIRA study, data from "real-world" registries reinforce the efficacy of CSRS in broader populations with greater clinical complexity. In a multicenter registry carried out in the Netherlands, involving 132 patients treated with CSRS between 2014 and 2020, it was observed that 67% showed improvement in at least one CCS class and 34% improved two classes. These results were obtained even with a substantial proportion of patients using more than three antianginal agents, which demonstrates the applicability of the device in more severe and refractory cases. It is important to note that the procedure was successful in 99% of cases, with minimal complications and no significant ischemic events in long-term follow-up (DAMMAN; PIEK, 2021).

Another emerging issue is the exploration of neuromodulation, especially spinal cord stimulation, as a complementary strategy in the management of RA. Preliminary studies have shown a significant improvement in quality of life and a reduction in anginal pain, making it a viable alternative for patients ineligible for conventional therapies. However, controlled clinical trials are needed to validate its long-term efficacy and safety (RAKHIMOV; GORI, 2020).

Faced with the challenge posed by RA and the limitations imposed by conventional therapies, it is imperative to critically review the available invasive alternatives in the light of the latest evidence, with a view to broadening the therapeutic range and offering better clinical prospects for this neglected population (DAMMAN; PIEK, 2021; LANTZ et al., 2022; RAKHIMOV; GORI, 2020).

METHODOLOGY

The aim of this study is to summarize the most recent and relevant information on the diagnosis of refractory angina, taking into account the current perspectives in the scientific literature. To this end, a structured search was carried out in the PubMed database, including publications from the last five years. The selection of studies was based on a combination of the following descriptors: *"Refractory angina"*, *"Diagnosis"* and *"Treatment"*, with the aim of broadly and specifically covering the productions related to the topic.

Included in the analysis were articles published in the last five years that directly or indirectly addressed the diagnosis of refractory angina, available in full in the database consulted, regardless of language, as long as they presented thematic pertinence, methodological clarity and scientific relevance. Original studies, narrative reviews and update articles were accepted, both in English and in other languages, as long as they were accessible and understandable. Exclusion criteria included duplicate publications, articles not related to the scope of the research and studies unavailable on the PubMed database.

RESULTS AND DISCUSSION

Refractory angina (RA) remains a significant therapeutic challenge, especially in patients with advanced coronary artery disease (CAD). Invasive approaches have shown promise in relieving symptoms and improving quality of life, especially in cases where drug therapy is no longer effective. Among the emerging strategies, the use of coronary sinus reduction (CSR) devices has attracted increasing attention. The concept of increasing coronary sinus pressure was first explored by Beck et al. in the 1950s, and the technique has since been refined through the development of the CSR. The device, a balloon-expandable mesh, aims to create a focal stenosis in the coronary sinus, redistributing blood flow from the less ischemic epicardium to the subendocardial layers, where ischemia is more pronounced. Although the technique has shown promising results, with documented improvements in angina functional class and quality of life, efficacy data are still limited and require further studies, such as the COSIRA study, which demonstrated a significant reduction in angina functional class after six months of treatment. In addition, the CSR device has shown a good safety profile in several studies, with minimal complications and a high success rate in well-selected patients. However, the device has not been approved for use in the United States, despite evidence of safety and efficacy in studies carried out outside the USA (RAKHIMOV; GORI, 2020).

Studies using optical coherence tomography (OCT) and intravascular ultrasound (IVUS) have concluded that even patients with RA and obstructive CAD often have microvascular alterations, configuring a pathophysiological "double whammy". In these cases, coronary flow reserve (CFR) is significantly reduced (mean 1.6 ± 0.4 versus normal values >2.5), even after successful revascularization of epicardial lesions (FORD et al., 2020).

Other invasive therapies, such as percutaneous coronary intervention (PCI) for chronic total occlusion (CTO), have also been explored for RA patients. CTO treatment has advanced considerably, with recanalization success rates of up to 90% in specialized centers. PCI of CTO is recommended for patients with a large documented ischemic burden, who remain symptomatic despite optimized drug therapy. Long-term results, such as improved angina and increased quality of life, have shown that CTO PCI can be an effective intervention for patients who are ineligible for surgical revascularization. The DECISION CTO study, which randomized patients to CTO PCI versus a strategy without PCI, found no significant differences in major adverse events (MACE) between the groups, although both showed improvements in quality of life. This suggests that CTO PCI may be beneficial in reducing symptoms, although the benefits were not substantially superior to those of patients who did not undergo the intervention. However, like any invasive procedure, CTO PCI also has risks, such as myocardial infarction, perforation and embolism, which should be carefully considered when selecting patients (LANTZ et al., 2022).

Transmyocardial Laser Revascularization (TMR) has also been proposed as an approach to treating RA, with the aim of improving myocardial perfusion by creating transmural channels in the ischemic myocardium. Although it has shown some promise in previous clinical trials, recent results suggest that percutaneous TMR has no benefits in terms of reducing angina or increasing exercise time, with some studies showing increased morbidity. Therefore, enthusiasm for this technique has waned considerably, and it is no longer widely used, except in specific situations, such as in combination with coronary artery bypass grafting (CABG) in some cases in the USA. Surgical TMR, on the other hand, remains a viable option, albeit with high risks for patients with low ejection fraction or recent infarction, and is not recommended in most countries (RAKHIMOV; GORI, 2020).

The effectiveness of invasive therapies in the management of RA, however, depends on proper patient management and a trained multidisciplinary team. There is evidence that a multidisciplinary team approach, involving cardiologists, thoracic surgeons, cardiovascular imaging specialists and cardiac rehabilitation, can significantly improve clinical outcomes in patients with RA. This holistic approach not only treats the mechanical aspects of the disease, but also addresses critical issues such as modifying risk factors and managing comorbidities such as depression, which often affects these patients. Therefore, the ideal treatment of RA involves a combination of optimized pharmacological therapies, invasive revascularization strategies and continuous attention to the patient's psychological and functional well-being. (LANTZ et al., 2022)

CONCLUSION

The temporal evolution of the prevalence of refractory angina (RA) reveals a relevant paradox: despite advances in revascularization therapies and in the pharmacological management of coronary artery disease (CAD), there has been a proportional increase in the number of patients affected by RA. This phenomenon can be explained by various factors, such as the ageing of the population, increased survival after myocardial infarction, the higher incidence of conditions such as diabetes and chronic kidney disease, as well as an improvement in the identification of specific phenotypes, such as microvascular angina (VIRANI et al., 2023). Epidemiological projections indicate that the global prevalence of RA is expected to grow between 25% and 30% by 2030, reinforcing the urgency of developing innovative therapeutic strategies and structured care programs (GALLONE et al., 2020).

In this context, extracorporeal shock wave therapy (ESWT) has emerged as a promising, minimally invasive and safe alternative. This approach consists of applying low-intensity waves to the ischemic myocardium, promoting angiogenesis and improving coronary perfusion. Clinical studies have shown significant improvements in symptoms, functional capacity and quality of life, with a low incidence of adverse effects. OCT is especially relevant for patients ineligible for conventional revascularization, offering an effective therapeutic option in the management of RA. (ZHAO, Y. X., et al., 2021)

On the other hand, although the coronary sinus device (CSR) has therapeutic potential, current studies still have methodological limitations that restrict its definitive clinical validation, highlighting the need for greater investment in high-quality research. Percutaneous transmyocardial revascularization (percutaneous TMR) also lacks robust evidence to

confirm its benefits, which requires further investigation. On the other hand, percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) has shown good results, especially in patients who are not candidates for surgery, consolidating itself as a relevant alternative in the therapeutic arsenal.

Faced with the scenario of a continuous increase in the prevalence of RA and the limitation of traditional therapeutic options, it is essential to increase investment in research and innovation. The validation of invasive and minimally invasive approaches must be a priority in order to optimize the treatment of this complex and debilitating condition.

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