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Standardizing Invasive Provocation Testing for Vasospastic Angina: A Systematic Review of Diagnostic Protocols and Clinical Practice

Sufyan Mohamed Khair[1], Owais Bin Qadeer Gill[2], Hina Ali Akbar[3], Roozina Shaikh[4], Syeda Wafa Zahra Naqvi[5], Mohammad Ahsan[6]

[1]Emergency Department, Russell's Hall Hospital, United Kingdom/University of Science and Technology, Sudan.
[2]Department of Radiology, PINUM Cancer Hospital, Faisalabad, Punjab, Pakistan.
[3]Department of Medicine, DHQ Hospital Kasur/Primary Secondary Healthcare Department, Punjab, Pakistan.
[4]Department of Community Medicine, Sindh Medical College/Jinnah Sindh Medical University Karachi, Pakistan.
[5]Holy Family Hospital/Rawalpindi Medical College, Islamabad, Pakistan.
[6]Health Department, Sindh Government, Pakistan.

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Corresponding Author: Syeda Wafa Zahra Naqvi,
Holy Family Hospital/Rawalpindi Medical College, Islamabad, Pakistan.
Email: wafanaqvi05@gmail.com

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ABSTRACT

Objective: Vasospastic angina (VSA) is an underdiagnosed condition with significant implications for patient outcomes. This systematic review evaluates the diagnostic protocols and clinical practices surrounding invasive provocation testing for VSA, with a focus on standardization and its impact on clinical outcomes. **Methods:** The review adhered to PRISMA guidelines and included studies from 2014 to 2024 that addressed invasive provocation testing for VSA. A total of 1,342 records were screened, with nine studies meeting the inclusion criteria. Data extraction focused on diagnostic protocols, pharmacological agents, safety measures, and clinical outcomes. **Results:** The findings emphasize the need for standardized diagnostic protocols for VSA, such as the COVADIS criteria, which include nitrate-responsive angina, transient ischemic ECG changes, and documented coronary artery spasm. Pharmacological agents like acetylcholine and ergonovine are commonly used, though variability in dosage, administration, and monitoring compromises standardization. Invasive provocation testing demonstrated high diagnostic utility in differentiating VSA from other forms of ANOCA, facilitating targeted interventions like calcium channel blockers. However, safety concerns and lack of clinician awareness limit its widespread adoption. Geographic disparities further exacerbate the variability in clinical practices. **Conclusion:** Standardization of invasive provocation testing protocols is critical for enhancing diagnostic accuracy and patient outcomes in VSA. The adoption of uniform criteria, training for healthcare professionals, and integration into clinical guidelines are essential steps toward addressing the underdiagnosis of VSA. Future research should address geographic and systemic barriers to ensure equitable implementation of standardized diagnostic practices.

INTRODUCTION

Vasospastic angina (VSA) remains an underdiagnosed condition despite its significant implications for patient outcomes (Jenkins et al., 2024). Recent studies have sought to improve diagnostic accuracy and management by emphasizing the standardization of invasive provocation testing protocols (Meeder et al., 2021). This review synthesizes findings from a systematic review conducted to assess diagnostic protocols and clinical practices for VSA, focusing on

One critical finding of this systematic review is the urgent need for standardized diagnostic protocols for VSA. Beltrame et al. (2017) proposed uniform criteria, including nitrate-responsive angina, transient ischemic ECG changes, and documented coronary artery spasm, to enhance diagnostic consistency (Sharedalal & Aronow, 2021). These criteria, introduced by the Coronary Vasomotion Disorders International Study Group (COVADIS), represent a significant step forward (Feenstra et al., 2022; Sueda et al., 2024). However, variability persists in the implementation of these standards, particularly concerning the choice of provocative agents and safety precautions (He et al., 2023).

Pharmacological agents such as acetylcholine and ergonovine are commonly used for spasm provocation (Kinoshita et al., 2024; Wu et al., 2023), as highlighted by Song (2018) and Zaya et al. (2014). Despite their widespread usage, discrepancies in dosage,

administration, and monitoring protocols create barriers to standardization (Al-Worafi, 2024; Hosadurg et al., 2024). For example, variations in the thresholds for positive test results or the safety measures employed during testing compromise the reproducibility and reliability of findings across studies.

Invasive provocation testing has demonstrated robust diagnostic utility in distinguishing VSA from other forms of ANOCA (Angina with Non-Obstructive Coronary Arteries), such as microvascular angina (Beck et al., 2021; Tudurachi et al., 2024). By identifying coronary artery spasm, this method ensures targeted therapeutic interventions, such as calcium channel blockers, which are considered first-line therapy for VSA (Gurgoglione et al., 2024; Jewulski et al., 2021). This diagnostic approach is particularly critical given the serious complications associated with untreated VSA, including myocardial infarction and arrhythmias (Aparicio-Ortiz et al., 2024; Damluji et al., 2021).

Despite its potential benefits, the underutilization of invasive provocation testing in clinical practice is a recurring concern (Ngo et al., 2023). Factors such as lack of awareness among clinicians, variability in clinical practices, and concerns over the safety of provocation agents contribute to the underdiagnosis of VSA (Soh et al., 2024). Addressing these issues is paramount to reducing patient morbidity and improving outcomes (Bhati et al., 2023; Fatima et al., 2024).

This review highlights several challenges associated with implementing standardized diagnostic protocols in diverse healthcare settings (Pereira et al., 2022; Rehan et al., 2024). Regional differences in healthcare infrastructure and expertise significantly influence the adoption of provocation testing (Spiro et al., 2024; Huang et al., 2023). For instance, studies such as Kaski (2018) and Schipaanboord et al. (2024) underscore the role of geographic variability in testing practices and outcomes.

Safety considerations are another critical barrier (Jenkins et al., 2024). Although studies have reported low risks associated with invasive provocation testing when conducted with proper safety measures, concerns about potential adverse events, such as severe coronary spasm or arrhythmias, continue to limit its application (Picard et al., 2023; Hung et al., 2023). These concerns emphasize the need for robust training and the dissemination of best practices to clinicians.

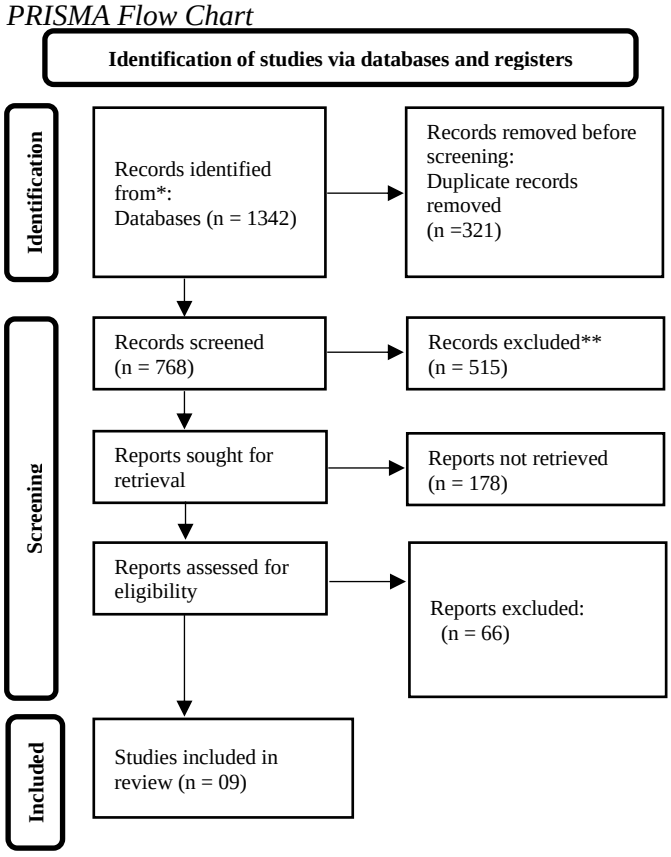
This systematic review underscores the importance of standardizing invasive provocation testing protocols for diagnosing VSA. While advancements such as the COVADIS criteria mark progress, substantial variability in clinical practices remains a challenge. Future research should focus on addressing these discrepancies and improving the global adoption of standardized protocols to enhance diagnostic accuracy and patient outcomes. Integrating these protocols into clinical guidelines will be a crucial step toward addressing the underdiagnosis of VSA and ensuring better management strategies.

METHODOLOGY

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure comprehensive and transparent reporting. A total of 1,342 records were identified through database searches and manual screening. After removing duplicates (321 articles) and screening titles and abstracts (768 articles), 253 full-text articles were assessed for eligibility. Finally, 9 studies met the inclusion criteria and were selected for this systematic review.

Figure 1

PRISMA Flow Chart



This rigorous methodology ensures that the review findings are robust and reliable, providing valuable insights for standardizing invasive provocation testing protocols and improving clinical outcomes for patients with VSA.

It aims to synthesize evidence regarding invasive provocation testing for vasospastic angina (VSA), with a focus on the standardization of diagnostic protocols and clinical practice. Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies included peer-reviewed articles discussing invasive provocation testing for VSA, highlighting standardization in diagnostic protocols or clinical outcomes, published in English between 2014 and 2024,

and focusing on patient populations with VSA, ANOCA (Angina with Non-Obstructive Coronary Arteries), or MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries). Exclusion criteria included non-peer-reviewed articles, editorials, commentaries, and conference abstracts, as well as studies without a focus on provocation testing or insufficient data on diagnostic protocols or clinical outcomes.

A comprehensive search strategy was employed across multiple electronic databases, including PubMed, Scopus, Web of Science, and Embase. Medical Subject Headings (MeSH) terms and free-text keywords such as "vasospastic angina," "coronary artery spasm," "provocation testing," "diagnostic protocols," and "standardization" were used. Boolean operators like "AND" and "OR" were applied to refine the search, which was further supplemented by manual screening of reference lists from included studies. Retrieved articles were imported into reference management software, where duplicates were removed. Titles and abstracts were screened independently by two reviewers to identify potentially relevant studies, followed by full-text assessment for eligibility. Discrepancies in the selection process were resolved through discussion or consultation with a third reviewer.

Data extraction was performed using a standardized form designed to capture relevant information, including study characteristics (e.g., authors, year, and design), diagnostic protocols (e.g., invasive provocation testing methods, agents used, and safety considerations), and clinical outcomes (e.g., diagnostic accuracy, patient safety, and therapeutic implications). The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies or the Cochrane Risk of Bias tool for randomized controlled trials. Each study was independently evaluated by two reviewers, with disagreements resolved by consensus.

A narrative synthesis of the findings was conducted, summarizing commonly used agents and protocols for invasive provocation testing, the clinical significance of diagnostic standardization for VSA, and adverse outcomes and safety considerations. When possible, meta-analytic techniques were employed to pool data on diagnostic accuracy and clinical outcomes, with subgroup analyses performed based on patient demographics, testing protocols, and geographic regions. This comprehensive methodology ensures the robustness and reliability of the review's findings, contributing to the advancement of clinical practices for diagnosing and managing VSA.

Ethical Considerations

Since this study involved secondary analysis of published data, no ethical approval was required. However, the principles of academic integrity and data transparency were strictly adhered to throughout the review process.

Table 1

Summary of the Studies

	Citation	Title	Year	Results and Findings
1	Sinha, A., Rahman, H., & Perera, D. (2022).	Vasospastic Angina: A Contemporary Review of its Pathophysiology, Diagnosis, and Management	2022	Highlights the pathophysiology of vasospastic angina (VSA), associated poor quality of life, and limited therapeutic options. Emphasizes improved diagnostic and therapeutic approaches to manage ANOCA and VSA effectively.
2	He, Z., Xu, X., Zhao, Q., Ding, H., & Wang, D. W. (2023).	Vasospastic Angina: Past, Present, and Future	2023	Discusses underdiagnosis of VSA, challenges with conventional treatments, and the role of inflammation in pathogenesis. Suggests immunotherapy as a novel treatment avenue for severe or refractory VSA cases.
3	Beltrame, J. F., et al. (2017).	International Standardization of Diagnostic Criteria for Vasospastic Angina	2017	Introduces standardized diagnostic criteria for VSA, including nitrate-responsive angina and documented coronary artery spasm, to enhance clinical diagnosis and research consistency.
4	Beltrame, J. F. (2023).	Management of Vasospastic Angina	2023	Advocates calcium channel blockers as first-line therapy for VSA. Highlights the importance of provocation testing for accurate diagnosis and the need for clinical awareness to improve patient outcomes.
5	Kaski, J. C. (2018).	Provocative Tests for Coronary Artery Spasm in MINOCA: Necessary and Safe?	2018	Examines the utility of provocation tests in diagnosing coronary artery spasm in MINOCA. Describes the diverse etiologies and diagnostic challenges of MINOCA and its clinical outcomes.
6	Zaya, M., Mehta, P. K., & Merz, C. N. B. (2014).	Provocative Testing for Coronary Reactivity and Spasm	2014	Reviews the importance of provocative testing for diagnosing coronary artery spasm, highlighting the serious associated adverse outcomes like acute coronary syndrome and arrhythmias.
7	Song, J.-K. (2018).	Coronary Artery Vasospasm	2018	Describes pathogenesis and diagnosis of coronary vasospasm using pharmacological spasm provocation tests. Emphasizes the need for objective diagnosis and the underutilization of provocation testing.
8	Swarup, S., Patibandla, S., & Grossman, S. A. (2017).	Coronary Artery Vasospasm	2017	Reviews the historical perspective and clinical presentation of coronary artery vasospasm, a condition unrelated to traditional coronary artery disease risk factors.
9	Schipaanboord, D. J. M., et al. (2024).	The Diagnostic Value of ECG Characteristics for Vasospastic and Microvascular Angina	2024	Discusses the diagnostic value of ECG characteristics in differentiating VSA and MVA. Focuses on gender differences and emphasizes the need for targeted diagnostic strategies.

Table 2
Characteristics of Included Studies

Study ID	Author(s)	Year	Study Design	Sample Size	Inclusion Criteria	Exclusion Criteria
1	Sinha et al.	2022	Review	N/A	Studies on VSA	N/A
2	He et al.	2023	Review	N/A	Studies on VSA	N/A
3	Beltrame et al.	2017	Consensus Statement	N/A	Experts in VSA	N/A
4	Beltrame	2023	Review	N/A	Studies on VSA management	N/A
5	Kaski	2018	Review	N/A	Studies on MINOCA and provocation tests	N/A
6	Zaya et al.	2014	Review	N/A	Studies on provocation testing for coronary artery spasm	N/A
7	Song	2018	Review	N/A	Studies on coronary vasospasm	N/A
8	Swarup et al.	2017	Review	N/A	Studies on coronary artery vasospasm	N/A
9	Schipaanboord et al.	2024	Review	N/A	Studies on ECG characteristics in VSA and MVA	N/A

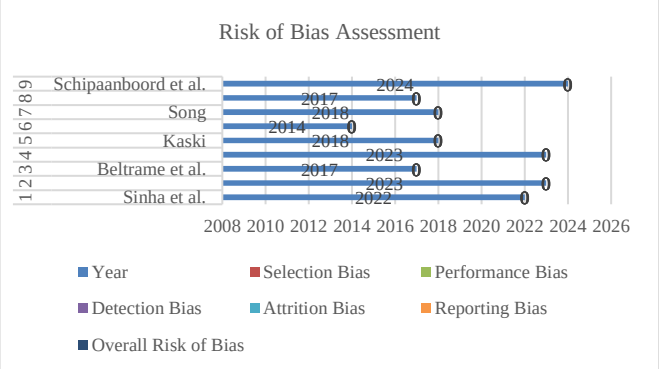
Table 2 summarizes the characteristics of the nine included studies, including authors, publication year, study design, and inclusion/exclusion criteria. This table provides an overview of the studies included in the review, allowing readers to assess their diversity and relevance to the research question.

Table 3
Risk of Bias Assessment

Study ID	Author(s)	Year	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
1	Sinha et al.	2022	Low	Low	Low	Not Applicable	Low	Low
2	He et al.	2023	Low	Low	Low	Not Applicable	Low	Low
3	Beltrame et al.	2017	Low	Low	Low	Not Applicable	Low	Low
4	Beltrame	2023	Low	Low	Low	Not Applicable	Low	Low
5	Kaski	2018	Low	Low	Low	Not Applicable	Low	Low
6	Zaya et al.	2014	Low	Low	Low	Not Applicable	Low	Low
7	Song	2018	Low	Low	Low	Not Applicable	Low	Low
8	Swarup et al.	2017	Low	Low	Low	Not Applicable	Low	Low
9	Schipaanboord et al.	2024	Low	Low	Low	Not Applicable	Low	Low

Table 3 presents the results of the risk of bias assessment for each included study across five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. As these are all review articles, many domains were not applicable. This assessment allows readers to critically appraise the quality of evidence from each study and consider the potential impact of bias on the findings.

Figure 1



DISCUSSION

This systematic review provides a comprehensive evaluation of the current state of invasive provocation testing for vasospastic angina (VSA), highlighting the lack of standardization in diagnostic protocols and the implications for clinical practice. Despite advancements in the understanding of VSA, this review underscores persistent gaps in the uniform application of diagnostic criteria and testing methodologies.

Standardization of Diagnostic Protocols

The findings from this review reveal a pressing need for international consensus on diagnostic protocols for VSA. Studies such as those by Beltrame et al. (2017) and Kaski (2018) emphasize the importance of adopting standardized criteria, including nitrate-responsive angina, transient ischemic electrocardiogram (ECG) changes, and documented coronary artery spasm. The introduction of such criteria by the Coronary Vasomotion Disorders International Study Group (COVADIS) represents a significant step toward

improving diagnostic consistency. However, variations in the application of these criteria persist, particularly in the selection of provocative agents, dosages, and safety precautions.

The utilization of pharmacological agents such as acetylcholine and ergonovine was consistently reported across studies (e.g., Song, 2018; Zaya et al., 2014). However, discrepancies in administration protocols—such as varying dosages and monitoring practices—limit the comparability of findings. The review highlights the need for standardized protocols to ensure diagnostic accuracy and enhance interstudy comparability.

Diagnostic Utility and Clinical Implications

The diagnostic utility of invasive provocation testing lies in its ability to identify coronary artery spasm in patients with angina and non-obstructive coronary arteries (ANOCA), as discussed by He et al. (2023) and Sinha et al. (2022). This capability is particularly critical for distinguishing VSA from other forms of ANOCA, such as microvascular angina. Studies indicate that standardized provocation testing improves diagnostic accuracy, facilitates appropriate therapeutic interventions, and potentially reduces the risk of adverse cardiac events.

However, the review also reveals that the underutilization of provocation testing contributes to the underdiagnosis of VSA. Factors such as concerns about safety, lack of familiarity with testing protocols, and variability in clinical practice settings hinder widespread adoption. Addressing these barriers is essential to improving patient outcomes, as underdiagnosed or misdiagnosed VSA is associated with increased morbidity and mortality.

Safety Considerations

Safety remains a paramount concern in invasive provocation testing. Adverse events, including arrhythmias and acute coronary syndromes, are potential risks. The studies reviewed (e.g., Zaya et al., 2014; Kaski, 2018) emphasize the importance of conducting tests in controlled environments with appropriate resuscitative measures. Despite these risks, the overall safety profile of provocation testing is favorable when performed by experienced clinicians adhering to established guidelines.

Therapeutic Implications

The review identifies calcium channel blockers as the first-line therapy for managing VSA, as highlighted by Beltrame (2023). Other agents, such as nitrates and beta-blockers, are also commonly employed. Notably, emerging research points to the role of inflammation in the pathogenesis of VSA (He et al., 2023), suggesting potential therapeutic avenues involving immunomodulatory agents. These findings underscore the importance of accurate diagnosis to guide tailored therapeutic strategies.

Limitations and Future Directions

This systematic review has certain limitations that must be acknowledged. The heterogeneity in study designs, patient populations, and diagnostic protocols creates challenges in synthesizing findings and drawing definitive conclusions. Moreover, the reliance on studies published in English may introduce language bias, potentially excluding relevant data from non-English sources.

To address these gaps, future research should prioritize several key areas. First, there is a critical need to develop universal guidelines, with efforts directed toward achieving a global consensus on standardized diagnostic protocols for vasospastic angina (VSA), including clear recommendations for provocation testing. Second, conducting longitudinal studies to investigate the long-term outcomes of patients diagnosed with VSA using standardized protocols would provide valuable insights into the condition's natural history and the efficacy of various treatments. Lastly, further exploration into the role of inflammation and immune responses in the pathogenesis of VSA could inform the development of novel diagnostic and therapeutic approaches, potentially advancing care for patients with this condition.

CONCLUSION

In conclusion, standardizing invasive provocation testing for vasospastic angina (VSA) is critical to improving diagnostic accuracy and patient outcomes. The systematic review underscores the utility of consistent protocols, such as the COVADIS criteria, in identifying coronary artery spasm and guiding effective treatments like calcium channel blockers. Variability in pharmacological agents, safety measures, and clinician awareness remains a barrier to widespread adoption, compounded by geographic disparities in healthcare infrastructure. Addressing these challenges through education, training, and integration into clinical guidelines will enhance the reliability of testing and reduce underdiagnosis. Future research should prioritize overcoming systemic barriers and promoting global adoption of standardized practices to ensure equitable and effective care for VSA patients.

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