

Systematic Review

Modifiable risk factors of vasospastic angina: a systematic literature review

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ABSTRACT

Vasospastic angina is caused by transient coronary spasms unrelated to exertion, which may even occur at rest (classically at night) and promptly responds to short acting nitrates. It is thought to be caused by inherent generalised hyper reactivity of the smooth muscle cells of epicardial vessels to various stimuli. Being comparatively less studied, the risk factors for VSA vary considerably from obstructive or atherosclerotic cardiac disease. However, coronary vasospasm can occur in non stenosed arteries, atherosclerotic arteries as well as sub critically stenosed arteries which can result in significant overlap between the risk factors and underlying pathophysiology. 1-14% of AMI can be caused by non-obstructive, or 'functional' coronary artery disorders like vasospastic angina but VSA continues to be underdiagnosed and less well understood than obstructive coronary artery disorders. This prompted us to study the existing literature for modifiable risk factors of coronary artery vasospasm so that an emphasis can be made on proper lifestyle modifications and avoidance of vasospastic agents in susceptible individuals. Smoking proved to be the most important risk factor whereas recreational drugs and drugs used for treatment of certain medical disorders have also been shown to associate with coronary vasospasm. Medical personnel, therefore, need to be more vigilant in history taking as well as investigating cardiac chest pain in which traditional investigations end up being normal so that an early diagnosis of vasospastic angina can be made and appropriate steps taken to improve the quality of life of patients.

Keywords: Coronary artery spasm, Vasospastic angina, Variant angina, Prinzmetal angina

INTRODUCTION

Vasospastic angina, described by Prinzmetal and his colleagues in 1959 against the commonly known classic

angina described by Heberden, and thereafter referred to as variant angina is angina caused by transient coronary spasms unrelated to exertion, which may even occur at rest (classically at night) and promptly responds to short acting

nitrate.^{1,2} Due to the vast diversity in the presentation of patients with vasospastic angina, the Coronary Vasomotion Disorders International Study group (COVADIS) specified a diagnostic criteria consisting of three components, 'nitrate-responsive angina, transient ischemic electrocardiographic (ECG) changes in the absence of obvious causes for increased myocardial oxygen demand, and angiographic evidence of coronary artery spasm.³

Vasospastic angina is thought to be caused by inherent generalised hyper reactivity of the smooth muscle cells of epicardial vessels to various stimuli as well as microvascular dysfunction and endothelial dysfunction.⁴⁻⁷ Coronary vasospasm can occur in non stenosed arteries, atherosclerotic arteries as well as sub critically stenosed arteries which can make it challenging to study the underlying pathophysiology of coronary vasospasm.⁸ Moreover, non-obstructive causes of cardiac insult can include non-cardiac causes like renal impairment to myocardial disorders like Takotsubo syndrome.⁹

Obstructive or structural cardiac disease has received extensive medical attention throughout history which has resulted in a tremendous body of knowledge about the guidelines, screening and management of obstructive coronary artery disease. Functional cardiac disorders, on the other hand, have not been so fortunate. And patients with functional cardiac disorders, given the transience of symptoms, are not only underdiagnosed but have also been categorised as psychoneurotic patients at times.¹⁰ Consequence being the under popularity of provocative testing for ruling out or diagnosing vasospastic angina in patients with cardiac chest pain.

The predominant proportion of acute MI patients have obstructive coronary artery disease (CAD) which classically, does not go undiagnosed. However, 1-14% of AMI can be caused by non-obstructive, or 'functional' coronary artery disorders like vasospastic angina. Not only has the functional aetiology been less studied, but the risk factor and triggers for it vary considerably from atherosclerotic or obstructive cardiac disease sometimes, to the extent that it resembles the profile of non-cardiac patients.^{11,12}

Traditionally vasospastic angina was considered relatively benign with a good prognosis but it is increasingly becoming clear that it might not be the case.¹³ Vasospastic angina can result in a myriad of adverse cardiac events in the absence of flow limiting structural coronary artery lesions. These can range from myocardial infarction and life threatening arrhythmias to syncope and presyncope.¹⁴ Given, vasospastic angina, if untreated can also be potentially fatal, resulting in cardiac arrest and sudden that death.¹⁵ It is therefore, paramount to determine the impact of modifiable risk factors for vasospastic coronary artery disease to work on early diagnosis and lifestyle

modification. Modifiable risk factors are the ones that can be prevented from occurring by life style modifications including Exercise, appropriate control of weight and avoidance of smoking.¹⁶ This article will focus on the modifiable risk factors for Vasospastic angina (VSA), also known as Prinzmetal angina and variant angina, which is an important functional cardiac disorder causing significant cardiac morbidity and mortality.

METHODS

Search strategy for this systematic literature review, we developed a search strategy to identify relevant literature. This search strategy was tailored for two databases: PubMed and Google Scholar and the search terms used were the following 'Vasospastic angina' OR 'coronary vasospasm' OR 'coronary artery spasm' OR 'coronary spasm' OR 'Prinzmetal angina' OR 'variant angina' OR 'angina pectoris'. All searches spanned from database inception till 2020, and included journal articles, review papers, case reports and literature reviews.

Selection criteria the selection criteria were based on the PRISMA statement. The search mainly focused on mapping the existing literature on vasospastic angina with regards to modifiable risk factors. The search span was from year 1959 to 2020. All articles before 1959 were excluded from the search. The search was mainly focused on the modifiable risk factors only. Thus, any articles on non-modifiable risk factors were excluded. A total of 299 articles were searched and after exclusion a total of 23 articles were extracted for this systemic literature review.

Quality assessment the study is based only on original case reports, research articles and literature reviews. For maintaining the quality of the review, all duplications were checked thoroughly. Abstracts of articles were checked deeply for analysis and purification of the articles to ensure the quality and relevance of academic literature included in the review process. A careful evaluation of each research paper was carried out at a later stage.

Only studies on human coronary vasospasm were included which resulted in exclusion of one paper on Guinea pigs. Furthermore, after the filtration of duplicate records, 6 more articles were removed from the study. We selected 23 articles after assessing each article on the aforementioned inclusion and exclusion criteria. Figure 1 shows the literature inclusion and exclusion at every stage (PRISMA statement)

Data extraction in the data extraction phase, 23 articles were selected and the characteristics extracted were: articles must be original paper, review paper and case reports, article must be on modifiable risk factors for coronary artery spasm. Papers on non-modifiable factors like ethnicity and genetics were excluded, extracted articles were published between 1959 and 2020.

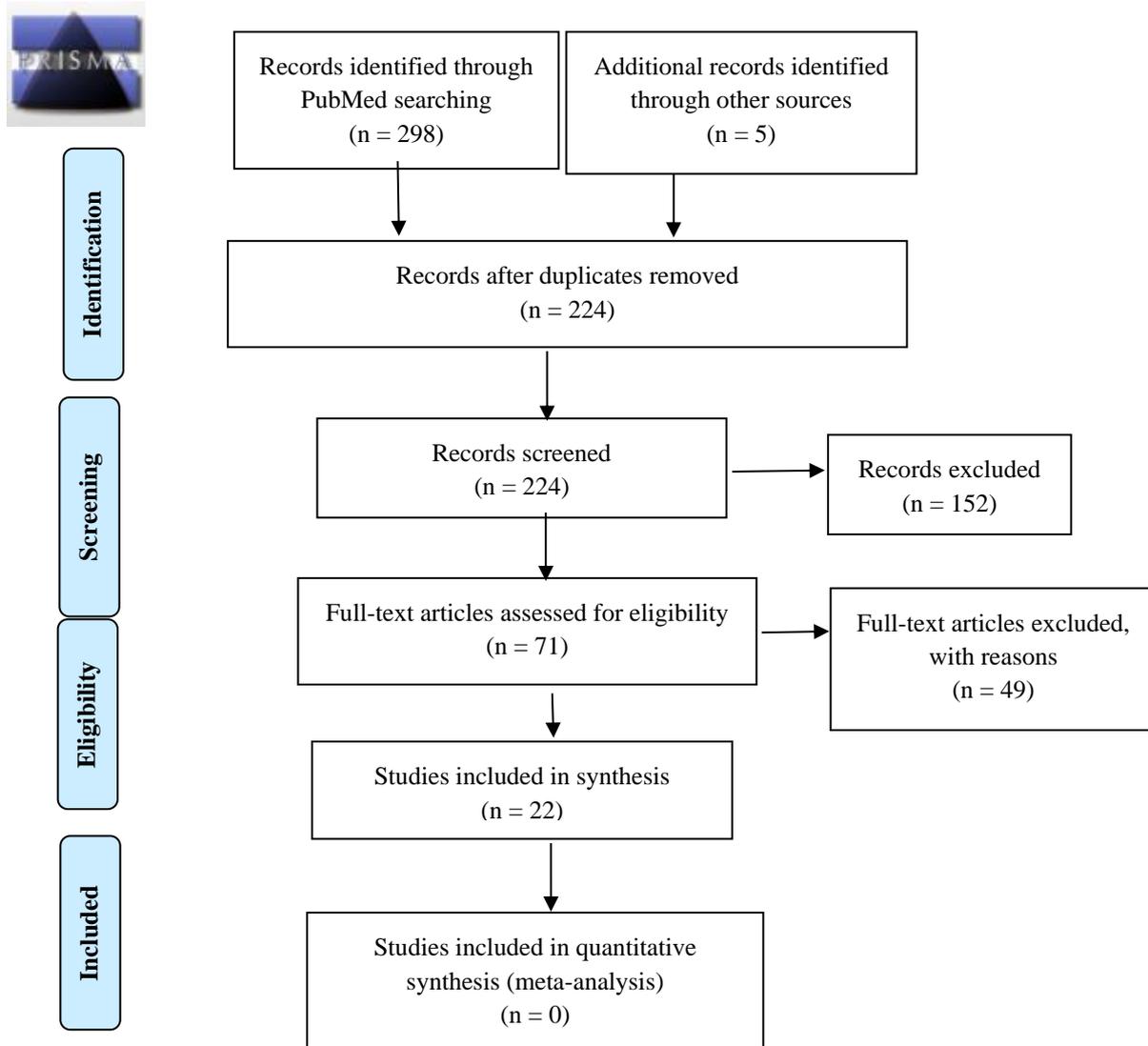


Figure 1: PRISMA flow chart.

RESULTS

The literature search revealed 303 potentially suitable publications (Figure 1). A total of 152 publications (50.1%) were excluded because they reported on treatment/ management/ diagnosis of vasospastic angina (exclusion criteria); another 79 studies (26%) were excluded because they were duplicates, and 49 articles (16.1%) were excluded because they reported on non-modifiable risk factors or full text article was not available. Lastly, one (0.32) article reporting on vasospasm in guinea pigs was also excluded. The remaining 22 publications (7.2%), including 26618 patients were analysed. These 22 publications included 5 case reports and 1 case series.

Identified modifiable risk factors

A total of 13 categories were identified, of which 4 were individual case reports and one was a case series as shown

in table 1. The most frequently identified risk factor in vasospastic angina was smoking, identified in 49% (423 of 863). Dyslipidaemia associated with vasospasm was reported in 75% (33 of 44) of the patients. Iatrogenic triggers of vasospasm include catheter induced 30% (30 of 7317) and pericardial manipulation which was an isolated case report. A case series reported 3 patients having coronary vasospasm due to burn injury. Two further case reports were on hyperthyroidism and food borne botulism resulting in coronary vasospasm.

Two significant psychological associations were also found, type A personality 22.6% (22 of 97) and alexithymia 31% (31 of 100). Hyperventilation 25% (25 of 30) and magnesium deficiency 38.8% (7 of 18) were also important risk factors for development of coronary vasospasm. Lastly, 100 patients with drug induced vasospasm were also identified.

Table 1: Characteristics of included studies.

Modifiable factor	N (%)	Reference number
Smoking	423 (49)	12, 17, 18, 19, 20, 21, 22, 23, 24, 25
Drugs	101 (0.08)	20, 26
Dyslipidemia	33 (75)	17, 22
Post-partum hemorrhage	1	27
Catheter induced	30 (0.41)	28
Burn injury	3	29
Food borne botulism	1	30
Type A personality	22 (22.6)	31
Exercise	5 (0.08%)	32
Pericardial Manipulation	1	33
Alexithymia	31 (31)	34
Hyperventilation	25 (83%)	35
Magnesium deficiency	7 (38.8%)	36
Hyperthyroidism	1	37

DISCUSSION

Besides the role of pharmacological therapy, reducing occurrence of modifiable risk factors is a paramount in terms of vasospastic angina. Modifiable risk factors are those factors which can be prevented from occurrence by bringing positive changes in lifestyle i.e., exercise, healthy diet, avoidance of smoking and maintaining optimum weight.³⁸ The most common modifiable factors in literature for vasospastic angina are smoking, BMI, dyslipidaemias, coronary artery diseases.³⁹ Another study has reported modifiable risk factors of vasospastic angina including dyslipidaemia, use of certain recreational drugs, magnesium deficiency, hyperventilation, exercise, hyperthyroidism, post-partum haemorrhage, food borne botulism and burn injuries. Moreover, some iatrogenic factors such as catheterisation and pericardial manipulation were also identified as a risk for vasospasm in epicardial vessels.⁴⁰

Smoking has the strongest correlation with vasospastic angina, even more than its association with atherosclerotic coronary artery disease.²⁴ In addition to tobacco smoking, marijuana/weed smoke inhalation has also been found to be a contributory factor in the development of vasospastic angina which may lead to myocardial infarction.^{41,42} Dyslipidaemia had a positive correlation with vasospastic angina. Since coronary vasospasm usually occurs on a background of atherosclerosis, it is unsure exactly how much a role does dyslipidaemia play directly in the development of coronary vasospasm. Some over-the-counter medications including drugs for migraine, nonsteroidal anti-inflammatory drugs, pseudoephedrine,

ephedra containing dietary supplements have been identified as possible triggers for VA.⁴³⁻⁴⁶ Hypersensitivity to amoxicillin was also reported as a possible trigger for VA.⁴⁷ Some racial differences are also present that make people susceptible to vasospastic angina. Asian races mostly Japanese have high incidence of vasospasm of coronary artery as compared to Caucasians. The former has three to four times higher incidence than the latter. The mean age of presentation for the Prinzmetal angina is 45 to 75 years of age. Women are more prone to get Prinzmetal angina as compared to males.⁴⁸

In pregnancy, vasoconstrictive agents used to induce the labour can lead to the vasospasm of the coronary artery. These agents include bromocriptine, ergonovine and prostaglandins. Other factors that can lead to the vasospastic angina during pregnancy or in postpartum period include the elevation in the level of renin angiotensin from uterine hypo perfusion and endothelial function impairment.⁴⁰ In light of the recent increase in the consumption of such substances, especially by young adults, it is imperative that further trials should be conducted about their possible role in the pathophysiology of vasospastic angina. In cases of non-occlusive ischemic chest pain, a thorough history taking should be encouraged among medical practitioners. As the use of such illicit substances is getting more and more prevalent in the society.⁴⁹

An important aspect is the overlap between the pathophysiology of VSA and occlusive arterial disease. There is strong evidence that in most cases, atherosclerosis and endothelial dysfunction always work in background along with the vasospasm leading to ischemia/myocardial infarction.⁸ In some cases cardiac arrhythmias can develop along with arterial vasospasm, which further exacerbates the ongoing ischemia.⁸ This not only makes it challenging for academia to study the disorder but also makes it difficult for clinicians in guiding treatment in patients with co-existing disease. As there is a gulf of difference between the number of well conducted trials about Occlusive Arterial Disease and Vasospastic phenomenon, we hope that this article can serve as a pointer for researchers to direct future research on this topic.

CONCLUSION

This study prompts the existing literature for modifiable risk factors of coronary artery vasospasm so that an emphasis can be made on proper lifestyle modifications and avoidance of vasospastic agents in susceptible individuals. Smoking proved to be the most important risk factor whereas recreational drugs and drugs used for treatment of certain medical disorders have also been shown to associate with coronary vasospasm. Medical personnel, therefore, need to be more vigilant in history taking as well as investigating cardiac chest pain in which traditional investigations end up being normal so that an early diagnosis of vasospastic angina can be made and

appropriate steps taken to improve the quality of life of patients.

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