3-1-2021

Coronary Vasospasm: Not Gone But Often Forgotten

Michael Savage

Tabitha Moe

JACC: CASE REPORTS VOL. 3, NO. 3, 2021

EDITORIAL COMMENT

Coronary Vasospasm

Not Gone But Often Forgotten*

Michael P. Savage, MD,[a] Tabitha G. Moe, MD[b]

It has been more than 60 years since the initial description of vasospastic angina by Prinzmetal et al. (1). This seminal report was a series of 32 patients with a clinical syndrome characterized by angina occurring at rest associated with transient ST-segment elevation and prompt relief with nitroglycerin. Classified as a "variant form of angina" to distinguish it from the classic exertional angina of Heberden, the researchers astutely postulated that the cause of these attacks was a "temporary increased tonus" in large coronary arteries.

Although the prevalence of coronary artery spasm (CAS) is unknown, evidence suggests that it remains underdiagnosed and undertreated. A large registry study showed that 62% of patients undergoing elective cardiac catheterization for suspected coronary artery disease had no obstructive disease (2). A prospective study of 124 patients with typical angina but angiographically normal coronary arteries evaluated the frequency of provocable CAS using intracoronary acetylcholine (3). Epicardial CAS was demonstrated in 28% of patients. An additional 34% of patients had evidence of microvascular spasm. Similarly, in the CorMICA (Coronary Microvascular Angina) trial, acetylcholine testing induced epicardial vasospasm in 37% of patients with angina but no obstructive coronary artery disease (4). Despite the accruing evidence for CAS as a frequent cause of chest pain in patients with relatively normal coronary angiograms, provocative testing with acetylcholine or ergot derivatives is infrequently performed in contemporary practice. In addition to recurrent symptomatic episodes, CAS may cause myocardial infarction or sudden cardiac death, and therefore, failure of diagnosis can have potentially dire consequences.

Another variation on the theme of unrecognized CAS is seen in patients with chest pain syndromes and significant angiographic stenosis. Vishnevsky et al. (5) described a series of patients referred for percutaneous coronary intervention (PCI) with >70% stenosis on angiography that resolved after administration of intracoronary nitroglycerin. PCI was deferred, and patients were successfully treated with medication. The importance of considering CAS during diagnostic cardiac catheterization was further illustrated by Mohammed et al. (6), who found that in patients with prior coronary artery bypass grafting (CABG) for left main stenosis, 4.1% had no evidence of left main disease on follow-up coronary angiography, suggesting that vasospasm was responsible for the original lesion (6). Other investigators have reported even higher rates of unrecognized left main vasospasm in patients referred for CABG (7). These studies underscore the importance of intracoronary nitroglycerin during diagnostic coronary angiography and before PCI to avert unnecessary revascularization procedures (8). It is notable that current PCI guidelines neglect to mention the use of intracoronary nitroglycerin, which has been dubbed the "forgotten stepchild of cardiovascular guidelines" (5).

This issue of *JACC: Case Reports* presents 2 case studies of patients with coronary vasospasm offering different, important perspectives. The report by Arps et al. (9) reinforces past lessons on the importance of clinical vigilance for the role of vasospasm in chest pain syndromes, and the report by Pereyra et al. (10) points the way toward future novel approaches for the treatment of CAS.

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

From the [a]Thomas Jefferson University, Philadelphia, Pennsylvania, USA; and the [b]University of Arizona College of Medicine, Phoenix, Arizona, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.01.022

Arps et a. (9) describe a 69-year-old man undergoing cardiac catheterization for unstable angina 7 years after CABG. Initial injection of the vein graft to a diagonal branch demonstrated a high-grade proximal stenosis and was complicated by ventricular fibrillation. After resuscitation, PCI was initiated, but repeat angiography following coronary guidewire placement revealed complete return of vein graft patency, indicating that the original stenosis was due to vasospasm. A common perception is that spasm of aortocoronary venous bypass grafts is relatively rare outside of the early post-operative period. However, cases of vein graft spasm have long been recognized (11,12). Kafka et al. (13) reported vein graft spasm in 24 of 1,264 (1.9%) patients undergoing routine post-CABG surveillance angiography. The location of spasm was typically in the proximal grafts, which were often technically difficult to engage, suggesting that catheter-induced spasm was the proximate cause in many of the cases.

This case report has valuable take-home lessons. The possibility of CAS needs to be considered even in cases where it may be least expected. Vein graft spasm, although uncommon, does occur, and failure to make the diagnosis could lead to unnecessary stenting (8). The present report is a case in point—vasospasm was not initially considered, as PCI had commenced, until repeat angiography showed spontaneous resolution of the stenosis. A more advisable action during this procedure would have been to administer intracoronary nitroglycerin first before proceeding with PCI precisely for this reason (5). Fortunately, CAS was recognized, and the patient was treated successfully with medication. PCI and stents are generally not recommended for the treatment of CAS in the absence of severe atherosclerotic disease. In patients with CAS, PCI does not eliminate the need for continued antispasm medication because spasm has the propensity to reoccur outside of the stented segment (14).

Management of vasospastic angina includes avoidance of precipitating factors, especially cigarette smoking and drugs that potentiate coronary vasoconstriction, such as cocaine, sympathomimetic agents, ergot alkaloids, and nonselective beta-blockers (15). Magnesium deficiency has also been associated with vasospastic angina. Calcium-channel blockers and nitrates are the mainstays of therapy for CAS. Occasionally, patients fail to achieve an adequate response despite combination therapy with these drugs. In Japan, where CAS is more prevalent, the incidence of intractable vasospastic angina exceeds 13% (16). One strategy for dealing with refractory vasospastic angina is to use different calcium-channel antagonists (dihydropyridine and nondihydropyridine) in combination. There is a paucity of data on the efficacy of this approach, and new alternative options are needed to address the difficult problem of vasospastic angina refractory to conventional therapies.

The case report by Pereyra et al. (10) describes the novel use of riociguat to successfully treat a 77-year-old woman with refractory vasospastic angina. Riociguat is an oral drug, a soluble guanylate cyclase stimulator approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) group 1 patients. It is the only agent approved by the U.S. Food and Drug Administration for WHO group 4 patients with chronic thromboembolic pulmonary hypertension. The drug has been shown to improve exercise capacity and WHO functional class and to delay clinical worsening in patients with PAH (17,18).

In this case study, riociguat was used off label to treat longstanding vasospastic angina that was refractory to multiple conventional drugs. Riociguat promotes vasodilation via cyclic guanosine monophosphate, which is produced in lung parenchyma by guanylate cyclase in response to nitric oxide. Riociguat increases the activity of soluble guanylate cyclase by 2 mechanisms: it sensitizes soluble guanylate cyclase to endogenous nitric oxide and also directly stimulates guanylate cyclase receptors independent of nitric oxide (18). That the vasodilatory effects occur systemically and not only in the pulmonary circulation allows its potential as a therapeutic agent in the treatment of coronary vasospasm. Other agents affecting this nitric oxide pathway may also be potential therapeutic targets. In the United States, riociguat remains on patent and is not a preferred agent by many insurance providers, resulting in what is often a cost-prohibitive therapy for patients with PAH.

Larger controlled studies are necessary before riociguat can be recommended for the treatment of CAS. The drug has notable side effects and drug interactions. Secondary to the systemic effects of vasodilation, hypotension, headaches, and vasomotor symptoms are not uncommon. The application may be limited in patients with elevated left ventricular end-diastolic pressure (LVEDP) because it is likely to worsen LVEDP. Riociguat potentiates the blood pressure–lowering effect of nitroglycerin, which is particularly problematic for patients with CAS because its use is contraindicated “with nitrates or nitric oxide donors in any form” (19). Riociguat utilizes the CYP3A pathway. Therefore, ketoconazole and protease inhibitors increase circulating levels of riociguat. Conversely, nicotine exposure decreases circulating

levels of riociguat. For smokers, dosage adjustments may be necessary unless smoking cessation can be achieved. Bioavailability may be affected by antacids containing magnesium or aluminum hydroxide, which limit absorption. Particular caution is required in women of child-bearing age. The drug is pregnancy category X and requires additional monitoring for all women of reproductive potential.

In conclusion, coronary artery spasm remains alive and well. The case studies presented in this issue of *JAAC: Case Reports* serve to underscore the continued challenges in the diagnosis and treatment of this affliction. Continued cognizance of the often sneaky role of vasospasm in chest pain syndromes is vital to ensure its clinical recognition and appropriate therapy.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Michael P. Savage, Jefferson Angioplasty Center, Thomas Jefferson University Hospital, 111 South 11th Street, Suite 6210, Philadelphia, Pennsylvania 19107, USA. E-mail: michael.savage@jefferson.edu. Twitter: @DocSavageTJU.

REFERENCES

1. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris I. A variant form of angina pectoris. Am J Med 1959;27:375–88.

2. Patel MR, Petersen ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

3. Ong P, Athanasiadis A, Borgulya G, et al. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal Coronary Vasomotion in Patients With Stable Angina and Unobstructed Coronary Arteries). J Am Coll Cardiol 2012;59:655–62.

4. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMICA trial. J Am Coll Cardiol 2018;72:2841–55.

5. Vishnevsky A, Julien HM, Fischman DL, et al. Unrecognized coronary vasospasm in patients referred for percutaneous coronary intervention: Intracoronary nitroglycerin, the forgotten stepchild of cardiovascular guidelines. Catheter Cardiovasc Interv 2017;90:1086–90.

6. Mohammed AA, Yang A, Shao K, et al. Patients with left main coronary artery vasospasm inadvertently undergoing coronary artery bypass grafting surgery. J Am Coll Cardiol 2013;61:899–900.

7. Ilia R, Shimony A, Cafri C, et al. Angiographic characteristics of catheter induced spasm of the left main coronary artery. Am J Cardiol 2016;117:571–3.

8. Vishnevsky A, Fischman DL, Savage MP. Intracoronary nitroglycerin: recognizing coronary spasm first and foremost to avoid unnecessary coronary stents. Expert Rev Cardiovasc Ther 2017;10:727–8.

9. Arps K, Chakravarti MD, Hess CN, Rao SV. Ventricular fibrillation due to aortocoronary vein graft spasm during angiography: case report and literature review. J Am Coll Cardiol Case Rep 2021;3:388–91.

10. Pereyra VM, Seitz A, Hubert A, et al. Repurposing riociguat for treatment of refractory angina resulting from coronary spasm. J Am Coll Cardiol Case Rep 2021;3:392–6.

11. Victor MF, Kimbiris D, Iskandrian AS, et al. Spasm of a saphenous vein bypass graft: a possible mechanism for occlusion of the venous graft. Chest 1981;80:413–5.

12. Walinsky P. Angiographic documentation of spontaneous spasm of saphenous vein coronary artery bypass graft. Am Heart J 1982;103:290–2.

13. Kafka H, Fitz Gibbon GM, Leach AJ. Aortocoronary vein graft spasm during angiography. Can J Cardiol 1995;11:211–6.

14. Tarabe Y, Ito E, Suzuki K, et al. Limited role of coronary angioplasty and stenting in coronary spastic angina with organic stenosis. J Am Coll Cardiol 2002;39:1120–6.

15. Pichard F, Sayah N, Spagnoli V, Adjedj J, Varenne O. Vasospastic angina: a literature review of current evidence. Arch Cardiovasc Dis 2019;112:44–55.

16. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina). Circ J 2014;78:2779–801.

17. Ghofrani HA, Galie N, Grimminger, et al. Riociguat for the treatment of pulmonary artery hypertension. N Engl J Med 2013;369:330–40.

18. Khaybullina D, Patel A, Zerilli T. Riociguat (Adempas): a novel agent for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. P T 2014;39:749–58.

19. Adempas (riociguat). Prescribing information. Bayer Healthcare Pharmaceuticals, Inc., January 2018.

KEY WORDS acute coronary syndrome, chest pain, coronary angiography, myocardial ischemia, pulmonary hypertension, stenosis, treatment