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ISCHEMIC HEART DISEASE

CLINICAL CASE

Myocardial Perfusion and Angina Improvement Following Allopurinol Therapy in a Patient With Coronary Artery Fistula

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ABSTRACT

BACKGROUND Coronary artery fistulas (CAFs) can lead to ischemia and angina in the absence of obstructive coronary artery disease. There is no evidence supporting a noninterventional approach to improve ischemia or alleviate symptoms for patients with refractory angina associated with CAFs.

CASE SUMMARY An 85-year-old woman presented with angina functional class 3 despite being on 3 antianginal medications. Myocardial scintigraphy showed reversible hypoperfusion in the left ventricle's lateral, inferolateral, and inferior walls. A coronary angiogram showed no obstructions; however, a CAF was found. Considering the patient's frailty and unsuitability for cardiac intervention, she was enrolled in a high-dose allopurinol protocol, which led to a significant improvement in symptoms, exercise capacity, and myocardial perfusion.

DISCUSSION This case highlighted allopurinol as a potential alternative for alleviating ischemia and angina in patients with CAF deemed not good candidates for cardiac interventions. (JACC Case Rep. 2025;30:105010)

HISTORY OF PRESENTATION

An 85-year-old woman with chronic coronary syndrome presented with worsening angina, classified as Canadian Cardiovascular Society (CCS) class 3, which required her to use nitrates frequently (twice a week). Antianginal medications were optimized and included the maximum tolerated doses of metoprolol, trimetazidine, and a long-acting nitrate. Calcium channel antagonists were tried, but they had to be withdrawn because of poor tolerability. She was also receiving treatment for cardiovascular risk factors.

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ABBREVIATIONS AND ACRONYMS

ANOCA = angina with no obstructive coronary artery disease

CAF = coronary artery fistula

CCS = Canadian Cardiovascular Society

LV = left ventricle

RA = refractory angina

VE/VCO_2 = ventilatory equivalent of carbon dioxide

VO_2 = volume of oxygen

During the physical examination, her heart rate was 52 bpm, her blood pressure was 130/60 mm Hg, and there were no signs of heart failure.

PAST MEDICAL HISTORY

The patient presented with systemic arterial hypertension, dyslipidemia, peripheral arterial disease, and a history of acute myocardial infarction that was treated with percutaneous coronary intervention on the left anterior descending and right coronary arteries. In addition, she suffers from sarcopenia and frailty. Her quality of life was significantly affected by chest pain experienced during daily activities.

DIFFERENTIAL DIAGNOSIS

In patients with multiple cardiovascular risk factors, obstructive coronary artery disease is typically regarded as the primary cause of myocardial ischemia in the context of angina pectoris. However, there is a significant overlap between the risk factors associated with atherosclerosis and angina with no obstructive coronary artery disease (ANOCA).[1] This overlap particularly pertains to microvascular dysfunction and arterial vessel spasm. It is important to be cautious and thorough in the diagnostic approach, as specific cardiomyopathies, especially hypertrophic and infiltrative diseases like amyloidosis, may represent potential differential diagnoses. Coronary anatomical anomalies are a less common cause of angina in the elderly.

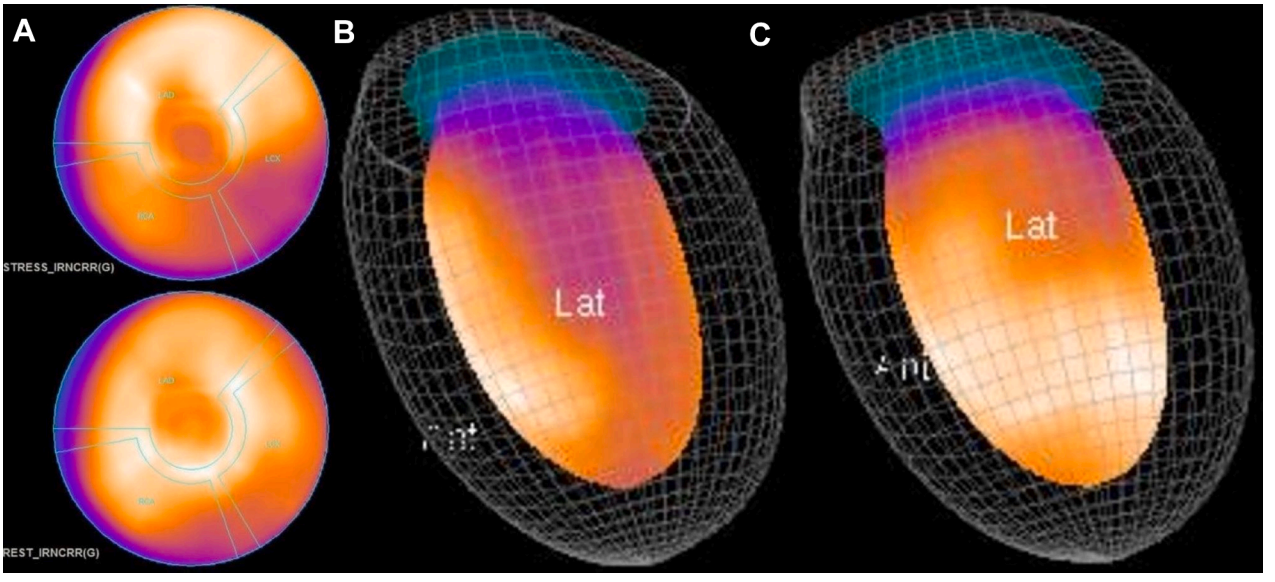
TAKE-HOME MESSAGES

- Coronary artery fistulas can be a rare cause of angina with no obstructive coronary artery disease and refractory angina in the elderly.
- Allopurinol can improve angina symptoms, enhance exercise tolerance, and increase myocardial perfusion.

INVESTIGATIONS

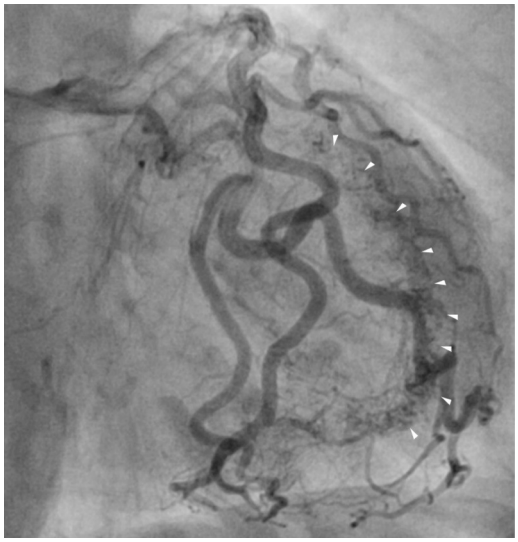
Stress myocardial perfusion scintigraphy showed reversible hypoperfusion in the left ventricle (LV)'s lateral, inferolateral, and inferior walls, as illustrated in **Figure 1**. The LV ejection fraction was preserved. Following this, a coronary angiogram was performed, which reassuringly revealed no coronary obstructions and confirmed the patency of stents. However, it also identified a coronary artery fistula (CAF) leading to the LV cavity in the ischemic territory, as shown in **Figure 2** (Video 1). This CAF had been

FIGURE 1 Baseline Myocardial Stress/Rest Perfusion Scintigraphy



(A) Composite image of all segments. Reversible hypoperfusion in the lateral, inferolateral, and inferior left ventricle walls. (B) Lateral and inferior walls show ischemia at stress. (C) Normal perfusion at rest.

FIGURE 2 Coronary Angiogram



No epicardial obstructions. Coronary artery fistula draining into left ventricle (white arrow heads) in the territory of lateral, inferolateral, and inferior walls. Source (author's): https://www.ahajournals.org/doi/10.1161/circ.150.suppl_1.4146119.

present in her previous coronary angiogram, indicating that it was likely a congenital anomaly.

MANAGEMENT

Despite the general recommendation of fistula occlusion for adults with ischemia, we faced a unique situation with our octogenarian patient. Her frailty ruled out cardiac intervention, leading us to implement our allopurinol protocol, tailored for patients with refractory angina (RA). The inclusion criteria for this protocol are meticulously designed to ensure the safety and efficacy of the treatment. They include angina classified as CCS 2 or higher, use of at least 3 antianginal medications, any positive ischemic test, an LV ejection fraction >35%, and a glomerular filtration rate above 30 mL/min.

The initial treatment phase lasts 4 weeks and involves administering allopurinol at 300 mg daily, followed by 600 mg daily for the subsequent 8 weeks. After 12 weeks, we reassess the patient's symptoms and functional tests. Figure 3 illustrates the treatment protocol flowchart.

In the baseline cardiopulmonary test, angina onset occurred at 6 minutes 38 seconds under a workload of 3.6 metabolic equivalent of task. The peak volume of oxygen (VO_2) was 16 mL/kg/min, and the ventilatory equivalent of carbon dioxide (VE/VCO_2) slope was 33 (a normal VE/VCO_2 slope is typically below 30). Table 1 provides a list of the equipment utilized for investigation.

OUTCOME AND FOLLOW-UP

After 3 months, the patient's ability to tolerate physical activity has significantly improved. The threshold and intensity of angina have improved, now classified as CCS class 2. The need for nitrate has reduced, with usage decreasing to approximately twice a month. New scintigraphy showed normalization of myocardial perfusion (see Figure 4), and a cardiopulmonary test indicated an increase of 4.1 minutes in the time to angina onset, allowing the patient to achieve an additional 1.7 metabolic equivalent of tasks of effort before experiencing angina. The VO_2 peak remained unchanged at 16 mL/kg/min, while the VE/VCO_2 slope decreased by 3 points, reaching 30. No significant differences were observed in ST-segment depression. Table 2 compares the exercise parameters before and after treatment. It is important to note that no other therapies, including additional antianginal drugs

FIGURE 3 Institutional Allopurinol Protocol for Refractory Angina

AA = antianginal drug; CCS = Canadian Cardiovascular Society; GFR = glomerular filtration rate; LVEF = left ventricle ejection fraction.

TABLE 1 Equipment List

Test	Equipment
Myocardial perfusion scintigraphy	Tomography study with Sestamibi ^{99m}Tc Pharmacological stressor: dipyridamole Equipment: VENTRI I (baseline test), INFINIA (post-treatment test)
Cardiopulmonary test	Performed on treadmill (Vyaire Vyntus CPX-GE CardioSoft V6.71) Balke protocol 1.5 mph
Coronary angiogram	Arterial access: right radial artery, puncture catheter size 6-F, hemostasia with radial compression strap Contrast: nonionic low-osmolarity iodine contrast, 80 mL

such as ranolazine or ivabradine, were given to this patient during the protocol and follow-up period. **Figure 5** (Video 2) summarizes the history of this clinical case.

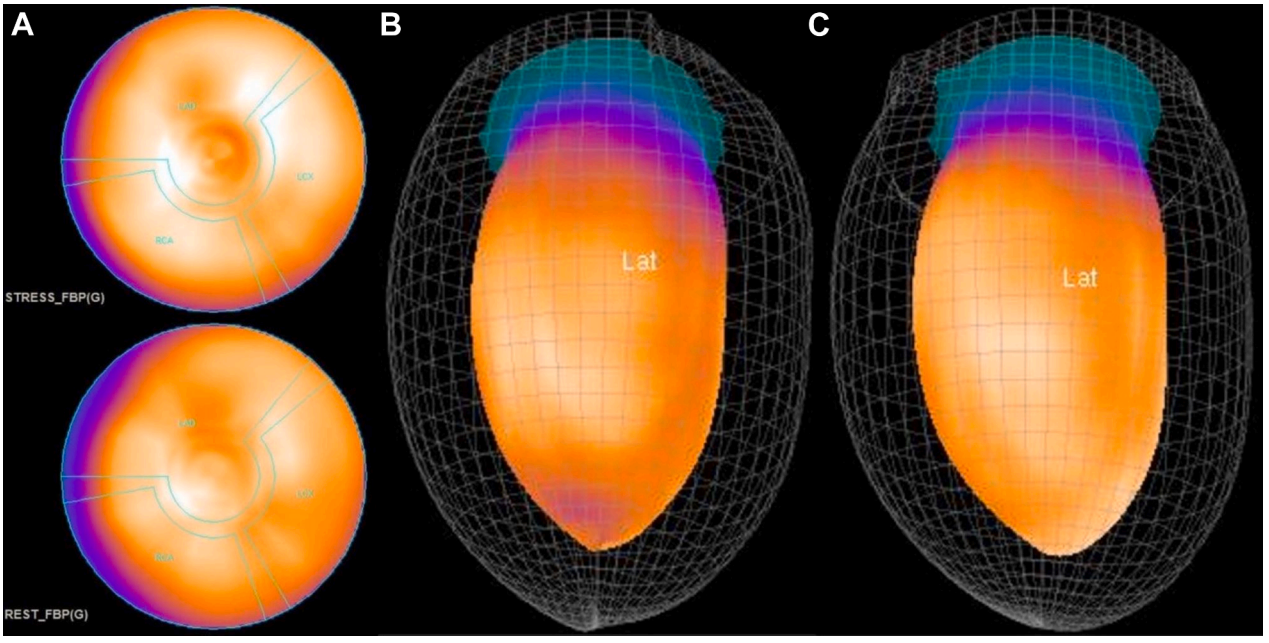
DISCUSSION

RA is a complex and debilitating condition characterized by persistent chest pain lasting more than 3 months, caused by myocardial ischemia despite the use of 2 or 3 antianginal medications and myocardial revascularization procedures.[2] A notable phenotype of RA is ANOCA, which can be triggered by various factors including abnormal epicardial or microvascular reactivity (impaired vasodilation or increased vasoconstriction), and anatomical arterial anomalies.[1] The connection between RA and CAFs is rarely reported, and there is limited documentation on the use of conservative treatment, especially in elderly patients.

In the context of vessel anomalies, CAFs are connections between the coronary arteries and heart chambers or other blood vessels, accounting for nearly half of all coronary anomalies and representing the most common type of hemodynamically significant coronary lesion. These conditions can lead to heart failure, myocardial ischemia, and arrhythmias.[3] CAFs are estimated to be present in approximately 0.002% of the population and can be identified in up to 0.25% of angiograms, underscoring their rarity and the unique challenges they present in diagnosis and treatment. In approximately 3% of CAF cases, the fistula drains into the LV cavity, potentially leading to the coronary steal phenomenon, which may manifest as ANOCA. Symptoms tend to be more prevalent with advancing age. Large and/or symptomatic fistulas should be treated through open surgery or percutaneous transcatheter embolization.[3]

Allopurinol, a xanthine oxidase inhibitor, is a noteworthy option in noninvasive treatments for

FIGURE 4 Post-Treatment Myocardial Stress/Rest Perfusion Scintigraphy



(A) Composite image of all segments. Undetected reversible hypoperfusion. (B) Normal perfusion at stress. (C) Normal perfusion at rest.

TABLE 2 Cardiopulmonary Parameters on baseline and After Allopurinol

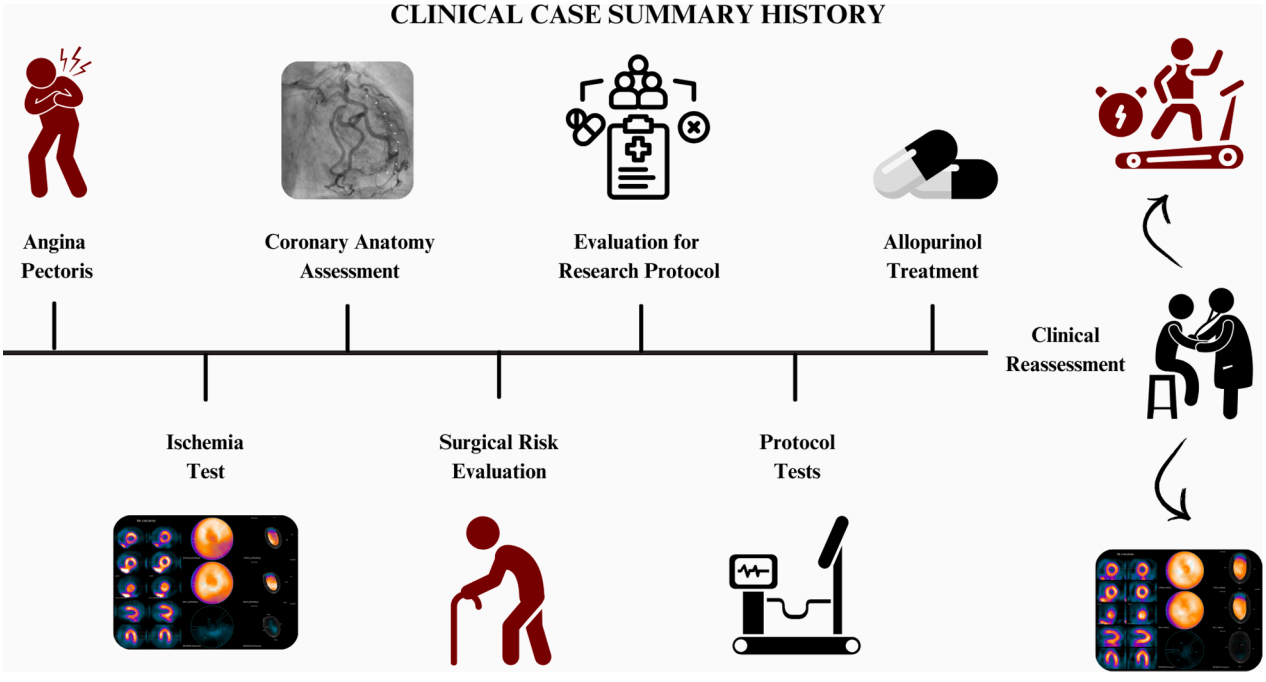
Test Parameters	Baseline	Post-Treatment
Angina onset (exercise duration)	06:38 min	10:44 min
Angina onset (workload)	3.6 METs	5.7 METs
VO_2 peak (mL/kg/min)	16	16
VE/VCO_2 slope	33	30

MET = metabolic equivalent of task; VE/VCO_2 = ventilatory equivalent of carbon dioxide; VO_2 = volume of oxygen.

patients with RA.[4] While studies have produced conflicting results, high doses of allopurinol have been shown to significantly enhance endothelial function,[5,6] increase exercise tolerance,[4] and improve angina symptoms in patients with chronic coronary syndromes.[7,8] The potential benefits of allopurinol in those patients may stem from its ability to reduce oxidative stress.[6] By reducing oxidative stress, allopurinol may improve myocardial efficiency and reduce oxygen consumption, a key factor in chronic coronary syndromes.[5] Moreover, the effects of allopurinol on arterial function and its implications for oxygen utilization could be interconnected. Increased oxygen consumption may occur, predominantly when xanthine oxidase is upregulated and nitric oxide synthase is downregulated, a common metabolic state in ischemic tissues. Therefore, allopurinol, with its potential to improve also myocardial perfusion by minimizing vasomotor dysfunction, offers a promising avenue for therapeutic intervention. The patient described may have experienced improved myocardial perfusion due to improvement in endothelial function. This improvement could serve as a therapeutic target for addressing the 2 leading causes of angina involved: coronary microvascular disease and the steal phenomenon associated with chronic angina.

Noman et al[4] conducted a randomized clinical trial demonstrating that patients with stable angina, obstructive coronary artery disease, and documented ischemia experienced a significant increase in exercise capacity after 6 weeks of treatment with 600 mg of allopurinol daily. However, there is currently a

FIGURE 5 Clinical Case Summary History



This image illustrates the patient's history in the order of events from its clinical presentation, through the process of investigation and decision-making to clinical reassessment after treatment.

lack of data regarding the use of allopurinol for patients with ANOCA, particularly in cases where rare anatomical factors, such as CAF, contribute to ischemia. In the APEX (effects of allopurinol on exercise capacity, coronary and peripheral endothelial function, and natriuretic peptides in patients with cardiac syndrome X) trial,[9] high-dose allopurinol did not improve exercise capacity and coronary or peripheral endothelial function in 19 patients with syndrome X, although angina pectoris was not included as an outcome measure. This underscores the need for further research in this area.

The ALL-HEART (allopurinol versus usual care in UK patients with ischemic heart disease) study was the most extensive study investigating the potential cardiovascular benefits of allopurinol, which involved over 5,000 patients with ischemic heart disease who did not have gout.[10] The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The study found no superiority of the allopurinol intervention compared to the control. In addition, one secondary outcome assessed the quality of life using the Seattle Angina Questionnaire-Angina Domain, which yielded neutral results. Several limitations in this trial might have impacted the findings. For instance, there was a high treatment discontinuation rate of 57% in the allopurinol group despite no significant differences in adverse events compared to the control group. Furthermore, the trial participants were largely asymptomatic, with <50% experiencing any angina and fewer than 17% reporting angina classified as CCS 2 or higher.

Our report discusses the case of a frail octogenarian patient with RA presently diagnosed with ANOCA possibly secondary to CAF and/or coronary microvascular dysfunction. The patient underwent medical optimization with allopurinol, leading to remarkable improvements in angina symptoms, exercise tolerance, and myocardial perfusion. In the context of RA and ANOCA, a careful combination of various antianginal medications, especially those that enhance endothelial function, such as allopurinol, may help control symptoms and improve myocardial perfusion and exercise tolerance.

CONCLUSIONS

This case report aims to highlight the potential for RA to arise from CAFs and advocates for a conservative approach to treating myocardial ischemia in high-risk patients. It specifically emphasizes the role of allopurinol in alleviating ischemic symptoms in cases of ANOCA and coronary anomalies such as CAFs.

The lack of robust evidence regarding the effectiveness of allopurinol in improving ischemic symptoms or enhancing coronary blood flow in chronic coronary syndromes underscores the urgent need for well-designed randomized controlled trials that assess symptom outcomes to clarify its potential benefits and provide high-quality evidence regarding its role in managing coronary artery disease. Importantly, for its low cost, allopurinol may represent a valuable therapeutic option for RA patients, particularly in developing middle- to low-income countries where chronic coronary syndromes are highly prevalent.

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KEY WORDS allopurinol, coronary artery fistula, coronary vessel anomalies, myocardial ischemia, myocardial perfusion, stable angina

APPENDIX For supplemental videos, please see the online version of this paper.