ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–7
https://doi.org/10.1093/ehjcr/ytac440

CASE REPORT
Coronary heart disease

Implantation of the coronary sinus reducer for refractory angina due to coronary microvascular dysfunction in the context of apical hypertrophic cardiomyopathy—a case report

Kevin Cheng [1,2]*, Georgia Keramida[2], A John Baksi[2], and Ranil de Silva [1,2]

[1]Vascular Science, National Heart and Lung Institute, Imperial College London, Cale Street, London SW3 6LY, UK; and [2]Royal Brompton Hospital, Sydney Street, Chelsea SW3 6NP, London, UK

Received 22 June 2022; first decision 23 August 2022; accepted 2 November 2022; online publish-ahead-of-print 7 November 2022

Background Refractory angina leads to a poor quality of life and increased healthcare resource utilization. In this growing population of patients, multiple mechanism(s) of ischaemia may co-exist, including functional disorders of the coronary microcirculation. There are few evidence-based effective therapies resulting in a large unmet clinical need.

Case summary A 38-year-old woman with refractory angina was referred with daily chest pain despite multiple anti-anginal medications and previous percutaneous coronary intervention. Cardiac magnetic resonance imaging demonstrated apical hypertrophic cardiomyopathy (HCM). Rubidium-82 positron emission tomography (PET) with regadenoson stress confirmed significant myocardial ischaemia in the apex and apical regions (16% of total myocardium) with a global myocardial perfusion reserve (MPR) of 1.23. Coronary angiography confirmed patent stents and no epicardial coronary artery disease. Therefore, the mechanism of ischaemia was thought attributable to coronary microvascular dysfunction (CMD) in the context of HCM. In view of her significant symptoms and large burden of left-sided myocardial ischaemia, a Coronary Sinus Reducer (CSR) was implanted. Repeat PET imaging at 6 months showed a marked reduction in ischaemia (<5% burden), improvement in global MPR (1.58), symptoms, and quality of life.

Conclusion In refractory angina, ischaemia may be due to disorders of both the epicardial and coronary microcirculations. The CSR is a potential therapy for these patients, but its mechanism of action has not been confirmed. This report suggests that CSR implantation may reduce myocardial ischaemia and improve symptoms by acting on the coronary microcirculation. The efficacy of CSR in patients with CMD and its mechanism of action on the coronary microcirculation warrant further investigation.

Keywords Refractory angina • Coronary microvascular dysfunction • Hypertrophic cardiomyopathy • Angina pectoris • Myocardial ischaemia • Coronary sinus reducer • Case report

ESC Curriculum 3.1 Coronary artery disease • 3.3 Chronic coronary syndrome • 2.3 Cardiac magnetic resonance • 2.5 Nuclear techniques

* Corresponding author. Tel: +44 020 7351 8626, Email: kevin.cheng@imperial.ac.uk
Handling Editor: Dimitrios A. Vrachatis
Peer-reviewers: Adam Hartley; Rita Pavasini
Compliance Editor: Debbie Falconer
Supplementary Material Editor: Ayse Djahit

Learning points

- Refractory angina can occur in the context of multiple mechanisms of myocardial ischaemia involving both the epicardial and microvascular coronary circulations.
- The coronary sinus reducer is a potential novel therapy that may be able to reduce ischaemia and improve symptoms by altering the coronary microcirculation.
- Further studies are needed to investigate the specific effect of the coronary sinus reducer on the coronary microcirculation.

Introduction

Refractory angina is a rapidly growing clinical problem associated with life-limiting symptoms, poor quality of life, and increased utilization of healthcare resources.[1] Defined as chronic chest pain (≥ 3 months duration) in the context of coronary artery disease and ischaemia that is refractory to optimal medical, interventional, and surgical treatments,[2] contemporary accurate epidemiological data are lacking but estimates suggest 0.6–1.8 million patients in the USA. In England, the incidence is estimated at ∼16, 500 per year. Few evidence-based therapies exist for these patients. Novel effective therapies are needed to meet the large and growing unmet clinical need. The Coronary Sinus Reducer (CSR), an hourglass-shaped metallic device, is a potential treatment; however, its mechanism of action remains unproven. We present a case of refractory angina secondary to coronary microvascular dysfunction (CMD) in which CSR improved symptoms and quality of life with associated improvement on rubidium-82 positron emission tomography (PET) stress perfusion imaging.

Timeline

Age 35–37	Onset of symptoms: left-sided chest pain radiating to neck and arms. Severe pain, clammy with nausea, and vomiting. Attendances at accident & emergency, normal serum markers.
	Recurrent symptoms. Occurs whilst walking dog but also randomly. Referred to local cardiology service.
	Local stress perfusion cardiac magnetic resonance imaging (MRI) showed concentric left ventricular hypertrophy (LVH) with patchy late gadolinium enhancement in apical segments suggestive of apical hypertrophic cardiomyopathy (HCM). Perfusion defect in apical septum and apical inferior wall.
	Coronary angiogram with percutaneous coronary intervention (PCI) to right coronary artery. Ostial left anterior descending (LAD) plaque with negative fractional flow reserve.
Age 38–40	Referred to Specialist Angina Service due to increasing symptoms, breathlessness, pain at rest. Daily sublingual glyceryl trinitrate (GTN) use which eases pain.
	Repeat cardiac MRI for tissue characterization showed a normal LV systolic function, no RWMAs and mid-apical LVH (maximum LV wall thickness 15 mm). Raised native T1 values in hypertrophied apical segments (1105 ms at apical anterior wall and 1115 ms at apical lateral wall at 1.5 T). No systolic anterior motion of the mitral valve or left ventricular outflow tract obstruction (LVOTO). Overall cardiac MRI findings in keeping with apical HCM phenotype.
	Anti-anginal medications: bisoprolol 5 mg OD, nicorandil 5 mg BD, amlodipine 5 mg, ISMN 60 mg OD, and ranolazine 500 mg BD.
	Nitrates used with caution given diagnosis of HCM but continued given no evidence of LVOTO and provided symptomatic benefit.
	Recurrent daily symptoms. Optimize anti-anginal medications: ranolazine 750 mg BD, nicorandil 30 mg BD, amlodipine 10 mg OD, ISMN 60 mg BD, bisoprolol 10 mg OD, and ivabradine 5 mg BD.
	Risk factors modified with atorvastatin 80 mg ON, ezetimibe 10 mg OD, candesartan 8 mg OD, spironolactone 25 mg OD, evolocumab injection 40 mg fortnightly.
	PCI to LAD with some improvement in symptoms thereafter.
	PET Rb82 showing antero-apical stunning during adenosine infusion with profound inducible perfusion abnormality in antero-apical region (LAD territory) amounting to 16% regional ischaemic burden.
Age 41	Chest pain two to five times a day. Can last from 10 min to 2 hr. Responds after 2–3 puffs of sublingual GTN spray. Canadian Cardiovascular Society (CCS) Class 3. Quality of life score of 33 on Seattle Angina Questionnaire (SAQ).
	Heart rate 90bpm. Ivabradine uptitrated to 7.5 mg BD.
Age 42	CSR implantation.
	6-months follow-up repeat PET Rb82 showing significant improvement of perfusion in all apical segments. Ischaemia burden <5% of myocardium.
	Associated with reduction in frequency of angina (CCS Class 1). Quality of life score of 47 on SAQ.

Case presentation

A 38-year-old woman with refractory angina, elevated body mass index (40 kg/m^2), hypertension, hyperlipidaemia, type 2 diabetes, ex-smoker (20 pack years) and strong family history of premature coronary and peripheral artery disease was referred. Previous stress perfusion cardiac magnetic resonance imaging (MRI) at her local referring hospital had raised the suspicion of apical HCM as it had shown concentric LVH with patchy late gadolinium enhancement in the apical segments and perfusion defects in the apical septum and apical inferior wall. Subsequently, she had undergone percutaneous coronary intervention (PCI) to her right coronary artery (RCA) and left anterior descending (LAD) artery (see timeline).

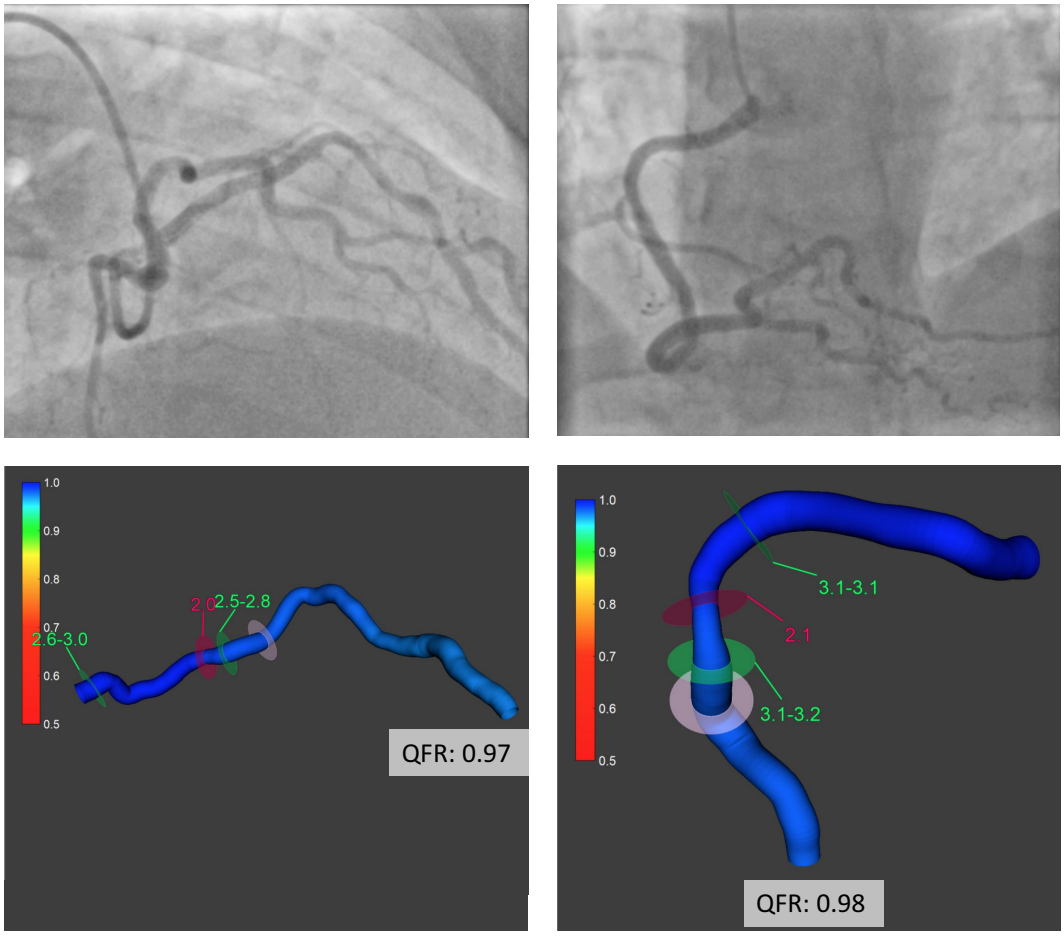

Figure 1 Top: angiographic images showing non-obstructed left anterior descending and right coronary arteries. Bottom: Angiography-derived quantitative flow ratio (QFR) confirming non-obstructed coronary arteries (QFR in left anterior descending 0.97; right coronary artery: 0.98).

Her other medical history included polycystic ovarian syndrome, idiopathic episodes of anaphylaxis, obstructive sleep apnoea and deep vein thrombosis.

She suffered life-limiting symptoms of chest pain occurring two to five times a day [Canadian Cardiovascular Society (CCS) Class 3] which was responsive to sublingual glyceryl trinitrate. Her symptoms continued despite uptitration to maximally tolerated doses of guideline-directed anti-anginal drug therapy, with associated poor quality of life. Physical examination was unremarkable.

Up to date coronary angiography revealed patent stents and no flow-limiting epicardial disease by Angio-quantitative flow ratio [0.97 (LAD) and 0.98 (RCA)] (*Figure 1*). Repeat cardiac MRI confirmed normal left ventricular (LV) systolic function without regional wall motion abnormality and mid-apical LV hypertrophy (maximum LV wall thickness 15 mm) consistent with apical hypertrophic cardiomyopathy (HCM) (*Figure 2*). There was no systolic anterior motion of the mitral valve or LV outflow tract obstruction.

A Rubidium-82 PET stress perfusion scan showed normal regional wall motion and rest perfusion. There was significant antero-apical stunning with profound inducible perfusion abnormality in the antero-apical region. The ischaemic burden was quantified at 16% of the total myocardium.

At Heart Team discussion, coronary microvascular dysfunction (CMD) secondary to apical HCM was considered as the mechanism of ischaemia. CSR implantation was recommended given her refractory symptoms, poor quality of life and left-sided myocardial ischaemia. This was performed via a 9Fr sheath placed in the right internal jugular vein under ultrasound guidance. Mean right atrial pressure was 9 mmHg. Coronary sinus dimensions were appropriate for CSR implantation which was delivered to the appropriate target and inflated to 4 atmospheres with an excellent angiographic result and no immediate complications (*Figure 3*). She was discharged the same day on ticagrelor for 6 months and lifelong aspirin.

At 6-month follow-up, she reported a significant reduction in anginal frequency, now occurring two times per week (CCS Class 1). Her quality of life as measured by the Seattle Angina Questionnaire (SAQ) had also markedly improved [+14 points (42.4%)]. A repeat Rubidium-82 PET perfusion scan showed a significant improvement in the apex and all apical segments at stress which was completely normalized at rest (*Figure 4*). The ischaemic burden was <5% although there was residual apical akinesia on stress. Quantitative analysis of myocardial perfusion showed significant improvements across all coronary artery territories (*Figure 4*) with greatest improvements in MPR observed in the most ischaemic myocardial segments at baseline (*Figure 5*). At 1-year follow-up, she was no longer limited in her daily activities and was able to exercise to a greater extent (CCS class 1; quality of life score of 47 on SAQ).

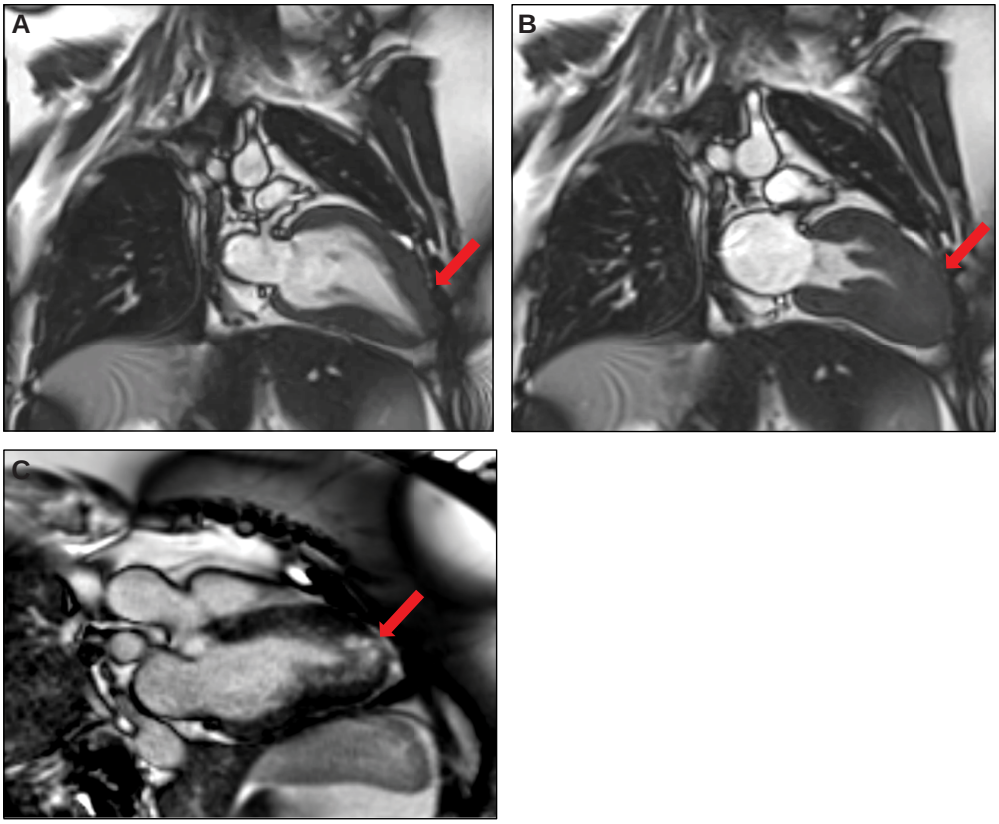

Figure 2 Cardiac magnetic resonance imaging showing apical hypertrophy in (*A*) diastole and (*B*) apical cavity obliteration in systole consistent with a diagnosis of hypertrophic cardiomyopathy. (*C*) Late gadolinium enhancement showing apical fibrosis.

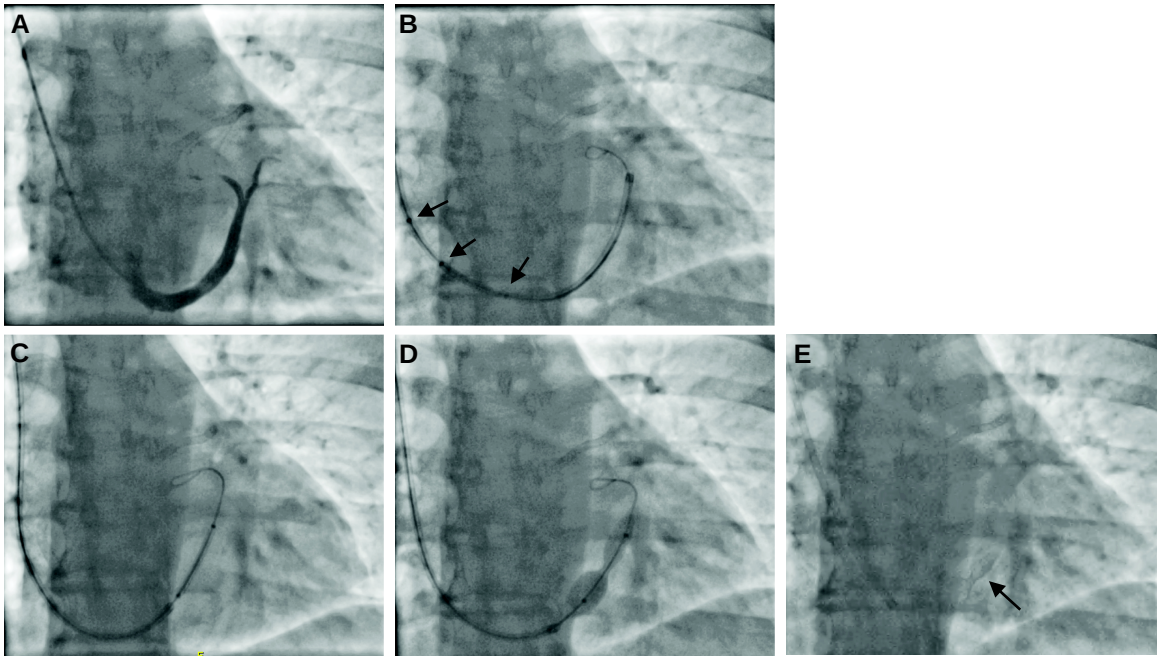

Figure 3 (*A*) Coronary sinus venogram. (*B*) Guide in coronary sinus. Distal and proximal markers (arrows) of Coronary Sinus Reducer device in the right atrium. (*C*) Coronary Sinus Reducer advanced into position. (*D*) Device deployment, balloon inflated to 4 atmospheres. (*E*) Coronary Sinus Reducer device *in situ* (arrow). Total procedure duration was 48 minutes with 60 ml of iodinated contrast used.

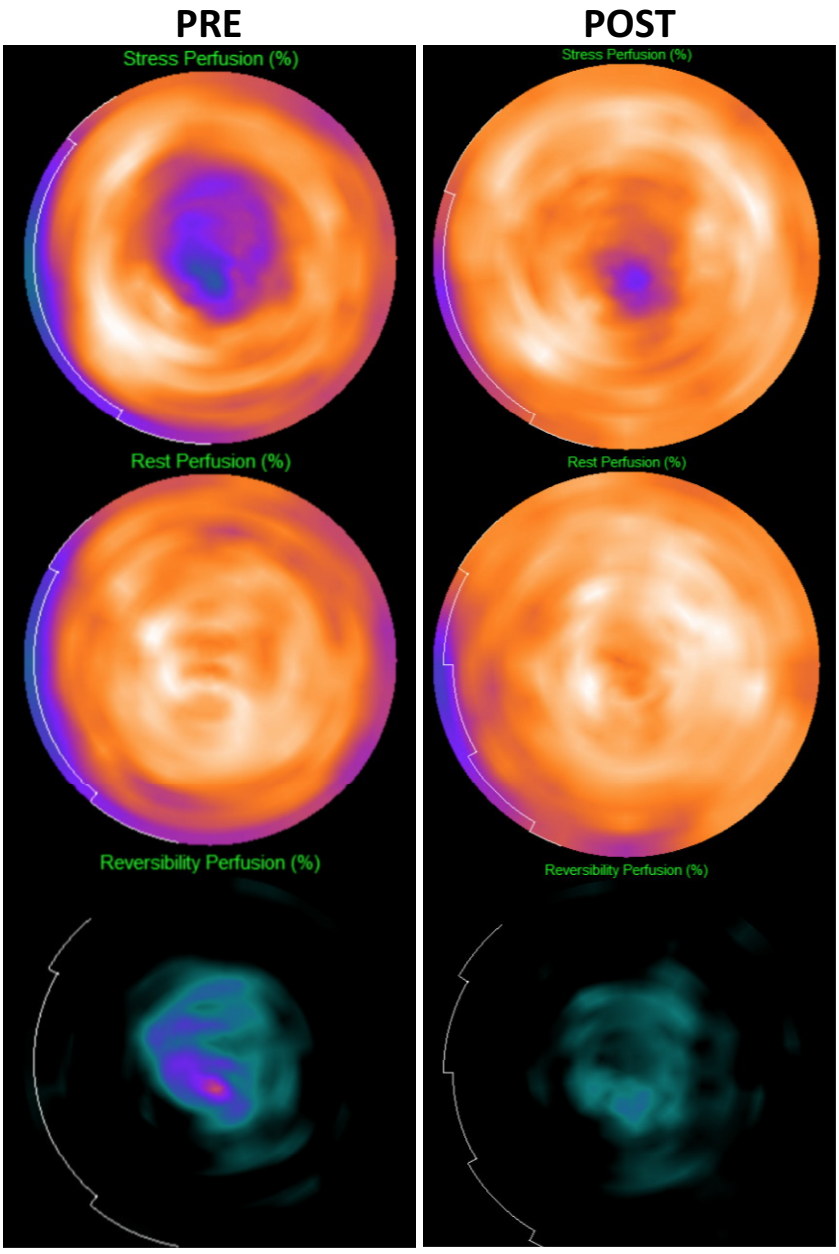

Figure 4 Below: Table showing myocardial blood flow stratified by coronary artery distribution after Coronary Sinus Reducer implantation (values before Coronary Sinus Reducer implantation shown in parentheses) after heart rate correction. Right: Rubidium-82 positron emission tomography images showing a reduction in ischaemic burden from 16% pre to <5% post Coronary Sinus Reducer implantation.

Discussion

This case suggests that CSR implantation may improve symptoms of angina by significantly reducing ischaemic burden, improving rest and stress myocardial blood flow and MPR through an effect on the coronary microcirculation. In this patient without flow-limiting epicardial disease, the large burden of ischaemia pre-implant is most likely to arise from CMD which is well-known to occur in HCM.[3]

Current use of CSR in refractory angina secondary to advanced coronary artery disease

In patients with refractory angina due to advanced epicardial coronary disease, both randomized, double-blinded, sham-controlled trial and large registry data show that CSR implantation improves symptoms and quality of life.[4–6] European Society of Cardiology guidelines[7] provide a Class IIb (Level of evidence B) recommendation with recent

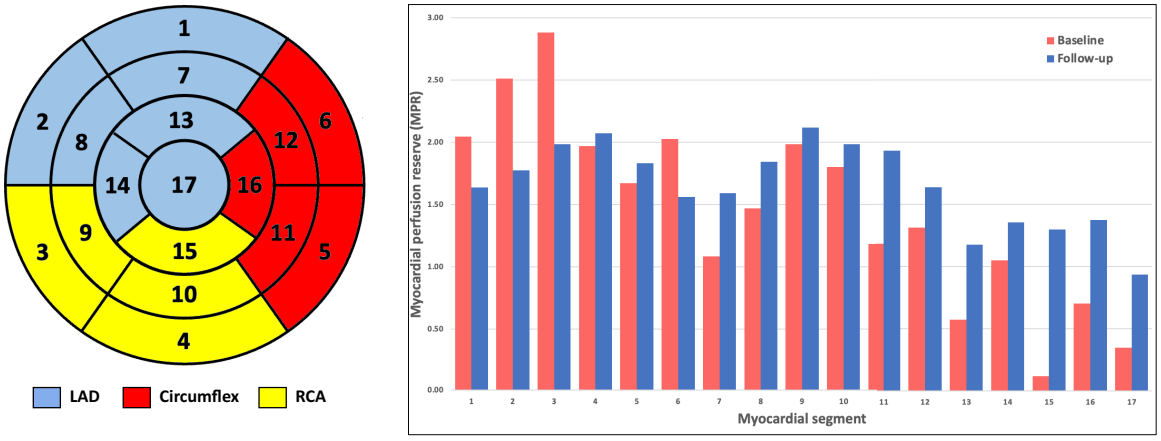

Figure 5 Left: 17-segment American Heart Association model of myocardial segments with corresponding coronary territories—left anterior descending (LAD), right coronary artery (RCA), circumflex. Right: Graph showing baseline (bars on left) and follow-up (bars on right) myocardial perfusion reserve as assessed by Rubidium-82 positron emission tomography showing changes in myocardial perfusion reserve by myocardial segment. Greatest improvements were seen in segments with the lowest baseline myocardial perfusion reserve.

National Institute for Health and Care Excellence guidance[8] issued for this indication. In the USA, a randomized, double-blinded, sham-controlled pivotal trial (Efficacy of the COronary SInus Reducer in Patients With Refractory Angina II [COSIRA-2]; NCT05102019) of CSR implantation for patients with refractory angina secondary to advanced coronary artery disease will be powered for the primary outcome of change in total exercise duration on treadmill exercise testing and further clarify the clinical benefit of this device.[9]

The CSR is hypothesized to raise venous backpressure which dilates subendocardial vessels, recruits capillaries, reduces microvascular resistance and redistributes blood to ischaemic myocardium. However its precise mechanism of action remains unconfirmed. Early evidence suggests that CSR implantation is associated with improvements in myocardial ischaemia although no adequately-powered study has demonstrated this to date.[10,11] Preliminary work also suggests that CSR implantation may improve diastolic function, exercise performance and reduce healthcare costs however further studies are needed.[12–14]

CSR in refractory angina secondary to coronary microvascular dysfunction

Identifying the mechanism(s) of ischaemia in each patient with refractory angina is essential so therapies can be rationally individualized to address the underlying pathophysiology. In clinical practice, a large proportion of patients with refractory angina have ischaemia secondary to disorders of the coronary microcirculation. Our observations from this case suggest that CSR implantation can directly impact the function of the coronary microcirculation and has potential to reduce ischaemia and symptom burden for appropriately selected patients with CMD. Other mechanistic studies suggest that that intermittent coronary sinus occlusion can recruit collaterals and improve regional myocardial blood flow into ischaemic subendocardium.[15] Preliminary non-controlled studies in patients with refractory angina despite complete revascularization and non-obstructive epicardial coronary disease suggest that CSR implantation may improve semi-quantitative indices of myocardial perfusion.[11]

Conventionally, CSR has been indicated for patients with ischaemia in myocardial territories supplied by the left coronary circulation given that the posterior interventricular vein that drains the RCA distribution enters the coronary sinus close to its os in a location proximal to the neck of the CSR. The effects of CSR on right coronary ischaemia have not been systematically investigated. In this report, quantitative myocardial blood flow assessment by PET demonstrated improvements in perfusion in both the left and right coronary artery territories. However, further studies investigating the differential effects on the left and right coronary circulations are needed.

What does this case add?

This case highlights the need to consider dysfunction of the coronary microcirculation as a cause of ischaemia in patients with refractory angina. The CSR is a percutaneous device that may act on the microcirculation to improve myocardial perfusion and may represent a biologically-plausible treatment for CMD, which can occur in a wide variety of cardiac conditions. This case directly demonstrates the effect of CSR implantation on improving objective measures of myocardial perfusion in a patient with CMD. Further systematic evaluation of the effects of CSR implantation on CMD is needed.

Lead author biography

Dr Kevin Cheng is a Cardiology Registrar at the Royal Brompton Hospital, London, and an Academic Clinical Fellow at Imperial College London. His research focuses on coronary sinus reducer implantation, clinical trials, coronary physiology assessment, and conditions affecting the coronary microcirculation.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

References

1. Henry TD, Satran D, Hodges JS, Johnson RK, Poulose AK, Campbell AR, Garberich RF, Bart BA, Olson RE, Boisjolie CR, Harvey KL, Arndt TL, Traverse JH. Long-term survival in patients with refractory angina. *Eur Heart J* 2013;**34**:2683–2688.
2. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, Follath F, Hellemans I, Herlitz J, Lüscher T, Pasic M, Thelle D. The problem of chronic refractory angina; report from the ESC joint study group on the treatment of refractory angina. *Eur Heart J* 2002;**23**:355–370.
3. Timmer SA, Knaapen P. Coronary microvascular function, myocardial metabolism, and energetics in hypertrophic cardiomyopathy: insights from positron emission tomography. *Eur Heart J Cardiovasc Imaging* 2013;**14**:95–101.
4. Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, Vrolix M, Agostoni P, Engstrom T, Labinaz M, de Silva R, Schwartz M, Meyten N, Uren NG, Doucet S, Tanguay J-F, Lindsay S, Henry TD, White CJ, Edelman ER, Banai S. Efficacy of a device to narrow the coronary sinus in refractory angina. *N Engl J Med* 2015;**372**:519–527.
5. Verheye S, Agostoni P, Giannini F, Hill JM, Jensen C, Lindsay S, Stella PR, Redwood S, Banai S, Konigstein M. Coronary sinus narrowing for the treatment of refractory angina: A multicentre prospective open-label clinical study (the REDUCER-I study). *EuroIntervention* 2020;**17**:561–568.
6. Ponticelli F, Khokhar AA, Leenders G, Konigstein M, Zivelonghi C, Agostoni P, van Kuijk J-P, Ajmi I, Lindsay S, Bunc M, Tebaldi M, Cafaro A, Cheng K, Ielasi A, Patterson T, Wolter JS, Sgura F, De Marco F, Ioanes D, D'Amico G, Ciardetti M, Berti S, Guarracini S, Di Mauro M, Gallone G, Dekker M, Silvis MJM, Tarantini G, Redwood S, Colombo A, Liebetrau C, de Silva R, Rapezzi C, Ferrari R, Campo G, Schnupp S, Timmers L, Verheye S, Stella P, Banai S, Giannini F. Safety and efficacy of coronary sinus narrowing in chronic refractory angina: insights from the RESOURCE study. *Int J Cardiol* 2021;**337**:29–37.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
8. Coronary sinus narrowing device implantation for refractory angina. Interventional procedures guidance [IPG712]. National Institute for Health and Care Excellence 2021. Available from: https://www.nice.org.uk/guidance/ipg712.
9. Efficacy of the Coronary SInus Reducer in Patients With Refractory Angina II (COSIRA-II). US National Library of Medicine [ClinicalTrials.gov]. Available from: https://clinicaltrials.gov/ct2/show/NCT05102019.
10. Giannini F, Palmisano A, Baldetti L, Benedetti G, Ponticelli F, Rancoita PMV, Ruparelia N, Gallone G, Ancona M, Mangieri A, Tzanis G, De Cobelli F, Del Maschio A, Colombo A, Esposito A. Patterns of regional myocardial perfusion following coronary sinus reducer implantation: insights by stress cardiac magnetic resonance. *Circ Cardiovasc Imaging* 2019;**12**:e009148.
11. Giannini F, Baldetti L, Ielasi A, Ruparelia N, Ponticelli F, Latib A, Mitomo S, Esposito A, Palmisano A, Chieffo A, Colombo A. First experience with the coronary sinus reducer system for the management of refractory angina in patients without obstructive coronary artery disease. *JACC Cardiovasc Interv* 2017;**10**:1901–1903.
12. Szekely Y, Topilsky Y, Bazan S, Revivo M, Banai S, Konigstein M. The impact of coronary sinus narrowing on diastolic function in patients with refractory angina. *Int J Cardiol* 2019;**291**:8–12.
13. Zivelonghi C, Konigstein M, Azzano A, Agostoni P, Topilski Y, Banai S, Verheye S. Effects of coronary sinus Reducer implantation on oxygen kinetics in patients with refractory angina. *EuroIntervention* 2021;**16**:e1511–e1517.
14. Gallone G, Armeni P, Verheye S, Agostoni P, Timmers L, Campo G, Ielasi A, Sgura F, Tarantini G, Rosseel L, Zivelonghi C, Leenders G, Stella P, Tebaldi M, Tespili M, D'Amico G, Baldetti L, Ponticelli F, Colombo A, Giannini F. Cost-effectiveness of the coronary sinus reducer and its impact on the healthcare burden of refractory angina patients. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:32–40.
15. Ido A, Hasebe N, Matsuhashi H, Kikuchi K. Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia. *Am J Physiol Heart Circ Physiol* 2001;**280**:H1361–7.