‘Targeted Therapies for Microvascular Disease’

Dr Adam Bland MBBS, MMed, BAppSc[1,2]

Dr Eunice Chuah MBBS, BBiomedSc[1,2]

Dr William Meere MBBS[1,2]

Dr Thomas J Ford MBChB (Hons), PhD[1,2,3]

- [1] Cardiology department, Gosford Hospital - Central Coast LHD, Gosford, NSW
- [2] The University of Newcastle - Central Coast Clinical School, Gosford, NSW
- [3] University of Glasgow, ICAMS, Glasgow, UK

Correspondence

Tom.ford@health.nsw.gov.au, Department of Cardiology, The University of Newcastle - Central Coast Clinical School, 75 Holden St, Gosford, NSW, Australia, 2250

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Key Words

CMD, INOCA, Angina, Ischaemia, Management

Key Points

- Coronary microvascular dysfunction (CMD) is a common contributor to INOCA when the microcirculation cannot meet myocardial oxygen demands. CMD typically results from impaired vasodilation and/or excessive vasoconstriction.
- Invasive assessment of the coronary microcirculation can stratify anti-ischaemic therapy to improved patient outcomes. Beta-blockers are the cornerstone of therapy for angina due to CMD.
- Management of CMD includes combination of pharmacological therapy and cardiovascular risk factor modification including lifestyle interventions. Pharmacological treatment may be divided into anti-atherosclerotic therapy and anti-anginal therapy.
- Further large clinical trials are required to determine effects of current management strategies, as well as proposed novel therapies.

Synopsis

Coronary microvascular dysfunction (CMD) is a common cause of INOCA that results in an inability of the coronary microvasculature to meet myocardial oxygen demand. This typically relates to mechanisms including impaired vasodilation or excessive vasoconstriction. CMD is challenging to diagnose and manage due to a lack of mechanistic research and targeted therapy. Recent evidence suggests we can improved patient outcomes by stratifying anti-anginal therapies according to the diagnosis revealed by invasive assessment of the coronary microcirculation. This review article appraises the evidence for management of

CMD which includes treatment of cardiovascular risk, anti-anginal therapy and therapy for atherosclerosis.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality affecting 126 million worldwide individuals (approaching 2% of the earth's population)[1]. Obstructive epicardial CAD has been the focus of most research in the era of coronary interventions. Patients with ischaemia but no obstructive coronary artery disease (INOCA) have largely been overlooked until recently in part related to challenges in diagnosis, poorly understood pathophysiology, and variable management of the syndrome[2]. Coronary microvascular dysfunction (CMD) is one endotype of INOCA along with vasospastic angina, mixed INOCA and non-cardiac chest pain[3]. Chest pain with no obstructive CAD previously was under the umbrella term of cardiac syndrome X (CSX), however, INOCA is now a preferred umbrella term replacing the ambiguous term CSX in recognition of better understanding of the endotypes that may co-exist to drive myocardial ischemia[4,5].

Approximately 50% of diagnostic coronary angiograms for patients at high risk of CAD demonstrate unobstructed coronary arteries. Many of these patients have abnormal stress testing, unstable angina and non-ST-elevation myocardial infarction[6,7]. Up to two thirds of INOCA patients undergoing functional coronary angiography are subsequently demonstrated to have CMD, diagnosed by demonstrating reduced coronary flow reserve (CFR) or elevated microvascular resistance[8]. Non-invasive testing of these patients often shows reduced myocardial perfusion reserve (MPR) on cardiac magnetic resonance imaging (CMR) or positron emission tomography (PET) [8-10]. INOCA is a particularly relevant diagnosis in women presenting with angina in whom unobstructed coronary arteries is a more common finding that in their male counterparts.[11] The COVADIS working group has helped with some unifying

definitions including microvascular angina (MVA) being the preferred diagnostic term for angina patients without flow limiting CAD but in whom invasive or non-invasive tests show evidence of coronary microvascular dysfunction (CMD)[12,13].

(See figure 1)

Despite the absence of epicardial obstruction, CMD remains associated with higher major adverse cardiovascular events (MACE) including cardiovascular mortality, as well as higher repeat angiography, higher levels of depression and lower quality of life[2,9,12,14-16]. Patients with CMD however, remain largely under treated due to difficulties over recent decades in establishing a widely accepted diagnostic criteria, and subsequently large trials and guidelines addressing CMD management are lacking[9,17,18]. This review aims to discuss the evolving management of CMD including the role of targeted therapies.

Treatment targets for microvascular dysfunction

Coronary blood flow incorporates three distinct compartments. Larger epicardial arteries appreciable on diagnostic coronary angiogram range from approximately 500µm up to 5mm or greater[18,19]. The microcirculation consists of Intermediate pre-arterioles (~100 to 500µm diameter), and smaller intramural arterioles (< 100µm in diameter)[18,19]. The coronary microcirculation alters blood flow to meet cardiac myocyte metabolic demand, with increased demand and flow causing vasodilation, and decreased demand and flow causing

vasoconstriction. Proximal arteriolar stretch receptors or distal arteriolar local metabolites dictate these alterations in arteriolar size[18].

CMD results from an inability of the microvasculature to meet cardiac myocyte demand, resulting in ischaemia and angina. Traditional cardiovascular risk factors remain the same for CMD including hypertension, dyslipidaemia, diabetes mellitus, ageing and smoking[18]. However, CMD also has significant predisposition for women[3,16,20]. Aggressive reversible risk factor modification, whilst limited in evidence, is accepted to be fundamental to CMD management[3,18,21]. CMD is also associated with increased mild epicardial atherosclerosis which may suggest a reason for increased levels of MACE associated with this disorder, but further highlights the need for risk factor optimisation[22,23]. Other specific disorders predispose to microvascular dysfunction including hypertrophic cardiomyopathy and idiopathic dilated cardiomyopathy. Treatment of these unique situations is outside the scope of this review.

CMD is heterogenous in its pathophysiology, clinical presentation, and response to therapy[3]. The inability of the coronary microcirculation to meet cardiac myocyte demand in CMD can be because of excessive vasoconstriction, or inadequate vasodilation[24]. Invasive angiographic provocation testing can help direct and individualise pharmacological therapy for CMD. Endothelial dysfunction results in vasoconstriction and can be demonstrated with intracoronary acetylcholine during coronary angiography[24]. Epicardial vasoconstriction detected with acetylcholine represents vasospastic angina which can co-exist with CMD, and is best treated with calcium channel blockade[25]. If there is no epicardial vasoconstriction to acetylcholine, but symptoms or electrocardiogram signs of ischaemia are reproduced (or to

adenosine), this indicates endothelial dependent CMD and again suggests likely benefit to calcium channel blockade[24].

CFR is the ratio of coronary blood flow at maximal dilation (commonly after intracoronary adenosine) compared to blood flow at baseline, which is reduced in CMD. It suggests impaired ability of the microvasculature to dilate and accommodate increased coronary flow during demand resulting in angina[18]. This is termed endothelial independent CMD[24]. Beta blockers are recommended first line for CMD, especially is impaired vasodilation is suspected[21]. Subsequently individuals with mixed endothelial independent CMD and either endothelial dependent CMD or vasospastic angina require combination therapy[17]. Confirming the diagnosis of CMD at time of angiography and titrating therapy to the endotype of CMD has demonstrated angina and quality of life improvement, and subsequently should be pursued[26].

(See Figure 2)

Given the lack of large clinical trials, management of CMD is based on weak evidence and much of the direction for treatment has been made from trials concerning INOCA or CSX. These pathologies do not exclude vasospastic angina and some non-cardiac causes of chest pain, rendering them unreliable when applying to CMD[24]. Despite this, widely accepted management principles include a combination of risk factor modification, anti-atherosclerotic therapy, and anti-angina therapy[17]. Novel therapies are being trialled for this

chronic disorder without a cure, particularly as some individuals may have limited benefit to standard care resulting in significant residual morbidity and poor quality of life.

1 - Reversible risk factors

Cardiac rehabilitation and physical exercise

Though outside the scope of this review of pharmacological therapy, the role of physical activity and cardiac rehabilitation cannot be emphasised enough. Cardiac rehabilitation may help with illness understanding[27] and alleviate some of the understandable fear that comes with a diagnosis of angina. Neuromodulation in this way may improve symptoms and alleviate anxiety to reduce pain[28]. Cardiac rehabilitation has been shown to have benefit in coronary angina, and exercise has been demonstrated to improve endothelial dysfunction[61]. A small trial of 13 subjects completed a 6 week cardiovascular conditioning program and low fat diet, which demonstrated improved myocardial flow reserve through improving vasodilatory capacity and resting blood flow[62]. A systematic review involving 8 trials looking at exercise prescription for angina in individuals with non-obstructive coronary artery disease, showed improvements in oxygen uptake, angina severity, exercise capacity and quality of life[63]. Whilst this is not specifically CMD and may include patients with vasospastic angina, it would suggest likely benefit in the CMD population.

Hypertension

Hypertension is associated with lower CFR and subsequent predisposition to CMD[29]. A trial with 137 subjects demonstrated treatment with antihypertensive therapy down to a normal blood pressure significantly improves CFR suggesting microvascular functional improvement

but this data did not capture angina change[29]. Perindopril therapy in 14 hypertensive patients for 12 months has demonstrated regression of periarteriolar fibrosis and improvement in coronary reserve[30].

Dyslipidaemia

Inverse correlations were observed between CFR and total lipid levels including LDL using PET scanning, suggesting LDL can contribute to CMD[31]. In another study, 25 patients with familial hypercholesterolaemia were found to have significant reduction in myocardial blood flow and CFR using PET scanning[32].

Smoking

In a study with 354 subjects, smoking has been shown to be associated with a significant reduction in transthoracic echocardiogram detected coronary flow reserve, suggesting microvascular dysfunction[33]. Furthermore, another small trial with 19 subjects demonstrated and average reduced CFR of 21% using PET scan in smokers, which improved following vitamin C to suggest oxidative stress is likely involved in some element of pathogenesis of CMD[18,34].

Diabetes Mellitus

Microvascular dysfunction is a known feature of diabetes resulting in retinopathy, nephropathy and neuropathy[18]. Type 1 and 2 diabetes mellitus have been shown to have reduced coronary vasodilator function predisposing to CMD[35]. Obesity, which is commonly associated with diabetes, predisposes to coronary atherosclerotic burden[36]. A small randomised trial of 33 subjects with INOCA found significant microvascular function

improvement with metformin therapy, suggesting potential improvements of CMD in hyperglycaemia reduction[37].

2 - Anti-atherosclerotic therapy

Aspirin

Inhibits platelet aggregation but also prevents the vasoconstrictive effects of thromboxane A2. The 2019 European Society of Cardiology guidelines for management of chronic coronary syndromes support at least one antiplatelet agent in diffuse epicardial atherosclerosis but in primary microvascular angina there is no robust evidence supporting a role of aspirin[38].

Statin therapy

Statins are associated with anti-inflammatory and anti-atherosclerotic effects[9]. Atorvastatin has been demonstrated to improve CFR in patients with slow coronary flow[39]. The 2019 European Society of Cardiology guidelines for management of chronic coronary syndromes suggest using statins in those with MVA[38].

Angiotensin converting enzyme inhibitors (and Angiotensin receptor blockade)

Act to block the vasoconstrictive effects of angiotensin II which can reduce vascular tone and promote vasodilation[23]. In a randomised trial on 78 women with confirmed CMD, quinapril therapy was associated with reduction in angina frequency as well as improved coronary flow reserve (CFR) in invasive testing[40]. Combination therapy of ramipril and atorvastatin added to diltiazem in a randomised trial with 45 patients was shown to reduce

frequency of angina in patients with Cardiac Syndrome X, suggesting likely some benefit in the CMD population, although CMD was not confirmed[41].

3 - Anti-anginal therapy

Beta Blockers

Beta blockers reduce myocardial oxygen demand and prolong diastolic filling, improving the chance of coronary flow meeting demand[9,18]. There are limited trials for beta blocker use in CMD. A comparison trial between propranolol and verapamil investigated 16 patients with angina and normal coronary arteries on angiography, but no confirmed CMD. It found a significant reduction in angina in the beta blocker arm compared to placebo, but not in verapamil suggesting beta blockers were superior to calcium channel blockade in this population[42]. A small 10 patient trial comparing atenolol, amlodipine and nitrate therapy in Cardiac syndrome X, showed angina improvement in the beta blocker population, but not in the nitrate or calcium channel blocker populations[43]. Beta blockers are recommended for MVA in the 2019 European Society of Cardiology guidelines for management of chronic coronary syndromes[38].

Nitrates

Act on arteriolar endothelium to cause vasodilation. Whilst traditionally prescribed for angina, accumulating evidence seems to suggest negligible benefit and even potential harm with the use of long-acting nitrates on MVA[44,45]. Reduced responsiveness from coronary arteries, steal syndrome from redistribution of blood flow to areas of adequate perfusion,

and poor medication tolerance and have all been suggested as potential reasons for the lack of nitrate benefit in MVA[44,45].

Calcium Channel Blockers (CCB)

Act to cause coronary vasodilation and are particularly effective in coronary vasospasm[25]. Limited trial benefit exists in CMD and diltiazem has been shown to not improve CFR in MVA[9,46]. Verapamil and Nifedipine use have been shown to improve angina symptoms in patients with angina and normal angiographic coronary arteries, but this did not remove patients with vasospastic angina[47]. CCB are recommended after Beta blockers in patients with MVA according to 2013 ESC guidelines[21].

Percutaneous coronary intervention (PCI)

Addressing epicardial coronary obstruction of significant lesions with PCI when co-existent pathology exists may be important in the overall management of CMD[21]. Invasive physiological vessel interrogation allows appraisal of each coronary compartment and may predict improvement in epicardial blood flow after PCI of a coronary stenosis. [44,48] Invasive coronary physiology predicts ischaemia relief but has not been shown to predict reduction in angina frequency.[49]

4 - Novel Therapies

Ranolazine

Improves myocardial perfusion by decreasing sodium and calcium overload through late sodium channel blockade, promoting myocardial relaxation[23]. Multiple mixed trial results

where small benefits in CFR have been demonstrated[50], as well as no benefit in others but benefit in angina symptoms[51]. Requires larger trials.

Ivabradine

Reduces heart rate thought I_f channel inhibition at the sinoatrial node. A small trial of 46 patients found symptomatic improvement of angina in ivabradine, but no change in microvascular function[51].

Phosphodiesterase Inhibition

Sildenafil has been shown to improve CFR in women with CMD with the significant improvement being in those with a CFR of < 2.5, but this was not clinically correlated with angina severity[52].

Rho-Kinase Inhibition (Fasudil)

Endothelin A receptor activates rho-kinase, eventually leading to vasoconstriction. Intracoronary fasudil, a rho-kinase inhibitor, improved angina and features of coronary ischaemia in endothelin dependent CMD[53].

Zibotentan

Is an endothelin A receptor antagonist, preventing the coronary vasoconstrictive effects of endothelin 1, which is often elevated in those with MVA[54]. It is currently undergoing phase 2 trials into its effect on exercise tolerance in MVA[54].

Coronary sinus occlusion

Coronary sinus occlusion can encourage retro filling of blood into the coronary microcirculation[55,56]. One such pressure controlled intermittent coronary sinus occlusion

device has been shown in the ST elevation myocardial infarction population to preserve microvascular function[55]. Another device to narrow the coronary sinus improved symptoms and quality of life in patients with refractory angina who weren't candidates for revascularisation[56].

Spinal cord stimulation

Electrical stimulation is thought to modulate pain fibres and possibly alter coronary blood flow. A small trial with 8 patients found small benefits in angina frequency in cardiac syndrome X with the use of transcutaneous electrical nerve stimulation (TENS)[57]. Spinal cord stimulation has been demonstrated in a small trial of 7 subjects to improve angina and exercise tolerance in INOCA patients[58].

Tricyclic Antidepressants (Imipramine, Amitriptyline)

Aim to reduce nociceptive stimuli leading to reduced angina severity[44]. For consideration in treatment resistant MVA possibly due to enhanced pain perception.

Hormone replacement

Given the predisposition in the post-menopausal women population, oestrogen deficiency has been suggested as a cause to CMD[9]. A small trial of 35 women demonstrated a reduction in angina symptoms in postmenopausal women and INOCA, but did not alter endothelial dysfunction[59].

Cognitive behavioural therapy

CMD is often associated with a degree of anxiety and mood disorders given the chronicity. Autogenic relaxation training in 53 women demonstrated improvements in symptom frequency with cardiac syndrome X[60]. A small systemic review of 6 trials suggested a modest

benefit predominately in the first 3 months of psychotherapy in individuals with chest pain and normal coronary arteries mainly focusing on cognitive behavioural framework. However, these patients had no formal CMD diagnosis made and their pathogenesis could be broad.

(See Figure 3)

Conclusion

CMD remains a challenging condition to manage due to heterogenous pathophysiology, presentation, and response to therapy. Awareness of CMD is improving but therapeutic randomised trials of therapy are lacking. Invasive assessment of the coronary microcirculation can stratify anti-ischaemic therapy to improved patient outcomes. Beta-blockers remain the cornerstone of therapy for angina due to CMD. The role of non-pharmacological interventions including cardiovascular risk factor modification, lifestyle interventions and cardiac rehabilitation is central to management. Further research is needed to assess traditional and novel pharmacological therapies on symptoms and clinical events in the various CMD endotypes.

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