Review Article

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Microvascular Angina-An Enigma

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Abstract

Prognosis of patients with Microvascular angina is not as benign as is considered despite normal coronaries. It contributes to increased suffering, health care costs and may have role in long term increased cardiovascular risk. There is increasing consensus about underlying coronary microvasculature abnormality with or without other risk factors. A lot more research and clinical work is required to develope effective and optimum treatment to alleviate the symptoms and improve microvascular function. In this review we have discussed the prevalence, pathophysiology and available investigative and treatment modalities and present limitations and need of further studies and research about coronary microvascular dysfunction.

Keywords: Angina; CFR; Coronary; Microvascular; Syndrome X.

As coronary angiography (CAG) became widely practiced since 1960s, many patients have undergone CAG because of angina on exertion with clinical diagnosis of coronary artery disease (CAD). It is seen that not all patients with clinical suspicion of CAD had obstruction of coronary arteries. Up to 40% of patients undergoing CAG fall into this category[1], having normal or near normal coronary arteries at angiography and no evidence of coronary vasospasm. As many as 50% to 65% of these patients with chest pain without obstructive CAD are believed to have coronary microvascular dysfunction (CMD), also known as microvascular angina [2-5]. CMD is defined as impaired vasodilatation of arterioles, leading to an inadequate increase in blood flow from rest to stress. The term "Microvascular Angina" (MVA) was coined by Cannon and Epstein [6]. They thought that dysfunction of small intramural prearteriolar coronary arteries is central to the pathogenesis, hence used the term. The term "cardiac syndrome X" is used for patients with anginal chest pain and ST-segment depression or perfusion abnormality during stress despite normal coronary arteriogram. The cardiac Syndrome X is characterized by angina predominantly on excretion, a positive electrocardiogram (ECG) response to exercise testing, normal coronary arteries at angiography and absence of epicardial coronary artery spasm and of known causes of microvascular dysfunction such as left ventricular hypertrophy, systemic hypertension, and valvular heart disease. Often the term microvascular angina and cardiac syndrome X are used interchangeably however microvascular angina is an identifiable pathophysiological mechanism whereas there is no universal mechanism described for cardiac syndrome X. The lack of definitive evidence of ischemia in some patients with syndrome X has focused attention on alternative nonischemic causes of cardiac-related pain, including a decreased threshold for pain perception—the so-called sensitive heart syndrome [7]. So it is prudent to use the term microvascular angina instead of syndrome X to avoid ambiguity. Irrespective of the definition used (whether exercise-induced ischemic changes are present in the ECG or not), patients with angina with normal coronary angiograms show a distinct female preponderance [8,9]. Even after correcting for body surface area, women have smaller coronary arteries. This can seriously affect symptoms from anything that reduces diameter such as stenosis or endothelial dysfunction. Most women with diagnosis of

microvascular dysfunction have estrogen deficient state i.e. PCOS or post menopausal women. But how estrogen affect the microvasculature is still speculative. In WISE study [10], 42% of women with anginal chest pain in the absence of obstructive CAD had coronary microvascular dysfunction.

Pathophysiology

The mechanisms proposed include endothelial cell and smooth muscle dysfunction i.e. microvascular dysfunction, diffuse atherosclerosis, platelet dysfunction, inflammation local or systemic, estrogen deficiency and abnormal pain perception. Involvement of coronary arterioles with diameter less than 500 M sparing epicardial arteries is responsible for reduction of myocardial perfusion and clinical spectrum in microvascular angina. The impaired vasodilatation of arterioles with inadequate blood flow in response to stress causes structural and functional changes to myocardium and angina. Even in the absence of atherosclerosis and vasospastic disease, coronary microvascular dysfunction (CMD) can lead to transient myocardial ischaemia as in patients with coronary artery disease (CAD), cardiomyopathy (CMP) or in Takotsubo syndrome and there may be overlap of atherosclerosis, vasospasm and microvascular dysfunction in significant proportion of patients.

Camici and Crea [11]divided coronary microvacsular dysfunction into 4 types depending on presence or absence of obstructive CAD (type 1 and type 2 respectively), involvement of myocardium (Type 3) and whether iatrogenic (type 4). Microvascular angina can also be classified as primary or secondary where primary microvascular angina is diagnosis of exclusion while secondary form occurring in association with specific cardiac or systemic diseases with cardiac involvement. Microvascular angina can also be classified on the basis of clinical presentation as stable or unstable with stable form related to effort while unstable form occurring at rest or on minimal exertion or increasing type of angina.

Risk factors for microvascular angina include gender, aging, hypertension, diabetes, obesity, insulin resistance, early menopause, smoking, lipid abnormalities and chronic inflammation resulting in endothelial dysfunction, smooth muscle dysfunction and vascular remodeling. Abnormal endothelium dependent and non-endothelium-dependent microvascular dilatation results in decreased myocardial perfusion, ischaemia and angina. Systemic lupus erythematosus and rheumatoid arthritis are characterized by an inverse correlation between coronary flow reserve (CFR) and C-reactive protein concentrations suggesting that chronic inflammation may contribute to microvascular abnormalities. Disorders of nitric oxide metabolism, dysregulation of numerous mediators including inflammatory cytokines, estrogen, or adrenergic receptors, and alterations in the expression or production of local vasoactive substances such as angiotensin II and endothelin are other plausible mechanisms contributing to microvascular dysfunction.

Assessment and Diagnosis

It is important to rule out other causes of chest pain like gastroesophageal reflux disease, musculoskeletal pain, pericardia or pleural involvement and psychogenic and functional involvement. Diagnosis of primary MVA also requires the exclusion of significant lesion of epicardial coronary arteries on angiography and ruling out coronary spasm or other abnormalities like bridging before labeling as primary microvascular angina.

Though it is not feasible to image coronary microcirculation directly or catheterize resistance vessels, there are noninvasive and invasive methods to assess coronary microcirculation. In fact, indirect parameters such as myocardial perfusion and perfusion reserve provide an index of microvascular function. Until now percutaneous angiography has been the traditional invasive method to assess micro circulation using blush score, use of flow wire and calculation of CFR. Now with advancement in science and technology we are able to assess microvascular function non invasively with modalities like myocardial contrast study in conjunction with trans thoracic echo, cardiac magnetic resonance imaging(CMR) and PET scan. PET scan is valuable in measuring absolute myocardial perfusion and perfusion reserve to assess microvascular dysfunction. In one of the recent analysis [12] Marinescu et al proposed a definition of CMD, as CFR or myocardial perfusion reserve (MPR) <2.5 using PET, CMR, intracoronary (IC) Doppler wire, or thermodilution methods in the presence of angina or symptom equivalent, exclusion of epicardial CAD with stenosis 50% or no evaluation of CAD and absence of known structural heart disease or heart failure.

Treatment

Treatment for microvascular angina is mainly directed at risk factor reduction, symptomatic and

targeting coronary microvasculature to improve myocardial perfusion. Non pharmacological measures are equally important in improving endothelial dysfunction and improving coronary microcirculation like Smoking cessation, weight loss, Mediterranean diet and physical exercise. Strict glycaemic control also reduces microvascular disease to a greater extent. Treatment with quinapril an angiotensin convertase enzyme inhibitor (ACEI) was shown to improve CFR by Pauly et al in a double-blind placebo-controlled trial where as kaski et al and motz et found improved stress test parameters in their studies. Statins due to their pleotropic action including anti-inflammatory and antioxidative action may help in improving endothelial function and microvascular tone. Metformin by reducing Insulin resistance can improve microvascular dysfunction and needs large scale trials. Despite inconsistent response to Beta-blockers in patients with microvascular angina they are the first line treatment and more effective in reducing exercise related symptoms and anginal episodes. Nebivolol causes release of nitric oxide at endothelial level and improves coronary flow reserve in addition to its beta blocking property and needs large scale studies in patients with microvascular angina. Due to conflicting results from various studies and unproven role calcium antagonists are used as add on or second line therapy. Oral Nitrates have no proven action at micro vasculature and doubtful role in isolated microvascular dysfunction with sublingual nitroglycerin reducing angina in less than 50% of patients with micro vascular angina.

Newer Drugs and Other Treatment Modalities

Nicorandil causes arterial vasodilatation by opening potassium channel and improves myocardial perfusion. Many trial have shown improved TIMI score in primary percutaneous coronary intervention (PCI) and improving no reflow with use of parenteral nikorandil. Despite symptomatic benefit, due to fewer studies of nikorandil in patients with microvascular angina large scale trials are warranted before its routine use in these subsets. Trimetazidine is a 3-ketoacyl coenzyme A thiolase inhibitor decreasing free fatty acis(FFA) oxidation and has favorable impact in patients with primary stable MVA in terms of reducing anginal episodes and improving effort tolerance as seen in small studies and needs further evaluation. Ivabradine is funny channel inhibitor acting on sinus node and improves symptoms in patient with microvascular angina through unknown mechanism. Ranolazine is late sodium current inhibitor, may improve diastolic function and was shown to have beneficial effects in patients with primary stable MVA though it has no direct effect on endothelial function or coronary flow. Sildenafil causes endothelium-dependent dilatation of arterioles and vascular smooth muscle relaxation by inhibition of the breakdown of cyclic guanosine monophosphate. One of the studies had statistically significant improvement in coronary flow in patient's of microvascular angina with CFR less than 2.5 but no benefit if baseline CFR was >2.5. Aminophylline is adenosine receptor antagonist increasing exercise-induced chest pain threshold and has favourable impact to reduce angina by redistribution of coronary flow. Imipramine is serotonin and noradrenalin uptake inhibitor reducing visceral pain and may be tried in patients symptomatic for angina despite optimum medications. However its side effect profile may limit its widespread use. By altering central pain processing in cerebral cortex and improving tone of coronary microvasculature through local spinal circuits spinal cord stimulation may have positive impact and can be tried as last resort. Trans cutaneous electrical nerve stimulation has shown to reduce symptoms in some patients with refractory micro vascular angina.

According to ESC guidelines beta blockers, aspirin and statins are first line therapy while Calcium channel blockers are second line as alternative to β blockers in patients not tolerating or responding to β blockers.

Future

Routine use of CFR or MPR with a cutoff 1.5 and 2.5 seems to help stratify patients with CFR or MPR >2.5 ruling out CMD while a CFR <1.5 affirming CMD. According to Suwaidi et al [13] value of <1.5 is suggestive of endothelial-dependent dilation and <2.5 for endothelial-independent dilation in patients with angina but normal coronaries. There is need of validation of imaging techniques with large randomized trial in various ethnic groups over widespread geography in patients with chest pain without obstructive CAD. Also large studies are required with newer agents.

Conclusion

Even though patients with normal coronaries have better prognosis as compared to those with obstructive CAD, those with proven microvascular

angina and microvascular dysfunction are associated with poorer prognosis and can result in significant morbidity and contribute even to mortality. At present the treatment for microvascular dysfunction is mainly directed at reduction and treatment of risk factors and use of current day antianginals. Large scale randomised trials with newer promising agents are required to expand the armamentarium against microvascular angina.

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