Coronary Microvascular Dysfunction: An Update
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Abstract:
Structural and functional abnormalities of the microcirculation can impair myocardial perfusion which is called coronary microvascular dysfunction and the resulting ischemia is known as microvascular ischaemia. Most of the researches have focused on the epicardial coronary arteries while addressing angina pectoris. Although the importance of the coronary microcirculation in maintaining appropriate myocardial perfusion has been recognized for several decades, the substantial morbidity of coronary microvascular dysfunction (CMD) has not been appreciated until recently. It is not possible to diagnose of microvascular angina clinically with the current knowledge. Resting or exercise electrocardiogram is nondiagnostic. Imaging with speckle tracking in echocardiography may reveal focal diastolic and/or systolic dysfunction. Other noninvasive investigations includes Contrast stress echocardiography, 99Tc-sestamibi imaging cardiovascular magnetic resonance (CMR), Nuclear magnetic resonance spectroscopy may show some degree of abnormality. Invasive methods like intracoronary adenosine and acetylcholine test may guide us to diagnose CMD. No guideline directed medical therapy is still available for the CMD. Risk factors modification like smoking cessation and weight-loss may improve endothelial dysfunction and CMD. Beta blockers, calcium channel blockers, Angiotensin converting enzyme inhibitors and statin are now used in different clinical condition related to microvascular angina. After these medical treatment patient with microvascular angina have higher risk of MACE compared with people without angina. So, physicians must be aware of this potentially fatal but under recognized clinical entity.

Key Words: Coronary Microvascular Dysfunction (CMD), Update.

University Heart Journal 2020; 16(1): 43-49

Introduction:
Coronary angiography is found to be normal in about 30% of cases who present with chest pain. & this percentage is even higher in woman1. Structural and functional abnormalities of the microcirculation can impair myocardial perfusion which is called coronary microvascular dysfunction and the resulting ischemia is known as microvascular ischaemia2,3. Most of the researches have focused on the epicardial coronary arteries while addressing angina pectoris. Although the importance of the coronary microcirculation in maintaining appropriate myocardial perfusion has been recognized for several decades, the substantial morbidity of coronary microvascular dysfunction (CMD) has not been appreciated until recently. Studies have found that CMD itself is associated with higher rates of MACE irrespective of presence of obstructive CAD4,5,6. According to Camici and Crea, CMD are classified CMD into four subtypes: (i) CMD without myocardial diseases and obstructive CAD, (ii) CMD in myocardial diseases, (iii) CMD in obstructive CAD, and (iv) iatrogenic CMD. The underlying mechanisms of CMD vary according to clinical context and some of them can even overlap. The aim of this article is to provide an update on CMD based on published literature in recent years.

Risk Factors & Pathophysiology
CMD is associated with hypertension, dyslipidemia, smoking, insulin resistance & diabetes and accelerated by early menopause and obesity. CFR is also reduced with aging. Coronary microvascular abnormality are more pronounced in female than male (66% vs. 60%)8

Although microvascular function appears similar in women and men by Index of microcirculatory resistance (IMR), CFR is lower in women due to higher resting coronary vasomotor tone.8

Endothelial dependent and independent coronary vasodilatation are also significantly impaired in chronic
Studies have shown that endothelial dysfunction can be improved by good glycemic control in patients with no obstructive epicardial CAD.

Inflammation also adversely affect coronary microvascular responses as evidenced by raised C-reactive protein in patients with microvascular angina. CMD is also common in patients with systemic lupus erythematosus and rheumatoid arthritis.

In HCM, medial hypertrophy, intimal hyperplasia, and decreased luminal size of the micro vessels cause CMD and myocardial ischemia.

In Takutsubo syndrome, microvascular constriction with subclinical CMD are augmented by endothelial dysfunction.

In myocarditis, chest pain is due to myocarditis induced coronary vasoconstriction and direct infection of endothelial and/or vascular smooth muscle cells may also contribute.

In aortic stenosis, CFR is adversely affected by reduced diastolic filling time, increased diastolic filling pressure and intramyocardial pressure which ultimately lead to reduced sub-endocardial perfusion, increased intramyocardial systolic pressure, and delayed myocardial relaxation after systole.

In infiltrative cardiac diseases like amyloidosis, myocyte hypertrophy and perivascular fibrosis & endothelial deposits cause MVD & increased microvascular resistance.

CMD may present with obstructive atherosclerotic coronary arteries. Stable IHD patient may share common risk factors for microvascular dysfunction and these may lead to concomitant presence of both. In ACS patient MVO results from the combination of four factors: (i) distal atherothrombotic embolization; (ii) ischaemic injury; (iii) reperfusion injury; and (iv) individual susceptibility of coronary microcirculation to injury.

CMD after PCI occur due to coronary vasoconstriction and embolization of coronary microcirculation & same phenomenon also happen after coronary artery bypass grafting (CABG). (Figure-2)

Diagnosis
It is not possible to diagnose of microvascular angina clinically with the current knowledge. Electrocardiogram may show non specific ST T wave change, and exercise electrocardiogram is nondiagnostic. Regional wall motion abnormalities are usually not found in echocardiography. Radio-isotope imaging can detect only severe localized disease. So non-invasive techniques need high index of clinical suspicion to detect CMD. Currently, diagnosis requires presence of normal epicardial coronaries, CFR less than 2.5 on adenosine induced hyperemia, and absence of spasm of epicardial coronaries on acetylcholine challenge test.
Clinical Profile
Clinically it is very difficult to clearly differentiate microvascular angina from angina that results from isolated epicardial coronary artery disease. The clues to suspect CMD are symptoms persistence despite complete revascularization symptoms disproportionate to angiographic findings, poor response to nitroglycerine & cessation of effort. Patients with microvascular coronary spasm usually have symptoms during night or early morning while at rest.

In cardiac syndrome Y, abnormally high microvascular resistance causes rest angina & coronary slow flow is usually found.

No research work has been done on angina equivalent. The role of microvascular dysfunction in ST elevation myocardial infarction is also not clear. Chronic, diffuse, persistent, and progressive coronary microvascular dysfunction can produce global diastolic and/or systolic dysfunction with normal coronary angiogram in DCM patients.

Non-invasive method
Resting electrocardiogram does not demonstrate significant changes even during chest pain. In microvascular coronary spasm, borderline ischemic electrocardiogram changes may be found. Microvascular angina may be suggested by chest pain with ischemic ECG changes without any wall motion abnormality on echocardiography. Adenosine induced early long axis diastolic dysfunction may be found in tissue Doppler imaging. Strain rate imaging with speckle tracking may reveal focal diastolic and/or systolic dysfunction. Exercise ECG is usually nonconclusive. Slow recovery or unsatisfactory response to sublingual nitrates may suggest microvascular dysfunction. Flow in left anterior descending coronary artery can be assessed by Doppler echocardiography. Coronary flow velocity is measured at baseline and again after adenosine induced maximal hyperemia. Difference is taken as representative of coronary flow reserve (CFR). In absence of epicardial coronary artery disease, increased flow is taken as an indirect marker of dilatation of coronary microvasculature in response to adenosine. Other noninvasive investigations includes: Contrast stress echocardiography, 99Tc-sestamibi imaging, cardiovascular magnetic resonance (CMR), Nuclear magnetic resonance spectroscopy.

Invasive methods
While diagnosing primary microvascular angina, it should be established that epicardial coronary arteries are normal in structure & function. Acetylcholine and adenosine respectively cause endothelium dependent and endothelium independent vasodilatation of epicardial coronaries. Microvascular dysfunction is often associated with epicardial coronary artery disease. While fractional flow reserve (FFR) determines functional significance of a coronary lesion, corrected thrombolysis in myocardial infarction (TIMI) frame count quantifies coronary blood flow. Slow flow may be present in case of advanced & extensive coronary microvascular dysfunction. It is also present in case of diffuse spasm, increased coronary vasomotor tone or micro embolization. Microcirculation can be assessed qualitatively by Myocardial blushing, though it’s sensitivity is low.

Suspected vasospastic angina can be provoked by intracoronary injection of acetylcholine. Appearance of angina and ECG changes without spasm of epicardial coronary artery suggests coronary microvascular spasm.
But it frequently coexists with spasm of epicardial coronaries. Right coronary artery is most susceptible to vasospasm. Therefore, assessment of coronary microvascular function only in left anterior descending coronary may be insufficient. Index of microcirculatory resistance (IMR) is calculated as distal coronary pressure multiplied by the hyperemic mean transit time. It has got some limitations of its own.

As none of the diagnostic tests are conclusive of CMD, clinical correlation is of paramount importance for detection of CMD. (Figure-3)

Fig.-3: Diagnostic algorithm. Abbreviations: Ach, acetylcholine; ACS, acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; IMR, index of microcirculatory resistance; FFR, fractional flow reserve; TMT, treadmill stress test.

Treatment of Coronary Microvascular Dysfunction
No guideline directed medical therapy is still available for the CMD. Risk factors modification like smoking cessation and weight-loss may improve endothelial dysfunction and CMD. Perindopril and indapamide for may be prescribed in the absence of myocardial diseases and obstructive coronary artery disease. Statins and angiotensin converting enzyme (ACE) inhibitors should be present as first line of treatment in MVA. Calcium antagonists do not improve CFR and show inconsistent effects on symptoms, while beta-blockers appear to reduce chest pain. Ranolazine is also beneficial for MVA. Imipramine may give symptomatic improvement in case of altered cardiac pain perception. (Figure-4)

Finally, spinal cord stimulation and enhanced external counterpulsation may be tried in case of refractory angina. Menopausal hormone therapy may improve emotional wellbeing in postmenopausal women with angina and ‘normal’ angiograms; yet, there is no symptom benefit for this patients.

In HCM, alcohol septal ablation may improve CFR and septal endocardial-to-epicardial MBF. While drug treatment offers no benefit in enhancing myocardial perfusion.

In dilated cardiomyopathy, beta-blockers, but not calcium antagonists or ACE inhibitors likely to improve CMD. Allopurinol may also have beneficial effect on CMD.

No study is yet to be performed to evaluate the role of any intervention on CMD in acute myocarditis but beta-blockers & ivabradine may be helpful by selectively reducing the heart rate & increasing diastolic filling time. But this theoretical benefit must be translated into clinical trials.

A-ch, acetylcholine test; AFD, Anderson-Fabry’s disease; AS, aortic stenosis; BG, blush grade; CABG’, coronary aortic bypass graft; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; COCM, congestive cardiomyopathy; HCM, hypertrophic cardiomyopathy; MVA, microvascular angina; MVO, microvascular obstruction; PET: positron emission tomography; pPCI, primary percutaneous coronary intervention; PVB, Parvovirus B9; RF, risk factors; STR,
ST segment resolution; Tn, troponin; TTDE, transthoracic Doppler echocardiography. It is unknown the incremental prognostic value of coronary microvascular dysfunction in addition to that conveyed by risk factors.\(^7\)

Attempts should be made to promote collateral growth in case of refractory angina which may favorably influence outcome & symptoms. Therapeutic interventions able to promote collateral growth may have an impact on outcome and also on symptoms. Though gene therapy offered some hope but the results of randomized controlled trials are not promising. Moreover to promote collaterals, intra-myocardial administration of progenitor vascular cells should be validated through trials.

In ACS two small randomized studies\(^46\) found a beneficial effect of manual thrombus aspiration vs. the standard procedure in improving myocardial reperfusion. The concept of intracoronary adenosine administration is promising. Ischemic conditioning, in particular, ischemic post-conditioning\(^47\) and remote pre-conditioning\(^48\) are also beneficial.

**Conclusion:**

Patients with microvascular angina have higher risk of MACE compared with people without angina. Physicians must be aware of this potentially fatal but under recognized clinical entity. *Extensive research work should be carried out to identify* suitable non-invasive methods for evaluation of microvascular and endothelial function. Now a day’s PET, MRI or CT perfusion, and contrast-enhanced Doppler echocardiography is a potential modality. Though till now guideline directed treatment is not available but treatment should address the underlying pathophysiology. So it can be concluded that CMD is a true clinical entity rather than a mystery or an academic curiosity.

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