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Review Article

Etiopathogenesis of microvascular angina: Caveats in our knowledge

S.R. Mittal

Department of Cardiology, Mittal Hospital & Research Centre, Pushkar Road, Ajmer, Rajasthan 305001, India

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ABSTRACT

Nearly 50% of subjects of coronary artery disease suffer from coronary microvascular dysfunction. Various etiopathogenetic factors have been proposed by different workers but no hypothesis can explain the genesis of microvascular angina in all patients. We have made an attempt to review the literature to find caveats in our knowledge so that future studies can be better designed.

Since it's recognition, microvascular angina was considered synonymous with cardiac syndrome X resulting in several controversies. Cardiac syndrome X is defined as typical angina with positive stress test but normal coronary angiogram.[1] Now it is clear that there are several causes for angina or angina like discomfort with normal coronary angiogram. Microvascular angina is a subset with specific etiopathogenesis and therapeutic implications.[2,3] Coronary microvascular dysfunction is suspected by a positive physical or pharmacological stress test using electrocardiography/cardiac MRI/SPECT or PET.[4] Coronary flow reserve less than 2.5 on adenosine induced maximal hyperemia suggests microvascular dysfunction.[5] Coronary flow reserve in left anterior descending coronary artery can be assessed non-invasively using transthoracic Doppler echocardiography.[2] Invasively, coronary microvascular dysfunction can be evaluated by index of microcirculatory resistance.[6] Several issues, however, need to be addressed for further refinement of diagnosis and decision about management strategy in an individual patient.

1. Documentation of myocardial ischemia

Objective evidence of myocardial ischemia, however, has not been observed in all cases inspite of ischemia like ST-T changes on exercise electrocardiograms.[7] Reasons for the low sensitivity of presently available non invasive methods (stress test, echocardiography & radio-isotope perfusion imaging) to detect ischemia in cases of microvascular angina are not clear.[8,9]

It appears that sensitivity and specificity of different methods needs re-evaluation in the context of microvascular angina. Etiopathogenesis, prognosis and management may be different in patients with evidence of myocardial ischemia than in those without evidence of myocardial ischemia.[10]

2. Role of abnormal pain perception

Abnormal pain perception has been proposed as an underlying mechanism for chest pain in patients with microvascular

E-mail address: sarweshwarm@gmail.com.
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angina.[4,11] High incidence of anxiety and panic attacks and relief with imipramine, transcutaneous stimulation and spinal cord stimulation are considered to support such mechanism. However, there are some difficulties in accepting this hypothesis.

(i) Most of the studies were performed in cases of syndrome X. Coronary microvascular dysfunction was not documented.
(ii) As the studies included cases of syndrome X, more females were studied by default. Anxiety and panic attacks are more frequent in females.
(iii) Most of the studies have shown partial symptomatic relief in some patients. There is no objective evidence of improvement in microvascular dysfunction. Symptomatic relief could be because of placebo effect.
(iv) Imipramine is an antidepressant. It is possible that responders had occult depression with somatic localization rather than microvascular angina.

It is possible that some patients of microvascular angina (specially females) have abnormal pain perception as a comorbidity. It is also possible that acute adrenergic drive during a panic attack can produce transient microvascular spasm. These possibilities need documentation.

3. Role of autonomic dysfunction

Increased adrenergic activity has been observed in some patients of cardiac syndrome X.[12] However, coronary adrenergic hyperreactivity has not been documented.[13] Plasma catecholamine levels have been found to be normal[14] and alpha blockade has not been shown to increase myocardial blood flow in patients of cardiac syndrome X.[15] It has been postulated that parasympathetic impairment could produce microvascular dysfunction through its' influence on endothelial function.[16] However, Frobert et al[17] found no evidence of autonomic dysfunction in patients of cardiac syndrome X with positive exercise test. Etiological significance of autonomic dysfunction is, therefore, not clear. Stress cardiomyopathy has been shown to be associated with coronary microvascular dysfunction in the affected area in small number of selected patients.[18] However, ischemia itself can also increase microvascular resistance.[19] Inspite of these limitations and conflicting observations in literature, some possibilities deserve further evaluation.

(i) Some subjects can have hyperdynamic myocardial response to beta adrenergic stimulation.[20] This may produce chest pain specially, in subjects with abnormal pain perception.
(ii) Transient increase in adrenergic activity can produce coronary microvascular spasm.[2] Transient autonomic dysfunction has been shown to precede ST segment depression in patients with syndrome X.[21]
(iii) It is possible that sympatho-vagal imbalance can produce increased coronary microvascular resistance at rest and decreased dilatory capacity during stress. Such pathophysiology can produce effort angina.

4. Role of inflammation

Higher levels of circulating intercellular adhesion molecule – 1 and high sensitivity CRP have been observed in some cases.[22,23] Some issues, however, need to be clarified.

(i) There is no evidence that subjects with presence of inflammatory markers are more prone to have isolated coronary microvascular dysfunction without involvement of epicardial coronaries.
(ii) There is no evidence of any correlation between presence, duration and magnitude of abnormality in inflammatory markers and coronary microvascular dysfunction.
(iii) Is coronary microvascular dysfunction present only in patients having higher levels of inflammatory markers due to systemic vasculitis? Will inflammatory process not involving vessels also produce coronary microvascular dysfunction?
(iv) Will management of systemic inflammation retard or revert coronary microvascular dysfunction?
(v) Do other markers of inflammation e.g. raised ESR or gammaglobulins also correlate with coronary microvascular dysfunction?

5. Role of cardiovascular risk factors

(i) Systemic hypertension is associated with interstitial fibrosis and myocyte hypertrophy.[24] These factors can also produce angina with normal coronary angiograms. How to differentiate these possibilities from microvascular angina?
(ii) Diabetes mellitus is associated with microvascular dysfunction.[25] However, diabetics also have impaired myocardial metabolic function[26] which may produce angina even in absence of microvascular dysfunction. How to differentiate?
(iii) Common cardiovascular risk factors are frequently present in patients with coronary microvascular dysfunction.[27–29] However, there is poor correlation between risk factors and severity of coronary microvascular dysfunction.[30–32] On the contrary, coronary microvascular spam has been found to be more common in white, females with lower body mass index, lower frequency of smoking and relatively higher levels of HDL.[33,34]
(iv) Initial impression of higher incidence in females was derived from studies of patients of syndrome X. Studies comparing coronary flow reserve in response to adenosine have, however, found similar incidence in both sexes.[35]It is also not clear if there are any other sex differences in microvascular angina.
(v) Reason for isolated/dominant initial localization of pathology to microcirculation in some patients and epicardial coronaries in other patients is not clear. Genetic predisposition of microcirculation might be important.[36,37]