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Pathophysiology of Coronary Microvascular Dysfunction

Review Article

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Abstract

Coronary microvascular dysfunction is a group of disorders with heterogenous pathophysiology. At present there are no methods to pinpoint the underlying structural and functional disorder in a given patient. Identification of exact pathophysiology is necessary to tailor correct diagnostic approach and therapeutic modality.

Keywords: Angina; Coronary Artery Disease; Ischemic Heart Disease; Microvasculature; Syndrome X

Introduction

Coronary microvascular dysfunction is considered when there is angina with normal coronary angiogram, coronary flow reserve is less than 2.5 on adenosine induced hyperemia and there is no spasm of epicardial coronaries on acetylcholine provocation. Possibility of primary coronary microvascular dysfunction can be considered only after excluding secondary causes like

- Obstructive coronary artery disease by OCT / IVUS /PET
- Myocardial diseases like HCM , DCM
- Iatrogenic - Post PCI, Post CABG

Underlying pathophysiology is heterogenous. This is responsible for nonuniform response to different diagnostic tests and therapeutic approaches.

(a) Gender Differences

Structural differences in microvasculature and coronary reactivity have been observed between two sexes [1]. It is not clear if there are any sex differences in pathophysiology and risk factors [2]. Pathogenesis of such differences and their clinical relevance in microvascular angina is not clear.

(b) Site of Lesion

Presently, all vessels not seen on coronary angiography are grouped as "microvessels". Anatomically these include epicardial prearterioles, intramyocardial arterioles and subendocardial capillaries [3]. Lesion at any site will increase microvascular resistance. Capillaries do not dilate in response to adenosine due to absence of smooth muscles. Therefore, they are the site of maximum microvascular resistance during hyperemia [4]. Further, problems at the level of interstitium or myocytes will also present as angina with normal coronary angiograms. Opherk et al. [5] found swelling of mitochondria on electron microscopy of left ventricular biopsy. Arterioles, metaarterioles, capillaries and venules were normal. Etiopathology, clinical and laboratory profile, response to different therapies and prognosis may differ according to site of lesion. Rinkevich et al. [6] compared myocardial contrast echocardiography in women with syndrome X and controls. They indirectly concluded that coronary resistance vessels are the site of microvascular abnormality. However at present, there are no methods that can pinpoint the site of lesion in vivo.

(c) Structural Alterations

Microvascular dysfunction could be due to several structural alterations -

(i) Rarefaction - Reduced number of arterioles and capillaries per unit of myocardium [7]. Myocardial infarction, hypertension, diabetes and end stage dilated cardiomyopathy are associated with

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reduced myocardial capillary density [8]. These conditions are, however, also associated with several other pathologies that can produce angina.

(ii) Interstitial infiltration [8]

(iii) Perivascular fibrosis [9]

(iv) Medial hypertrophy: On transarterial left ventricular endomyocardial biopsy, Opherk et al found occasional small arteries with a media with more than two muscle cell layers [5].

(v) Atherosclerosis [7]

(vi) Microembotization: Plaque and vessel wall constituents including lipid, matrix, endothelial cells, fibrin and platelet thrombi can embolize following thrombolysis or intervention [10]. Preexisting microvascular disease may reduce the adaptive capacity to embolization. Such reduction in adaptive capacity may be related to underlying disease eg diabetes or vasculitis. Genetic factors may also predispose an individual's microcirculation to decreased capacity to accommodate particulate matter.

Myocyte alteration:

Strategy for management may differ depending on pathology. Opherk et al. [5] found no evidence of small vessel disease on transarterial left ventricular endomyocardial biopsy of patients with syndrome X. Endomyocardial biopsy has been found to have low sensitivity [5]. It could be due to patchy distribution of disease [11]. However, quantitative measurement of coronary artery size with adenosine, acetylcholine and nitroglycerine has revealed similar measurements in left anterior descending and circumflex arteries suggesting a diffuse rather than localized pathology [12]. Low yield of endomyocardial biopsy could also be due to the fact that endomyocardial biopsy can study only endocardium and adjacent myocardium. Pathology of epicardial prearterioles and myocardial arterioles are not evaluated. Vessels between 110-200 u are not accessible to electrone microscopic examination [5]. It is also possible that structural alteration are not present in all cases. Microvascular angina may result from functional abnormalities without detectable structural abnormality [13].

(d) Functional Alterations

Several distrubances of microvascular function can be involved in genesis of microvascular angina.

(i) Increased resting tone. In some patients it can be indirectly suspected if there is abnormal cardiac adrenergic nerve function at rest [14] or there is slow flow phenomenon on coronary angiography with reduced coronary sinus oxygen saturation [15]. This may be present even when symptoms are relatively quiescent and may be transient [16]. There is, however, no noninvasive method to suspect this possibility. Clinical significance in microvascular angina is not clear.

(ii) Hypercontractile response to various stimuli [15,17]. Ergonovine injection, mental stress, cold pressor and hyperventilation have been shown to cause constriction of coronary microcirculation. Exercise has also been shown to cause abnormal coronary vasomotion in patients with normal coronary arteries and reduced coronary flow reserve [18]. However, response to various stress stimuli in laboratory may not correlate with events of daily life. It may result in false positive as well as false negative results.

(iii) Transient spasm [19]. Transient diffuse microvascular spasm has been proposed as an explanation for angina with ST segment elevation in presence of normal epicardial coronary arteries during intracoronary administration of acetylcholine. However most of the patients are likely to have isolated or concomittant spasm of epicardial coronaries. Literature on isolated coronary microvascular spasm is scanty and response to acetylcholine in catheterization laboratory may not correctly represent events occurring outside the laboratory.

(iv) Decreased capacity to dilate - endothelium dependent and/or endothelium independent [20].

(v) Compression of intramyocardial vessels by the intramyocardial pressure.

Several factors govern flow in microcirculation [21] Table 1. Abnormalities of some of these factors has been observed in some clinical studies [22-26]. Decreased coronary dilatory capacity has been concluded by reduced coronary blood flow response to various pharmacological agents [5,20]. Response to acetylcholine is considered to represent reduced nitric oxide release from endothelium. However acetylcholine also has direct vasoconstriction effect [27]. Further, it may not affect the metabolic pathway of nitric oxide in some cases [28]. Adensoine and dipyridomole produce endothelium independent vasodilation through relaxation of smooth muscle cells. There could be several yet unknown factors. Response to few pharmacological agents may not correctly represent response to various stimuli of day to day life. Identification of exact functional alteration and it's cause will help in development of specific therapy.

(e) Rheological Disorders

As capillaries are the site of maximum resistance during

Table 1: Factors governing microcirculation.

(1)	Extravascular compression	(a) LVEDP (b) RVEDP
(2)	Local physical factors	(a) Myogenic regulation (b) Flow mediated vasodilation
(3)	Metabolic factors	(a) Vasodilators - Adenosine, Endothelium dependent hyperpolarizing factor, Nitric oxide, Prostacyclin (b) Vasoconstrictors - Endothelin, Thromboxane A_2, Hypoxia, Acidosis.
(4)	Neural control	(a) Cholinergic mediated vasodilation (b) Beta-2 mediated vasodilation (c) Alpha-1 mediated vasoconstriction (d) Neuropeptide-y induced constriction
(5)	Rheological factors	(a) Blood viscocity (b) Erythrocyte deformability (c) Oxyhemoglobin dissociation
(6)	Cellular factors	(a) Membrane sodium- hydrgen exchanger (b) Rhokinase activity (c) Endothelial progenitor cell function (d) Activity of vascular smooth muscle cells (e) Activity of calcium channels

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hyperemia, factors that hamper blood flow through capillaries can also contribute to microvascular angina. These include

(i) Increased blood viscosity. Common causes are increased hematocrit & lipids [29]. Rinkevich et al. [6], however, observed no difference in hematocrit between patients of syndrome X and controls.

(ii) Erythrocyte diameter, charge and deformability [30].

(iii) Defect of oxyhemoglobin dissociation

(f) Disorder of Cellular Mechanisms

Endothelial progenitor cells and circulating endothelial cells have the potential for repair of endothelium [31]. Women with decreased coronary flow reserve have been shown to have lower number and decreased function of CD 34 cells [31]. Further studies are needed to define role of these cells in pathophysiology of microvascular angina.

Vascular smooth muscle cells play an important role in vascular reactivity [32] and their abnormality could be involved in increasing resting microvascular tone or decreasing vasodilatory response. Airway hyperresponsiveness [33] and esophageal motility disorder [34] have been observed in some cases of syndrome X. Diffuse disorder of smooth muscle responsiveness has been proposed. Further work is needed to find role of vascular smooth muscle cell hyperresponsiveness in microvascular angina.

(g) Association of Systemic Microvascular Dysfunction

Strain et al. [35] compared skin microvascular response to heating and ischemia among men with refractory angina and controls. Skin microvascular function was impaired in individuals with refractory angina. It is possible that microvascular angina is part of systemic microvascular dysfunction. Pathophysiological significance of this observation needs evaluation of microvasculature in different vascular territories in patients with documented microvascular angina.

Conclusion

Microvascular angina is a group of disorders with hetrogenous pathophysiology. At present, no specific investigations can be advised as multiple factors may exist in the same patient. Various groups of drugs are used to tackel this condition but no therapy is uniformly effective because of hetrogenous pathophysiology. Identification of exact pathophysiology will help in deciding correct diagnostic and therapeutic approach in a given patient. Future studies should be directed towards development of techniques to define pathophysiology in a given patient.

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