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Review Article

Ischemia of Non-Obstructive Coronary Artery Disease: Need to Address in our Patient Population

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Abstract

Ischemia of non-occlusive coronary artery disease (INOCA) not an uncommon phenomenon, exist in our patient population which did not address well. Many of the stable angina and or unstable angina patient, whose coronary angiogram revealed significant coronary stenosis (>70%) are being treated by PCI with drug eluting stent. On the contrary, quite a significant proportion of patient, who are found to have non-significant coronary lesion (<50%) or essentially normal epicardial coronaries. These group of patients with angiographic evidence of non-occlusive CAD, remain undiagnosed of their exact etiology of angina. As a result, recurrence of anginal chest pain leading to repeat hospitalization impaired quality of life and the expenditure. Women are significant number in this category, labelled as syndrome X. Many of the scientific literature, has labeled it as Ischemia of Non obstructive Coronary artery Disease. Notably, Microvascular angina is due to ischemia driven mismatch of demand and supply in the myocardium. Microvascular Dysfunction (MVD) and Coronary vascular spasm or Vasospastic Angina (VSA) are the main pathogenic causes of INOCA. With the advent of Imaging physiology, and its availability in Bangladesh, many of the center can assess INOCA and its severity by FFR, iFR, DFR and transthoracic Doppler study of the coronaries. Therefore, we recommend evaluating INOCA patient by available technical assistance and to address the issue and patients suffering with repeated hospitalization and financial expenditure.

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Bangladesh with an estimated population over 170 million, many are suffering from life threatening cardiovascular events like acute myocardial infarction, Stable Angina, Unstable Angina. Many dies before reaching the hospital and many could not afford the treatment expenses. Thus, death from cardiovascular disease is number one leading cause of death in this part of world.

Angina pectoris, most common symptoms of ischemic heart disease, affects 112 million people globally and among these, 70% of population undergoing coronary angiogram, do not have documented obstructive CAD.[1-3] Many of the studies documented that coronary microvascular dysfunction (CMD) and epicardial vascular dysfunction are additional pathophysiologic mechanism of IHD. CMD and epicardial vasospasm, alone or in combination with coronary artery disease (CAD) are adjunctive to myocardial ischemia. These group of patients continue to experience recurrent angina with impaired quality of life, leading to repeated hospitalizations, unnecessary CAG, and adverse cardiovascular outcomes.[4-5]

Cardiac ischemia may also be caused by vascular dysfunction without angiographic evidence of CAD, a condition recently termed INOCA (ischemia of non-occlusive coronary artery) disease. In INOCA, mismatch of demand supply in myocardium caused by CMD and or epicardial coronary artery spasm (vasospastic angina, VSA).[6]

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Coronary microvascular dysfunction refers to the subset of disorder affecting the structure and function of the coronary microcirculation, serve as key mediators of patient symptoms, is prevalent in patients across a broad spectrum of cardiovascular risk factors. With the advent of medical technologies, available resources, Cath lab facilities in many of the big cities, interventional cardiologist expertise, and drug eluting stents, acute Myocardial Infarction patient are benefitting by Primary angioplasty (pPCI) in many of the centers. Successful flow re-stabilization with better myocardial salvage depends on reduced door to balloon time of less than two hours.

In the global pandemic of Covid-19, strategy in treating AMI patient from pPCI has changed to pharmacoinvasive therapy, like other parts of developed world and as per ACC/ AHA/ESC guideline recommendation.

To date, most of the Coronary angiogram registries include obstructive CAD.[7] Few registries include patient longitudinal outcome data.[8] Nonobstructive CAD is atherosclerotic plaque that will not expect to obstruct flow or induce angina, is found in 10-25% patient undergoing CAG.[9] Although these are labelled as insignificant, prior studies mentioned that majority of the plaque ruptures and resultant MI arises from non-obstructive plaque.[10-13]

Historically, obstructive CAD has been the primary focus of CAD management as its role in causing ischemia associated anginal chest pain.[14,15] Obstructive CAD usually correspond to extensive CAD associated MI. However, recognition that ruptured plaque, rather than the occlusive plaque is genesis of MI, arise from non-obstructive CAD.[10,12,13,16] Non obstructive CAD is associated with significant risk of MI and all-cause mortality.[17] This group patient constitutes 10% AMI and referred as MI with Non-Obstructive coronary arteries, termed MINOCA.[18]

Microvascular angina (MVA) is the clinical manifestation caused my microvascular dysfunction. Myocardial ischemia may result from structural remodeling of the vasculature leading to fixed reduced microcirculatory conductance or vasomotor disorders affecting the coronary arterioles causing dynamic obstruction.[19,20] Microvascular angina and vasospastic angina may coexist together with worst prognosis.

Microvascular dysfunction related to impaired smooth muscle relaxation is an endothelium-independent mechanism for cardiac ischemia.[21] Microcirculation accounts for 70% of resistance within the coronary circulation and ineffective smooth muscle relaxation prevents demand-related increases in flow. These group of patients are theorized to present with exercise or stress related angina.[22] Endothelial-independent microvascular dysfunction is studied by measuring coronary flow reserve using transthoracic Doppler echocardiography, Myocardial contrast Echocardiography, PET, Intracoronary Doppler or CMR following induced vasodilatation with an endothelium-independent agent such as adenosine or dipyridamole.[23-28] Endothelial-dependent dysfunction is caused by pathologic constriction of a vessel or vascular bed. Diffuse distal epicardial and microvascular constriction causes ST depression and angina at rest or stress. Anginal chest pain or ECG changes may precede diffuse epicardial constriction, indicating that it may instigating effect that propagates proximally.[29,30]

In unselected population referred for angina, less than 10% have obstructive CAD. In a large US study, for suspected angina and or positive stress test, 39% patient have non-obstructive CAD.[31] This frequency was higher in women (50-70%, compared to men (50-70%).

Microvascular angina due to coronary artery spasm were prevalent in Japanese population. frequency of multiple coronary spasm (>2 spastic arteries) by provocative testing in Japanese (24.3%), Taiwanese 19.3%), markedly higher than those in Caucasians (7.5%). Interestingly VAS prevalent in men than women of age 40-70yrs.[32] Epicardial vasospasm has origin in hyper-reactive epicardial coronary segment that undergoes maximal contraction when exposed to vasoconstrictor stimulus, such as smoking, drugs, peaks in blood pressure, cold exposure, emotional stress and hyperventilation.[33]

Microvascular dysfunction could develop before epicardial artery stenosis and could coexist with angiographically significant coronary artery stenosis. Diabetes mellitus, dyslipidemia, HTN and clinical conditions might have been associated with MVD.

Nonobstructive CAD is not "insignificant" rather associated with significant and quantifiable risk of cardiovascular mortality and morbidity. The stable non obstructive CAD patient population excluded from many of the major cardiac prevention studies. Therefore, empirical evidence is lacking whether these group of patients will benefit from secondary prevention therapies with antiplatelet and statins.[34]

The prognosis of INOCA is far from benign. Angina of non-obstructive CAD associated with impaired quality of life, higher risk of disability, healthcare cost with repeated hospitalization and coronary angiogram. In WISE (Women's Ischemia Syndrome Evaluation) study, persistent chest pain, smoking, CAD severity, DM and QTc interval were significant independent predictor of cardiovascular events defined as CV death, MI, Congestive heart failure or stroke.[35] In a cohort of patients undergoing elective CAG, nonobstructive CAD, compared with no apparent CAD, was associated with a significantly greater 1-year risk of MI and all-cause mortality.[36]

INOCA patient might present with wide spectrum of symptoms and signs, like angina occurring with obstructive CAD, may complain of breathlessness, pain in between shoulder blades, nausea, weakness and or sleep disturbances. This group of patients should not be leveled or classify as non-cardiac, since Women have much higher prevalence of INOCA.

As we know that functional or structural abnormalities of the coronary can be responsible for impaired myocardial perfusion and ischemia, in the absence of large epicardial coronary artery disease.[37] In the ESC CCS 2019 guideline first line of testing is non-invasive testing and common non-invasive technique assessing ischemia related large regional differences in LV perfusion and or wall motion in epicardial perfusion territories by single photon emission computed tomography or dobutamine stress echo.[38]

Transthoracic Doppler echocardiography (TDE) as a tool to measure CFVR, has the advantages of being non-invasive, widely available, performed at bedside, without radiation exposure, not time consuming. Among the three coronaries, LAD most interrogated, followed by PDA. Technical feasibility for LAD is high 90% in experienced hand, PDA is lower and LCX is most challenging due to its anatomy.[39,40]

Coronary flow reserve is the ratio of hyperaemic blood flow in response the various vasoactive stimuli divided by resting blood flow. Reduced CFVR is an indicator of CMD. Coronary flow velocity reserve (CFVR) is a useful tool to measure CMD. Patient with or without DM with a CFVR<2 has worse prognosis despite normal LVE EF, preserved wall motion during dipyridamole stress test and angiographically significant coronary stenosis.[41] Non-endothelial dependent dysfunction may be assessed by noninvasively, acetylcholine can only be administered during invasive testing and is supported IIa recommendation. The 2019 ESC CCS guideline recommend IIa for guide wire based CFVR microcirculatory resistance measurement in patients with persistent symptoms.[38]

In invasive testing, invasive coronary flow reserve (iFR) can be assessed by intracoronary doppler tipped guidewire or thermodilution techniques to measure coronary blood flow velocity at rest and in response to adenosine (endothelium-independent) and acetylcholine (endothelium-dependent) vasodilation.[42] Fractional flow reserve (FFR) provides a surrogate measure of flow limitations and stenosis-level physiological obstruction and calculated as the ratio between coronary pressure distal to a stenosis and aortic pressure during hyperemia. FFR represent pressure ratio across a stenosis during hyperemia, it is a relative index of epicardial conductance and may influenced by CMD and diffuse atherosclerosis. CMD may increases microvascular resistance and may pseudo normalize FFR.[43]

Instantaneous wave-free ratio (iFR) uses wave intensity analysis to identify the mid-late diastolic instantaneous-wave free interval over which the iFR is computed. iFR is a pressure-derived index of stenosis severity, obtained in diastole without adenosine and it can be useful in evaluation of CMD.[44]

Treatment of anginal symptoms in patient with INOCA is challenging. Short acting Nitrates may be effective since long acting may be ineffective and intolerable due to stealing effect. For microvascular spasm following acetylcholine

testing calcium antagonist should be considered as first line therapy. In patients with MVA and reduced CFR and or increased IMR betablocker, calcium channel blocker ACEi or ARB would have been good choice. Nicorandil a vasodilator acting via nitrate and potassium channel activation.[45] Ranolazine, an antianginal agent improves myocyte relaxation,[46] and trimetazidine also improve symptoms in this group of patients. Role of Ivabradine efficacy in MVA poorly investigated.[47]

Lifestyle modification is a very important and key determinant in improving anginal chest pain or angina equivalent symptoms due to CMD and VSA. Stopping of smoking, weight reduction, avoidance of excess carbohydrate intake, avoidance of cholesterol rich food with brisk regular walk would be beneficial in reducing the angina. Eating healthy diet, avoidance of any stressful condition, sound and sufficient sleep would offer additive improvement of symptoms in INOCA patient.

Ischemia of non-occlusive CAD is not an uncommon clinical entity that causing anginal chest pain induced by angina, either due to coronary microvascular dysfunction (MVD) and or vasospastic angina (VSA). Literature has documented, that after PCI of a significant stenotic lesion, patient may have ongoing angina, for which re-look CAG revealed stent patency without any occlusive or new lesion either in stented territory or other non-stented territory. From this view, it is evident, or we may conclude that these group of patient has microvascular disease, that are the key factor in inducing anginal chest or angina equivalent symptoms, or some instances may lead to heart failure.[48]

In our common practice, we found approximately 14% patient having non-occlusive CAD (% stenosis <50% angiographic eye-ball estimation), 11% essential normal epicardial coronaries (our unpublished CAG data of 5174 patients). So, we found many of the patients are admitting with chest pain with angina or angina equivalent symptoms and many are swapping from one doctor to other. Many may be ignorant or non-compliant to the medication and lifestyle modification. Some patients might have repeated coronary angiogram.

Time has changed, in Bangladeshi Cardiology interventional era. Many of the big city Hospital, has modern facilities with cardiac catheterization laboratory and expert interventional cardiologist. Some center has IVUS, FFR, iFR and DFR facilities. Some of the center can assess non-invasively CFR by Transthoracic Doppler Echocardiography (TDE) study by a technically skilled echocardiographer, since TDE is addressed in LAD in majority cases, followed by PLB and most difficult in LCX due to its anatomic location.[49] Invasively, patient with normal epicardial coronaries, coronary flow can be assessed by intracoronary Acetylcholine with careful observation and documentation of chest pain and ECG changes. In patient with non-obstructive CAD (stenotic lesion <50% by angiographic view), FFR with adenosine, iFR or DFR without adenosine may provide information and diagnosis of INOCA. No doubt, if we do these tests, it will benefit patient from anginal chest pain with repeated hospitalization and or in severe cases from myocardial infarction (MINOCA),[50] boost up patient psychologically and alleviate symptoms with the improvement of quality of life.[43]

To our knowledge, INOCA is not well addressed in our clinical practice. Therefore, we may recommend forming a common consensus, set a standard protocol to evaluate these group of patients, find out the underlying pathology by available non-invasive and invasive means. Thus, to provide or ensure healthy life, improvement of angina or angina equivalent symptoms, avoidance of consequences of MI and or heart failure from INOCA.

Conflict of Interest - None.

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