



A 'Diamond' Approach To Personalized Treatment Of Angina

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1. ABSTRACT

Chronic stable angina is the most common manifestation of ischaemic heart disease in the developed world and is associated with impaired quality of life and increased mortality. The pathogenesis of stable angina is complex and often, albeit not always, involves flow-limiting epicardial coronary artery stenoses (atheromatous plaques) that reduce the ability of the coronary circulation to deliver appropriate blood supply to the myocardium. The coronary microcirculation can also play an important role. An imbalance between myocardial oxygen supply and metabolic oxygen demand causes the symptoms of angina pectoris and represents a major therapeutic target. Rational treatment requires a multi-faceted approach combining lifestyle changes, aggressive management of modifiable coronary artery disease risk factors, pharmacological therapy and myocardial revascularization when appropriate. Despite modern therapies, many patients continue to suffer from angina. Several new anti-anginal drugs have been introduced that might allow more effective symptom control. These novel agents have specific mechanisms of action and fewer side effects compared to conventional drugs.

Keywords:- chronic stable angina, pathogenesis of angina, Treatment

2. INTRODUCTION

Current treatment strategies for chronic stable angina aim to control symptoms, reduce the ischaemic burden and improve prognosis by preventing the progression of atherosclerotic coronary artery disease (CAD) and its consequences. Ideally, the treatment of angina should be tailored to the individual patient's needs, taking into consideration the characteristics and severity of symptoms, the location, severity and functional significance of coronary artery stenoses, the presence of co-morbidities and patient preference. For each individual patient, the efficacy of the agent and their side effects, together with patient compliance, are important determinants for the success or the failure of a given treatment.



Fig. no 01

3] PATHOPHYSIOLOGICAL AND PATHOGENIC MECHANISM

1. : DETERMINANTS OF CLINICAL PRESENTATION :-

The pathogenesis of angina is often multi-factorial. The basic underlying mechanism that leads to angina is an imbalance of myocardial oxygen supply and demand. This often occurs as a direct result of flow-limiting CAD, but it can also be due to coronary artery spasm limiting blood supply, coronary microvascular dysfunction and/or several other contributing mechanisms. To a great extent, the underlying pathogenic mechanism determines the pattern of clinical presentation, leading to effort-induced angina, mixed angina or angina at rest.

2. EFFORT-INDUCED ANGINA:-

Long-standing obstructive epicardial CAD causes angina by providing a fixed limitation of coronary blood flow, which prevents physiological matching of coronary blood supply to exercise-induced increases in myocardial metabolic demand. A stenosis of 50% or more in the left main coronary artery, or 70% or more in another major epicardial artery, is defined as 'obstructive'. Symptoms of effort-induced stable angina resulting from flow-limiting coronary stenoses often occur at a predictable and reproducible threshold, triggered by physical activity and/or emotional stress. The Canadian Cardiovascular Society (CCS) grading of angina is a functional classification of exercise tolerance that can be related to metabolic equivalent units (METs) and it is used in the assessment of exercise stress testing.

3. MIXED ANGINA:-

The imbalance of myocardial oxygen supply and demand in angina can also result from combined mechanisms. Excessive coronary artery vasoconstriction at the site of organic stenoses manifests clinically as 'mixed angina pectoris', in which patients present with variable-threshold effort angina and occasionally angina at rest.

4. MICROVASCULAR ANGINA:-

Coronary microvascular resistance is the main determinant of coronary flow reserve (the ratio of maximal induced myocardial flow to resting coronary blood flow). Abnormal vasodilatory responses of the coronary microcirculation can cause effort-related angina (microvascular angina). It is important to note that as few as 38% of patients without previously known heart disease who undergo elective diagnostic coronary angiography are found to have obstructive CAD.⁶ In many of these patients with typical angina symptoms, exercise-induced myocardial ischaemia is caused by coronary microvascular dysfunction.

Patients with cardiac syndrome X — defined as typical exertional angina, positive stress test responses and normal coronary angiograms — experience transient myocardial ischaemia resulting from impaired endothelial function, which leads to abnormal coronary microvascular vasodilatation, increased coronary vasoconstriction, or both.

In the ACOVA (Abnormal Coronary Vasomotion in patients with stable angina and unobstructed coronary arteries) study, approximately two-thirds of patients without significant epicardial CAD had positive intra-coronary acetylcholine tests for distal epicardial or microvascular spasm. Clinicians should be encouraged to think about the possibility of microvascular dysfunction or coronary microvascular spasm in patients who present with typical angina despite having angiographically normal coronary arteries.

5. OTHER CONTRIBUTING MECHANISMS: -

Following transient myocardial ischaemia, impaired diastolic relaxation and increased wall tension caused by calcium overload, which results from intracellular acidosis, and activation of late inward sodium currents worsens the oxygen imbalance and prolongs the angina episode. Further metabolic derangement, including

abnormalities of substrate supply and utilisation, enzymatic activities and mitochondrial function, can also contribute to the pathogenesis. Aortic stenosis, hypertrophic

cardiomyopathy, severe anaemia and thyrotoxicosis (when present) are other potential contributory factors that can worsen myocardial ischaemia

4. TREATMENT OF CHEST PAIN EPISODES:

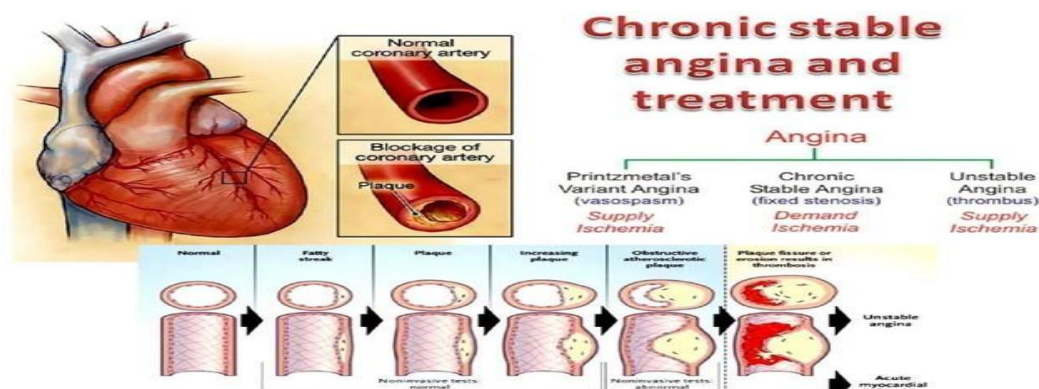


Fig. no 02

Episodes of angina are best treated with sublingual glyceryltrinitrate (GTN). GTN acts as a nitric oxide donor, causing systemic and coronary vasodilatation. GTN is rapidly absorbed in the sublingual mucosae and its effects usually occur within 2–10 minutes. Common side effects of sublingual nitrate administration are headaches, dizziness, hot flushing and nausea. Contraindications for the use of GTN include aortic stenosis, hypertrophic cardiomyopathy, systemic hypotension and co-administration with phosphodiesterase-5 inhibitors (eg sildenafil). GTN is recommended for all patients with stable angina, unless contraindicated. When prescribing GTN, patients should be given advice regarding how and when to use GTN and potential side effects that they may experience. They should be advised to inform their doctor if the symptoms are not controlled. GTN can also be useful in preventing episodes of exertional angina when used prior to undertaking physical exertion.

1. FIRST-LINE ANTI-ANGINAL DRUGS

β -adrenergic receptor blockers (beta-blockers) and calcium-channel blockers are considered to be first-line anti-anginal drugs and have been shown in many studies to prevent angina and myocardial

ischaemia. The TIBET (Total Ischaemic Burden European Trial) study showed that atenolol produced

similar anti-anginal benefits when compared to slow-release nifedipine; no significant additional benefits were seen when the two agents were combined. In the APSIS (Angina Prognosis Study in Stockholm) study, patients with stable angina treated with either metoprolol or verapamil had similar rates of

cardiovascular events and mortality. The choice between these two drug classes is generally guided by contraindication, the presence of co-morbidities and patient preference. If one of these agents is not well tolerated, the other can be tried instead. If combination therapy is required, the use of a non-heart-rate limiting dihydropyridine calcium channel blocker (eg., amlodipine or slow-release nifedipine) is recommended.

The anti-anginal actions of beta-blockers result from a reduction in heart rate, contractility and blood pressure, which result in a reduced myocardial oxygen requirements. Also, by lowering the heart rate, the diastolic component of the cardiac cycle is prolonged, which improves myocardial flow. For maximal

efficacy, long-acting, cardioselective betablockers that have no intrinsic sympathomimetic activity are preferred. The dose should be titrated to achieve a target resting heart rate of 50–60 beats per minute.

The prognostic benefit of beta-blockers in angina has been extrapolated from studies of post myocardial infarction but has not yet been documented in stable angina.

The potential benefits of beta-blocker therapy are often limited by side effects and contraindications. Among the most common side effects of beta-blockers are fatigue, dizziness, syncope, bronchospasm, hyperglycaemia, depression and erectile dysfunction. These agents are contraindicated in patients with reactive airway diseases, severe

bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension, acute heart failure and peripheral vascular disease. Beta-blockers are not generally used in patients with vasospastic angina

because of the possibility that unopposed α -adrenergic receptors might have unwanted effects. Abrupt withdrawal of beta-blockers can cause rebound myocardial ischaemia.

Calcium channel blockers act on L-type Ca^{2+} receptors and lead to systemic and coronary vasodilatation, reducing afterload and improving myocardial blood flow. Like beta blockers, non-dihydropyridines (eg., verapamil and diltiazem) have additional anti-anginal effects through reductions in heart rate and contractility. Long-acting preparations are preferred. Common side effects of blockers include dizziness,

headache, fatigue, flushing, abdominal pain, nausea and peripheral oedema. Like beta-blockers, non-dihydropyridine, calcium channel blockers are contraindicated by severe bradycardia, 2nd or 3rd degree heart block, sick sinus syndrome, hypotension and acute heart failure.

Examples:

Beta blockers

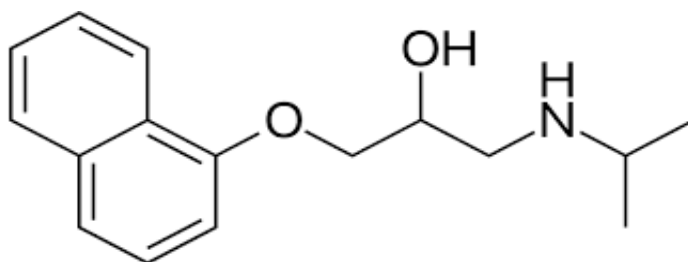
Reduce the heart rate and force of the heartbeat, which lowers blood pressure and improves blood flow.

Beta blockers are often well tolerated, but they can cause side effects like fatigue, impotence, and bradycardia.

Nitrates

Dilate blood vessels in the heart and elsewhere in the body, which improves blood flow to the heart muscle and relieves angina symptoms.

Calcium channel blockers



Also known as calcium antagonists, these drugs relax and widen blood vessels to improve blood flow

2. : SECOND-LINE ANTI-ANGINA THERAPIES :-

For patients whose symptoms are not well controlled by beta-blockers and calcium-channel blockers, or if contraindications exist for these agents, several options supported by NICE guidelines⁴ are available.

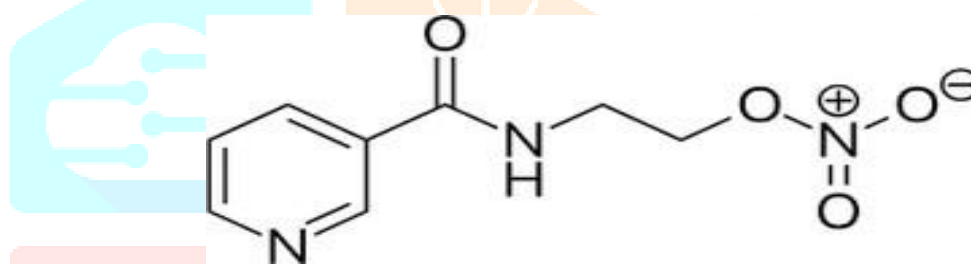
These include: vasodilators such as long-acting nitrates and nicorandil, a drug that selectively slows the heart rate; ivabradine, and ranolazine, an agent that acts on the fast sodium current to improve

cardiac metabolism. When and in which order these second-line agents are used in clinical practice is based on several variables, including pathogenic mechanisms, patient characteristics and co-morbidities, drug interactions and patient preference. Adverse effects of long-acting nitrates reported recently require consideration before these drugs are prescribed for a given patient.

Exampals :

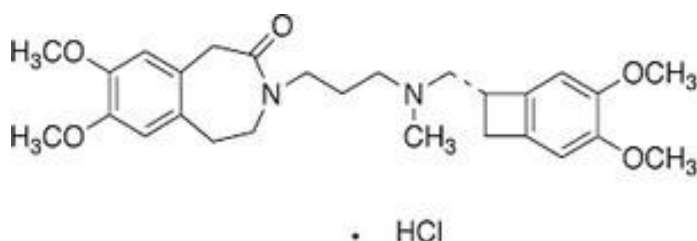
1. NICORANDIL

Nicorandil acts as both a nitric oxide donor and a sarcolemmal K^{+} -adenosine triphosphate (K-ATP)-dependant channel opener, causing K^{+} efflux and subsequent hyperpolarisation and inhibition of L-type Ca^{2+} channels, leading to systemic and coronary vasodilatation.



The cardio-protective properties of nicorandil might be due to ischaemic preconditioning mediated by activation of mitochondrial K-ATP channels. Common side effects of nicorandil are headaches, dizziness, nausea, vomiting and flushing. Metformin might antagonise the effects of nicorandil.

2. IVABRADINE:-



Ivabradine inhibits I_f channels, thereby affecting the intrinsic pacemaker cells of the sino-atrial node. When activated by hyperpolarisation

in diastolic range voltages and by adrenergically driven increases in cyclic adenosine

monophosphate, the I_f channel, causes an inward Na^{+}/K^{+} ionic current across the sarcolemma, leading to spontaneous depolarisation of myocytes in the sino-atrial node. Inhibition of the I_f current lowers the heart rate. Ivabradine is more effective in patients who have increased I_f channel activity.

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