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A Review On Neuro-Pharmacological Perspective Of Angina Pectoris

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ABSTRACT:- Angina Pectoris is a common clinical symptom that often results from ischemia of the heart muscle due to the occlusion of the coronary artery. The typical manifestation of angina pectoris is often described as chest pain that is characterized by a retrosternal crushing, burning or squeezing sensation. Normally, the pain is continuous, deep and diffuse. However, one typical characteristic of angina pectoris is that the chest pain is not consistent with the development or severity of the myocardial ischemia: patients with severe myocardial ischemia may feel weak or no angina pectoris.[1] Dysfunction of cardiac autonomic nervous system is considered as one of risk factors for coronary atherosclerotic heart disease. Heart rate variability may play a crucial role in estimating the correlation between damage of coronary artery and dysfunction of autonomic nerve system. Heart rate variability which means alteration of intervals among continuous sinoatrial node beats including R-R interval, is a non-invasive, practical and reproducible test for detecting autonomic nervous system function. In a study of Feng et al, [3] they indicated from heart rate variability indicators that compared with control group, dysfunction of cardiac autonomic nervous system was found widely in patients suffered stable angina pectoris, especially for those who has lower parasympathetic nerve activity.[3]

Keywords: *nucleus of the solitary tract (NTS), transient receptor potential vanilloid-1 (TRPV1) receptors, nuclear factor kappa b (NF-kb*)

I. Mechanism of Pain in Angina Pectoris

The nucleus of the solitary tract (NTS), located in the medulla oblongata, is an important nucleus for processing cardiac nociception. Nociceptive information from the heart can be directly forwarded to the NTS through the afferent fibers of the vagal nerve. In addition, sympathetic afferent fibres can transmit cardiac Nociceptive information to the dorsal horn of the spinal cord and then to the NTS through ascending pathways. Pericardial application of algogenic compounds (e.g., adenosine, capsaicin, and bradykinin) or temporary occlusion of the left coronary artery significantly increases c-Fos expression in the NTS, suggesting that the NTS is important for the central regulation of angina pectoris after a heart attack.[1] Furthermore activation of thinly myelinated A_δ-fiber and unmyelinated C- fiber cardiac sympathetic afferent nerves during myocardial ischemia is responsible for the transmission of information from the heart to the brain that ultimately elicits the perception of cardiac pain and evokes excitatory cardiac-cardiovascular reflex responses. The endogenously produced ischemic metabolites, including endothelin, protons, extracellular ATP, thromboxane A_2 , serotonin (5HT), histamine, Reactive oxygen species (ROS), and bradykin (BK), excite cardiac spinal afferent nerves during ischemia and reperfusion in an interactive and multifactorial fashion. Some mediators, like ATP and 5-HT are specific for ischemically sensitive afferent nerves, whereas others, like BK, ROS, and histamine, are nonspecific, as they stimulate both ischemically sensitive and insensitive afferent nerve endings. [2] The endogenous opiod systems in the brain and spinal cord, which function as atypical inhibitory neurotransmitters or neuromodulators, have been extensively studied. However, the functional effects of this system on peripheral sensory nerve activity have been investigated less extensively. Several sources of evidence suggest that peripheral opiods may be crucial in the regulation of cardiac spinal afferent nerve activity during myocardial ischemia. For instance, cardiac myocytes, sympathetic nerves, and leukocytes can synthesize and store opiod peptides as well as their precursors. Leukocytes that accumulate in the area of coronary arterial plaques release large quantities of opiods when they are activated during plaque disruption. Clinical studies have documented increased concentrations of coronary opiod peptides in patients with unstable angina pectoris or undergoing coronary angioplasty. Hence, myocardial ischemia leads to the production and release of opiod peptides that have the potential to contribute to the regulation of cardiac spinal afferent nerve activity during ischemia. [2] Spinal cardiac afferent fibers mediate typical angina pain via pathways from the spinal cord to the thalamus and ultimately cerebral cortex. Spinal neurotransmission involves substance P, glutamate, and transient receptor potential vanilloid-1 (TRPV1) receptors; release of neurokinins such as nuclear factor kappa b (NF-kb) in the spinal cord can modulate neurotransmission. Vagal cardiac afferent fibers likely mediate atypical angina pain and contribute to cardiac

ischemia without accompanying pain via relays through the nucleus of the solitary tract and the C1-C2 spinal segments. The psychological state of an individual can modulate cardiac nociception via pathways involving the amygdala. Descending pathways originating from nucleus raphe magnus and the pons also can modulate cardiac nociception. Sensory input from other visceral organs can mimic cardiac pain due to convergence of this input with cardiac input onto spinothalamic tract neurons. Reduction of converging nociceptive input from the gallbladder and gastrointestinal tract can diminish cardiac pain. [4] In other studies the occurrence of craniofacial pain during myocardial ischemia, with or without an acute myocardial infarction, was associated with ischemia within the inferior wall. This result suggests the involvement of the vagal afferent system in the mechanisms of craniofacial pain of cardiac origin[5], the most common craniofacial locations during cardiac ischemia were the throat, the left mandible, the right mandible, left temporo-mandibular joint, ear region, and the posterior teeth. [5] Moreover, sympathetic hyperactivity is linked with several adverse cardiovascular events in patients with acute coronary syndrome. Sympathetic activity increases early in the process of ischemia through two mechanisms. One originates from the central nervous system and leads to enhanced sympathetic activity. The other mechanism originates at the infarct zone and leads to B receptor up regulation and catecholamine super sensitivity. Nevertheless, sympathetic hyperactivity accompanied by an underlying myocardial structural damage is likely to increase the ventricular repolarization duration measured as QT interval on the body surface electrocardiogram.[6]

In distinction to most other muscular beds, the oxygen extraction from the coronary circulation by the myocardium is nearly maximal, even at rest, with around 70% of oxygen being extracted, compared with around 30% elsewhere. Consequently, in order to supply the four to fivefold increase in oxygen delivery that the myocardium requires under conditions of exercise or stress, blood flow must increase by a similar amount. Normally this is achieved by a beautifully coordinated vascular response involving neural, chemical and physical factors such as shear stress acting on several different regions of the coronary circulation. Normally adjustments in the size of the epicardial coronary arteries make only a small contribution to this process; however, when the flow of blood is limited by stenosis in the epicardial coronary artery, a mismatch between myocardial oxygen demand and supply inevitably occurs. This rapidly results in a decrease in the adenosine triphosphate (ATP) to adenosine diphosphate ratio and generation of adenosine, which in turn leads to further dilatation of coronary pre-arterioles. Normally this would increase coronary blood flow and restore homeostasis, but when the epicardial artery is significantly stenosed, no further blood supply is available and the adenosine levels rise significantly. These high levels activate sympathetic cardiac afferent neurons, probably through the use of A_1 subtype of the adenosine receptor. The resulting neural outflow appears to be responsible for the resulting sensation of visceral pain or discomfort, which manifests clinically as angina pectoris.[7]

There is little evidence for the existence of visceral nociceptors. When considering the rules that bind somatic pain, of which we have a more extensive understanding, it becomes clear that the phenomenon we call 'visceral pain' does not necessary adhere to the same criteria. In case of somatic pain, following peripheral tissue damage sufficient to mount a pain response, there are predictable sequelae. Not all visceral pain is related to tissue injury. Cardiac syndrome X, a poorly understood pain condition in which angina pectoris is described in the absence of coronary artery disease (thereby carrying almost no risk of myocardial infarction) is neurologically distinguishable from angina associated with ischemic heart disease. It has long been recognised that there is no connection between stimulus intensity (in the case of angina pectoris this is assumed to be myocardial ischemia) and perceptual intensity. Mild myocardial ischemia may generate severe and prolonged episodes of angina, and yet the phenomenon of silent (painless) ischemia and even infarction is well known. [7]

Visceral Pain is mediated by the autonomic nervous system. As mentioned above, studying autonomic function in humans is challenging, and is often invasive, which has limited our understanding. There is extensive autonomic innervation of the heart; the effects of efferent stimulation are well recognised. Vagal stimulation reduces heart rate and has a negative inotropic effect, whereas sympathetic stimulation does the opposite. In case of cardiac pain it seems that afferent sympathetic nerve activity, principally activated by adenosine, as discussed above, is responsible for the bulk pain signalling from the heart to the spinal cord and brain. The vagus nerve appears to have a minor role in afferent pain transmission. Afferent sympathetic neurones pass from the myocardium to either the superior or inferior cardiac plexus, from which they pass without synapsing through the sympathetic ganglion chain to the dorsal horn of the spinal cord. Here they connect predominantly to neurones in lamina I, although additional connections are made to lamina V. Incoming somatic nociceptive fibres are known to synapse with the same lamina I neurones (in addition to their laminae II and III connections), and it is possible that this is the point at which the crosstalk occurs between somatic and visceral afferent pathways, giving rise to the referred pain which characterises angina pectoris. Because of the extensive connections between cardiac sympathetic plexi, sympathetic ganglion chain and spinal cord (from the upper cervical ganglion to as far down as the sixth or seventh thoracic segment), it is easy to understand how angina may be expressed over such a large potential proportion of the upper body. [7] There are extensive afferent

neuronal connections from the trachea-bronchial tree, the lungs, the oesophagus and the stomach that connect to the spinal cord at the same segmental levels as cardiac afferent fibres. In lamina I of the dorsal root entry zone the afferent autonomic neurones may send connecting branches one or two segmental levels rostrally and caudally. These branches may synapse onto a 'transmitter' cell, which also receives synapses from incoming sensory nociceptive neurones, the principle synaptic connections of which are in laminae II and III (substantia gelatinosa). It seems likely that the incoming angina information gains access to the recognised rostral pathways that conduct pain information by this common connection in the lamina I. However, there are also opportunities for information transfer with the lamina I transmitter cell's own connections with the spinothalamic tract and also the possibility of crosstalk between deeper pain connections in lamina V and the afferent sympathetic neurones that also connect with other neurones in lamina V. The poor localization of the pain is most likely due to the diffuse nature of the convergence of visceral autonomic inputs onto common 'transmitter' cells used by both visceral and somatic afferents and the subsequent failure of the sensory cortex to project the incoming information accurately onto the 'body map' sometimes visualized as the 'sensorimotor homunculus'. In addition, the inability of these common spinal routes to classify the incoming autonomic information as nociceptive leads to wide individual variations in character and intensity of perception, as well as location. Many patients refuse to describe their angina as painful, preferring instead to use such terms as 'discomfort', 'pressure', or 'heaviness'.[7]

In other perspective of Angina pectoris due to Coronary vasospasms; coronary arteries are able to adjust the blood supply to the heart during different loading conditions by either vasoconstriction or vasodilation. In patients with vasospastic angina there is an abnormal vasoconstrictive response. Different pathogenic mechanisms have been proposed as the underlying cause. The most common are vascular smooth muscle cell (VSMC) hyperactivity, endothelial dysfunction, low grade inflammation and altered autonomic nervous system response, and these may in turn be modified by genetic factors. Vascular smooth muscle cells (VSMC) hyperactivity is thought to be the main pathophysiological substrate for spasms and early studies of human coronary anatomy have shown that all coronary vessels, including the microvessels, have a similar wall structure that includes a layer of vascular smooth muscle cells. Animal studies using light and electron microscopy have provided insights into the mechanics of vascular smooth muscle cells during spasm. They show that radial rearrangement of the medial vascular smooth muscle cells, because of their own concentration, and resultant medial thickening folding of the internal elastic lamina create a piston effect to narrow the lumen. The molecular pathways leading to spasm are still not fully understood, but the rho-kinase pathway has emerged as important in the genesis of spasm.[9] Autonomic nervous system; the relationship between autonomic nervous system and coronary spasm is complex. An increase in both the sympathetic and parasympathetic tone is able to induce coronary spasm. An increase in sympathetic activity may cause coronary spasm through an increase in noradrenaline, the neurotransmitter of efferent sympathetic nerve fibres, causing vasoconstriction by stimulating vascular smooth muscle cells. As the parasympathetic innervation derives from the adventitia of the vessel, alterations in neuronal nitric oxide (NO) synthase may play an important role in this setting. Endothelial dysfunction with abnormalities in nitric oxide release and its reduced bioavailability combined with hyperactivity of VSMCs may be an important factor in developing coronary spasm. However, it is important to remember that endothelial dysfunction alone is not sufficient to explain the phenomenon of coronary spasm because it requires the activation of vascular smooth muscle cells. Biomarkers of low grade inflammation such as C-reactive protein, CD40 ligand and interleukin 6, have shown to be elevated in patients with vasospastic angina compared with patients with non-vasospastic angina. Low grade inflammation may cause up regulation of rho-kinase, leading to spasm. This may also explain the link between cigarette smoking and angina, because cigarette smoking has also been shown to be associated with low grade inflammation. Several genetic polymorphisms have been described as potentially involved in the predisposition for coronary spasm. Most of these mutations concern the gene encoding for NO synthase, but mutation in other molecules responsible for modulation of vascular tone have also been suggested.[9]

II. Treatment of Angina Pectoris

The pharmacological prevention of exertional symptoms of angina has classically involved the use of agents that reduce myocardial oxygen demand and/or increase myocardial oxygen supply in response to exercise. The anti angina include: organic nitrates, β-blockers, and calcium channel blockers.[10]Organic nitratesDespite being in use for more than 100 years, the mechanism of action of organic nitrates remains uncertain. Traditionally, their primary mechanism of action was felt to be secondary to preload reduction mediated by potent venodilator effects. Preload reduction can reduce myocardial oxygen demand by reducing left ventricular chamber size, and as a consequence systolic and diastolic wall stress. Furthermore, when given using dosing regimens that avoid nitrate tolerance, these agents reduce blood pressure and increase conduit artery distensibility, actions that can reduce myocardial oxygen consumption. Although nitrates dilate conduit epicardial arteries, their ability to

increase coronary blood flow in the setting of obstructive coronary stenosis remains uncertain. Finally, although never investigated in humans, in vitro and animal data suggests that nitrates and other nitric oxide donors may be able to improve left ventricular efficiency, favourably altering the ratio of myocardial oxygen consumption per unit work. Examples of organic nitrates include: *sublingual nitroglycerine, isosorbide mononitrate and isosorbide dinitrate, and Intravenous Nitroglycerine*. [10]Sublingual nitroglycerine is typically prescribed for the relief of acute attacks of angina, while isosorbide dinitrate is generally effective when taken prior to activity in patients with refractory effort angina. [10] Nitroglycerine does not release nitric oxide directly, as compared to sodium nitroprusside. The organic nitrates react with intracellular sulfhydryl groups (from methionine or cysteine) and enzymes to produce Nitric oxide or the intermediate S-nitrosothiol, which is reduced to nitric oxide. Thus nitrates are prodrugs that undergo enzymatic denitrification within the vascular wall, mostly significantly by mitochondrial aldehyde dehydrogenase. Nitric oxide then activates smooth muscle guanylyl cyclise, raising cyclic guanosine monophosphate (cGMP) levels to inhibit calcium entry into the muscle cell and relax muscle filaments. Nitric oxide also acts to inhibit potassium channels; hyperpolarizing muscle membranes and activating light chain phosphatase, both of which effect relaxation, and may account for a significant proportion of vasodilation.[12]

β- Adrenergic blockers

Adrenergic receptors are a class of G-coupled receptors stimulated by the catecholamines, and those in the β- family have most effects mediated by adenylyl cyclise. Specific β_1 effects include increased heart rate and contractility, increased automaticity and conduction velocity, release of rennin from juxta-glomerular cells, and lipolysis. β_2 –adrenergic receptor stimulation relaxes smooth muscle in the bronchi and elsewhere, dilates peripheral, coronary, and carotid arteries and promotes glycogenolysis and gluconeogenesis, among other actions. All β- blockers are effective against angina pain because they lower heart rate, blood pressure, and contractility, thereby reducing myocardial oxygen demand. As such, guidelines indicate that they should be used as first line therapy in patients without prior MI and when a previous MI has been sustained unless contraindications exist. In addition, because of their negative chronotropic effect, β- blockers prolong diastole, raising coronary artery blood flow and myocardial perfusion.[12]

β- Blockers have become a mainstay in the treatment of coronary disease and are effective in the therapy of exertional angina. Their mechanism of action is based primarily on reducing myocardial oxygen demand in response to exercise by decreasing heart rate, blood pressure, and myocardial inotropic responses. Further, via negative chronotropic effects, they can improve coronary blood flow by increasing the duration of diastole, the period during which coronary blood flow occurs. Examples of β- blockers are divided into: non selective β- adrenergic blockers such as *propanolol, timolol, nadolol and pindolol*, and β- 1 selective adrenergic blockers such as *Atenolol, metoprolol, bisoprolol and acetabulol.* β- Blockers with partial sympathomimetic activity (Pindolol and Acetabulol) have been promoted for use in patients with stable angina; however they appear to be less effective and are no longer in common clinical use.[10]

Calcium channel blockers

Calcium channel blockers prevent calcium from entering into the heart muscle cells, and into the smooth muscle cells that cause blood vessels to constrict. By reducing calcium influx, calcium channel blockers cause these muscle cells to 'relax'. This is relaxing effect results in the dilation of blood vessels, and a reduced force of contraction of the heart muscle. Some calcium channel blockers also slow the sinus node and the rate at which the heart's electrical impulse transmits through the AV node. These effects make calcium channel blockers useful in treating some arrhythmias.[11]

All the effects of calcium channel blockers (blood vessel dilation, reduction in heart muscle contraction, and slower heart rate) reduce the amount of oxygen required by the heart muscle. Reducing the amount of oxygen used by the heart allows the heart to function longer without developing ischemia, even when blood flow through the coronary arteries is partially blocked by an atherosclerotic plaque. In patients with stable angina, calcium channel blockers usually increase the amount of exercise that can be performed before angina occurs. Calcium channel blockers can be especially useful in patients with prinzmetal's angina (coronary artery spasm) since they can directly prevent spasm of the coronary arteries. There are two types of calcium channel blockers namely; the dihydropyradines and non- dihydropyradines. [11]

The Dihydropyradines drugs include nifedipine, nicardipine, felodipine and amlodipine; these drugs cause significant dilation of blood vessels and relatively little effect on the heart muscle and heart rate. They are most useful for treating hypertension. [11]The non- dihydropyradines drugs include verapamil and diltiazem. Verapamil affects the heart muscle and is particularly effective in slowing the heart rate, but has little effect on blood vessels. It is not very useful for hypertension but is quite good for angina and cardiac arrhythmias. Diltiazem has modest effects on both the heart muscle and the blood vessels. It tends to be tolerated better than most other

calcium blockers. All the calcium blockers have been used for treating angina. However, the most commonly used calcium blockers are the longer-acting forms of diltiazem and verapamil, amlodipine, or felodipine. [11]
Nifedipine especially its short acting forms, should generally be avoided in patients with angina, since the pronounced blood vessel dilation produced by this drug can increase in adrenaline, leading to a more rapid heart rate, and consequently an increase in cardiac oxygen requirements (which can increase the chances of developing cardiac ischemia). In general, while calcium channel blockers are useful for relieving angina, they are considered to be inferior to beta blockers. [11] Current recommendations are:

- Calcium blockers should be tried in patients who cannot tolerate beta blockers.
- Calcium blockers should be added to beta blockers in patients who have insufficient relief of symptoms with beta blockers. [11]

Newer, non-traditional anti-ischemic agents
Nicorandil is structurally a nicotinamide derivative with a nitrate moiety and a dual mechanism of action. First, it increases potassium ion conductance by opening adenosine triphosphate (ATP) - sensitive potassium channels, in turn activating the enzyme guanylate cyclise. Second, nicorandil shares the smooth muscle-relaxing property of nitrates to vasodilate, lowering preload through venodilation. The drug also reduces afterload and promotes expression of endothelial nitric oxide synthase. Its use is associated with improved myocardial function during ischemia- reperfusion, protection of myocardium during ischemia, shortened action potential duration, and prevention of intracellular calcium toxicity, of importance in modulating ischemic cell damage and death. In the impact of Nicorandil in Angina (IONA) study of 5,126 patients with angina, nicorandil produced a significant 17% reduction in hospitalization for chest pain, MI, and CAD death. The drug also prolongs time to the onset of angina and ischemic ECG changes, extends exercise duration, and reverses ischemia-related impairment in regional wall motion. In the multicenter, randomized SNAPE trial comparing it to isosorbide mononitrate, nicorandil was found to be both safe and efficacious in treating angina by 70-80%. [12]
Ivabradine is a prototype of specific bradycardic agents and the only one in use and under current clinical investigation. These compounds selectively inhibit the inward sodium- potassium 'I_f current', an important pacemaking current in SA node cells, to slow the rate of diastolic depolarization and lower heart rate. Ivabradine does not affect contractility, AV nodal conduction, nor alter hemodynamics. Phase II studies confirmed the bradycardic effect of Ivabradine at rest and during exercise, as well as angina efficacy. The BEAUTIFUL trial found that in patients with CAD, LV dysfunction, and heart rates > 70bpm, Ivabradine was able to lower the risk of acute myocardial infarction and need for revascularization by one third, even when therapy was considered optimal. The ASSOCIATE trial found that Ivabradine resulted in significant improvements in exercise capacity relative to placebo in patients with stable angina pectoris receiving beta-blocker therapy whether their resting HR was above or below 65 beats per minute. [12]

Trimetazidine a member of the class of '3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors', is a metabolic modulator that improves myocardial energetic at several levels, partially inhibiting β- oxidation of fats by decreasing activity of mitochondrial enzyme 3-KAT. The drug raises myocardial glucose utilization, prevents a decrease in ATP and phosphocreatine levels in response to hypoxia or ischemia, preserves ionic pump function, minimizes free radical production, and protects against intracellular calcium overload and acidosis. It raises coronary flow reserve, lowers frequency of angina episodes, improves exercise performance, and spares the use of nitrates without changes in the heart rate, negative inotropic, or vasodilator actions. The TIGER study confirmed the usefulness of this agent in elderly patients resistant to traditional anti-ischemic agents with effects mediated through hemodynamic changes. A Cochrane review of 1,378 patients found that the drug was extremely well tolerated and agreed with the above-mentioned findings. Multiple intracellular metabolic and electrophysiological benefits have created an interest for possible use in Heart failure and idiopathic dilated Cardiomyopathy. [12]

Rolanazine is a piperazine derivative that inhibits the late sodium channels, not only lowering total inward sodium flux but also the subsequent intracellular calcium overload. Early ranolazine trials confirmed a significant prolongation in exercise duration to angina and to ST-segment depression in angina patients. [12]
Ranolazine exerts antianginal and anti-ischemic effects without changing hemodynamic parameters (heart rate or blood pressure). At therapeutic levels, ranolazine inhibits the late phase of the inward sodium channel (late I_{Na}) in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^+-Ca^{2+} exchange. Decreased intracellular calcium reduces ventricular tension and myocardial oxygen consumption. It is thought that ranolazine produces myocardial relaxation and reduces anginal symptoms through this mechanism although this is uncertain. At higher concentrations, ranolazine inhibits the rapid delayed rectifier potassium current (I_{Kr}) thus prolonging the ventricular action potential duration and subsequent prolongation of the QT interval. [13]

III. IN CONCLUSION

It's really difficult to explain the mechanism of Angina pectoris as a visceral pain, but by this critical review of research papers it explained different pathophysiological mechanisms of Angina pectoris. It's because of this different mechanisms facilitated the discovery of Anti-anginal drugs. My recommendation is to further improve our comprehension in these mechanisms as Angina pectoris is a common cardiovascular symptom affecting patients with ischemic heart disease which is responsible for cardiovascular mortality worldwide, for example in China alone *'It is estimated in the "Report on Cardiovascular Disease in China, 2011" that there are about 230 million patients with CVD, including 200 million patients with hypertension, 7 million patients with stroke, 2 million patients with myocardial infarction, and 4.2 million patients with heart failure. There are 3 million cases of death of CVD each year, accounting for 41% in total'*.[21] Thus by understanding paying attention to it, will help us to improve the cardiovascular morbidity and mortality.

REFERENCES:

[1] Jing li, et at, the excitatory synaptic transmission of the nucleus of solitary tract was potentiated by chronic myocardial infarction in rats. PLOS/ ONE 10(3):e0118827.doi:10.1371/journal.pone.0118827

[2] Liang-Wu Fu and John C. Longhurst, Functional role of peripheral opioid receptors in the regulation of cardiac spinal afferent nerve activity during myocardial ischemia.

[3] Am J Physiol Heart Circ Physiol. 2013 Jul 1; 305(1): H76–H85

[4] Jun Feng, Ailing Wang et al, Altered heart rate variability depend on the characteristics of coronary lesions instable angina pectoris. Anatol J Cardiol 2015; 15: 496-501

[5] Foreman RD, Garrett KM, Blair RW, Mechanisms of cardiac pain. Compr Physiol. 2015 Apr; 5(2):929-60. doi: 10.1002/cphy.c140032.

[6] Marcelo Kreiner, Ramon Alvarez, et al, Cranial facial pain of cardiac origin is associated with Inferior wall ischemia. J Oral Facial Pain Headache 2014; 28:317-321.doi:10.11607/ofph.1257

[7] Amer A. Hasanien,et al, Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula. J Electrocardiol. 2013 Jul-Aug; 46(4): 336–342.

[8] Austin Leach and Mike Fisher, Myocardial ischaemia and cardiac pain – a mysterious relationship. Br J Pain. 2013 Feb; 7(1): 23–30.

[9] Manabu Matsumoto et al, Decreased Serum Ghrelin Levels in Patients with Acute Myocardial Infarction. Tohoku J. Exp. Med.,2013, 231,235-242

[10] Peter Ong, Ahmed Aziz, et al, Structural and Functional Coronary Artery Abnormalities in Patients With Vasospastic Angina Pectoris. Circulation journal Vol. 79 (2015) No.7 1431-1438

[11] John D. Parker, Stable Angina Pectoris: The Medical Management of Symptomatic Myocardial Ischemia. Canadian Journal of Cardiology 28 (2012) S70–S80Circulation
By Richard N. Fogoros, MDOctober 17, 2016https://www.verywell.com/calcium-channel-blockers-for-treating-angina-1745910

[12] Richard Kones, Recent advances in the management of chronic stable angina II. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization. Vasc Health Risk Manag. 2010; 6: 749–774.

[13] CH Peters, et al Effects of the antianginal drug, ranolazine, on the brain sodium channel Nav1.2 and its modulation by extracellular protons. British Journal of Pharmacology (2013) 169 704-716.

[14] Richard Kones, Recent advances in the management of chronic stable angina II. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization. Vasc Health Risk Manag. 2010; 6: 749–774.

[15] Kones R, Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. Vasc Health Risk Manag. 2010 Aug 9; 6:635-56.

[16] van Dam RM, Willett WC. Unmet potential for cardiovascular disease prevention in the United States. Circulation. 2009;120:1171–1173. [PubMed]

[17] Grundy SM. Prevention of atherosclerotic cardiovascular disease: why are the benefits of lifestyle therapies neglected. Dialogues Cardiovasc Med. 2005;11:73–86.

[18] Fox K, Garcia MA, Ardissino D, et al. for Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG) Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006;27:1341–1381. [PubMed]

[19] Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina –summary article: a report of the American College of

Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina) J Am Coll Cardiol. 2003;41:159–168. [PubMed]

[20] O'Rourke ST. Nitro vasodilators: pharmacology and use in the treatment of myocardial ischemia. Am J Pharm Educ. 2002;66:177–180.

[21] Hua Li a,b , Junbo Ge ,Cardiovascular diseases in China: Current status and future perspectives . IJC Heart & Vasculature 6 (2015) 25–31