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Angina pectoris: Revisiting an Age Old Menace

Srikanta Chandra*[1], Preeta Bose[2], Abhishek Jana[2], Tathagata Roy[2], Arabinda Nayak[3], Somsubhra Ghosh[4]

[1]Jakir Hossain Institute of Pharmacy, Miapur, Murshidabad – 742225, West Bengal, India

[2]Department of Pharmaceutical Technology, JIS University, Kolkata – 700109, West Bengal, India

[3]Gupta College of Technological Sciences, Asansol, Burdwan – 713301, West Bengal, India

[4]NSHM Knowledge Campus, A Group of Institute, Behala, Kolkata – 700053, West Bengal, India

Corresponding Author:Srikanta Chandra,Jakir Hossain Institute of Pharmacy,Murshidabad,742225,Email:srikanta.chandra95@gmail.com,Contact No:8250919674

Abstract: As we know angina pectoris is looming large in USA & other industrialized countries.*American Heart Association*(AHA) defined angina pectoris as aclinicopathological condition occurred due to transient reversible myocardial ischemia. Angina mainly three types one is stable angina second things that is variant or prinzmetal angina rest one is unstable angina. The general physiological conditions can be seen in the disease are multiferrous spread over squeezing, tightness or pain in the chest, jaw or neck, dizziness, fatigue, sweating.Epidemiologically angina pectoris got a huge impact on the world wide health condition. So here we are determined to narrowing down angina pectoris in our researchhead. As per the specifications in the reports the root cause of occurrence in the case of angina pectoris is often difficult because of the multifactorial etiology underpinning the condition which shows close to identical overview. The curtail causes may be figured ascholesterol deposition in the coronary artery which is also called atherosclerosis and vasoconstriction or vasospasticity of coronary artery.Since, Organic nitrate group of drugs such as Isosorbidedinitrate, Isosorbidemononitrate plays a pivotal role another group of drug that is calcium channel blocker such as Amlodipine, Diltiazemare used for management of angina pectoris.

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Introduction :

As we know Ischemic Heart Disease (IHD) is a risk persisting from past. According to *American Heart Association* (AHA) IHD is defined as a clinicopathological condition due to imbalance between imbalance between oxygen supply to the myocardium & oxygen demand of the myocardium.(Elanthendral R et al.2019) Ischemia have three criteria one is oxygen supply is reduced,other nutrition supply is reduced & another things that is impaired washout of waste product is reduced.(Albrecht Suzanne.2013)Apart from that isolated hypoxemia means only oxygen supply is reduced for that reason ischemia is too dangerous rather than isolated hypoxemia. (Chiara de Waureet al.,2013) Since, 99% case ischemia is associated with left ventricle not right ventricle because left ventricle thickness 1.5 cm whereas right ventricle thickness 0.3-0.5 cm, another pivotal point that is left ventricle produce 0-125 mm Hg pressure on the other hand right ventricle produce 0-25mm Hg pressure.(Saikumar K et al.,2020) However, left ventricle produce high tension that's why needs more oxygen on the opposite side right ventricle produce less tension that's why needs less oxygen compared to left ventricle.(Ford J Thomas et al.,2018) Angina pectoris is a clinicopathological condition resulting from transient reversible myocardial ischemia. Angina pectoris mainly three types one is Stable angina which is also called effortinduced angina or typical angina another one that is variant or prinzmetal or vasospastic angina rest is called unstable angina. Stable angina occurs due to formation ofatheromatous plaque obstruct 70% lumen in the coronary artery. Main reason of variant angina coronary artery vasoconstriction or vasospasm.(Ford J Thomas et al.,2018)Since , unstable angina associated with atheromatous plaque formation but another pivotal reason platelet & fibrin stick on the atheromatous plaque & produce a dynamic obstruction that's why unstable angina are too dangerous compared to stable angina.(Vadivelan Ramachandran et al.,2020) Epidemiologically angina pectoris got a huge impact on the world wide health condition.The general physiological conditions can be seen in the disease are multiferrous spread over chest pain, squeezing, tightness or pain in the chest, jaw or neck, dizziness, fatigue, sweating.(Kevin Cheng et al.,2016) Glycerin trinitrate, Isosorbidemononitrate, Amlodipine, Atenelol plays a pivotal role in management of angina pectoris as per as pharmacological aspects (Wee Yong et al.,2015).

Epidemiology: A Brief Over View

There is long range variation between the incidence rates of Angina pectoris. In Europe country incidence rates range from 5.1/100,000 (Romania) to 81.5/100.000.In Asia incidence

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was lower 0.1-6.8/100.000.(BA Mack Molly et al.,2014)On another side in intermediates rates between 0 to 18.2 people from the population of 100.000 are suffering in USA. However, current report indicating 61,000 patients are suffering from angina pectoris only in Sweden.Botucatu Medical School in Brazilconductedan epidemiological study evaluated the prevalence andincidence of angina pectoris in micro region of Sao Paulo State. Since, in the year of 1984 Khosla et al., conducted first study in India specifically in north India at the state of Haryana.(Gonzalez-FerreiraIgnacio.,2014)In that study 21,971 people participated and found around of 42.9 coronary artery disease patients. Up next 15 years later another study was conductedin Punjab by Soodetal.,.But it's incidence was calculation takes 1 year and it has been reported that 7.02people out of 100.000 people having angina.(Kuller L et al.,2011) In Australia it was 7.33, 23.68 and 14.00 per 100.000 where as inAsia the data shows of the cases are 0.76, 1.37 and 0.54respectively. (Kuller L et al.,2011)Data from middle east specially population studies from Turkey, Kuwait and Israel indicating an increased rate of 4.8 per 100.000 population in Kuwait and 6.04 people in Israel respectively. However, that is round 5.9/ 100.000 in Turkey and 168 people from same amount of population in Israel respectively bin.(RN McGillion Michael et al.,2009)The prevalence of angina pectoris rising very rapidly in japan research study showing from 2.9/100.000 individually in the year of 1986 to 13.5/ 100.000. quadrupled from 8.57 people from 100.000 population in 1997 to 30.87/100.000 individuals in 2005. In 9 year'stime period the growthof angina pectoris getting nearly tripled from 2.36/100,000 people in 1998 to 7.30/100,000 individuals in Chinese governedHong kong in 2006. Angina pectoris prevalence also increased in Singaporemarkedly from 2.3 people from 0.1 million population in 1990 to 7.2 per 0.1 million individuals in 2005.(Dai Xuminget al.,2016)The geographical variation is more common for angina pectoris. However, pediatric patients who are suffering from angina pectorisin NetherlandsandSweden are more common rather than Myocardial infraction. In Scotland angina pectoris isnot unknown rather than England. In India subcontinent the growth of angina pectoris is quite large on the society through the recent past.Coronary artery disease mayshown below the age of 20-25 years varies between 25-40 % it also affects irrespective of sex. In South Indian girls are effected less with Coronary artery disease rather than girls of southern part of India. Most studies reporting the incidence of angina pectoris (3/5) were from the Grate Bretain,with a predominant SA migrant group. The remaining two studies from Canada described the SA pediatric population and one study compared non – immigrants to.(Gorlin Richard et al.,1965) The incidence of angina pectoris in SAs was very much lower than Caucasian,except for one Canadian pediatric study.The Benchimol study

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reported that among other groups within the same environment as SA, still the SA showing lesser incidence rate than others .In United Kingdom two different studies has been done on the case of incidence over two different time durationwhich indicating an uplifts in the incidence of angina pectoris in the SA population from 1.3 to 2.4 people from 0.1 million in East London and 2.2 to 3.2 per 0.1 million individuals in Leicester . In 1989 for the last time incidence study on immigrants in United Kingdom has been published. (Fuchs M. Richard et al.,1982)

Pathophysiology: A Lacunae Revisited

Epidemiologically angina pectoris has a greater prevalence in the world population. So it has been decided by us to zero in on angina pectoris in our work ahead. As suggested in the literature study the course of the angina pectoris is often complicated due to the multifactorial etiology under pinning the condition which demands closer over view. The pivotal contours may be featured as cholesterol deposition in the coronary artery which is also called atheroma means it's a fibro fatty plaque formed in intima and coronary artery vasoconstriction or vasospasm. Atherosclerosis is a major problem in developed and developing countries. Fatty substance is found in the central core of the plaque which is covered by fibrous cap. (QuingWang .,2005)Atherosclerosis consists of two important parts ; atherosis that means deposition of fat fallowed by several sclerosis and macrophagesmeans fibrosis layer consists of smooth muscle cells , leukocyte & connective tissue.Cholesteroldeposition in intima and smooth muscle bellow it causesformation of these plaques. Then plaques grow up with the proliferation of fibrous tissues & the surrounding smooth muscle block the artery & reduce blood flow for this reason developed relative ischemia. Since another pivotal point is that platelet is stick on the cholesterol blood flow reduced other nutrients supply also reduced & impaired washout of waste product is reduced for this reason severe ischemia occurs & which is too dangerous rather than stable angina.(Almontashiri M.A Naif.,2017)Since different gene are responsible for coronary heart disease namely SORT I, PPAP2B, IL6R, NFKB1, APOB, ZEB-ACO74093, VAMP5-VAMP8-CGCX,ABCG, MRAS, GUCYIA3, EDNRA,SLC22A4-SLC22A5, TCF2 I, SLC22A3-LPAL2-LPA, PHACTRI, KCKN5,PLG,ZC3HCIHDAC9,LPL,TRIBI,CDKN2BASI,ABO,CYPI7AI-CNNM2-NT5C2, KIAAI462, CXCLI2, PDGFD,SH2B3,COL4AI-COL4A2, FLTI, HHIPLI, ADAMTS7, FURIN-FES,RAII-PEMT-RASDI,SMG6,LDLR, KCNE2 ⁽ChekalinaNataliyaet al.,2018) Mutation & polymorphism of these genes are one of the pivotal point beyond pathogenesis of angina pectoris . PPAP2B means Lipid phosphate phosphohydrolase3(LPP3) also known as

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phospholipid phosphatase3 (PLPP3) &phosphatidic acid phosphatase type 2B (PAP-2b or PPAP2B) is an pivotal enzyme in humans which is encoded by the PPAP2B gene on chromosome 1.(Christiansen Krogh Morten et al.,2018)Since it is spreads in different tissue. However, LPP3 is a cell surface glycoprotein that hydrolyzes extra cellularly phosphatidic acid (LPA) & short chain phosphatidic acid. Its have a specialized function that it regulate vascular & embryonic development by inhibiting a wide range of human disease such as cardiovascular disease & cancer. Increased risk factor of coronary artery disease is associated withthe genePPAP2B is contain 27 loci.(Gordon W. Joseph et al.,2011) Interleukin 6 (IL - 6R) is an inflammatory cytokine that produced from T cells , macrophages & adipocytes & it promotes inflammatory response through circulating soluble or membrane boundinterleukin -6 receptor on monocytes ,hepatocytes & endothelial cells.Since C – reactive protein & fibrinogen these synthesis stimulated by IL6R signalling , high circulating concentrations of IL-6 were associated with increased risk factor of coronary artery disease.Toclizumab is a pivotal pharmacological agents which is a monoclonal antibody it blocks both membrane bound & circulating IL6 R that's why inflammatory reaction is reduced & C- reactive protein & fibrinogen concentration is reduced. Thus we can used Toclizumab in management of coronary heart disease because its reduce articular inflammation & promote disease remission.(Hua Lei et al.,2020)The nuclear factor NFKB is a super family of transcriptional factors which plays an key role in regulating inflammation.(Ozbilum Nil et al.,2013) It is activated through reactive oxygen intermediates, hypoxia/ anoxia, hyperoxia, cytokines, protein kinase C activators, mitogen –activated protein kinase(MAPK) activators. The family of NFKB consists with the member p52, p50, p65 c-Rel&RelbB which forms different homo & heterodimers , the most pivotal common active form that is p50 or p52/RelA heterodimer.(Sun Xiao-Yu et al.,2013)NFKB consist different protein such as IKBδ& IKBβ another one. Then it phosphorylate & activate genes & produce vasoconstriction. Cholesterol deposition is one of top most pivotal reason to generate fixed obstruction into the intima of the coronary artery. Since familial hypercholesterolemia (FH) is an autosomal dominant disease at the molecular level by the presence of mutations of the receptor gene consists of low density lipoprotein & increased high risk of (Wu Wenjing et al. 2015)apolipoprotein B 100 is an autosomal dominant inherited disease due to mutation in the geneapoB. Three gene mutation such as R3500Q, R3500W, & R35331 C reduce the binding of LDL particles to the LDLRand cause the disease. Vesicle associated membrane protein5 & Vesicle associated membrane protein 8 are associated with high risk of coronary artery disease. On another side coronary syndrome X depress ST Segmentation in

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case of effort induced angina. Smoking, hyperlipidemia, hypertension, obesity atrial fibrillation, age, sex, family history, prothrombotic factors, elevated serum lipoprotein, elevated serum homocysteine are the high risk factors for formation of atheromatous plaque in the intima of the coronary artery & fixed obstruction associated there for this reason relative ischemia occurs. Since different studies shows that coronary artery disease and ischemic stroke is associated with each other. Coronary artery disease lasts 15 sec to 15 mins when it cross this duration cardiac cell under goes to necrosis & myocardial ischemia occurs Chromosome 9p21.3 were identified as susceptibility loci for coronary artery disease.(Yu Jieet al.,2016) Since another pivotal point is that a variant single nucleotide polymorphism (SNP) rs9818870 in the muscle RAS(M-ras) oncogene homologous gene (MRAS) on chromosome 3q22.3 was recently found& mutation of this chromosome increased risk of coronary artery disease. (Zdravkovic S et al., 2007) Briefly, transcription factor 7 like 2 (TCF7L2) gene polymorphism increased the risk factor for coronary artery disease. (Sousa.P Gustavo Andre et al.2009) Another study shows that rs7903146 protein polymorphismis responsible for cardiovascular disorder. (BellisariiIachini .F et al.,2003)KCEN2 gene or potassium voltage –gated channel subfamily E regulatory subunit 2, this gene expressed in heart & muscle &its having a different function such as maintain heart rate, regulate neurotransmitter, neuronal excitability etc. mutation of this gene associated with cardiac arrhythmia & coronary artery disease.(Corwin Steven et al.,2001) The ADAMTS7 gene which is found on chromosome 15:78,203-78,431,759,811, & has a 5 transcripts,10 paralogues, 79 orthologues& is a member of family which is associated with 67 phenotypes.(Daiber Andreas et al.,2015)1686 amino acid protein ADAMTS7 which contain a single prodomain, a peptide& a metalloproteinase domain, a disintegrin – like protein & a thrombospondin type-1 motif. Then it cleavage of the prodomain& it binds with a2-macroglobulin, connective tissue growth factor & cartilage oligomeric matric protein. ADAMTS7 which is produced & secreted by macrophages. Then it effects as proteolytic enzymewhich degrades the vessel wall's extracellular matrix to cleave thethrombospondinwhich is a vascular extracellular matrix protein that ultimately leads to CAD.(Fares Hassan et al.,2016)

Treatment of Angina Pectoris (AP) and Emerging Challenges :

We can manage angina pectoris followed by two aspects one is non pharmacological& another one is pharmacological aspects. Under non pharmacological aspects life style changes like monitored dieting, exercise may provide major benefit& psychological

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intervention also deployed to control the functional aspects of the disease. On the other hand Organic nitrate namely Isosorbidemononitrate,Isosorbidedinitrate , dihydropyridine group of calcium channel blocker such as Amlodipine , β-blocker namely Atenelol, Propranolol, Metoprolol still considered as a corner stone of the therapy as per as pharmacological aspects. (BallaCristina et al.,2018)Organic nitrate is the primary choice drug which has a salutary therapeutic effect against angina pectoris. Since,Glyceryltrinitrate is the first organic nitrate which was discovered byAscanioSobero in the year of 1847(Fox Kim et al.,2006)Organic nitrate denitrated enzymatically in smooth muscle to convert into nitric oxide. Then it activates guanylylcyclase and increased cGMP level form GTP. Dephosphorylates myosin light chain kinase & dephosphorylated myosin light chain kinase does not able to activates myosin. Then myosin is not able to interact with actin,relaxation of vascular smooth muscle occurs. (Rowe .G.G et al.,1990)Organic nitrate are lipid soluble, well absorbed from buccal mucosa, intestine, skin.(Silva Franca .S Maria et al.,2014) All nitrates except Isosorbidemononitrate undergoes extensive first pass metabolism in liver. Nitrate are classified into different category one is short acting another one is long acting based upon their site of administration. To prevent first pass metabolism organic nitrates are given in sublingual route, transdermal route.However organic nitrate associated with plethora of adverse effects such as fullness in head, headache, throbbing, palpitation, dizziness. On the other hand another group of drug that is calcium channel blocker (CCB) namely Amlodipine , Verapamil, Nifedipine plays a instrumental role for management of angina pectoris. (Tarkin .M Jason etalet al.,2016)Basically it is used for variant or prinzmetalangina because its produce vasodialation . Amlodipine which is a dihydropyridine group of drug its block L-type (Long Lasting Current Located Calcium Channel. Release NO from vascular endothelium cells then it activates guanylylcyclase.Guanylylcyclase convert GTP to cGMP& increased cGMP level . Then dephosphorylate Myosin Light Chain Kinase (MLCK) that's why myosin is not activated & actin - myosin interaction does not occurs & vascular smooth muscle & cardiac muscle relax.Since Amlodipine associated with different types such as flushing, dizziness, headache, peripheral edema,hypotension. However it is used for angina pectoris, hypertension, cardiac arrhythmia, hypertrophic cardiomyopathy. β- blocker such as Atenelol, Propranolol , Metroprolol plays an important role beyond the management of angina pectoris . β- blocker blocks β1 adrenergic receptors of the heart decrease cardiac output , force of contraction , heart rate & blood pressure, decrease of oxygen demand of myocardial muscle of heart.K^+ channel opener such as Nicorandil have plays a instrumental role beyond the management of angina pectoris. Intracellular concentration of K^+ is much

higher compared to extracellular K^+concentration. K^+ channel opening results in K^+ outflow & Hyperpolarization occurs that's why vascular & visceral smooth muscles relax.(FalaseB et al.,2001)However Nicorandil is associated with different types of adverse effects like headache, nausea, vomiting, postural hypotension.Since, Trimetazidine is a newer drugs which has an ameliorative property against angina pectoris. Briefly, all antianginal drugs are effects on the blood vessels but Trimetazidine does not associated with blood vessels. It blocks mitochondrial Long chain 3 keto acyl thiolase ($_{LC3KAT}$) which is involved in fatty acid metabolism .Due to this blockage of fatty acid metabolism myocardium start utilizing the glucose for ATP production .It have been seen that fatty acid oxidation requires more oxygen than glucose oxidation thus blocking of myocardial fatty acid oxidation reduces oxygen demand of heart . Dipyridamol another group of drugs which is a coronary vasodialator& increased blood flow through coronary artery. It inhibits uptake of adenosine in erythrocyte & other tissues which allow metabolically released adenosine which is a coronary vasodialator to accumulate in plasma.(ChruscielPiotr et al.,2014)

Conclusion: As we know angina pectoris is an emergent nuance in present scenario. From this review we concluded that organic nitrate is a first line drugs which is having a salutary therapeutic effect on angina pectoris .However β- blocker , Calcium Channel Blocker (CCB) ,K^+ channel opener plays a pivotal for management of angina pectoris as per as pharmacological aspects.

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