

Recent trends in “Coronary Artery Disease”

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Abstract

Coronary artery disease (CAD) is the most common type of heart disease, killing 382,820 people in 2020. About 20.1 million adults age 20 and older have CAD (7.2%) and 2 in 10 deaths from CAD happen in adults less than 65 years old. In the United States, someone has a heart attack every 40 seconds and every year, about 805,000 people have a heart attack. Of these, 605,000 have a first heart attack, 200,000 happen to people who have already had a heart attack and 1 in 5 heart attacks are silent, heart disease cost the United States about \$229 billion each year from 2017 to 2018. High blood pressure, high blood cholesterol, and smoking are the key risk factors for heart disease. Several other medical conditions and lifestyle choices can also put people at a higher risk, including diabetes, overweight and obesity, unhealthy diet, physical inactivity and excessive alcohol use. Sometimes, coronary artery disease develops without any classic risk factors. Inflammation is a key driver of its pathogenesis and targeting the inflammation represents a novel therapeutic option beyond the management of conventional cardiovascular risk factors.

Keywords: coronary artery disease; etiopathogenesis; stem cell therapy; nanotechnology; mitochondria-targeted cardioprotective compounds

Introduction

Coronary artery disease (CAD) remains one of the most common causes of morbidity and mortality [1], and the worldwide burden is set to reach 47 million disabilities by the year 2020 as projected by World Health Organization (WHO). In United States, 9 lakhs subjects suffered of CAD in 2016 and in > 35 years age group, the CAD causing one-third of deaths [2], close to 50% in western nations.

Risk factors

The rising incidence of CAD is a new phenomenon in developing countries and in western studies, there is a significant role of various nutrients, the fat, saturated fat and cholesterol are the causation of CAD [3]. INTERHEART - South Asia study identified the risk factors in Indians as abdominal obesity, insulin resistance, smoking, hypertension, diabetes, psychosocial factors and lack of physical activity which are more common in urban areas, accounts for 89% of acute myocardial infarction in Indians [4]. Indians are known to have the highest coronary artery disease (CAD) and rheumatic heart disease remains in epidemic proportions in India with an estimated prevalence of 1.5-2 per 1000 individuals. Global Burden of Disease study state age-standardized CVD death rate of 272 per 100000 population in India which is much higher than that of global average of 235 [5]. The traditional Indian diet is low in fat content and cannot be the sole cause for the high prevalence of CAD in Indians. The modifiable risk factors such as consumption of coconut oil has high amount of saturated fat and thought to be highly atherogenic [6], but recent studies state that no specific role of coconut oil in the causation of CAD [7-8]. Repeated heating of coconut oil leads to

increased lipid levels and lipid peroxidation in cholesterol fed rats. The results indicate that thermally stressed oils increase the atherosclerotic tendency in experimental animals by inducing oxidative stress. The common practice of repeatedly using the oil for frying may generate free radicals which are harmful for our health [9]. Animal fat was not an important etiological factor and the vegetarians are not protected by high intake of unsaturated fatty acids [10].

Etiopathogenesis

The exact reason for the high and increasing incidence of CAD among Indians [11] remains elusive and other etiologies such as the infectious or inflammatory conditions such as Endomyocardial fibrosis (EMF) provide an insight in its analysis [12]. Endomyocardial fibrosis is a reaction of endocardium to various insults, mainly of infectious origin causing damage to the endothelial lining of heart, blood vessels serous cavities and it is immunologically mediated [13] similar to rheumatic process and sometimes both coexist in the same individual. This ‘acute inflammation of the heart’ (Inflammatory hypothesis) results in myocardial damage, vasculitis with ECG changes of ischemia, infarction, conduction disturbances, atrial or ventricular arrhythmias in > 30% of cases [14].

Cardiotropic viruses were first implicated in the pathogenesis of CAD in 1968 and coxsackie B4 virus infection in mice was shown to produce acute coronary arteritis [15],[16]. Recent febrile illness due to seropositive *C. pneumoniae* and *H. pylori* shown to possess elevated levels of fibrinogen and a risk factor for CAD [17]. Finland study (1980) showed that elevated levels

of IgG, IgA to C. pneumoniae with angina pectoris and anti-chlamydial IgM with acute myocardial infarction. C. pneumoniae infects endothelial cells, smooth muscle cells, monocytes/macrophages and induces inflammatory reactions that are commonly observed in atherosclerosis. Seroepidemiological studies in Finland and other periequatorial countries, the PCR, Immunocytochemical staining and electron microscopy identified the presence of C.pneumoniae in atherosclerotic lesions of healthy, young, south african adults. Helicobacter pylori causes peptic ulceration & CAD and in autopsy, the presence of H.pylori and C. pneumoniae genomic materials were identified in coronary arteries of myocardial infarct cases. Sudden onset of arrhythmias in children, young adults and older age group herald the lesions of EMF in echocardiography similarly with infarction episodes. Biomarkers (propeptides and telopeptides) released during synthesis and degradation of collagen type I and III of extracellular matrix (ECM), the structural components of myocardium are used to identify fibrosis to assess the efficacy of medications [18].

During infection, plasma to move towards hypercoagulable state, plasma clotting factors increase, increased procoagulant activity at the level of vascular endothelium, shifting of prostaglandin metabolism towards thrombosis happened and changes in lipid metabolism [19] such as serum triglycerides & VLDL increase during the acute phase of infections, the LDL-cholesterol and HDL decrease concomitantly and the endothelium is directly damaged by lipopolysaccharide. Lipopolysaccharides affects circulating & tissue macrophages, increasing their production of free radicals which oxidises the LDL. Oxidised LDL [20] transforms the macrophages into “foam cells” and lipid accumulating monocytes (foam cells) appear in the media of vessel walls in pathogenesis of atherosclerosis and the cell lines infected by viruses such as herpes simplex (HSV), cytomegalovirus (CMV), Epstein-Barr virus are having transforming abilities. HSV can infect fetal smooth muscle cells and promote accumulation of cholesteryl esters and lipids in some cells. CMV-specific genomes have been detected in smooth muscle cells cultured from segments of restenosed coronary artery following angioplasty is a significant factor in post-transplant arteriopathic changes and the cardiac allograft vasculopathy (CAV) [21] and resembles conventional atherosclerosis. Prevalence of CAD rates in COVID-19 infection is between 4.2 and 25 percent in most series from China with an increased risk of poor prognosis [22]. The virus has large spikes of viral membrane glycoproteins on the surface and a unique furin-like cleavage site on the spike protein, plays a crucial role in viral cell entry. Transmembrane protease, serine 2 (TMPRSS2) enzyme is needed to activate the spike protein and a serine protease enzyme inhibitor blocks viral entry into the host cell and this phenomenon can be exploited for developing a treatment of COVID-19 in the future. The angiotensin converting enzyme 2 receptor (ACE-2), to which SARS-CoV-2 binds for entry into cells, found in vascular endothelium and smooth muscle, activating inflammatory and thrombotic pathways, leading to microangiopathy [23]. Thrombocytopenia with elevated D-dimer and C-reactive protein, lymphopenia, eosinopenia and elevated neutrophil counts, increased troponin in severe COVID-19 are consistent with a virus-associated microangiopathic process. Competitive blockage of angiotensin-converting enzyme 2 by the SARS-CoV-2 virus down-regulates angiotensin-converting enzyme 2 expression leading to uncontrolled blood pressure [24], RAAS dysregulation and hypoxia induced myocardial injury. In India, Mumbai witnessed a six-fold rise in deaths related to heart attacks in the first six month of 2021 during the second wave of Covid-19 as compared to the previous year". In the period between January-June 2021, nearly 3,000 people lost their lives to heart attacks every month which was around 500 in 2020. Nearly 23.8% (17,880) of the total 75,165 deaths recorded till June last year in Mumbai were attributed to heart attacks," the report said. Covid-19 is an inflammatory disease which has the potential to destabilize plaques in the coronaries and can also cause microvascular damages. Covid-19 typically causes inflammation of the endothelium which is termed as 'Covid Endotheliitis'. This endotheliitis is the cause of increased thrombotic events

thereby leading to the increase in the cardiac mortality and morbidity seen in the second wave [25].

Preventive measures

Nutritional support

Avoid concentrated juices, sugared beverages, saturated fats, obesity, malnutrition, and cachexia among other influences. Polyphenols, leguminous seeds containing plant protease inhibitors, as well as proteins, such as whey protein or jackfruit seed protein, could be incorporated in the daily diet. Bioactive polyphenols, such as EGCG (epigallocatechin gallate), GCG (gallic acid) are common constituents of green tea, quercetin is found abundantly in apples while hesperetin is present in citrus foods. Citric acid, a metabolite with anti-inflammatory activity, antiplatelet aggregation and has direct cardiomyocyte protective effects [26]. Ketogenic diets, tea bioactives, zinc and other micronutrients are essential.

Medications

The important steps to prevent and decrease the risk of CAD is to reduce the chance of getting this disorder by epidemiological measures, advice of blood thinning medications such as small daily dose aspirin (75 to 100 mg orally [27]), statins, nitrates and antibiotics in susceptible individuals. Immediate anticoagulation with low-molecular-weight heparin has been recommended to reduce the risk of thrombotic disease and this approach might also reduce COVID-19-associated ischaemic episodes [28], but it must be balanced against the risk of intracranial haemorrhage, including haemorrhagic transformation of an acute infarct. In unvaccinated COVID-19 patients, prophylaxis with heparin at the intermediate/high dose did not reduce primary outcome compared with the low dose but increased the risk of major hemorrhagic events [29]. Treatment by inhalation of fibrinolysis-related substances [30], such as tPA (also has anti-inflammatory effect) and plasminogen, can be administered at any stage of COVID-19 without concerns about bleeding. and improve alveolar ventilation by resolving fibrin-containing exudates in the pulmonary alveolar space and dissolving fibrin thrombi at the level of the microcirculation near the alveoli. The routine use of RAS inhibiting medications, the ACE inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists in hypertensive patients are shown to reduce fibrosis in humans. Vaccines with angiotensin II effects (RAS vaccine) effectively decreased cardiac fibrosis in immunized mice, Ang II signaling was inhibited and the anti-Ang II antibodies increased [31],[32] Ivabradine, an oral medication provides selective heart rate reduction by inhibiting the f-channels of the sinoatrial node and it effectively reduces the fibrosis, circulating Ang II and aldosterone levels [33] in animal models. Antiviral and anti-inflammatory agents have no benefit beyond standard of care and associated with cardiovascular side effects.

Novel treatment strategies

1. The stem cell therapy

Improve blood supply to the ischemic areas of heart, promote cardiac cell regeneration by a direct or paracrine factors and the stem cells decrease cardiac fibrosis and cardiac muscle apoptosis. Following injection of mononuclear stem cells in patients with myocardial infarction, there is an improvement in LV ejection fraction, exercise capacity, decrease in scar tissue and a reduction in mortality in a 5-year follow up occurs. “cardioclusters”. are cocktails of cells that include cardiac progenitor cells, mesenchymal stem cells, endothelial progenitor cells and fibroblasts. They have the potential to promote cardiac cell regeneration in disease states such as CAD when cell function is reduced. Thus, stem cell therapy continues to be a promising treatment modality in both acute and chronic CAD [34],[35].

2. Nanotechnology

Nanomedicine leads to an interesting and promising direction in the treatment of coronary artery disease. HDL (high density lipoprotein) are

thought to have a protective role since they are involved in the transportation of cholesterol away from the peripheral tissues. Nanotechnology has been used in the synthesis of a dimyristoyl phosphatidyl choline, mimics the surface characteristics of HDL [36] by mediating the removal of cholesterol from the peripheral tissue and transport it to the liver, showed significant reduction in plaque volume and cholesterol content in aorta [37] in animal models. Nanoparticle-based-antithrombotic agents phenylalanyl-L-prolyl-Larginyl-Chloromethyl ketone, perfluorocarbon-core nanoparticle, collagen IV nanoparticles) improve collagen formation, reducing oxidative stress by mimicking Annexin A (a glucocorticoid regulatory protein) in animal model.

Nanobacteria is the unit or member name of a former proposed class of living organisms, the specifically cell-walled microorganism now discredited, with a size much smaller than the generally accepted lower limit for life (about 200 nm for bacteria, like mycoplasma). They were found in 200-million-year-old sandstones taken from 3-5 kilometres below the seabed. When the rocks were opened, the nanobes multiplied and grew in the laboratory. Tests showed that they contain DNA (deoxyribonucleic acid), the molecule which contains the instructions for life. They were discovered by Philippa Uwins at the University of Queensland, Australia. Molecular mimicry with genetic predisposition leading to autoimmune damage to endothelial lining of the heart and blood vessels. Pathogen-triggered calcification could play a role in CAD. Recent reports suggest that infectious blood nanobacteria (NB) emerge to be such a trigger [38] and treatment with nanobacteria promising with reversal of calcific deposits within the vasculature.

Nanotechnology during PCI promote healing by inducing endothelialization of the stent and reduce restenosis and restore the injured vessel. Nano-sized hydroxyapatite coating, carbon nanoparticle coated stents with consistent release of sirolimus, pitavastatin, magnetic silica nanoparticles with rapamycin exhibit endothelialization in vitro-studies. Biodegradable/bioabsorbable stents using antibody coated nanoparticles which recruit endothelial progenitor cells are under study. Anti-proliferative drugs can be delivered using nanoparticles specifically at the site of PCI, to thwart neo-intimal genesis. Antimitotic drug (paclitaxel) in the form of albumin - based nanoparticles with significant antiproliferative effects can reduce restenosis and neointimal hyperplasia and platelet adhesion in animal models. Weekly intravenous injection of Pitava-NP increased fibrous cap thickness [39] and decreased the number of buried fibrous caps in the atherosclerotic plaques with reduced macrophage accumulation (Mac-3) and monocyte chemoattractant protein-1 (MCP-1) expression. Intravenous treatment with Pitava-NP at the time of reperfusion reduced infarct size in 24 h after reperfusion. Intravenous treatment with Pitava-NPs for three consecutive days ameliorated the LV remodeling 4 weeks after myocardial infarction. Gene eluting stents are used to overcome restenosis, in-stent thrombosis and delayed endothelialization.

3. Mitochondria-targeted cardioprotective compounds

The coenzyme Q10 (CoQ10) (or ubiquinone) is the only endogenously synthesized liposoluble antioxidant. Besides its role in electron transfer chain, the fully reduced form (ubiquinol) exerts a well-characterized lipid peroxidation-inhibitory effect, whose therapeutic potential has largely been investigated in CVD. In several animal models of acute cardiac ischemia and HF, CoQ10 treatment resulted in attenuation of mitochondria structural damage, increase of high energy substrates, improved endothelial function, and mitigation of adriamycin cardiotoxicity [40]. Isosteviol (IST) is a bioactive diterpenoid extracted by *Stevia rebaudiana* that has a variety of biological activities targeted at the CVS, including anti-hypertensive, anti-hyperglycemic, antioxidant, and anti-inflammatory effects. It restores mitochondrial membrane potential, morphological integrity, and biogenesis; decreased ROS (reactive oxygen species) levels; and upregulated the expression of antioxidant enzymes [41]. In addition, IST relieved IR (ischemia and reperfusion) injury in rodent hearts and isolated pig hearts and these observed beneficial effects of IST can be attributed to stimulation of

the mito-KATP channel, since a selective mito-KATP inhibitor abolished its protective action [42]. A lipid-polymeric nanocarrier (LPN) for mitochondrial-targeted delivery of TN (Tanshinone) has been recently developed. The formulation consists in a PLGA-TN mixture enclosed in a lipophilic shell formed by TPP linked to a D- α -tocopheryl-PEG-succinate (TPGS) moiety, an FDA-approved biocompatible excipient widely used for drug delivery [43].

4. Phytochemicals

The pathological processes of myocardial I/R injury include apoptosis, autophagy, and irreversible cell death caused by calcium overload, oxidative stress, and inflammation. Eventually, myocardial I/R injury causes a spike of further cardiomyocyte injury that contributes to final infarct size (IS) and heart failure as well as all-cause mortality within the following 12 months. Adjuvant intervention to improve myocardial salvage and cardiac function calls for further investigation. Phytochemicals are non-nutritive bioactive secondary compounds abundantly found in Chinese herbal medicine and improve myocardial I/R injury without compromising the clinical efficacy or to even produce synergy. Resveratrol is the natural compound, mainly extracted in fruits, such as peanut, grape, berry and carry a potentially cardioprotective property against myocardial I/R injury via regulating inflammatory, angiogenesis, energy metabolism, mitochondrial function, and cardiomyocyte apoptosis [44]

5. Pinocembrin

A major flavonoid derived from propolis [45] has antioxidant effect, reduction of calcium overload, inhibition of inflammation and myocardial cell apoptosis and plays a role in the treatment of myocardial ischemia and reperfusion injury. It exerts its antiarrhythmic effect by increasing the activity of Ca^{2+} - Mg^{2+} -ATPase. The clinically used inotropes worsen the reperfusion stunning and provoke arrhythmias by increasing the cytosolic calcium level.

6. Levosimendan

Is a calcium sensitizing inodilator [46], increases the myofilament calcium sensitivity without increasing myosin-ATPase activity. It is also a PDE (phosphodiesterase inhibitor) and K-ATP channel opener, do not increase the cytosolic calcium when given in low concentrations. It also induces changes in cAMP to cGMP ratio, an increase in cGMP level, decrease the increase in cytosolic calcium during ischemia and protects from arrhythmic episodes. It is a cardioprotective inotrope by virtue of its ATPase sparing and K-ATP channel opening properties, protects the ischemic myocardium while at same time improving reperfusion, mechanical function without elevating cytosolic calcium level.

7. Antioxidants

Direct induction of lipid peroxidation has arrhythmogenic effect on the heart. The stress affects the Na^{+} , K^{+} -ATPase activity, accelerates thermodenaturation of this enzyme, plays a key role in maintaining the transmembrane potential and electrical stability of the heart. Antioxidants prevent cardiac fibrillation during acute ischemia and reoxygenation of the heart [47].

8. Antibiotics

Azithromycin given once weekly in clinical trials since a single dose may require 10 days for elimination and generally well tolerated during long-term prophylaxis and gastrointestinal symptoms and superinfection by candidiasis may also occur. In ACADEMIC trial (Azithromycin in coronary artery disease elimination of myocardial infection with chlamydiae), there was a reduction in markers of inflammation such as C-reactive protein, TNF- α , IL-1, 6, but antibody titers were unchanged after 6 months of therapy with azithromycin. (500 mg daily for 3 days, then weekly). Azithromycin

600mg/week- short, 3 months therapy [48] was safe and well tolerated and 33% reduction in death or myocardial infarction at 6 months. Clarithromycin appears to reduce the risk of ischemic cardiovascular events in patients presenting with acute non-Q-wave infarction or unstable angina [49]. Antibiotics eradicate the *C. pneumoniae* from epithelial cells and not from monocytes and *C. pneumoniae* in lymphocytes was less susceptible to antibiotics [50]. In STAMINA trial (south thames trial of antibiotics in myocardial infarction and unstable angina), the additional metronidazole had improved outcome and complete eradication may take 1-year of treatment (long-term therapy) since the organism is resistant to antibiotics when engulfed within the monocytes.

9. Statin treatment

Statins are used for secondary prevention to reduce coronary heart disease (CHD) events. Antigen presenting cells such as dendritic cells and macrophages have recently been detected in atherosclerotic plaques. Toll-like receptors expressed on the surface of these cells, have been implicated in ongoing inflammatory responses in the plaques. Anti-inflammatory effect of atorvastatin, via Toll-like receptor 4 (TLR4) at 10 microM significantly attenuated NF-kappaB activation within 24 hours while at lower doses of 0.1 and 1 microM, treatment time had to be prolonged up to 48 hours for a significant inhibition to occur. The attenuation of NF-kappaB by atorvastatin occurred in a MyD88 dependent fashion [51]. In the randomized controlled trials (RCTs) reviewed, initiation of moderate-intensity therapy (lowering LDL-C by approximately 30% to < 50% Alirocumab [54], a monoclonal antibody produced by recombinant DNA technology block the LDL regulator protein (PCSK9-Proprotein Convertase Subtilisin/Kexin Type 9 [55]), reduce the LDL cholesterol to 66-73% when combined with atorvastatin and atorvastatin alone cause reduction by 17% only.

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