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# FROM ATHEROSCLEROSIS TO CABG

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**Abstract:** Ischemic heart disease (IHD) is diagnosed in approximately 30-34% patients who undergo surgery. In other words, 1 out of 3 patients scheduled for surgery is an IHD patient. Cardiovascular diseases are in fact the main health problem in Iran. From 44 million surgeries performed in the US in 2003, 6.8 million were related to the cardiovascular system, 467,000 were related to coronary artery bypass grafting (CABG), and 93,000 were valve-related. The annual cost of coronary artery diseases in the US is nearly $142 billion (2, 3, 4, 9). Coronary artery bypass grafting (CABG) is a common treatment method for ischemic heart disease. This surgery is not only essential to survival, but also relieves the angina pains and helps increase the quality of life (5-9)

**Key Words:** Ischemic heart disease, Atherosclerosis, CABG

## ATHEROSCLEROSIS

Atherosclerosis is a type of arteriosclerosis or hardening of vessels caused by atheromatous plaque formation in the vessel walls. Félix J. Marchand became popular in the 80s when he used this term. The term is derived from the Greek word "Athero" which means porridge or gruel which describes the lipid-rich soft inflammatory substance that is generally seen in atherosclerotic lesions. Sclerosis is derived from scarring or hardening. This condition leads to the narrowing or blockage of blood vessels and ultimately stroke, heart attack, and death. The prevalence of cardiovascular disease, whose main reason is atherosclerosis, is 1 out of 3 Americans, and has imposed over 400$ billion directly and indirectly which account for 8% of the total annual health expenditure per capita (10).

## ATHEROSCLEROSIS RISK FACTORS

Environmental and genetic risk factors include family history, high levels of LDL in the blood, high blood pressure, smoking, gender, race, diabetes, obesity, high-fat diet, excessive alcohol consumption, and sedentary life style. All these risk factors are involved in the risk of developing the disease. Atherosclerosis is an insidious disease that takes many years to develop symptoms. Narrowing of blood vessels due to atherosclerotic plaque. The plaque is formed in the vessel and bulges towards the lumen and narrows the lumen compared to healthy vessels. The reduced lumen diameter disrupts blood flow.

Humans have been dealing with atherosclerosis for thousands of years. Microscopic and macroscopic evidence have been found of the vascular lesions in the aorta, carotid, coronary and femoral arteries in Egyptian mummies (11,12).

The symptoms of vascular lesions were first described in 1912 by the American physician, James B. Herrick, when his articles on clinical features of myocardial infarction were published in the Journal of the Medical Association of America. Before the twentieth century, atherosclerosis was a rare condition that occurred in few people, but in less than 100 years, it became the number one cause of death in the United States. New technologies and innovations changed the active lifestyle to a sedentary one. Manual labor was replaced by machines or was facilitated by them. Cars, washing machines, lifts, and vacuum cleaners become usual appliances. Changes in diet accompanied lifestyle changes, and fatty foods such as butter, cheese, ice cream, hamburgers, fries, and chips also become the main component of Western foods. Life expectancy increased by 30 years. At the end of the 20$^{th}$ century, life expectancy was increased to from 44-45 years in men and 49-50 years for women in 1900 to 74-75 for men and 79-80 for women in 1999 (13,14). All these changes in the American lifestyle have contributed to the increased prevalence of atherosclerosis.

## PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis process begins in infanthood with the induction of fat veins in vessels (15). Fat veins are composed of monocytes from macrophages and T lymphocytes (16). The number of fat veins increases until adolescence and early adulthood. More advanced damages form in the mid-twenties. They progress with age. The clinical symptoms of this disease manifest when advanced plaques appear. Its frequency also increases with age during 50s and 60s. At the time, it is accepted that atherosclerosis is a chronic inflammatory disease (17 & 18). The expression of VCAM-1 is critical in the beginning of this disease. Resulting damages are

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reduced in rats with VCAM-1 lack. Its expression leads to the increase of T-cells and monocytes in endothelial ulcer sites. Then, accumulated lococytes reinforces inflammatory reaction through releasing Monocyte Chemo-attractant Protein-1 (MCP-1). This protein collects further lococytes, activates them, and gives rise to the proliferation and increase of smooth muscle cells (20). The multiplication of macrophages induces further cytokine release and its outflow into the mid layers of vessels. The topical activation of monocytes leads to both the progress of cytokine-mediated atherosclerosis and the oxidation of low-density lipoprotein. Lower level of chronic inflammation is a major objective of atherosclerosis research. It is seen that many useful effects of statin are also mediated by their ability to change sequential (cascade) inflammatory paths (21). Inside and outside the vessel, cholesterol moves by sticking to carrier protein in form of LDL. If LDL exists in subintimal space, it can pass through blood flow without any changes. Yet, it can also be oxidized and entrapped by oxygen free radicals at the inflammation time. It seems that all Lipoxygenases (LOs), Myeloperoxidases (MPO), inducible Nitric Oxide Synthesis (iNOS), and NADPH oxidases are involved in LDL oxidation. They are expressed by macrophages (22). Oxidized LDL (oxLDL) is bound with phagocyte receptors on macrophages and brought into cell (23). Macrophages absorb high amounts of oxLDL. They reserve extra cholesterol as cholesterol ester particles. They transform cells into cellular foam. The absorption of oxLDL reduces foamed cells' movement. It also decreases the accumulation of lipid-rich cells in inner membranes or intima. Foamed cells also secrete other cytokines. They absorb further monocytes and lead to the proliferation of smooth muscle cells. This plaque gradually develops through the accumulation of foamed and smooth muscle cells in intima. Some of them attach proteoglycans in subintimal space. LDL is attached oxidized proteoglycans. Then, it is detected by phagocyte receptors on macrophages. Lipid-filled macrophages are transformed into foamed cells. They are entrapped in vessels' walls. These foamed cells release cytokines. They, in turn, attract more monocytes to this area and lead to the proliferation of smooth muscles cells in blood vessels. Depending on morphology, plaque can be stable, fibrous, or apt to detachment. When growing, stable plaques can induce chronic problems like angina and, then, vessel lumen narrowness. Yet, they are generally considered to be a benign disease (24 & 25).

In other words, asymptomatic and unstable platelets can be disintegrated, their contents be exposed to blood flow, and cause coagulation cascade. This creates a thrombus on the surface of the platelet and can block blood vessels in the platelet or convert them into smaller vessels, which leads to myocardial infarction or stroke. The platelets which are highly at the risk of rupture have generally a large lipid core, thin fibrous cap, a large number of inflammatory cells, especially macrophages, lipid peroxide and some vascular smooth muscle cells. In other words, stable platelets that are resistant to disruption are more fibrosed and containing more smooth muscle cells compared to unstable platelets (26-29).

**DIAGNOSIS AND TREATMENT OF ATHEROSCLEROSIS**

Not generally until its complications such as loss of sensation in the distal regions of the body, chest pain, myocardial infarction or death from loss of blood pressure in the tissues occur that Atherosclerosis can be diagnosed. Currently, the degree and location of obstruction is determined using X-ray angiography with contrast intensification in which a dye is injected into the blood circulation and the blood flow is imaged. The regions where blood flow is restricted are colorless due to platelets. This technique has maintained its golden standard for assessing cardiovascular diseases. This imaging technique is limited in the sense that it cannot measure platelet coverage and to provide information about the morphology or platelet stability (30-34).

It does not seem that the sensitivity of the platelet depend on its size. Therefore, small asymptomatic platelets sensitive to rupture may remain in the conventional X-ray angiography. Newer technologies avail themselves of the current computerized (CT) or MRI tomography for angiography which provide more accurate images. Angiograms are still limited in terms of the information they provide. Targeted imaging techniques which directly carry the contrast agents or radio tracer to atherosclerotic platelets. These techniques allow high-resolution imaging such as MRI or PET which are individually used as non-invasive platelet imaging. Current treatments for Atherosclerosis try to reduce the symptoms of the disease or slow down its progression. Cholesterol-lowering drugs such as Reductase HMG-CoA (3-hydroxy-3- methylglutary l coenzyme A) inhibitors or statins are used to reduce cholesterol synthesis and increased clearance of LDL through the liver, which causes a general reduction in blood cholesterol. The use of statins means a 60 percent reduction in myocardial infarction and a 17 percent reduction in stroke (36) but it has not yet become a treatment as was hoped at the time of its discovery and has its own side effects (37). Anticoagulants such as heparin, warfarin, low-dose aspirin, and direct thrombin inhibitors are used for the prevention of thrombus formation caused by platelet rupture. These drugs are administered systematically and have potential side effects such as severe bleeding, Thrombocytopenic and drug reactions. Heparin, a commonly used

anticoagulant, has varied effects on patients in the hospitals. This effect may be due to the fact that it connects to many plasma proteins such as fibronectin and Von Wilde brand factor and is also neutralized by platelet factor 4 and histidine-rich glycoproteins which are released by activated platelets. This opens only limited treatment avenues for patients receiving sub-therapeutic doses and puts them at high risk of recurrent cardiac incidences and bleeding in patients taking therapeutic doses (38).

Surgeries done to remove lumen stenosis or abnormal artery stenosis due to atherosclerosis include subcutaneous transluminal coronary angioplasty, bypass or endarterectomy. Angioplasty is applied to return normal blood flow through affected artery. It includes the insertion of balloon into the narrowed area of vessel and widening it by pushing atherosclerosis plaque. Then, a naked metal stent can be placed in the vessel to keep it open. It prevents from artery swing and provides a skeleton for the regeneration of endothelial cells (39&40). Unfortunately, lumen stenosis or %50-narrowness of vessel happens in %40 patients during 6 months after subcutaneous transluminal angioplasty anew (41).

Recently, drug-carrier stents have contributed to the reduction of re-stenosis risk by alleviating the proliferation of smooth muscle cells or intensifying the regeneration of endothelial cells in vessels. They both decrease scar formation in damaged vessels (42&43). Re-stenosis process is not well-understood. Further modifications are being made on stents such as changing the constituents of stents and the type of medication they carry. Endarterectomy is usually done in cerebral vessels diseases where a severe reduction is induced in cerebral blood reserve; (carotid endarterectomy) or for treating peripheral vessels diseases (deficient blood reserve in legs). A blunt (non-sharp) tool is used for removing the mid and internal layers of blood vessels in the place where plaque is located. These stages are significant in blood flow-back through vessel. Yet, there is still the risk of serious side effects of these stages such as infection, apoplexy, bleeding, and thrombus (44).

Accordingly, this treatment will not be administered, unless with highly acute disease symptoms. Bypass surgery is usually done in patients with coronary stenosis in cardiac vessels of other vessels severely damaged or calcific vessels to relieve the obstruction. Normally, an alternative blood path is made by binding an intact vein from patient's leg, arm, chest, or abdomen or synthetic tubes to vessels. In some cases, an artery is redirected by being cut and attached to another area where blood flow is more necessary yet there is a lack of parallel blood flow. Serious side effects can occur after bypass surgery including the reduction of perceptual performance, apoplexy or infection. The present forms of atherosclerosis diagnosis and treatment have efficiency limitations. There are serious risks in applying them. The purposeful transmission of imaging factors and medications to atherosclerosis plaque can help the better management of this complicated disease (45).

## CORONARY ARTERY BYPASS GRAFTING SURGERY (CABG)

Coronary Artery Bypass Grafting Surgery (CABG) is a protective standard method developed for patients with coronary artery disease (46). This complicated method of re-vascularization (re-opening vessels) and the advances of coronary surgeries (like inventions of surgical, and anesthetic techniques, qualitative improvements, cardiac cares promotion, the application of artery duct and the improvement of pre- and post-surgery cares) have reduced the side effects, mortality, and blockage rate of attachments (47).

Annually, over 600,000 patients undergo CABG in the US. The first human CABG was done on a beating heart in 1960. Yet, after the advent of cardiovascular machines or Cardio-Pulmonary Bypass (CPB), Off Pump Coronary Artery Bypass Grafting (OPCABG) became practically obsolete. Now, it is replaced with Conventional Coronary Artery Bypass Grafting (CCABG). However, OPCABG was again introduced in 1980s. In 1990s, it was acknowledged that it has become popular (48). Now, recent technical improvements in surgery have turned OPCABG (with 20-25% CABG) into a routine method in the US (49).

## CCABG OR CONVENTIONAL CORONARY ARTERY BYPASS GRAFTING

It is acknowledged that CBP considers CABG a very effective and safe treatment for CAD. This procedure creates an artificial circulation after certain procedures are carried out and, therefore, surgery can be performed when the heart has stopped beating (cardioplegic arrest) and does not bleed (which will substantially protect it against ischemic injury). Nevertheless, many studies have suggested CBP can cause problems related to CABG and mortality (50-52).

Some of the most important clinical concerns related to CBP are as follows:

1. Post perfusion syndrome resulting from contact between blood constituents and artificial surfaces along the bypass path, and paradoxical (crossed) embolism and reperfusion injuries
2. Neurological and neuropsychological problems that, on average, can increase hospital expenses for rehabilitation and outpatient services by 5 to 10%

3. Higher incidence of postoperative chest infections
4. Blood loss during or after surgery, use of blood products, and the long duration of surgery (53)

**OPCABG OR OFF-PUMP CORONARY ARTERY BYPASS GRAFTING**

OPCABG has been introduced as a technique capable of reducing postoperative complications and mortality and is thought to be a valuable and relatively useful technique for patients at high risk of pump-related complications. It has been reported that OPCABG offers better myocardial protection, lower rates of pre- and post-operative complications, and that it reduces neurologic deficits resulting from hyper perfusion during CPB, embolic events caused by CPB pump, and paradoxical (crossed) embolism (54). Moreover, beating heart surgery makes it possible to maintain functional integration of the systems in the main body organs, and reduces rates of mortality and complications. Therefore, patients undergoing OPCABG will be hospitalized for a shorter period and will have lower expenses (55). There is little definitive and documented data to prove the superiority of the off-pump technique over the on-pump one, and available information on the effectiveness of the off-pump technique obtained from previous studies is contradictory and makes off-pump CABG an unreliable substitute for the on-pump one in the United States (56). Nevertheless, a meta-analysis performed by Reston *et al.,* showed that rates of heart infarction before surgery, stroke, reoperation due to bleeding, kidney failure, and death after OPCABG were lower compared to those after CABG (57). Moreover, OPCABG reduces hospital stay, atrial fibrillation, and wound infection. Therefore, this research concluded that it seemed off-pump coronary artery bypass decreased hospital stay and complications and mortality resulting from the surgery compared to the on-pump technique, and it was noted that rates of repeat treatment interventions in CCABG were lower. CABG is a unique procedure among very complicated surgeries as it is performed 10 times more than abdominal aortic aneurism repair in the United States, 150 times more than esophagectomy, and 2.5 times more than carotid endarterectomy (58).

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