
Chronic Coronary Artery Disease

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Coronary insufficiency (CI) is the state in which an imbalance occurs between the supply and demand of oxygen, which prevents adequate maintenance of the metabolic needs of the myocardium, resulting in ischemia of several degrees of intensity.

CI has numerous causes among which are cardiac valvular diseases (aortic stenosis), hypertrophic cardiomyopathy, microvasculature diseases (diabetes mellitus, syndrome X), anomalous origin of coronary arteries, and coronary fistulas. However, the most important cause, because of its frequency and the resulting morbidity and mortality, is atherosclerotic obstructive CI. Therefore, this discussion will be specifically about coronary atherosclerosis. The main objective is not to suggest practical applications for specific situations, but to outline concepts, based on critical analysis of data in the literature, which may provide a basis for conducting further investigation and for providing treatment of coronary artery disease (CAD).

Pathophysiology

Human atherosclerosis is a chronic, progressive and systemic process characterized by an inflammatory and fibroproliferative response of the arterial wall caused by aggression against the arterial surface. As a systemic process, it frequently attacks all arterial beds, including the aorta and its main branches: carotid, renal, iliac and femoral arteries. Among the risk factors (RF) for arterial lesions are hypercholesterolemia, arterial hypertension (AH), diabetes, smoking, immunological and inflammatory reactions, and individual genetic susceptibility¹.

The coronary vascular alterations present in atherosclerosis derive from three fundamental components: 1) endothelial dysfunction, which starts early, altering the reactivity of the vessel and causing paradoxical vasoconstriction following stimuli with acetylcholine, and exacerbation of reactivity to epinephrine and angiotensin; endothelial dysfunction also leads to loss of the natural antithrombotic properties and of the selective permeability of the endothelium; 2) obstruction of the lumen of the vessel by

the atherosclerotic plaque and 3) thrombosis at the location of the lesion. Any of these could individually trigger CI, but they often occur at the same time.

Response of the arterial wall to aggressive agents

Endothelial cells play several physiological roles in maintaining the integrity of the arterial wall and constitute a permeable barrier through which diffusion and exchanges or active transportation of several substances occur. They provide a non-thrombogenic and non-adhesive surface for platelets and leukocytes; they operate to maintain vascular tonus by releasing nitric oxide (NO), prostacyclin (PGI₂) and endothelin-1; they produce and discharge growth factors and cytokines and maintain the integrity of the basal membrane rich in collagen and proteoglycans on which they are supported². Alterations in one or more of these functions represent initial manifestations of endothelial dysfunctions and may trigger cellular interactions with monocytes, platelets, smooth muscle cells and lymphocytes, causing an atheromatous plaque to be formed^{3,4}.

One of the triggering factors of endothelial dysfunction is hypercholesterolemia, followed by the increase in transportation by transcytosis of LDL to the intima; this is followed by the accumulation of such lipoproteins both in their native form and in the oxidized form, with peroxidation of the phospholipids composing them, and forming particles and compact mycelia or larger vesicles named extracellular liposomes⁵. The cytotoxic effect of the lipoproteins causes endothelial dysfunction, which translates into hyperplasia of the basal layer, which detaches itself from the endothelium, and also the proliferation and reorganization of the extracellular matrix now containing the liposomes. Another consequence is the stimulation of the endothelium to cause chemotaxis and adherence of molecules of leukocytes to the endothelial surface^{3,6}.

Several studies⁷⁻¹⁰ have shown the presence of molecules that induce the adherence of leukocytes to atherosclerotic lesions in their various evolutionary phases. These molecules attract leukocytes, more specifically monocytes, and are expressed and detected on the surface in the initial phases of arterial lesions or on lesion prone areas, such as those next to junctions of arterial branches. Among the main adhesion molecules we can identify the vascular cell

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adhesion molecule-1 (VCAM-1); the intercellular adhesion molecule-1 (ICAM-1); the E-selectin, also called acute phase adhesion molecule; and the endothelium-leukocyte adhesion molecule (ELAM-1), among others. The belief is that the discharge of adhesion molecules is regulated by cytokines synthesized in small concentrations by the arterial endothelium. Important among these are interleukin-1 (IL-1), interleukin-4 (IL-4), alpha tumor necrosis factor (TNF- α) and gamma interferon (INF- γ). During endothelial dysfunction, the concentration of cytokines rises, stimulating the production of adhesion molecules, thus favoring the recruiting and adhesion of monocytes to the endothelial surface.

Luscinskas et al⁹ studied the sequence of events triggered by the interaction of monocytes and endothelial cells activated by IL-4. Four distinctive phases can be noticed. The first, called the *rolling phase*, establishes the initial contact between monocytes and the endothelial surface in normal hemodynamic conditions, and is mediated by L-selectin; the interaction is with the glycidic part of the glycoproteins present in the leukocyte membrane. The second phase, called the *stop phase*, is characterized by the activation of monocytes, caused by chemotaxis and/or accessory molecules that activate adhesion molecules. Once activated, such molecules are connected to the monocytes, characterizing the strong adhesion phase, also called *stop phase*. This stage depends on integrins, such as alpha4B1, present in the monocytes and endothelial VCAM-1. Adhered monocytes can spread on the apical surface of the endothelium, which represents the third phase, called *spreading*. This process depends on beta2 integrins synthesized by monocytes and on ICAM-1 and/or ICAM-2 present in the endothelial cells. The monocytes that have already spread migrate to intercellular junctions and gain subendothelial space by diapedesis; this final phase is known as the *diapedesis phase* and seems to be dependent on the endothelium-platelet cell adhesion molecule (EPCAM-1) expressed in leukocytes and endothelial cells. The adhesion molecules can foster endothelial lesions by reducing the distance between monocytes and endothelial cells, and easing the attack of the oxygen active species, such as superoxide anion, hydrogen peroxide and hydroxyl radicals originated from activated monocytes, constituting an added factor favoring atherogenesis¹¹.

High concentrations of plasmatic LDL ease the penetration of these particles into the subendothelial area. In contact with the endothelial cells, macrophages or smooth muscle cells, the LDL particles suffer progressive oxidation; initially only of their lipids (minimally oxidized LDL) and later also of their protein component (totally oxidized LDL - LDL_{ox})¹². The particle becomes recognizable by acetylated receptors¹³ and CD-36¹⁴, an LDLox receptor, on the surface of macrophages. Such receptors are not regulated by the intracellular cholesterol concentration; so, macrophages incorporate large particles of LDLox and become rich in lipid content. Then foam cells are formed and they are characteristic of the fatty streak, which is the earliest lesion known at the onset of atherosclerosis. Table I provides a summary of the

Table I - Development of the fatty streak

1)	Lipoprotein transportation
2)	Lipoprotein retention
3)	Lipoprotein modification
4)	Monocyte adherence
5)	Monocyte migration
6)	Monocyte differentiation
7)	Formation of foam cells

process of fatty streak formation. LDLox performs important actions, such as: forming foam cells, producing substances that promote chemotaxis like the monocyte chemotaxis protein - which attracts monocytes to the subendothelial area, reducing the recirculation of resident monocytes, which retain monocytes in the sub-endothelium; and finally, oxidized LDL is toxic to the tissues⁶. This toxicity results in a structural lesion in the endothelium.

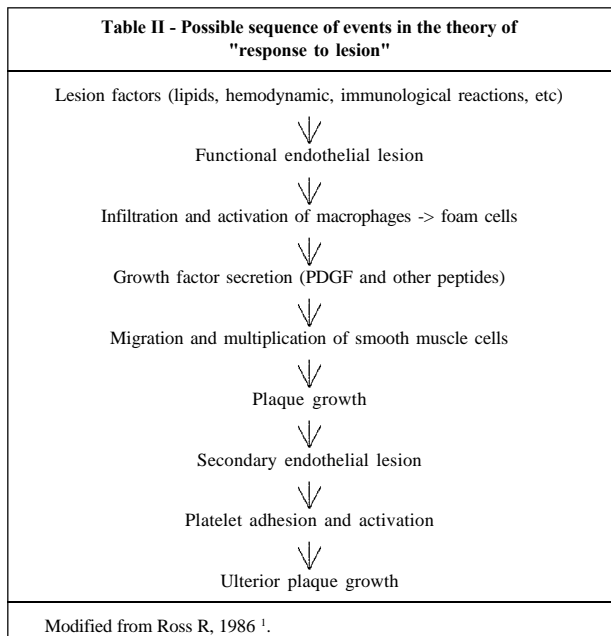
Among the alterations caused by the presence of LDLox is also the production of interleukin-1, stimulating the migration and proliferation of smooth muscle cells of the media layer. When these migrate to the intima layer, they proliferate and start producing not only cytokines and growth factors, but also extracellular matrix, mainly composed of collagen and proteoglycans, which will form part of the fibrous cap of the mature atherosclerotic plaque³. The endothelial erosion induced by LDLox can also cause the formation of platelet microthrombi, which will in turn produce growth factors, such as the platelet-derived growth factor (PDGF)³. At this moment the endothelium may present extensive lesions, true erosions. The interaction between platelets, endothelium, smooth muscle cells and macrophages will determine the degree of cellular proliferation, extracellular matrix secretion, and consequently the extension of the mature plaque. Table II presents the main phases of formation of the atherosclerotic plaque¹.

Anatomy of the atherosclerotic plaque

The evolution of the fatty streak atherosclerotic lesion into the fibrous plaque is quite slow. Pathological studies in human beings and animals have shown that the growth of the atherosclerotic plaque initially occurs towards the outer part of the vessel. Glagov et al¹⁵ have demonstrated remodeling of the arterial wall in atherosclerotic plaques, with wall expansion towards the outside and lumen preservation in the beginning of the process. Therefore, the plaque can take years in this continuous remodeling process until it causes luminal stenosis.

The mature atherosclerotic plaque shows, in addition to cells, two distinctive structural components: a slightly dense lipid nucleus and the fibrous cap, which is its fibrotic component. This fibrous component represents about 70% of the plaque's total size¹⁶⁻²¹, and the larger the plaque is, the less prone it is to rupture. The fibrous cap is basically formed by smooth muscle cells, extracellular matrix and inflammatory

Table II - Possible sequence of events in the theory of "response to lesion"



cells. The matrix consists of collagen, elastin, proteoglycans and protein microfibriles. Cytokines and growth factors regulate the synthesis of the matrix components ¹.

The lipid nucleus is hypocellular and rich in extracellu-

lar lipids, mainly crystals and cholesteryl esters. Its pathogenesis is controversial, for it can derive both from lipids imprisoned in the extracellular space and from the necrosis or apoptosis of the foam cells ¹⁹. The content of this lipid nucleus is highly thrombogenic. When in contact with the blood stream, due to rupture of the fibrous cap or endothelial erosion, the phenomena of platelet adhesion and aggregation occur, along with generation of thrombin and fibrin, with superjacent thrombus formation, representing the common starting point of acute coronary syndromes. Table III illustrates the phases of formation of atherosclerotic plaque, according to the classification of the American Heart Association ²².

The sequence of progression of lesions, from type I to type IV is by the progressive accumulation of lipids. This evolution is slow; it starts in the first decade of life and goes until the third decade; this is the silent period of the disease. When it reaches phase IV, it grows by the accelerated accumulation of smooth muscle cells and collagen, going on to type V lesion; or in a more abrupt way, by instability, with the occurrence of ruptures and thrombosis or hematoma and then lesions type VI are formed. In the latter, the thrombi can become incorporated into the lesion, which grows and becomes again type V. This oscillation between type V and VI plaques is the main gradual occlusion mechanism of advanced lesions in medium caliber arteries.

Table III - Phases of atherosclerosis (American Heart Association classification) ²²

Type of lesion	Characteristics
Initial lesions	
Type I	Increase in the number of macrophages and appearance of foam cells, distributed at random. These are present in 45% of children up to 8 months old.
Type II (fatty streak)	First visible lesion. Layers of foam cells and drops of fat inside the the smooth muscle cells, and in the extracellular space and minute lipid particles with rough and heterogeneous aspect. These are present in 65% of teenagers.
Ila	With intimal thickening. Lesions tending to progress.
Ilb	With tunica intima thinner and few smooth muscle cells.
Intermediary lesions	
Type III	Lesions similar to those of Type II, together with extracellular lipid collections.
Advanced lesions	
Type IV (atheroma)	The confluence of the lipid collections of type II lesions creates an extracellular dense accumulation of fat in a well-determined area of the tunica intima, the lipid nucleus. There is no marked fibrous tissue nor presence of complications such as flaws on the surface of the plaque or thrombosis. Between the lipid nucleus and the endothelial surface, there is the extracellular matrix rich in proteoglycans and cells, such as lymphocytes, macrophages and foam cells. Usually they are not associated with the vessel's lumen stricture. On the contrary, there may be an increase in diameter when measured from the adventitia.
Type V	When the fibrous capsule develops, it usually causes lumen stricture and can suffer fissures, hematomas or thrombosis.
Va (fibroatheroma)	Fibrous tissue containing the lipid nucleus. New lipid nuclei can appear in different locations and planes, creating an asymmetric lesion.
Vb	Calcification of the fibrous nucleus or of other parts of the lesion.
Vc	Absence or minimal presence of lipid nucleus.
Complicated lesion	
Type VI	These are usually type IV or V lesions presenting rupture on the surface, hematoma or hemorrhage and also thrombus.
VIa	Surface rupture
VIb	Hematoma or hemorrhage
VIc	Thrombosis
VIabc	Rupture, hemorrhage and thrombosis.

Atherosclerotic plaque instability factors: the vulnerable plaque

The instability of the atheromatous plaque, although unpredictable in regard to time, has reasonably defined markers: the composition and relationship of the lipid nucleic mass with the total lesion mass; the thickness of the fibrous cap and the presence of inflammatory activity. Other factors are the degree of stenosis and the hemodynamic disorder related to it.

Instability happens more often with plaques whose nuclei are rich in more fluid lipids²³ and with a larger mass in relation to the lesion¹⁹. As for the thickness of the fibrous cap, instability occurs in thinner plaques and in the junction with the normal wall of the vessel, the "shoulder"²⁴; in addition, unstable plaques present smaller amounts of collagen and glycosaminoglycans compared with more stable plaques. These characteristics are more frequently associated with ruptures, fissures and thrombosis and occur more often in acute syndromes. Patients with stable angina have the accumulation of extracellular matrix as the main mechanism for arterial obstruction.

The fibrous cap of ruptured plaques shows activated macrophage infiltration, indicating inflammation where the rupture is located²¹. T-lymphocytes are also present in the fibrous cap, attracted by adhesion molecules expressed in the endothelium²⁵. In eccentric plaques, the inflammatory cells are mainly located in the shoulder area, which is the place most likely to rupture. A study made with samples gathered by atherectomy, in patients with stable and unstable angina and non-Q AMI demonstrated that arteries responsible for acute syndromes contained more macrophages than samples responsible for stable angina²⁶. According to Libby²⁵, the IF-gamma produced by lymphocytes blocks collagen production by the smooth muscle cells. On the other hand, activated macrophages cause extracellular matrix degradation; both factors contribute to the weakening of the plaque's fibrous cap.

Macrophages may degrade the extracellular matrix through two distinct mechanisms: fagocytosis or metalloproteinases secretion; these are enzymes able to digest almost all substances present in the extracellular matrix^{27,28}. The metalloproteinases operate in a neutral pH in the extracellular space, where they are released as proenzymes²⁸. So far, twelve different enzymes from the metalloproteinase family have been identified, each with a preferential substrate, but not a single one. Collagen type I, a prominent component of the fibrous cap, can be degraded by metalloproteinases 1 and 8²⁹. Galis et al³⁰ have demonstrated that it is on the plaque's shoulder area that there is an excess of activity. Increased activity of metalloproteinases 2 to 9 has also been documented in human plasma, in unstable angina³¹. The macrophages are not the only cells able to produce and secrete these enzymes. Smooth muscle cells also discharge metalloproteinases, thus also contributing to the homeostasis of the fibrous cap.

Recent studies have shown that patients with unstable angina and AMI have high levels of C-reactive protein and amyloid-A protein, reflecting a systemic inflammatory

Author	No	<50%	50%-70%	>70%
Unstable angina				
Ambrose et al ³⁷	25	72	16	12
Acute infarction				
Ambrose et al ³⁷	23	48	30	22
Little et al ³⁸	41	66	31	3
Giroud et al ³⁹	92	78	9	13
Nobuyoshi et al ⁴⁰	39	59	15	26
Average	65	20	15	

process^{32,33}. This rise, even in normal individuals, was related to a higher incidence of myocardial infarction and strokes³⁴. The same authors have shown that the reduction of the risk of the first AMI, through the use of aspirin, seems to be related to a lower level of C-reactive protein, suggesting the possibility that anti-inflammatory drugs may contribute to the prevention of cardiovascular diseases.

An intriguing finding concerns the level of stenosis in unstable plaques; it was noticed that patients with acute coronary syndromes show a predominance of slight (<50%) or moderate (<70%) lesions³⁵⁻⁴⁰. Table IV below illustrates this fact.

Several explanations have been suggested for acute syndromes involving slight to moderate lesions³⁵. Among these are the higher ratio of these lesions in relation to the total number of lesions and the absence of collateral circulation. Another theory is that the tension on the fibrous cap

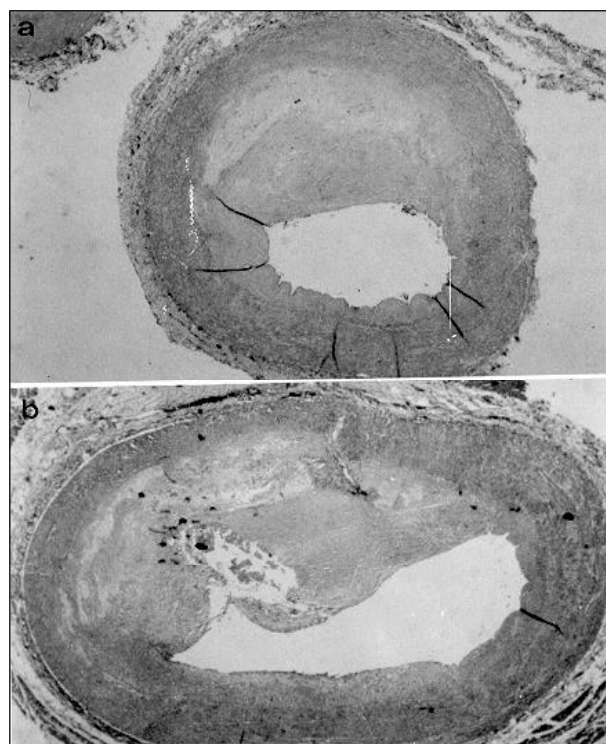


Figure 1 - Representative sections of stable (A) and unstable (B) plaque. A) See the significant thickness of the fibrous cap. B) See the site of plaque rupture. (Material from the Pathology Laboratory of Incor).

is directly proportional to the diameter of the artery and to the intracoronary pressure, according to Laplace's law²⁴; therefore, the tension is higher in smaller lesions than in larger ones, due to the luminal ray. Figure 1 exemplifies stable and unstable lesions.

Coronary reserve, obstructive lesion and ischemia

As an atherosclerotic lesion develops in an epicardial artery, luminal tightening occurs. In significant obstructions the vessel begins to greatly resist coronary flow. Within physiological limits of perfusion pressure, the coronary auto-regulation allows arteriolar resistance adjustments to maintain the proper balance between flow and demand for myocardial oxygen⁴¹. As the resistance of the epicardial artery increases due to a higher degree of stenosis, the distal arteriolar resistance declines to keep the flow at normal levels. When the arteriolar vasodilation reserve is exhausted, the myocardial perfusion is linearly dependent on the perfusion pressure. In such conditions, drops in arterial pressure (AP) can induce ischemia⁴².

The decline of coronary reserve starts when lesions occupy at least 70% of the vessel diameter. In concentric lesions, the coronary flow depends on the degree of the lesion and perfusion pressure. In eccentric lesions, the degree of obstruction can be dynamic, because the part of the plaque least affected by the atherosclerotic process may suffer dilation or constriction, and thus vary the effective vessel lumen.

The reduction of the coronary reserve is progressive; initially ischemia occurs in intense oxygen demand situations (tachycardia, exercises), and then in situations of lower demand until the coronary reserve is totally impaired when the lesion occupies 90% of the vessel diameter.

Collateral circulation

Collateral circulation is blood circulation between two vessels without an intermediary capillary network. The mechanisms responsible for the development of collateral circulation are not well known. Ischemia and the pressure gradient between normal and obstructed vessels seem to be important, because the irrigation of the area supplied by collateral vessels is more deficient in endocardial layers. The functional significance of collateral circulation has been assessed in various manners. The backward flow following acute coronary occlusion in dogs varies from 8 to 36% of the normal flow. This flow may increase up to 40% with the use of drugs, such as verapamil, during acute ischemia⁴³. Collateral vessels that have developed slowly also respond to vasodilating drugs and to tachycardia⁴⁴. With collateral coronary circulation, between 28 and 50% of silent coronary occlusions in humans are not accompanied by a ventricular mechanical deficit, suggesting that the presence of pre-existing collateral circulation may protect the myocardium⁴⁵.

On the other hand, myocardial scintigraphy studies with thallium-201, during exercise, have shown that when there is an occlusion of the anterior descending artery, the anterior myocardial area shows signs of ischemia in the occlusion, even in the presence of collateral circulation. The other areas are totally protected by collateral circulation, as demonstrated by Baroldi⁴⁶, who noticed that in 44% of the patients with up to two occluded vessels there was no histological evidence of a myocardial infarction. This suggests that collateral circulation may be adequate at rest but insufficient during intense exercise, mainly when the area irrigated by the occluded artery is large. Right after an infarction, collateral circulation may appear; however, only later does this collateral circulation influence ventricular mechanical function. For protection from the beginning, it should be present before the occlusion.

Risk factors

Advanced age, family history of CAD and male sex are commonly recognized RF^{47,48}. As for AH, MacMahon et al⁴⁹ demonstrated in a metanalysis of more than 400,000 persons that a close correlation exists between hypertension, systolic or diastolic, and CAD. It is a very prevalent factor among patients with CAD. Although its control is followed by decreased mortality due to stroke, lower incidence of kidney insufficiency and heart failure, a great reduction in acute coronary events has not been proved. On the other hand, the metabolic alterations present in diabetes mellitus⁵⁰, the generalized glycolysation of proteins, insulin resistance and the alteration of the metabolism of the remaining chylomicrons, lead to accentuated and diffuse atherosclerosis of all vessels. Atherosclerosis is even greater, however, in average and small caliber arteries. Thus, atherosclerosis is the cause of 80% of deaths^{50,51} in persons with diabetes. Persons with non-insulin dependent diabetes mellitus (NIDDM) (type II diabetes), although they have lower levels of glycemia, have greater cardiovascular risk than those with insulin-dependent diabetes mellitus (IDDM) (type I diabetes), because atherosclerotic alterations in their arteries are greater⁵². These same disturbances seem to be responsible for endothelial dysfunction and microangiopathy. Control of post-prandial glycemia and the resulting metabolic disturbances that follow it has proven to be the most effective way of reducing complications in persons with diabetes^{52,53}.

Cigarette smoking, another risk factor, alters LDL⁵⁴, reducing the endothelium-dependent relaxation induced by acetylcholine, in a similar way to oxidized LDL, without altering the non-endothelium dependent relaxation. Both active and passive smoking⁵⁵ are associated with the development of several clinical forms of CAD and diffuse atherosclerosis in men and women.

The rate of progression of atherosclerosis, determined by measuring the thickness of the layers media and intima of the carotid artery in the Atherosclerosis Risk In Communities (ARIC) Study, in relation to those that are normal, was 50% higher in active smokers⁵⁶, 25% in ex-smokers and 20% in

individuals exposed to passive cigarette smoke. The impact of cigarette smoking was greater in persons with diabetes and hypertension. The duration and degree of exposure, but not the exposure continuation or interruption, correlated with the progression of atherosclerosis. The benefits of smoking cessation and the decrease in coronary events are well established. Hasdai et al⁵⁷ showed a higher incidence of non-Q wave infarction and of death in patients who continued smoking compared with ex-smokers and non-smokers. In women the increase in cigarette smoking coincides with an increase in the incidence of atherosclerosis.

Dyslipidemia is perhaps the most frequent RF⁵⁸. Countless experimental and epidemiological studies^{59,60} have established the influence of hyperlipemia on the development of atherosclerosis and its cardiovascular complications. In some cases it is linked to genetic alterations (see below); but in most cases it is due to an increased intake of saturated fat.

The relationship between triglycerides and coronary disease is somewhat controversial⁶¹. In a univariate analysis, triglycerides usually predict the disease, but when other RF, mainly HDL levels, are factored into multivariate analysis, triglyceride loses its predictive power. However, a recent study⁶² indicates that even within levels considered normal, individuals with triglyceride levels >100mg/dl have more coronary events in the long-range than those with levels <100mg/dl. This is very suggestive of the long-range predictive value of hypertriglyceridemia.

A sedentary way of life and obesity go hand in hand^{63,64}. Regular exercise reduces considerably the incidence of coronary events; however, a cumulative effect has not been noticed, except in preventing obesity from the fifth decade in life on. Of practical importance is the demonstration that even light intensity exercise as often as twice a week, although it does not lead to physical conditioning, does positively influence lipid profiles⁶⁵. On the other hand, body mass indexes >27 are associated with an increase in total and cardiovascular mortality, mainly in young people⁶⁶. Emotional stress related to the work environment, personal and family problems^{67,68} is also a RF.

It is important to note that in about 35% of the documented cases of CAD, traditional RF are not found⁶⁹. Certain "genetic alterations" have already been identified⁷⁰⁻⁷³ that are responsible for dyslipoproteinemia causing atherosclerosis; among these are familial dysbetalipoproteinemia, combined familial hyperlipemia, apolipoprotein A-I, A-I and apoC-III deficiency. One special condition is the occurrence of low HDL (<35mg/dl), especially when followed by increased triglycerides; it is found in approximately 4%-5% of the population. In the Prospective Cardiovascular Munster Study (PROCAM)⁷⁴ it was associated with a 6-fold increase in the incidence of coronary events. A variation of apoA-I (delta K107) was associated with this syndrome. Increases of lipoprotein(a) (Lp(a))⁷⁵, of fibrinogen⁷⁶ and plasma homocysteine⁷⁷⁻⁸¹ may contribute to some cases of CAD. The relationship of homocysteine and atherosclerosis was first reported in 1969, when McCully⁸² demonstrated precocious atherosclerosis in children with homocystinuria. Later on,

the infusion of homocysteine in laboratory animals demonstrated the rapid formation of typical vascular lesions. The confirmation of hyperhomocysteinemia as a RF for arterial disease came from clinical studies, showing the association of elevated homocysteine levels with peripheral vascular disease, stroke and coronary disease⁸⁰⁻⁸¹.

Some infectious agents, such as the bacteria *Chlamydia pneumoniae*, and certain viruses have been suggested as possible causal agents^{82,83}. However, it is not clear yet if they are causal agents or simply coincide with or heighten the already on-going process. Clearly, the issue of RF is still open for discussion. In 1981, Hopkins and Williams⁸⁵ identified 246 possible coronary RF. It is possible that even more may be discovered.

Certain groups of RF are frequently found in one individual. Stress combined with smoking, hypertension or both are often found in the same individual. A sedentary life, obesity and hypercholesterolemia are also another commonly found group of RF. This grouping of RF is important, because the risk of coronary events increases, not in a simple additive way, but in a geometrical progression.

Clinical syndromes in coronary artery disease

Necropsy studies in children and adolescents⁸⁶, in soldiers who participated in the Korean^{87,88} and Vietnam⁸⁹ wars, and adults approximately 25 years old, victims of sudden death (SD)⁹⁰, clearly indicate that coronary atherosclerosis begins in adolescence and its initial alterations date back to childhood. However, its clinical manifestations only show up during adulthood, more frequently from the fourth decade of life on. It may then be concluded that the disease presents a long period of silent evolution, before the manifestation of clinical CI, which can take various forms, including the following:

a) **Stable angina** - Repeated anginal attacks, which can develop over months or years are referred to as stable angina. An increase in myocardial oxygen consumption (MVO₂), usually due to physical exertion or emotions, triggers ischemia. It is relieved by rest or the use of vasodilators. The threshold for angina may vary. When the ventricular function is normal, as it frequently is, stable angina is compatible with an acceptable quality of life.

b) **Heart failure** - Heart failure associated with CAD is mainly due to two conditions: ischemic cardiomyopathy and LV akinesia/dyskinesia (aneurysm). The ischemic cardiomyopathy is the ventricular dysfunction with diffuse hypocontractility and dilation of ischemic cause. It can be a consequence of the replacement of fibrosis in areas where multiple, small infarctions have occurred, or of global myocardial dysfunction due to chronic ischemia and hibernation. The state of myocardial hibernation⁹¹⁻⁹³ is of great practical importance, for it indicates the presence of persistent ischemia with viable myocardium, therefore liable to recovery by restoring the blood flow.

The other segment of patients with heart failure secondary to coronary disease are those with akinesia or ventricular aneurysm. This type of heart failure is a segmentary mechanical ventricular dysfunction following an infarction. When it is extensive, the aneurysm ends up causing dysfunction of normal, not infarcted segments, leading to chronic CI. Aneurysms cause serious alterations in the ventricular geometry, being also a cause of ventricular arrhythmias.

c) **Silent ischemia (SI)** - About 3% of the normal population and 30% of asymptomatic patients experience silent ischemia (SI) following an infarction of the myocardium^{94,95}. Most angina patients experience multiple ischemic episodes of painless ischemia, which amounts to 75% to 92% of the total ischemic load. SI can be diagnosed by an ergometric test (ET) and Holter monitor. The prognosis depends mainly on the size of the risk area. SI is particularly troublesome because patients do not experience the classic warning sign: pain. Therefore, they may be at serious risk without knowing it. That is why it is the cause for SD in many cases.

d) **Acute coronary ischemia** - Unstable angina, non-Q wave infarction, and infarction with Q-wave are characteristics of acute coronary ischemia. They are related to atherosclerotic plaque rupture and thrombosis superimposition in the areas of ischemia. Thrombosis of short duration or in combination with partial arterial occlusion is associated with instances of unstable angina; more persistent thrombosis and total occlusion are associated with myocardial infarction. These thromboses can occur both in patients with a history of prior angina or can be the first manifestation of CAD.

e) **Sudden death (SD)** - As indicated by the name, SD is an event that naturally evolves to death, which is not always observed in other forms of acute ischemia. Approximately 1/3 of CAD patients die of SD, which can be due to primary malignant arrhythmias, such as ventricular tachycardia degenerating into ventricular fibrillation or ventricular fibrillation associated with acute ischemia⁹⁶.

It must be stressed that in CAD there is no precise relationship between anginal symptoms and the extension of the coronary or ventricular function impairment. It is quite common to find patients with recent angina who maintain practically normal physical activities until the onset of the symptoms. Coronary angiography reveals important bi- or tri-arterial lesions in such patients. It is obvious that these lesions developed long before the symptoms. On the other hand, the ventricular mechanical function may be little altered or even entirely normal. This can be explained because ischemia is segmentary or because collateral circulation allows for natural compensation of the coronary obstruction. Hence, certain patients with serious coronary lesions can maintain practically normal physical activities for a long period of time. However, when symptoms or signs of heart failure occur, significant ventricular dysfunction is present.

Coronary disease in women - CAD in women occurs about 10 years later than it does in men⁹⁷. This is attributed

to the protective effect of female hormones during the women's reproductive years, because no difference exists in the prevalence of RF and type of lesion between men and women⁹⁸. However, the seriousness of the clinical presentation does not differ between the sexes. Actually, it is suggested that the post-AMI evolution is worse in women than in men⁹⁹. However, more careful analyses show that this worse evolution is mainly due to other factors, such as more advanced age and diabetes, and not the female sex¹⁰⁰ per se.

But cardiovascular disease is the greatest cause of death in women, even higher than total mortality due to uterine, breast, and ovarian cancers^{101,102}. Therefore, CAD treatment in women must not differ from that in men, because the disease has similar evolution or prognosis in both sexes.

Prognosis

Ejection fraction of the left ventricle - Random comparative studies of clinical and surgical treatments have proved the undeniable value of measuring ejection fraction (EF) for the prognosis of CAD^{103,104}. In patients clinically treated in the Coronary Artery Surgery Study (CASS)¹⁰⁵, the survival rate over 4 years was 92% for EF >50%, 83% for EF 35-49%, but only 57% if EF was <35%. Hueb et al¹⁰⁶ reported that patients with few symptoms and preserved ventricular function who had refused surgery showed similar results as those in CASS. Therefore, EF must always be quantified when establishing a CAD prognosis. Figure 2 illustrates the relationship of EF versus survival rate.

Coronary artery anatomy - Usually, the higher the number of arteries with critical lesions, the worse the long-term prognosis^{103,104}. The European Coronary Study Group¹⁰⁷,

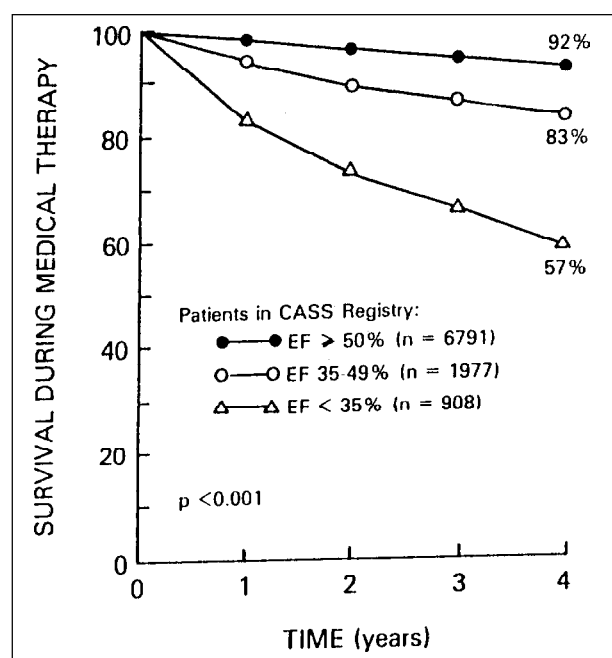


Figure 2 - Survival to ejection fraction ratio in patients clinically treated in the CASS registry (Reproduction allowed¹⁰⁶).

however, has shown that critical lesions (>50%) in the left coronary trunk or the presence of proximal lesions in the two great branches of the left coronary artery, the anterior interventricular branch and the circumflex branch together with lesions in the right coronary artery show a higher mortality rate than other subgroups. This mortality is reduced with myocardial revascularization. Later, patients in CASS with few symptoms and presenting uni-, bi- or tri-arterial lesions had a low mortality rate if they also had a good ventricular function, an EF over 45% visualized by contrast ventriculography or by radioisotopes.

In addition to the prognosis, knowing the coronary anatomy is fundamental in deciding about the best treatment, whether clinical or revascularization by angioplasty or surgery. Not only it is important to know where the lesions are located, but also the characterization of the distal beds and the presence of collateral circulation are valuable elements in determining treatment.

Risk area— The myocardial area that can be affected by ischemia when coronary occlusion occurs is called the risk area. The knowledge of coronary artery anatomy or the extension and intensity of ischemia in myocardial scintigraphy using Thallium-201 or SESTAMIBI-Tc99m allows us to quantify the risk area⁹³. However, it is also important to analyze non-ischemic areas, because they are responsible for ventricular adaptation when coronary occlusion occurs. It is well documented that larger risk areas have a worse prognosis¹⁰⁸.

Electrophysiological status - The frequent occurrence of ventricular arrhythmia, i.e., over 30 ventricular extrasystoles per hour, recurrent ventricular tachycardia, the presence of low voltage potentials in the final part of the QRS complex in the high resolution electrocardiogram, in patients with left ventricular aneurysm or left ventricular dysfunction, are associated with a higher incidence of cardiovascular death and SD^{109,110}.

Age - In chronic CAD the influence of age is not simple. On the one hand results from CASS showed a higher survival rate in 7 years among young people (84% versus 75% for males and 90% versus 77% for females)¹¹¹. However, the disease is, in relative terms, more serious and has a worse prognosis in young people; perhaps because in this age group two of the most important RF are prevalent: smoking and family history of CAD. The Brazilian Medicine, Angioplasty, or Surgery Study (MASS)¹¹², which analyzed the influence of medical treatment, angioplasty and surgery in patients with critical lesions in the anterior interventricular branch of the left coronary artery, revealed a high rate of progression in non-critical lesions in younger patients, most of whom developed tri-arterial lesions at the end of the 3 years of the study. Whereas the Gruppo Italiano Per lo Studio Della Streptokinase Nell' Infarto Miocardio-2 (GISSI-2)¹¹⁰ reported that with acute myocardial infarction advanced age is a bad prognostic factor.

Diagnosis

A clinical history may provide important information for the diagnosis of CAD. Anginal pain, fatigue, dyspnea, and palpitations are the most common complaints. Typical angina is the most easily diagnosed. Identification of triggering and relief factors, its duration and characteristic location and irradiation are indispensable for the diagnosis of typical angina. It is associated with coronary disease in 90% of men over 55 years old and 80% of women in this same age group^{112a}. When the pain has some, but not all of the classic characteristics, it is called atypical angina and is associated with coronary disease in 50% of the patients over 50 years old. However, many symptoms mirror angina. SI, where the patient can be totally asymptomatic must not be overlooked. Family history should include history of infarction and SD, in men who are close relatives below 55 years of age, and in women also who are close relatives below 65 years of age. Life style habits can indicate significant RF. But physical examination usually adds little to the diagnosis. Except in instances of heart failure, the physical examination is noticed only for being normal, which ironically contrasts with the potentially lethal situation.

Non-invasive examinations - Technical aspects will not be discussed here, but only several peculiarities of major interest to the cardiologist in general.

Electrocardiogram at rest - Most patients with heart failure are within normal standards. However, the presence of inactive areas suggesting a previous infarction, inverted T waves, downslope of the ST segment and left ventricular hypertrophy are associated with a higher cardiovascular mortality rate in the long-range¹¹³. The presence of extrasystoles, mainly those of ventricular origin, may suggest coronary disease. Conduction disorders both atrial-ventricular and fascicular may occur, but these do not contribute to the detection of coronary disease because they are unspecific.

ECG Stress test (ST)— Considering the low cost, simplicity, sensitivity and specificity, and prognostic value of this test, and also considering the prevalence of CAD in the population group to be studied, the ST is very useful in tracking and stratifying coronary atherosclerotic disease and has an excellent level of reliability¹¹⁴. The interpretation of the ST must include not only the analysis of the electrocardiogram, but also the hemodynamic and clinical variables. It is used to track CAD in suspect cases and, as a screening tool in individuals who are beginning physical exercise programs or patients with RF. Therefore, it predicts a poor prognosis when positive in low loads, when the arterial pressure does not rise adequately and the work tolerance is less than six minutes.

Radioisotopes - The versatility of radioisotopes allows them to be used to detect ischemia, fibrosis and to evaluate the LV mechanical function. Thallium 201 or SESTAMIBI-Tc99m scintigraphy, due to its high specificity, sensitivity and

positive and negative predictive value is considered a fundamental exam in identifying the presence of coronary disease⁹³. Fixed uptake defects suggest areas of predominant fibrosis, while reversible defects suggest an ischemic process and viability of the myocardial cells. Alterations in the balance between supply and demand of O₂ that allow the induction of ischemia and evaluation of the viability may be triggered both by exercise and drugs such as dipyridamole. The contrast reinjection techniques, late reading and tomographic cuts contribute to increase this method's analytical capacity¹¹⁵. It also allows an estimate of the extension of the risk area. As it is well known, this has great prognostic value, for the larger the area, the worse the prognosis.

The use of deoxyfluoroglucose, with radioactive fluoride, of long-chain fatty acids, with C14, or of labeled ammonia permit the evaluation of the integrity of cellular metabolism, the presence of ischemia, and the quantification of the residual coronary flow in hypocontractile or akinetic areas fed by coronaries with critical lesions⁹³. Currently available computer software allows simultaneous appraisal of the presence of ischemia, ventricular volumes and ventricular segmental contraction. It is undoubtedly a method of immense value. The only restrictions are its cost and availability.

Resting and stress echocardiogram - The resting echocardiogram has considerable application in the diagnostic and non-invasive prognostic determination of the coronary atherosclerotic disease¹¹⁶. It allows the detection of segmental thickness and motility alterations (hypokinetic, akinetic or aneurysmal areas), which are characteristic of CAD, in addition to allowing for the evaluation of volumes and ventricular mass, and also the EF, which is of acknowledged prognostic value.

However, it was the use of physical stress, or rather, pharmacological stress^{116a} that opened great perspectives for echocardiography. When administering dobutamine in increasing doses (up to 40µg/kg/min), three responses may be triggered: progressive improvement of the contraction, initial improvement followed by a worsening, and finally, progressive worsening^{116b}. The response considered typical of the presence of ischemia with viability in hypokinetic areas is the initial improvement followed by a worsening of the contraction. However, the lack of an adequate window, more common in the age bracket of coronary disease patients, can prevent resting echocardiograms from being made or impair their technical quality. Physical exercise can also be used to provoke ischemia, but the increase of movements in the thorax, both due to hyperpnea and the exercise, makes this exam more difficult to conduct.

Echocardiogram with the use of micro-bubbles - The development of stable micro-bubbles, not related to the occurrence of systemic emboli and that reflect the ultrasound rays, causing a contrast in relation to the blood and neighboring tissues, hail a new non-invasive era in the diagnosis and determination of ischemia and ventricular function¹¹⁷. Intracavitary bubbles allow ventriculography

with contrast and, bubbles in the intratissular vessels, allow visualization of myocardial perfusion. The technical hindrance to the use of micro-bubbles is their low commercial availability, a higher number of patients with inadequate thorax for the exam in the age bracket to be investigated, and the low specificity for perfusion defects on lateral wall. Rapid technical development in this area is expected, which will widen the use of this method.

Coronary angiography - The definitive exam for the diagnosis of coronary obstructive atherosclerosis is coronary angiography. It also permits the evaluation of ventricular function. It should be performed when there is reasonable suspicion of coronary disease, to explain precordial pain of possible ischemic origin, to establish the prognosis, and whenever any intervention is considered, whether by catheter or surgery. It should be stressed that it is an invasive exam, and despite its low risk, serious complications may occur, such as systemic embolism, arterial dissections, ventricular fibrillation and death. Studies relating the level of stenosis with the triggering of ischemia have shown that lesions > 70% are correlated with the decrease of coronary flow reserve. Furthermore, certain characteristics of the lesions can be appraised. According to Ambrose et al¹¹⁸, the lesions may be concentric, eccentric type I (asymmetric tightening with smooth borders and large neck) and eccentric type II (asymmetric with thin neck or irregular borders or both). The lesions most often found in patients with unstable angina are the eccentric type II. These, then, are the lesions most likely to become unstable. The presence of a lesion equal to or above 50% in the trunk or the presence of proximal lesions above 70% in the three main branches, the latter with systolic dysfunction of the left ventricle, are indicators of the worst prognosis with isolated clinical treatment.

Important contributions to the understanding of the physiopathology of coronary disease were the studies of endothelium-dependent coronary vasomotion, visualized during coronary angiography. Paradoxal vasoconstriction was thus documented, after the administration of acetylcholine, in segments with stenosis and pre-stenosis¹¹⁹, with irregularities or being angiographically normal in coronary atherosclerotic patients.

Magnetic resonance imaging - Magnetic resonance imaging (MRI) has been used in two instances to evaluate patients with coronary atherosclerotic disease: cellular metabolic study and cardiac form and function¹²⁰. The spectrographic analysis of phosphorus compounds allows us to measure the relationship between the phosphocreatine cellular deposits and adenosine triphosphate (ATP). So, in myocardial ischemia there is decrease in the peak of phosphocreatine, and in fibrotic areas there is absence of both. This method is limited because it is used only on the anterior wall, as in other positions the presence of the thoracic muscles, with a high content of these compounds, becomes the main source of the spectrum held. To the study of the cardiac form and function, images synchronized with the

cardiac cycle. are obtained in the T1 or anatomic relaxation phase. The result is high fidelity ventriculography. More recently, non-invasive coronary evaluation with the use of helicoidal tomography¹²¹ is being used as a convenient way of detecting coronary atherosclerosis, but the method is not a routine clinical application.

Treatment

The great options for CAD treatment include clinical/medicinal treatment, angioplasty and surgical revascularization. The clinical treatment is obviously always used, as neither PTCA nor surgical revascularization interferes in the metabolic process of the basic disease.

Clinical treatment

Nitrates - Nitrates are prodrugs that need to be converted into nitric oxide (NO) in the endothelial and smooth muscle cells¹²², in order to have their vasodilating effects. Their basic action is the relaxation of vessel smooth muscle. Their availability in the venous, oral, sublingual and transdermic forms makes them especially versatile. Their vasodilating action starts quickly, lasting less in the arteries than in the veins, where it lasts for hours. Nitrates act through various mechanisms: they redistribute the coronary flow preferably to the myocardial hypoperfused zones, they counteract vasospasm, reduce the venous return, the preload, the ventricle wall tension, and therefore reduce MVO₂; they also promote platelet antiaggregation. They are excellent for treating stable and unstable angina, SI, ischemic cardiomyopathy and post-AMI angina. Their most undesirable side effects are headache and hypotension; the latter is more common and more of a concern with older patients. Pulmonary ventilation/perfusion defects and methemoglobinemia were also reported, but their clinical importance is questionable.

Important characteristics are the development of tolerance and recovery of its action in a short period of time¹²³. To prevent medical intolerance "free intervals" of 12 hours every 24 hours should be observed. Despite its proven action in the relief and prevention of ischemic symptoms and in the increase of tolerance to physical exercise, the decrease in mortality with the use of nitrates still has not been demonstrated¹²⁴.

Beta-blockers - The stimulatory effects of the beta-receptors by catecholamines are upset by beta-blockers. Two large receptor classes are known: beta 1 and beta 2. The beta 1 receptors, predominantly cardiac, when stimulated respond with an increase in heart rate (HR), in contractility and A-V conduction, release renin through the juxtaglomerular kidney cells and induce lipolysis in adipocytes. The stimulation of beta 2 receptors causes bronchodilation, vasodilation and glycogenolysis.

Because they block the action of catecholamines, beta-blockers are efficient drugs for the treatment of angina,

essentially because they reduce MVO₂, due to the reduction of HR. This also increases the diastolic period, increasing the coronary perfusion period. It has likewise been demonstrated that although beta-blockers reduce total coronary flow, they improve endocardial perfusion, therefore favoring the myocardial region most affected by ischemia. They are also very efficient medicines for the treatment of AH and arrhythmias dependent on the sympathetic action. It has also been demonstrated that they reduce SD and re-infarctions post-AMI¹²⁵. They also reduce pressure increase and heart rate during effort. Therefore, they are especially useful in effort angina. However, their undesirable effects can be extremely limiting. These include weakness; sleep and mood alterations; sexual dysfunction, with impotence and retrograde ejaculation; bronchospasm; peripheral circulatory insufficiency; precipitation of heart failure; induction or intensification of cardiac blockades; and intensification of hyperglycemia induced by insulin.

Cardio-selective blockers, such as atenolol and metoprolol, act preferably on beta 1 receptors, having less effect on beta 2; therefore, they reduce MVO₂ with fewer effects on the bronchia, peripheral circulation or glycogenolysis. On the other hand, the non-selective, such as propranolol and nadolol, block the beta 1 and beta 2 receptors. Cardioselectivity, however, from the clinical point of view is relative.

Some beta-blockers, such as labetalol, carvedilol and bucindolol, also cause vasodilation^{126,127}. Carvedilol specifically has shown beneficial effects in treating chronic heart failure, partially because of its vasodilating effects. On the other hand, sotalol has a significant anti-arrhythmic effect (classes II and III types), and therefore is useful for the treatment of angina associated with ventricular arrhythmias.

Individual tolerance to beta-blockers can vary considerably. Metoprolol and propranolol can cause very intense effects (intense bradycardia) in certain people, known as "poor metabolizers"; this is due to a particular genetic polymorphism that affects about 10% of the white population. Therefore, it is always advisable to start therapeutics with low dosages of these substances. As far as metabolism is concerned, beta-blockers, especially propranolol, can increase triglycerides and reduce HDL, without altering LDL. This should be considered when patients with CAD and dyslipidemia are prescribed this medication¹²⁸.

Calcium channel antagonists - Ca⁺⁺ ions are essential for contraction of the cardiac muscle and the vascular smooth muscle. Ca⁺⁺ blockers represent a heterogeneous group of substances that block the movement of the Ca⁺⁺ ions through the slow channels of the cellular membranes in cardiac and smooth muscle cells. They are classified into three basic classes: dihydropyridines, whose prototype is nifedipine; phenylalkylamines, of which verapamil is the prototype, and benzothiazepines, of which diltiazem is the prototype. Phenylalkylamines also delay channel recovery, and therefore depress cardiac pacemakers and the transmission of electrical stimuli. Therefore, it also has anti-arrhythmic effects. This does not occur with dihydropyridines,

and hence these have little effect on the conduction system. Producing coronary and systemic vasodilation, dihydropyridines increase the supply of oxygen to the myocardium and decrease MVO_2 by reducing peripheral resistance and systolic stress¹²⁹. The coronary dilating action is especially important in spastic angina or with variable threshold angina. The blockade of Ca^{++} entrance has a negative inotropic effect; however, this is counterbalanced by the sympathetic stimulation induced by hypotension. Nifedipine has a higher systemic vasodilating effect than verapamil and diltiazem. Nifedipine mainly reduces the systolic pressure, so its beneficial effect is primarily due to afterload reduction and also to the increase of the coronary flow. Fast action formulations have been held responsible for the increase in cardiovascular events, but this does not apply to drug slow-release formulations.

On the other hand, verapamil reduces HR and myocardial contractility. It can therefore cause a decrease in the cardiac output and heart failure, in patients with ventricular dysfunction, while those with normal function tolerate it well. It is contraindicated in patients with sinus node disease and in atrioventricular node disease.

Diltiazem has intermediary actions between nifedipine and verapamil. It is a systemic vasodilator, but it can also increase coronary flow. Its depressing action over cardiac function is less than verapamil's. Besides being very efficient as an anti-anginal drug, it produces few undesirable side effects. When administered in the acute phase of a myocardial infarction it reduced mortality, except in the presence of ventricular dysfunction, when mortality increased¹³⁰.

"Second generation" Ca^{++} ¹²⁹ antagonists (nicardipine, isradipine, amlodipine, and felodipine) are derived from dihydropyridine. Usually they have a higher peripheral vasodilating action than those of the "first generation". Amlodipine starts acting slowly and has a long half-life (36 hours); it causes important peripheral and coronary vasodilation, being especially useful in cases of hypertension and angina. It has been used even in heart failure, but in this condition its role is not yet well defined.

It was demonstrated experimentally and in men that Ca^{++} antagonists may have an anti-atherogenic effect^{131,132}. New coronary lesions were less frequent in patients taking nifedipine than in those in the control group. However, this action needs further investigation. Despite the beneficial effects common to all Ca^{++} antagonists, a decrease in cardiovascular mortality with their extended use has not been demonstrated.

Calcium channel antagonists have wide use in patients who undergo coronary anastomoses with arterial conduits in order to avoid spasms of the grafts and after coronary angioplasties, and in patients for whom beta-blockers have been contraindicated. The most common undesirable side effects are lower limb edema, headache, intestinal obstipation, dyspepsia, and more rarely, gum hypertrophy.

Angiotensin-converting enzyme inhibitors - Angiotensin-converting enzyme inhibitors prevent the conver-

sion of angiotensin I to angiotensin II in circulation. Their hemodynamic actions are due to arterial vasodilation, which increase cardiac output; they also act on the lung and venous beds, reducing the pre-load. Such effects favorably influence the cardiac remodeling following an infarction^{133,134}. The use of this type of medication is beneficial in the acute phase of extensive infarctions, because it prevents ventricular dilation and reduces mortality both by heart failure and by SD. Theoretically, blocking the renin-angiotensin system on the atherosclerotic lesion areas has a beneficial influence on the evolution of the lesions, because angiotensin, besides being a potent vasoconstrictor, is also a growth factor for smooth muscle cells¹³⁵. Therefore, it is useful in cases of angina with heart failure or AH. Its main side effects include: dry cough due to an increase in the bradykinin half-life in the bronchial tree; and hypotension by vasodilation, mainly present when associated with other hypotensive drugs.

Aspirin - Platelets play an important role in triggering acute coronary episodes and in the growth of atherosclerotic lesions (see "Anatomy of the Atherosclerotic Plaque"). Among platelet aggregation stimuli is the production of thromboxane A_2 by the platelets themselves. Aspirin blocks its formation by interfering with its synthesis from arachidonic acid and interferes little with the production of prostacyclin by the endothelial cells¹³⁶.

Because aspirin operates on the key mechanism of formation and growth of the intra-arterial thrombus, it is capable of reducing the number of fatal and non-fatal events in patients with coronary disease¹³⁷ and currently is a fundamental part of CAD therapeutics. Other anti-platelet medications are sulfapyrazone, ticlopidine and pentoxifylline. The great problem with antiplatelet therapies, mainly aspirin, is the tendency to promote bleeding, which can cause hemorrhages, including strokes. Therefore, drugs should be used very carefully in individuals prone to such phenomena.

The most modern antiplatelet agents are the glycoprotein IIb/IIIa blockers, which act in the final common pathway of platelet action in thrombus formation¹³⁸⁻¹⁴². The studies of these types of drugs were made in principally acute syndromes. However, their role as oral agents for treatment of chronic coronary insufficiency is yet to be established.

Finally, it should be mentioned that in many patients combination therapy, including the simultaneous use of the medications cited above, is necessary to control symptoms; their use should always be individualized.

Treatment of the underlying disease - The treatment of the underlying disease of atherosclerosis, requires extensive life style changes by people who have known and modifiable RF. It is well known that AH, a sedentary life, emotional stress, active and passive smoking, dyslipidemia, and obesity must be controlled. Moderate and continuous physical exercise should be encouraged. However, improper exercise or exercise beyond individual tolerance may trigger acute coronary accidents. An exercise program should,

therefore, be developed for each individual based on that person physiological, electrical and hemodynamic parameters. The recommended diet aims for a lower intake of animal fats, and favors fruits, vegetables, and legumes. The influence of the global control of RF was appraised in the Stanford Coronary Risk Intervention Project (SCRIP)¹⁴³, in the U.S.A. In SCRIP, patients underwent global control of RF for four years; it was possible to control all of them, except smoking. Even so, lower rates of new coronary lesions were noticed at coronary angiography in the control group compared with the non-control group. The reduction of fat intake had the greatest effect.

The European Action on Secondary Prevention Through Intervention (EUROASPIRE)¹⁴⁴ study demonstrated that, despite the great prevalence of modifiable RF and those of genetic influence, in only 21% of the cases were the patients relatives tracked for coronary disease RF. This suggests that preventive measures are still imperfect and need to be improved.

However, the greatest contribution to the control of atherosclerosis and its manifestations has been interventions that reduce total serum cholesterol. Among these, statins have been the first medicines to greatly reduce hypercholesterolemia with long-term tolerance by most patients. Several clinical studies have shown that the treatment of intense or moderate hypercholesterolemia reduces coronary events, coronary mortality, global mortality, hospitalizations and the need for angioplasty or revascularization surgeries. These findings apply both to men and women, diabetics and non-diabetics, smokers and non-smokers, older or younger patients^{145,146}. Furthermore, angiographic studies have documented the decrease in the progression of lesions, lower occurrence of new lesions, and even the regression of lesions in some patients¹⁴⁷. Significant alterations in arterial vasomotion have also occurred with statin therapy; furthermore, this improvement can be reached in only one month of statin use¹⁴⁸. This suggests that the lipid lowering treatment is perhaps indicated in acute syndromes; this hypothesis, however, must be tested. A 29% reduction in strokes was also documented¹⁴⁹ in patients treated with statins and followed for more than three years. More recently, such results have also been noticed in patients with only hypercholesterolemia, but without documented CAD. The extended use of cholesterol lowering drugs has not coincided with an increase in incidences of cancer or violent deaths¹⁴⁹.

Patients with hypertriglyceridemia as the primary risk factor, followed by hypercholesterolemia or low levels of HDL-cholesterol are best treated with fibrates (benzafibrate, gemfibrozil, phenofibrate and etofibrate), which reduce triglycerides, increase HDL-cholesterol and reduce cholesterolemia. Its use in coronary disease patients was followed by a reduction in cardiovascular mortality^{150,151}. Therefore, the treatment of dyslipidemia plays an essential role in the control of CAD.

Antioxidants and vitamins

Oxidative stress plays an important role in the pathophysiology of atherosclerosis¹⁵². Antioxidants have been experimentally shown to protect against the alterations brought on by oxidative stress. Diets rich in antioxidant substances, such as beta-carotene, alpha tocopherol (vitamin E) and ascorbic acid (vitamin C), are consumed by populations with a low incidence of coronary atherosclerosis, which supports the oxidation theory¹⁴⁷. However, only a randomized study, the Cambridge Heart Antioxidant Study (CHAOS)¹⁵³, has demonstrated that vitamin E is capable of reducing the incidence of new coronary events, specifically non-fatal AMI. Therefore, the diet containing these substances is considered more important than supplements.

Flavonoids, substances present in grape juice, red wine and other red fruits, have an anti-inflammatory and antioxidant effect. In various studies they have been shown to reduce the incidence of atherosclerotic lesions¹⁵⁴. Probuocol, a lipid-lowering agent with a powerful antioxidant effect has been proven to reduce atherosclerosis in experimental animals¹⁵⁵ and the coronary restenosis following angioplasty¹⁵⁶. The unquestionable clinical demonstration of the beneficial effect of antioxidants in CAD treatment, however, still requires new data. Specific studies are currently underway.

Estrogens

The epidemiological evidence of the lower prevalence and incidence of coronary atherosclerosis in women in their reproductive years and of its later increase, the beneficial effects of the chronic use of estrogens in the lipid profile and of the recovery of endothelium dependent vasodilation in acute estrogen administration led to the development of studies to prove the usefulness and safety of hormone replacement therapy for women in menopause. The most recent carefully controlled study, the Heart and Estrogen/progestin Replacement Study (HERS)¹⁵⁷, however, has not proved that the use of 0.625mg of estradiol and 2.5mg of progesterone reduces the incidence of coronary events. On the contrary, the use was followed by an increase in coronary events in the first year, only decreasing in subsequent years; furthermore, hormone therapy was followed by a threefold increase in the risk of thromboembolic phenomena and biliary lithiasis. Therefore, the use of hormone replacement therapy for the specific purpose of treating CAD does not seem justified.

Genetic predisposition and CAD treatment

Undoubtedly a family history of CAD, showing genetic predisposition to the disease, is a weighty risk factor^{59,60}. Genetic predisposition is present in approximately 20% of CAD cases. Alterations in the formation of HDL genes, in LDL receptors, and in apo-E receptors, among others⁷⁰⁻⁷³, have already been identified.

The fundamental concept concerning treatment is that genetic predisposition is not an isolated determinant of the occurrence or evolution of the disease. That is to say, environmental factors interact with genetic factors and they jointly influence the course of CAD. As a consequence, even individuals with genetic predisposition for CAD should treat other RF, such as hypertension, smoking, sedentariness, etc. On the other hand, the absence of genetic factors does not grant immunity against CAD; in such cases, strictly environmental factors can cause atherosclerosis.

Coronary angioplasty

In several randomized studies^{158,159}, coronary angioplasty has been shown to have a similar effect as surgery and clinical treatment on the incidence of death or infarction. Compared with surgery, it is associated with a higher need of new procedures, especially in the first year post-intervention. However, after this initial phase the evolution is very good. An important advance has been the use of stents, intracoronary expansible prostheses, which have increased the frequency of the primary success and reduced the incidence of restenosis following hospital discharge. They are presently used routinely with PTCA, being used in at least 50-70% of the cases at our institution. PTCA indications have been expanded considerably; currently interventions in multiple vessels, in patients with ventricular dysfunction and the elderly are successfully made in centers with good experience. Although initial indications were preferably for proximal lesions, =3mm diameter, with extension below 2cm and in segments free of branches or curves, these indications have been periodically revised in view of the experience acquired and of new technical developments. Another point to be carefully noticed is the experience and competence of the operator and the service as a whole. The restenosis problem, about 40% in conventional PTCA (balloon)^{158,159}, continues without solution, despite innumerable technical and pharmacological therapies. Two recent studies suggest that the anti-oxidant probucol¹⁵⁶ significantly reduces restenosis, while multivitamins do not affect it. This may seem to justify its use in PTCA. However, there is no doubt that PTCA is a remarkable advance in treating CAD. Indications for its use should always be made jointly between the clinical physician and interventionist.

Myocardial revascularization surgery

Revascularization is widely indicated, as an elective procedure, for thousands of patients due to its confirmed reduction of symptoms and increase in survival rates in certain subgroups¹⁶⁰. With the improvement of myocardial protection and oxygenating techniques, the incidence of death and transoperative myocardial infarction in elective surgeries in patients with no ventricular dysfunction is around 1% and less than 4%, respectively. Following surgeries in patients with myocardial dysfunction or aneurysms followed by a marked decrease in the EF, the mortality rate rises to about 6%.

Currently, more seriously ill and older patients are being operated upon than in the past. Despite the marked decrease in surgical complications with improved techniques, because of the advanced age and serious illness of current surgical patients, the number of such patients has increased so much that they have influenced the global mortality rates, mainly in referral hospitals. Associated procedures, cardiac or not, repeat surgeries, renal insufficiency and age >75 years increase postsurgical morbidity and mortality.

An important development in surgical technique has been the use of grafts from the internal thoracic artery, which has a higher probability of remaining pervious in most patients, 90% in five years¹⁶¹. Multiple arterial grafts are currently frequently used.

Surgical trauma has been reduced by tactics that do not use extra-corporeal circulation and, more recently, by minimally invasive surgeries. The initial results are encouraging. However, as in all new surgical or invasive techniques, there is a learning curve and the smaller extension of the surgical field can be a limitation to the wider use of these new approaches.

The frequent occurrence of disabling angina in patients with preserved ventricular function, but without an appropriate coronary bed for bypass surgeries, has led to the use of the laser to perform transmyocardial passages. Initially these passages were thought of as forerunners of sinusoids that would take the blood from inside the ventricle to the inside of the myocardium, i.e., a reptilian-like transformation of the mammalian heart; however, apparently its main action is to stimulate the formation of new vessels, not always from inside the heart.

Finally, the ventricular geometrical reconstruction proposed and systematized by Jatene¹⁶² has contributed even more to the anatomical and functional recovery of ventricles with large aneurysmal or dyskinetic areas.

Suggestions for practical approaches

Some general guidelines for the treatment of those at risk for CAD can be outlined: 1) middle-aged men and women should be evaluated for CAD risk, since the disease has a silent evolutionary period; 2) sons and daughters of CAD patients should be checked even earlier, preferably during adolescence, as the disease starts very early and has a strong family trend; 3) when patients are suspected of having CAD because of important RF or history suggestive of angina, non-invasive tests should be performed, such as ECG stress test, radioisotopes, or stress echocardiogram; 4) coronary angiography should be performed when suspicion of CAD exists based on clinical history or non-invasive tests. Performing coronary angiography assumes some intervention like PTCA or surgical revascularization is being considered. On the other hand, the indication for coronary angiography may leave out non-invasive exams like stress tests and radioisotopes, when the angina history is sufficiently typical; 5) women should be checked as carefully as men, naturally respecting certain peculiarities related to sex; 6) the choice of form of treatment should take into account

the current knowledge about the CAD natural history, prognostic determinants, efficiency of the treatments available and individual conditions of the patients, such as age, associated diseases and occupation; 7) in the case of invasive treatments, the experience and competence of the local services are fundamentally important; 8) notwithstanding the form of treatment, one must remember that CAD is basically a progressive metabolic disease, whose control must be sought in the long-term. Recent information indicates that its natural course can be modified for the better by controlling RF.

Conclusion

Significant advances have recently occurred in the comprehension of CAD pathophysiology. The development of the disease and its multiform clinical manifestations are currently better understood. Acute conditions originating from plaque instability are interpreted through

cellular alterations. The investigative processes are being transformed and improved. This has allowed earlier diagnoses. The CAD treatment has improved: PTCA and surgical revascularization have undergone significant technical progresses. However, perhaps the greatest contributions are the prevention studies, which have shown it is possible to alter the material course of atherosclerosis, decreasing its progression and even inducing plaque regression. Nevertheless, great challenges still persist: the identification of the real causes of atherosclerosis, early detection of lesions prone to destabilization, correct quantification of the degree of stenosis, the most efficient and safest treatment of the acute cases, and mainly the control of the underlying disease, atherosclerosis. The contributions of molecular biology in the diagnosis and treatment of atherosclerosis are still not defined; but there are certainly reasons for great hope, of advances in this area which should occupy great research efforts in the next years.

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