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Review Article

# Pros and Cons of Metabolic Alterations in Hypertension Treatment

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## Abstract

Systemic arterial hypertension, in addition to increasing the probability of occurrence of coronary artery disease, is one of the main factors that predispose to its development and progression; it is also a fact that most deaths of patients with systemic arterial hypertension are due to coronary heart disease. The role of insulin in increasing the activity of the sympathetic nervous system, in the greater retention of sodium and in the proliferation of smooth muscle cells (muscle hypertrophy) is well described, which can ultimately not only trigger but also exacerbate systemic arterial hypertension. Therefore, when we approach arterial hypertension, we must consider it as an "inherited" syndrome of metabolic, hemodynamic and genetic abnormalities and always remember that the simple reduction in blood pressure levels may not interfere with the other factors that contribute to coronary artery disease. The hypotensive drugs that may be the cause of all this negative picture are diuretics and beta-blockers, which, by the way, are the most commonly used drugs in the large multicenter studies included in the metaanalysis by Collins et al. The diuretics that have been shown to alter the lipid profile are thiazides. They have an average elevation of 34 mg/dl in triglycerides and 11 mg/dl in total cholesterol. Beta-blockers versus lipid metabolism produce elevation of total cholesterol (LDL-col-e and VLDL-col) and triglycerides. They work by inhibiting the activity of adenyl cyclase in fat cells and reducing the hydrolysis of fatty acids and triglycerides. Beta-blockers with intrinsic sympathomimetic activity do not seem to have a negative effect on the lipid profile of hypertensive patients.

**Keywords:** hypertension; metabolic changes; cholesterol; triglycerides; pharmacological treatment

## Introduction

Systemic arterial hypertension (SAH) and dyslipidemia are proven to be the major risk factors for coronary artery disease (CAD) [1]. Hypercholesterolemia is frequently found during the clinical investigation of SAH, and the association of the two pathologies acts synergistically, increasing cardiovascular risk [2]. We will discuss the peculiarities of this association and the appropriate ways to approach it from a therapeutic point of view.

## Epidemiological data

Large epidemiological studies [3-5] have shown that the risk of cardiovascular mortality increases with cholesterol levels - in the 55-year-old man the risk is 0.6%/year for a cholesterol level of about 245 mg/dl, falling to 0.2%/year for a level of 180 mg/dl. They also showed the existence of a positive and synergistic correlation between these serum total cholesterol (TC) values and blood pressure (BP) levels [6-11]. SAH, in addition to increasing the probability of CAD occurrence, is one of the main factors that predispose to its development and progression; it is also a fact that most deaths of patients with SAH are due to coronary heart disease. Published data [12] have shown that 40% of all individuals with BP>140/90 mmHg or who use antihypertensive medication have serum TC levels higher than 240 mg/dl; and 46% of those with TC>240 mg/dl also have BP>140/90 mmHg. A frequent association of hypertension with hypertriglyceridemia and hypoalphalipoproteinemia, described by Reaven and known as Syndrome X, has also been reported.

The result of the meta-analysis carried out by Collins et al. [13], which included 14 studies on the treatment of SAH, with about 45,000 patients and a median follow-up time of 5 years, demonstrated a 42% reduction in the risk of stroke versus a decrease of only 14% in the risk of myocardial infarction and/or death from CAD. The explanation for this unexpected phenomenon, a small reduction in the risk of myocardial infarction, since antihypertensive

therapy has been proven to "protect" the patient against progression to more severe levels of SAH and its deleterious consequences, would be the occurrence of adverse metabolic effects of the drugs used [14], in association with the fact that coronary heart disease is multifactorial. In view of these data, we came to the conclusion that the treatment of SAH is not simply limited to the reduction of blood pressure levels; our goal is the protection of the so-called target organs, not forgetting the endothelium, which plays a major role in increasing cardiovascular risk in the association of the pathologies in question.

Although it is not our intention to study in depth the pathophysiology of arterial hypertension, we believe it is important to discuss, even if briefly, a "metabolic element" common to the association of SAH and dyslipidemia: insulin resistance. Insulin resistance begins with the occurrence of decreased glucose uptake, with consequent hyperinsulinemia as a response (there is an increase in insulin secretion by the pancreas and a decrease in extraction by the liver). The role of insulin in increasing the activity of the sympathetic nervous system, in the increased retention of sodium and in the proliferation of smooth muscle cells (muscle hypertrophy) is well described, which can ultimately not only trigger but also exacerbate SAH. It is important to emphasize that the existence of an associated genetic predisposition is reported and already well accepted as "scientific truth" - there are several studies carried out with normotensive children of hypertensive parents (with essential arterial hypertension), which demonstrated a higher occurrence of insulin resistance when compared to control groups. Therefore, when we approach arterial hypertension, we should consider it as an "inherited" syndrome of metabolic, hemodynamic, and genetic abnormalities, and always remember that a simple reduction in blood pressure levels may not interfere with other factors that contribute to CAD [15] (Table 1).

**Table 1:** Effects of antihypertensive drugs on various risk factors for coronary artery disease

| | Carbohydrate metabolism | | | Lipids | | | Electrolytes | |
|---|---|---|---|---|---|---|---|---|
| | Insulin resistance | Glucose | Insulin | Total Cholesterol | HDL-col | Triglycerides | Potassium | Magnesium |
| Diuretics | - | - | - | 0 / - | 0 | - | - | - |
| Beta-blockers | - | - | - | 0 | - | - | - | 0 |
| Angiotensin-converting enzyme inhibitors | 0 / + | 0 / + | + | 0 / + | 0 / + | 0 | 0 | 0 |
| Alpha-1 adrenergic blockers | + | + | + | + | 0 / + | + | 0 | ? |
| Calcium Antagonists | 0 | 0 / + | + | 0 | 0 | 0 | 0 | ? |
| (+) Favorable effect (-) Unfavorable effect (?)Effect not known (0) No effect | | | | | | | | |

**Adverse effects of antihypertensive drugs**

The presence of metabolic alterations, such as glucose intolerance and lipid alterations (often hypertriglyceridemia), is more "common" in treated hypertensive patients, reflecting possible adverse effects of hypotensive agents [16]," on tissue sensitivity to insulin; obesity and sedentary lifestyle, factors that can be modified, also contribute to this picture.

The hypotensives that may be the cause of all this negative picture are diuretics and beta-blockers, which, by the way, are the most commonly used drugs in the large multicenter studies included in the metaanalysis by Collins et al. [13].

**Diuretics vs Lipid Metabolism**

The diuretics that have been shown to alter the lipid profile are thiazides. They have an average elevation of 34 mg/dl in triglycerides and 11 mg/dl in TC [17]. Although these alterations are very discrete and allow a return to the baseline value when the drug is discontinued, we know that they are due to interference with the production, release and action of insulin, which makes these drugs so deleterious. They also increase the action of lipoprotein lipase, which hydrolyzes triglycerides and very low-density lipoproteins (VLDL-col), increasing the production of low-density lipoprotein cholesterol (LDL-col) and TC.

**Beta-blockers vs Lipid metabolism**

They produce an increase in TC (LDL-col-e and VLDL-col) and triglycerides [18].

They work by inhibiting the activity of adenyl cyclase in fat cells and reducing the hydrolysis of fatty acids and triglycerides.

Beta-blockers with intrinsic sympathomimetic activity (ISA) do not seem to act negatively on the lipid profile of hypertensive patients [12].

**Favorable effects of antihypertensive drugs in relation to the modification of atherosclerosis**

We know that the theory of "endothelial injury" is the common basis for the actions of SAH and dyslipidemia in the arterial wall and that the atherogenic "marker" of both is insulin resistance [19].Therefore, as previously discussed, we should seek the institution of an antihypertensive therapy also aiming at the regression of vascular structural alterations; it is important to have an integrated view that links SAH to atherosclerosis [20], even if, apparently, hypertension is not present by essentially numerical criteria. The preservation of vascular integrity, combined with the concern not to cause metabolic damage, assumes a higher priority and, in this regard, agents that potentially have an antiproliferative and/or protective role on the arteries can produce the expected clinical benefits [21]. Calcium antagonists (CaA) and angiotensin-converting enzyme inhibitors (ACEI) are the best options for the treatment of dyslipidemic hypertensive patients [14,20,22].

**Calcium antagonists**

Calcium is clinically and experimentally involved in the progression of atherosclerotic injury and also seems to be responsible, according to the theory of excessive calcium uptake (especially mitochondrial calcium

overload), for a cell death mechanism common to several injuries [23]; several CaA were able to act effectively in this process.

Studies carried out in Japan, previously, had already shown that, in rabbits, arteries that had induced atheromatous lesions could be injured by calcium; Injections of calcium salts into these rabbits led to the disintegration of the inner elastic membrane of the vascular wall. It was also found that the ratio between lipid content and the presence of calcium in aortic and coronary lesions was 30 to 65% in the aorta and about 4 to 5% in the coronary arteries, compared to more than half of calcium in the coronary arteries (dry weight of the plaques). With proven antiatherosclerotic and vasculoprotective effects and having been shown to be effective in reducing the development of atherosclerosis in rabbits, it was necessary to verify whether CaA also had these effects in men, since the injury model is different [23]. Clinical studies have recently shown that the chronic use of this class of hypotensive agents in patients with incipient coronary artery disease significantly reduced the appearance of new lesions detectable by coronary angiography, when compared with placebo (the formation of new lesions seems to depend on cellular calcium) [24-26]. The clinical study carried out with Nicardipine (CaA) [27] presented interesting results: this drug did not show any effect in delaying or regressing the atherosclerotic lesion already installed, but in those patients who had minimal lesions (<20% obstruction) there was an extraordinary reduction. Similarly to this reported study, the INTACT (International Trial on Antiatherosclerosis Therapy) [28] performed with a dihydropyridine CaA nifedipine - showed the same results, also reducing the formation of new lesions.

CaA would then act by decreasing endothelial damage and inhibiting the proliferation and migration of smooth muscle cells; Isradipine also appears to have positive effects on platelet aggregation and fibrinolytic activity [25].

**Angiotensin-Converting Enzyme Inhibitors**

The scientific interest in studying SAH in its initial phase, even before blood pressure changes are verified, is evidenced in the large number of publications on the subject. The Dutch Hypertension and Offspring Study [29] was conducted to describe the important etiological mechanisms in the "onset" of hypertension. The findings suggested that the alterations that appeared in the early stages would occur in renal hemodynamics: renal vasoconstriction and the presence of a more "active" renin-angiotensin-aldosterone system. There is also evidence that the increase in serum angiotensin-converting enzyme (ACE) is associated with an increased risk of myocardial infarction (independent genetic marker) [30]; the same evaluation can be made for angiotensin II [30,31].Therefore, the use of ACEI as antihypertensive drugs in dyslipidemic hypertensive patients is due not only to the neutrality factor in the lipid profile [32], but also to their actions in attenuating the vasoconstrictive effects of angiotensin II and the sympathetic nervous system on the coronary bed, in the possible inhibition of LDL-col oxidation, in the increase in bradykinin levels (increase in nitric oxide production; antiproliferative effects) and in the control of ACE levels.

## Drug Interactions

The interactions known or theoretically possible to occur are [33,34]:

a. Decreased LDL-col reduction with the combined use of bile acid sequestrants and thiazide diuretics;
b. Interference with the hypotensive action of various antihypertensive drugs when used concomitantly with nicotinic acid, aspirin, or nonsteroidal anti-inflammatory agents;
c. Potential adverse effect of thiazide diuretics on hyperglycaemia when administered together with nicotinic acid.

**Familial dyslipidemic arterial hypertension syndrome**

The grouping of high BP with other metabolic factors is described using various headings, such as Insulin Resistance Syndrome, Syndrome X and, more recently, Familial Arterial Hypertension, which would be present in about 12 to 16% of essential hypertensive patients and in 1 to 2% of the general population [35]. The population studies left no doubt as to the existence of a maintained association, and not merely a casual or dependent on possible adverse effect of antihypertensive treatment, between high blood pressure levels and altered lipid profile. The classic Utah study [35, 36] showed that patients with early CAD studied had lipid abnormalities. Of the alterations found, the most common were low HDL-col and hypertriglyceridemia (twice as high LDL-col). In this study, the occurrence of Dislipemic Familial Hypertension ranged from 21 to 54% and Combined Familial Hyperlipidemia from 36 to 48%. Williams et al. [37] observed a higher prevalence of hyperlipidemia in middle-aged men with familial hypertension, which suggested a genetic character for this alteration. After the report made by the National Heart Lung and Blood Institute (USA) of the study carried out in 514 pairs of twins, in which the occurrence of Dislipemic Arterial Hypertension Syndrome was about three times higher in monozygotic patients, the genetic character (in a polygenic context) of the syndrome became evident. Although genetic factors are important in determining the variation between individuals in lipid levels and BP, these are also strongly influenced by environmental factors - particularly diet; It seems that we can achieve a reduction in blood pressure with the use of diets with reduced lipid content and rich in polyunsaturated fatty acids. It is postulated that there is a "strong action" of the sympathetic nervous system based on the recognized capacity of vasoconstriction by adrenergic stimulus, added to the reduction of lecithin-cholesterol acyltransferase - LCAT and LDL-col receptors [38]. There are also studies on transmembrane ion exchange that have suggested an alteration in the caton transport, secondary to a structural alteration of the membrane (for example, the cholesterol-phospholipid ratio of the platelet membrane of essential hypertensive patients is significantly high). We also have lipase-lipoprotein deficiency (heterozygous) appearing as the possible "promoter" of this syndrome. It is important that we investigate the occurrence of this syndrome in all essential hypertensive patients with a family history, since the risk for CAD is four times higher than that of each pathology separately.

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## Conflict of interest

None.

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