Arterial hypertension and coronary artery disease

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Abstract

The relation between arterial hypertension and coronary artery disease is analyzed. The importance of other concurrent risk factors of atherosclerosis and the less remarkable efficacy of antihypertensive treatment in what concerns coronary artery disease are both emphasized.

Endothelial dysfunction related to several risk factors is mentioned as a key factor to functional and structural alterations of coronary arteries. Coronary pathophysiology in hypertensive heart disease is further discussed and several mechanisms responsible for ischemia, mainly subencordial, in left ventricular hypertrophy are described. Special emphasis is given to the potential importance of prevention and regression of left ventricular hypertrophy and interstitial fibrosis in improving coronary reserve and ventricular function.

Finally, the therapeutic measures available to potentially break the causal link between arterial hypertension and coronary artery disease are referred.

Key words: hypertension, coronary artery disease, atherosclerosis, endothelium, left ventricular hypertrophy, coronary reserve.

There is a close relation between hypertension and atherosclerosis,[1,2] being well defined the paramount importance of a blood pressure increase, on the atherosclerosis development and/or its worsening.[3,4] Therefore, experiments in laboratory animals have demonstrated that atherogenesis induced by hyperlipidaemia could be speed up by an increase on blood pressure,[5,6] and that such increase can take to an increase of the arterial wall pressure would favor the passage of albumin and lipids to the artery walls[7]. More recently it became evident the existence of endothelial dysfunction in hypertension what seems to have a crucial role in the pathophysiology of the vascular structural changes both in hypertrophy as atherosclerosis.[8,9,10]

Already in 1928, Bell and Clawson[11] and a few years afterwards, Murphy.[12] in necropsy studies, had pointed out the relation between hypertension and atherosclerotic coronary disease. Also Lober[13] in 1953 in a study on the pathogenesis of "coronary atherosclerosis" mentioned, also in the autopsies study, that the degree of coronary atherosclerosis found in a group of hypertensive patients, 40-49 years of age, was so severe as the one found in normotensive subjects over 60 years of age.

However, it was especially since the Framingham study[14] and the Pooling Project[15] that it was shown that cardiovascular atherosclerotic lesions occur with a 2- 3- fold higher frequency in hypertensive than in normotensive subjects, in the same age group.

In the specific case of coronary disease any one of its manifestations are more frequent in hypertensive patients and the risk of appearance is related with the hypertension severity.

Nevertheless, although hypertension treatment benefits have been well evident regarding reducing mortality due to cerebrovascular disease, heart failure and kidney failure, regarding the coronary disease, the benefits seen are less than expected.[16,17] There are studies not showing any benefit at all. There are several explanations for this fact, including the following ones:[16,21]

1 - Inadequate control of blood pressure, as it has been verified in most studies, although it is achievable a control on the pressure values with therapy, they are higher than the normotensive population.

2 – Curve in J or U of the relation between diastolic arterial pressure and coronary mortality.

3 - Coexistence of very old atherosclerotic lesions needing much longer periods of pressure control to improve.

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4 – Coexistence of other risk factors to coronary disease which were not duly treated or prevented.

5 – Possibility of not existing, in reality, a causal relationship between hypertension and atherosclerosis (what is contrary, for instances, to the inexistence of atherosclerosis on coronary arteries with origin in the pulmonary artery or due to the fact that it only exists atherosclerosis in the pulmonary circulation when in presence of pulmonary hypertension).

6 – Non interference in the therapy of differential pressure (as it has been suggested by Safar at al.).[16]

7 – Adverse effects by the therapeutic agents which are against the benefit of reducing blood pressure (changes on lipidic profile, electrolytic, carbohydrates and purines metabolism; non regression of the left ventricular hypertrophy – LVH).

I call especially the attention to the fact that the relation between hypertension and coronary disease is a complex one, although hypertension is undoubtedly a risk factor to the coronary disease, there are other risk factors that often co-exist with high blood pressure interacting and influencing in a complex manner the development, maintenance and evolution of the atherosclerotic disease.

It is in fact frequent the coexistence in a hypertensive patient of other coronary risk factors, what would lead, by an additive effect, to a higher risk[17.] Some studies have shown, on the other hand, the existence of a significant relation between blood pressure values and cholesterol levels,[18] especially in certain groups (men aged from 20 to 29 years old) what raises the hypothesis of a possible influence of this association in the mechanism responsible for the higher coronary risk with a higher blood pressure.

Also recently it has been demonstrated in laboratory animals that the increase in cholesterol induced by a certain diet was followed by structural and functional arterial changes which might contribute to a higher pressure increase induced by a catecholamine infusion.[19]

Another aspect of this very important problem and discussed is the curve in J.

Cruickshank[20] has verified, while assessing several essays, that an increase on the coronary mortality occurred when the diastolic pressure values decreased beyond 85-95 mmHg. Also the researchers in the Framingham study have recently verified the existence of a U curve when relating coronary disease and diastolic arterial pressure in patients with a previous myocardial infarction.[21]

Contrary to these findings MacMahon[22] in a meta-analysis of big therapy essays has verified the existence of a progressive cardiovascular reduction, being this a continuous and linear ratio without identifying any value for which the risk would be stable or deteriorated with a decrease on blood pressure.

In the last few years it has been made evident the crucial role of the endothelium in the atherosclerosis pathogenesis.[22,24] Both in hypertension[10,23,25] as in dyslipidaemia[26,27] changes were demonstrated both in the constricting and/or "relaxing" arterial "mechanisms" endothelium dependent, where the former take predominance over the latter, whether on the production of certain vasoactive substances and growth factors to platelets and by the endothelium cells and/or smooth muscle, which would lead to structural changes where are included, obviously the coronary arteries.

Thus it has been demonstrated that hypertension has important effects on the arterial intima leading to an endothelial lesion or dysfunction[10,24,25] (although the endotelial changes can be a cause and not an hypertension effect), as for instances, an increase on its permeability, higher blood platelet adhesion, changes on the responsible factors by the vascular contraction/relaxation as it has been referred, proliferation of muscle cells migrating from the media to the intima, white blood cells adhesion and a subendothelial accumulation of monocytes/macrophages[28] what before hyperlipidaemia will contribute to the formation of an atheroma plaque. The increase on the tension of the artery walls

caused by hypertension leads, on the other hand, to a stimulation of muscle cells of the tunica media that will be contributed by several growth factors, occurring also an increase synthesis of collagen fibers, changes which will originate the increase on the tunica media thickening.

Recently has been demonstrated that normotensive subjects with hypertensive relatives had already shown changes in the endothelium function[29] what seems to support its role in the future increase in pressure.

On the other hand, sometime ago, it was also published a work[30] demonstrating that in hypertensive patients, regardless of high or normal cholesterol values, it was higher the susceptibility to LDL to oxidation. Oxidized LDL, as it is known, have a crucial role in the development and speeding up of atherosclerosis,[31] contributing to the endothelial dysfunction

(decrease on NO production and higher endothelin production) and for the monocytes recruitment (due to its chemotactic properties) and stimulating the proliferation of smooth muscles cells proliferation of the tunica intima.

Also, the metabolic changes existing in hypertension have been studied, having emerged the hypothesis to consider hyperinsulinism, or the resistance to insulin the link between hypertension, obesity, dyslipidaemia and type II diabetes, for instances, referring to its possible role in the atherosclerosis pathogenesis in general or the coronary disease in particular.[32,33.]

The genetic understanding and the physiopathology relating to the metabolic changes with essential hypertension can be of importance, for instances, in the definition of certain patients sub-groups regarding the risk and therapeutic approach.

One of the most delicate problems while interpreting the epidemiologic data mentioned previously, it is to distinguish the related accidents with atherosclerosis of epicardial coronary arteries of the related with left ventricular hypertrophy that can co-exist and it is know to be an independent risk.

In reality there are hypertensive patients with typical angor and/or ischemia electrocardiographic changes while resting or after effort, showing coronariographies without significant changes. To a better understanding of this situation it is an advantage to have present the coronary physiology of the hypertrophic heart.

In humans, the most important works are those by Strauer et al., [34,35] which verified that the coronary flow in resting hypertensive patients, opposite to what was described in laboratory animals, increased by around 18% regarding the controls. Coronary resistances, on their turn, were also increased in around 38%. Perfusion pressure was increased by 56%. There was a slight increase, not significant, of the arteriovenous difference and an increase on the oxygen consumption quoted in 21%.

Usually, when there is an increase on the O_2 consumption, there is a reduction of the coronary resistances and an increase of the coronary flow, in a way to respond to the energetic needs added to the left ventricle. Hypertensive cardiopathy would be thus a particular and unique case, as increase on the flow needed to a higher O_2 consumption by a hypertrophic myocardium was made against increased coronary resistances.[35]

In the hypertensive cardiopathy it existed a decrease in the coronary reserve for 72% of normal, if there was no coronary disease and for 42% of normal, if simultaneously there was a coronary disease. These authors[34,35], have verified also that the decrease of the coronary reserve was not related with the hypertrophy degree but it was reducing as the systolic stress was increasing (negative correlation highly significant).

Although there are works where no coronary structural changes were verified, pointing as causes to explain the decrease of the coronary reserve, the increase of the extravascular component of the coronary resistance during diastole,[36] and/or the functional increase of the vascular tonus being described, as it was mentioned, changes in the production of vasoactive substances by the vascular endothelium (reducing the NO production, the hyperpolarization factor and prostacyclin and/or increase on the endothelin production or the vasoconstricting prostaglandins),[24,37-39] being the responsible for this last change, most authors[34,35,40,41] name as causes, on one hand, the fact that coronary vessels do not follow the growth of cardiac muscle fibers, and on the other hand, the structural changes of coronary small arteries and arterioles which are thickened with a reduced lumen. It is evident that for such structural changes it will contribute likewise the endothelial dysfunction and the consequent higher production of mitogenic factors.[23-25,28].

There would be therefore a reduction on the coronary regulation capacity and myocardial ischemia in hypertensive patients with normal coronariographies, would be also related with a coronary microangiopathy e with an increase on O2 consumption.

Strauer[35] has ascertained that in spite of the increase on O2 consumption that can be explained by the absolute increase of the left ventricular mass, great changes in this consumption were seen pointing out for another component as responsible for such addition. This other component would the systolic stress - as the left ventricle would dilate, the ratio mass/volume would decrease and the stress would improve, increasing also the O2 consumption. It was then explained why hypertrophic hearts keeping or increasing their contractility had less O2 consumption that hearts with reduced contractility: stress in the former would be less than in the latter.

Therefore, the increase in the systolic stress would

lead, on one hand, to a higher decrease on the coronary reserve, and on the other hand, to an increase on O2 consumption.

Besides, the ratio capillary-fiber is kept 1:1 in the hypertrophic heart, what will increase the average distance for the O2 diffusion.[40,42]

The coronary reserve reduction is, therefore, related with several factors, the most important of which, in accordance with Strauer[35] works is the hypertrophy in the tunica media of small arteries and arterioles presenting a parallelism with a reduction on the coronary reserve. This author in a study of myocardial biopsies has shown that there was an increase of 60% in the media thickness and its relation with the radius[43] . Although there was a relation between the structural changes of the small coronary arteries and a decrease on the coronary reserve, it was verified, however that, in the presence of left ventricular hypertrophy the coronary reserve was not normal even when there was no evidence of vascular changes in biopsies what could be secondary to the already quoted endothelial dysfunction.

The region that most resents the decrease of the coronary reserve is the subendocardial once that, even in the normal heart, there is a reduction of auto-regulatory capacity in this area. When hypertension is followed by the left ventricular hypertrophy there is then a marked change in the lower limit of the coronary auto-regulatory curve (right and upwards deviation).[44]

The haemorrheology changes described in the arterial hypertension, contributing both to the cardiac hypertrophy and to the increase on blood viscosity, are other the factors that can influence direct or indirectly changes on the coronary reserve in the hypertensive patients.[45]

The issue of the ratio between the left ventricular hypertrophy and the myocardial ischemia it is more complicated a bit more by the fact of the very coronary disease can lead on its own of hypertrophy. Whether by the increase on the wall "stress", reducing the complacency and an increase on the O2 consumption secondary to the regional or global dilation of the left ventricle, whether by the change in metabolism of myocardial fibers or neuro-humoral factors secondary to episodes of recurring ischemia, it would have an activation of the protein synthesis in viable myocardial areas and with appropriate blood flow and consequently, a left ventricular hypertrophy.[46]

Also the existing ratio between LVH and ventricular dysrhythmia is complex,[47] and it will depend, at least partially of a reduction on the coronary reserve as it has been demonstrate by some authors when verifying that the number of extrasystoles and the arrhythmia complexity were progressively higher with a decrease on the coronary reserve.[48]

In a recently published work,[49] it has been demonstrated the importance of an increase of interstitial fibrosis present in LVH, while reducing the coronary reserve, as this will only be normalized when it would be induced not only a reducing in the thickening on the arteries wall but also a reduction on the perivascular fibrosis.

It is important to remember that the remission of the left ventricular hypertrophy and the tunica media hypertrophy of coronaries small arteries and arterioles can contribute to preventing a congestive cardiac failure, as the secondary cardiac failure to arterial hypertension can be partially related with recurring myocardial ischemia induced or favored by this change on the microcirculation, having as examples the frequent episodes of silent ischemia demonstrated by some authors,[50] which will lead to the loss of contractile elements and an increase on interstitial fibrosis.

After reviewing the complexity of interrelations between arterial hypertension and coronary disease and the multiple queries still existing we can refer to the strategies that according to Dunn and Pringle[51] and Raplan,[52] should be implemented to break the link between hypertension and coronary disease:

- Prevention of arterial hypertension and LVH
- Monitoring more often blood pressure, mainly in the first few hours of the morning
- Precise definition of arterial hypertension and the varied atherosclerosis therapies
- Optimization of hypertension treatment

a) Early identification

b) Definition of optimum levels of arterial pressure to be reached

c) Appropriate choice of therapy

- LVH regression and a preservation of the left ventricle preservation
- To treat all present coronary risk factors together

It is to be pointed out the importance that anti-hypertensive therapy may have if it succeeds to normalize the endothelial dysfunction that seems to play a crucial role in the hypertension vascular changes.[10,24,26]

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