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Arterial hypertension and coronary artery disease

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Introduction

The influence of blood pressure (BP) on the risk of coronary artery disease (CAD) has been demonstrated by prospective epidemiological studies including large populations and randomized therapeutic trials. Arterial hypertension (HTN) is a modifiable risk factor that may cause all clinical manifestations of CAD. It increases the risk of coronary atherosclerosis by 3 and more than 35% of patients hospitalized for acute coronary syndrome have a history of hypertension (1-3). Angina may occur in hypertensive patients with or without coronary atherosclerotic lesions. The links between the two pathological entities are known but their relations are complex and still under investigation. HTN influences both directly and indirectly CAD, by causing arterial remodeling, limiting coronary vasomotricity, accelerating atherogenesis, promoting the development of atheromatous plaques and their complications (cracking or rupture). The entanglement with other risk factors has a determining role in the high prevalence of this pathological association. In addition, left ventricular hypertrophy (LVH), an independent risk factor, indirectly increases myocardial oxygen consumption and metabolic demands of the myocardium, promotes ischemia by creating functional abnormalities of coronary flow and arteriolar rarefaction. The reduction in the coronary flow reserve is constant in the hypertensive patient (4). In an ischemic hypertensive patient, the recommended target values of diastolic blood pressure and the choice of a preferred therapeutic class are still under debate.

Epidemiological data

Three types of arterial BP values are associated with cardiovascular risk: systolic pressure, diastolic pressure and pulse pressure.

In middle-aged and elderly subjects, total and vascular mortality are strongly correlated with BP, starting at 115/75 mmHg. A meta-analysis, based on 61 prospective observational studies, including more than one million adults, shows that death from CAD is low for a systolic pressure of 115 mmHg and a diastolic pressure of 75 mmHg (5). Recently the association of arterial pressure with various manifestations of coronary disease was studied in 1, 25 million subjects over 35 years without a history of cardiovascular disease. The lowest risk of coronary heart disease was observed in subjects aged 30 to 79 years, with the lowest systolic and diastolic pressures (90-114 mmHg and 60-74

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mmHg) (6). Systolic blood pressure is better indicator of cardiovascular risk than diastolic blood pressure. The Benetos study has highlighted the predictive value of pulse pressure. A pulse pressure> 60 mmHg is the best independent predictor for coronary events, infarction or stroke (7).

To assess the blood pressure level, the French High Authority for Health ("La Haute Autorité de Santé") recommends the self-measurement of blood pressure and proposes to use MAPA to evaluate nocturnal variations, resistant hypertension, search for masked hypertension and eliminate a white coat effect. After ambulatory measurement, HTN is defined by a 24-hour mean value equal to or greater than 120 / 80mmHg. In addition to BP levels, coronary risk depends on other modifiable risk factors (dyslipidemia, diabetes, smoking, overweight) and unmodifiable risk factors (age, sex, and vascular inheritance). Atherogenic risk factors frequently accumulate in the same patient multiplying the cardiovascular risk. Also, the concept of global cardiovascular risk is used for the assessment and treatment decision in current European guidelines for the management of hypertension (8). Normal high pressure (systolic BP 130-139 mmHg or diastolic BP 85-90 mmHg) compared to optimal blood pressure (PAS <120 and PAD = 80mmHg) according to the classification of JNC -VI, multiplies the risk of cardiovascular disease by 2.

LVH is an independent risk factor, leading to diastolic dysfunction, atrial and ventricular arrhythmias. Its prevalence depends on diagnostic techniques and the population studied. The electrocardiogram offers good specificity but low sensitivity. The current reference method is echocardiography for predicting cardiovascular risk and determining therapeutic options (9). The relationship between cardiovascular risk and left ventricular mass index is continuous; an LVH at echocardiography is to be considered from 125 g/m^2 in men and 110 g/m^2 in women. LVH impairs coronary circulation and increases coronary vascular resistance due to elevated perfusion pressure. There is a reduction in arteriolar lumen due to hypertrophy of the media and intimal proliferation, a decrease in intramyocardial capillary density, and vascular and perivascular fibrosis. In addition to the mechanical factor, hormonal agents are also involved, such as angiotensin II – by activation of the tissue renin-angiotensin system, endothelin and growth factors such as beta-TGF.

Atherosclerosis, coronary artery disease and hypertension

Coronary atherosclerosis is common, early, severe and extensive in hypertensive patients. Angina pectoris is four times more common in hypertensive subjects than in subjects with normal BP (10-11). The relationship between the incidence of coronary events and blood pressure is linear, continuous and independent of other cardiovascular risk factors. In hypertensives aged 40 to 69, each increase of 20 mmHg for systolic or 10 mmHg for diastolic BP doubles the cardiovascular risk for values between 115-75 and 185/115 mmHg (12).

Coronary artery exposure to pulsatile pressure alters endothelial function with release of thromboxane A2 and decreases the vasodilatation capacity of coronary arteries.

LVH alters the microcirculation, the intracoronary hemodynamics, and decreases the vaso-dilatation reserve (14). This finding can be confirmed by a negative response during intracoronary injection of acetyl choline or dipyridamole.

HTN itself and LVH facilitate the ischemic process and stress-induced myocardial ischemia is possible even in the absence of atherosclerotic lesions (14-15).

Blood pressure figures in patients with coronary atherosclerosis are at the origin of a controversy regarding a possible J – shaped curve describing increased risk of coronary events for low diastolic arterial pressures in atherosclerotic patients with LVH. A possible mechanism would be the abolition of coronary flow self-regulation. The combination of low diastolic pressure, LVH, and coronary artery stenosis makes the endocardial layers very sensitive to ischemia. Epicardial artery stenosis> 50% decreases distal perfusion pressure and in this situation, self-regulation preserves coronary flow by vasodilation. Arterial stenosis> 80% leads to ischemia in the sub-endocardial region due to the abolition of this auto-regulation (15). Because the coronary perfusion occurs mainly during the diastole, hypertensives with a history of CAD and LVH should not have the diastolic pressure lowered <80 mmHg.

Detecting cardiac complications of hypertension has been improved by advances in cardiac imaging.

Myocardial ischemia in hypertensive patients may remain silent for a long time or present as either stable angina or acute coronary syndrome. The Framingham study revealed a significant proportion of silent infarc-

tions detected by systematic electrocardiographic tracing, particularly in women (16).

In a hypertensive patient, always look for LVH. Its detection is based on ECG and echocardiography. ECG offers good specificity (90%) but low sensitivity while the repolarization impairments caused by LVH may mask ischemia changes. Ambulatory ECG recording is useful for detecting silent ischemia in asymptomatic hypertensive patients during daily activities.

Stress test can be recommended, as it evaluates the cardiac repercussions of hypertension, its exercise -induced variations and can detect myocardial ischemia associated with LVH. The appearance of a horizontal or descending ST segment depression > 2 mm after the J point is a criterion of positivity if resting ECG is normal, especially if the electrocardiographic anomaly is associated with anginal pain. CAD likelihood increases with ST depression amplitude, its persistence during the recovery phase and if it appears at a low exercise threshold. ST segment elevation in the absence of a history of myocardial infarction is highly suggestive of severe transmural ischemia due to either proximal arterial stenosis or spasm on a coronary artery. The occurrence of polymorphic premature ventricular beats on exertion in a hypertensive patient has a poor prognosis and is correlated with the risk of sudden death.

For the detection of ischemia - related myocardial hypoperfusion, thallium 201 myocardial scintigraphy during exercise or using dipyridamole can be used to evaluate the extent and severity of ischemia. It is reflected on the images acquired immediately after exercise by hypofixation in the territory irrigated by the stenotic coronary artery, followed by total or partial correction on the late images of redistribution. The sensitivity and specificity are excellent (approximately 90%); however in the presence of an important LVH, exercise scintigraphy loses its specificity (75%) and sensitivity (85%).

The results of ischemia detection tests should be interpreted according to Bayes' theorem. Their positive predictive value rises to 90% in patients with high overall cardiovascular risk. The discrepancy between the functional data of exercise myocardial scintigraphy and coronary angiography can arise in two situations: either false positive test results or microcirculation alterations leading to a reduction of the coronary flow reserve, in the absence of significant epicardial atheromatous lesions.

Two-dimensional echocardiography using Doppler can detect LVH and analyze diastolic and systolic functions in a hypertensive patient. It is the reference method because of its high sensitivity (95%) and its specificity, which reaches 98% . It allows for the calculation of the volume, wall thickness of the left ventricle, ventricular mass indexed to body mass. It provides information on the morphology of the ventricle, distinguishing concentric, symmetrical or asymmetric LVH and eccentric hypertrophy with dilation of the ventricular cavity. Diastolic disfunction results in prolongation of the isovolumic relaxation time, decreased speed and volume of fast ventricular filling, and increased atrial contribution to ventricular filling. Stress echocardiography has a very high sensitivity for detecting ischemic areas with segmental ventricular kinetic alterations.

The difficulties of detecting myocardial ischemia by non-invasive techniques explain the frequent use of imaging (coronary CT or coronary angiography) in hypertensive patients at risk with LVH. Severe single or multi vessel lesions of type B2 or C are often observed.

The clinical presentation of the different types of acute coronary syndromes in a hypertensive patient is often modified by the immediate development of a ventricular dysfunction. HTN predisposes to complications during the acute phase of myocardial infarction - facilitating rhythm disorders, larger myocardial necrosis, ventricular dysfunction and myocardial rupture.

Prevention and treatment

In a hypertensive patient, prevention and treatment of coronary artery disease are based on the same therapeutic principles as in non-HTN patients. First, in any hypertensive patient suffering from CAD, it is necessary to apply appropriate lifestyle and dietary measures based on a healthy lifestyle, a reduction of the sodium intake, a loss of weight if necessary, the definitive cessation of smoking, regular physical exercise (one hour of walking, 5 days a week) and correction of dyslipidemia or normalization of blood glucose. The cardiovascular risk increases with the number of risk factors. In a 50 to 60-year-old smoker patient with HTN, LVH on the ECG and a low HDL cholesterol, the 10-year cardiovascular risk is 55% (17). In these patients at high

risk, blood pressure must be lower than 140 / 90mmHg or 130mmHg after a stroke or carotid artery disease and particularly in cases of diabetes or renal failure (17). On the other hand, diastolic BP must not be durably lowered <80mmHg.

Is there a class of BP lowering medication to prioritize for the prevention of myocardial ischemia when treating hypertension?

A recent meta-analysis investigated the effect of antihypertensive therapy on the occurrence of cardiovascular events. In trials comparing antihypertensives to placebo or no treatment, the reduction in the rate of coronary events under medical treatment ranged from 18 to 28% (absolute reduction of 7 events per 1000 patients treated for 5 years) (18). When stratifying according to systolic BP, it appeared that a systolic pressure <130mmHg was better than a pressure >130mmHg (-21 vs -16%).

In a recent meta-analysis of Law and Al., in patients without a history of cardiovascular disease a reduction of 10 mmHG systolic and 5mmHg diastolic BP was associated with a 21% reduction of the risk of coronary artery disease. Depending upon the therapeutic class used, the significant decreases in coronary artery disease were -16% with diuretics, -13% with angiotensin converting enzyme inhibitors (ACEI), -12% with betablockers, -17% with inhibitory calcium, - 6% with angiotensin antagonists (19-20).

For CAD prevention, in a comparison evaluating the effects according to the therapeutic class, ACEI were superior to all other classes, that have similar effects on coronary risk. The five main antihypertensives classes cause the same reduction in the risk of coronary disease. The results of the SPRINT randomized study underline the interest of a fall in systolic blood pressure: in non-diabetic subjects with a high cardiovascular risk, 20% of them with known cardiovascular disease, a target systolic pressure of less than 120 mmHg compared to a target of less than 140 mmHg, resulted in a highly significant reduction of 25% in cardiovascular events, a 17% non-significant decrease in myocardial infarction, a very significant reduction of 38% of cases of heart failure, 43% of cardiovascular mortality and 23% of overall mortality. The arterial pressure achieved in SPRINT at one year was 121/69 mmHg in the intensive care group and 136/76 in the standard treatment group.

Finally, what should the BP therapeutic targets be for hypertensive patients with CAD?

- Antihypertensive therapy targeting systolic BP <140 or 130 mmHg is recommended by international guidelines. Blood pressure <130 mmHg should be the target in hypertensive patients at risk, especially in patients with a history of myocardial infarction, peripheral atherosclerotic disease, a history of stroke, diabetes, renal failure or proteinuria (22). The diastolic pressure must not be <80mmHg;
- All BP lowering medication classes are equivalent and effective in the prevention of cardiovascular complications, the decrease in risk being related to the decrease in blood pressure. Long term target BP maintenance is more important than the choice of drug. If BP is not controlled at the optimal dosage of a single antihypertensive drug, a complementary action medication will be added. Some drugs are beneficial because of their antihypertensive effect and their anti-anginal effect. Thiazide diuretics transiently decrease BP but their deleterious metabolic side effects are to be taken into account for prolonged use. On the other hand, they may be combined with other therapeutic classes, in order to potentiate their effect, in particular with ACEI or calcium channel blockers;
- Beta-blockers are the preferred drugs because they reduce heart rate, are effective anti-anginal drugs, improve exercise tolerance and, after myocardial infarction, the prognosis. Also, during the acute phase of myocardial infarction, they decrease the necrotic mass and the risk of myocardial rupture. These are first-line drugs for hypertensive patients with coronary insufficiency according to the main guidelines (23). Their relative contraindications are sinus node dysfunction, asthma or severe bronchopulmonary disease. In patients with left ventricular failure after myocardial infarction, their use must be delayed: their intravenous prescription should be reserved for patients with active hypertension or ischemia. After the acute phase if the patient has ventricular dysfunction, carvedilol, metoprolol bisoprolol

and nebivolol should be the preferred option;
- Calcium inhibitors reduce myocardial oxygen consumption by decreasing peripheral arterial resistance, increase myocardial oxygen supply by dilating coronary arteries (24). In addition, non-dihydropyridines, such as diltiazem and verapamil, reduce the heart rate and prolong the duration of diastole. They are an alternative to betablockers. The INVEST trial comparing verapamil to atenolol in stable CAD patients, showed identical effects on mortality and infarction occurrence in both treatment groups (24). In contrast, short-acting nifedipine should be avoided in CAD patients. The contraindications for diltiazem and verapamil include low heart rate, atrioventricular block, sinus disease and ventricular systolic dysfunction (left or right) (25);
- ACEI improve prognosis in coronary heart failure patients, stable angina patients, and high-risk diabetics. Their prescription is a Class IA recommendation after a myocardial infarction associated with ventricular dysfunction or overt heart failure, in patients with diabetes or chronic renal failure (26). In the acute phase of an infarction they prevent cardiac remodeling, heart dilatation and reduce mortality. A BP <130/80mmhg is acceptable at the hospital exit. The HOPE trial showed the favorable effect of ramipril compared to placebo in high-risk patients with a 20% decrease in cardiovascular events (27).
- Angiotensin receptor antagonists, in the setting of ACEI intolerance, are recommended for cardiovascular risk reduction in HTN patients with stable angina, heart failure or diabetes. In the ONTARGET study, in high-risk patients, telmisartan was equivalent to ramipril for cardiovascular prognosis, while a 20% decrease in diastolic pressure did not result in a significant increase in coronary events (28).

Conclusions

For hypertensive patients with coronary artery disease, achieving the blood pressure target values according to current guidelines generally requires a combination of several therapeutic classes. Several combinations potentiate their blood pressure lowering effect without increasing the risk of side effects. Additionally, in hypertensive CAD patients, care must be taken to combine effective anti-platelet therapies, statins and control diabetes. Depending on the coronary artery disease, revascularization procedures (interventional or surgical) should always be performed when necessary.

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