Hypertension and coronary artery disease: current status

Coronary artery disease (CAD) constitutes the leading cause of death and is a major cause of morbidity and impaired quality of life worldwide; hypertensives compared to normotensives have a higher risk of cardiovascular events and death mainly due to atherosclerotic plaque rupture and subsequent thrombosis. The main objectives of this review are to update on the clinical need to identify asymptomatic CAD and to describe the pathophysiology of myocardial ischaemia in hypertension.

The clinical need to identify asymptomatic CAD

CAD has a long asymptomatic latent period. Many subjects, even those with an advanced form of the disease, do not show symptoms before experiencing a major event such as sudden cardiac death, unstable angina, myocardial infarction, or congestive heart failure [3, 6, 7]. Additionally, there is clinical practice the common need to exclude CAD in asymptomatic hypertensives who undergo preoperative risk assessment, who present with a new-onset atrial fibrillation, or who are on clinical work-up episodes of ventricular tachycardia or syncope [6, 7]. Based on the above, the aim of this newsletter is to provide an approach to risk assessment of CAD in asymptomatic hypertensive patients.

Pathophysiology of myocardial ischaemia in hypertension

In hypertensive patients, myocardial ischaemia is caused by anatomical and pathophysiological factors different to those of 'classic' CAD [3, 8]. Apart from the atherosclerotic obstruction of the large epicardial coronary arteries, reduced vasodilator capacity of the coronary microcirculation, caused mainly by arteriolar hypertrophy and endothelial dysfunction, is very often present [3, 8]. Furthermore, coronary flow reserve is reduced in hypertensives due to several pathophysiologic mechanisms such as increased haemodynamic load, left ventricular (LV) mass and end-systolic stress, inadequate angiogenesis, extracellular compression, reduction in the overall maximal cross-sectional area of the microcirculatory bed along with subclinical inflammation, endothelial dysfunction, and activation of the sympathetic nervous system and the renin angiotensin system [3, 8]. From a clinical point of view, reduced coronary flow reserve could lead, at least during the period of stress, to reduced subendocardial coronary perfusion and ischaemia, and impaired diastolic and systolic functions [3, 8]. Additionally, adverse alterations of the haemodynamic and platelet-related mechanisms of platelet aggregation contribute to a prothrombotic state and CAD clinical events [8].

All the above-mentioned mechanisms lead to an imbalance of myocardial oxygen demand and supply in hypertension, and contribute to either the clinical expression of ischaemic events or to silent ischaemia [12–14]. The latter is very common in patients without adequate blood pressure (BP) control as well as in elderly untreated hypertensives, suggestive of a pronounced ischaemic burden [12–14]. However, the data on the prognostic significance of silent ischaemia is sparse and contradictory. In the Baltimore Longitudinal Study of Aging, there was no association of transient ischaemia with cardiac end-points [13], but in a Swedish study of men born in 1914, the presence of silent ischaemia constituted a strong predictor of cardiac events [14]. Nowadays, if clinical data on transient silent ischaemia is available, it should only be used cautiously in terms of assessing the global ischaemic myocardial burden.

Assessment of CAD risk in hypertension: combining risk scores and target organ damage

In the setting of asymptomatic hypertensive individuals, a diagnosis of CAD should be guided by total cardiovascular risk [4–7]. According to the ESH guidelines [4, 5], high-risk hypertensives are defined as those with systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg, diabetes (types 1 and 2), a severely elevated single risk factor or more than three cardiovascular risk factors [4, 5]. Additionally, in intermediate-risk hypertensives, a 12-lead ECG is predictive of events in asymptomatic adults, and that a 12-lead ECG is predictive of events in asymptomatic adults, and that specific findings such as left ventricular hypertrophy (LVH), QRS prolongation, ST-segment depression, T-wave inversion and Q waves are indicative of the augmented likelihood of adverse cardiovascular events along with the presence of arrhythmias [7, 15]. Most importantly, ECG reclassifies risk compared to standard assessment in the Women’s Health Initiative and in the Cleveland Clinic study [7].

Resting cardiac echocardiography

In asymptomatic hypertensive patients, echocardiography is essential for CAD risk assessment and detection of LVH [4, 5]. For a hypertensive individual, the MAST study found that 15% of the patients had significant left ventricular hypertrophy (LVH), using the 1995 ESH criteria. In 3,664 asymptomatic high-risk hypertensive patients, 10-year cardiovascular mortality was 1.6%, decreased to 0.7% in patients with LVH compared to 2.0% in those without LVH (p=0.02). In a recent study on 8,477 hypertensive patients, 14% had LVH, those with LVH had a 3-fold higher cardiovascular risk (4, 5). Additionally, both ejection fraction and LV fractional shortening predict cardiovascular events as well as LV systolic function (transmural blood flow or tissue Doppler imaging). Segmental defects of LV wall contraction may be due to prior silent infarction or ischaemia and should be further investigated [4, 5, 7].

Blood vessels

Carotid intima-media thickness

Carotid intima-media thickness evaluation predicts the incidence of cardiac events. More specifically, the ARIC study found that for every 0.1-mm increment of intima-media thickness, the risk of death of myocardial infarction was augmented by 26% [4, 5, 7]. Notably, the link between carotid intima-media thickness and events is linear and continuous and the use of the cut-off point value of >0.9 mm is a conservative estimate.

Arterial stiffness

Carotid-to-femoral pulse wave velocity is an independent predictor of coronary events in hypertension. Although the relationship of stiffness to events is continuous, the cut-off point of >12 m/sec is commonly used [4, 5].

Kidney

Glomerular filtration rate

Renal dysfunction assessed by estimated glomerular filtration rate (eGFR), using either the Cockcroft-Gault or MDRD formulas, is related to adverse outcome [4, 5, 16]. In a hypertensive population, eGFR between 15-59 ml/min/1.73 m² augmented by 66% the risk for events, even after adjustment for LVH and baseline confounders [16]. In the ADVANCE trial, a 50% decrease in eGFR increased by 2.2-fold the risk of cardiovascular events and, in concordance with the VALUE trial, underscored the predictive value of eGFR [4, 5, 17].

Microalbuminuria

In hypertensive microalbuminuria, even below the established threshold values (albumin to creatinine ratio <30 mg/g), there is a cardiovascular predictive value and there is a continuous relationship of CAD risk with levels as low as 3.9 mg/g in men and 7.5 mg/g in women [4, 5]. This may be due to the fact that albuminuria reflects generalized vascular dysfunction and is a unique integrator of endothelial irregularities, inflammatory activation and atherosclerosis progression [18].

Functional testing for CAD

Exercise electrocardiography

Exercise ECG is indicated in hypertensives with average and high risk assessment of asymptomatic CAD [7, 8]. In hypertension, diastolic dysfunction, LV hypertrophy, increased wall stress and subendocardial ischaemia commonly decrease the specificity and sensitivity of exercise testing [3, 8]. Meta-analysis has shown that this test has low sensitivity and specificity of 68% and 77% respectively, while other works have shown specificity as high as 90% [3, 8]. Exercise tolerance is decreased in patients with poor BP control, and severe systemic hypertension may cause exercise-induced ST depression in the absence of atherosclerosis, reducing diagnostic accuracy [3, 8]. Furthermore, hypertensives with bundle branch block, atrial fibrillation and signs of left ventricular hypertrophy or ischaemic disease in resting ECG, along with orthopaedic problems that would preclude maximal effort on the bicycle or treadmill, should be excluded from exercise testing [20]. However, despite the relatively low sensitivity, an exercise test has an excellent negative predictive value and is ideal for the initial screening of average and high risk hypertensives.

Myocardial perfusion imaging

Stress myocardial perfusion imaging may be considered in high-risk hypertensive patients, especially if they are diabetic [7]. In 3,664 asymptomatic high-risk patients re-
ferred for stress myocardial perfusion imaging, those with >7.5% myocardial ischaemia had an annual event rate of 3.2% [21]. The accuracy of perfusion is high (sensitivity of 85–90% and specificity of 70%), and comparable to stress-echocardiography in hypertensive patients. The sensitivity of myocardial perfusion imaging compared to stress-echocardiography [8, 22, 23]. However, because of the time, cost and radiation exposure, a nuclear test might not be more competitive especially in the setting of asymptomatic hypertension [7].

**Stress-echocardiography**

Stress-echocardiography is not indicated in asymptomatic low-risk adults or in average-risk ones unless the exercise ECG test performed in the latter group is positive, ambiguous, non-diagnostic, submaximal or inconclusive [3, 7]. Stress echocardiography can be performed with dynamic forms of exercise, including treadmill and bicycle, as well as with pharmacologic stress, most often using dobutamine and dipyridamole [24]. The diagnostic performance of the test is highly dependent on the expertise of the physician, and on positioning as well as interpretation, of the images [24].

A poor acoustic window makes any modality of stress echocardiography unfeasible to perform, and specific contraindications to dipyridamole (or adenosine) echocardiography include the presence of severe conduction disturbances and bronchopneumopathie disease. Additionally, dobutamine causes an increase in systolic BP in the majority of patients and should be used judiciously in hypertension [24].

Cumulative evidence suggests that in hypertension stress-echocardiography has excellent predictive value [22, 23, 25] and that among stressors, dobutamine may yield better diagnostic accuracy compared to dipyridamole [3, 8, 22, 23]. The low sensitivity of dipyridamole stress in hypertensive patients with a higher specificity to myocardial perfusion scintigraphy [3, 23], whereas in patients with LVH and right bundle branch block, dipyridamole shows increased diagnostic accuracy [22, 23]. The low sensitivity of dipyridamole stress in single vessel disease can be resolved with the atropine protocol [8].

Patients with a negative stress-echocardiography test are expected to have either normal coronary arteries or anatomically minor and prognostically benign forms of CAD; thus coronary angiography can be safely avoided.

Computed tomography for coronary calcium

Evaluation of coronary calcium could be considered in asymptomatic hypertensives with average and high risk in men older than 40 years and women older than 50 years [7]. Average-risk patients with an elevated coronary calcium score > 300 have a 2.8% annual rate of cardiac death or myocardial infarction [7]. However, due to the issue of radiation and in the present era of cost-effectiveness, this modality cannot be encouraged in the setting of asymptomatic hypertensives.

**Proposed algorithm for identification of CAD in asymptomatic hypertensives: a three-step approach (Figure 1)**

**First step: risk classification**

In order to better evaluate an asymptomatic hypertensive patient for the presence of significant CAD, a thorough history and clinical examination is needed. Moreover, an ECG is performed, as well as rest echocardiographic examination, in parallel with a search for target organ damage according to current guidelines [4, 5]. Based on all the above, the patient is classified as low, average or high/very high risk.

**Second step: functional testing for CAD**

In low-risk individuals, no further testing is considered. For patients in the average and high-risk groups, an exercise ECG test is done if applicable according to the established criteria. In the low-risk patients, stress-echocardiography or myocardial perfusion imaging in single- or vessel-level modalities are considered the initial step. Based on negativity for ischaemia of the functional stress-test, the patient is advised to continue current treatment. However, an asymptomatic hypertensive patient with a positive stress-test should be referred for coronary angiography.

**Third step: coronary angiography**

In the small fraction of patients referred for coronary angiography, if significant epicardial CAD is found, ischaemia-driven revascularisation in order to improve the prognosis should be implemented.

**Summary**

The purpose of screening for possible CAD in asymptomatic hypertensive patients is to prolong life and improve its quality because of early detection. Furthermore, assessment of risk for asymptomatic CAD in hypertension aids clinicians in making evidence-based decisions on the intensity of lifestyle and pharmacological interventions, in order to reduce adverse events and optimise cardiovascular care. From another point of view, if a certain hypertensive individual based on estimated risk for significant CAD, no unjustified testing is performed, in order to spare resources. Nevertheless, a reduction of risk factors should be attempted in all hypertensives, while identification of functional impairment by stress-tests may further improve patients’ compliance. Finally, in the rare cases of obstructive epicardial CAD in asymptomatic hypertensives, ischaemia-driven revascularisation can ameliorate the long-term cardiac outcome.

**References**

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