INSIGHTS INTO THE PATHOPHYSIOLOGIC FEATURES OF HYPERTENSIVE HEART DISEASE

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Abstract: *Arterial hypertension is an important risk factor for cardiovascular, cerebrovascular and renal disease, being a considerable public health problem of our society. Even though when we're considering hypertensive heart disease we are used to think in left ventricle modifications (ventricular hypertrophy) there's growing evidence of both atrial and large vessels pathophysiological changes, too. The early recognition of cardiovascular fibrotic modifications requires a rigorous control of associated risk factors as well as the intensification of medical treatment given the exposure of this patients to an increased number of ischemic events, heart failure, stoke or arrhythmias.*

Cuvinte cheie: *hipertensiune arterială, fibroza miocardică, rigiditate arterială*

Rezumat: *Hipertensiunea arterială constituie un factor de risc important pentru afectarea cardiovasculară, cerebrovasculară şi renală, constituind o reală problemă de sănătate publică a societăţii actuale. Deşi atunci când vorbim despre afectarea cardiovasculară a pacienţilor hipertensivi ne gândim în primul rând la modificările suferite de ventriculul stâng (hipertrofia ventriculară stângă), există din ce în ce mai multe dovezi care susţin atât afectarea atriilor cât şi a vaselor mari. Evidenţierea apariţiei modificărilor de tip fibrotic la nivel cardiovascular impune un control foarte riguros al factorilor de risc şi intensificarea tratamentului medicamentos, dată fiind expunerea acestor pacienţi la producerea de evenimente de tip ischemic, insuficienţa cardiacă, accident vascular cerebral sau aritmii.*

Arterial hypertension is one of the leading causes of preventable premature death, being the most common risk factor for serious cardiovascular conditions such as myocardial infarction, heart failure and stoke. Because of the increased longevity and increased prevalence of smoking, physical inactivity and unhealthy food, arterial hypertension projects itself as one of the most important public health issues, the World Health Organization (WHO) data estimating 1.5 billion affected people by 2025, meaning almost one third of the globe population (29.2%).(1) The early recognition of the heart and vessel disease in hypertensive patients has both diagnostic and prognostic implications, the current imagistic techniques being able to evaluate the ventricular myocardial modifications (hypertrophy, ischemia, fibrosis), the atrial myopathy and the vascular changes.

Ventricular remodelling

Discrete changes in left ventricle structure and geometry appear early in arterial hypertension's evolution. The most emphasized was the left ventricle hypertrophy because many studies correlated this aspect with an increase in morbidity and mortality of those patients which were more prone to stoke, atrial fibrillation, myocardial infarction and heart failure. The main pathophysiological process involved in producing left ventricular hypertrophy in hypertensive patients comprises on one hand cardiomyocite hypertrophy and on the other hand an exaggerate accumulation of the fibrous tissue both interstitially and perivascular. The excess of interstitial myocardial collagen seems to be due to an impairment between increased synthesis and reduced collagen degradation, in the myocardium being detected mostly type I and type III collagen. The main triggers involved in the imbalance between synthesis and degradation of myocardial collagen are haemodynamic, humoral and genetic factors.(2) In vivo and in vitro studies revealed that chronic pressure overload on the left ventricle walls is definitely a stimulus for procollagen type I synthesis and its deposition. As for the humoral factors, it has been shown that hypertensive patients have an excess of collagen stimulating synthesis molecules (angiotensin II, aldosterone, TGF-β, endothelin I) and a decrease in inhibitory molecules of the collagen turn-over (bradikinin, nitric oxide, prostaglandins).(2) The contribution of the genetic factors in myocardial hypertrophy and fibrosis cannot be ignored. The fact that patients with AA genotype for angiotensin II type I receptor (A 1166 C – AT1) have an increased collagen volume fraction than patients with AC/CC genotype was first observed on mice and then confirmed on humans. The importance of detecting myocardial fibrosis resides in its impact on myocardial function. Seems that a two-three fold increase in collagen volume fraction is associated with an increase of diastolic rigidity, producing diastolic dysfunction and more than a four fold increase is associated not only with diastolic stiffness but also systolic stiffness conducing to systolic dysfunction.(2) Also, the perivascular disposition of collagen fibers is associated with a reduction of coronary flow reserve. Myocardial fibrosis can be detected by using invasive methods such as endomyocardial biopsy, but this has a reduced accessibility. Non-invasive methods already validated by comparison with collagen volume fraction determined by quantitative morphometry are serum markers of collagen synthesis (the carboxy-terminal propeptide of procollagen type I, the carboxi-terminal propeptide of procollagen type III) or serum markers of collagen degradation (C-terminal telopeptide of procollagen type I); the C-terminal propeptide type I has by now the best correlation with collagen volume fraction results.

Imaging techniques bring their contribution in the evaluation of hypertensive heart disease. Echocardiography detects myocardial hypertrophy, fibrosis generating a particular

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texture by increasing the acoustic impedance of the myocardium. Another method with increased reproducibility for left ventricle (LV) measurements is computer tomography but the gold standard for LV mass measurement remains cardiac magnetic resonance (CMR). CMR is able to detect fibrosis on late gadolinium enhancement (LGE) sequence, a recent study showing that half of hypertensive patients with left ventricular hypertrophy exhibit patchy enhancement on LGE imaging.(3,4)

Atrial remodelling

For many years the researchers focused especially on the effects of arterial hypertension on the left ventricle. Given the evolution of imaging techniques, is now proved that chronic exposure of the left atrium to an increased afterload induces structural and functional modifications at this level, determining atrial dilation and dysfunction. It has been shown that neuro-endocrine stimulation with sustained release of natriuretic peptides, AT II and aldosterone generates remodelling both at the ventricular and atrial level. Fibrosis is the hallmark of the atrial structural remodelling (5), generating a reduction in atrial contractility and an arrhythmogenic substrate, atrial fibrillation being a common arrhythmia in patients with a long evolution of the arterial hypertension. Echocardiography is the most accessible technique for the evaluation of the left atrium function; we measure left atrium (LA) volumes which offer information about the reservoir, the pump and the conduit functions of the LA, but we can also measure various Doppler parameters that quantify the systolic function of the left atrium (e.g.: LA systolic force – a useful index for the assessment of atrial contribution to diastolic performance of the left ventricle). The new myocardial imaging techniques such as tissue Doppler, strain and strain rate bring their contribution in the LA function assessment, the A' value measured at the level of the interatrial septum immediately below the mitral annulus showing a very good correlation with LA ejection fraction and LA ejection force in patients with various degrees of diastolic dysfunction.(6)

Vascular remodelling

Hypertensive patients have modifications both at the microcirculation level, but also at the level of large arteries.

Endothelial dysfunction characterized by the disruption of the balance between vascular relaxing endothelial factors (nitric oxide) and factors that determine vascular constriction and a prothrombotic status (endothelin I, thromboxane) was shown in many studies on hypertensive patients with left ventricular hypertrophy using flow mediated vasodilation at the brachial artery level. Sustained increase of the arterial pressure combined with neurohormonal effects determine a vessel wall remodelling process that will contribute to a further perpetuation of the arterial hypertension. The hallmark of the vascular remodelling in arterial hypertension is considered the relative thickening of the vascular media to the vascular lumen diameter; the eutrophic remodelling of small arteries consequently determines an increase in systemic vascular resistance.(7) As for the large vessels, besides the medial hypertrophy of the smooth muscle cells, a decrease in elastin fibers and an increase in collagen and fibronectin fibers occurs, contributing to the increase in vascular stiffness. The importance of the arterial rigidity evaluation resides in the direct relation between the arterial stiffness and the extension of the atherosclerotic process. Initially, the aortic stiffness was evaluated using parameters that were taking into account the systolic and diastolic diameters of the ascending aorta measured at a level of three centimetres above the aortic valve (aortic strain and aortic distensibility).(8) The gold standard for quantification of arterial stiffness is now considered the pulse wave velocity (PWV) method and there are studies showing that carotid-femoral PWV is a predictor for cardiovascular mortality and for all cause mortality, independent of age or diabetes in hypertensive patients.(9)

Conclusions:

Arterial hypertension is an important risk factor for cardiovascular, cerebrovascular and renal disease, being an important public health issue, considering the increasing incidence projected by the WHO statistics. Fibrosis is the key pathologic process in patients with persistent arterial hypertension, expressed at the level of ventricular myocardium (even in non-hypertrophied hearts), atriums and large vessels. The presence of fibrotic tissue has prognostic implications, being associated with ischemic events, heart failure, ventricular and atrial arrhythmias and strokes. The rigorous correction of associated risk factors (smoking cessation, weight control and a healthy diet) as well as the early initiation of medical therapy using eventually angiotensin converting enzyme inhibitors or angiotensin II type I receptor blockers which proved in some studies reduction of the degree of myocardial fibrosis (10) should contribute to limitation of the cardiovascular disease progression and the reduction of the adverse events related to arterial hypertension.

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