Diastolic Heart Failure in Hypertension: Possible Preventive Benefits of Nebivolol Beyond Lowering Blood Pressure

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ABSTRACT

Arterial hypertension is one of the most prevalent cardiovascular diseases and one of the most important causes of heart failure with low or preserved ejection fraction. Although many drugs are highly effective in lowering blood pressure, the optimal treatment for preventing progression to heart failure is still uncertain. Beta-blockers, a class of drugs with well-established indications and benefits for both hypertension and heart failure seem to show different pharmacological properties with different consequences on the cardiovascular hemodynamic. The third class beta-blocker nebivolol, by its particular mechanism of vasodilatation mediated by nitric oxide release, has been proven to provide substantial benefits beyond the effect of blood pressure lowering, such as reversal of endothelial dysfunction, improvement of ventricular-arterial coupling, improvement of coronary flow reserve and an overall improvement of the diastolic function which is independent of the changes in ventricular geometry. Thus, nebivolol seems to be superior to other “classical” beta-blockers for the reversal of subclinical left ventricular dysfunction in hypertensive patients, before the onset of overt heart failure. This could be an important fact to take into consideration especially for the early stages of heart failure with preserved ejection fraction for which the optimal management is not established yet.

Keywords: beta-blockers, nebivolol, diastolic dysfunction, longitudinal function, conduit arterial stiffness

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arterial stiffness, plasma volume, neuro-hormonal status or various genetic aspects (2). Left ventricular (LV) hypertrophy involves the myocytes but also the interstitial tissue, and the increased amount of interstitial fibrosis plays an important role in the development of cardiac dysfunction in hypertensive disease. The LV hypertrophy and interstitial fibrosis reduce the ventricular compliance and, finally, leads to diastolic dysfunction. Also, the structural changes of the coronary arteries and the increase of the myocardial mass contribute to the decrease of the coronary flow reserve. Diastolic dysfunction among hypertensive patients, especially the elderly with persistent raised blood pressure values, is present in at least one of four subjects (3).

The development of some new diagnostic tools, such as tissue Doppler imaging (TDI) or the assessment of brain natriuretic peptide (BNP) have raised the hypothesis that, in fact, in hypertension the subclinical diastolic dysfunction might precede the development of left ventricular hypertrophy. The BNP values, which are progressively increased proportionally to the degree of diastolic dysfunction, are raised in patients with diastolic heart failure independently of the magnitude of the LV myocardial mass (4). Also, TDI studies sustain the hypothesis of an early diastolic dysfunction in hypertensive heart. Some study findings showed that early diastolic annular velocities (Em), as well as the systolic myocardial velocities (Sm) are indexes of LV function, being strongly dependent both on the regional amount of interstitial fibrosis and the myocyte beta-adrenergic receptor density, as determined by TDI echocardiography, along with transmural endomyocardial biopsy (5).

There are also many evidences from studies that the conduit arterial stiffness is increased in arterial hypertension. The increased brachial pulse pressure is an independent marker for the cardiovascular risk, especially for myocardial infarction, congestive heart failure and cardiovascular death and its predictive value is influenced both by the raised systolic pressure and the low diastolic pressure (6). The arterial stiffness influences the propagation velocity of the pressure wave generated by the cardiac contraction, which is generally augmented in hypertension; consequently, the pressure wave reflects and is transmitted back to the heart in a shorter time, so that it increases the pressure of the anterograde wave and reduces the blood flow. At the aortic level, wave reflection is responsible for the augmentation of the pressure in the late systole and, by this mechanism, it increases additionally the cardiac load and affects the coronary flow (2). The conduit arterial stiffness contributes to the myocardial ischemia by altering the ventricular-arterial coupling and, in hypertensive patients, microvascular ischemia and interstitial fibrosis determine subendocardial dysfunction (7).

Studies of myocardial architecture have shown that shortening occurs first in the fibers from the longitudinal axis followed by shortening in the circumferential axis. At present, no noninvasive technique can simultaneously assess all the components of myocardial motion and there is a debate regarding the relative importance of each. However, there is a uniform agreement regarding the role of longitudinal shortening which is an integral part of the global contractile function and has a good correlation with the overall ejection performance of the ventricle (8). Subendocardial function of the left ventricle is governed by the longitudinal myocardial fibers whereas the radial function is due mainly to the contraction and relaxation of the mid-wall circumferential fibers. Many studies have shown that in patients with arterial hypertension there is a significant impairment of the longitudinal LV function by comparison with normal age- and sex-matched patients (9) both at rest and during peak stress test with dobutamine, even in the presence of a normal ejection fraction and no proof of coronary heart disease (10) and all these changes induced by arterial hypertension have to be taken into consideration for diagnosis, monitoring and especially for choosing the optimal treatment. There are also some findings suggesting that the longitudinal LV dysfunction might be reversed, at least partially, by the antihypertensive treatment, irrespective of the drugs used to lower the blood pressure, and, by this, the progression to overt heart failure might be attenuated (11). Moreover, beyond a similar efficiency in lowering blood pressure, different drug classes or even individual drugs that have special pharmacological properties might have an additional benefit on the cardiac systolic and/or diastolic subclinical dysfunction.

The optimal management of diastolic dysfunction, from its early stages until the decompensation of heart failure (with or without de-
increased EF) remains relatively empirical. The therapeutic objectives include the improvement of the hemodynamic filling status, concerning both the preload and the afterload. Most patients with predominantly diastolic heart failure have symptoms not at rest, but in a direct relationship with stress conditions. Tachycardia, in particular, shortens the time necessary for the global LV filling and, by this, induces the raising of the left atrial pressure; consequently, when diastolic dysfunction is present, avoiding tachycardia and controlling the heart rate is important. A slower heart rate induces the prolongation of the LV filling time, counterbalancing the resistance of a rigid ventricle to the diastolic filling flow and, afterwards, providing a better stroke volume. Even if recent guidelines highlight some limitations of traditional beta-blockers as a choice for antihypertensive treatment, these limitations do not appear to be shared by the new generation of beta-blockers with vasodilator activity (such as carvedilol-by concomitant alfa-adrenergic blocking activity and nebivolol-by additional direct vasodilatation). By reducing heart rate and myocardial ischemia and also central pulse pressure and aortic stiffness better than atenolol, these agents could be indicated in particular in the management of the diastolic dysfunction (12-13).

Nebivolol has additional vasodilatation properties by inducing the release of nitric oxide (NO), one of the most powerful lusitropic agents. It has a demonstrated benefit on the endothelial dysfunction in hypertension, improving the small arteries distensibility index and increasing the endothelium-dependent cutaneous vasodilation after acetylcholine, an effect not observed for atenolol (14). The observation that nebivolol enhances or restores NO-mediated vasodilatation in hypertensive patients has important therapeutic implications in view of the well-established protective role of NO against cardiovascular risk factors, and particularly the development of atherosclerosis. The increased release of NO in the vessels of the skeletal muscles may also increase their dilatory capacity and thus improves the muscle perfusion during exercise (15). In 2003, Nodari et al published the results of a prospective randomized trial comparing two 6 months-regimens of treatment with nebivolol and atenolol in hypertensive patients with diastolic dysfunction and no evidence of coronary heart disease, assessed by hemodynamic parameters measured both at rest and at peak stress. Those parameters were obtained from a cardiopulmonary stress test, with the placement of a Swan Ganz catheter and echocardiographic assessment. It was showed that nebivolol is associated with a superior improvement of the hemodynamic status, both at rest and at peak stress, differences that seem to be related to a better improvement of the diastolic function. Both drugs decreased significantly the blood pressure and the heart rate at rest and at peak stress and the LV mass, but only for nebivolol there were found a decrease of the VE/VCO2 ratio (minute ventilation/CO2 production) and an increase of the early/late transmitral diastolic flow (E/A) ratio, peak VO2 and VO2 at the anaerobic threshold (15). The differences between the two beta-blockers could be explained by the vasodilator activity secondary to NO release induced by nebivolol, observed also in other similar studies, but these results were based upon direct hemodynamic measurements of the filling pressures, at rest and at peak stress, and the maximal capacity of exercise in patients with predominantly diastolic heart failure.

It is also known that the drugs increasing the NO activity reduce significantly the arterial reflected wave. In a study published in 2008 that included 40 hypertensive untreated subjects, randomized to receive atenolol 50 mg or nebivolol 5 mg daily for 4 weeks, the conduit arterial stiffness was evaluated by carotid-femoral pulse wave velocity (PWV, Complior) and the reflected wave (the augmentation index Aix) by applanation tonometry (Sphygmocor). The results extended previous observations that in hypertension nebivolol decreases not only the aortic stiffness but also the reflected wave and the central aortic pulse pressure (16).

Metoprolol is a “classic” β1-selective beta-blocker, much more used in Europe than atenolol and with many strong evidences regarding benefits in heart failure treatment. In 2011, Vinereanu et al published the results of the EN-EYS study, a randomized PROBE design trial of 60 hypertensive patients, all having left ventricular hypertrophy and no evidences of coronary heart disease, treated for 6 months with nebivolol and metoprolol, respectively. By performing an assessment with standard echocardiography and dobutamine stress test with TDI, cardiac systolic and diastolic function, includ-
ing the contractile reserve, were examined in dynamics. It was found that the longitudinal early diastolic function, evaluated by the longitudinal early diastolic velocities at TDI, and also the flow propagation velocity at color M-mode were improved significantly only in patients treated with nebivolol (by 16% and 34% respectively, both p<0.05). Moreover, although the influence on the systolic function was not significant for both drug regimens, nebivolol increased significantly the longitudinal displacement and the ejection time, thus providing a more favorable global hemodynamic profile (11).

Several studies published recently by Galderisi et al showed that the coronary flow reserve (CFR), which is due to epicardial coronary stenoses but also to the coronary microvascular dysfunction, affects both the early relaxation and the filling pressures independently of the presence or absence of LV hypertrophy (17). Unlike the first and second-generation beta-blockers, which have controversial influences on the coronary flow, the drugs of the last generation, such as nebivolol, improve the coronary flow reserve, probably by a decrease in coronary resistance (18). Nebivolol improves also filling pressures (evaluated by measuring the ratio between early diastolic transmitral flow and early annular velocity, E/Em ratio) independently of the presence of LV hypertrophy. After 3 months of treatment, nebivolol increased significantly the Em values and decreased the E/Em ratio, which correlated with the increase of CFR; the association between the changes of CFR and those of filling pressures suggest a possible common mechanism for the improvement of the coronary microvascular function and the stimulation of myocardial NO release induced by this drug (19). The effects of nebivolol on the diastolic function seem to be related also to the duration of the treatment, being not significant after 4 weeks but significant after treatment periods of minimum 3 months.

As for the metabolic effects, known to be overall unfavorable for the beta-blockers class, the 2013 ESH/ESC guidelines highlights the fact that the new vasodilating generation affects insulin sensitivity less than metoprolol and nebivolol has recently been shown not to worsen glucose tolerance compared with placebo and when added to hydrochlorothiazide (13).

Overall, the favorable hemodynamic profile of nebivolol, as described by the new investigations (preservation of cardiac output, prolonged ejection time, reduction of peripheral resistance and improved diastolic function) appear to have clinically relevant benefits on the impairment in systolic and/or diastolic function often complicating early the evolution of hypertension (20).

**CONCLUSIONS**

The detection and prevention of the subclinical cardiac systolic and diastolic dysfunction in arterial hypertension are still an important objective for attenuating the progression to overt heart failure, both with low and preserved ejection fraction. For the heart failure with low EF, the current guidelines provide specific indications and several beta-blockers of second and third generation, such as nebivolol, have a well-established place in the global treatment. Instead, the optimal management of the heart failure with preserved EF, especially in its early, subclinical stages, is not well established, so that the knowledge and the appropriate choice of drugs with beneficial long-term effects is important. Large ongoing or future trials are expected to provide more clarified data.

**Abbreviations list**

LV = left ventricular
TDI = tissue Doppler imaging
BNP = brain natriuretic peptide
EF = ejection fraction
CFR = coronary flow reserve
E = early diastolic transmitral flow wave
A = atrial diastolic transmitral flow wave
Em = early diastolic annular velocity
Am = late (atrial) diastolic annular velocity
S = systolic myocardial velocities (at TDI)

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