Should we prescribe “vasodilating” beta-blockers in Marfan syndrome to prevent aortic aneurysm and dissection?

Da li bi trebalo da propisujemo „vazodilatirajuće“ beta blokatore kod sindroma Marfan za sprečavanje aneurizme i disekcije aorte?

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Key words: marfan syndrome; aortic aneurysm; aortic rupture; therapeutics; adrenergic beta-antagonists.

Introduction

The Marfan syndrome (MFS) was named after Antoine Bernard-Jean Marfan (1858–1942), a French pediatrician, who described the syndrome in a 5-year-old girl in 1896. There is a great deal of interest in medical therapy for MFS, which protects the aorta and prevents or delays surgery.

MFS is a hereditary connective tissue disorder, with the incidence of 2–3 in 10,000 live births worldwide. Approximately 15%–30% of MFS patients are due to de novo genetic mutations, but it is mostly inherited as an autosomal dominant trait, due to mutations in the fibrillin-1 gene. Fibrillin-1 is the major constituent of microfibrils, which are components of extracellular matrix, as well as of elastic fibers. Thus, in MFS connective tissues are looser than usual, damaging the support structures of the entire body. Elastin fibers are abundant in elastic arteries: up to 40% of the wall of the thoracic aorta. In MFS the amount of elastin in the aortic wall is decreased (quantitative disorder), together with a loss of elastin’s normally highly organized structure (qualitative disorder). In systole, aorta normally expands, stretching the elastic fibers and enables a portion of a stroke volume to be stored. The aorta recoils during diastole (i.e. elastic fibers return to their original size, bringing back the aorta to its unexpanded diameter), so that blood continues to flow forward from the aorta to the periphery during diastole, thus creating a nearly continuous peripheral blood flow. This is named the buffering (Windkessel) function of the aorta. The proximal aorta provides more than half of the “buffering” capacity of the entire arterial system, and the aorta and some of the proximal large vessels store about 50% of the left ventricular (LV) stroke volume during systole. The Windkessel model was proposed in 1899 by Frank. Buffering function allows blood flow to be converted from an intermittent, pulsatile flow to a more steady and laminar one, protecting sensitive end-organs from the detrimental effects of excessive pressure pulsatility.

Aortic elasticity with consequent buffering function is very useful: it protects ascending aorta from an abrupt increase of wall tension during systole, reduces LV afterload, and improves both LV relaxation and coronary blood flow. Thus, fibrillin is the primary component of the microfibrils that allow tissues to stretch repeatedly without weakening. In MFS, the impaired microfibrils do not help the elastic fibers spring back and the vulnerable, weak aorta gets stretched out over time by the force of the blood. As it widens, the aorta weakens additionally.

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Aortic dissection is major cause of death in Marfan syndrome

At 30 years of age, men with MFS have an annual risk of death of about 2%, and women have a risk of about 1%, 20–40-fold increased risk compared with the United Kingdom population of the same age. The mean age at death in affected people is 44 years for men and 47 years for women, and about 70% die from acute CV complications, mainly AoD.

It is not a surprise, having in mind that in MFS aorta is impaired and aorta is the largest and the strongest artery in the body, carrying roughly 200 million liters of blood through the body in an average lifetime. A clinical hallmark and the major cause of morbidity and premature death in MFS was and remains aortic root dilation and associated aortic regurgitation, dissection, and rupture. Vice versa, MFS is one of the most important risk factors for AoD especially in the young.

Beta-blockers are standard therapy for aortic dissection

As a result of earlier detection, better follow-up and both surgical and medical treatment, average life expectancy in MFS have been increased by 30 years or more. Beta-blockers (BBs) retard the rates of aortic dilatation and AoD in MFS. The story started in 1959, when it was announced that reserpine had prevented aortic rupture in susceptible turkeys, and continued in 1965, with successful treatment of AoD without surgery, i.e. with antihypertensive drugs. The experience with propranolol ability to slow aortic root dilatation and dissection in MFS was published in 1971.

BBs are the standard treatment for MFS, since the only randomized clinical trial of Shores et al. suggests that BBs should remain the first-line treatment of aortic dilatation in MFS. In a small (17 patients) randomized double-blind trial, the ACE inhibitor perindopril reduced aortic stiffness and even aortic root diameter compared to placebo when given to adult MFS patients in addition to BB treatment for 24 weeks.

To our knowledge, there is no more randomized, double-blind clinical trials with other drugs published, but a couple of them (mostly with angiotensin receptor blockers) are ongoing. One interesting trial compares effects of losartan vs. nebivolol vs. the association of both on the progression of aortic root dilatation in MFS. Losartan antagonizes TGF-β, which has been shown to prevent aortic elastic fibre degeneration. Nebivolol exerts antistiffness effects, and aortic stiffness is increased and relates to aortic disease progression in MFS.

BBs in uncomplicated arterial hypertension: not the first-line antihypertensives anymore

BBs have been used in arterial hypertension (AHT) for decades, but their role in uncomplicated AHT was challenged for the first time in 1998. “The time has come to admit that BBs should no longer be considered appropriate for the first-line therapy of uncomplicated AHT.” Compared with other antihypertensives, BBs are less effective for preventing CV events in patients with uncomplicated AHT. Moreover, two recent meta-analyses showed that despite reducing brachial BP, BBs was not effective in reducing CV events when compared with either placebo or other antihypertensive agents. BBs increases peripheral vascular resistance, which in turn may increase central aortic pressure and wall stress.

BBs lower central aortic BP to a lesser degree even when BP measured by sphygmomanometry is reduced substantially. Given the strong relationship between central aortic BP and target organ damage, the effectiveness of BBs may be overestimated in practice on the basis of conventional BP measurements alone. Despite a “beneficial” effect on the brachial BP, which is surrogate end point, BBs failed to favorably affect the clinical end point, i.e., coronary artery disease and CV mortality and all-cause mortality. The increase in the augmentation index reported after BBs result s in increased central systolic BP in hypertensive patients. Thus, BBs could have a deleterious effect on LV-aortic coupling, LV afterload, LV hypertrophy, and, ultimately, the risk of CV events. The fall in pulse
rate is an obvious mechanism for the higher central BP with BB-based therapy noted in the Conduit Artery Function Evaluation (CAFE) study.\(^{45}\)

BBs’ side effects are also important, including: precipitation of diabetes mellitus, little effect on regression of LV hypertrophy, likely failure to improve endothelial function, weight gain and decrease in exercise endurance.\(^{35,46}\) Thus, National Institute for Clinical Excellence downgraded BBs from the first-line drug choice for uncomplicated AHT. In head-to-head trials, BBs were usually less effective than a comparator drug at reducing major CV events, in particular stroke. Atenolol was the BBs used in most of these studies and, in the absence of substantial data on other agents, it is unclear whether this conclusion applies to all BBs. BBs are not a preferred initial therapy for AHT. However, BBs may be considered in younger people, particularly: those with an intolerance or contraindication to angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, or women of child-bearing potential, or people with evidence of increased sympathetic drive.\(^{47}\)

On the contrary, European Society of Hypertension and of the European Society of Cardiology recommended: “BBs may still be considered an option for initial and subsequent antihypertensive treatment strategies. ...they should not be preferred, however, in hypertensives with multiple metabolic risk factors including the metabolic syndrome.”\(^{48}\) Contemporary titles in leading medical journals give us also picture about current status of BBs: “Beta-blockers in hypertension: adding insult to injury”?\(^{49}\), “Hypertension in the elderly: a compelling contraindication for β-blockers”?\(^{50}\), “Beta-blockers in hypertension—The emperor has no clothes”?\(^{37}\).

**Importance of central aortic (and carotid) blood pressure**

Although the differences between central (aortic and carotid) and peripheral BP have been known for decades, the consequences of decision-making based on peripheral rather than central BP have only recently been recognized.\(^{50}\) Although brachial measurement may accurately determine diastolic BP, it does not necessarily reflect systolic BP. This is mainly attributed to the fact that BP waveform is distorted as it travels outward from the heart due to the presence of wave reflections from the peripheral arteries.\(^{51}\) Brachial systolic and pulse pressures tend to overestimate central systolic and pulse pressures, especially in younger subjects who have more pronounced amplification, but also in older people, especially with tachycardia, exercise, use of vasoactive agents, or in those with systolic heart failure.\(^{52,53}\) The superior prognostic utility of central compared with brachial BP was demonstrated in an unselected geriatric population\(^{54}\) in patients with coronary artery disease, in patients with end-stage renal failure, etc.\(^{55}\) Moreover, young African-American men have greater central BP, despite comparable brachial BP compared with young white men.\(^{14}\)

Central (aortic and carotid) pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of CV disease. It is aortic systolic BP that the LV encounters during systole (afterload), and the aortic pulse during diastole is a determinant of coronary perfusion.\(^{14,51,52}\) More and more clinical studies suggest that central BP may provide additional information regarding CV risk beyond peripheral BPs.\(^{50–52,55–58}\) Recent findings suggest that the pulsatile component of BP (when represented by central pulse pressures or central pulsatility) is one of the most important factors determining event-free survival, because it accelerates atherosclerosis and leads to plaque rupture in coronary arteries.\(^{50}\) Recent large-scale trials have shown that central hemodynamics may provide a worthwhile treatment target.\(^{52}\) ACE inhibitors, angiotensin receptor blockers and dihydropyridine calcium blockers diminish central BP.\(^{59}\)

Effects on central pressures may not be evident by pressure measurements in the periphery, because the reflected wave is added to a different part of the central waveform. This may explain why drugs with similar reduction in peripheral pressures have a differential impact on CV outcomes.\(^{52}\) Important multicenter trials gave rise to the hypothesis that blockers of the renin–angiotensin system, may reduce CV outcomes beyond (peripheral) BP control, perhaps by decreasing also central BP and protecting from subclinical organ damage.\(^{52}\) Besides, there is compelling evidence regarding the detrimental effect of BBs (mainly atenolol) on central BP.\(^{59}\) However, the prognostic role of central as opposed to peripheral BP needs to be further confirmed in more large-scale observational and interventional studies.\(^{48}\).

**Blood pressure in the aorta (central blood pressure) is important for aortic dissection genesis**

The strong argument for the abovementioned statement comes from the fact that AHT is recognized as the most important cause of AoD.\(^ {34}\) Central pulse pressure is a major determinant of ascending aorta dilation in MFS.\(^ {40}\) Over time, and presumably as a consequence of central BP and waves acting on the stiff aortic wall, the aortic diameter enlarges, which increases the risk of AoD.\(^ {3}\) In patients with malignant AHT, reducing BP to normal but not reducing the rate of change in the central arterial pressure with respect to time (dP/dt) did not prevent AoD but apparently increased its risk.\(^ {21,61}\) The theoretical reason suggested for the beneficial effect of BBs on Marfan aortas was the decrease in the rate of change in central arterial pressure (dP/dt).\(^ {3}\) Central pulse pressure, which takes into account wave reflections and aortic stiffness, is a better determinant of ascending aorta diameter than brachial pulse pressures in MFS patients, independently of age and body surface area.\(^ {6}\)

**Vasodilating BBs decrease also central (aortic) blood pressure and they are recommended in arterial hypertension**

Atenolol may even increase central BP.\(^ {59,62}\) Hemodynamic effects of vasodilating BBs clearly differ. Carvedilol and labetalol appear to cause vasodilation through α-1 receptor blockade; nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide bioactivity. Their favorable hemodynamic profile includes reduction of pulmonary vascular resistance, while maintaining or improving cardiac output, stroke volume, and LV function, whereas nonvasodilating BBs tend to raise pulmonary vascular resist-
tance and reduce cardiac output and LV function. Compared with conventional BBs, vasodilating BBs have beneficial hemodynamic effects including decreased pressure wave reflection from the periphery, leading to decreases in central aortic BP 42, 63–65. Nebivolol improves endothelial function, leading to a reduction in arterial stiffness, with beneficial hemodynamic effects including reductions in central aortic BP 42, 62, 63. Central hemodynamic at rest and during exercise were recorded 1 h and 2 h after carvedilol tablet and the results indicated a combined BBs and vasodilating effect 66.

Besides, vasodilating BBs have been preferred in AHT due to metabolic profile 66, 67, 68. Namely, non-vasodilating BBs have higher potential to elevate blood glucose and cholesterol level. The risk which should not be neglected, as Messerli et al. 69 warn: in uncomplicated AHT, diuretics and BBs should no longer be considered for the first-line treatment. The trade-off of lowering BP at the expense of increasing risk for diabetes mellitus by up to 10% yearly is not acceptable. The risk for diabetes mellitus is greater with atenolol, in the elderly, and in studies in which BBs were less efficacious antihypertensive agents and increased exponentially with longer duration on BBs 67. BBs have been shown to inhibit pancreatic insulin secretion (via β-2 receptors), worsen insulin resistance, cause weight gain, diminish peripheral blood flow, and lead to increased glycogenolysis (by unopposed α-2 action), all of which are implicated in adverse glycemic control. This is not a class effect, and BBs with intrinsic sympathomimetic effects, β-1 selective blockers with β-2 agonist properties, and newer noncardioselective BBs with vasodilating properties (such as carvedilol) have minimal effects on glycemic control 67.

Metabolic studies evaluated the effects of vasodilating BBs, such as dilevalol, carvedilol and celiprolol, on insulin sensitivity and the atherogenic risk factors. None of them decreased insulin sensitivity, as has been described for the BBs with and without β-1 selectivity. This supports the idea that peripheral vascular resistance and peripheral blood flow play a central role in mediating the metabolic side effects of the BBs, as the vasodilating action (either via β-2 stimulation or α-1 blockade) seems to more than offset the detrimental effects of the blockade of β (or β-1) receptors 70. Indeed long-term CV outcome in AHT treated with carvedilol or nebivolol is still not known 65.

Vasodilating BBs decrease also central (aortic) blood pressure: should not they also be considered in Marfan syndrome to prevent aortic aneurysm and aortic dissection?

Our idea is: if BBs with better impact upon central BP are preferred in AHT, why should not they also be preferred in MFS to prevent aortic aneurysm and AoD? Namely, central BP means BP in the aorta, where also the prevention target in MFS is. If vasodilating BBs have the advantage in AHT due (among others) to better performances at this particular site (aorta), they may be also better suited for MFS as well. Metabolic profile of vasodilating BBs may be additional argument to consider them as the first line choice for patients with MFS, because prevention is expected to be prolonged, usually life-long.

A word of caution is needed, because neither we have a definite proof from large trials that central BP is clearly superior prognosticator, nor that vasodilating BBs improve outcomes in terms of survival and freedom from myocardial infarctions and strokes better than classical BBs.

Finally, there are two premises, i.e. sentences from the literature. The first is: central pulse pressure is a major determinant of ascending aorta dilation in MFS 6. The second follows: compared with conventional BBs, vasodilating BBs have beneficial hemodynamic effects including decreased pressure wave reflection from the periphery, leading to decreases in central aortic BP 63. The conclusion is obvious from the premises: vasodilating BBs may have the advantage in preventing aortic complications in MFS. Indeed, to obtain a valid conclusion, promises should be checked.

A PubMed search for terms: “central blood pressure Marfan” retrieved 11 papers, and for “central blood pressure Marfan beta blocker” only two (30th March. 2010). None of them had evaluation of the potential role of vasodilatory BBs in the prevention of aortic aneurysm and AoD in MFS.

Conclusion

In the recent guidelines for arterial hypertension BBs (in the absence of compelling indications) have been removed from the first-line antihypertensive therapy – in part due to insufficient efficacy in decreasing central BP. It is probable that central (aortic) BP reduction is central for the prevention of aortic dilatation, AoD and rupture in MFS. Thus, the same inefficacy of classic BBs to decrease central BP may be the reason to consider them less effective in the prevention of aortic aneurysm and AoD in MFS. On the other hand, vasodilating BBs might have larger efficacy in decreasing central BP and thus in delaying aortic complications in MFS. Metabolic profile of vasodilating BBs should be another argument to use them in MFS, because a prolonged application is expected. This issue deserves more attention, in order to better prevent catastrophic diseases (aortic aneurysm and AoD) in MFS. Indeed, randomized controlled trials as well as large registries’ data are needed to obtain a more precise answer.

REFERENCES


Received on December 8, 2010. Accepted on April 8, 2011.