Beta-blockers: focus on mechanism of action

Which beta-blocker, when and why?

Frauke GORRE[1], MD; Hans VANDEKERCKHOVE[2], MD

[1]Department of Cardiology, University Hospital Ghent; [2]Department of Cardiology, General Hospital St. Lucas, Ghent, Belgium.

Beta-blockers are a heterogeneous group of antihypertensive agents. What they have in common is competitive antagonistic action on beta-adrenoreceptors (B1, B2 and B3). They differ in their receptor selectivity, intrinsic sympathomimetic activity (ISA), vasodilating properties and metabolism. Antihypertensive mechanisms and effect differ according to receptor-specificity and ISA, where differences in duration of action also have to be considered. An unfavourable metabolic profile of beta-blockers was reported based on studies describing the metabolic side effects of weakly-selective or non-selective agents. Newer generation beta-blockers appear to have a metabolic neutral profile. In systolic heart failure, three agents proved to improve survival up to 30%, mainly because of B1-blocking and/or vasodilating properties. The position of beta-blockers in treating diastolic heart failure remains uncertain. Beta-blocker therapy in coronary artery disease also leads to uncontested survival benefit, the cardioprotective mechanism largely due to rate reduction. This paper aims to describe the basis of heterogeneity of the available agents and to translate this into their applicability in different cardiovascular diseases, with focus on the underlying physiopathological mechanisms.

Keywords: *Adrenoreceptor – beta-adrenoreceptor antagonist – sympathetic nervous system.*

Mechanism of action and classification of beta-blockers

Adrenoreceptors. The mechanism of action of beta-blockers (BBL) is heterogeneous, incompletely understood and different for available agents[1]. As a basic principle, BBL antagonize adrenergic stimulation of beta-adrenoreceptors (B-AR) in a competitive way through their structural similarities to catecholamines. In addition to stimulating B-AR (B1, B2 and B3), catecholamines also stimulate alfa-adrenoreceptors (A-AR) (A1 and A2)[2,3]. B3-AR remain inactivated in basal conditions but impose negative inotropic effects in intense adrenergic stimulation. They also mediate lipolysis and thermogenesis. Catecholamines affect the *cardiovascular system* by influencing the central nerve system (preganglionic neurons), sympathetic ganglia (postganglionic neurons), the heart, peripheral arteries and the kidney (figure 1). The orthosympathetic nerve system is affected both on the central and peripheral level. Activation of central A2-AR inhibits sympathetic activity, which is further modulated at postganglionic neurons, where noradrenergic release is inhibited by presynaptic A2-AR stimulation (a negative feedback mechanism) but stimulated by activating B2-AR[3,4]. The heart contains B1-AR in excess to B2-AR in a 70/30 ratio. Stimulating B1 and B2-AR results, via cAMP-dependent intracellular pathways, in positive inotropic, chronotropic, lusiotropic and dromotropic effects[3]. Adrenoreceptors on smooth muscle cells in arterial walls mediate vasoconstriction (A2-AR) and vasodilation (B2-AR). At the renal level, release of renine out of juxtaglomerular cells is B1-AR mediated and sympathetic stimulation of the adrenal medulla results in epinephrine release. Adrenoreceptor-dependent mechanisms *outside the cardiovascular system* are, among others, regulation of carbohydrate metabolism through hepatic and skeletal muscle glycogenolysis (A1- and B2-AR), pancreatic insulin release (B2-AR) and lipolysis (B1 and B3-AR), tremor (skeletal muscle contraction through B2-AR stimulation) and bronchodilation (B2-AR mediated relaxation of smooth muscle cells).

The effect of beta-blockade on the heart is heterogeneous. The *anti-ischaemic mechanism* will be discussed later. In addition, there is *anti-arrhythmic* activity. Beta-blockage decreases spontaneous depolarization

Address for correspondence: Dr. Frauke Gorré, Department of Cardiology, University Hospital Ghent, De Pintelaan 185, BE-9000 Gent, Belgium. E-mail: frauke.gorre@ugent.be

Received 4 June 2010; accepted for publication 8 June 2010.

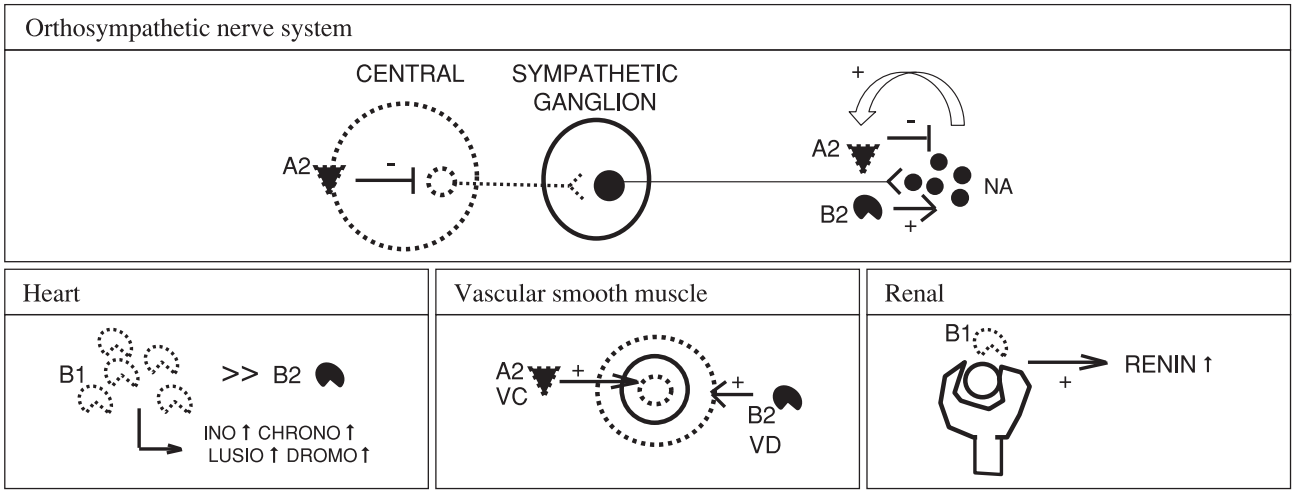

Fig. 1. – Adrenoreceptor-mediated effects of catecholamines on the cardiovascular system. A2: alpha-2 adrenoreceptor; B1: beta-1 adrenoreceptor; B2: beta-2 adrenoreceptor; Chrono: chronotropy; Dromo: dromotropy; Ino: inotropy; Lusio: lusiotropy; NA: noradrenalin; VC: vasoconstriction; VD: vasodilation.

Table 1. – *Overview of pharmacologic properties of different beta adrenoreceptor antagonists.*

	Receptor selectivity		B1-ISA[3]	Metabolism		Vasodilatory mechanism		
	B1[1] selective	B1- SI[2] (ref 6)		Renal	Hepatic	Alpha lytic	NO[4]	B2[5]-ISA
Acebutolol	O		O	O				
Atenolol	O	16		O				
Bisoprolol	O	30		O	O			
Carvedilol		4			O	O		
Celiprolol	O	33	O	O				O
Labetalol					O	O		
Nebivolol	O	295		O	O		O	O
Metoprolol	O	8			O			
Pindolol			O	O				
Propranolol		2			O			
Sotalol				O				

Molecules with vasodilating properties are located in the grey area. [1]Beta 1. [2]Selectivity index (as given in reference 6). [3]Intrinsic sympathomimetic activity. [4]Nitric oxide. [5]Beta 2.

of pacemakers, causes prolongation of sinus node cycle length, atrioventricular conduction times and atrioventricular refractory period, a class II anti-arrhythmic activity. Sotalol has class III anti-arrhythmic properties, with prolongation of the action potential of the myocardial cells, and thus QT interval[2]. Other anti-arrhythmic mechanisms are reduction of myocardial ischaemia and catecholamine-induced hypokalaemia. Finally, *left ventricular structure and function* is modulated by reducing myocardial ischaemia and catecholamine-related release of free fatty acids in myocardial adipose tissue, modulating myocardial gene expression, inhibiting myocardial apoptosis and reducing myocardial oxidative stress[1].

Receptor selectivity and vasodilating properties. Due to excess B1-AR compared to B2-AR in the heart, B1-selectivity is often referred to as "cardio"-selectivity. No organ contains only B1- or B2-AR and no agent is completely B1-selective[2,3]. Cardioselectivity is dose-dependent, with selectivity decreasing when doses increase. *First-generation beta-blockers* are non-selective agents. *Second-generation agents* bind more to B1- compared to B2-AR, a selectivity that is different for the different agents available. *Third-generation or vasodilating beta-blockers* are structurally different from classic BBL, leading to A1-blocking, B2-stimulating, NO-generating, anti-oxidant and/or anti-inflammatory properties[3,5]. The vasodilatory activity leads to improvement of endothelial function and antihypertensive action with little effect on cardiac output. Their effect on various clinical end points has yet to be described. The mechanism of vasodilation of each molecule is different and shown in table 1.

Intrinsic sympathomimetic activity (ISA). BBL with ISA are agents having partial agonist (thus catecholamine) activity on certain B-AR[2]. B1-ISA on the

heart is most evident at rest with absent negative chronotropic effects in the resting state. On the renal level, B1-ISA reduces suppression of renine-release. A partial B2-ISA (e.g. nebivolol) induces vasodilation by acting on smooth muscle cells of the peripheral vessels. Electrically, BBL with ISA lower the threshold for ventricular fibrillation.

Metabolism. Lipophylic agents undergo hepatic clearance, have long half-lives and penetrate the blood brain barrier, causing more central neurologic side effects. Hydrophilic products undergo renal clearance, have shorter half-lives resulting in multiple-day dosage and only penetrate the blood brain barrier when doses are high. Agents with mixed profile undergo both hepatic and renal clearance[2].

Table 1 offers an overview of some of the properties discussed in a selection of frequently used agents.

Beta-blockers and hypertension

The blood pressure-lowering mechanism is incompletely understood. As a basic mechanism, a cardio-inhibitory effect reduces cardiac output. This in turn is followed by a baroreflex-mediated proportional increase in peripheral vascular tone to maintain blood pressure. This "vascular resistance" is described in B1-selective as well as non-selective agents, thus not depending on B2-blocking action[2,3]. Lowering of blood pressure finally occurs because of incompletely understood late lowering of peripheral vascular tone, minutes to hours after oral intake of the BBL. This way, agents with ISA can lower blood pressure at rest while preserving cardiac output. Possibly, inhibition of the abovementioned presynaptic B2-AR on noradrenergic nerve endings – thus reducing circulating noradrenaline levels – contributes to the late vasodilation but this cannot explain the effect in B1-selective blockage[2]. Other possible blood pressure-lowering mechanisms are a B1-AR-mediated decrease in adrenal medulla catecholamine release or anti-renin activity in conditions with high circulating renin, and thus catecholamine concentrations.

Are all beta-blockers equally effective? Most authors consider antihypertensive action of different agents to be equal when administered in equipotent doses[4]. However, antihypertensive activity is dependent on ISA, with reduced lowering of blood pressure at rest but not during exercise-induced sympathetic activation[7], and B1-selectivity because of reduction in peripheral vasodilation and unopposed alpha-mediated vasoconstriction in non-selective products[8]. Also, duration of action of the different agents has to be considered, as a once-daily dosage regimen of short-acting agents (e.g. atenolol) results in absence of activity in early morning, when most cardiovascular and cerebrovascular events occur[9].

Are beta-blockers as effective as other classes of antihypertensive agents? A 2008 Cochrane review, with the BBL studied in reviewed articles mainly being non-selective propranolol and moderately selective atenolol, concludes that the antihypertensive potency of BBL is superior to placebo but inferior to diuretics, calcium channel blockers (CCB) and inhibitors of the renin-angiotensin-aldosterone system (RAAS-i)[10]. There was no survival benefit compared to placebo. Incidence of stroke was higher with the BBL studied than other antihypertensive agents, probably due to lesser blood pressure reduction. Studies with newer generation agents in primary hypertension are needed.

A so-called ***"pseudo-antihypertensive property" of beta-blockers*** has been described in, among others, the CAFE trial, which reports in a subgroup of the ASCOT population a higher central aortic pressure in the atenolol/thiazide arm versus the amlodipine/perindopril arm, despite a similar reduction in brachial pressures[11]. This is largely due to heart rate lowering in beta-blockade, with in-creasing amplitudes of reflected arterial pressure waves as heart rate decreases[12], and is a possible explanation for less favourable results on regression of left ventricular hypertrophy with BBL compared to other antihypertensive drugs[13]. This pseudo-antihypertensive effect is not as pronounced in super-selective and vasodilating, but less heart rate-lowering nebivolol[5].

Hypertension and age. Increased sympathetic activity in hypertensive young adults seems to be associated to body mass index and insulin resistance, resulting in increased peripheral vascular resistance and mainly diastolic hypertension[14]. In the elderly, raised levels of circulating catecholamines are secondary to a reduced B-AR (and thus BBL) response[15]. Hypertension in elderly subjects is mainly systolic and secondary to reduced arterial compliance, not increased vascular resistance[14]. In the elderly, BBL are not first-line agents in the treatment of hypertension but proved to be beneficial in coronary artery disease and heart failure, indications for which they are under-used[15]. Changing pharmacokinetics should be taken into account when using BBL in an elderly population.

The metabolic issue

Effects on glucose metabolism. The diabetogenic effect of non-selective beta-blockage results from a decrease in pancreatic insulin secretion, decreased insulin sensitivity secondary to a reduced peripheral blood supply, increased body weight and increased gluconeogenesis through glycogenolysis secondary to unopposed alfa 2 activity. The definition of the term "new onset diabetes" (NOD), meaning newly arisen diabetes mellitus under antihypertensive treatment, is vague and often not specified in studies. A large

meta-analysis studied the prevalence of NOD in a hypertensive population treated with BBL, with the BBL being studied (propranolol, metoprolol, atenolol) being not or only moderately selective[16]. Beta-blockage resulted in an approximately 30% increased risk of NOD compared to placebo and a 20% increased risk compared to CCB and RAAS-i. When comparing BBL to thiazide diuretics, data are less uniform, reporting neutral[17,18] to less diabetogenic effects[16] of BBL. Data concerning diabetogenic effects of non-thiazide diuretics are lacking[19]. The diabetogenic profile of BBL does not represent a class effect. Receptor selectivity is important, with decreasing negative metabolic impact with increasing B1-selectivtiy[20]. BBL with vasodilating activity also show little or no metabolic side effects. There is no consensus regarding the significance of antihypertensive therapy-induced diabetes on major end points[15]. The negative impact of hyperglycaemia on cardiovascular end points is possibly (partially) compensated for by the antihypertensive action of the therapy, although in general a negative prognostic significance of new diabetes in hypertensive patients receiving therapy is assumed[17,18].

Effects on lipid metabolism. First- and second-generation BBL are considered "atherogenic" because they influence the distribution of the different subgroups of lipids unfavourably (lowering HDL, increasing LDL and triglyceride). The lipase responsible for degrading triglycerides is inhibited by unopposed A-AR stimulation in beta-blockade[2]. HDL-lowering possibly is ISA-dependent[13]. Third-generation BBL exert a neutral or beneficial effect on the lipid profile. Data concerning impact on outcome are lacking.

Beta-blockers and heart failure

Pathophysiology. Myocardial systolic dysfunction is associated with neurohumoral hyperactivity (sympathetic nerve system and renin-angiotensine-aldosteron system (RAAS), amongst others)[3]. Although beneficial in the early stages of heart failure, by contributing to preservation of inotropy, eventually this results in negative cardiac remodelling and progression of heart failure. In heart failure, increased serum concentrations of norepinephrine, angiotensine II, aldosterone, endothelin, vasopressin and cytokines are observed, all negatively influencing cardiac structure and function. In the setting of sympathetic hyperactivity, a protective adaptation by downregulation of B1-AR has been described. The role of B2- and B3-AR in heart failure is less clear. No downregulation of B2-AR occurs, with a possible role for these receptors in anti-apoptotic mechanisms. The importance of heart rate lowering in itself, independent of attenuation of sympathetic tone, remains unclear. Time course of changes in myocardial structure and function after initiation of BBL was studied in 26 patients with dilated cardiomyopathy receiving RAAS-i. Initiating treatment with metoprolol in a titrated manner initially leads to reduced left ventricular ejection fraction and increased left ventricular end systolic volume. These variables improved from a duration of therapy of one month and three months onward[21], respectively. After 18 months, reduced ventricular mass and improved geometry was reported. Next to neurohumoral effects of BBL in heart failure, anti-ischaemic properties are also to be considered and will be discussed later on.

Which beta-blocker, in what type of heart failure, and how? *In heart failure with reduced ejection fraction*, three molecules proved a reduction of about 30% in mortality and/or hospitalization: long-acting metoprolol succinate[22], bisoprolol[23] and carvedilol[24]. The beneficial effect is due to B1-blocking[8] and/or vasodilating actions. Agents with B1-ISA and non-selective molecules have a less favourable profile. B2-blockage leads to peripheral vasoconstriction with increased afterload due to unopposed alfa-action. The beneficial results of carvedilol, although being a non-selective molecule, can be explained by its alfa lytic activity. In this heart failure population there is a possible role for nebivolol (selective and vasodilating), as a similar survival benefit is suggested in a retrospective subgroup analysis of the SENIORS-trial, namely in a subgroup of patients with similar patient characteristics concerning age and ejection fraction as in the trials with metoprolol, bisoprolol and carvedilol[25]. *In managing heart failure with preserved ejection fraction*, the position of beta-blockers as well as other pharmacologic therapies remains unclear. The underlying mechanisms differ from those in heart failure with reduced ejection fraction[26]. Until now, no therapy could prove a beneficial effect on mortality. For now, focus is on the underlying mechanisms and co-morbidities (hypertension, diabetes, coronary artery disease, obesity, etc.) along with control of volaemia through diuretics[27]. Initiation of beta-blocker therapy in heart failure must happen in a carefully titrated manner. The CIBIS-III trial showed that the common sequence of initiating ACE-inhibitors before BBL is as good as the opposite order[28].

Beta-blockers, coronary artery disease and the importance of heart rate

Pathophysiology. Myocardial ischaemia results out of imbalance between oxygen supply and oxygen demand. Increased adrenergic tone associated with cardiac ischaemia induces lipolysis and thus higher plasma and myocadial concentration of free fatty acids[2], with oxygen demands being higher in metabolizing free fatty acids compared to carbohydrates. Haemodynamic changes also increase oxygen demand, most importantly increases in heart rate and blood pressure (pressure-rate

product). Areas of ischaemic myocardium are less oxygenated because of catecholamine-induced alteration of coronary perfusion, with redistribution of blood supply away from ischaemic areas and shortened duration of diastole. Also, platelet aggregation is increased. The cardioprotective effect of betalysis in coronary artery disease is largely based on its heart rate-lowering effect. This has been studied mainly in post-myocardial infarction settings, in which reduced incidence of re-infarction and all-cause mortality showed proportional to reduction in heart rate[29]. In the absence of symptoms of heart failure, non-dihydropiridin calcium antagonists also reduce the risk for cardiac events and mortality post myocardial infarction. A placebo-controlled study with timolol showed a mortality reduction of 41.6% in the timolol arm, but mortality for a given heart rate was similar for timolol and placebo[30]. Pathophysiologic mechanisms underlying the cardioprotective effect of heart rate reduction are, amongst others, beneficial effects on the arterial wall because of lesser mechanical pulsatile stress and lesser pro-inflammatory processes secondary to oscillating shear stress on the endothelium[29], resulting in slowed progression of coronary atheromatosis, increased plaque stabilization and arterial compliance. Next, there is a beneficial modulation of the abovementioned myocardial oxygen balance. Betalysis increases coronary artery tone, a B1 effect possibly secondary to the reduced oxygen demand at lower heart frequencies[31]. The impact of first- and second-generation BBL on coronary flow reserve (CFR) in hyperaemic states is not clear, study results are not uniform. Amongst vasodilating BBL, carvediol and nebivolol have been shown to increase CFR, not solely due to decreased flow at rest.

Effects of betalysis in different subgroups. Most guidelines are based on studies dating from the pre-revascularization era. *Betalysis in chronic, stable coronary artery disease* improves symptoms, not survival[1,14]. *In ST-elevation acute myocardial infarction (STEMI)*, complete infarction is established 12 to 24 hours after onset[2]. Betalysis in the early stages of infarction relieves symptoms and reduces infarct size and frequency of arrhythmias, the effects on short-term mortality being unclear[1,2]. Betalysis in secondary prevention, initiated a few days to a month after acute myocardial infarction, is associated with a survival benefit of 20 to 25% by reducing cardiac mortality, sudden death and re-infarction. A placebo-controlled benefit has been shown for propranolol, metoprolol, timolol, acebutolol and carvedilol[1]. The indication for betalysis in *non-ST-elevation acute coronary syndromes* was largely extrapolated from data in STEMI and small studies in unstable angina, and aims to control ischaemia and prevent evolution to STEMI[32]. *In vasospastic angina* BBL are contra-indicated because of associated elevation in resting coronary artery tone. In the *perioperative management of high-risk non-cardiac surgery* guidelines advise patients with a high risk profile to continue beta-blockers when already administered or to initiate them up to a week prior to surgery, in a titrated manner, thereby avoiding hypotension and bradycardia and associated peri-operative mortality[33].

Conclusion

In understanding the proper use of beta-blockers in cardiovascular pathology, their mechanism of action has to be understood. One should consider receptor selectivity, vasodilating properties and duration of action when choosing a certain agent. In hypertension, the position of beta-blockers remains a point of discussion, with available data largely based on studies with older molecules and studies with newer generation agents lacking. Beta-blockers have established a solid position in the treatment of arrhythmias, heart failure and coronary artery disease. The profile of third-generation agents with vasodilating properties is promising and they begin to prove beneficial in large outcome studies.

Conflict of interest: none declared.

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