REVIEW

Cardiovascular Therapeutics

Cardio-Selective Beta-Blocker: Pharmacological Evidence and Their Influence on Exercise Capacity

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SUMMARY

For the past 40 years, beta-blockers have been widely used in cardiovascular medicine, reducing morbidity as well as mortality. Beta-blockers are currently used in a number of cardiovascular conditions such as systolic heart failure, postmyocardial infarction, and in prevention and treatment of arrhythmias. They are not recommended as the first line antihypertensive therapy, particularly in the elderly, unless there are specific indications. Despite the benefits of beta-blockers, tolerability concerns in patients with co-morbidities have limited their use. Some of these problems were overcome with the discovery of cardioselective beta-blockers. The third generation beta-blockers have additional properties of vasodilatation and advantages in terms of minimizing the adverse effects of beta-blockers. Some of the advantages include improvement of insulin resistance, decrease in cholesterol as well as alleviation of erectile dysfunction. Acute treatment with beta-blockers modifies local muscular metabolic properties and impairs endurance exercise capacity whereas the influence of chronic is debated controversially.

Introduction

β-adrenoceptor blocking agents (beta-blockers) were first discovered in 1962 by Sir James Black at the Imperial Chemical Industries in the United Kingdom [1]. The development of propanolol is considered one of the most important contributions to clinical medicine and pharmacology and Sir Black was consecutively awarded the Nobel prize in 1988. In combination with ACE inhibitors, antiplatelets and statins beta-blockers were proven to reduce cardiovascular mortality and morbidity by as much as 90% in acute coronary syndromes [2].

Beta-blockers have evolved ever since form their origin as treatment for angina and cardiac arrhythmia to be very successful therapeutics in large variety of diseases as hypertension, glaucoma, migraine just to name a few. However, the mechanism of action of beta-blockers probably differ within the class and are not fully understood yet. Newer third generation beta-blockers exhibit additional properties including the improvement of insulin resistance, decrease in cholesterol as well as alleviation of erectile dysfunction.

Furthermore, cardiovascular conditions are common in the general population and thus are also common in athletes or patients who are physically active. When choosing a drug for these patients, providers should choose an agent that has favorable effects on blood pressure and minimal detrimental hemodynamic change during exercise. This review discusses the pharmacological properties of cardioselective beta-blockers, their clinical use in cardiovascular medicine as well as their influence on exercise capacity.

Mechanism of Action of Beta-Blockers

β-adrenergic receptors are essential regulators of cardiovascular homeostasis. Three different types of beta-receptors have been identified by molecular pharmacology: β1, β2, and β3 are variably distributed in different tissues [3, 4]. β1 receptors are predominantly located in the heart and make up to 75% of an all b-ARs, while β2 receptors are found in vascular and bronchial smooth muscle [5]. β3 receptors are located in the adipocytes where they are presumed to be involved in the fatty acid metabolism [6, 7]. In addition, ß3-adrenoceptors have been described in

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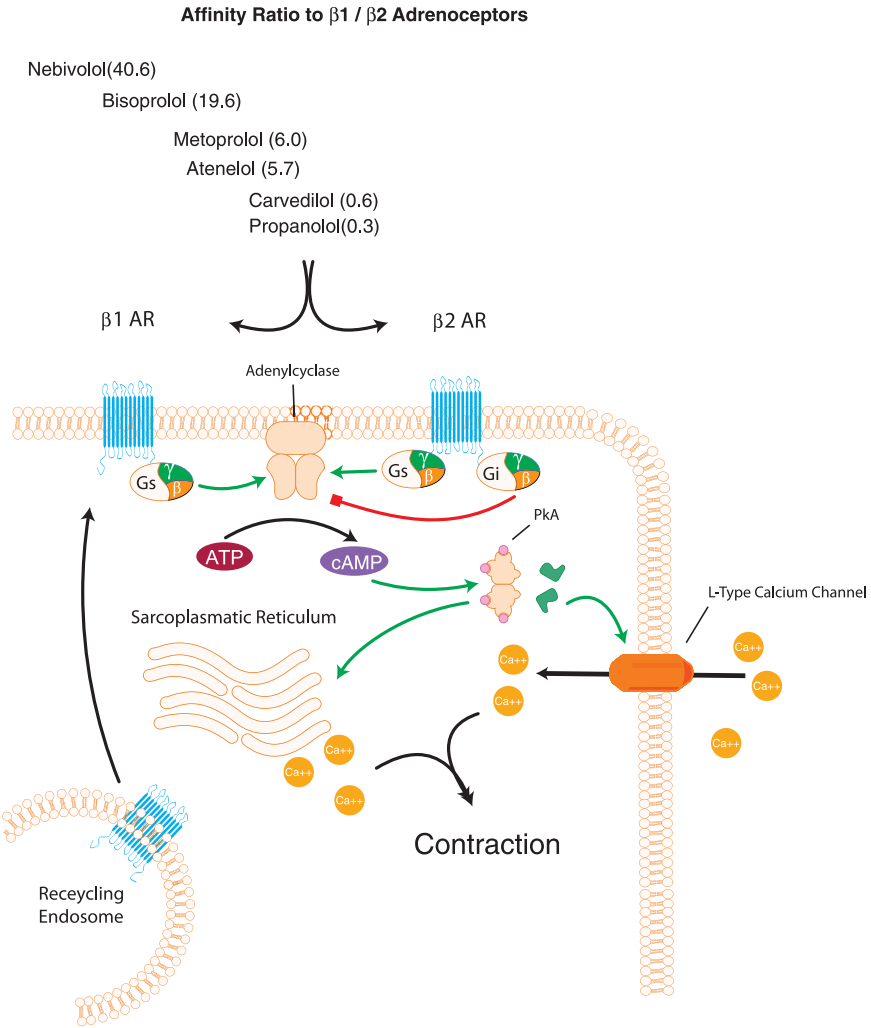

Figure 1 Comparison of the affinity ratio to the β1 and β2-adrenoceptor for currently available beta blockers and intracellular signal transduction. Under agonist action β1 and β2 receptors promote the formation of cAMP by interacting with adenylate cyclase via activation of the Gs protein. Moreover β2 receptors have also been found to couple with Gi and decrease adenylcyclase activity. cAMP facilitates the PKA phosphorylation which then activates the calcium release channel (ryanodine receptor) as well as the SERCA activity. Increased cytosolic calcium results in an increased contraction of the heart muscle cell.

cardiomyocytes, where they make up a population of about 5% of the ß-AR [8], as well as in endothelial cells [9]. Furthermore, a putative β4 receptor has been reported to exist in the heart [10], however there is now evidence that this putative receptor is another activation status of the ß1-AR [11].

All beta-blockers cause a competitive inhibition of the β receptor and counter the effects of catecholamines. The β2-adrenoceptor, like the β1-adrenoceptor, is a G-protein coupled receptor that couples to Gαs-proteins. If activated it stimulates an increase in intracellular cAMP via the adenylyl cyclase (Figure 1) [12]. Moreover the cyclic AMP Q1 (cAMP) response element binding protein (CREB) is activated by beta-adrenoceptor signaling [13]. cAMP, the second messenger, activates protein kinase A (PKA) which phosphorylates the membrane calcium channel and hence increases calcium entry into the cytosol. In addition, PKA enhances calcium release from the sarcoplasmic reticulum. The increase in calcium loading leads to an positive inotropic effect. The lusitropic effect is caused by phosphorylation of troponin I and phospholamban by PKA, which increase the calcium reuptake by sarcoplasmic reticulum [14].

Chronically increased noradrenaline levels induce downregulation of β1-adrenoceptors and alter signal transduction [15]. In failing human hearts noradrenaline concentration is increased in left ventricular biopsies [16], which leads to a reduction of myocardial β1-AR as a hallmark of CHF. β1-AR downregulation is associated with a reduction in the re-uptake of [11C]-hydroxyephedrine by neural terminals in the myocardium [17]. Thus the less efficient disposal of catecholamines from the synaptic cleft contributes to myocardial β-AR downregulation. In parallel with the alterations of the ß1 (as well as the ß2)-AR an upregulation of Gi-proteins has

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been described [18]. All these reactions result in a massive depression of cardiac contractility. ß3-AR expression has been shown to be upregulated and this further contributes to the depression of cardiac force by the release of nitric oxide, which has been shown to impair cardiac force of contraction [19].

Clinical Pharmacology

Beta-Blockers are in general well absorbed after oral administration [20]. The plasma half-life of beta-blockers is significantly shorter than their biologic half-life with esmolol having the shortest half-life of about 10 min [21]. The water-soluble beta-blockers (e.g., Atenolol) have in general longer half-lives, tend to be nonmetabolized, and excreted unchanged via the kidney [22]. In contrast, Lipid-soluble beta-blockers (e.g., metoprolol) have shorter half-lives and are metabolized mainly in the liver [23].

Currently, beta-blockers can be categorized based on their receptor affinity and hemodynamic properties: the absence or presence of cardioselectivity and vasodilatory effects. The mechanisms of vasodilation are vasodilation mediated either via nitric oxide (carvedilol, nebivolol) or via α receptor blockade (labetalol, carvedilol) [24]. Carvedilol and nebivolol are in addition antiproliferative, antioxidant and block the expression of several genes involved in myocardial damage [25]. Nebivolol reduces interleukin-1alpha, cyclooxygenase-2 (COX-2), and tumor-necrosis-factor (TNF)-alpha-induced protein, while the beta-blocker metoprolol increases inflammatory genes [26]. Tumor necrosis factor-α (TNF-α) is a pluripotent mediator of inflammation involved in atherogenesis inducing a pro-inflammatory activation of macrophages [27]. COX-2 is an inducible enzyme that is expressed in response to inflammatory cytokines and is responsible for the synthesis of proinflammatory PGs such as PGE2, which is chemoattractant for leukocytes [28].

Another criterion that distinguishes a smaller group is the presence of intrinsic sympathomimetic activity (ISA). These beta-blockers have lately been suspected to increase peripheral vascular resistance and attenuate the decreases in heart rate and cardiac output that may negate any benefit in a cardiovascular disease population [29]. Examples of beta-blockers with this property are acebutol and pindolol.

Noncardioselective beta-blockers such as propanolol cause an equal blockade of β1- and β2-adrenergic receptors while vasodilating effects are absent [30]. Beta-blocker such as atenolol and metoprolol have a higher affinity for the β1 receptor and are therefore deemed cardioselective. Nevertheless, with increasing doses some β2 effects may appear [30]. These beta-blockers have no vasodilatory properties. Noncardioselective beta-blocker as carvedilol exerts equal blockade of the β1- and β2-adrenergic receptors, while exhibiting vasodilating properties due to α1-receptor blockade [31]. One of the newest agents is the cardioselective and vasodilating beta-blocker Nebivolol. Nebivolol has demonstrated to have the highest cardioselectivity of any currently available beta-blocker [32]. In addition, nebivolol exhibits vasodilatory properties not related to α1-receptor blockade but instead the vasodilatation mediated by nitric oxide (NO) [33].

A recent pharmacological study has shown that several of beta-adrenoceptor antagonists of the first and second generation currently in clinical use for hypertension, heart disease and, more recently, heart failure have poor selectivity between adrenoceptor subtypes 1 and 2 in whole-cell assays [34].

Table 1 Use of beta-blockers in AHA/ESC guidelines

Strong evidence	
Secondary prevention post-MI	- improve survival (I A) - prevention of sudden death (I A) - prevention of re-infarction (I A)
Chronic heart failure (CHF)	- prolong survival (I A)
Some evidence	
Acute myocardial infarction (AMI)	- relief of ischemic pain (I B) - control arrhythmia (I B) - prevention of sudden death (I C) - limit infarct size (IIa A)
Weak evidence	
Hypertension (HTN)	- recommendation as first-line therapy in uncomplicated HTN withdrawn - (currently guidelines are debated)

Clinical Uses and Comparisons

The benefit and clinical indications of beta-blockers have been clearly defined in many cardiovascular conditions and clinical settings (Table 1). In patients at risk for coronary vascular disease a meta-analysis of 18 randomized long-term, placebo-controlled trials found treatment with beta-blockers associated with a reduction in the risk of stroke by 29%, coronary heart disease by 7%, and heart failure by 29% [35]. In a large meta-analysis in post-MI patients beta-blockers proved to reduce significantly morbidity and mortality, regardless whether selective or nonselective beta-blockers were used [36].

Beta-blockers are among the standard therapy for heart failure patients [37], although only bisoprolol, metoprolol, and carvedilol have proven themselves in large randomized trials [38–40]. Some studies suggest that beta-1 selective blockers have a slightly greater antihypertensive effect than the nonselective blockers. Evidence that beta-2 blockade does not contribute to the antihypertensive effect of beta-blockade originates from a study with the beta-2 selective blocker ICI 188 551 [41]. Support is drawn from early observations that adrenaline in presence of beta-2 blockade produces a greater rise in blood pressure compared to its beta-2 vasodilator action [42]. Beta-2 blockade may antagonize the modest background vasodilator effect of circulating adrenaline that explains the 2–3 mmHg greater fall in blood pressure seen with beta-1 blockade as opposed to nonselective block [43]. Beta-blockers with ISA seem to have a reduced clinical benefits in post-MI patients, so that these agents should be avoided in this population [36]. Furthermore, these agents have also been observed to have a negative effect on heart failure in high-risk patients [44].

The anti-arrhythmic effects of beta-blockers are mainly related to their capacity to inhibit beta-receptor-mediated adrenergic neural activation [45]. The ability of the beta-blockers to slow conduction and increase atrioventricular node refractoriness is useful

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Table 2. Comparison of beta-blockade affecting exercise capacity

Study	Drug	Condition	Results
Dubach 2002	Bisoprolol	Heart failure	Exercise capacity ↑
Issa 2007	Bisoprolol	Heart failure	Exercise capacity unchanged
Nodari 2003	Atenolol	Heart failure	Exercise capacity unchanged
	Nebivolol	Heart failure	Exercise capacity ↑
Patrianakos 2005	Nebivolol	DCM	Exercise capacity ↑
Diehm 2011	Nebivolol	Heart failure	Exercise capacity unchanged
Dalla Libera 2010	Nebivolol	Heart failure	Prevents muscle wastage thus improves exercise capacity
Patrianakos 2005	Nebivolol	Heart failure	Exercise capacity ↑
	Carvedilol	Heart failure	Exercise capacity ↑
Suazzi 1999	Carvedilol	Heart failure	No effect, pulmonary dysfunction improved
Agostini 2002	Carvedilol	Heart failure	Exercise capacity ↑
Volterrani 2011	Carvedilol	Heart failure	Exercise capacity unchanged
Nessler 2008	Carvedilol	Heart failure	Exercise capacity ↑
Witte 2005	all	Heart failure	Exercise capacity ↑
Beloka 2008	Bisoprolol	Healthy	Exercise capacity ↓
Vankees 2000	Bisoprolol	Healthy	Exercise capacity ↓
Van Bortel 1992	Nebivolol	Healthy	Exercise capacity unchanged

in the prevention and treatment of supraventricular arrhythmias [46]. These drugs are also effective in arrhythmias related to excessive cardiac adrenergic stimulation such as those associated with thyrotoxicosis, pheochromocytoma, exercise, and emotional stress [47–49]. Beta-blockers can prevent exercise-induced augmented ventricular ectopy in patients with coronary artery disease and treat arrhythmias associated with the mitral valve prolapse syndrome [50]. Furthermore, they are effective in reducing the number and complexity of ventricular contractions after myocardial infarction. Several studies have demonstrated a reduction in the incidence of sudden death after myocardial infarction [51].

Effects on Glucose and Lipid Metabolism

Diabetes and adipositas are growing concerns in the western societies but also in developing countries. In patients with diabetes and/or adipositas differences among beta-blockers may have significant clinical implication. Some studies suggest that beta-blockers even raise the risk of occurrence of diabetes as well as of dyslipidemia [52]. Metabolic changes involve blood sugar, $HbA1^c$, insulin-sensitivity, triglycerides, VLDL, and HDL, and are closely associated with beta-2 blockade [53]. Various mechanisms are discussed to explain these negative metabolic effects of beta-blockers. For once beta-blockers produce unopposed α1-adrenergic receptor activity, which may induce vasoconstriction, decrease skeletal blood flow, and reduce insulin-stimulated peripheral glucose uptake [54, 55]. Furthermore, beta-blockers may inhibit insulin secretion from pancreatic beta-cells [56]. Weight gain is another proposed mechanism of insulin sensitivity deterioration with beta-blockers, as beta-blockers are associated with increased body weight in numerous large studies [57] while weight gain is closely connected to insulin sensitivity reduction [58].

The nonselective beta-blockers (e.g., timolol and propranolol) are the most susceptible to cause these changes, followed by partially beta-1 selective agents (e.g., metoprolol and atenolol). In contrast in highly beta-1 selective agents (e.g., nebivolol [59] or bisoprolol [60]) the metabolic disturbances involving blood sugar, insulin-sensitivity, and lipids are almost completely absent [61]. This also applies for agents triggering alpha-blockade (e.g., carvedilol) [62] or beta-2 intrinsic sympathomimetic activity (e.g., nebivolol) [63]. Current guidelines for the management of hypertension emphasize beta-blockers as preferred agents for patients with concomitant diabetes [64].

Lately, there has been interest in the beta-3 receptor and especially in its role in obesity and diabetes. The beta-3 adrenoceptors are found in adipose tissue and in the skeletal muscle [65, 66]. Agonists at the beta-3 receptor lead to increased fat oxidation, lipolysis, and insulin sensitivity. On the other hand, blockade of beta-3 receptors are associated with weight increase and unfavorable metabolic changes [53].

Thus, beta-blockers differ regarding their influence on glucose or fat metabolism with respect to their molecular pharmacological mechanisms. These differences should be taken into account when treating cardiovascular patients with additional metabolic diseases.

Impact on Skeletal Muscle Adaptation and Exercise Capacity

The above-described influence of ß-blockers on glucose and fat metabolism may also influence skeletal muscle adaptation in situations of acute and chronic exercise and thus exercise capacity. The effects of beta-blockade on adaptations to aerobic exercise have been studied in healthy and hypertensive subjects under both acute and chronic conditions (Table 2, Figure 2).

Acute treatment with beta-blocking drugs modifies local muscular metabolic properties [67] and impairs endurance exercise capacity resulting in an increase in perceived exertion, lower VO2max, and lower work rate [68, 69]. Especially the

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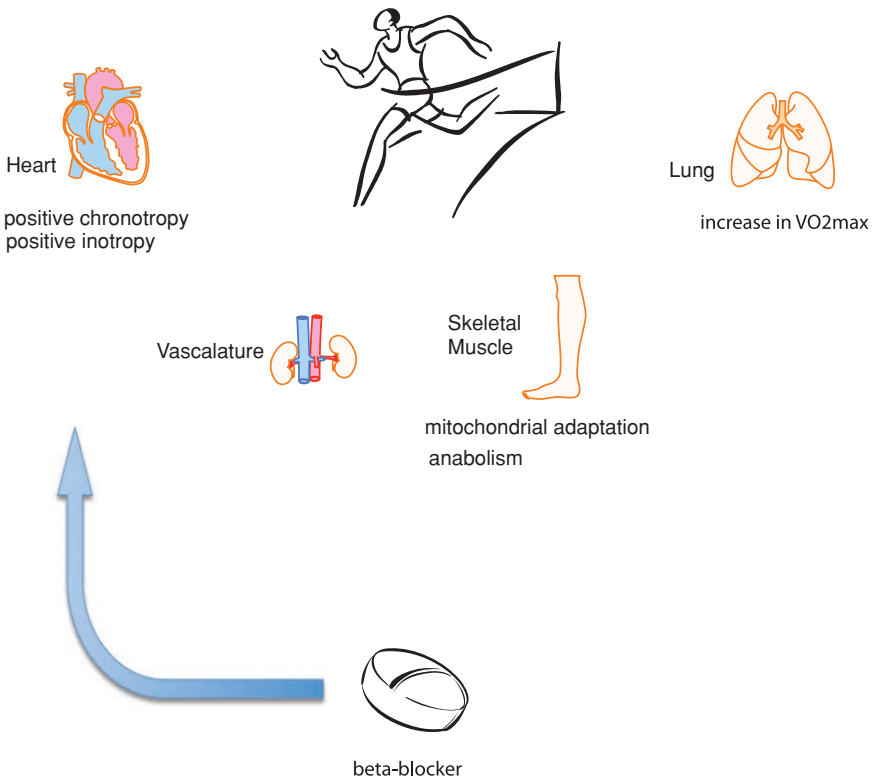

Figure 2 Treatment with beta-blockers affects physical activity. Beta-blockers reduce heart rate both in rest and under exertion. Acute treatment with beta-blocking drugs modifies local muscular metabolic properties and impairs endurance exercise capacity resulting in an increase in perceived exertion, lower VO2max and lower work rate. Nonselective beta-blockers can increase lactate levels during exercise through b2-associated peripheral vosoconstriction.

nonselective inhibitors, which also antagonize beta-2-receptors, can restrict aerobic training effects [70].

In normal subjects, beta-blocker treatment with metoprolol is associated with a decrease in sub maximal exercise $\dot{V}_E$ and in maximum O_2-uptake (VO_{2max}) [69]. However, as described above, differences may exist depending on the underlying molecular pharmacological effects of the respective ß-blocking agent. Nebivolol, for example, does not impair exercise capacity in healthy persons [71].

Depression of exercise capacity by at least some beta-blocking agents is due to limitation of oxygen convection to the muscles by decreased chronotropy and inotropy [72]. However, by a relative decrease in cardiac output and O2-transport the muscle metaboreflex during exercise may be enhanced, thus leading to increased chemosensitivity and activation of the sympathetic nervous system [72, 73].

Recent studies reported a marked increase of MSNA after acute ß-blockade associated with unchanged values of arterial blood pressure and baroreflex sensitivity. Acute ß-blockade also alters the oscillatory characteristics of MSNA, thus decreasing its effectiveness on peripheral vasoconstriction [74]. This reaction may counteract the above-mentioned suppression of the cardiopulmonary system and may contribute to an upregulation or at least compensation of exercise capacity when treated with ß-blocking agents. Data from animal studies confirm that beta2-blockade may impair the adaptation to endurance exercise to a greater extent than beta1-blockade [75]. In accordance metoprolol compared with carvedilol provided a greater effect in LV ejection fraction at rest and in LV stroke volume and stroke work during exercise. In contrast, carvedilol produces greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise [25].

Aside from the different physiological effects, ß-blocker treatment may also alter skeletal muscle und resting conditions as well as skeletal muscle adaptation toward exercise. It has been shown, for example, that one of the suggested mechanisms are mitochondrial adaptations. Mitochondrial function (succinate dehydrogenase and citrate synthase activity) can be increased by endurance exercise, while the response to training can be attenuated when animals or healthy subjects are treated with selective or nonselective beta-blockers. The impaired mitochondrial response may be due to a beta2-receptor-mediated decrease in PGC-1 [76, 77]. However, there is also evidence that ß-blockers like nebivolol (Libera, Vescovio 2010) or carvedilol (Della, Libera 2005) stop skeletal muscle wastage which is a common co-morbidity in heart failure patients.

Exercise-induced dyspnea in patients with heart failure may be related to sympathetic nervous system activation involving an increased metabo- and/or chemosensitivity [78]. Whether or not this mechanism plays a role in exercising normal subjects remains

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unclear. Studies by Beloka et al. suggest that decreased aerobic exercise capacity under beta-adrenergic blockade goes along with decreased ventilation regardless of the present metabolic rate [72]. Moreover, beta-blockade was shown to reduce the sensitivity of arterial chemoceptors to potassium stimulation during exercise, thereby modulating the regulation of exercise ventilation [79], although effects could be secondary to reduced cardiac output [80]. Duration of beta-blocker treatment prior to exercise testing seems not to significantly alter exercise responses [81].

Furthermore, beta-blockers affect the pulmonary mechanical function as well as gas diffusion. The respiratory system is characterized by a significant predominance of β2 receptors, in the airways and the alveoli [82]. Beta-receptors located in the alveoli influence gas exchange efficacy by regulating fluid reabsorption from the alveolar surface. Therefore, different β-receptor affinities result in different effects on the carbon monoxide diffusing capacity (DLCO). Long-term bisoprolol treatment leads to higher DLCO values because of changes in the active membrane transport under alveolar β2-receptor control [83]. In addition, carvedilol reduces hyperventilation by reducing peripheral chemoreflex sensitivity as suggested by increased PaCO2 with normoxia [84].

Overall, beta1-selective beta-blockers are preferable to nonselective agents for patients engaged in exercise training. Furthermore, beta-blockers affect several pathways or systems that ultimately can reduce exercise capacity during training.

Perspective

Beta-blockers are an important class of drugs that are widely recommended for the management of cardiovascular disease, heart failure, and hypertension. However, pharmacological differences among beta-blockers impact use in everyday practice. The clinical rationale for using beta-blockers is to antagonize the beta-1-adrenoceptor signaling to reduce the rate and force of cardiac muscle contraction. However, the beneficial mode of action in heart failure is still not understood. In an aging society, with increasing cardiovascular morbidity and thus rising use of beta-blockers, it is important to obtain information about the degree of physical impairment by the use of these drugs. This is especially true among young and physically active patients. In addition, people are increasingly taking more physical exercise as a consequence of the growing awareness of the importance and the lifestyle aspects of exercise.

Although highly selective beta-1-antagonists do exist, most of the beta-blockers available for clinical use are also antagonists at the beta 2-adrenoceptors, which are expressed at high levels in the airways, causing bronchospasm as a major side-effect of this therapeutic class. In a study by Baker the binding of a wide range of beta-adrenoceptor antagonists to stably expressed 1- and 2- adrenoceptors in an identical mammalian cell culture environment was measured [85]. It was shown that although great variation in the potency of clinically used beta-blockers for all receptor subtypes exist, these agents only showed little selectivity between 1 and 2 subtypes. Therefore, the clinical benefit of beta-blockers especially in heart failure is unlikely to be attributed to receptor affinity alone. Other factors, such as longevity of action at the receptors, presumably also play an important role.

Moreover, there is another controversy emerging for beta-blockers—the paradoxical hypothesis that beta-blockers might actually be beneficial in asthma is now being tested in clinical trials [86]. These studies were initiated after long-term exposure was shown to reduce lung sensitivity in a mouse model of asthma.

While research is moving forward we need to learn more about the complex pharmacology of adrenoceptors. Beta-blockers and exercise effects of it are still a matter of ongoing research. Lack of research evidence regarding possible drug and exercise interaction necessitates the close monitoring of patients undergoing pharmacotherapy. This includes tracking heart rate, rating of perceived exertion and blood pressure before, during and after exercise sessions. Overall there is clearly great potential for the development of beta-blockers with greater selectivity and less side-effects for a wide range of indications.

Conflict of Interest/Disclosure Statement

The authors have no conflicts of interest that are relevant to the content of this study.

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