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THE ACUTE AND CHRONIC EFFECTS OF BETA BLOCKADE ON DYNAMIC EXERCISE PERFORMANCE AND CARDIAC ADAPTATION TO DYNAMIC EXERCISE TRAINING

H. Bart Robbins, B.S.

APPROVED:

Major Professor

Committee Member

Committee Member

Chair, Department of Integrative Physiology

Dean, Graduate School of Biomedical Sciences

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H. Bart Robbins, B.S.

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Introduction

Widespread use of beta-adrenergic blocking agents as treatments for hypertension, ischemic heart disease and postmyocardial infarction has raised many questions concerning the effect of these drugs during exercise. Since exercise is often prescribed as an adjunct treatment in combination with beta blockade, the effect of these drugs on cardiac function during exercise is important to know. It is also important to ascertain if patients taking beta blockers will benefit from chronic dynamic exercise training the same way as normal subjects or if they should be viewed differently.

This review of the current biomedical literature is meant to elucidate the cardiac effects, both acute and chronic, of beta-adrenoceptor blockade during dynamic exercise. The acute effects during dynamic exercise and the compensatory mechanisms in the cardiovascular system will be outlined. I will further explore if and how beta blockade significantly affects cardiac adaptation to chronic exercise training. By reviewing the current literature I will show what is already known and will demonstrate where current knowledge is lacking and where further research is needed.

There are two questions which will be addressed by this research. The first question is: "What happens to the cardiovascular system during dynamic exercise when a beta blocker is present in the system?" This question deals with the acute effects of such agents on exercise performance and cardiac

function. The second question is: "What effect does beta blockade have on the cardiac adaptations to chronic dynamic exercise training?" This question examines areas of cardiac adaptation that have been postulated to be mediated by beta-adrenergic receptor stimulation (e.g. myocardial hypertrophy). I hypothesize that the acute effects of beta blockade on exercise performance are minimal, while the chronic effects on cardiac adaptation to dynamic exercise training may be significant.

Role of cardiac beta-adrenergic receptors during exercise

To adjust to the disturbance in resting homeostasis imparted by the exercise stimulus, a number of regulatory systems are called upon to return the body to a new level of homeostasis. Principal among these is the central nervous system, which is capable of making very rapid adjustments to large segments of the body. Specifically, the sympathetic nervous system and the adrenal glands play prominent roles in the acute response to the exercise. This is mediated via the release of the catecholamines epinephrine and norepinephrine, which have very powerful regulatory properties that exert control over a number of critical physiological and metabolic functions central to the ability to sustain physical exercise. Included among these responses are their capacity to affect cardiac function and metabolism, redirect blood flow to working muscles, and alter substrate mobilization and utilization.

These responses are specific to the target tissue involved as well as the type of adrenergic receptor (alpha-1 and alpha-2; beta-1 and beta-2) to which the catecholamines bind. Catecholamines are the first messengers of beta-adrenergic signaling that integrate and amplify chemical signals from outside the sarcolemma to effectors within the myocyte. This signal-transduction pathway involves the sequential interaction of beta-adrenergic receptors, G proteins, and adenylyl cyclase. Agonist binding to beta receptors causes interactions of receptors with coupled stimulatory GTP-binding regulatory G proteins (Gs), which, in turn, interact with membrane-bound catalytic subunits of adenylyl cyclase to increase intracellular concentrations of adenosine 3′,5′-cyclic monophosphate (cAMP). Intracellular cAMP then stimulates cAMP-dependent protein kinase, which signals multiple effectors in the nucleus and sarcoplasmic reticulum, contractile proteins, and ion channels, all serving to increase inotropy in ventricular myocytes and both chronotropy and inotropy in atrial cells (1,2)

Beta-1 and beta-2 receptors differ in their principal locations, in their relative sensitivity to norepinephrine and epinephrine, and in the functions that they mediate. The distribution of beta-adrenergic receptors in the heart has been determined both pharmacologically (3) and by quantitation of mRNA levels (4). In mammals both beta-1 and beta-2 receptors are expressed in the heart, with beta-1 predominating at an ~3:1 ratio in ventricles and an ~3:2 ratio in atria and conduction tissue (5).

Although they constitute a minority of the receptors in the human heart , beta-2 receptors are more efficiently coupled to adenylyl cyclase than beta-1 receptors (3). Beta-1 receptors are located at postsynaptic sites and have less affinity for the neurotransmitter norepinephrine than for the adrenal medullary hormone epinephrine. Both inotropic and chronotropic responses are mediated by beta-1 receptors. Recent work by Rohrer et al. (6) injected the anticholinergic atropine into beta-1 knockout mice and demonstrated that although vagal withdrawal is responsible for significant increases in heart rate, up to levels seen in mild to moderate exercise, the exercise-induced tachycardia present at moderate to heavy exercise workloads is predominantly mediated by beta-1 receptor stimulation.

Beta-adrenergic blocking agents

Beta blocking drugs bind reversibly with beta receptors to block the response to sympathetic nerve impulses and circulating catecholamines. Beta blockers are classified as either cardioselective or non-selective on the basis of their relative affinity for beta-1 and beta-2 receptors. Those with relatively strong affinity for beta-1 compared to their affinity for beta-2 receptors are considered cardioselective. Those with equal affinity for the two beta subtypes are deemed non-selective. Several of these drugs are currently available and the most commonly studied ones historically have been the nonselective agent propranolol and the cardioselective drug, metoprolol (7). Newer drugs in this class include carvedilol which also possesses alpha-1 blocking

properties. The medical indications for these drugs include hypertension, angina pectoris and cardioprotection following myocardial infarction.

Normal cardiovascular changes during acute dynamic exercise

The increase in cardiac output during exercise in normal subjects depends on increases in heart rate and stroke volume. However, an increase in stroke volume is the major component at low levels of exercise, while tachycardia is predominant at higher levels (8). This increase in cardiac output serves to meet the increased oxygen demands of working muscle, since dynamic exercise requires aerobically produced energy. According to the Fick principle, oxygen consumption (VO_2) = heart rate x stroke volume x (A-V O_2 difference), where A-V O_2 difference represents the difference in oxygen content between arterial and mixed venous blood. These are the variables most commonly measured when doing dynamic exercise research and they can all be measured both directly and indirectly. It is important in the setting of beta blockade research to remember that changing one variable (i.e., heart rate) while maintaining VO_2 constant requires compensatory changes in one or more of the remaining variables.

Several other metabolic and physiologic changes take place during dynamic exercise but it is beyond the scope of this paper to address them all. It is acknowledged however, that while cardiac output is increased by catecholamines, these substances also alter distribution of blood flow through alpha 1-, alpha 2- and beta 2-adrenergic receptors on vascular smooth muscle

(9). This allows the body to perform more work without a concomitant increase in cardiac output.

Acute effects of beta blockade during dynamic exercise

Studies have shown that beta-adrenergic blockade significantly reduces heart rate both at rest and during exercise (10). The degree of reduction varies depending on the drug and the dose used. Studies of older subjects (17), patients with hypertension (11), and patients with coronary artery disease (12) have all shown a significant decrease in heart rate at rest and during dynamic exercise with beta blockade. Animal models using rodents, dogs, and swine also noted similar declines in heart rate.

Changes seen in exercise performance and cardiac output are not as consistent. Although most authors find minimal changes in these parameters (11), others have demonstrated a significant decline (13). The previously cited study by Rohrer et al. (6) complimented the traditional pharmacological approach to studying receptor function with a genetic approach . They employed genetic ablation of beta-1 expression to allow for an unambiguous test of beta-1 function in the mouse. Based on its role in regulating cardiac inotropism and chronotropism, they expected that beta-1 function would be critical for maintaining both resting and maximal stress cardiovascular function. However, in mice lacking the beta-1 receptor they unexpectedly found that basal cardiovascular indices were essentially unaltered and, furthermore, that the capacity to perform graded treadmill exercise as

measured by VO_2max and total distance run, was normal. The failure to impact exercise performance occurred despite the fact that chronotropic reserve was severely blunted.

It is believed that increases in stroke volume and A-V O_2 difference compensate for the potentially negative effects of heart rate reduction due to beta-adrenergic blockade during exercise. The mechanism responsible for this paradoxical increase in contractility in the face of a relative decrease in beta receptor stimulation can be explained by the increased ventricular filling time and the Frank-Starling mechanism. Bevilacqua et al. (14) measured cardiac output by the CO_2 rebreathe method and found that during all levels of exercise, untrained subjects were able to maintain cardiac output despite large reductions in heart rate caused by beta blockade. This was accomplished by increasing stroke volume progressively to almost twice the levels achieved during placebo.

Results from pilot studies in my lab (22) found a trend toward decreased cardiac output with a significant increase in A-V O_2 difference when six subjects were intravenously administered the beta-1 blocker esmolol during submaximal bicycle exercise at 40% and 70% of VO_2max. Femoral arterial and venous blood O_2 content was not measured directly in this study but was calculated from respiratory gas O_2 and CO_2 concentrations and cardiac output data obtained with the acetylene rebreathe technique.

Another mechanism which would give similar results without an increase in tissue oxygen extraction from arterial blood, is the redistribution of cardiac output. The marked increase in plasma catecholamines seen with beta blockade at moderate to high exercise workloads act on alpha-adrenergic receptors in vascular smooth muscle and cause constriction of small arterioles. This occurs in working muscle as well as other vascular beds despite beta blockade (9). Pirnay et al. (15) evaluated femoral venous O_2 content directly during heavy exercise with and without beta blockade in subjects of varying fitness levels and reported that beta blockade reduced exercise femoral venous O_2 content in untrained subjects to levels similar to those observed in unblocked trained subjects.

Joyner et al. (16) noticed that these compensatory increases in stroke volume and A-V O_2 difference associated with beta blockade in untrained subjects are qualitatively similar to the changes in stroke volume and arterial-mixed venous O_2 difference that result from prolonged intense endurance exercise training. They hypothesized that trained individuals had already maximized these compensatory mechanisms and, therefore, they would be more hindered by beta blockade. In their study they compared trained and untrained subjects and found the ability to exercise submaximally was unaffected by beta blockade in both subject groups, while maximal exercise was affected more by beta blockade in trained subjects. At 60% of VO_2max both groups demonstrated large increases in stroke volume, which maintained

cardiac output at >94% of the unblocked values, meaning that minimal increases in A-V O_2 difference were required to maintain submaximal, steady-state VO_2. Since VO_2max was affected by propranolol more in trained vs. untrained subjects, this indicates that, from 60% VO_2max to VO_2max, trained subjects were either less able to make further hemodynamic adjustments (i.e., increase stroke volume) to increase cardiac output or, were unable to further increase A-V O_2 difference when compared with untrained subjects.

Cardiac adaptation to chronic dynamic exercise training:

Chronic dynamic exercise is known to elicit adaptations in the cardiovascular system that ultimately enable the trained person to achieve greater maximal levels of aerobic performance as reflected by an increase in maximal cardiac output and oxygen consumption. A significant amount of effort has been spent on elucidating the factors that underlie these adaptations.

Numerous studies have shown training induced improvements in maximal and submaximal work capacity are accompanied by several central cardiovascular adaptations which are considered to be signatures of the trained state. These fundamental adaptive changes, were recently confirmed in trained cyclists by magnetic resonance imaging and include a resting and submaximal exercise bradycardia, increased stroke volume, an increase in left ventricular end-diastolic dimension, and increases in left ventricular mass (18).

It should be emphasized that the effects of chronic exercise on stroke volume, heart rate and myocardial mass are generalizations that do not necessarily represent consensus viewpoints (23). This is not surprising because the body of evidence for or against specific adaptations of the heart to training are derived from studies across several different species using chronic exercise paradigms that vary significantly with respect to modality, intensity, and duration. The information presented above regarding the effects of chronic dynamic exercise training on ventricular morphology and function is meant only to serve as a point of reference so that the following review of and speculation about the possible cellular mechanisms of these cardiac adaptations can be discussed.

Considerable attention has been devoted to characterizing how a training-induced increase in maximal stroke volume is achieved, and a single consensus conclusion regarding the global mechanism(s) underlying this adaptation has been elusive. Some suggested mechanisms are: (1) augmented myocardial contractile function, (2) increased intrinsic compliance of the myocardium, (3) increased end-diastolic filling pressure secondary to training-induced blood and plasma volume expansion, (4) an increase in left ventricular chamber dimension secondary to myocyte growth.

While research exists to support each of these mechanisms there is a compelling body of evidence supporting the idea that these changes are largely due to an increase in intrinsic left ventricular chamber dimension (18-

21). Under conditions where training induces increased cardiac dimensions, it is thought to occur by myocyte hypertrophy as opposed to cardiocyte hyperplasia, because adult ventricular cardiocytes appear to be terminally differentiated and unable to re-enter the mitotic cell cycle (24).

Role of beta-adrenoceptors in exercise-induced cardiac hypertrophy

The possible mechanism for this cardiac hypertrophy is the subject for much research and the exact mechanism is not yet clearly understood. Repeated bouts of dynamic exercise disrupt cellular homeostasis which could lead to adaptive changes in levels of expression of specific proteins. It is possible that exercise associated alterations in the levels of specific intracellular constituents (e.g. second messengers, ions, and transcription factors) within the myocytes, selectively activate increased levels of expression of specific proteins. Conceivably, increases in ventricular dimensions would then establish a new level of myocardial homeostasis, decreasing subsequent exercise induced disturbances. Several factors present during dynamic exercise may provoke such cardiac adaptations. Alpha-adrenoceptor stimulation, increased stretch of the myocardium, and beta-adrenoceptor stimulation have all been proposed as possible inducers of hypertrophy. While evidence exists for each of these pathways the current discussion will be limited to the beta-adrenoceptor mediated mechanism.

In vivo, the role of catecholamine mediated beta receptor stimulation in cardiac growth regulation is difficult to evaluate independently of the

catecholamines' hemodynamic and inotropic effects. The alpha receptor mediated increase in peripheral resistance, by itself, might lead to cardiac enlargement via increased wall stress as postulated by the "stretch" hypothesis. To avoid this confusion, numerous studies have been done using cultured cell preparations..

As stated earlier, during intense exercise plasma levels of circulating catecholamines rise abruptly and stimulate beta-adrenergic receptors in the heart. This in turn causes increased adenylyl cyclase activity and a subsequent rise in intracellular cAMP. Studies have examined the effects of superfusing cultured ventricular myocytes with various elements of the beta stimulation cascade including the second messenger cAMP (28). Zhou et al. (29) investigated whether a cell permeable analogue of cAMP, dibutyryl cAMP (dbcAMP), can mimic the hypertrophic effect of beta2-adrenoceptor stimulation on cultured adult cardiomyocytes. They found that dbcAMP increased the rate of protein synthesis by ~38% compared to control cultures. Moreover, forskolin, a direct activator of adenylyl cyclase, also increased the rate of protein synthesis by ~22%. They further noted that the hypertrophic action of the non-specific beta agonist isoprenaline on cultured cardiomyocytes could be abolished by addition of Rp-cAMP, an antagonist of cAMP-dependent protein kinases. These results indicate that beta2-dependent induction of cellular hypertrophy on cardiomyocytes is mediated by cAMP and protein kinase A. Such research has demonstrated cardiac hypertrophy in

the presence of beta receptor stimulation. However, the application of these results to the physiologic condition of dynamic exercise can be debated.

A closer simulation of "real world" conditions is in vivo animal studies done with norepinephrine infusion at levels which do not induce hypertension. Chiba et al. (25) found that although body weight did not differ between control dogs and those continuously infused for two months with subhypertensive doses of norepinephrine (0.04 mg/kg/day), the heart weight and the heart to body weight ratio were both significantly increased in the infusion group compared with those in the control group. When pursuing this possibility it is important to remember that catecholamines stimulate both alpha- and beta-adrenoceptors which make it difficult to differentiate any beta-specific effect. Some authors have avoided this potential confounder by infusing the beta-agonist isoproterenol instead of norepinephrine. Although the results are often impressive, its relevance to the current discussion are suspect, since constant infusion with exogenous isoproterenol bears little resemblance to the transient increase in plasma catecholamines seen during intermittent bouts of dynamic exercise.

A better approach has been the addition of alpha- and/or beta-adrenoceptor antagonists to exogenous catecholamine infusion. Using this technique, Zierhut and Zimmer (27) demonstrated significant increases in the left ventricular weight/body weight and RNA/DNA ratios in rats receiving a constant intravenous infusion of norepinephrine combined with the alpha-

blocker prazosin with no increase in mean arterial pressure. Furthermore, the authors noted that although combination of norepinephrine and the calcium channel blocker verapamil, resulted in considerable reduction of mean arterial pressure and total peripheral resistance, the development of cardiac hypertrophy and the elevated RNA/DNA ratio were not significantly influenced. This data makes a strong argument for a beta-adrenergic mediated stimulus independent of alpha-adrenoceptors or hemodynamic parameters.

The best way to analyze the role that beta-adrenoceptors play in exercise induced cardiac hypertrophy would be to randomly divide healthy human subjects into four groups and then aerobically train two of the groups. One training group and one control group would receive beta blockers and the other groups would not. After sufficient training stimulus the cardiac parameters would then be measured and any differences between groups could be attributed to lack of beta receptor stimulation. Such a study was not found in my MEDLINE search of the past ten years of biomedical literature, although an animal study of similar design was located (30). That study evaluated the effects of eight weeks of endurance training (treadmill running at 0.5 m/s, 20% grade) on gross and microscopic alterations of rat heart muscle under the presence of either cardioselective (metoprolol) or non-selective (propranolol) beta-adrenergic blockade. It was shown that non-selective beta blockade with propranolol prevented the normal growth of the heart so that ventricular weights were significantly lower than those of the other training

groups. In addition, the response of the heart in rats undergoing metoprolol-training combination was not different from that seen in the rats trained without beta blockade. The authors concluded that blockade of both beta-1 and beta-2 receptors during training is necessary to produce the "atrophying" effect observed. This is further supported by Zhou's work (29) with cultured adult cardiomyocytes which showed that the increased rate of protein synthesis seen with isoprenaline was completely abolished in the presence of either the non-specific beta-antagonist propranolol or the beta2-specific antagonist ICI 118,551, but not influenced by the cardioselective antagonist atenolol.

A well designed prospective study using beta blockade and aerobic training was completed by Ades et al. using hypertensive human subjects (26). M-mode echocardiographic studies were performed at rest in three subject groups, (metoprolol, propranolol, placebo), before and after ten weeks of aerobic conditioning. Left ventricular end-diastolic dimensions, end-systolic dimension, septal thickness, posterior wall thickness, and heart mass were unchanged in all three groups following training. The authors noted that the increase in VO_2 seen in the placebo group (+24%) was larger, though not significantly, than the conditioning effects seen in the metoprolol group (VO_2 +8%). However, there was no conditioning-induced changes in resting stroke volume or in measures of cardiac anatomy. In contrast, the propranolol group did not demonstrate any training effect at all, as assessed by changes in aerobic capacity, stroke volume or cardiac dimensions. While these results

speak to a possible difference between beta-1 and beta-2 blockade and diminished training adaptation, the small sample size (N=31) and relative short training period make it difficult to achieve significant data.

Besides recognizing factors that evoke the hypertrophic response, it is important to identify the signal transduction pathways that transmit the hypertrophic signal to the nucleus and then induce specific changes in cardiac gene expression. One current model shows external hypertrophic stimuli such as catecholamines induce a receptor-mediated increase in cAMP which is transmitted by sequential phosphorylation of intermediate factors to mitogen-activated protein (MAP) kinase. The phosphorylated MAP kinase is then translocated into the nucleus, where it phosphorylates specific transcription factors that in turn activate or repress transcription of specific cardiac genes (31, 32). Much active research is currently underway to further clarify and describe the cardiac hypertrophic phenomenon at the molecular level.

Conclusion

This review of the current biomedical literature has discussed the decrease in heart rate that accompanies administration of beta blockers, both at rest and during exercise. It was shown that submaximal exercise performance can be maintained despite this relative bradycardia, by increases in stroke volume via the Frank-Starling mechanism and increases in oxygen extraction at the tissue level. These adaptations appear to be more limited at

high workloads in trained subjects, who have already maximized these compensatory mechanisms.

It was further demonstrated that exercise-induced cardiac hypertrophy may be partially mediated by catecholamine stimulation of beta-adrenergic receptors and the intracellular second messengers produced by such stimulation. There appears to be some attenuation of the adaptation to dynamic exercise training with beta blockade. There also appears to be a difference between the two sub-types of beta receptors, with beta-2 showing a stronger influence on cardiac hypertropy than beta-1. With this current evidence I would recommend that patients who must take beta blockers while participating in conditioning programs should be given a cardioselective agent when possible.

Future studies should look at this question by using human training protocols that are of adequate intensity and duration to elicit changes in myocardial dimensions. It would be worthwhile to use both cardioselective and non-selective agents to better differentiate the effects of the two receptor sub-types and help clinicians choose the best agent for their patients who must take these medications while participating in dynamic exercise programs.

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