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New Aspects on Training Bradycardia

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Dedicated to Professor Torsten Teorell

ABSTRACT

Rats were trained by treadmill running after chemical sympathectomy with 6-hydroxy-dopamine or during chronic beta receptor blockade. Contrary to untreated trained animals, sympathectomized rats did not get a reduction of the intrinsic heart rate after training despite an increased heart weight. In contrast, no cardiac hypertrophy occurred after training during beta adrenergic blockade but the heart rate during exercise was reduced in these animals. It is concluded that the training-induced bradycardia contains a lowering of the intrinsic heart rate and that this is not dependent on the stimulation of cardiac beta receptors or the magnitude of heart rate increase during exercise. The results also indicate that there is not a causal relationship between the training-induced bradycardia and cardiac hypertrophy. The latter conclusion is supported by an echocardiographic study in humans where no correlation was found between IHR and cardiac dimensions.

INTRODUCTION

A low heart rate (HR) at rest and during exercise at submaximal work loads is an effect of endurance training that has been recognized since long ago and since the beginning of this century attributed to an altered autonomic nervous activity, mainly an increased vagal tone (17). Recent investigations have shown that a lowered rate of the cardiac pacemaker (intrinsic heart rate, IHR) is part of the explanation to this bradycardia seen in physically trained individuals (18,4,9).

Still, however, the mechanisms for the lowering of IHR through training are known, and the investigations to be reported were undertaken to identify some factors of importance for this adaptation. We prefer to look upon physical training as an adaptation to an increased physical activity resulting in an increased capacity to perform this activity. Hereby follows that the circulatory and other adjustments at each exercise occasion, repeated at certain

intervals and for a sufficiently long duration induce the "training effects". By manipulation of the cardiovascular adaptation at each training session (e.g. the increase of oxygen consumption, stroke volume or HR) it would be possible to draw conclusions about the importance of these different factors for the development of training effects, in this context the training bradycardia and reduction of IHR.

In this paper are summarized such longitudinal training studies that have been carried out in rats. In a previous cross-sectional human study we have found evidence for a training-induced decrease of IHR also in man (9). As in many other studies we also found greater roentgenological heart volumes in trained than in untrained persons. We have now performed an echocardiographic study of endurance athletes to investigate whether there is any causal relationship between IHR and cardiac dimensions.

MATERIAL AND METHODS

Rats were trained by treadmill running. A method for recording of ECG during exercise and an exercise test for rats with stepwise increased treadmill speed to test the efficiency of the training program were developed (5). One group of rats was trained after chemical sympathectomy with 6-hydroxydopamine (6-OH-DA)(10). Littermate untreated rats were trained simultaneously. Both treated and untreated rats, littermates to the training ones, were kept as sedentary controls (16).

In a similar study one group of training rats and one sedentary group were instead treated with metoprolol, a cardioselective beta receptor antagonist (1) orally during the training period (11).

After a training period all rats were exercise-tested. In order to measure the IHR a denervation was performed including 6-OH-DA treatment, cutting of the vagus nerves and spinal cord destruction (pithing)(15). At the end of the experiment the hearts were weighed.

In a separate study hearts from trained and sedentary rats were investigated also in a modified Langendorff preparation, to ensure that the heart rates measured in pithed preparations represent the true intrinsic HR (12).

In the human study seven competitive cyclists of national elite class were investigated. They had been training regularly for 7-11 years and trained 600-1000 km/week at the time of the study. Physical characteristics are given in Table 1. They performed a maximal exercise test with determination of maxi-

mal oxygen consumption with the Douglas bag method and with recording of heart rate and blood pressure during exercise. On a separate day the test was repeated after the administration of atropine sulphate 0.04 mg/kg body weight and propranolol hydrochloride 0.25 mg/kg body weight as described previously (9).

TABLE 1. Physical characteristics and maximal oxygen uptake ($\dot{V}O_2$ max) in seven competitive cyclists.

	Age y	Height cm	Weight kg	$\dot{V}O_2$max l/min	$\dot{V}O_2$max ml/kg/min
Mean	24	179	68	4.9	72
±1 SD	±3	±7	±5	±0.6	±5

The echocardiographic examination was performed by one investigator (E.N.) before the exercise test. A 3 mHz ATL (Advanced Technology Laboratories) mechanical sector scanner was used for both 2-dimensional imaging and M-mode. All recordings were performed with the subject in the left lateral recumbent position, except for right ventricular dimension which was studied with the subject supine. The measurements on the M-mode recordings were performed following the recommendations of the American Society of Echocardiography (14). Echocardiographic stroke volume was estimated with the cube method. Left ventricular mass was calculated according to Bennett & Evans (2).

Standard statistical methods were used.

RESULTS

Exercise heart rate and intrinsic heart rate in rats.

At the exercise test after the training period trained untreated animals had significantly lower HR than the sedentary ones. Also after denervation and in isolated hearts there remained a significant HR difference between trained and sedentary rats (Fig 1).

There was an exercise HR difference also between sympathectomized trained and untrained rats. However, the treatment with 6-OH-DA resulted in higher HR than were found in untreated animals so that the HR of trained treated animals were similar to those of the untreated sedentary ones (Fig 2). In these animals there was no significant HR difference between trained and untrained rats after cardiac denervation or isolation.

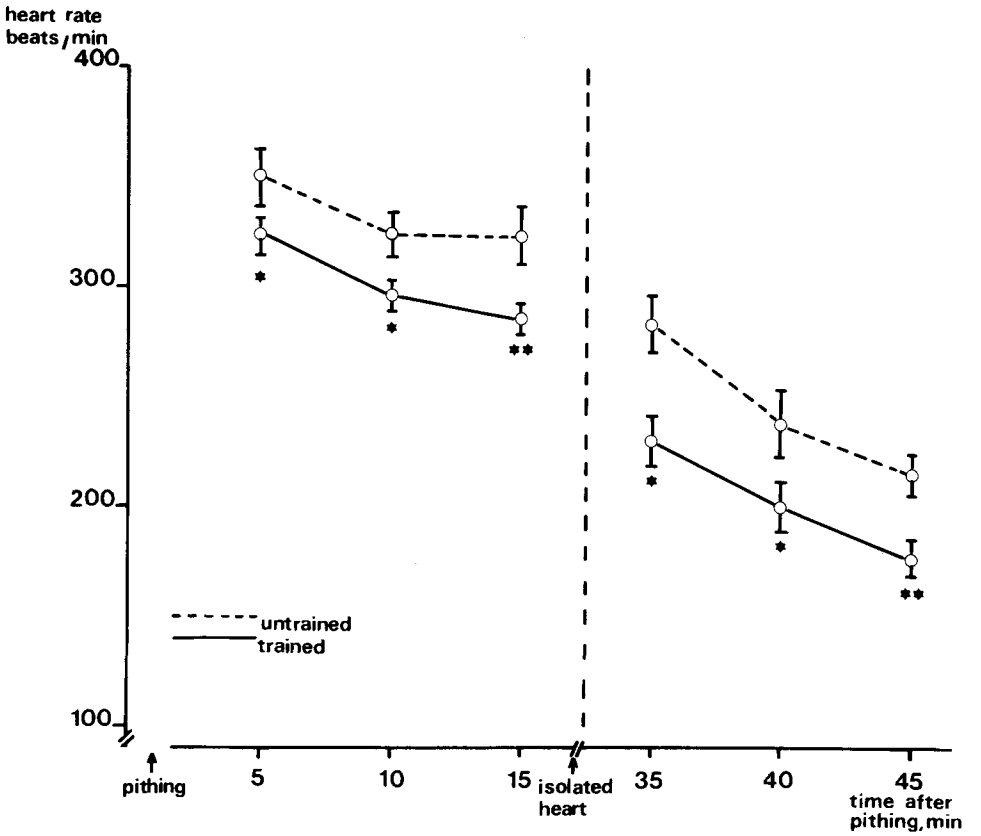

Fig 1. Heart rates in untreated trained and untrained rats after denervation (6-OH-DA, vagotomy and pithing) and in the isolated heart, mean values ±SEM. * $p<0.05$, ** $p<0.01$. From (12).

The metoprolol treated rats performed the exercise test three days after withdrawal of metoprolol, when plasma concentrations of the drug were shown to be negligible. Untrained rats had similar heart rates to the untreated sedentary ones. The trained metoprolol treated rats had significantly lower HR than both the sedentary animals and the trained untreated ones (Fig 3). In this study there was a slight but not significant IHR difference between trained and untrained rats, both in the untreated and the metoprolol treated group.

Heart weights of rats after training

In untreated animals, the average heart weight was significantly greater in the trained than in the untrained group (1.079 g ± 0.020 (S.E.) vs. 0.935 ± 0.014, $p<0.001$). Also the heart weight / body weight ratio (hw/bw) was greater in the trained animals, 3.811 0/00 ±0.062 vs. 3.293 0/00 ±0.069, $p<0.001$).

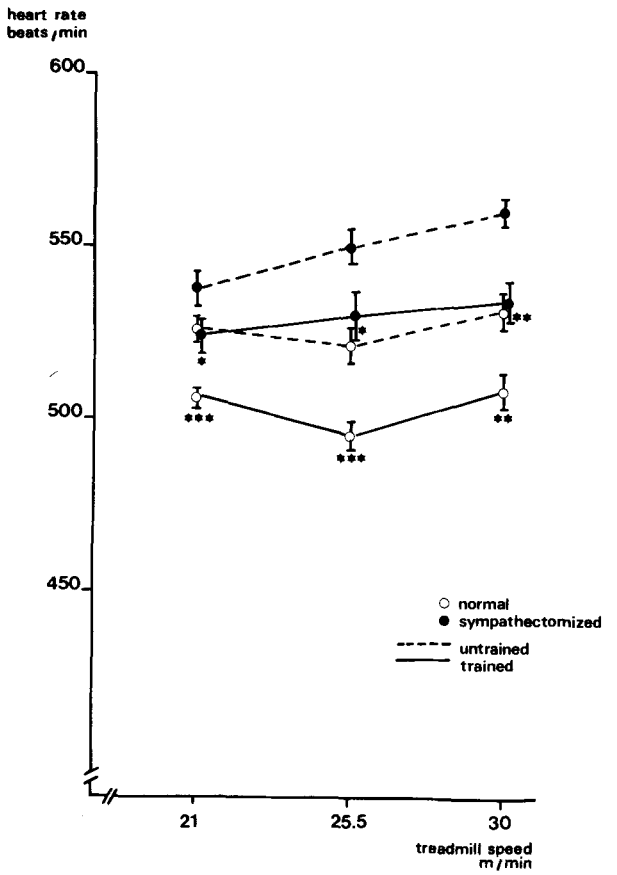

Fig 2. Heart rates during exercise at 3 different work loads in trained and untrained, untreated and sympathectomized rats, mean values ±SEM. Asterisks denote statistically significant differences compared to corresponding untrained group. * $p<0.05$, ** $p<0.01$, *** $p<0.01$. From (12).

6-OH-DA treated trained rats also had a significantly increased hw/bw ratio in one investigation (16) and both hw and hw/bw in the other study (12). Rats trained during chronic beta blocker treatment did not exhibit a cardiac hypertrophy (11).

IHR and cardiac dimensions in endurance athletes.

Heart rates and echocardiographic dimensions are listed in Table 2. The relation between IHR and left ventricular mass or left ventricular inner dimension is illustrated in Fig 4, showing that there was no striking correlation between these cardiac dimensions and IHR.

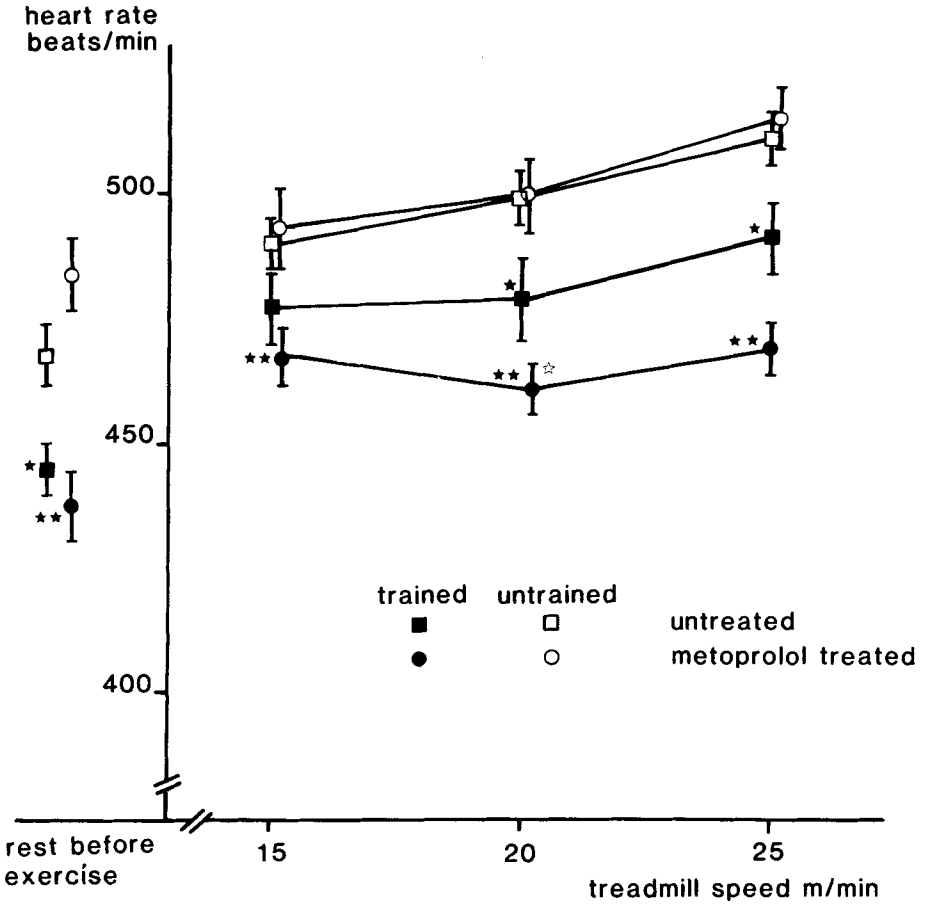

Fig 3. Heart rates at rest and during exercise at three different work loads in untreated rats and in metoprolol treated rats after withdrawal of metoprolol, mean values ±SEM.

★ : significant difference between trained and corresponding untrained group.

☆: significant difference between trained metoprolol treated and trained untreated group.

★,☆: $p<0.05$ ★★,☆☆: $p<0.01$

DISCUSSION

The group of endurance athletes is homogenous as regards physical characteristics and work capacity. Thus it is not representative of the general population but within this group there was no correlation between IHR and LV mass or LV inner dimension. This is in accordance with our animal experiments and findings by others (21) of a poor correlation between heart weight and heart

TABLE 2. Heart rates and echocardiographic dimensions in seven competitive cyclists.

	HR rest b/min	IHR b/min	LA mm	RVID mm	IVS mm	LVID mm	LVPW mm	LV-mass g	SV ml
Mean	52	81	37	18	12	58	12	380	130
±1 SD	±5	±13	±2	±4	±1	±3	±1	±65	±15

LA = left atrium; RVID = right ventricular inner diameter; IVS = interventricular septal thickness, LVID = left ventricular inner diameter; LVPW = left ventricular posterior wall thickness, SV = echocardiographic stroke volume.

rate. This indicates that IHR is not determined by cardiac dimensions only. The present animal experiments show that an increase in heart weight may occur without a lowering of IHR, as in the sympathectomized trained animals and that a training-induced bradycardia can develop without an increase of cardiac mass, as was seen in the metoprolol group. All this speaks against the bradycardia and reduction of IHR as direct effects of an increased LV dimension of myocardial mass.

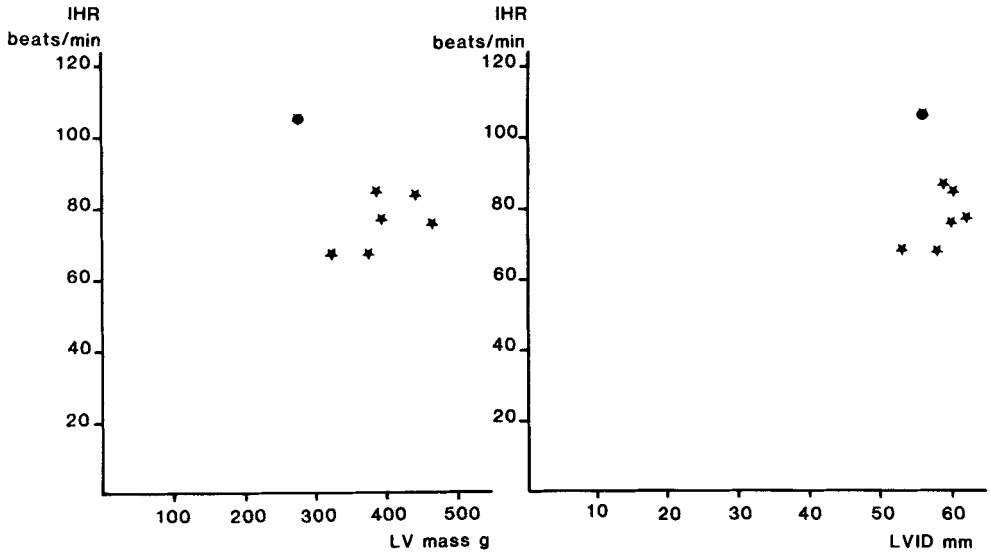

Fig 4. Relation between IHR and left ventricular (LV) mass estimated by echocardiography (left) and between IHR and left ventricular inner dimension (LVID)(right) in seven competitive cyclists.

Which cardiovascular adjustments during each exercise session may then act as stimuli for a reduction of exercise and intrinsic HR? This can not yet be completely answered but the hypothesis of the repeated heart rate increase above a certain level can be rejected since beta receptor blockade did not prevent the development of training-induced bradycardia. Likewise, 6-OH-DA treated animals that contrary to the beta blocked ones have an increased HR response to exercise (16) did not get a reduction of exercise HR or IHR. Chronic atropine treatment, resulting in repeated periods of tachycardia, is also reported not to alter the intrinsic rate of isolated atria in rats (7). A direct effect of catecholamines at the cardiac beta receptors is also unlikely since the development of training bradycardia was enhanced despite a diminished beta stimulation in trained rats receiving metoprolol. However, indirectly the adrenergic nerves are essential for the reduction of IHR since in the 6-OH-DA treated rats training did not have this effect. In accordance with this are the findings by Paynter et al (13) that a training-induced resting bradycardia did not occur in immuno sympathectomized rats.

It is well known from many animal species that the HR increases in response to acute mechanical stretch of the atria (8). The hypothesis has been set forth by Frick et al (6) and Blomqvist and Lewis (3) that this HR response to stretching may be reduced as an adaptation to the repeated atrial dilatation resulting from the increased venous return during exercise and that this phenomenon explains the lowered setting of IHR and also HR at rest and submaximal exercise after endurance training.

The results from training after pretreatment with 6-OH-DA or training during beta receptor blockade fit into this hypothesis. In 6-OH-DA treated animals the enhanced tachycardia during exercise shortens diastole, thereby preventing an increased diastolic filling and the reduction of IHR. The negative chronotropic effect of the beta-blockade on the other hand would augment the atrial dilatation because of increased stroke volumes during exercise.

Thanks to the contributions of Teorell (19, 20) it is known that there exists in the heart not only an electromechanical but also a mechanoelectrical coupling of events. The reported results support the theory that this relationship can undergo adaptation and imply that a diminished HR response to atrial stretch could be the mechanism for the lower IHR setting in trained individuals.

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