Differential Effect of Physical Exercise Routines on Ventricular Myosin and Peripheral Catecholamine Stores in Normotensive and Spontaneously Hypertensive Rats

Heinz Rupp

The influence of the adrenergic system on the population of ventricular myosin isoenzymes under physiological conditions was assessed by subjection of normotensive and spontaneously hypertensive rats (SHR) to different types of physical exercise that increased the activity of the peripheral adrenergic system to varying degrees. The routines, which were 5–6 weeks in duration, involved the mild exercise of enforced swimming (2×90 min/day), spontaneous running (daily, about 15 km/10–12 hr) that resulted in absolute ventricular hypertrophy, and enforced running of low intensity (daily, 2×1.8 km/3 hr) but associated with marked stressors. Swimming and spontaneous running reduced the high blood pressure of SHR, whereas enforced running increased it. In both strains, the myosin isoenzymes were redistributed in the direction of V, after swimming but not after running. In SHR, therefore, reduction of pressure load seems insufficient for induction of a higher proportion of V1. The unique and, until now, unexplained effect of swimming was attributed to the pronounced activation of the peripheral adrenergic system as judged from catecholamine stores of ventricles and adrenal glands. Only swimming increased the norepinephrine content of ventricles and adrenal glands in normotensive rats. Swimming also had the strongest influence in SHR. Further evidence for the influence of the adrenergic system came from the effect of selective cardiac β-blockade with atenolol (50 mg/kg/day). The diminished adrenergic drive of the heart reduced the proportion of V1 to a greater extent in the swimming rats than in the sedentary rats. Taken together, the data demonstrate that substantial changes in adrenergic activity occur under physiological conditions associated with an altered myosin heavy-chain expression. (Circulation Research 1989;65:370–377)

The myocyte can react to an altered functional load or neuroendocrine status by remodeling the structure of subcellular organelles. A well-documented example is the redistribution of the myosin isoenzyme population toward V1 in the pressure-loaded rat heart, resulting in an improved economy of tension development1,2 at the expense of fast shortening.3–5 This change in phenotype is not an isolated event but is accompanied in a number of cases by functionally comparable alterations in the sarcoplasmic reticulum6 and represents a process that permits the myocardium to cope with a variety of loads. Although great progress has been made in the molecular biology of myosin,7,8 the functional loads and the associated signals that result in an altered myosin heavy-chain expression are still ill-defined. Especially little is known about the nature of the loads that can increase the proportion of V1. Among possible trigger mechanisms, catecholamines have been thought to play a role in the regulation of the myosin heavy-chain expression.9–12 However, only pharmacological interventions have been used, and there is no evidence for the involvement of catecholamines when the myosin expression is altered by a physiological load.

The possible influence of catecholamines was characterized by use of physical exercise, which intermittently activates the adrenergic system. Normotensive Wistar (N) rats and spontaneously hypertensive rats (SHR) were subjected to three exercise routines that were chosen to differ greatly with respect to their physical and psychological loads. Exercise was performed in the form of enforced swimming, known to be a mild type of exercise with a unique and-as-yet unexplained effect on myosin; running of high intensity performed spontaneously

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in large activity wheels; and enforced running of low intensity but associated with stressors due to the untypically low speed.13-17 The two running routines, which have opposite effects on the high blood pressure of SHR, have not previously been used together for study of the effects of exercise on the heart. Because an intermittent increase in peripheral adrenergic activity is known to result in higher catecholamine stores,18 the catecholamine content of the ventricles and adrenal glands was determined. If the adrenergic activity was a correlate of the altered myosin expression, then the exercise with the strongest influence on catecholamine stores would also be expected to have a marked influence on the myosin isoenzyme population. For a further substantiation of the role of the adrenergic system, swimming and sedentary rats were treated with atenolol, which provides a selective cardiac β-blockade but does not interfere with the sympathetic input into the vascular system.19 Because the adrenergic drive of the heart is greater during exercise than in the sedentary state, β-blockade should have a more pronounced effect in the exercised rats.

Materials and Methods

Male 21-week-old N rats and SHR (Ivanovas, Kissleg, FRG) were received 2 weeks before the start of the experiments and were housed in a 21-23° C room with a 12-hour light-dark cycle. Enforced routines were performed during the light phase. Rats received a standard chow (“Ssniff” of Plange, Soest, FRG) and tap water ad libitum.

Exercise Routines

An exercise routine of swimming in 35° C water with a calculated density of 30 rats per square meter surface area was started with 10 min/day and increased daily in 10-minute steps. When a duration of 100 minutes was reached, two sessions of 50 minutes each were performed. The swimming time was further increased each day by 10 minutes to a maximum of two 90-minute sessions per day.20 The rest period between the two swimming routines was 4 hours. The swimming routine was also performed by rats treated with atenolol in the drinking water (50 mg/kg/day). In all groups, attrition of swimming rats averaged 5%. The rats of the spontaneous running routine were housed individually in standard cages to which were attached custom-made revolving wheels of 0.6 m diameter and 0.4 m width. The rats had free access to the wheels and ran spontaneously. The running distance was recorded by counters connected to the wheels. Enforced running was performed in synchronously motor-driven wheels of 0.6 m diameter and 0.4 m width. Enforced maximum daily running time at a speed of 10 m/min was two 3-hour sessions separated by a 4-hour rest. All experimental routines lasted for 5-6 weeks.

Blood Pressure

Systolic arterial pressure was measured in the conscious rat by the tail-cuff method.21 For detection of the pulse, a piezoresistive pressure transducer (Rhema, Hofheim, FRG) connected to an oscilloscope was used. The tail of the rat was warmed to 38-39° C during the measurement by warming the box that contained the pressure transducer. The cuff (30×11 mm) was attached to the base of the tail. The rats were habituated over 2 weeks to the measurement procedure, during which the rat was held loosely by hand under a black cloth; restraining devices resulted in less consistent values. Blood pressure was determined every 4-5 days in the morning before the exercise period. The mean value of at least four readings was taken as the blood pressure value. The indirect pressure readings were validated by use of a cather-tip manometer.22 For detection of any excitement, the ECG was recorded sporadically during blood pressure measurement by positioning the rat on two conducting plates connected to a differential input storage oscilloscope. Heart rates were typically in the range of 360-380 beats/min.

Myosin Isoenzymes and Catecholamine Stores

The animals were killed by decapitation, and the hearts were excised, washed with saline, blotted, and weighed. The left ventricles were frozen and stored in liquid nitrogen. Adrenal glands were excised, blotted, and also stored in liquid nitrogen. Myosin isoenzyme populations were determined using pyrophosphate gel electrophoresis23 as described previously.20 Quantification of individual components was based either on peak height or, in the case of a low proportion of Vβ, on integration of the resolved individual components after the envelope was fitted to three gaussian curves. Catecholamines were determined by high-performance liquid chromatography that used a Waters M 6000 A pump (Millipore Corp., Milford, Massachusetts) and a Metrohm 64 electrochemical detector (Metrohm, Herisau, Switzerland) operating at +0.7 V versus Ag/AgCl reference electrode. Separation was performed on a Nucleosil 5 C18 column (Macherey-Nagel, Düren, FRG). The eluent contained 60 mM citric acid/acetate (pH 4.0), 1 mM di-n-butylamine, 0.1 mM Na2EDTA, and 0.9 mM 1-octanesulfonic acid in 95:5 (vol/vol) water and methanol. Samples were prepared by use of the alumina extraction procedure described by Refshauge et al.24 Identical results were obtained when the supernatant of the homogenate24 was injected directly after centrifugation for 20 minutes at 160,000g.

For statistical evaluations, normality of the distributions was verified by David’s test and equality of variances by Bartlett’s test.25 Multiple comparisons were performed by analysis of variance and the Scheffe test or the rank test of Kruskal and
Results

The exercise routines had a differential influence on blood pressure and, thus, on the pressure load of the heart (Figure 1). Swimming greatly normalized the high blood pressure of SHR when assessed either by the indirect method (Figure 1) or invasively with a catheter (not shown). At the end of the swimming protocol, body weight was lower than that of sedentary rats (Figure 2). Blood pressure also was reduced by spontaneous running (Figure 1). Rats ran undisturbed in activity wheels attached to their home cages. After 3 weeks, the rats ran about 15 km daily in 10–12 hours, which corresponds to 23 m/min on average. In N rats, both routines had a smaller effect on blood pressure. In contrast with swimming, spontaneous running had no significant influence on body weight (Figure 2). The effect of enforced running in wheels rotating at the low speed of 10 m/min on blood pressure depended on the exercise duration. When the running time was 3 hr/day, blood pressure remained unaltered. However, when two daily routines of 3 hours each, corresponding to a total running distance of 3.6 km, had to be performed, the pressure increased significantly in SHR (Figure 1). As in spontaneous running, body weight was not significantly different when compared with sedentary rats (Figure 2).

The SHR exhibited hypertrophied left ventricles compared with N rats (Figure 2). In both strains, a significant increase in ventricular weight was induced by spontaneous running but not by enforced running (Figure 2). After the swimming exercise, ventricular weight was not significantly different compared with the sedentary rats, although body weight was reduced (Figure 2).

Swimming exercise increased the weight of adrenal glands in both strains, whereas spontaneous running led to a higher adrenal gland weight only in SHR. Enforced running had no significant effect (Figure 2).

In sedentary SHR, the proportion of V3 was higher than in N rats (Table 1). After the swimming exercise, the proportion of V3 was reduced in both strains. Neither spontaneous nor enforced running had a significant influence. In the N rats, however, the proportion of V3 was slightly higher after enforced running than after spontaneous running. The influence of β-blockade was studied only in swimming rats. Atenolol reduced the proportion of V3 in sedentary and swim-exercised rats (Table 2); however, the effect of atenolol was greater in the rats subjected to swimming exercise. Body weight and ventricular weight were not further affected by atenolol treatment (not shown).

Swimming exercise induced an increase in the norepinephrine content of left ventricles in N rats and SHR (Figure 3). By contrast, spontaneous running did not significantly affect the norepinephrine content in N rats and reduced the content in SHR. Enforced running had no significant influence on either strain. The total ventricular contents of epinephrine (41.8±15.6 ng) and of dopamine (46.2±13.9 ng) did not differ significantly within the two strains, and no consistent changes were observed after the exercise routines (not shown).

In N rats, the swimming exercise induced an increase in the content of norepinephrine of adrenal glands (Figure 4). Neither running routine had any

Wallis. Values are mean±SD; statistical significance was assumed at \( p<0.05 \).
significant influence. In sedentary SHR, norepinephrine and dopamine content was significantly higher than in N rats. Swimming markedly increased the norepinephrine content and, to a smaller extent, the content of epinephrine and dopamine in SHR. The running routines resulted only in a significantly higher content of epinephrine, which was still smaller than that of swim-exercised SHR. After the enforced running, the total epinephrine content was higher even though the weight of adrenal glands was not significantly changed. Information on the functional loads involved in the routines was gained by calculation of the ratio of epinephrine to norepinephrine (Figure 5). In SHR, the ratio decreased after swimming, corresponding to a higher proportion of norepinephrine. A significant decrease occurred in N rats when the density of rats swimming together was doubled (not shown). Spontaneous running had no effect on the ratio. The proportion of epinephrine increased in both strains after the enforced running.

### Discussion

In swimming exercise, the physical load is considered to be mild, corresponding to 50–65% of the aerobic capacity.20 In male rats, swimming results in an unchanged ventricular weight associated with a reduced body weight.27 When the ventricular weight of the swimming rats was compared with that of paired-weight rats, a small ventricular hypertrophy became evident.27 Although enforced swimming in a group results in pronounced interaction between rats, leading to situations of longer diving when compared with rats swimming individually, no increase in right ventricular weight typical of pronounced hypoxia20 was detected in this group (not shown). Invasive measurements of blood pressure by use of a catheter indicated that both systolic and diastolic blood pressure were reduced at the end of the exercise routine (not shown). Because cardiac output was unchanged in the swim-exercised rats, the lower blood pressure has to be attributed to a reduction in peripheral vascular resistance.28 Despite the almost normalized blood pressure, the ventricular weight of swim-exercised SHR was not reduced, suggesting that normalization of pressure load is not sufficient for regression of cardiac hypertrophy. As an alternative model of physical activity that differs from swimming in as many functional parameters as possible but still reduces high blood pressure, a spontaneous running routine was devised in wheels with a 1.0-m diameter, which permitted the rats to run on a nearly flat area. The maximum daily running distance of about 15 km was performed in 10–12 hours, corresponding to an average speed of 23 m/min. This speed would correspond to 76% of maximum aerobic power, reached at a running speed of 54 m/min.26 It should be noted, however, that only one out of three rats ran in a manner as shown in Figure 1. The rats were selected in the first 2 days of the routine. If they ran 200–400 m/day, then they increased their total running distance to about 15 km/day. The daily

### Table 1. Myosin Isoenzyme Populations of Left Ventricles of Sedentary and Exercised N Rats and SHR

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>V1 (%)</th>
<th>V2 (%)</th>
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<tr>
<td>N rats</td>
<td></td>
<td></td>
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<tr>
<td>Sedentary</td>
<td>5</td>
<td>20.4±7.6</td>
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<td>Swimming</td>
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<td>17.9±2.8*</td>
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<td>28.9±2.0</td>
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<tr>
<td>Enforced running</td>
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<td>24.7±5.1</td>
<td>29.4±1.7</td>
<td>45.9±6.7</td>
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<td>SHR</td>
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<td>28.2±2.0</td>
<td>23.1±4.4</td>
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<tr>
<td>Swimming</td>
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<td>33.7±1.3*</td>
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<td>49.5±2.8</td>
<td>27.5±1.1</td>
<td>23.0±2.1</td>
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</tbody>
</table>

N rats, normotensive rats; SHR, spontaneously hypertensive rats; n, number of animals.
* p<0.001 for exercised vs. sedentary rats.
† p<0.05 for rats of spontaneous vs. enforced running.
‡ p<0.05 for exercised vs. sedentary rats.

### Table 2. Effect of Atenolol Treatment on Myosin Isoenzyme Populations of Left Ventricles of Swim-Exercised and Sedentary N Rats

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>V1 (%)</th>
<th>V2 (%)</th>
<th>V3 (%)</th>
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<tr>
<td>Sedentary</td>
<td>7</td>
<td>19.6±3.5</td>
<td>26.6±2.9</td>
<td>53.8±6.0</td>
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<tr>
<td>Swimming</td>
<td>7</td>
<td>5.4±1.2*</td>
<td>16.1±3.0*</td>
<td>78.5±4.1*</td>
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<tr>
<td>Sedentary, atenolol-treated</td>
<td>7</td>
<td>31.5±6.2†</td>
<td>27.9±1.1</td>
<td>40.6±7.1†</td>
</tr>
<tr>
<td>Swimming, atenolol-treated</td>
<td>7</td>
<td>16.9±5.9</td>
<td>26.2±4.0</td>
<td>56.9±9.9</td>
</tr>
</tbody>
</table>

N rats, normotensive rats; n, number of animals.
* p<0.001 vs. untreated sedentary rats.
† p<0.01 vs. treated sedentary rats.
maximum running distance was greater than that of the routine described by Suzuki et al., in which the maximum distance was 8 km/day. This difference can most probably be accounted for by the larger diameter (×3) of the revolving wheels employed in the present approach. The routine of spontaneous running, which has reinforcing properties, was exceptional with respect to its effect on ventricular mass. Enforced running routines generally did not produce an increase in absolute ventricular weight. Only enforced running with sprints of very high intensity induced cardiac hypertrophy. In contrast with spontaneous running, however, one would also have to take into account the ill-defined effect of stressors associated with enforced running.

High-speed interval training. The third type of physical activity was chosen to see the possible effect of stressors associated with an enforced running routine. In this instance, the exercise intensity was low when compared with typical running routines. Running was enforced with a steady speed of 10 m/min, which was lower than that observed during spontaneous running. To keep pace with the slowly revolving wheel, the rats typically ran a short distance on the upslope of the wheel, paused until they were taken to the downslope, and then ran again. The low degree of control associated with such a situation most probably caused the increase in blood pressure, which was also observed by Suzuki et al. In this respect, it should be pointed out that although the swimming routine was also enforced, no attempts were made to interfere with the typical behavior of swimming rats, which consists of sporadic floating and drownproofing. Thus, although the rats had to swim, they coped well with the experimental situation.

Although both spontaneous running and swimming reduced blood pressure with the same time course, only swimming increased the proportion of V1. It can be concluded that reduction of pressure load is not sufficient for reduction of the high proportion of V1 typical of SHR. In accordance, treatment of SHR with the vasodilating drug hydralazine for up to 12 weeks completely normalized blood pressure but had either no significant effect or only slightly reduced V1. Therefore, the increased blood pressure of the SHR with the enforced running routine is not necessarily linked to a higher proportion of V1. Also, when the unchanged ventricular weight is considered, one would not expect an effect on the isoenzyme population. Thus, the increase in the proportion of V1 after swimming seems to be unique for this type of exercise and involves a signal that also operates in the presence of pressure load.

Because thyroid hormones represent a fast-acting trigger for the expression of myosin α-heavy chains, one could infer that the effect of swimming exercise was mediated by an increase in circulating thyroid hormones.

**Figure 3.** Total norepinephrine (NE) content of left ventricles of normotensive (N) rats and spontaneously hypertensive rats (SHR) after different exercise routines. *p<0.05; ***p<0.001 for exercised rats vs. corresponding sedentary rats.

**Figure 4.** Total epinephrine (E), norepinephrine (NE), and dopamine (DA) content of adrenal glands of normotensive (N) rats and spontaneously hypertensive rats (SHR) after different exercise routines. *p<0.05; ***p<0.001 for exercised rats vs. corresponding sedentary rats.

**Figure 5.** Ratio of concentrations of epinephrine (E) and norepinephrine (NE) in adrenal glands of normotensive (N) rats and spontaneously hypertensive rats (SHR) after different exercise routines. *p<0.05; **p<0.01 for exercised rats vs. corresponding sedentary rats.
hormones. However, serum thyroid hormones were not affected in a manner that could account for the increase in the proportion of $V_1$ (H. Rupp and R. Wahl, unpublished data); therefore, other mechanisms must be assumed. In view of the evidence that pharmacological interventions interfere with the influence of endogenous catecholamines and the fact that depletion of myocardial norepinephrine by chemical sympathectomy can alter the myosin isoenzyme population (H. Rupp and R. Wahl, unpublished data), the exercise routines could be expected to differ with respect to their influence on peripheral adrenergic activity. Besides by the determination of the activity of enzymes involved in catecholamine biosynthesis, it is possible to draw conclusions on the peripheral adrenergic activity by measurement of catecholamine stores. Because a repeated pronounced stimulation of the adrenergic system results in an adaptive increase in norepinephrine stores, higher norepinephrine stores can be considered as indicative of loads that lead to a high adrenergic drive. The present data show that only swimming can increase the total norepinephrine content of ventricles in both N rats and SHR. A higher norepinephrine content has been reported by Ostman-Smith for swimming N rats. By contrast, enforced running of high intensity (37 m/min) did not affect norepinephrine content.

For a further examination of the differential influence of the exercise routines on peripheral adrenergic activity, catecholamine stores were determined in adrenal glands. In contrast with ventricles, in which a higher norepinephrine content most probably arises from increased stores of existing nerve fibers, adrenal glands can increase in size. This was most prominent in the case of swimming N rats. An increase in adrenal mass, however, does not necessarily correspond to higher norepinephrine and epinephrine stores because the medulla accounts for only a small fraction of total volume. As in the case of the ventricles, the swimming exercise had a pronounced influence on adrenal catecholamine stores, and only swimming induced a marked increase in the norepinephrine content. SHR exhibited a stronger response, in accordance with the well-documented "hyperresponsivity" of this strain, which exhibits a higher proportion of norepinephrine even under normal cage activity. The high adrenergic activity arising from swimming is also reflected in increased activity of the biosynthetic enzymes tyrosine hydroxylase and dopamine $\beta$-hydroxylase. The high adrenergic drive during swimming most probably arises from a combination of muscular activity and heat loss due to water immersion; however, water immersion on its own had no influence on myosin ATPase activity and most likely did not affect catecholamine stores either. The greater norepinephrine stores of adrenal glands are typical of experimental loads that substantially increase peripheral adrenergic activity and, in an adaptive response, induce an increase of the biosynthetic capacity leading to norepinephrine. Thus, after repeated immobilization of rats, the norepinephrine content was greatly increased, whereas the epinephrine content was unaltered during a 4–6-week period. Also, after intermittent exposure to cold, the norepinephrine content was increased. Compared with the swimming exercise, the biosynthetic pathway was probably activated to a lesser extent by the running routines. Spontaneous running did not significantly increase the norepinephrine content and, therefore, did not affect the ratio of epinephrine to norepinephrine. Enforced running increased the proportion of epinephrine, which was pronounced in the case of SHR, and most probably was attributable to the low degree of control and the ensuing adrenal-cortical response. This argument is reinforced by the finding that the synthesis of epinephrine depends essentially on glucocorticoids. An increase in the proportion of epinephrine has also been observed after a procedure involving stressors arising from shock-induced aggression in sedentary rats (H. Rupp, unpublished data).

Taken together, the data suggest that the myosin isoenzyme population can be affected by exercise only when the routine has a marked influence on peripheral adrenergic activity (Table 3). As shown by the catecholamine content of ventricles and adrenal glands, this condition was far better fulfilled by the swimming exercise than by the spontaneous or enforced running. The stressors associated with enforced running did not have a great effect on the isoenzyme population. Experimental stressors in the absence of physical activity were found to slightly increase the proportion of $V_1$. This mechanism could contribute to the higher proportion of $V_1$ in N rats of the enforced routine as compared with those of the spontaneous running routine. The marked difference in adrenergic drive between the swimming and running routines could also explain the puzzling fact that although swimming had to be

<table>
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<tr>
<th>CLASS</th>
<th>Left ventricle</th>
<th>Adrenal gland</th>
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<tr>
<td>$V_1$ (%)</td>
<td>Weight</td>
<td>NE content</td>
</tr>
<tr>
<td>Swimming</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Spontaneous running</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Enforced running</td>
<td>↓</td>
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N rats, normotensive rats; NE, norepinephrine; •, increased; ●, unchanged as compared with sedentary rats.
rated as moderate exercise, it increased myosin ATPase activity, whereas enforced running routines had either no effect or only a small effect.\textsuperscript{13,14} Further support for a link between myosin expression and adrenergic activity comes from the effect of $\beta$-blockade. Because adrenergic activity in rats is lower under normal cage activity than during exercise, one would expect the effect of $\beta$-blockade to be greater in the swim-exercised rats. Accordingly, atenolol treatment led to a greater reduction in $V_i$ in the swim-exercised rats than in the sedentary rats. The fact that the increase in the proportion of $V_i$ did not completely vanish in swimming rats suggests that either $\beta$-blockade was not complete or that additional triggers were operating independently of $\beta$-adrenergic receptors. In view of the finding that feedings of low amounts of sucrose can increase the proportion of $V_i$, probably via an altered fuel metabolism,\textsuperscript{4} the possibility that the high adrenergic activity during swimming could act via a metabolic switch should be considered. The nature of the subcellular signals leading to an altered myosin expression requires further investigation.

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KEY WORDS • myosin • ventricular isoenzymes • exercise • catecholamines • hypertension • blood pressure
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