Effect of Physical Training on Exercise-Induced Hyperkalemia in Chronic Heart Failure

Relation With Ventilation and Catecholamines

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Background The exercise-induced rise in arterial potassium concentration ($[K^+]_a$) may contribute to exercise hyperpnea and could play a role in exertional fatigue. This study was designed to determine whether the exercise-induced rise in $[K^+]_a$ is altered in patients with chronic heart failure (CHF) and whether physical training affects K^+ homeostasis.

Methods and Results We evaluated 10 subjects with CHF (ejection fraction, 23±3.9%) and 10 subjects with normal left ventricular function (NLVF) who had undergone previous coronary artery graft surgery (ejection fraction, 63±8.6%). Subjects performed an incremental cycle ergometer exercise test before and after a physical training or detraining program. Changes in $[K^+]_a$ and ventilation ($\dot{V}_E$) during exercise were closely related in both groups. Subjects with CHF did less absolute work and had reduced maximal oxygen consumption ($\dot{V}O_2max$) compared with subjects with NLVF ($P<.01$). Exercise-induced rises in $[K^+]_a$, $\dot{V}_E$, norepinephrine, lactate, and heart rate were greater at matched absolute work rates in subjects with CHF than in subjects with NLVF ($P<.01$). However, when the rise in $[K^+]_a$ was plotted against percentage of $\dot{V}O_2max$ to match for relative submaximal effort, there were no differences between the two groups. Physical training resulted in reduced exercise-induced hyperkalemia at matched submaximal work rates in both groups ($P<.01$) despite no associated change in the concentration of arterial catecholamines. At maximal exercise when trained, peak increases in $[K^+]_a$ were unaltered, but peak concentrations of catecholamines were raised ($P<.05$). The decrease in $\dot{V}_E$ at submaximal work rates after training was not significant with this incremental exercise protocol, but both groups had an increased peak $\dot{V}_E$ when trained ($P<.01$).

Conclusions Exercise-induced rises in $[K^+]_a$, catecholamines, and $\dot{V}_E$ are greater at submaximal work rates in subjects with CHF than in subjects with NLVF. Physical training reduces the exercise-induced rise in $[K^+]_a$ but does not significantly decrease $\dot{V}_E$ during submaximal exercise with this incremental cycle ergometry protocol. The reduction in exercise-induced hyperkalemia after training is not the result of altered concentrations of arterial catecholamines. The pathophysiological significance of the increased exercise-induced hyperkalemia in CHF and the mechanisms of improved K^+ homeostasis with training have yet to be established. (***Circulation.*** **1994;89:1144-1152.**)

Key Words • potassium • exercise • heart failure • catecholamines

Patients with chronic heart failure (CHF) ventilate more for a given work rate[1] and experience early muscle fatigue.[2-4] Several studies have suggested that a disturbance in the metabolic state of the exercising muscle in CHF may affect both the ventilatory response and the early onset of fatigue.[3,5,6] Exercise-induced hyperkalemia, which follows potassium (K^+) release from the skeletal muscle, may contribute to exercise hyperpnea.[7,8] There is a strong correlation between the increase in arterial potassium concentration ($[K^+]_a$) and ventilation ($\dot{V}_E$) during exercise,[9,10] and because hyperkalemia has been shown to stimulate $\dot{V}_E$ in the anesthetized cat by excitation of the peripheral chemoreceptors,[11,12] this relation could be causal. It has also been suggested that K^+ depletion from the skeletal muscle during exercise plays a role in muscle fatigue,[13,14] which is a prominent symptom in CHF.[2-4] The first aim of this study was to determine the $[K^+]_a$, ventilatory, and metabolic responses to exercise in patients with ischemic CHF and to compare these results with data from subjects with normal left ventricular function (NLVF).

Recent research has shown that improved physical fitness can be achieved in patients with CHF[15-19] or left ventricular dysfunction.[20,21] Patients with CHF have altered skeletal muscle biochemistry and histology,[4-6] and the predominant response of physical training appears to involve adaptations in the skeletal muscle.[15] There is also evidence from uncontrolled studies that exercise-induced hyperkalemia is reduced in trained compared with untrained normal men,[22,23] possibly because of an increase in the concentration of skeletal muscle Na^+-K^+ pumps.[24] It is therefore possible that the training effect in the skeletal muscle in CHF may include decreased K^+ release. Exercise-induced hyperkalemia could be modulated by the activity of the sympathetic nervous system,[25-27] although there are conflicting results concerning the spillover of catecholamines into the plasma after training.[28,29] The second aim of our study was to determine the effects of physical training on the $[K^+]_a$, catecholamine, and other responses to exercise in patients with CHF and subjects with NLVF. Some of the results reported have been presented previously in abstract form.[30]

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TABLE 1. Clinical Characteristics of the 20 Participants

	CHF Subjects (n=10)	NLVF Subjects (n=10)
Age, mean y	58±9.9*	58±4.6*
Ischemic heart failure, n	10	...
Coronary graft surgery, n	6	10
Ejection fraction, %	23±3.9*	63±8.6*
Medication, n		
Frusemide	9	...
Amiloride	7	...
ACE inhibitors	9	...
Warfarin	6	...
Aspirin	4	10
NYHA status		
I	...	10
II	6	...
III	4	...
Trained/detrained, n	5/5	5/5

CHF indicates chronic heart failure; NLVF, normal left ventricular function; ACE, angiotensin-converting enzyme; and NYHA, New York Heart Association.
*Values are mean±SD.

Methods

Subjects

Ten male subjects with stable CHF and 10 male subjects with NLVF participated in the study. Subjects with CHF had symptoms of CHF and systolic left ventricular dysfunction (ejection fraction, <30% by radionuclide ventriculography) secondary to ischemic heart disease. Subjects with NLVF (ejection fraction, >50%) who had undergone previous coronary artery bypass graft surgery were selected so that the major difference between the two groups was left ventricular function (Table 1). All subjects were physically inactive, and none were participating in exercise or training programs. All subjects were in sinus rhythm, able to perform cycle ergometer exercise to exhaustion, and achieve a respiratory exchange ratio of at least 1 during an initial screening test.[17,18] Subjects were selected only if they were limited by breathlessness or muscle fatigue, and none had evidence of exercise-induced myocardial ischemia or arrhythmias. All participants had been clinically stable and on unchanged medication for at least 3 months before the study, and none had intermittent claudication or chronic lung or valvular heart disease. All subjects had a normal venous [K^+], and none had resting hyperkalemia or hypokalemia during the previous year. Patients with diabetes or thyroid dysfunction or those taking β-blockers, β-stimulants, or digoxin were excluded because these interfere with K^+ homeostasis.[31-33] The clinical characteristics of the 20 participants are summarized in Table 1. The study was approved by the Central Oxford Research Ethics Committee.

Protocol

After the initial screening and exercise test, subjects underwent a second exercise test to further familiarize them with the protocol before the first invasive study. All exercise tests were performed at the same time of day with subjects on constant medication. For the initial invasive study, a 20-gauge brachial artery catheter was inserted in the nondominant arm with the subject under local anesthesia. Catheter patency was maintained by repeated flushing with heparinized saline (2 IU/mL). Upright cycle exercise took place on an electromagnetically braked ergometer (model KEM-3, Mijnhardt) with continuous ECG monitoring. Subjects breathed through a mouthpiece with the nose occluded. Ventilation was measured breath-by-breath using a turbine device and a Fleisch pneumotachograph.[34] Gas at the mouth was sampled continuously with a mass spectrometer and analyzed for P_{O_2} and P_{CO_2}. Ventilatory data were collected by a computer running a real-time data-acquisition program.[9]

The work rate during exercise for subjects with CHF was increased in 5-W/min steps until volitional exhaustion. This point was reached when a perceived effort rating (PER)[35] of 19 was achieved or a pedal frequency of 50 rpm could not be maintained. Subjects with NLVF undertook an identical incremental protocol to 75 W to serve as an absolute work rate control. After a 45-minute rest, the subjects with NLVF undertook an additional 10-W/min step test to exhaustion. This protocol was designed to match the exercise time of the group with CHF and therefore serve as a relative work rate control.

Arterial blood was sampled every minute during exercise and the first 5 minutes of recovery. The plasma was centrifuged within 15 minutes for K^+ analysis by flame photometry (model 943, Instrumentation Laboratory). Arterial blood lactate levels were measured immediately (model 23L, YSI). Arterial blood was sampled at 3-minute intervals and at peak exercise for analysis of P_{O_2}, P_{CO_2}, and pH (model 1306, Instrumentation Laboratory). Blood for the analysis of epinephrine and norepinephrine was also drawn at 3-minute intervals and immediately placed on ice. The plasma was centrifuged within 15 minutes and stored at −70°C. Catecholamine assay was subsequently undertaken by high-performance liquid chromatography with electrochemical detection.[36]

Subjects repeated identical studies when both trained and untrained.

Physical Training

Five subjects in each group undertook a training program, and five undertook a detraining program (Table 1). For the training program, the invasive exercise tests preceded and immediately followed physical training. For the detraining program, the first invasive exercise test immediately followed physical training, and then subjects had 8 weeks of restricted activity, avoiding exercise that produced breathlessness or fatigue, before completing the second test. The first invasive exercise test was preceded by at least two noninvasive tests, for screening and familiarization, in all instances.

Physical training consisted of 8 weeks of home-based cycle ergometry (Tunturi "Professional Ergometer") for 20 minutes a day, 5 days a week. A pulse-rate monitor (Micro Sports Lab Computer, Triadcolour) was used, and subjects increased the cycle resistance setting, maintaining a constant 50 rpm, until the heart rate was 70% to 80% of the previously determined maximum. This work rate was maintained for 20 minutes.[17] The program thus allowed for increases in exercise load as physical training progressed. Compliance was assessed by means of a revolution counter attached to the ergometer.

Statistical Analysis

Results are expressed as mean±SE unless otherwise stated. Data for comparison between groups and data for training effects within groups were analyzed independently. Differences between CHF and NLVF subjects in the measured variables at different work rates were initially assessed by ANOVA. This was followed, where appropriate, by unpaired two-tailed Student's t tests. Differences with training in the variables at different work rates were also first assessed by separate ANOVA within each of the two groups. This was followed by paired two-tailed Student's t tests. A value of $P<.05$ was considered statistically significant.

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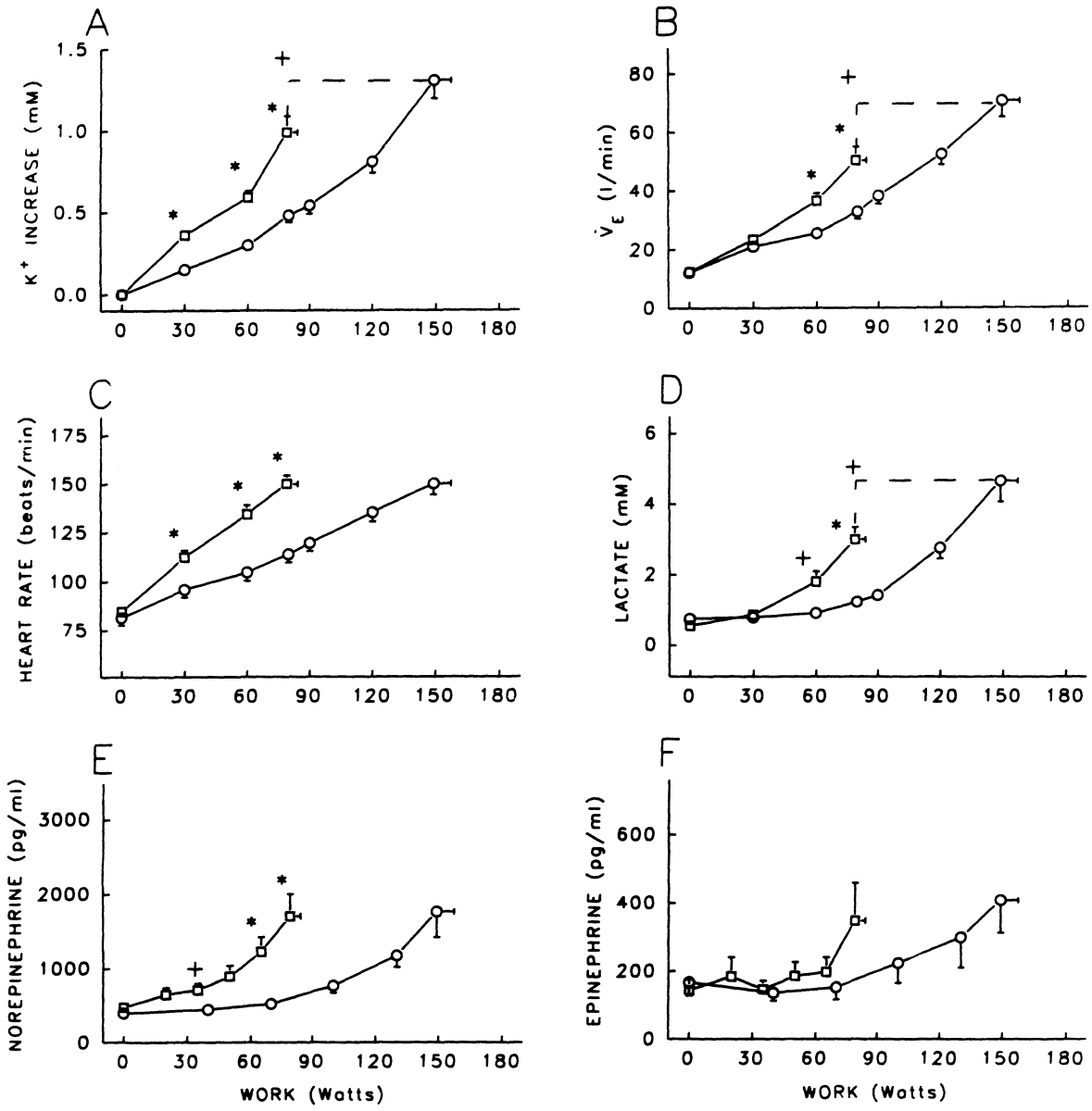

FIG 1. Plots of resting and exercise-induced rise in $[K^+]_a$, $\dot{V}_E$, heart rate, arterial lactate, norepinephrine, and epinephrine in subjects with chronic heart failure (CHF) (n=10) (□) and with normal left ventricular function (NLVF) (n=10) (○) in the untrained state. †$P<.05$, *$P<.01$ CHF vs NLVF. Dashed lines indicate comparisons of maximal data.

Results

Subjects with CHF and NLVF were of similar ages (Table 1). Those with CHF had substantially lower left ventricular ejection fractions assessed by radionuclide ventriculography. Resting $[K^+]_a$ was similar in both groups (3.98±0.14 versus 3.85±0.10 mmol/L), as was sodium concentration (137±1.0 versus 139±0.7 mmol/L). No significant side effects were encountered during the study, and no subject withdrew once physical training had begun. An 11th patient with CHF, who performed the initial invasive exercise study, was withdrawn before beginning training because of deterioration of his clinical condition. Medication remained constant throughout the study.

Comparison of Exercise Responses Between CHF and NLVF Subjects

Comparisons between the two groups are illustrated in the untrained state only (Fig 1), but identical trends were seen when the subjects were trained. The peak exercise work rate was lower in the CHF group than in the NLVF group (79.0±5.2 versus 149.0±8.1 W; $P<.01$). The $[K^+]_a$, heart rate, $\dot{V}_E$, lactate, and norepinephrine were all greater at matched submaximal work rates in subjects with CHF (Fig 1), as was the ratio of $\dot{V}_E$ to minute production of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) (45±3.0 versus 33±2.1 at 60 W; $P<.01$). The peak exercise-induced increase in $[K^+]_a$ was not as great in CHF as in NLVF subjects (0.99±0.10 versus 1.31±0.11 mmol/L; $P<.05$), and neither were $\dot{V}_E$ (50.3±4.7 versus 70.8±5.6 L/min; $P<.05$) or lactate (3.01±0.35 versus 4.68±0.60 mmol/L; $P<.05$) peaks. The peak $\dot{V}_E/\dot{V}CO_2$ was higher in the group with CHF (52±3.7 versus 43±4.5; $P<.05$). There was no difference between the two groups in peak heart rate (150±4.3 versus 150±5.7 beats per minute) or norepinephrine (1706±299 versus 1770±343 pg/mL) or epinephrine (348±112 versus

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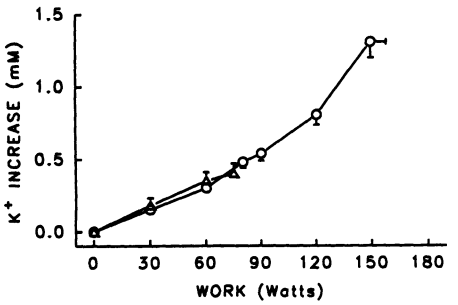

FIG 2. Plot of exercise-induced rise in $[K^+]_a$ in subjects with normal left ventricular function (n=10) in the untrained state during 5-W/min (△) and 10-W/min (○) step protocols. No comparison was $P<.05$.

409±96 pg/mL) levels. Mean arterial blood pressure increased from 89±3.7 mm Hg at rest to 111±3.8 mm Hg at peak exercise in the group with CHF and from 98±2.0 mm Hg to 128±3.2 mm Hg in the group with NLVF.

Fig 2 illustrates the exercise-induced increase in $[K^+]_a$ in the subjects with NLVF during the different 5- and 10-W/min protocols, again in the untrained state. The increase in $[K^+]_a$ was similar at matched absolute work rates with the two incremental cycle protocols.

Table 2 illustrates changes in arterial pH, Pa_{O_2}, and Pa_{CO_2} in the subjects when untrained. Arterial pH was higher at rest and during exercise in subjects with CHF than in those with NLVF. pH decreased progressively in both groups as exercise progressed. The Pa_{CO_2} was lower during exercise in the group with CHF than in the group with NLVF. The Pa_{O_2} remained constant throughout exercise in both groups.

Variables are plotted against percentage of O_2 consumption in Fig 3, again in the untrained state only, to give a comparison of the responses between the groups at matched relative effort. No difference is seen in the rises in $[K^+]_a$, heart rate, or catecholamines at submaximal levels of O_2 consumption. Lactate and $\dot{V}_E$ increase more rapidly in the subjects with NLVF when plotted in this way. The same differences in peak levels are seen as when the variables are plotted against absolute work rate (given in watts).

TABLE 2. Arterial Blood Gas and pH Changes in the 20 Participants (Untrained)

	Rest	75% $\dot{V}_{O_2}$max	Peak Exercise
CHF			
pH	7.43±0.01†	7.42±0.01*	7.40±0.01*
Pa_{O_2}, mm Hg	98±3.7	100±3.1	98±3.6
Pa_{CO_2}, mm Hg	35.6±1.2	34.9±0.9†	32.5±1.6
NLVF			
pH	7.41±0.01	7.39±0.01	7.35±0.01
Pa_{O_2}, mm Hg	98±2.0	100±3.2	100±3.5
Pa_{CO_2}, mm Hg	38.8±1.3	38.4±0.9	35.5±1.0

CHF indicates chronic heart failure; NLVF, normal left ventricular function. Values are mean±SE.
*$P<.01$, †$P<.05$ CHF vs NLVF.

Evidence for Physical Training

The physical training program was well tolerated, and both groups had a compliance of more than 90% (Table 3). The peak work rate increased significantly in both groups after training. The $\dot{V}_{O_2}$max increased in subjects with NLVF ($P<.01$), and there also was an upward tendency in the group with CHF ($P=.13$) (Table 3). No significant weight loss occurred in either group. Heart rate (Fig 4) was reduced at rest and during submaximal exercise. Peak heart rates were not affected by the training program. Arterial lactate levels were unchanged at rest but reduced at submaximal work rates after training (Fig 4). Peak lactate levels were increased in subjects with CHF after training (3.73±0.51 versus 3.01±0.35 mmol/L; $P<.05$) but not in subjects with NLVF (5.27±0.45 versus 4.68±0.60 mmol/L; $P=.14$). Both groups indicated improvements with training in their PER[35] during submaximal exercise.

Effect of Physical Training on $[K^+]_a$, $\dot{V}_E$, and Catecholamine Changes in Exercise

Fig 5 illustrates the exercise-induced rises in $[K^+]_a$, plotted as the increase in $[K^+]_a$ above resting levels; it is these increases that may be of physiological importance.[7] The exercise-induced rise in $[K^+]_a$ was reduced at submaximal work rates in both subjects with CHF and those with NLVF after physical training. There was no training effect on peak $[K^+]_a$ in either the CHF (1.11±0.11 versus 0.99±0.10 mmol/L; $P=.07$) or NLVF (1.40±0.11 versus 1.31±0.11 mmol/L; $P=.15$) groups. The decrease in $\dot{V}_E$ at submaximal work rates did not reach statistical significance after training (Fig 6), but the peak $\dot{V}_E$ was increased after training in both subjects with CHF (61.6±4.3 versus 50.3±4.7 L/min; $P<.01$) and those with NLVF (81.8±5.4 versus 70.8±5.6 L/min; $P<.01$). The $\dot{V}_{CO_2}$ was not altered by training at submaximal work rates (Fig 6). The increases in $\dot{V}_{CO_2}$max after training were not significant in either the group with CHF (1092±116 versus 981±62 mL; $P=.17$) or the group with NLVF (1824±67 versus 1729±128 mL; $P=.27$). The effect of training on the arterial concentrations of the catecholamines is shown in Fig 7. Resting and submaximal exercise levels of both epinephrine and norepinephrine were unchanged. The peak arterial norepinephrine concentration was increased after training in subjects with both CHF (2552±517 versus 1706±343 pg/mL; $P<.05$) and NLVF (3139±726 versus 1770±343 pg/mL; $P<.01$). Peak increases in arterial epinephrine concentrations after training did not reach statistical significance by paired Student's t tests because of considerable variations in absolute values between individuals. Nonparametric assessment of the increases (Wilcoxon signed-rank test; Fig 7) was significant in both the group with CHF (726±308 versus 348±112 pg/mL; $P<.05$) and those with NLVF (749±217 versus 409±96 pg/mL; $P<.01$).

Discussion

The new findings in this study are that the exercise-induced rise in $[K^+]_a$ is markedly increased in subjects with CHF compared with subjects with NLVF and that physical training in subjects with CHF and NLVF reduces the exercise-induced rise in $[K^+]_a$ at submaximal work rates without changing the concentrations of cir-

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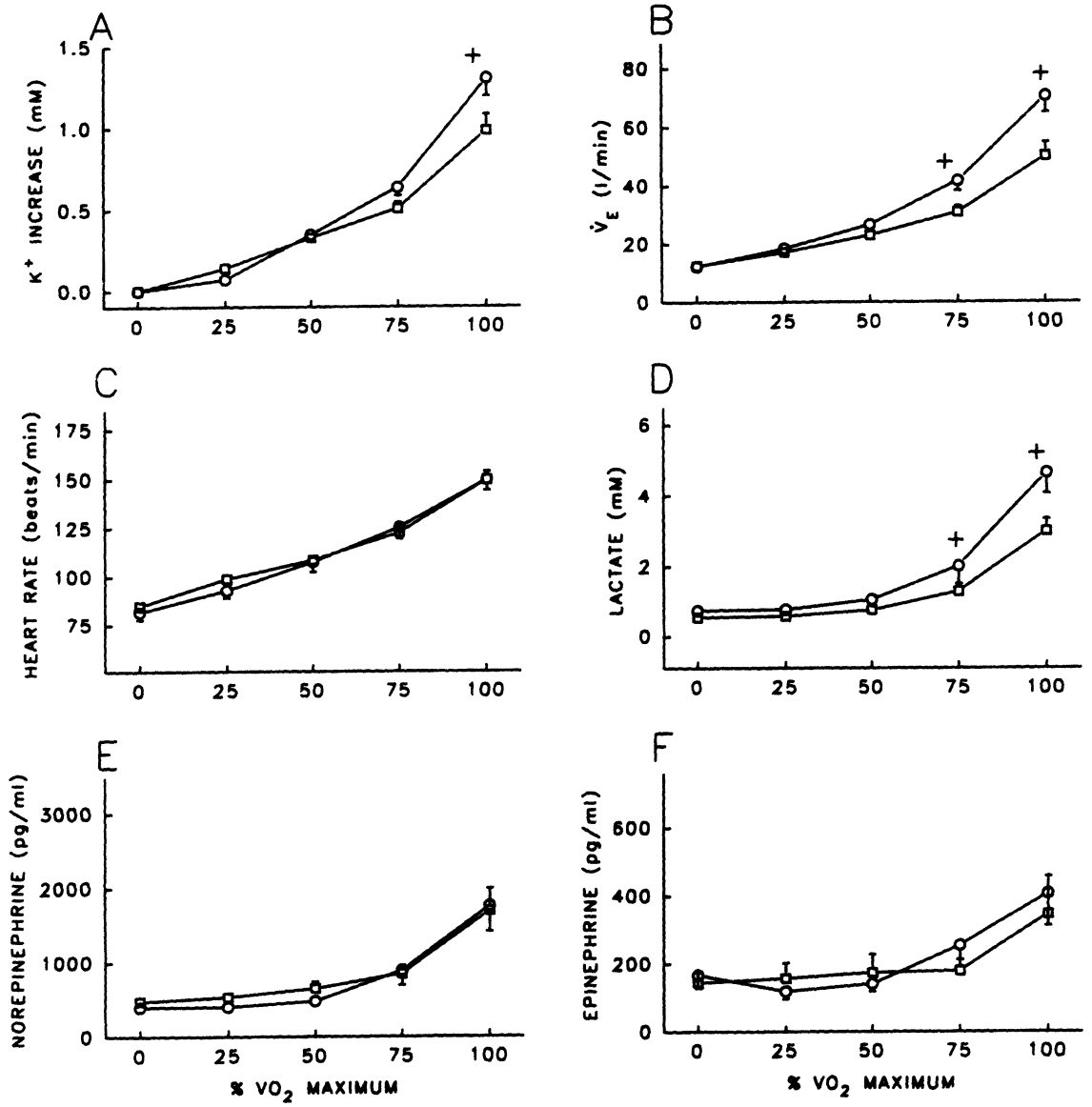

FIG 3. Plots of relations of $[K^+]_a$ rise, $\dot{V}_E$, heart rate, arterial lactate, norepinephrine, and epinephrine to O_2 consumption in subjects with chronic heart failure (CHF) (n=10) (□) and normal left ventricular function (NLVF) (n=10) (○) in the untrained state. †$P<.05$, CHF vs NLVF.

culating catecholamines. The decrease in exercise $\dot{V}_E$ after training was not significant with the incremental cycle exercise protocol used in this study.

Correlation Between $[K^+]_a$ and $\dot{V}_E$ Changes During Exercise and Recovery in CHF

A strong temporal correlation was found between $[K^+]_a$ and $\dot{V}_E$ changes during exercise in both subjects with CHF and those with NLVF. The time course of the rise in $[K^+]_a$ matches $\dot{V}_E$ more closely than that of lactate or norepinephrine, both of which have an initial "lag" at the start of exercise. This lag suggests that lactate and norepinephrine are unlikely to account for the rise in $\dot{V}_E$ with exercise. The close correlation between $\dot{V}_E$ and $[K^+]_a$, irrespective of training status, is in keeping with the possibility that K^+ may serve as a humoral signal in the drive to breathe.[7,8]

Use of Absolute Work Rate and Relative Effort in Comparing the Two Groups

Subjects with NLVF who had undergone previous coronary artery bypass graft surgery were selected to match the postischemic CHF group as closely as possible with respect to other possible manifestations of ischemic heart disease. The groups were also matched with respect to their approximate degree of physical inactivity before beginning the study. The major differences between the two groups were their left ventricular functions and drug therapies. The $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, heart rate, and lactate are increased at matched submaximal work rates in subjects with CHF compared with subjects with NLVF, as other investigators have reported.[1] Subjects with CHF also have increased exercise-induced hyperkalemia and greater arterial catecholamine concentrations than subjects with NLVF at submaximal work rates. Comparisons between the groups in this

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TABLE 3. Effect of Training on the 20 Participants

	CHF Subjects	NLVF Subjects
Work increase, %	16±2.8*	15±3.6*
Work untrained, W	79±5.2	149±8.1
Work trained, W	92±6.4	172±7.9
Peak $\dot{V}O_2$ increase, %	9±5.4	12±4.4*
$\dot{V}O_2$ untrained, mL · kg^{-1} · min^{-1}	13.4±1.2	20.1±1.0
$\dot{V}O_2$ trained, mL · kg^{-1} · min^{-1}	14.7±1.6	22.2±0.8
$\dot{V}O_2$ untrained, L/min	1.00±0.06	1.66±0.11
$\dot{V}O_2$ trained, L/min	1.09±0.12	1.80±0.07
Weight decrease, %	1.8±0.8	1.1±0.7
Weight untrained, kg	76.8±2.8	82.8±3.8
Weight trained, kg	75.2±3.0	81.8±3.4
Training compliance, %	90±6.4	95±6.3

Values are mean±SE.
*P<.01 trained vs untrained.

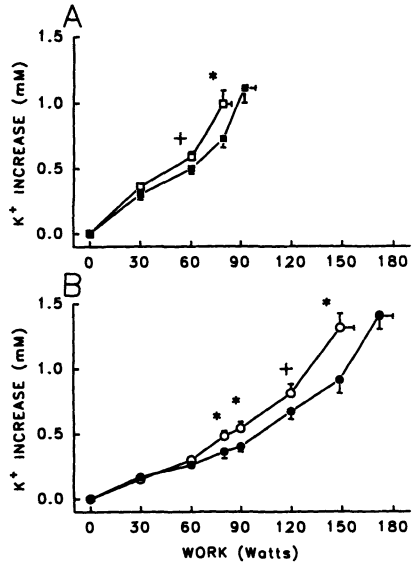

FIG 5. Plots of resting and exercise-induced rise in $[K^+]_a$ in subjects with chronic heart failure (n=10) (□) and normal left ventricular function (n=10) (○) in the untrained (hollow symbols) and trained (filled symbols) states. †P<.05, *P<.01 untrained vs trained.

study are demonstrated for the untrained state only, although identical trends were seen after training. The exercise-induced rise in $[K^+]_a$ is dependent on the absolute work rate; similar $[K^+]_a$ increments were found during two different incremental cycle exercise protocols.

There are several mechanisms that could be responsible for the increased exercise-induced hyperkalemia in CHF; these include possible differences in central and peripheral exercise hemodynamics between subjects with CHF and NLVF.[1,2,37] Alternatively, more K^+ may be lost by the muscle as a result of a greater number of action potentials for a given work rate or by activation of

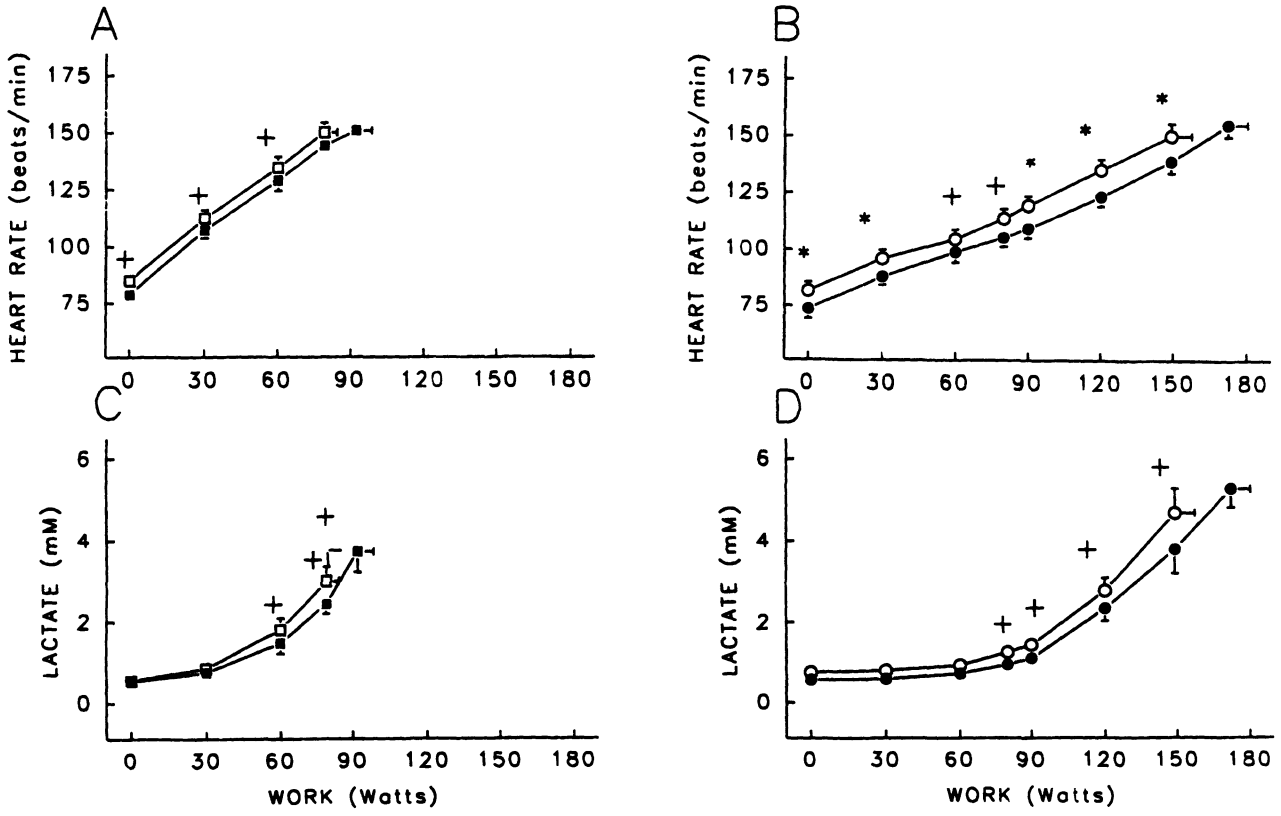

FIG 4. Plots of resting and exercise heart rate and arterial lactate in subjects with chronic heart failure (n=10) (□) and normal left ventricular function (n=10) (○) in the untrained (hollow symbols) and trained (filled symbols) states. †P<.05, *P<.01 untrained vs trained. Dashed lines indicate comparisons of maximal data.

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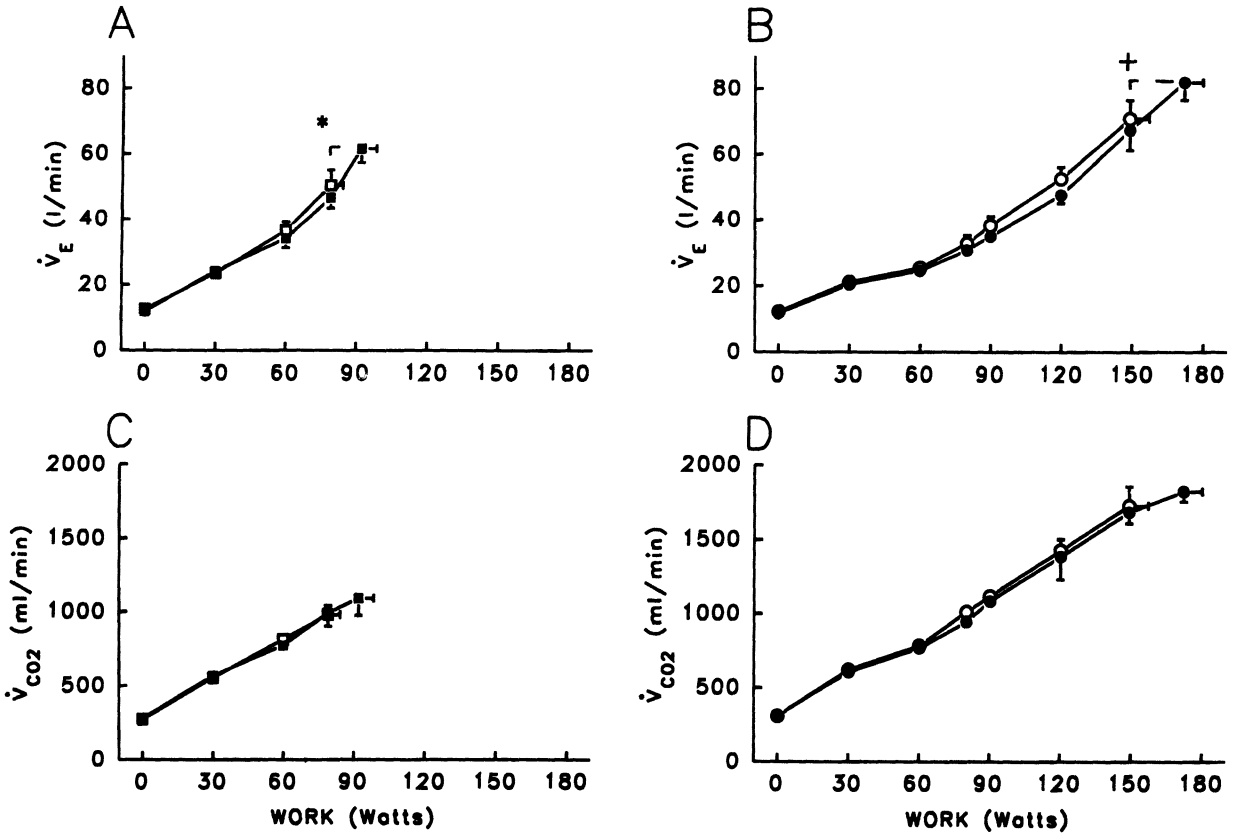

FIG 6. Plots of resting and exercise $\dot{V}_E$ and $\dot{V}_{CO_2}$ in subjects with chronic heart failure (n=10) (□) and normal left ventricular function (n=10) (○) in the untrained (hollow symbols) and trained (filled symbols) states. Dashed lines indicate comparisons of maximal data (†$P<.05$, *$P<.01$).

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Ca^{2+}-dependent or ATP-sensitive K^+ channels.[13,38,39] It is also possible that reuptake of K^+ after repolarization may be slow because of a decreased concentration of Na^+-K^+ pumps in the skeletal muscle of patients with CHF.[33] A decreased concentration of Na^+-K^+ pumps could be a direct consequence of the CHF condition or could be caused by diuretic therapy.[40] Furthermore, the possible effects of angiotensin-converting enzyme (ACE) inhibitors on exercise-induced hyperkalemia have not been studied.

The subjects with NLVF took about the same time (14.9±2.6 minutes) to reach exhaustion with the 10-W/min step protocol as did the subjects with CHF (15.7±3.4 minutes) with the 5-W/min step protocol. This assisted the comparison between the groups of measured variables at relative submaximal effort. One method for demonstrating differences in variables between groups at matched relative effort is to plot changes against percentage of O_2 consumption. This partly takes into account the work rate relative to the aerobic threshold.[41] We found no difference in exercise-induced $[K^+]_a$, heart rate, or catecholamine rises at submaximal levels of O_2 consumption, although $\dot{V}_E$ and lactate increased slightly more rapidly in the subjects with NLVF when plotted in this manner. These findings indicate that K^+ release, matched for relative effort, was similar in the two groups.

Effect of Training on $[K^+]_a$ and Other Exercise Responses in CHF

The physical training program described has been used successfully in the past in patients with CHF at our institution.[17-19] Both groups had lower heart rates and lactate levels at submaximal work rates after training. Subjects did more absolute work when trained and showed decreased PERs during exercise, which indicates a subjective improvement in the somatic stress being experienced.[35] Both groups increased their $\dot{V}O_2$max after training: subjects with NLVF by 12% ($P<.01$) and patients with CHF by 9% ($P=.13$). The 9% increase in the group with CHF, however, did not reach statistical significance, but the trend is in keeping with that observed by others.[15,19] The percentage improvements in $\dot{V}O_2$max after training in patients with CHF reported by some other investigators[15,19] have been surprisingly large and equal to those found in healthy subjects. The smaller improvement in $\dot{V}O_2$max found in the present study could be partly explained by differences in the study protocol. The patients who participated in the study of Sullivan et al[15] did not perform familiarization exercise tests before the baseline assessment. In addition, none of their patients detrained. Their patients did, on the other hand, undertake a more intensive training program than did the subjects in the present study. They also trained under supervision.

We have shown that physical training results in a reduced exercise-induced hyperkalemia at submaximal work rates in both patients with CHF and subjects with NLVF. There was no change in peak increases in $[K^+]_a$ in either group after training. A reduction in exercise-induced venous $[K^+]$ levels has been reported in uncontrolled studies involving comparisons between trained and untrained healthy human subjects.[23] The reduction in

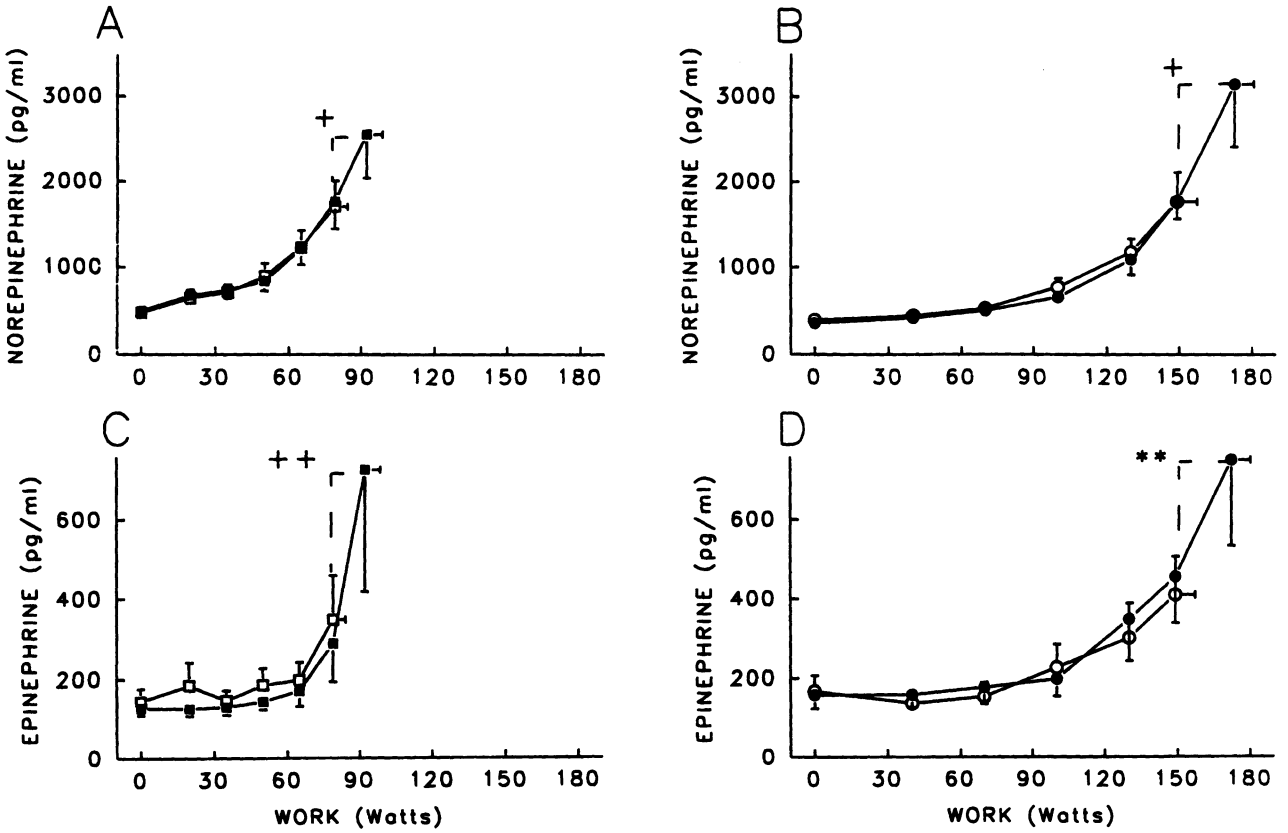

FIG 7. Plots of resting and exercise arterial norepinephrine and epinephrine in subjects with chronic heart failure (n=10) (□) and normal left ventricular function (n=10) (○) in the untrained (hollow symbols) and trained (filled symbols) states. Dashed lines indicate comparisons of maximal data (†$P<.05$ by paired Student's *t* test; ††$P<.05$, **$P<.01$ by Wilcoxon signed-rank test).

exercise-induced hyperkalemia after training could be the result of an increase in the skeletal muscle Na^+-K^+ pump concentration. An increased pump concentration has been described previously in trained compared with untrained healthy elderly men.[24] Although diuretics[40] and ACE inhibitors could alter exercise-induced hyperkalemia, the reduction in the rise of $[K^+]_a$ after training occurred while the doses of these medications remained constant. No patient received K^+ supplementation, although seven patients were receiving amiloride, a K^+-sparing diuretic, as well as frusemide.

The effect of training on $\dot{V}_E$ during submaximal exercise was similar to the effect of training on $[K^+]_a$, but the decreases in $\dot{V}_E$ did not reach statistical significance. Decreases in exercise $\dot{V}_E$ after physical training may be demonstrated using comparisons at constant work loads of long duration.[28,42] A reduction in the slope of $\dot{V}_E/\dot{V}CO_2$ has been reported previously after training subjects with CHF,[19] as has the finding that $\dot{V}_E/\dot{V}CO_2$ is increased in patients with CHF.[43]

Raised levels of catecholamines have a marked effect on K^+ homeostasis and may modulate the physiological effects of K^+ in exercise.[25-27] We are unaware of any previous studies on the effect of physical training on exercise levels of norepinephrine and epinephrine in patients with CHF. We found no changes in arterial catecholamine concentrations at submaximal work rates, but there was a significantly higher peak level after training. These data suggest that the beneficial effects of training on the exercise-induced rise in $[K^+]_a$ during submaximal exercise are not strongly associated with changes in catecholamines. There are conflicting data concerning the spillover of catecholamines into the plasma during exercise in healthy human subjects after training. Some investigators[29] have found that catecholamines increase, whereas Casaburi et al[28] found a reduction after training but used steady-state submaximal exercise testing.

In conclusion, a strong temporal correlation exists between exercise $\dot{V}_E$ and exercise-induced changes in $[K^+]_a$ in subjects with either CHF or NLVF. This correlation is closer than that observed between $\dot{V}_E$ and norepinephrine or that observed between $\dot{V}_E$ and lactate during exercise. Furthermore, exercise-induced hyperkalemia is greater at submaximal work rates in subjects with CHF than in subjects with NLVF. The exercise-induced rise in $[K^+]_a$ is, however, similar in the two groups when matched for relative effort. Physical training improves K^+ homeostasis in both groups by reducing exercise-induced hyperkalemia during submaximal exercise. Exercise responses at submaximal work rates after training, including the reduction in the rise in $[K^+]_a$, are not associated with changes in the levels of arterial catecholamines. The possibility should be investigated that the reduction in exercise hyperkalemia follows an increase in the concentration of Na^+-K^+ pumps in the skeletal muscle with physical training. The pathophysiological significance of the increased exercise-induced hyperkalemia in CHF also requires further study.

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