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Modifying Effects of Exercise on Clinical Course and Biochemical Response of the Myocardium in Influenza and Tularemia in Mice

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For a study of the interactions of strenuous physical exercise (daily swimming to exhaustion) and a viral as compared with a bacterial infection with regard to the clinical course and the biochemical response of the myocardium, influenza and tularemia of similar lethality were used in mice. In both infections, expected infection-induced catabolic alterations in the ventricular myocardium were evident 2 days before median lethality was achieved, with a more pronounced wasting in influenza than in tularemia. Exercise before inoculation (preconditioning) was beneficial in that the catabolic effects of both infections were limited and lethality in influenza was reduced. Thus, the myocardial protein-degrading effect of influenza did not occur with preconditioning, and oxidative tissue enzyme activities decreased less. In tularemia, cytochrome *c* oxidase activity was fully preserved with preconditioning, and activation of catalase was less pronounced. Exercise during ongoing infection counteracted the infection-induced decrease in the activities of glycolytic and oxidative enzymes in tularemia, but lethality and bacterial counts in the spleen were uninfluenced. Conversely, exhaustive exercise in influenza increased lethality and had no significant effect on cardiac enzymes. These exercise models caused no major alterations in activation of lysosomal enzymes (β-glucuronidase and cathepsin D).

Both skeletal muscle and the heart are essential determinants of physical exercise capacity (28). Although good physical fitness may reduce morbidity and mortality in certain diseases (5), it is not clear whether a high level of physical conditioning modifies the susceptibility or the metabolic responses to generalized infections or the factors affecting recovery time.

As to the effects of exercise performed during ongoing acute infection, there is evidence that such activity may worsen the outcome in certain infections that are located in structures specifically activated by the exercise, infections such as viral (15, 22) and parasitic (13) myocarditis or poliomyelitis (19). On the other hand, light physical activity programs in the acute phase of various bacterial, viral, and mycoplasma infections (9, 17) and even rather strenuous exercise in the early convalescence of hepatitis (12) do not seem to provoke complications or delay recovery. Similarly, strenuous exercise during acute tularemia in rats does not increase tissue damage, and the infection-induced catabolic effects on the myocardium are even counteracted (14). Hitherto published data do not allow for any general conclusions about possible benefits and hazards with more demanding physical activity in the acute phase of generalized infections.

Several aspects of the metabolic response of the host to the stress of any infection are stereotyped and predictable (W. R. Beisel [*in* M. C. Linder, ed., *Nutrition and Infection*, in press]), but in a recent study, important differences were observed in the response of the myocardium to influenza and tularemia (20). Thus, more pronounced tissue wasting and concomitant decreases in metabolic capacity occurred in influenza than in tularemia, the catabolic responses to these two infections possibly being mediated by different metabolic pathways (20).

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The first purpose of the present study was to determine whether physical conditioning before infection protected against the catabolic effects of a viral as compared with a bacterial infection. Lethality and biochemical responses of the myocardium were studied in trials 1 and 2. A second purpose was to study the effects of forced exercise in the acute phase of the same infections on myocardial histology, biochemistry, and lethality in trials 3 to 6. Influenza and tularemia of similar intensities were used in mouse models, since myocarditis is not a feature of these infections in resting rodents (14, 20).

MATERIALS AND METHODS

Animals. Male Swiss-Webster mice were used (Harlan, Sprague Dawley Inc.). Mice were maintained on a commercial diet (Wayne Lab Blox, Allied Mills, Chicago, Ill.) before and throughout the experiments and were housed in rooms maintained at 23 ± 1°C. Food and water were supplied ad libitum. The initial mean body weight for the groups of mice varied between 26.6 and 39.9 g (trials 1 to 6). Within each group in each infection, mice were preassigned to take part in the experiment for a total of 6 and 4 days post-inoculation with the influenza or tularemia infection, respectively, these timings representing comparable disease intensities (see below). Mice were randomized in groups (Table 1) that were sized to allow for losses due to lethality estimated for each group from preexperiments. Infected and control mice were studied simultaneously.

Infection. For trials 1, 3, and 5 (Table 1), on day 0, mice in light halothane anesthesia were inoculated intranasally with 0.1 ml of a 10-fold dilution of a mouse-virulent suspension of influenza virus, strain A/Aichi/2/68 (H3N2) delivered to a nose pad encompassing both nares. Virulence was achieved by serial passages in mice, and final products were produced in embryonated eggs and stored at −70°C (21). The thawed virus-containing allantoic fluids contained approximately $10^{8.7}$ egg median infectious doses per ml (21). To achieve the

TABLE 1. Experimental design and group treatment in six separate trials[a]

Group treatment	Treatment used (+) in trial(s):			
	1	2	3 and 5	4 and 6
Sham inoculation + no exhaustion + no preconditioning (controls)	+	+	+	+
Sham inoculation + no exhaustion + preconditioning	+	+		
Sham inoculation + exhaustion + no preconditioning			+	+
Influenza + no exhaustion + no preconditioning	+		+	
Tularemia + no exhaustion + no preconditioning		+		+
Influenza + no exhaustion + preconditioning	+			
Tularemia + no exhaustion + preconditioning		+		
Influenza + exhaustion + no preconditioning			+	
Tularemia + exhaustion + no preconditioning				+

[a] Each trial encompassed four groups of eight mice each. Trials 1 to 4 were biochemical studies, and trials 5 and 6 were histopathological studies. Plus signs, reading down, indicate which four groups were used in each trial.

desired dosage producing median lethality after 8 days in mice challenged by the respiratory route, we diluted the virus in heart infusion broth containing 250 U of penicillin G and 250 μg of streptomycin per ml. In the bacterial infection, mice were challenged intraperitoneally with an 0.2-ml suspension of 3.40×10^4 (trial 2), 4.15×10^4 (trial 4), or 3.75×10^4 (trial 6) CFU of nonwashed *Francisella tularensis* per ml, live vaccine strain that had been grown on solid fortified glucose-cysteine-blood agar (25). Although the strain of *F. tularensis* we used is attenuated in comparison with wild strains, the dose and route of administration had been shown in preexperiments to produce a median lethality at 6 days post-inoculation in Swiss-Webster mice.

Control mice were administered similar volumes of heart infusion broth containing antibacterial admixture intranasally in the influenza trials (trials 1, 3, and 5) or sterile tryptose saline (Difco Laboratories, Detroit, Mich.) intraperitoneally in the tularemia trials (trials 2, 4, and 6). Body temperatures were recorded before sacrifice by a rectally inserted thermocouple.

Swimming exercise. Both preinfection training and exhaustion during infection were performed by swimming mice in a plastic tank filled with tap water at a depth of 20 cm and strictly maintained between 33 and 35°C. All swimming was closely monitored by an experienced person who retrieved the mice in case they sank and were unable to return to the surface. The approximate point of exhaustion was established in preexperiments for both healthy and infected mice, and very few drowning deaths occurred.

Preinfection conditioning: trials 1 and 2. In a 6-week preinfection training program, some mice were forced to swim 6 days a week in three consecutive 2-week periods, the daily swimming time being gradually increased within each period from 45 to 75 min. To increase the load, the mice had no weight or a weight 3 or 5% of their body weight attached to their tails during the first, second, and third training period, respectively. The last training day was the day before inoculation with influenza virus or *F. tularensis*. These mice were allowed to rest during the course of the infections.

Exhaustion during infection: trials 3 to 6. Prior experience with the swimming task is important to maximize the ability of mice to swim effectively during an exhaustion study (14). Therefore, 2 days before scheduled inoculation, mice were placed in the water tank for short periods of familiarization before trials 3 to 6. Exhaustive exercise was achieved with one 50-min swimming session daily during the course of the infections starting on the day of inoculation (day 0) and ending on day 6 of influenza and on day 4 of tularemia. The load was constant, i.e., a weight of 3% of the body weight was attached. This exercise program was found to cause considerable exhaustion of the mice. The mean weight of noninfected sedentary control mice (unconditioned) was similar to that of trained control mice (preconditioned), i.e., 5 to 10% higher than that of exhausted control mice.

Sampling. Two days before median lethality was achieved, i.e., on day 6 of the influenza and on day 4 of the tularemia infection, eight mice from each group were anesthetized with halothane. In each mouse, the thoracic cavity was opened, the caval vein was severed, and blood was collected from the right pleural cavity by using heparinized pipettes. The heart and spleen were removed and put into ice-cold homogenization buffer (trials 1 to 4). The spleen was cleaned from connective tissue, rinsed, blotted on filter paper, and weighed. The myocardium was rapidly opened; atria, major vessels, and blood were removed, and the entire remaining ventricular muscle was cut into small pieces with a pair of scissors and homogenized in ice-cold homogenization medium (150 mM KCl, 50 mM $KHCO_3$, and 6 mM EDTA [pH 7.4]) with all-glass homogenizers operated manually. The entire procedure was performed at 0 to 4°C. The homogenates for acid hydrolase assays were made 0.1% with respect to Triton X-100 concentration. In trials 5 and 6, the myocardium was excised and placed in buffered 10% Formalin for routine histological processing and preparation of hematoxylin and eosin slides. The spleen (trial 5) was aseptically removed and immediately placed in ice-cold, pH 7.0 sterile tryptose saline (Difco). Then the spleen was homogenized and plated in 10-fold serial dilutions on solid fortified glucose-cysteine-blood agar plates for bacterial counts.

Assays. (i) Plasma. Blood plasma from ice was used in individual activity analyses of β-glucuronidase (GUase: EC 3.2.1.31) (Sigma Analytical Kit, Sigma Chemical Co., St. Louis, Mo.).

(ii) Tissues. The total myocardial contents of protein (after incubating 0.100 ml of homogenate with 0.100 ml of 20% KOH at 80°C for 60 min [23]), RNA, and DNA were measured (35). The RNA content was used as an indicator of the protein synthetic capacity in myocardium. The activities of lactate dehydrogenase (LDH: EC 1.1.1.27) (2), citrate synthase (CS: EC 4.1.3.7) (31), and cytochrome *c* oxidase (CYTOX: EC 1.9.3.1) (33) were used as measures of the glycolytic and oxidative capacities of myocardia. The activities of cathepsin D (Cat D: EC 3.4.23.5) (7) and GUase (1) were measured and considered as estimators of the lysosomal capacity related to degradative processes in myocardia. The activity of catalase (EC 1.11.1.6) was determined (trials 1 and 2) and considered as an enzymatic indicator of the degree of muscle wasting (32). The activity of catalase, as expressed by oxygen production, was measured by an oxygen electrode but otherwise was determined essentially as previously described (3). All assays, except those for plasma GUase and protein, RNA, and DNA were performed immediately. The latter were performed on homogenates

TABLE 2. Tissue weights and enzyme activities in myocardia and plasma and concentrations of protein, RNA, and DNA in myocardia in 32 sham-inoculated, unconditioned, nonexhausted control mice (trials 1 to 4)

Component	Unit	Mean ± SD
Body wt	g	32.7 ± 5.2
Spleen wt	mg	107 ± 22
Heart wt	mg	122 ± 21
Plasma GUase	U/ml	6.60 ± 2.50
Heart tissue variables (units per g of "wet" muscle)		
Protein	mg	164 ± 27
RNA	mg	2.76 ± 0.27
DNA	mg	1.77 ± 0.10
Glycolytic enzyme LDH	μmol/min	229 ± 27
Oxidative enzymes		
CS	μmol/min	233 ± 18
CYTOX	μmol of O_2 per min	6.17 ± 0.94
Lysosomal acid hydrolase enzymes		
GUase	nmol/min	17.9 ± 5.6
Cat D	μg of albumin per min	1,033 ± 135
Peroxisomal enzyme (catalase)[a]	μmol of O_2 per min	27.8 ± 8.2

[a] Measured in trials 1 and 2 (n = 16).

that had been frozen and thawed. All measured variables were calculated per gram of "wet" tissue and as total content (or activity) in the entire ventricular muscle.

Histopathological examination of the ventricular myocardium was performed, and the size and number of areas of myocyte necrosis and inflammatory cells were recorded.

F. tularensis cells were counted after incubation of plated homogenates of the spleen for 48 to 72 h at 37°C.

Statistics. The interacting effects of infection and preconditioning or infection and exhaustive exercise were calculated and evaluated for significance by means of two-way analysis of variance. Correlations were performed by using the least-squares method. The chi-square test was used when testing infection-induced differences in lethality between sedentary and preconditioned or exhausted groups of mice.

RESULTS

Tissue weights, enzyme activities in myocardium and plasma, and myocardial protein, RNA, and DNA concentrations in sham-inoculated, unconditioned, nonexhausted control mice are shown in Table 2.

Infection: trials 1 to 6. At the time of sacrifice, 2 days before median lethality was achieved, both infections had caused considerable wasting of body tissues, although this was more pronounced in influenza than in tularemia (Fig. 1). Wasting was reflected by losses of body weight averaging 26% ($P < 0.001$) and 15% ($P < 0.001$), respectively. Myocardial weight was lost (12%) only in the influenza infection, whereas spleen weight showed an increase (38%) only in tularemia.

Both infections caused degradation of cellular constituents in the myocardium, but the decrease of glycolytic and oxidative enzyme activity and of protein and RNA content was more pronounced in influenza than in tularemia. Myocardial DNA content was unaltered. The activity patterns of acid hydrolases did not reflect the more pronounced catabolic response in influenza, but catalase showed a greater activity increase in influenza. These results are in accordance with those of the accompanying study (20).

When examined microscopically (trials 5 and 6), all myocardial sections were diagnosed as being essentially normal tissue. A few mice scattered through all groups showed some minimal foci of mononuclear cells (lymphocytes or histocytes or both) at different sites. These foci were considered too minor to warrant a morphological diagnosis or to have meaningful functional effects. No myocardial fiber changes could be found.

Infection after preconditioning: trials 1 and 2. The present preinfection exercise program did not significantly affect the total myocardial contents of DNA, RNA, and protein (Fig. 2). Similarly, the total myocardial activities of LDH, CS, and CYTOX in sham-inoculated mice were unaltered, although numerical increases were observed for all three enzymes, averaging 5.0, 8.3, and 5.6%, respectively. The tissue activity of acid hydrolase enzymes and catalase were unaltered by this exercise.

In influenza, degradation of the total myocardial protein content was reduced 17% by preconditioning (Fig. 2), and the positive correlation between myocardial protein and RNA observed in noninfected mice was preserved only if the mice had undergone preconditioning (see Fig. 4A). In tularemia, on the other hand, the total protein content was not decreased, and the normal relation between myocardial protein and RNA seemed not to be disturbed by this infection (see Fig. 4B).

A similar trend of a protective effect of preconditioning before influenza infection was observed for the activities of both oxidative enzymes (Fig. 2). Similarly, the tularemia-induced decrease in myocardial CYTOX activity was significantly less pronounced in preconditioned than in unconditioned mice, whereas no significant differences were recorded for CS and LDH (Fig. 2).

The tissue-degrading enzymes GUase, Cat D, and catalase showed similar activities in preconditioned and unconditioned mice in influenza (Fig. 2). In tularemia, on the other

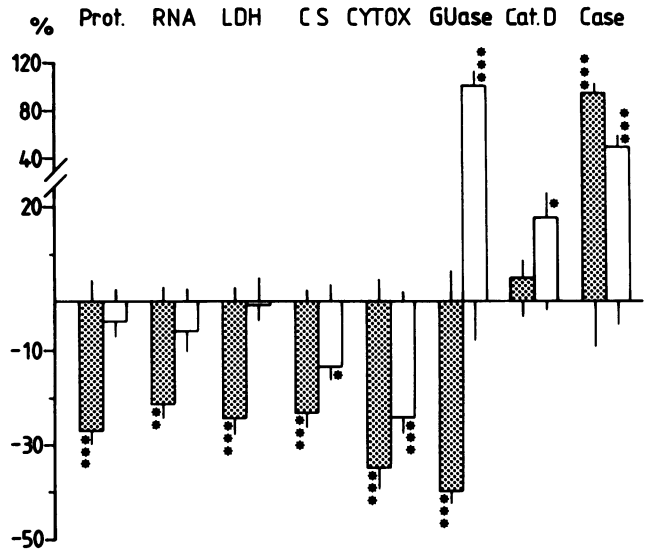

FIG. 1. Effects of influenza (▨) and tularemia (□) (trials 1 and 2, respectively) in unpreconditioned, nonexhausted mice on total myocardial protein and RNA content and on total myocardial LDH, CS, CYTOX, GUase, Cat D, and catalase (Case) activities. Results (mean ± SE) are expressed as percent deviation from those in sham-inoculated control mice, and asterisks indicate statistically significant differences (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$) from the controls.

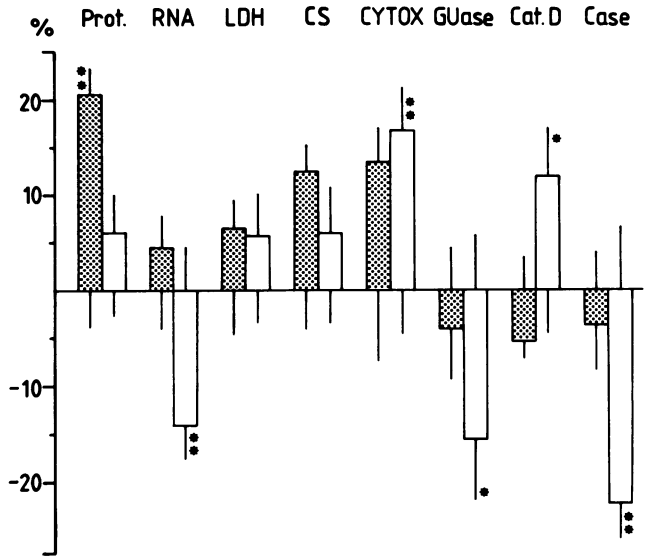

FIG. 2. Protective effects of preconditioning on the catabolic responses of total myocardial protein and RNA content and total myocardial LDH, CS, CYTOX, GUase, Cat D, and catalase (Case) activities to influenza (▩) and tularemia (□) in mice (trials 1 and 2). Results (mean ± SE) in infected preconditioned mice are expressed as percent deviation from those in infected unpreconditioned mice, and asterisks denote statistically significant differences (*, $P < 0.05$; **, $P < 0.01$) from the controls.

hand, myocardial activation of GUase and catalase was limited by preconditioning, but Cat D showed a greater response in preconditioned mice. As in unconditioned mice, the histological picture of the myocardium was normal in both infections.

In tularemia, the plasma GUase elevation was less pronounced in preconditioned (mean ± standard error, 151 ± 46 U/ml, $P < 0.05$) than in unconditioned mice (mean ± standard error, 264 ± 73 U/ml, $P < 0.001$). This preconditioning exercise regime did not affect the plasma enzyme activity in influenza.

Preconditioning did not affect lethality in tularemia, but in influenza, a nonsignificant (Ns) 25% lower lethality (13 compared with 9 of 16 mice survived) in preconditioned than in unconditioned mice was recorded at the time of sampling.

Exhaustive exercise in infection: trials 3 and 4. In sham-inoculated mice, the present program of exhaustive exercise increased the total myocardial RNA content by 6.3 or 11.6% ($P <$ Ns to 0.01) and the total protein content by 5.3 or 13.5% ($P <$ Ns to 0.01) on days 4 and 6, respectively (Fig. 3). In addition, this exercise regime increased the activities of LDH by 5.2 or 11.2% ($P <$ Ns to 0.05), CS by 10.4 or 12.5% ($P < 0.05$), and CYTOX by 11.4 or 16.5% ($P < 0.01$) after 4 or 6 days of exercise, respectively.

In influenza, a protein-sparing effect was observed, although exercise performed during this infection did not induce any increase in myocardial RNA content. The increased myocardial protein content with exercise in influenza was not enough to compensate for the degradation caused by the infection per se (Fig. 3). However, in tularemia, no significant effects on protein or RNA content were recorded with exercise. Further exhaustive exercise did not significantly change the correlation coefficients observed between total protein and RNA contents in unconditioned mice infected with influenza or tularemia or in sham-inoculated control mice (Fig. 4A and B).

In influenza, exhaustive exercise did not alter the responses of the myocardial metabolic enzyme activities to the infection (Fig. 3). On the other hand, in tularemia, the myocardium responded to exhaustion by increasing the activities of glycolytic and oxidative enzymes to fully compensate for the activity-reducing effects of the infection (Fig. 3), yielding results similar to those in noninfected, nonexhausted control mice.

Exhaustion caused no significant change in lysosomal enzyme activity in comparison with that caused by the infections (Fig. 3). Similarly, exercise was not associated with any change in the histological picture of the myocardium.

Spleen weight decreased by 20% ($P < 0.05$) when tularemia-infected mice were forced to exercise (trial 6). However, the total bacterial count in the spleen was similar in exhausted and nonexhausted mice (means ± standard errors were 7.12 ± 3.04 and 8.28 ± 0.48 $\log_{10}$ per entire tissue, respectively).

This exhaustion program did not alter disease-related lethality in tularemia, whereas in influenza there was a 33% higher lethality ($P < 0.05$) among exercising mice (8 compared with 13 of 15 mice survived).

DISCUSSION

Although the programs used for physical conditioning caused only minor to moderate myocardial training responses in noninfected mice, they had a substantial modifying impact on myocardial metabolism during influenza and tularemia. Thus, physical conditioning before infection limited the infection-induced catabolic responses in the myocardium to both infections and reduced lethality in influenza. Conversely, exhaustive exercise during infection increased lethality in influenza and did not influence myocardial glyco-

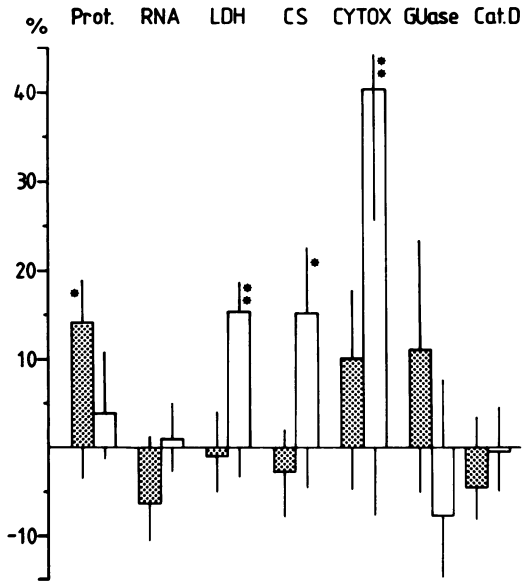

FIG. 3. Modifying effects of exhaustive exercise during ongoing acute infection on the responses of total myocardial protein and RNA content and on total myocardial LDH, CS, CYTOX, GUase, and Cat D activities to influenza (▩) and tularemia (□) in mice (trials 3 and 4). Results (mean ± SE) in infected exhausted mice are expressed as percent deviation from those in infected nonexhausted mice, and asterisks denote statistically significant differences (*, $P < 0.05$; **, $P < 0.01$) from the controls.

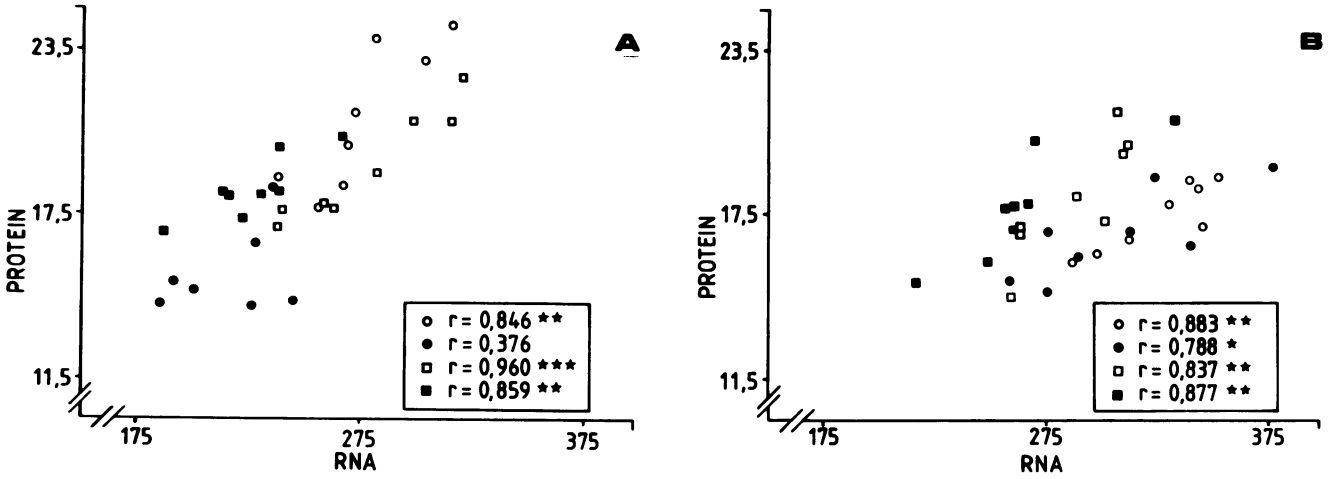

FIG. 4. Total myocardial protein content in relation to total myocardial RNA content in influenza (A) and tularemia (B) and in corresponding sham-inoculated control mice. The mice (trials 1 and 2) were divided into four groups: no preconditioning plus sham inoculation (○), no preconditoning plus infection (●), and preconditioning plus sham inoculation (□), and preconditioning plus infection (■). r, Correlation coefficient; asterisks indicate statistically significant values in each group (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).

lytic and oxidative enzyme activities, although protein degradation was counteracted. In tularemia, exhaustive exercise fully compensated for the infection-associated impairment of oxidative and glycolytic metabolic capacity of the myocardium, and lethality was unaltered.

At the time of study, both of the present infections had caused comparable disease intensities in unconditioned, nonexhausted mice as reflected by the similar lethality rates. The extent of tissue wasting and alterations in biochemical variables was similar to that in the accompanying study (20). Thus, myocardial protein degradation was more pronounced in influenza than in tularemia, the decreased RNA content in influenza suggesting this to be due mainly to decreased capacity for synthesis rather than activation of degradative processes, since lysosomal acid hydrolase activation occurred only in tularemia. Similarly, the oxidative and glycolytic capacities of the heart muscle deteriorated most in the influenza infection (Fig. 1). Another longitudinal study of the present infection models showed that the catabolic alterations occurred earlier and progressed faster in influenza than in tularemia of similar lethality. Neither infection was associated with histopathological signs of myocarditis (20).

The preconditioning program in noninfected mice evoked no measurable training responses in either oxidative or glycolytic pathways of the myocardium. This contrasts with findings in skeletal muscle of considerable adaptive increase in respiratory capacity in response to endurance exercise programs (18). Data from cardiac performance studies are not conclusive but suggest no major alterations in mitochondrial enzyme activity in response to physical conditioning (29). Nevertheless, the present preconditioning protected the myocardium from the catabolic effects of the infections. Thus, on a percentage basis, only about half of the normally occurring tularemia-associated deterioration of myocardial oxidative capacity was recorded after preconditioning. Nearly significant trends of a similar protective effect of preconditioning on oxidative enzyme activity were recorded, even in influenza. However, the most conspicuous effect of preconditioning in this infection was the virtually unaffected total myocardial protein content after the infection. Since preconditioning did not spare any myocardial RNA in these infections, an increased protein synthetic capacity seems less likely to explain the higher protein and enzyme values in conditioned as compared with nonconditioned mice with these infections. On the other hand, Young et al. (36) recorded an early 80 to 90% decrease in the protein synthetic rate of skeletal muscle ribosomes from *Salmonella typhimurium*-infected rats, although the decrease in RNA content was less pronounced. Thus, it cannot be ruled out that preconditioned mice in the present study were less susceptible to infection-induced reduction of the incorporation rate of amino acids into peptides by ribosomes.

Acid hydrolases, such as GUase and Cat D, are associated with cellular degradative processes and turnover of cellular constituents both under normal conditions and in various pathological states (4). Infection-induced alterations in the activities of these enzymes (Fig. 1) occurred to an extent expected from the accompanying report (20). Thus, acid hydrolase activation occurred only in tularemia, whereas in influenza, GUase activity even decreased. Preconditioning changed this pattern only in tularemia, but inconsistently so, as the activity of GUase was 15% lower in conditioned mice, and Cat D activity was 10% higher (Fig. 2). The magnitude of these changes was comparable to those observed when mice are adapting to inactivity. Cessation of training is associated with a decrease in GUase activity in mouse skeletal muscle of ca. 20% (26). This contrasts with the considerably greater acid hydrolase activation of ca. 100% that occurs in red skeletal muscle as a result of long-lasting treadmill exercise (34). Catalase has been proposed to be a valid indicator of the presence of skeletal muscle wasting (32). Consequently, the lower catalase activity observed in conditioned tularemic mice may indicate a lower rate of hydrogen peroxide formation and increased biochemical stability of the myocardial tissue and thus a limited tularemia-induced myocardial degradation. In influenza, on the other hand, preconditioning had no such effect on catalase (Fig. 2).

A lower disease intensity in preconditioned than in unconditioned mice may explain the less pronounced catabolic effects in the myocardium with preconditioning. The nonsignificantly lower lethality in influenza and the lower plasma GUase activity in tularemia in preconditioned than in unconditioned mice support this concept (8).

The mechanisms behind the protein- and enzyme-sparing

effects of preconditioning in influenza and tularemia cannot be explained by our results. The heart of a conditioned rat is better able to tolerate increases in afterload and hypoxia and can hypertrophy more rapidly than that of an unconditioned rat (10). These protective effects may be explained by increased myocardial vascularity and a subsequent increase in extraction of oxygen, nutrients, and essential components (29). The exhaustive exercise program used during ongoing infection caused, in noninfected mice, a small (ca. 10%) but significant myocardial increase in the oxidative and glycolytic metabolic capacities and of protein and RNA contents. This anabolic pattern was more pronounced than with the preconditioning program, possibly due to a detraining effect in the preconditioned mice, since they were resting 4 or 6 days after the last training session (26). Nevertheless, the biochemical training responses observed in the myocardia of noninfected mice exposed to the exhaustive program were minor compared with those that occur in skeletal muscle with various exercise treatments (18, 34). When exhaustive exercise was performed during tularemia, the biochemical effects of the program were exaggerated; for CYTOX, a 40% higher myocardial activity was recorded than in sedentary tularemia mice. Thus, the exercise compensated totally for the catabolic effects of tularemia, which supports the concept of an unaffected protein synthetic capacity but reduced energy accessibility in this infection. The fact that the relative exercise load was higher when performed during acute infection may have contributed to the more vigorous biochemical responses in the myocardia of tularemia-infected mice. However, our results support the concept of an additive type of relationship in the myocardium between the catabolic response of infection and the anabolic response of exercise in tularemia (14). In influenza, exhaustive exercise had a protein-sparing effect on the myocardium but no modifying effects on oxidative and glycolytic enzyme activities. Thus, the training response in enzyme activity of ca. 10% observed in noninfected controls did not limit the catabolic effect in this infection.

The activities of myocardial tissue-degrading enzymes were not altered with exercise in any of the present infections and thus cannot explain the different responses in myocardium when exercise was superimposed on the infections. However, previous findings of an early and profound decrease in protein synthetic capacity in Newcastle disease virus infection (30) and in influenza, but not in tularemia (20), accords with the present results. Thus, the lower protein synthetic capacity in influenza, as reflected by the reduced RNA content (Fig. 1), may explain the failure in achieving a cardiac training response during this infection.

The added stress of the exercise to that of the tularemia infection did not seem to change the intensity of the disease, since plasma GUase activity (8) and lethality were unaltered with exercise. In previous studies, spleen size has shown a correlation with the severity of tularemia in sedentary rodents (24). In the present study, there was no decrease in total bacterial counts in the spleen, although exhaustive exercise reduced the spleen size. In influenza, on the other hand, exercise increased disease lethality in the face of an unchanged plasma GUase activity. Thus, our data of forced exercise superimposed on influenza suggest no role for plasma GUase to explain the increased lethality in this infection. Similarly, other investigators have reported both increases and decreases of plasma acid hydrolases in an effort to define a role for these enzymes in the pathogenesis of death from infection (16). In coxsackievirus infections, exercise may provoke or aggravate myocarditis that increases lethality (22). In the present study, no histological signs of myocarditis could be found to explain the increased lethality in exhausted mice infected with influenza. However, increased viral replication and tissue damage in various other organs may have occurred or a delayed and decreased response in the production of interferon and antibodies. The latter has been noted with exercise in coxsackievirus infections (27). Further, exercise in humans causes the release of a circulating protein that exhibits endogenous pyrogen (EP) activity when injected into rats (6). EP has interesting implications, since it has been observed that bacterial but not viral disease causes release of EP (20), and EP-treated rats show increased resistance to bacterial infections (6). On the other hand, it seems that exercise augments K cell cytotoxicity and thus may indicate exercise-induced modulation of immune responses. Whether this applies to the present infection-and-exercise models remains to be investigated.

Forced swimming in small laboratory animals has been widely used for the study of exercise physiology (11), and with the exhaustion criterion used by us in this swimming model, the mice probably did not aspirate water. Accordingly, in preexperiments with these rodents, the histopathology of lungs was not altered by swimming to exhaustion. On the other hand, since the primary target of influenza infection is the epithelium of the respiratory tract, a plausible explanation to the higher lethality with exercise may be an increased inflammatory edema of the lungs resulting in decreased diffusion capacity for oxygen.

Nevertheless, decreased cardiac metabolic capacity after generalized infections may conceivably contribute to a deterioration of an individual's physical performance capacity. However, in the present study of cardiac metabolic capacity, it was found that a good physical condition protected the myocardium from the detrimental effects caused by either a viral or a bacterial infection, whereas myocardial responses to exercise in the acute phase of the infections were beneficial only in tularemia.

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