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# Physical Training Alters the Pathogenesis of Pacing-Induced Heart Failure Through Endothelium-Mediated Mechanisms in Awake Dogs

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**Abstract**

Background: Beneficial effects of exercise training on cardiovascular function in chronic heart failure (CHF) have been suggested previously, but the underlying mechanisms are unknown. We tested whether daily exercise training improves systemic hemodynamics and preserves endothelium-mediated vasodilator function during development of heart failure.

Methods and Results: Fifteen dogs were surgically instrumented for hemodynamic measurements. One group of dogs underwent 4 weeks of cardiac pacing (210 bpm for 3 weeks and 240 bpm during week 4), and another group underwent pacing plus daily exercise training (4.4 +/- 0.3 km/h, 2 h/d). Pacing-alone dogs developed CHF characterized by typical hemodynamic abnormalities, blunted endothelium-mediated vasodilator function in coronary and femoral circulations, and decreased gene expression of endothelial constitutive nitric oxide synthase (ECNOS, normalized to GAPDH expression; normal, 1.15 +/- 0.31 versus CHF, 0.29 +/- 0.08, P < .05). Exercise training preserved normal hemodynamics at rest, endothelium-mediated vasodilator function, and gene expression of ECNOS (0.72 +/- 0.16 versus normal, P = NS). Inhibition of NO synthesis (nitro-L-arginine) in exercise-trained dogs abolished the preserved endothelium-mediated vasodilation of epicardial coronary arteries and elevated left ventricular end-diastolic pressure (7.7 +/- 0.3 to 19 +/- 3.4 mm Hg, P < .05), suggesting that the preservation of resting hemodynamics was in large part due to preserved endothelial function concealing the underlying CHF state.

Conclusions: Long-term exercise training altered the natural history of heart failure due to rapid cardiac pacing. One of the underlying mechanisms is through the preservation of endothelial vasodilator function. (Circulation. 1997;96:2683-2692.)

Key Words: exercise, endothelium-derived factors, heart failure, circulation.

**Selected Abbreviations and Acronyms**

CBF = coronary blood flow

CD = coronary artery diameter

CHF = chronic heart failure

ECNOS = endothelial constitutive nitric oxide synthase

HR = heart rate

LAP = left atrial pressure

LV = left ventricle, left ventricular

LVEDP = LV end-diastolic pressure

LVSP = LV systolic pressure

MAP = mean arterial pressure

NLA = nitro-L-arginine

Endothelial dysfunction, characterized by blunted release of NO in response to chemical, humoral, or mechanical stimuli, has been documented to occur in experimental and clinical CHF. [1-4] This dysfunction, which has been observed in both peripheral and coronary vascular beds, [2-4] has been hypothesized to contribute importantly to the systemic vasoconstriction, the overall hemodynamic abnormalities, and the symptoms observed in CHF.

Results of several recent studies indicate that endothelium-dependent, NO-mediated vasodilator response to various stimuli can be enhanced by long-term exercise training in multiple vascular beds of normal animals. [5-7] If the same effect can be achieved in the CHF state, then it can be hypothesized that exercise training may improve hemodynamic status (and possibly symptoms) in that condition and that this may be partially mediated by a restoration of endothelial control of vascular tone. It may also be possible in this manner that physical training alters, in a beneficial manner, the natural history of heart failure. To date, however, relatively few data support these hypotheses.

The purpose of this study was to determine whether long-term treadmill exercise training influences systemic hemodynamics and endothelium-mediated vasodilator capacity during 4 weeks of rapid cardiac pacing, which normally induces severe CHF in dogs. In addition, we tested specifically whether NO-dependent pathways contribute to exercise-induced improvements in endothelial function during the progression of CHF. Three groups of dogs underwent rapid cardiac pacing; two of these groups also underwent daily exercise training, while the other group remained sedentary. After 4 weeks of rapid pacing, a time period that routinely induces severe CHF, we examined (1) systemic hemodynamics at rest, during exercise challenge, and in response to NO blockade; (2) coronary and femoral artery endothelial function in response to various stimuli; and (3) ECNOS gene expression in aortic endothelial cells. The overall results, which provided physiological, biochemical, and molecular information from a variety of vascular beds, support the idea that during the development of CHF in this model, long-term exercise training improves resting hemodynamics, improves endothelial function, and enhances ECNOS gene expression. Importantly, the data suggest that the improved hemodynamics are at least in part related to the restoration of endothelial function. Preliminary reports of these findings have been presented previously. [8,9]

## Methods

### Surgical Preparation

Fifteen dogs of either sex (10 male and 5 female) weighing between 26 and 32 kg were used for the main part of this study. Anesthesia was induced with thiopental 5 to 7 mg/kg IV and was maintained with 1.5% to 2.0% inhaled isoflurane mixed with oxygen. A thoracotomy was performed in the left fifth intercostal space by a sterile surgical technique. A Tygon catheter (Cardiovascular Instrument Corp) was placed in the descending thoracic aorta, and a second catheter was inserted in the left atrial appendage. A solid pressure gauge (P6.5, Konigsberg Instruments) was placed in the apex of the LV, and a Tygon catheter was also inserted into the LV for calibration of the solid pressure gauge during the experiment. A Doppler flow cuff transducer (20 MHz, 3.5 to 5 mm in diameter, Baylor College of Medicine) was implanted on the left circumflex coronary artery. A pair of sonomicrometer crystals (7 MHz, 1 x 2 mm) was sutured on opposing surfaces of the same artery. A hydraulic occluder was placed around the same artery distal to the flow transducer and sonomicrometer crystals. A screw-type unipolar myocardial pacing lead was placed on the LV. The wires and catheters were run subcutaneously to the back of the dog. The chest was closed in layers, and a chest tube was inserted to reduce the pneumothorax.

In 6 of the dogs, a second Doppler flow probe and a hydraulic occluder were placed on one of the femoral arteries in addition to the instrumentation detailed above. These dogs were used to study the effects of exercise training on a representative peripheral vascular bed.

The dogs were allowed to recover fully from surgery for at least 10 days and trained to lie quietly on a laboratory table.

### Experimental Design

Dogs were assigned to one of three groups: (1) 4-week rapid cardiac pacing alone with pacemaker turned off for 2 h/d (n = 5), (2) 4-week rapid cardiac pacing plus daily exercise training with pacemaker turned off during exercise training periods (n = 7), and (3) 4-week rapid cardiac pacing plus daily exercise training with pacemaker kept on during exercise training periods (n = 3). Three dogs with femoral artery instrumentation were in group 1, while the other 3 were in group 3.

After full recovery from the instrumentation surgery, baseline studies were performed that consisted of hemodynamic measurements made under two conditions: one with the dogs lying quietly on a table (defined as table experiments) and the other with the dogs running on a treadmill (defined as exercise challenge experiments). Table and exercise challenge experiments were performed on different days, and the order in which they were performed was randomized between dogs. After baseline measurements had been obtained, rapid LV pacing was initiated at 210 bpm for 3 weeks, followed by an additional week of pacing at 240 bpm with an external pacemaker (EV4543, Pace Medical, Inc). This rapid cardiac pacing regimen has been used previously to induce severe CHF. [4,10] During the pacing period, dogs randomized to one of the two exercise groups underwent exercise training (detailed below). After the 4-week pacing period, the hemodynamic measurements performed at baseline were repeated at least 40 minutes after the pacer was turned off [4] (both table and exercise challenge experiments). To determine the role of NO in the observed effects of physical training on systemic and coronary hemodynamics, an additional table experiment was performed on a separate day, in which hemodynamic measurements were made before and after administration of NLA, which is a competitive inhibitor of NO synthase. [2,4] On the final day of this experiment, the chest was opened to harvest endothelial cells immediately from the descending thoracic and abdominal aortas for assessment of ECNOS after the animals were killed by an overdose of pentobarbital sodium (120 mg/kg). The hearts of some of these animals were used in additional experiments (not described in this article [11]). Body weight and the weights of the LV free wall, right ventricular free wall, and septum were all measured.

## Hemodynamic Data Recordings

Hemodynamic measurements were obtained with common recording techniques. MAP and LAP were measured by attaching the previously implanted catheters to P23ID strain-gauge transducers (Statham Instruments, Inc). LVSP was measured with the previously implanted solid-state pressure gauges, which were calibrated in vitro against an electronic signal of known size and cross-calibrated in vivo with measurements of pressure from the LV and left atrial catheters. All the pressure transducers were calibrated in vitro against a mercury manometer with atmospheric pressure as zero and cross-calibrated in vivo with pressure recorded from the implanted arterial, left atrial, and LV catheters. Left circumflex CD and coronary or femoral blood flow were measured with the previously implanted sonomicrometer dimension crystals and Doppler flow transducer, respectively, with a pulsed Doppler system (System 6, Triton Technology Inc). Mean values of aortic pressure, atrial pressure, CD, and coronary or femoral blood flow were all determined on-line by use of 3-Hz averaging filters (DA26, Medtron Engineering). Data were recorded on an eight-channel thermal writing chart recorder (30-V8808-10, Gould Electronics), and periods of interest were digitized (Gateway 2000 486 computer equipped with a National Instruments analog-to-digital conversion system) for off-line analysis. Drift in the pressure gauges, dimension crystals, amplifiers, and chart recorder was eliminated by frequent calibration during table experiments; for treadmill exercise challenge experiments, transducers were calibrated immediately before and rechecked immediately after each training session.

## Protocols

### Daily Exercise Training

Long-term physical training consisted of running on a treadmill (Creative Horse Systems) 2 h/d: 1 hour in the morning and 1 hour in the afternoon. Each 1-hour training session was performed as follows: (1) 5-minute warm-up run at 2 km/h, (2) 50-minute endurance run at 4.4 +/- 0.3 km/h, and (3) 5-minute warm-down run at 2 km/h. In one group of trained animals, the pacemaker was turned off during exercise to provide natural stimulation to the cardiovascular system; of note, it was observed that in these animals, the intrinsic heart rate during treadmill exercise was comparable to the pacing rate (> 200 bpm). However, two features were built into the protocol to ensure that interruption of pacing during the 2-hour exercise period itself did not delay or lessen the degree of heart failure achieved by the pacing regimen. First, in the pacing-alone group, the pacer was turned off for 2 h/d (1 hour in the morning and 1 hour in the afternoon) to mimic the pacing regimen in the main group of exercise-trained animals. Second, in the second group of exercise-trained animals, the pacer was not turned off during the exercise training.

### Table Experiments

On the day of each experiment, a 19-gauge intravenous catheter was inserted in a peripheral vein of a back leg and attached to a piece of extension tubing for drug infusions. LVSP, LVEDP, MAP, LAP, HR, CBF, and CD were measured after the dogs were quiet and accustomed to the laboratory. To assess different aspects of cardiovascular properties and the vasodilator function of the coronary circulation, various interventions were performed, and drugs were injected intravenously in random order.

First, reactive dilation (the response of epicardial CD after release of a brief coronary artery occlusion) and reactive hyperemia (the response of coronary resistance vessels after release of the occlusion) were examined after release of 5, 10, 15, 20, and 30 seconds of coronary occlusion. The occlusion was performed by use of the previously implanted hydraulic occluder.

Second, multiple doses of acetylcholine (0.25, 0.5, 1, 5, 10, and 20 micro gram/kg, Sigma Chemical Co) were given as an intravenous bolus injection. To distinguish the role of receptor-mediated and flow-mediated components, [12] acetylcholine (5 and 20 micro gram/kg) was given in 6 of the dogs while CBF was kept constant by partial inflation of the previously implanted coronary hydraulic occluder in dogs with 4 weeks of rapid cardiac pacing plus daily exercise training.

Third, nitroglycerin at doses of 0.2, 0.8, 5, and 25 micro gram/kg was administered as bolus intravenous injections.

The responses of CD, CBF, and systemic hemodynamic parameters to the injections and after release of a brief coronary artery occlusion were examined. The epicardial CD was expressed as percent change from baseline to normalize the response. The dilation of epicardial coronary artery > 3% in response to nitroglycerin (5 micro gram/kg) was accepted for study. The change in mean CBF was presented as an absolute value because the change in flow was the direct stimulus for flow velocity-dependent dilation of epicardial coronary artery.

Finally, to assess the role of NO as a mediator of exercise-related improvements in hemodynamics, acetylcholine-induced (5 and 20 micro gram/kg), coronary occlusion-induced (15 and 30 seconds), and nitroglycerin-induced (25 micro gram/kg) dilation of circumflex coronary artery were examined before and after intravenous NLA administration. First, we determined the dose of NLA required to achieve total blockade of endothelium-mediated dilation of epicardial coronary artery in response to a 5-micro gram/kg IV bolus injection of acetylcholine. The initial dose of NLA was 30 mg/kg; additional injection of 25 mg/kg was administered as needed to block responses to the acetyl-choline. The average total dose of NLA required was 72 +/- 15 mg/kg. Immediately after the blockade was achieved, coronary artery occlusions, higher-dose acetylcholine, and nitroglycerin injections were performed. Systemic hemodynamics were also recorded before and after NLA at a dose of 30 mg/kg. This protocol was not performed under baseline conditions, only after the 4 weeks of pacing.

**Treadmill Exercise Challenge Experiment**

The dogs stood quietly on the treadmill for baseline hemodynamics. A five-stage exercise regimen was begun. Treadmill speeds of the five stages were 1.5, 3, 6, 9, and 12 km/h. Each speed was maintained for at least 5 minutes until hemodynamics reached a steady state (range, 5 to 7 minutes); the speed was then increased to the next higher level. Myocardial oxygen demand at each treadmill speed was estimated by calculating the rate-pressure product (LVSP times HR). Whether similar cardiac workloads were achieved during exercise challenge between groups was tested by use of this index. [13]

### Control Animals for Heart Weights and Molecular Assay

As will be detailed below, heart weights and ECNOS mRNA levels were examined in the different groups. Because retrieval of hearts and endothelial cells for this assay required animals to be killed, animals could not serve as their own controls for these parameters. Therefore, an additional group of 8 body weight- and age-matched normal animals were obtained from the same source as the other animals. These animals were anesthetized deeply, thoracotomy was performed, and the heart and aortic endothelial cells were harvested.

### ECNOS Gene Expression

ECNOS gene expression was assessed by Northern analysis. In brief, after perfusion with aerated sterile Medium 199 Plus in situ, aortas were collected from the dogs. Endothelial cells were scraped with a surgical blade, and total RNA was isolated by the method described by Chomczynski and Sacchi. [14] Total aortic endothelial RNA (15 micro gram) was electrophoresed in a 1% agarose and 15% formaldehyde gel. Prehybridization was performed with random-primed full-length bovine ECNOS cDNA (4.4-kb mRNA, $1 \times 10^6$ cpm/micro gram) and human GAPDH cDNA (1.3-kb mRNA, $1.2 \times 10^7$ cpm/micro gram). Optical densities of hybridization signals on x-ray films were measured by laser densitometry (Molecular Dynamics) for quantification of RNA levels. ECNOS transcript levels were expressed relative to GAPDH.

### Statistical Analyses

All results are expressed as mean +/- SEM. Within a group, each change was compared with its respective control. Changes in hemodynamic parameters between baseline and postpacing values were compared by one-way ANOVA. Changes in coronary and systemic hemodynamics due to an intervention on the control day were compared with the changes in the same intervention after rapid cardiac pacing plus daily exercise training by a

two-way ANOVA. A Tukey-Ciccheti or Duncan test was used for multiple comparisons, as appropriate. For measurements of ECNOS gene expression, an unpaired two-tailed Student's t test followed by a Bonferroni correction was used. Statistical significance was determined at $P < .05$.

This study was approved by the Institutional Animal Care and Use Committee of Columbia-Presbyterian Medical Center, and animals were cared for in accordance with the Guiding Principles for the Use and Care of Laboratory Animals (NIH publication 82-23, 1985).

## Results

### Daily Exercise Training Improves Resting Hemodynamics

Baseline systemic and coronary hemodynamics were measured (Table 1). In the group of dogs with cardiac pacing alone, severe CHF syndromes were developed. In contrast, dogs with the same cardiac pacing regimen plus daily exercise training showed only minor hemodynamic alterations at rest. Importantly, all baseline hemodynamic measurements except mean CBF obtained from dogs with cardiac pacing plus daily exercise training at rest were significantly different from these measurements obtained from the group of dogs with cardiac pacing alone.

| | Pacing Group (n=5) | | Exercise Group 1 (n=7) | | Exercise Group 2 (n=3) | |
|---|---|---|---|---|---|---|
| | Control | Pacing Alone | Control | Pacing+Ex 1 | Control | Pacing+Ex 2 |
| LVSP, mm Hg | 127±3 | 101±2† | 131±4 | 135±8* | 135±6 | 132±2 |
| LV dP/dt, mm Hg/s | 3176±255 | 1820±180† | 3153±142 | 2560±240* | 3039±388 | 2420±176 |
| LVEDP, mm Hg | 3±0.6 | 21±1.2† | 4±0.6 | 7.9±1.4* | 4±0.5 | 11±4.6 |
| MAP, mm Hg | 102±2 | 85±2† | 104±3 | 98±1* | 105±6 | 99±2 |
| HR, bpm | 89±8 | 132±11† | 91±3 | 100±9* | 88±7 | 104±12 |
| CBF, mL/min | 32±34 | 31±7 | 30±4 | 35±4 | 32±2 | 37±8 |
| Epicardial CD, mm | 3.38±0.4 | 3.48±0.3 | 3.32±0.2 | 3.66±0.1* | 3.43±0.4 | 3.64±0.2 |
| Response to acetylcholine 10 μg/kg | | | | | | |
| Epicardial CD, %Δ | 7.9±0.6 | 1.1±0.7† | 6.4±1.5 | 6.1±1.0* | 8.3±1.7 | 7.7±1.3 |
| CBF, ΔmL/min | 52±15 | 12±4† | 54±11 | 36±4* | 46±7 | 44±10 |

Pacing Group indicates dogs that were cardiac paced for 4 weeks but the pacer was turned off 2 h/d; Exercise (Ex) Group 1, dogs that were cardiac paced and exercise trained for 4 weeks but the pacing was discontinued during exercise training; and Exercise Group 2, dogs that were cardiac paced and exercise trained for 4 weeks but the pacing was continued during the training.
*$P<.05$ vs pacing alone; †$P<.05$ vs control.

Table 1. Baseline Hemodynamics and Endothelium-Mediated Dilation in Dogs With Three Different Pacing and Exercise Regimens

Heart weights were measured. Consistent with a previous study using the same rapid cardiac pacing regimen, [4] ventricular mass and ratio of mass to body weight increased as a result of 4 weeks of rapid cardiac pacing, and this was not altered by exercise training (Table 2).

| | Control (n=8) | Pacing Alone (n=5) | Pacing+Ex 1 (n=7) | Pacing+Ex 2 (n=3) |
|---|---|---|---|---|
| Body weight, kg | 26±0.7 | 25±1.2 | 26±1.7 | 28±1.3 |
| LV, g | 85±3.9 | 124±22* | 113±11* | 116±9 |
| LV/body wt | 3.3±0.2 | 4.4±0.8* | 4.0±0.4* | 4.5±0.8 |
| Right ventricle, g | 46±1.8 | 61±9.8 | 58±7.7 | 60±9.2 |
| Right ventricle/body wt | 1.7±0.1 | 2.1±0.3 | 2.1±0.2 | 2.0±0.5 |
| Septum, g | 37±1.6 | 42±6.7 | 52±2.9* | 54±3.5 |

Control, dogs were also used for Northern analysis of aortic ECNOS gene expression; Pacing Alone, dogs were cardiac paced for 4 weeks but the pacer was turned off 2 h/d; Pacing+Ex 1, dogs were cardiac paced and exercise trained for 4 weeks but the pacing was discontinued during exercise training; and Pacing+Ex 2, dogs were cardiac paced and exercise trained for 4 weeks but the pacing was continued during the training.
*$P<.05$ vs control.

Table 2. Body Weight and Heart Weight

As discussed in "Methods," a group of the dogs underwent rapid cardiac pacing plus daily exercise train ing with the pacer kept on during the training period. The results, summarized in Table 1, show that the preservation of systemic hemodynamics was independent of whether the pacer was turned off or on during the training period.

### Impact of Daily Exercise Training on Hemodynamic Responses to Treadmill Exercise Challenge

Data concerning the hemodynamic responses to exercise challenge are shown in Figure 1. Note that in this figure, control data (ie, data obtained before 4 weeks of pacing) from the pacing-alone and pacing-plus-exercise groups have been combined to simplify the presentation. With regard to these control data, there are two important points: (1) statistical analysis indicated no difference between control values between these groups,

and (2) data obtained after the 4-week pacing regimen were statistically compared with the corresponding control data from the respective group.

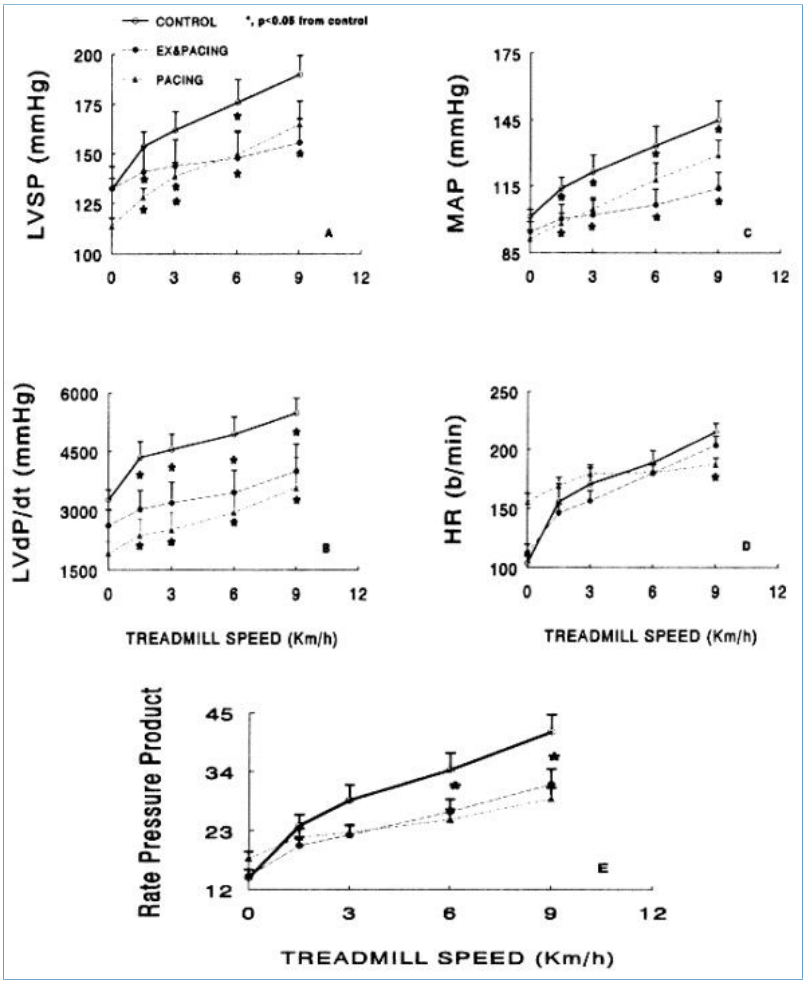


Figure 1. Responses of LVSP, MAP, LV dP/dt, and HR during treadmill exercise (EX) challenge (detailed in text).

In the control state before CHF, LVSP, LV $dP/dt_{max}$, MAP, HR, and rate-pressure product all increased in response to treadmill exercise challenge. In animals that underwent cardiac pacing alone, however, these hemodynamic responses were blunted. Exercise training, which improved resting values of LVSP, LV dP/dt, MAP, and HR, had only a limited effect on these parameters during exercise challenge. Rate-pressure product, which provides a rough estimate of myocardial oxygen demand, during exercise challenge was depressed after 4 weeks of cardiac pacing in both trained and untrained animals, but there was no difference between these two groups; this finding suggests that a similar degree of cardiac loading was achieved during exercise challenge in both of these groups. Thus, exercise challenge revealed the heart failure state in pacing-plus-exercise-training animals. It is noteworthy that none of dogs with pacing alone were able to run on the treadmill at a speed of 12 km/h, and all trained dogs were able to run at this speed; therefore, data obtained at this speed of the treadmill were not shown.

### Coronary Vasodilator Capacity Is Preserved by Daily Exercise Training

To test the hypothesis that exercise training improves endothelial function, coronary hemodynamics were measured in 7 dogs from the pacing plus exercise group, and results were compared with those of 5 dogs from the pacing-alone group. The responses of both epicardial CD and CBF to increasing doses of acetylcholine and to releases of brief coronary occlusions were markedly blunted in the pacing-alone group but nearly preserved in the exercise-trained animals (Figure 2). The preservation of the epicardial coronary artery responses was also not due to an effect mediated by changes in vascular smooth muscle sensitivity, because arterial dilation in response to nitroglycerin was not altered (Figure 3, top). To further test whether preserved endothelium-mediated epicardial coronary artery dilation was due to the increased CBF response, acetylcholine was administered while an occluder was simultaneously inflated in the pacing-plus-exercise-training group to keep the blood flow constant. When this was done, acetylcholine-induced vasodilation was still maintained in the trained animals compared with the control state (Figure 4). In contrast, smooth muscle function of the resistance vessels was impaired in pacing- alone hearts, as evidenced by a blunted CBF response to nitroglycerin, and this was also prevented by exercise training (Figure 3, bottom). Thus, exercise-mediated preservation of epicardial coronary artery dilation appears to be mediated by an effect on endothelial function, whereas the preservation

of CBF responses may be due to effects on both resistance-vessel endothelium and vascular smooth muscle (see "Discussion").

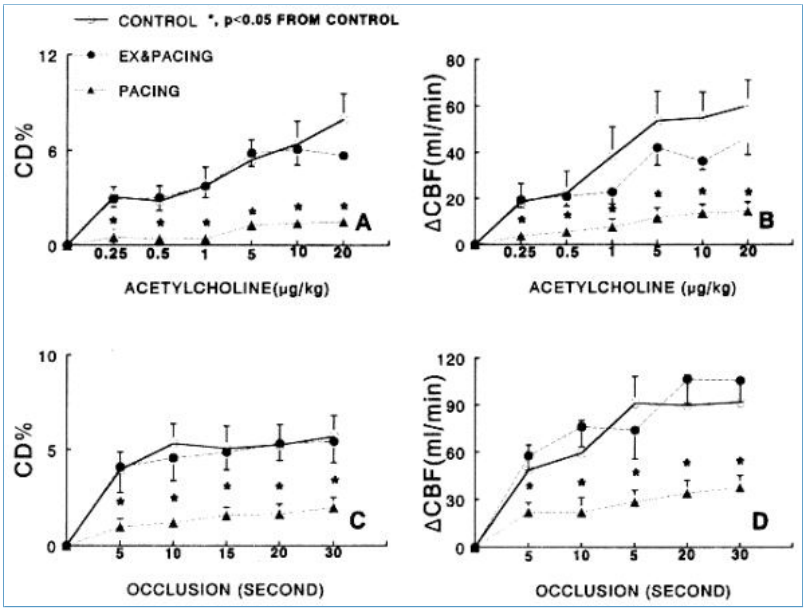


Figure 2. Dilation in epicardial CD and increase in CBF to acetylcholine (top) and to occlusion (bottom) were preserved in dogs with rapid cardiac pacing plus daily exercise (EX) training (n = 7) compared with dogs undergoing pacing alone (n = 5).

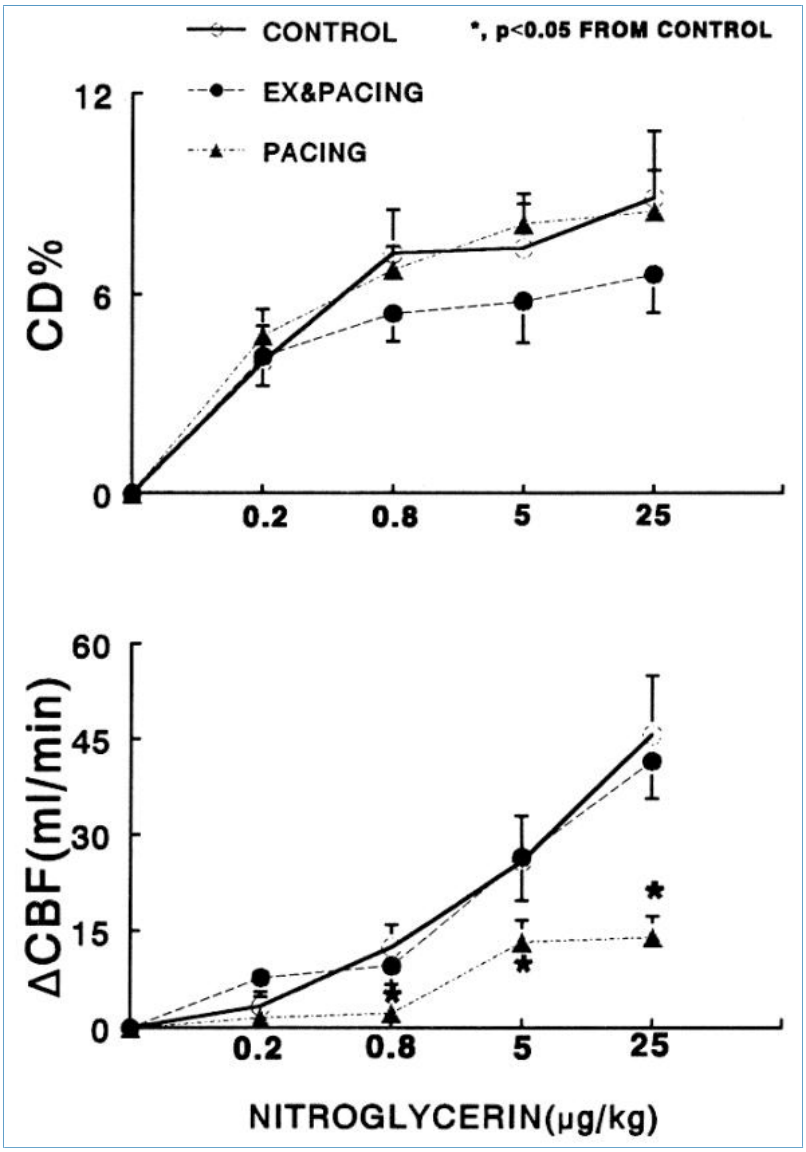


Figure 3. Nitroglycerin-induced dilation of epicardial CD (top) was not altered in either trained (n = 7) and untrained (n = 5) animals with rapid cardiac pacing. Impaired vasomotion of coronary resistance vessels, which was indicated as CBF (bottom), during heart failure was also prevented by daily exercise (EX) training.

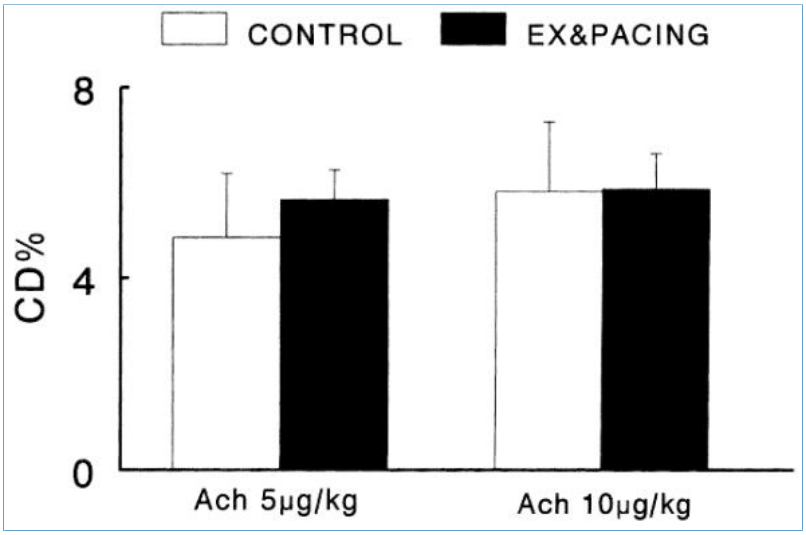


Figure 4. Response of epicardial CD to acetylcholine (Ach) at constant CBF. This dilation was not different before and after 4 weeks of cardiac pacing and exercise (EX) training regimen.

To examine vasodilator function in response to a physiological stress, changes in CD and CBF due to challenge treadmill exercise were also measured (Figure 5). Responses of both parameters were markedly blunted in pacing-alone dogs (n = 5), but this was nearly preserved in exercise-trained animals (n = 7). Thus, the effects of long-term exercise training on coronary properties are evident not only during pharmacological challenges but also during physiological stress.

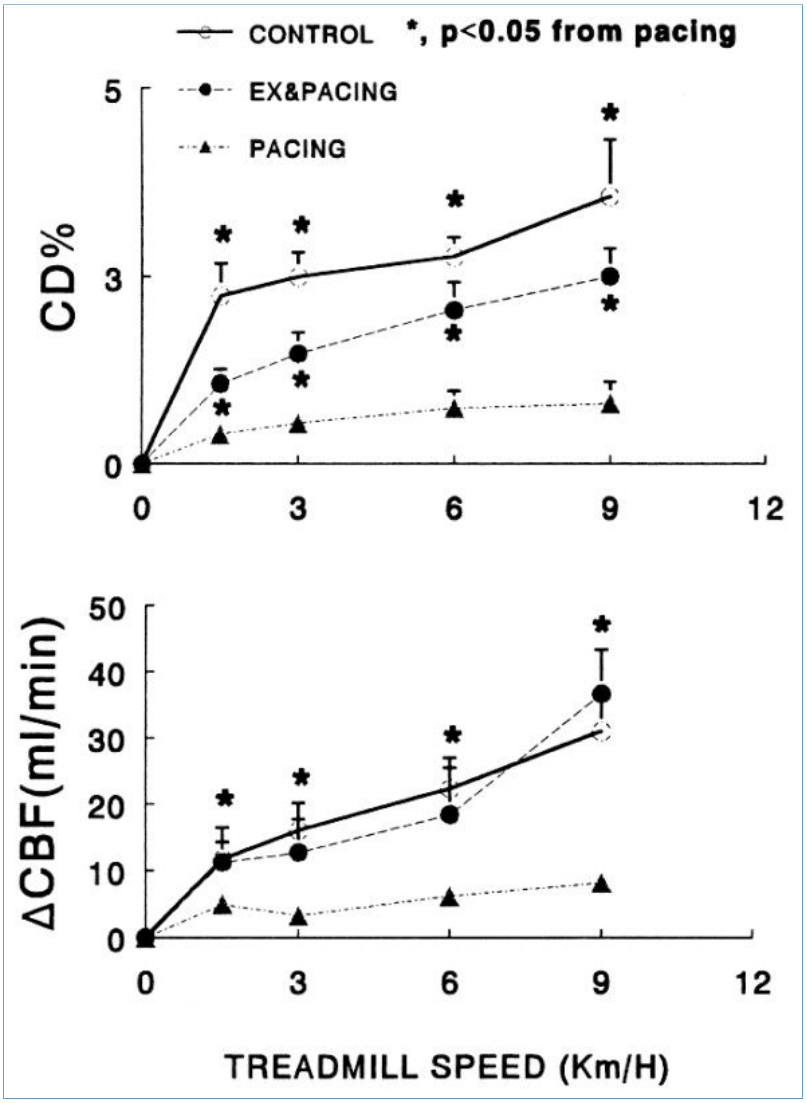


Figure 5. Responses of epicardial CD (top) and CBF (bottom) to treadmill exercise (EX) challenge were blunted in dogs with cardiac pacing alone (n = 5). Vasodilator function of coronary circulation was significantly improved in dogs with cardiac pacing plus daily exercise training (n = 7).

Again, it is noteworthy that both the vasodilator response and the increase in blood flow to a bolus injection of acetylcholine did not depend on whether the pacer was turned on or off during the periods of exercise training (Table 1).

### Peripheral Artery Vasodilator Capacity Is Also Preserved by Daily Exercise Training

Peak femoral blood flow responses to a brief femoral artery occlusion, to acetylcholine injection, and to nitroglycerin infusion were tested in the control state, after 4 weeks of rapid cardiac pacing alone (n = 3), and after 4 weeks of rapid pacing plus exercise training. The results, summarized in Table 3, show that as in the coronary vasculature, peak blood flow responses (expressed as a percentage of resting flow) were markedly blunted to all three interventions, but these were preserved by exercise training.

| | Pacing Alone | | Pacing+Exercise Training | |
|---|---|---|---|---|
| **Parameter** | **Control** | **4 Weeks** | **Control** | **4 Weeks** |
| Resting flow, mL/min | 61±14 | 39±11 | 69±13 | 35±4 |
| Release of 90-s occlusion, % | 135±19 | 18±12* | 175±55 | 115±21 |
| Acetylcholine, 20 μg/kg, % | 40±2 | 19±5* | 75±25 | 43±18 |
| Nitroglycerin, 25 μg/kg, % | 41±5 | 24±7* | 69±6 | 50±6 |

Values are expressed as percent changes from resting flow.
*$P<.05$ vs respective control.

Table 3. Femoral Artery Blood Flow Responses to Various Interventions

Exercise Training-Produced Improvements in Endothelial Function During Development of Heart Failure Are Mediated by NO

The impact of NO synthase antagonism by NLA on the epicardial coronary artery responses to pharmacological agents and brief periods of coronary occlusion was tested before and within 5 minutes after NLA administration in the pacing-plus-exercise-training animals (Figure 6). The open bars in the figure show the changes in CD to coronary occlusions (15 and 30 seconds) and to acetylcholine (5 and 10 micro gram/kg), which, as reviewed above, were similar to the responses in normal animals. As shown in the figure, these responses were markedly blunted by NLA. In contrast, nitroglycerin-induced epicardial coronary artery vasodilation was normal in these animals and was not affected by NLA. Thus preserved endothelial vasodilator capacity is mediated by mechanisms involving NO.

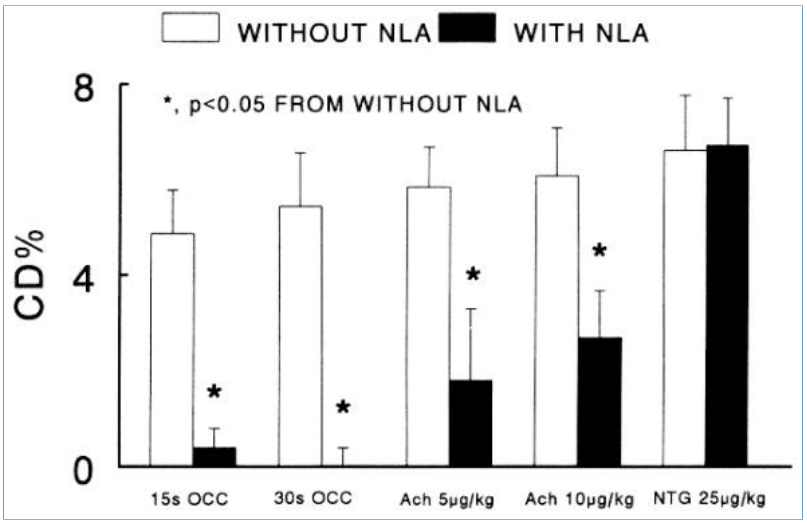


Figure 6. Preserved dilation of epicardial CD after release of 15-second (15s) and 30-second (30s) coronary artery occlusion (Occ) and acetylcholine (Ach)-induced dilation were eliminated by NLA in dogs with cardiac pacing plus daily exercise training (n = 7), but nitroglycerin (NTG)-induced dilation remained unchanged.

NO Partially Mediates Beneficial Effects of Exercise Training on Systemic Hemodynamics During Development of Heart Failure

Our results were consistent with those of a previous study [15] showing that NLA has a significantly blunted effect on resting hemodynamics in dogs that undergo pacing alone compared with normal animals (Table 4). In contrast, the pressor effects of NLA were comparable in normal dogs and in dogs that underwent pacing plus exercise training, indicating a preservation of endothelial function in the periphery. However, whereas LVEDP was not significantly affected in the control and CHF states, LVEDP increased significantly after NLA, suggesting a prominent role of NO in masking the CHF state in the exercise-trained animals. The results are summarized in Table 4.

| | Baseline | NLA |
|---|---|---|
| LVEDP, mm Hg | | |
| Normal | 4.9±0.6 | 7.7±0.3* |
| Pacing+exercise | 7.6±0.9 | 19±3.4*† |
| Pacing | 22±1.6 | 24±1.9 |
| LVSP, mm Hg | | |
| Normal | 134±4.1 | 167±6.1* |
| Pacing+exercise | 137±7.1 | 158±8.5* |
| Pacing | 104±8 | 114±4† |
| MAP, mm Hg | | |
| Normal | 100±2.0 | 124±3.6* |
| Pacing+exercise | 97±2.4 | 128±4.9* |
| Pacing | 85±3 | 96±8† |
| HR, bpm | | |
| Normal | 87±3 | 64±5* |
| Pacing+exercise | 108±9 | 86±4* |
| Pacing | 130±12 | 112±8*† |

Values are mean±SEM.
*$P<.05$ vs baseline; †$P<.05$ vs normal dogs.

Table 4. Responses of Systemic Hemodynamics to NLA in Normal Dogs, Dogs With Pacing Alone, and Dogs With Cardiac Pacing + Daily Exercise Training

Exercise Training Partially Preserves ECNOS Gene Expression During Development of Heart Failure

The results presented thus far suggest that one mechanism of the beneficial effects of exercise training during the development of CHF relates to preservation of the ability of endothelial cells to synthesize NO. To test this hypothesis, we examined whether there was a difference in ECNOS mRNA expression among the groups of animals. An example, shown in Figure 7, reveals a reduction in ECNOS expression in pacing-induced CHF that is partially preserved by exercise training. A summary of results obtained from 5 dogs in each group (Table 5) provides a quantitative confirmation of these results.

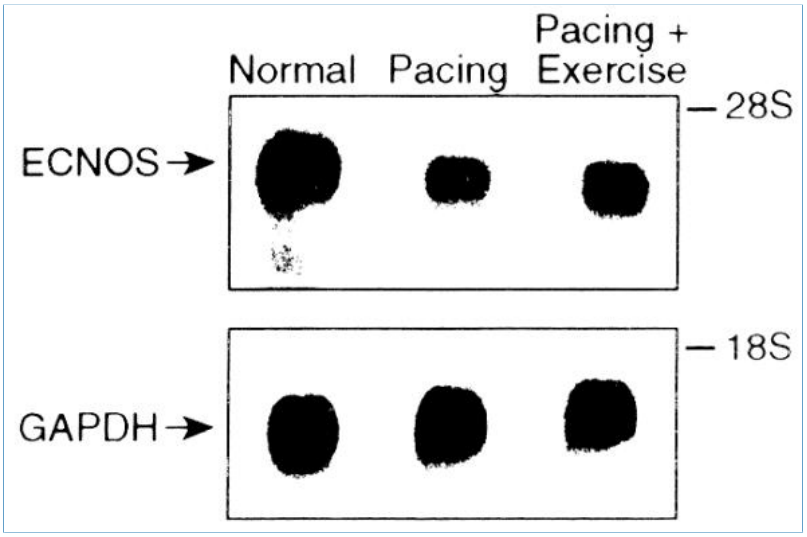


Figure 7. Northern blot shows that in dog with cardiac pacing plus daily exercise training (Pacing + Exercise), aortic ECNOS gene expression is preserved compared with untrained dog (Pacing). Normal indicates normal dog.

| | Ratio of ECNOS to GAPDH |
|---|---|
| Normal (n=5) | 1.15±0.31 |
| Pacing (n=5) | 0.29±0.08* |
| Pacing+exercise (n=5) | 0.72±0.16 |

Values are mean±SEM.
*$P<.05$ vs normal.

Table 5. Alteration of Aortic ECNOS Gene Expression in Dogs With Cardiac Pacing Alone and Dogs With Cardiac Pacing + Daily Exercise Training

## Discussion

Four weeks of rapid cardiac pacing in dogs ordinarily results in severe hemodynamic and clinical manifestations of CHF. This CHF state is not only due to the resulting primary impairment of ventricular contractile properties; secondary changes in the vasculature and other organ systems also contribute significantly. [1-4] The results of the present study reveal that daily exercise training instituted at the onset of rapid cardiac pacing preserves resting values of important hemodynamic parameters and alleviates clinical manifestations of CHF. Underlying these observations was a mild preservation of myocardial properties [11] and, most strikingly, a more significant preservation of both coronary and peripheral artery vasodilator capacity due to exercise training. Finally, many of the beneficial effects of training on the vasculature were related to a preservation of endothelial function, which, according to biochemical and molecular evidence, was specifically attributable to mechanisms involving NO.

Numerous studies over the past several decades have provided evidence that long-term exercise training has beneficial cardiovascular effects in both normal human subjects and normal experimental animals. [16-18] There is also increasing evidence that both central hemodynamic and peripheral metabolic factors are improved by long-term exercise training in the CHF state. [19-21] However, in most previous studies of exercise training, the training regimen has been introduced after CHF was already well established. This differs from the approach taken in the present study, in which exercise training was instituted before overt CHF. Accordingly, instead of addressing the question of whether exercise training improves hemodynamics once CHF is already established, we examined whether exercise training alters the natural history of disease progression. This is an important question because in a large number of patients who present with acute myocardial insults, heart failure develops over time.

This fundamental difference in when exercise training was instituted relative to the onset of disease may in part underlie the more dramatic effects of exercise training on the CHF state observed in the present study than in most previous studies. For example, previous studies have failed to show significant effects on LVEDP, heart contractile state, or MAP when training was instituted in a stable CHF state. [19,20,22] In contrast, the present results show that these and other factors (discussed below) are relatively preserved by exercise training during the development of CHF. Also, the preservation of hemodynamics was not limited to the resting state but was also apparent, although to a lesser degree, in the attenuation of HR and LV dP/dt responses during the hemodynamic stress of exercise challenge. It is interesting that these beneficial effects on systemic hemodynamics were present in the face of only a mild beneficial effect on ventricular pump properties per se, as evidenced by data presented in another report from our laboratory [11] and a previous study. [17] In contrast, our results indicate, on several levels and in different vascular beds, that a primary mechanism underlying many of these beneficial effects relates to a preservation of endothelial NO production.

Involvement of NO mechanisms was first suggested by the finding that competitive inhibition of NO production unmasked the CHF state, most notably evidenced by a marked rise in LVEDP. Although a rise in LVEDP is sometimes considered to reflect an acute decrease in ventricular contractile performance, this was apparently not the case in the present study, because there was no decrease in LV $dP/dt_{max}$ after NO inhibition. Furthermore, recent concepts suggest that an acute rise in LVEDP may be due primarily to an acute decrease in vascular capacity secondary to vasoconstriction. [23] Thus, the elevation of LVEDP after NO inhibition may reflect the importance of maintained or even enhanced vascular endothelial NO function (particularly in the venous system) due to exercise training and implies a compensatory role of this mechanism. LVEDP may also be elevated by increased afterload, but this is not likely to be the case, because although MAP was increased similarly by NO inhibition in normal and pacing-plus-training animals, LVEDP increased only in the latter group. NO inhibition may also affect the time course of ventricular relaxation, but available information suggests that even large changes in tau (the time constant of relaxation) do not have a significant affect on LVEDP. [23]

Consistent with previous studies in CHF, we observed defective endothelium-mediated vasodilation and decreased blood flow reserve in the coronary circulation; this was evidenced by blunted vasodilator responses to acetylcholine and to the release of a brief coronary artery occlusion. [2,4] These responses, which are both at least partially mediated by endothelium-derived NO, were preserved by daily exercise training. Although other factors, such as altered systemic hemodynamic responses, may have contributed to the preserved coronary responses after exercise training, it has been confirmed that the effects of acetylcholine on epicardial CD and

CBF are not altered after elimination of reflexes by beta- and alpha-adrenergic receptor blockade or ganglionic blockade. [12] Therefore, it is unlikely that systemic hemodynamic alterations play a critical role in the preserved endothelium-mediated coronary dilation that was elicited by acetylcholine in exercise-trained dogs. We further showed that these impaired vasodilator responses in the CHF state and their preservation by exercise training did not primarily involve changes in smooth muscle properties in large coronary arteries. This was because the vasodilator response of the epicardial coronary arteries to nitroglycerin was not altered either by CHF itself or by exercise training. Finally, we showed that despite constant CBF conditions, it was still evident that exercise training preserved the ability of acetylcholine to induce epicardial coronary artery vasodilation, suggesting that this effect primarily reflected preservation of endothelial function. The exercise training-induced preservation of endothelial function was also evident in the coronary circulation during the physiological stress of exercise challenge. Exercise challenge-induced epicardial coronary artery dilation is a flow-dependent phenomenon also mediated by endothelium-derived NO. [5,24,25] We showed in the present study that this response is blunted in dogs with rapid cardiac pacing-induced CHF and is near normal in dogs with cardiac pacing plus daily exercise training. Although myocardial oxygen consumption was not examined in our study and might be different at a given treadmill speed between each group of animals, our results clearly demonstrated that at least under our experimental conditions, coronary vasodilator capacity was impaired in dogs with cardiac pacing alone, and this capacity was preserved in dogs with cardiac pacing plus exercise training. Furthermore, several pieces of evidence suggest that the differences in coronary responses were not due to differences in myocardial oxygen consumption during exercise challenge. First, coronary vasodilation was abolished in dogs with pacing alone even at the highest treadmill speed (9 km/h). In contrast, trained dogs demonstrated significant increases in epicardial CD and CBF while running at the lowest speed (1.5 km/h). Second, the rate-pressure product, a rough index of myocardial oxygen consumption, was similar between trained and untrained animals at each treadmill speed after 4 weeks of cardiac pacing, indicating similar cardiac workloads and, in principle, similar myocardial oxygen demands. This finding is significant in that it demonstrates a preservation of endothelial function in the face of a physiological stimulation.

In addition to effects on endothelial function, other factors could have contributed to improved coronary vasoreactivity. These include changes in vascular smooth muscle properties and altered coronary microcirculation structure. With regard to the former, smooth muscle abnormalities were documented in CHF, as evidenced by attenuation of the CBF response to nitroglycerin. [4] As was the case for endothelial properties, these smooth muscle responses were preserved by exercise training in dogs with rapid cardiac pacing. The mechanisms underlying these smooth muscle abnormalities in the CHF state and their preservation by exercise training were not elucidated. [26]

Training-associated changes in microvascular structure were also not examined in the present study. Such changes include an increase in LV mass and increases in myocardial capillary density and coronary reserve. However, previous studies have indicated that in normal dogs, these types of changes do not occur until training periods significantly exceed 4 weeks. [27] In addition, myocardial hypertrophy itself generally reduces both coronary vasodilator capacity and coronary reserve. However, there were equivalent degrees of hypertrophy in pacing-alone dogs and in dogs with pacing plus exercise training, suggesting that the preserved coronary vasodilation properties were not related to a training effect on hypertrophy.

Endothelial dysfunction in CHF is a general phenomenon and is not limited to the coronary vasculature. Previous studies have shown that endothelial NO-mediated vasodilation of peripheral resistance vessels is impaired in CHF. [1,2] In normal animals, exercise training potentiates endothelial function of peripheral vessels. [7,28] Consistent with these previous findings, we showed that endothelial function in the femoral arterial bed (flow responses to acetylcholine and to release of brief arterial occlusions) was impaired in pacing-alone dogs. As in the coronary vasculature, endothelial function in this vascular bed was preserved by exercise training. Thus, the effects of long-term treadmill exercise training on endothelial function involve several vascular beds; however, the total extent of the effect was not defined in this initial study.

Exercise training-induced elevations of aortic EC-NOS have previously been demonstrated in normal dogs. [29] We showed in the present study that aortic ECNOS expression is depressed in dogs after 4 weeks of rapid cardiac pacing and that this expression was preserved by exercise training. It is important to note that this effect does not a priori extrapolate to other vascular beds (either the coronary or peripheral bed). Aortic endothelial cells (not coronary artery endothelial cells) were studied in the present work because it is not possible to obtained a large enough mass of pure coronary endothelial cells from a single heart to perform Northern blot analysis. Nevertheless, this finding provides molecular evidence for preservation of endothelial NO-mediated benefits of exercise training in at least one vascular bed. Examination of this phenomenon in different vascular beds will ultimately reveal whether this effect of exercise training is a general phenomenon or whether it is restricted to certain vascular beds. Also, the fundamental link between exercise training and alterations of ECNOS gene expression is unknown. Potential candidates include exercise training-induced alterations in circulating hormones and local autocoids or neuronal factors. [30] Another important possibility relates to the effects of intermittent increases in blood flow velocity during periods of exercise, which increase the shear stress imposed on vascular endothelial cells. [31] In vitro data have specifically shown that increased shear stress will upregulate ECNOS gene expression, increase the amount of NO synthase, and thus increase NO synthase activity. [31]

The primary potential limitation of the present study relates to the fact that in one group of exercise-trained dogs, the pacer was turned off during the 2 hours of treadmill exercise each day. It could therefore be

suggested that the less severe CHF state in those animals reflected a less severe insult to the myocardium. This issue was directly addressed by studies performed in a separate group of dogs in which the pacer was left on all the time, including the exercise training periods. No differences between these two groups were found, indicating that the preservation of hemodynamics was specifically related to the exercise training regimen and not to turning off the pacer for 2 h/d. Another potential limitation is that we did not specifically examine the effects of exercise training on autonomic function and whether some of the preservation of hemodynamics could have related to interactions between NO and sympathetic nerve function. Also, NO modulates sympathetic outflow [32] and may overcome alpha-adrenergic-mediated vasoconstriction. [33]

The physiological benefits of physical training have been recognized for many years. Long-term exercise training leads to lower incidence of cardiovascular disease, improved cardiac function, and an increase in exercise tolerance [18,30] in normal subjects. Beneficial effects of exercise training are now coming to be appreciated in the CHF state and, in particular, with regard to preservation of endothelial function. [34] Accordingly, experimental studies of the effects of exercise training on the natural history of heart failure have direct physiological and clinical significance. Specifically, these findings and the results of the present study raise the question of whether a rigorous exercise training program could be used as a therapy to improve patient symptoms when it is instituted in an early stage of CHF.

In summary, exercise training had a significant beneficial effect on the natural history of the CHF development in dogs that underwent 4 weeks of rapid cardiac pacing. This was manifested as a preservation of normal hemodynamics at rest, endothelium-mediated vasodilator function, and gene expression of ECNOS. Inhibition of NO synthase by NLA in exercise-trained dogs abolished the preserved endothelium-mediated vasodilation of epicardial coronary arteries and elevated LVEDP, suggesting that preservation of resting hemodynamics was due in large part to preserved endothelial function that concealed the underlying CHF state.

## Acknowledgments

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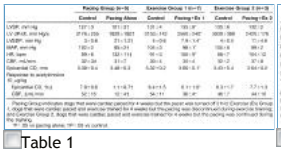
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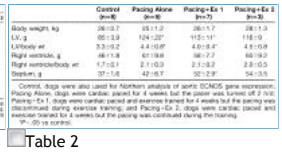
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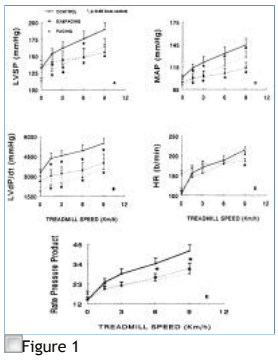


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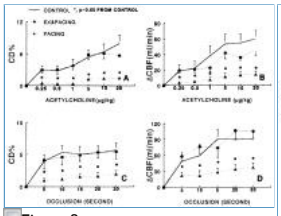

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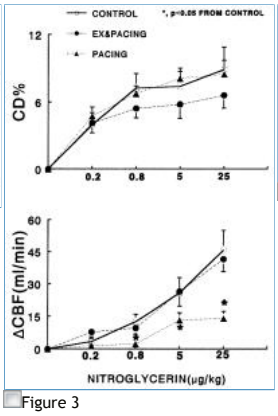


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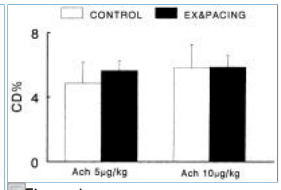


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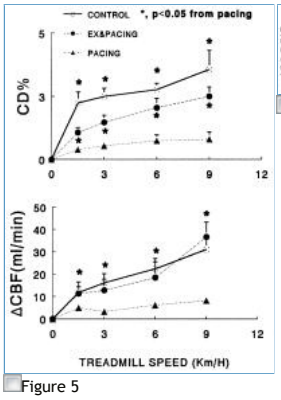


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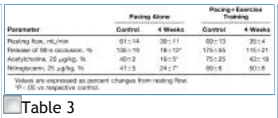

| Parameter | Pacing Alone Control | Pacing Alone 4 Weeks | Pacing+Exercise Training Control | Pacing+Exercise Training 4 Weeks |
|---|---|---|---|---|
| Resting flow, mL/min | 61±14 | 78±11 | 69±13 | 35±4 |
| Reserve of 90-s occlusion, % | 138±19 | 18±12* | 175±55 | 115±21 |
| Acetylcholine, 25 μg/kg, % | 40±2 | 19±5* | 75±25 | 43±19 |
| Nitroglycerin, 25 μg/kg, % | 47±5 | 24±7* | 69±8 | 50±6 |

Values are expressed as percent changes from resting flow.
*P<.05 vs respective control.

Table 3

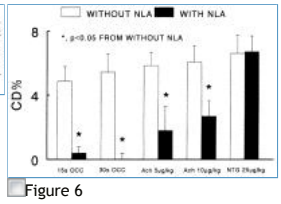


Figure 6

| | Baseline | NLA |
|---|---|---|
| LVEDP, mm Hg | | |
| Normal | 4.9±0.6 | 7.7±0.3* |
| Pacing + exercise | 7.6±0.9 | 19±3.4*† |
| Pacing | 22±1.6 | 24±1.9 |
| LVSP, mm Hg | | |
| Normal | 134±4.1 | 167±6.1* |
| Pacing + exercise | 137±7.1 | 158±6.5* |
| Pacing | 104±8 | 114±4† |
| MAP, mm Hg | | |
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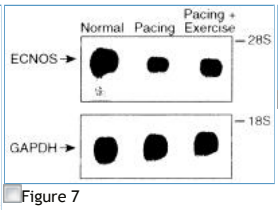


Figure 7

| | Ratio of ECNOS to GAPDH |
|---|---|
| Normal (n=5) | 1.15±0.31 |
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| Pacing + exercise (n=5) | 0.72±0.16 |

Values are mean±SEM.
*P<.05 vs normal.

Table 5

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