Impact of exercise training on ventricular properties in a canine model of congestive heart failure

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Todaka, Koji, Jie Wang, Geng-Hua Yi, Mathias Knecht, Richard Stennett, Milton Packer, and Daniel Burkhoff. Impact of exercise training on ventricular properties in a canine model of congestive heart failure. Am. J. Physiol. 272 (Heart Circ. Physiol. 41): H1382–H1390, 1997.—Exercise training improves functional class in patients with chronic heart failure (CHF) via effects on the periphery with no previously documented effect on intrinsic left ventricular (LV) properties. However, because methods used to evaluate in vivo LV function are limited, it is possible that some effects of exercise training on the failing heart have thus far eluded detection. Twelve dogs were instrumented for cardiac pacing and hemodynamic recordings. Hearts were paced rapidly for 4 wk. Six of the dogs received daily treadmill exercise (CHF$_{EX}$, 4.4 km/h, 2 h/day) concurrent with rapid pacing, while the other dogs remained sedentary (CHF$_S$). Hemodynamic measurements taken in vivo at the end of 4 wk revealed relative preservation of maximum rate of pressure rise (2,540 ± 440 vs. 1,720 ± 300 mmHg/s, $P < 0.05$) and LV end-diastolic pressure (9 ± 5 vs. 19 ± 4 mmHg, $P < 0.05$) in CHF$_{EX}$ compared with CHF$_S$. The hearts were then isolated and cross perfused for in vitro measurement of isovolumic pressure-volume relations; these results were compared with those of six normal dogs (N). Systolic function was similarly depressed in both groups of pacing animals [end-systolic elastance (E_{es}) values of 1.66 ± 0.47 in CHF$_S$, 1.77 ± 0.38 in CHF$_{EX}$, and 3.05 ± 0.81 mmHg/ml in N, with no changes in volume axis interceptors of the end-systolic pressure-volume relationship]. The diastolic myocardial stiffness constant, k, was elevated in CHF$_S$ and was normalized by exercise training (32 ± 3 in CHF$_S$, 21 ± 3 in CHF$_{EX}$, 20 ± 4 in N). Thus daily exercise training preserved in vivo hemodynamics during 4 wk of rapid cardiac pacing and was accompanied by a significant change in diastolic myocardial stiffness in vitro. These findings suggest that changes in heart function may contribute to the overall beneficial hemodynamic effects of exercise training in CHF by a significant effect on diastolic properties.

stiffness constant; pressure-volume relationship; maximal elastance; stress-strain analysis; myocardial oxygen consumption; collagen; relaxation

RESULTS OF RECENT clinical studies suggest that exercise training improves exercise capacity and quality of life in patients with chronic congestive heart failure (CHF) (4, 14). The results have further suggested that such improvement is achieved without any detectable restoration of ventricular systolic properties (5, 7, 24), suggesting a dominant effect of exercise training on peripheral factors also known to be important determinants of cardiovascular performance. Such peripheral effects include exercise-induced changes in vascular, skeletal muscle, and autonomic nervous system proper-

ties. However, methods used in the clinical setting to detect changes in ventricular properties have mostly been limited to an assessment of systolic function indexed by ejection fraction. It is well known that ejection fraction is neither a sensitive nor a specific method to detect subtle changes in ventricular function, especially in the setting of altered vascular properties (11). In contrast to conclusions derived from clinical studies, it has been shown that papillary muscle strength and the shortening velocity of isolated myocytes are enhanced in normal rats following chronic exercise training (17, 18, 25). Thus it is possible that an effect of chronic exercise training on ventricular function that has thus far eluded detection may exist in heart failure.

Therefore, the purpose of this study was to determine whether exercise training affects intrinsic left ventricular (LV) systolic or diastolic properties in dogs with rapid cardiac pacing-induced heart failure. One group of dogs underwent cardiac pacing alone, and a second group underwent cardiac pacing plus daily exercise training. We examined resting hemodynamics in awake dogs to test whether exercise training resulted in any objective improvement in systemic hemodynamics during the development of pacing-induced heart failure. The hearts of these animals were then excised, cross perfused, and instrumented with intraventricular balloons. Use of this preparation allows for assessment of ventricular contractile properties through accurate control and measurement of LV volume and pressure while providing an environment free of autonomic nervous system or changing humoral factors. The results indicated that exercise training attenuated the hemodynamic abnormalities ordinarily observed after 4 wk of rapid cardiac pacing in vivo and that this was accompanied by a small change in systolic ventricular function in vitro. However, diastolic myocardial stiffness was significantly decreased in paced animals which also underwent exercise training when compared with animals in the pacing alone group. This change in diastolic function associated with exercise training in paced animals, combined with the slight improvement in systolic function, resulted in a significant improvement in overall LV pump function as evidenced by an increase in workload capacity at any given filling pressure.

METHODS

Heart Failure Model and Exercise Protocol

Twelve mongrel dogs were anesthetized (1–2% inhaled isoflurane) and underwent aseptic surgery for chronic instrumentation via a left thoracotomy. A Konigsberg pressure

transducer was inserted into the LV through the apex, fluid-filled catheters were inserted into the left atrium, and the aorta and pacing wires were fixed to the LV free wall. After 2–3 wk of recovery, baseline hemodynamics were recorded with the dogs lying on a laboratory table in a resting, conscious state. The dogs assigned to the exercise group (CHF_{EX}, $n = 6$) were trained to run on a treadmill. Pacing was then initiated at 210 beats/min for 3 wk, followed by 240 beats/min during the 4th wk. During this 4-wk period, these dogs underwent daily exercise training, which consisted of running on the treadmill at submaximal speed (4.4 ± 0.3 km/h) 2 h/day (1 h in the morning and 1 h in the afternoon). The dogs assigned to the sedentary group (CHF_S, $n = 6$) were kept sedentary in cages while being paced with the same pacing regimen. After 4 wk of pacing or pacing plus exercise training, measurements of the resting hemodynamics were repeated at least 40 min after turning off the pacer. The hearts of these animals were studied as described below.

Isolated Heart Preparation

To test the effects of rapid ventricular pacing and/or exercise training on LV systolic and diastolic properties, the hearts of the CHF_{EX} and CHF_S animals and the hearts of six body weight-matched normal controls were studied using a standard isolated heart preparation. Details of this preparation have been provided previously (3). The heart from the dog of interest was excised and metabolically supported by blood provided from a second support dog. The femoral arteries of the support dog were cannulated and connected to a perfusion circuit consisting of two peristaltic pumps, a heater, a blood filter, and an air trap. The pressure in the aortic root of the isolated heart, which is the perfusion pressure for coronary flow, was measured and used as the feedback signal for a servo system that regulated the speed of the peristaltic pump and maintained perfusion pressure at ~80 mmHg. Blood traveled through the coronary vasculature of the isolated heart and returned to the support dog by gravity. Coronary flow was collected through a wide-bore cannula placed through the right atrium into the right ventricle and was measured by an in-line ultrasonic flowmeter (Transonic Systems model T108, Ithaca, NY). The difference between arterial and venous oxygen content ($A\text{-}V_{O_2}$) was measured on-line by a commercially available spectrophotometer (AVOX Systems, San Antonio, TX). Oxygen consumption of the whole heart was determined by multiplying coronary flow by $A\text{-}V_{O_2}$.

A water-filled balloon was placed within the left ventricle via the mitral valve. The volume of the balloon, and therefore of the ventricle, was controlled by a piston-pump servo system. A micromanometer (Millar Instruments model SPC-360, Houston, TX) placed within the balloon was used to measure ventricular pressure. The heart was paced from the LV apex at a constant rate (126 ± 11 beats/min) and was constrained to contract isovolumically. Blood temperature was kept at ~37°C by a heat exchanger.

All procedures were in accordance with institutional guidelines (Institutional Animal Care and Use Committee, Columbia University).

Isolated Heart Protocol

After isolation, the heart was allowed to stabilize for ~30 min. LV pressure, coronary blood flow, and $A\text{-}V_{O_2}$ were measured at several different volumes chosen to provide a range of end-diastolic pressures between <0 and a minimum of 15 mmHg. The volume steps between different settings were between 5 and 10 ml depending on the size of the

individual hearts. At each volume setting, enough time was allowed to attain steady-state conditions as judged from all signals recorded (usually 2–3 min). The data were acquired digitally at a sampling frequency of 1,000 Hz.

Data Analysis

Assessment of systolic properties. Systolic properties of the LV chamber were assessed in the isolated hearts by the linear end-systolic pressure-volume relationship (ESPVR)

$$P_{es} = E_{es}(V_{es} - V_0) \tag{1}$$

where P_{es} is end-systolic pressure, V_{es} is end-systolic volume, E_{es} is the slope of the ESPVR, and V_0 is the volume-axis intercept of the ESPVR.

Systolic properties were also assessed by the linear relationship between the maximum rate of LV pressure rise (dP/dt_{max}) and LV volume (13)

$$dP/dt_{max} = dE/dt_{max}(V - V_{int}) \tag{2}$$

where dE/dt_{max} and V_{int} are the slope and volume–axis intercept, respectively, of the relation and V is the isovolumic volume.

Assessment of diastolic properties. Diastolic properties were assessed by several indexes. First was the end-diastolic pressure-volume relationship (EDPVR), whereby the end-diastolic pressure-volume points were fit to a power function (16) as follows

$$P_{ed} = mV_{ed}^{\alpha} + n \tag{3}$$

where P_{ed} is end-diastolic pressure, V_{ed} is end-diastolic volume, and m, n, and α are the regression parameters. α has been shown to be a geometry- and mass-independent index of myocardial diastolic stiffness (15) and can be calculated by determining the slope of the linear relation between volume elasticity [$V(dP/dV)$] and P_{ed} (16), since it follows from *Eq. 3* that

$$V(dP/dV) = \alpha m V_{ed}^{\alpha} = \alpha(P_{ed} - n) \tag{4}$$

To further assess average diastolic myocardial properties, a stress-strain analysis was performed. Myocardial circumferential stress (σ) and natural strain (ϵ) were estimated by the following formulas (31), which assume a thick-walled spherical chamber

$$\epsilon = \ln (L/L_0)$$
$$\sigma = 1.355 LVP \, \pi r_i^2 / \pi(r_0^2 - r_i^2) \tag{5}$$

where $L = [(\frac{3}{4}\pi) \, [LVV + (4\pi/3) \, (r_m^3 - r_i^3)]]^{1/3}$, $L = L_0$ when $P_{ed} = 0$; r_i, r_m, and r_o are internal, midwall, and external radii of the LV, respectively, LVP is the left ventricular pressure, and LVV is the left ventricular volume. Each of the radii is determined from the equation for the volume contained within the respective sphere of interest: $r = (3V/4\pi)^{1/3}$. A specific gravity of 0.96 g/ml was assumed for myocardium. The average diastolic myocardial stiffness constant (k, which is analogous to the chamber index α explained above) was estimated by determining the slope of the line of regression between myocardial stiffness ($d\sigma/d\epsilon$) and stress (15)

$$d\sigma/d\epsilon = k\sigma + C \tag{6}$$

where C is a constant.

Assessment of active relaxation. The rate of diastolic relaxation was assessed by pressure half-time ($t_{1/2}$), which is the time for the LV pressure to fall from its value at maximum

negative dP/dt one-half of the way back to the end-diastolic pressure (EDP) (16). Because relaxation is a preload-dependent process, $t_{1/2}$ was measured at three different values of EDP.

Assessment of myocardial energetics. To determine whether exercise training resulted in any metabolic effects on the myocardium, the relationship between myocardial oxygen consumption (M$\dot{V}O_2$) and LV pressure-volume area (PVA) (22) was determined. M$\dot{V}O_2$ was calculated as detailed above. PVA was defined as the area circumscribed by ESPVR, EDPVR, and the systolic portion of the pressure-volume loop (which is a vertical line in the case of an isovolumic beat) on the LV pressure-volume diagram. Both M$\dot{V}O_2$ and PVA were normalized to 100 g LV mass and then fit to a linear equation

$$M\dot{V}O_2 = A\,PVA + B \tag{7}$$

where A is the slope and B is the intercept of the relation.

Assessment of LV pump function. To obtain an index of ventricular pump properties that simultaneously accounts for changes in both systolic and diastolic properties, overall LV pump function was assessed by determining the relationship between isovolumic PVA and EDP (23). The isovolumic PVA at a given preload represents the maximum mechanical energy-generating capacity of the LV at that preload and therefore as been regarded as a suitable parameter for indexing pump function in representation of the Frank-Starling law of the heart. When the ESPVR and EDPVR are specified by *Eqs. 1* and *3*, respectively, isovolumic PVA (PVA$_{\text{ISO}}$) can be reconstructed analytically as follows

$$PVA_{ISO}(V_{ed}) = \int_{V_0}^{V_{ed}} [E_{es}(V - V_0) - (mV^\alpha + n)]dV \tag{8}$$

where $V_{ed} = [(P_{ed} - n)/m]^{1/\alpha}$ (from *Eq. 3*).

Collagen content by hydroxyproline assay. As will be detailed in RESULTS, changes in diastolic stiffness were noted between the groups; to test whether this was related to changes in collagen content, myocardial collagen content was quantified using a hydroxyproline assay (30) with slight modifications. The LV free-wall samples from five CHF$_S$ and four CHF$_{EX}$ hearts were homogenized, hydrolyzed, and incubated with chloramine T. Samples from seven other normal dogs were used as control. The absorbance of the resulting solution at the wavelength of hydroxyproline chromogen (540 nm) was measured. To generate a standardization curve for the measurements, collagen samples of known concentrations were prepared from purified collagen of bovine Achilles tendon and absorbance was measured in the same manner as for the heart samples. Collagen content (expressed as a percentage of dry myocardial weight) was derived from this standard curve.

Statistics. Results are presented as means ± SD. Multiple linear regression analysis with Bonferroni's correction was used to test for statistical significance of differences among linear relations from the three groups. Two-way analysis of variance (ANOVA) was used for simultaneous comparison of hemodynamic parameters in CHF$_S$ and CHF$_{EX}$ at baseline and after 4 wk of pacing. For other comparisons between groups, one-way ANOVA with Tukey's post hoc test was used. $P < 0.05$ was regarded significant.

RESULTS

Resting Hemodynamics in Awake Dogs

Resting hemodynamic parameters were similar in the two groups of dogs after the instrumentation sur-

Table 1. *Hemodynamics in vivo*

CHF Group	0 wk	4 wk
LVEDP, mmHg		
Pacing	2.9 ± 2.2	18.7 ± 3.6*
Pacing + Ex	4.0 ± 1.6	9.4 ± 4.5*†
dP/dt_{max}, mmHg/s		
Pacing	3,320 ± 510	1,720 ± 300*
Pacing + Ex	3,150 ± 350	2,540 ± 440*‡
AoP, mmHg		
Pacing	100 ± 6	94 ± 7§
Pacing + Ex	104 ± 7	98 ± 5§
HR, min^{-1}		
Pacing	95 ± 15	139 ± 21*
Pacing + Ex	92 ± 6	113 ± 32*

Values are means ± SD. LVEDP, left ventricular end-diastolic pressure; dP/dt_{max}, peak rate of rise of left ventricular (LV) pressure; AoP, mean aortic pressure; HR, heart rate; Ex, exercise. *$P < 0.01$, §$P < 0.05$ for difference between weeks; †$P < 0.01$, ‡$P < 0.05$ for the interaction of groups and weeks; all statistics by 2-way analysis of variance.

gery but before the pacing regimen. CHF$_S$ generally showed signs and symptoms of CHF such as facial and abdominal wall edema, ascites, forced breathing, and appetite loss at the end of the 4-wk pacing regimen. Such overt signs were absent from the CHF$_{EX}$. Hemodynamic measurements obtained from CHF$_S$ and CHF$_{EX}$ at least 40 min after the pacer was turned off and in the conscious state are summarized in Table 1. LVEDP increased and dP/dt_{max} decreased as a result of the 4-wk pacing protocol in both groups. However, the changes in both parameters were significantly less marked for CHF$_{EX}$ than for CHF$_S$. For example, LVEDP increased by only ~5 mmHg in CHF$_{EX}$ compared with ~16 mmHg in CHF$_S$; dP/dt_{max} decreased by only ~20% in CHF$_{EX}$ compared with ~50% in CHF$_S$. Statistical analysis revealed a significant difference in these parameter values between CHF$_S$ and CHF$_{EX}$, indicating an attenuation of the heart failure state after rapid cardiac pacing due to the exercise training. Mean aortic pressure decreased and heart rate increased during 4 wk of pacing, but there was no difference between the two groups.

Average body and heart weights of the three groups of animals studied in the isolated heart protocol are shown in Table 2. The initial body weight was matched in the three groups. Both CHF$_S$ and CHF$_{EX}$ lost ~3 kg body wt during the 4-wk pacing period. RV mass was significantly larger in CHF$_S$ than in the normal group. Although other ventricular weight values tended to be larger in CHF$_S$, they did not reach statistical significance.

Assessment of Systolic Function

The isovolumic systolic and diastolic pressure-volume relations from all hearts studied are shown in Fig. 1. Although there were significant interanimal variations, pressure-volume relations of CHF$_S$ and CHF$_{EX}$ were generally shifted to the right as compared with those of normal hearts.

Average ESPVRs (Fig. 2*A*) show the differences between groups more clearly. These average relation-

Table 2. Body weight and heart weight

	Normal	Pacing	Pacing + Ex
BW_{org}, kg	26.3 ± 2.9	27.9 ± 4.9	29.4 ± 3.5
BW, kg	26.3 ± 2.9	$24.8 \pm 4.1^*$	$26.1 \pm 5.0^*$
RV, g	53.0 ± 6.0	$68.0 \pm 9.2†$	60.3 ± 9.7
LV, g	151.2 ± 16.5	181.0 ± 25.8	174.2 ± 35.3
RV/BW_{org}, g/kg	2.04 ± 0.37	2.51 ± 0.63	2.09 ± 0.48
LV/BW_{org}, g/kg	5.80 ± 0.86	6.58 ± 1.10	6.01 ± 1.48

Values are means $\pm$ SD. BW_{org}, original body weight; BW, body weight at death; RV, right ventricle; LV, left ventricle. $^*P < 0.05$ vs. original by paired t-test; $†P < 0.05$ vs. normal group by one-way analysis of variance and Tukey's test.

ships were generated by averaging volumes on fitted ESPVRs at common pressure. ESPVRs from both CHF_S and CHF_{EX} had shallower slopes compared with the normal group, with no significant differences in V_0 values. The differences in slopes (E_{es}) between normal and paced hearts were shown to be statistically significant by multiple linear regression (values presented in Table 3). There was no statistical difference in E_{es} between CHF_S and CHF_{EX}.

To test the effects of exercise training on contractile function using an index that also accounts for the speed of contraction (a factor that is disregarded by the ESPVR analysis), dP/dt_{max} was plotted against end-diastolic volume (EDV; Fig. 2B). As was the case for the ESPVR, the EDV-dP/dt_{max} relations had smaller slopes in CHF_S and CHF_{EX} compared with the normal group, with no difference in EDV axis-intercept values. These differences in slopes were shown to be statistically significant by multiple linear regression (Table 3). However, these relations did not differ between CHF_S and CHF_{EX}.

Assessment of Diastolic Function

The individual diastolic pressure-volume relations from all hearts studied are shown in Fig. 1. The
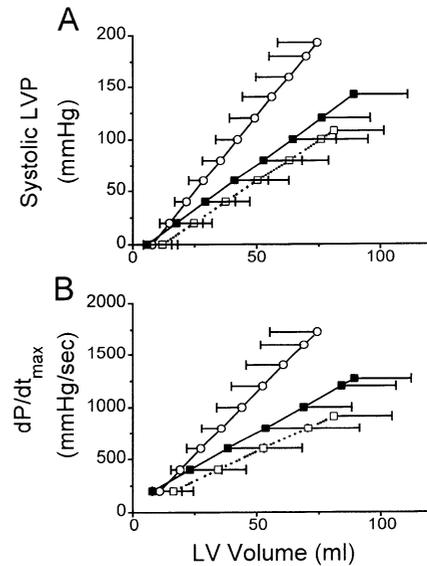
Fig. 2. Mean ($\pm$SD) LV end-systolic pressure (LVP)-volume relationships (A) and LV end-diastolic volume-maximum rate of pressure rise (dP/dt_{max}) relations (B) from the 3 groups. End-systolic pressure-volume relationships of the 2 pacing group hearts had lower slopes than normal. LV volume-dP/dt_{max} relations showed essentially the same result. There was a trend for improved systolic function in exercise-trained animals, but this did not reach statistical significance. ●, Normal; □, pacing; ■, pacing + exercise group.

end-diastolic points of CHF_S and CHF_{EX} were generally positioned to the right of those of the normal hearts. These differences are shown more clearly in the average EDPVRs shown in Fig. 3A. Although there was a strong trend for CHF_S and CHF_{EX} to have larger LV volumes than normal hearts, this difference did not reach statistical significance at any EDP (e.g., $P = 0.10$ at EDP of 20 mmHg).

Table 3. Parameters of systolic function, diastolic function, and energetics

	Normal	Pacing	Pacing + Ex
E_{es}, mmHg/ml	3.05 ± 0.81	$1.66 \pm 0.47^*$	$1.77 \pm 0.38^*$
V_0, ml	7.9 ± 3.6	11.9 ± 6.1	5.9 ± 9.8
dE/dt_{max}, mmHg$\cdot$ml$^{-1}\cdot$s^{-1}	26.4 ± 9.7	$12.0 \pm 4.0^*$	$13.8 \pm 3.8^*$
V_{int}, ml	2.5 ± 4.0	-1.8 ± 7.8	-7.5 ± 11.9
α	2.7 ± 0.69	$4.49 \pm 0.25†$	$3.16 \pm 0.42†‡$
k	20.4 ± 4.0	$32.4 \pm 3.2†$	$21.3 \pm 2.5†‡$
A, $\times 10^{-5}$ ml $O_2\cdot$beat$^{-1}\cdot$mmHg$^{-1}\cdot$ml^{-1}	1.73 ± 0.29	$1.46 \pm 0.41^*$	$1.15 \pm 0.47^*$
B, $\times 10^{-2}$ ml $O_2\cdot$beat$^{-1}\cdot$100 g LV^{-1}	3.89 ± 0.56	2.99 ± 0.52	3.44 ± 0.86

Values are means $\pm$ SD. E_{es} and V_0, slope and volume–axis intercept of end-systolic pressure-volume relation, respectively; dE/dt_{max} and V_{int}, slope and volume-axis intercept of dP/dt_{max}-end-diastolic volume relation, respectively; α, slope of volume elasticity-end-diastolic pressure relation; k, myocardial stiffness constant derived from myocardial stiffness-stress plot; A and B, slope and intercept of myocardial O_2 consumption and pressure-volume area relationship, respectively. $^*P < 0.01$, $†P < 0.05$ vs. normal group; $‡P < 0.05$ vs. pacing group by multiple linear regression analysis with Bonferroni's correction.
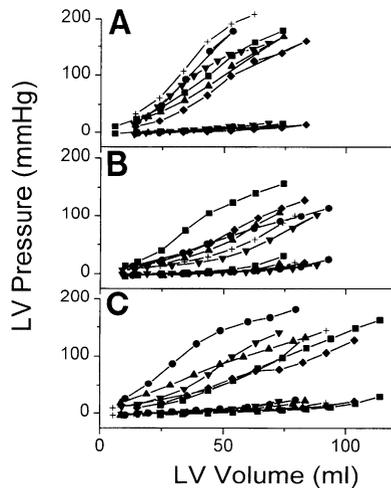
Fig. 1. Individual end-systolic and end-diastolic left ventricular (LV) pressure-volume points in normal ($n = 6$, A), in pacing alone ($n = 6$, B), and in pacing plus exercise ($n = 6$, C) dogs. Different symbols indicate data from different animals.
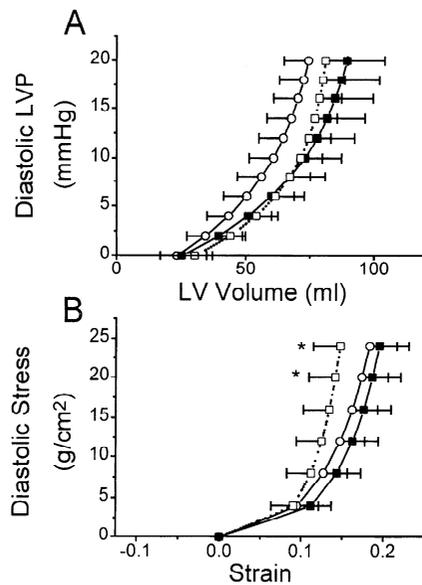
Fig. 3. Mean ($\pm$SD) LVP-volume relationships (A) and end-diastolic stress-strain relationships (B). There was no detectable difference among the groups in pressure-volume relations although the 2 pacing groups tended to have larger LV volumes. At highest stress levels, pacing alone group had statistically significant shift of stress-strain relation, indicating increased diastolic stiffness, which was normalized by exercise training. *$P < 0.05$ vs. pacing plus exercise.

Fig. 4. Volume elasticity [V(dP/dV)] plotted against LV end-diastolic pressure (EDP). Data points were pooled for each group, and means and 95% confidence intervals are shown. Slope of this relationship (normalized ventricular stiffness, α) was higher in pacing group compared with normal and pacing plus exercise groups. A: normal; B: pacing; C: pacing + exercise group.

Several analyses were performed to index passive myocardial properties. First, end-diastolic stress-strain relations were determined from the measured pressure-volume relation (Fig. 3B). As shown, the diastolic stress-strain relationship for CHF$_S$ was steeper than those of the other two groups, and the differences were statistically significant at high stress values; diastolic strain to achieve stresses of 20 and 24 g/cm^2 in CHF$_S$ were significantly smaller than those in CHF$_{EX}$ ($P < 0.05$ by one-way ANOVA and Tukey's test); there were only minor, statistically insignificant differences between normal and CHF$_{EX}$ hearts. These data suggest that diastolic stiffness was increased by 4 wk of rapid ventricular pacing but that exercise training could restore diastolic myocardial properties to normal.

To obtain a second index of changes in diastolic stiffness, we examined the relationship between volume elasticity [V(dP/dV)] and EDP (Fig. 4, data pooled from all hearts); the slope of this line, designated α, is a quantitative index of normalized ventricular stiffness [called the stiffness constant (15, 16)]. As shown in Fig. 4, the slope of the relationship was much steeper in CHF$_S$ compared with normal hearts, whereas it was more similar in CHF$_{EX}$ and normal hearts. The differences among the three groups were statistically significant ($P < 0.05$, multiple linear regression). The quantitative analysis, summarized in Table 3, revealed that α of CHF$_{EX}$ fell between the two extremes of the CHF$_S$ hearts and the normal hearts.

The stress-myocardial elastic stiffness (dσ/dϵ) relationship was also examined; the slope of this relationship provides a measure of myocardial stiffness. The results of this analysis, which were similar to those of the volume elasticity analysis (Fig. 4), were confirma-
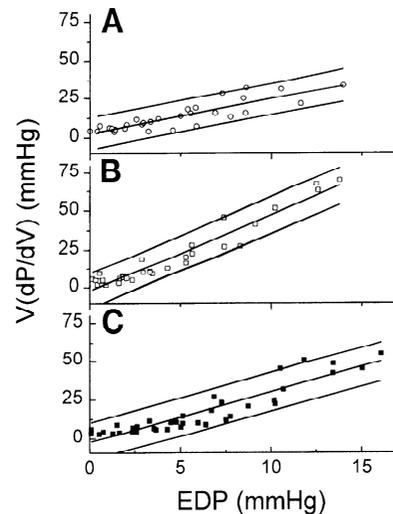
tory in showing that k of CHF$_S$ hearts was the highest, whereas that of CHF$_{EX}$ hearts fell between the extremes of the normal and CHF$_S$ hearts ($P < 0.05$, values reported in Table 3).

Thus three different analyses of diastolic myocardial properties revealed that diastolic myocardial stiffness increased following 4 wk of rapid ventricular pacing and that this change was largely prevented in paced animals that also underwent exercise training.

Relaxation

Active relaxation was assessed by the pressure half-time ($t_{1/2}$), which was measured at three different EDPs (Fig. 5). Although CHF$_S$ hearts tended to have longer $t_{1/2}$ values than normal or CHF$_{EX}$ hearts at all EDPs, these differences did not reach statistical significance ($P = 0.16$ at 10 mmHg).
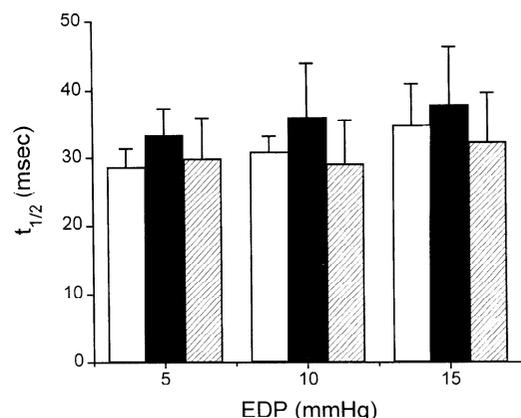

Fig. 5. Pressure half-time ($t_{1/2}$) at 3 EDP levels. Although $t_{1/2}$ tended to be longer in pacing group (solid bars) compared with normal (open bars) and pacing plus exercise groups (hatched bars), this did not reach statistical significance.
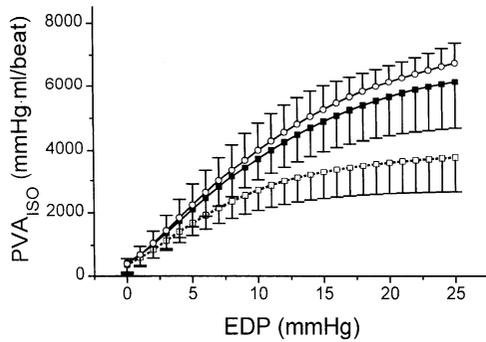
Fig. 6. Overall pump function curves. When possible maximum mechanical work (PVA$_{ISO}$) was plotted against EDP to index overall pump function by integrating systolic and diastolic ventricular properties, difference between pacing (□) and pacing plus exercise (■) groups became evident. O, Normal group. See text for detail.

Fig. 7. Mean (±SD) relationships between myocardial oxygen consumption (MV̇O$_2$) and LV pressure-volume area (PVA) in normal (O), pacing (□), and pacing plus exercise (■) groups. Relationship of the 2 pacing group hearts had shallower slope with no change in intercept compared with normal hearts.

LV Pump Function

As discussed, exercise training did not have a statistically significant effect on either end-systolic or end-diastolic ventricular pressure-volume relations when assessed in the isolated heart. Nevertheless, as shown in Figs. 2 and 3, there was a trend for a leftward shift in the ESPVR and a rightward shift in the EDPVR in hearts of trained animals compared with animals that only underwent rapid cardiac pacing. It is therefore possible that an index that simultaneously accounts for changes in both end-systolic and end-diastolic properties may be more significantly affected by exercise training. Accordingly, an index of overall LV pump function which simultaneously accounts for changes in end-diastolic and end-systolic ventricular properties was obtained from the relationship between isovolumic PVA and EDP. Isovolumic PVA provides an index of the theoretically maximum mechanical work the heart can perform at the specified EDP. The average (±SD) PVA$_{ISO}$-EDP relations from the three groups of hearts are shown in Fig. 6. As expected, PVA$_{ISO}$ increased with rising EDP. The PVA$_{ISO}$ curve for the CHF$_S$ group was shifted significantly downward compared with the normal group, indicating depressed overall pump capacity. However, the curve for the CHF$_{EX}$ group was similar to that of the normal hearts, suggesting improved pump function. Statistical analysis (ANOVA with Tukey's post hoc test) revealed that the CHF$_S$ pump function curve was significantly different from normal and CHF$_{EX}$ but that there was no significant difference between normal and CHF$_{EX}$. Thus there was a significant beneficial effect of exercise training on overall pump function capacity when evaluated by an index that simultaneously accounts for changes in systolic and diastolic properties.

Myocardial Energetics

Average MV̇O$_2$-PVA relations from each of the three groups are summarized in Fig. 7. Compared with the normal group, the relationships measured from CHF$_S$ and CHF$_{EX}$ hearts had smaller slopes with no difference in intercept (A and B, respectively, Table 3). There was
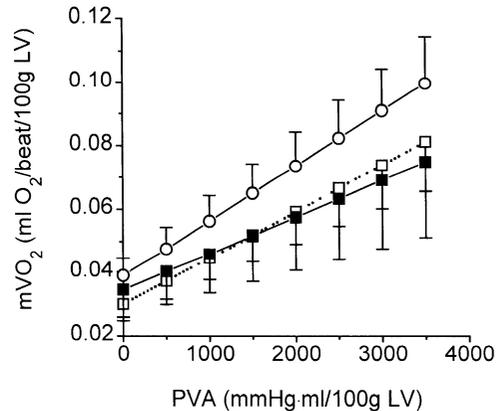
no detectable difference between CHF$_S$ and CHF$_{EX}$ hearts.

Myocardial Collagen Content

The left ventricular myocardial collagen contents are shown in Fig. 8. CHF$_S$ tended to have higher collagen content compared to normal dogs and CHF$_{EX}$ tended to have less collagen than that of CHF$_S$. These differences were of borderline statistical significance ($P = 0.09$ by ANOVA).

DISCUSSION

Exercise training attenuated the abnormalities of resting hemodynamics usually observed following 4 wk of rapid cardiac pacing in dogs. However, systolic LV function, as assessed by the ESPVR in isolated hearts, was depressed to similar degrees in pacing and pacing plus exercise-trained animals. On the other hand, exercise-training had a marked effect on diastolic myocardial stiffness, which was nearly normal in CHF$_{EX}$ but significantly increased in CHF$_S$. These changes were associated with mild (not statistically significant) changes in collagen content. However, when heart function was assessed by an index which depends upon both systolic and diastolic properties, significant preservation of overall pump function due to exercise training
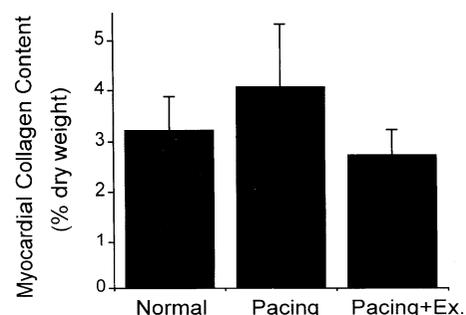

Fig. 8. Myocardial collagen content estimated by hydroxyproline measurement. Pacing alone group hearts tended to have larger collagen fraction ($P = 0.09$).

in rapidly paced hearts was revealed. Finally, exercise training did not prevent the changes in myocardial energetics observed after 4 wk of rapid pacing.

Results of several clinical studies have demonstrated that exercise training improves exercise tolerance, peak exercise oxygen consumption ($\dot{V}o_{2max}$), and functional class in patients with preexisting heart failure (2, 5, 7, 24). Although results of those studies employing hemodynamic monitoring have shown no significant effect of exercise training on resting LVEDP, LV ejection fraction, or dP/dt_{max} (7, 10), there have been reports of improved cardiac output during acute exercise in trained patients (5, 24). Similarly, results of available animal studies have revealed little effect on resting hemodynamics (6, 20), although one study showed improved resting dP/dt_{max} in cardiomyopathic Syrian hamsters (26). As in patients, $\dot{V}o_{2max}$ and cardiac output during peak exercise were improved in one of these animal studies (19). With failure to demonstrate marked effects of exercise training on ventricular function in heart failure, many investigators have focused on explaining the beneficial effects of exercise training in heart failure on peripheral effects, such as alterations in skeletal muscle metabolism and endothelial function (1, 9, 24). Indeed exercise training has been shown to provide marked hemodynamic benefits via these mechanisms. Consistent with these findings, our own studies have also demonstrated significant effects of exercise training on endothelial function in this same animal model (28, 33).

As in other studies, we observed a beneficial effect of exercise training on resting hemodynamics during the development of heart failure in awake dogs. Most notable of these was a marked blunting of the rise in LVEDP. Unlike most other studies, however, we observed a statistically significant effect of exercise training on in vivo systolic LV function, as evidenced by a relative preservation of dP/dt_{max}. Also, the effects on resting hemodynamics were greater than observed in prior clinical and experimental studies. There are many potential explanations for this apparent discrepancy. First, in our study, the exercise training regimen was started at the same time as the rapid pacing; training therefore began before the onset of heart failure, not after establishment of heart failure, as is normally the case in clinical studies. Thus our results show, in this animal model, that hemodynamic manifestations of heart failure can be attenuated by rigorous exercise training, not that exercise training can reverse hemodynamic abnormalities after heart failure is already established. Additional issues, such as differences in the causes of heart failure, the potential severity of heart failure, the intensity of the exercise regimens, and whether hemodynamic measurements were made under anesthesia, further complicate direct comparisons of our results to those of previous experimental and clinical studies.

It is noteworthy that, when assessed in the heart ex vivo, the magnitude of the beneficial effect of exercise training on systolic function was not significant. There are two possible explanations. First, the indexes we used to assess in vivo ventricular function (namely dP/dt_{max} and LVEDP) are also known to reflect changes in loading conditions. Therefore, those values are likely to be affected by peripheral changes known to be associated with exercise training (9, 24). Second, the fact that both anesthesia and the ex vivo surgical preparation depress systolic myocardial performance is likely to have influenced the findings. Although all hearts received similar treatment in this regard, it is apparent that assessment of systolic function in isolated hearts suffers from this limitation. Despite these limitations, useful information regarding systolic performance is obtained from these studies. Primarily, the overall shift of the ESPVR to the right in both groups of pacing dogs suggests that there was a significant effect of pacing on systolic function and LV enlargement despite the exercise training; this was evident even in the studies in the awake dogs. It is possible that the trend for exercise training to improve the end-systolic pressure-volume relation could have reached statistical significance had additional studies been done. However, the large P value ($P \sim 0.20$) for the comparison observed in the six animals studied in each group suggests that a much larger number of additional animals would have to be studied to observe what, in the end, would be a phenomenon whose magnitude may be of little physiological significance.

The effects of anesthesia and surgical preparation are much less important for assessment of passive ventricular properties. This is fortunate because it is very difficult to obtain detailed information about passive ventricular properties from the heart in vivo. There was a small, statistically insignificant shift toward larger volumes in the EDPVR induced by exercise training. However, our studies revealed significant changes in diastolic stress-strain relationships, the chamber stiffness constant (α), and the myocardial stiffness constant (k). All analyses indicated that myocardial stiffness was increased in paced hearts and that this was prevented by exercise training to such a degree that these indexes were nearly indistinguishable from those of normal hearts. Although these improvements in diastolic stiffness indexes may indicate a beneficial effect of exercise training, this may not be the case for the EDPVR shifts. LV enlargement, indexed by rightward shifts in the EDPVR, has been associated with increased mortality and arrhythmias (8, 21). Thus clinical implications of these effects of exercise training on diastolic function need to be investigated further.

A few previous reports using rapid-pacing pig or dog heart failure models failed to show an increase in diastolic stiffness constants (α or k) when EDP was matched (12, 26). The inconsistency with the present study pertaining to CHF_S may be due to two reasons. First, in the previous studies hearts were paced for only 3 wk. Second, most of the previous studies indexed myocardial stiffness from the pressure-volume data obtained during the diastolic portion of single beats and not from true steady-state end-diastolic pressure-volume points of variably loaded beats. Thus it is likely that these discrepancies are due to the fact that our

hearts were exposed to significantly longer pacing periods and we used more sensitive means of detecting changes in myocardial stiffness.

The beneficial effects of exercise training on passive stiffness are similar to those noted in a previous study of normal rats that underwent 16 wk of running-wheel exercise (32); it was found, despite development of significant LV hypertrophy, that the EDPVR shifted toward larger volumes and k and α decreased, indicating increased passive myocardial compliance. Two studies, both employing a rat infarct model of heart failure and exercise training via daily swimming, concluded opposite effects on diastolic properties. One study, which examined EDPVRs in ex vivo arrested hearts, showed an increase in chamber capacity manifested as a rightward shift in the EDPVR (6). In contrast, another study, which examined ex vivo arrested hearts fixed at 5 mmHg, showed hypertrophy of the noninfarcted septum and a decrease in ventricular cross-sectional area (20). Thus there are few data available concerning exercise training and diastolic function in experimental heart failure.

Similarly, the effects of exercise training on diastolic properties in patients have received very little attention. Results of one recent study indicated that exercise training in patients with heart failure resulted in an improved LV filling pattern and an increased exercise capacity in a certain subset of patients (2). Although improved active relaxation (shortening of isovolumic relaxation time) was suggested as the underlying mechanism, this could not be concluded solely based on the noninvasive echocardiographic measurements. Such findings could also be explained on the basis of improved passive properties. We found no statistically significant effect of exercise training on active relaxation.

The mechanism of decreased myocardial stiffness due to exercise training was not clarified in our study. We investigated whether changes in collagen content could have contributed to this phenomenon. We found that there was a trend for increased myocardial collagen content in the sedentary group of dogs paced for 4 wk. Consistent with this finding, Weber et al. (29) previously reported an increased myocardial volume fraction of collagen in pacing-induced canine heart failure, as well as qualitative changes in collagen fibers. In contrast, using a 3-wk rapid-pacing heart failure model, Komamura et al. (12) found no change in hydroxyproline content. Although collagen content differences between the different groups of dogs did not reach statistical significance, the trend for decreased collagen content in CHF$_{EX}$ compared with CHF$_S$ suggests that this may be a contributing factor. However, the absolute values of the differences were relatively small, and whether these alone could account for the marked changes in stiffness is unknown. In addition, it is likely important to examine how exercise affects other aspects of collagen properties, such as cross-linking, rate of collagen turnover, and relative proportions of collagen subtypes.

Because overall LV performance is dependent on systolic and diastolic properties, it is appropriate to examine the effect of exercise training on an index of overall heart function that accounts for both phases of the cardiac cycle, such as the EDP-PVA$_{ISO}$ relationship (23). Although this represents results of a theoretical analysis, we found that the subtle changes in end-diastolic and end-systolic properties yield a significant effect on this integrated index of overall function, particularly at high EDP. It is interesting that previous investigations in heart failure patients (5, 24) and in rats with old myocardial infarction (19) suggested that cardiac output was improved by exercise training during acute maximal exercise but not at rest. This may be because acute exercise shifts the working point of the ventricle toward higher filling pressures where more significant differences in diastolic properties manifest their effects on overall pump function.

The reduced slope of the $\dot{M}\text{V}\text{O}_2$-PVA relationship in both groups of CHF dogs is consistent with results of a previous investigation that used the same model (31). Although this is a consistent finding, the interpretation remains uncertain. Although a decrease in slope has been interpreted as indicating an effective increase in metabolic efficiency of contraction, a biochemical link (e.g., altered myosin adenosinetriphosphatase kinetics) has not been established and the finding remains phenomenological in nature. Nevertheless, because the changes in energetics associated with rapid pacing are considered beneficial (i.e., suggestive of improved efficiency) and exercise training did not alter the effect of rapid pacing on this index, it seems unlikely that beneficial effects of exercise training on heart function were mediated by an effect on myocardial energetics, at least as can be detected by the $\dot{M}\text{V}\text{O}_2$-PVA relationship.

In conclusion, the present results suggest that exercise training attenuates the CHF manifestations uniformly observed following 4 wk of rapid cardiac pacing. Previous studies have shown, in large part, that such benefits of exercise training are related to effects on peripheral metabolism (1) and endothelial function (9). We have shown, however, that small changes in systolic properties and larger changes in diastolic myocardial properties also occur due to exercise training. These effects on systole and diastole resulted in larger changes in overall LV pump function, especially at high preload pressures, as assessed by an index that accounts for both phases of the cardiac cycle. The findings suggest that the effects of exercise training on heart function will be most evident at high filling pressures, a notion which is consistent with some previous clinical and experimental data (5, 19, 24). These findings contrast to most prior studies, which failed to show any effect of exercise training on heart function. These findings, particularly those related to overall pump function, suggest that changes in heart function may contribute to the overall beneficial hemodynamic effects of exercise training in CHF.

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