TEN WEEKS OF RAPID VENTRICULAR PACING CREATES A LONG-TERM MODEL OF LEFT VENTRICULAR DYSFUNCTION

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Objective: Rapid ventricular pacing produces a reliable model of heart failure. Cessation after 4 weeks of rapid ventricular pacing results in rapid normalization of left ventricular function, but the left ventricle remains persistently dilated. We present novel data that show that prolonged rapid ventricular pacing (10 weeks) creates a model of chronic left ventricular dysfunction.

Methods: In 9 dogs undergoing 10 weeks of rapid ventricular pacing, left ventricular function and volumes were serially assessed by using 2-dimensional echocardiography and pressure-volume analysis for 12 weeks after cessation of pacing.

Results: Increased end-diastolic volume and decreased systolic and diastolic function were seen at the end of pacing. By 2 weeks of recovery from rapid ventricular pacing, end-diastolic volume and ejection fraction were partially recovered but did not improve further thereafter. Load-independent and load-sensitive indices of function obtained by pressure-volume analysis at 8 and 12 weeks of recovery confirmed a persistence of both systolic and diastolic dysfunction. In addition, left ventricular mass increased with pacing and remained elevated at 8 and 12 weeks of recovery. Four of these dogs studied at 6 months of recovery showed similar left ventricular abnormalities.

Conclusion: Ten weeks of rapid ventricular pacing creates a long-term model of left ventricular dysfunction. (*J Thorac Cardiovasc Surg* 2000;119:834-41)

To study new surgical therapies for end-stage dilated cardiomyopathy, a stable, long-term animal model analogous to the human condition needs to be developed. One potential model is rapid ventricular pacing. This model produces a reliable model of left ventricular (LV) dysfunction and leads to heart failure (HF) within 1 to 2 weeks of initiating pacing.¹⁻⁶ Congestive HF develops with signs of venous congestion, systolic and diastolic LV dysfunction, and an increase in ventricular volumes.¹⁻⁸ Neurohumoral profiles obtained in this model have shown abnormalities consistent with an activated sympathetic system.^{2,3,9} Most reports have

used pacing protocols for 2 to 4 weeks. Several recent studies have assessed the short-term recovery (typically 1 month) after cessation of pacing.^{1,3-5,8-15} Unfortunately, they have shown that termination of rapid ventricular pacing results in a rapid normalization of load-sensitive indices of global cardiac function, neurohumoral profiles, and hemodynamics, whereas abnormalities of cardiac size and individual myocyte function persist.

We hypothesized that prolonging the insult to the myocardium would result in more significant changes in the cellular and molecular processes inducing HF in this model, and more severe permanent LV dysfunction would then result. Accordingly, this study was conducted to assess the long-term recovery after prolonged rapid ventricular pacing. This study used serial echocardiography and pressure-volume (PV) analysis to obtain novel longitudinal information about cardiac function, volumes, and energetics after cessation of prolonged rapid ventricular pacing.

Material and methods

All animals used in this study received care in compliance with the "Guide for the Care and Use of Laboratory Animals"

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Experimental design. Nine heartworm-free adult mongrel dogs (22–30 kg) were studied. All dogs underwent baseline 2-dimensional echocardiography and PV analysis as described below. After pacemaker implantation, the dogs were subjected to rapid ventricular pacing at 215 beats/min for 10 weeks to ensure development of HF. At the end of pacing, studies were repeated in all dogs. Pacemakers were removed at peak failure (HF). Seven of 9 dogs (2 dogs were killed at the 10-week study point of rapid ventricular pacing because of complications during data collection) were observed during recovery from rapid ventricular pacing by using biweekly echocardiograms for 8 weeks, and a final echocardiogram was obtained at 12 weeks. PV analysis was conducted in these 7 dogs at 8 and 12 weeks of recovery. Two additional dogs underwent echocardiograms and PV analysis only at 12 weeks of recovery. Terminal studies in a subset of these dogs ($n = 4$) were carried out at 6 months after cessation of rapid ventricular pacing. Symptoms of cardiac failure (extremity edema, ascites, and anorexia) present in all dogs by the time of peak failure were treated with daily digoxin (0.125 mg) and furosemide (20 mg) along with thrice weekly aspirin (80 mg) for the last 9 weeks of the rapid pacing period and the first week of recovery.

Echocardiography. Each animal was mildly sedated with acepromazine (0.05 mg/kg) before we obtained echocardiograms. Two-dimensional transthoracic echocardiograms taken with an ACUSON 128XP echocardiograph (Acuson Corporation, Mountain View, Calif) were then obtained under awake conditions. Both short-axis and apical 4-chamber and long-axis views were obtained and stored for later analysis.

Anesthesia. One hour before either PV analyses or pacemaker insertions, each animal was premedicated intramuscularly with acepromazine (0.1 mg/kg) and glycopyrrolate (INN: glycopyrronium bromide; 0.001 mg/kg). General anesthesia was induced with ketamine (10 mg/kg) and diazepam (0.5 mg/kg) administered intravenously and maintained after endotracheal intubation with inhaled oxygen (3 L/min) and isoflurane (1%–2%). Cefazolin (25 mg/kg administered intravenously) was given prophylactically before the skin incision and again just before the termination of all procedures.

PV analysis. PV analysis was conducted after achievement of anesthesia as follows. A 7F multielectrode dual-field conductance catheter (Sentron Europe BV, Maastricht, The Netherlands) and a 5F micromanometer-tipped catheter (Millar Instruments, Inc, Houston, Tex) were placed under fluoroscopic guidance along the long axis of the LV cavity by sterile cutdowns of the carotid and right femoral arteries.

Similarly, 20-mL occlusion catheters (Applied Vascular, Laguna Hills, Calif) were placed at the junction of the superior and inferior venae cavae with the right atrium through the right jugular and right femoral veins. A balloon-tipped pulmonary artery catheter was placed through the left jugular vein.

Volume measurements were obtained by using the conductance catheter technique.^{16–22} All hemodynamic signals and the electrocardiographic tracing were processed by using an analog amplifier (Gould, Inc, Cleveland, Ohio) digitized at 200 Hz and stored on computer disk for offline analysis.

All data were collected with the ventilator held at end-expiration. For determination of the end-systolic and end-diastolic PV relationships and the preload recruitable stroke work (PRSW) relationship²³ (the slope of stroke work vs end-diastolic volume [EDV]), the 20-mL balloons in the venae cavae were temporarily inflated to alter preload, as described previously. All incisions were then closed primarily.

Pacemaker insertion. After a recovery period of no less than 3 days after the initial PV analysis, each dog was administered general anesthesia and underwent placement of specially modified ventricular pacemakers (model IS-1; Medtronic, Inc, Minneapolis, Minn) designed to maintain prolonged pacing rates at 215 beats/min. Through a right anterior thoracotomy, a 2-cm $\times$ 3-cm section of the apical pericardium was excised, and a unipolar pacing lead (model IS-1, Medtronic, Inc) was secured to the LV apex. The lead was then tunneled subcutaneously to a subfascial pocket under the right rectus abdominis and connected to the implantable pacemaker. A right thoracostomy tube was then placed, and all incisions were closed in layers. The tube was removed after 1 hour while the dog was under anesthesia. Animals were allowed to recover for at least 7 days, after which pacing was initiated at a rate of 215 beats/min for 10 weeks.

Data analysis. Two-dimensional echocardiographic LV volumes were calculated by using the modified biplane Simpson rule.²⁴ Cardiac shape was assessed by examining the ratio of the short-to-long axis area in diastole. All hemodynamic data were analyzed offline by using custom software. Parallel conductance from extracavitary structures was derived from saline calibration, as previously described.¹⁹ Volume gain was set to unity. Measured parameters were heart rate, stroke volume, peak and end-diastolic LV pressures, and pulmonary artery pressures. Derived parameters included cardiac output, stroke work, maximum and minimum rates of pressure change (maximum dP/dt and minimum dP/dt), and the time constant of isovolumic pressure decay (τ). This constant was calculated by using a nonlinear regression, as previously described.²⁵ The end-systolic and end-diastolic PV relationships and the PRSW data were derived by using the caval inflow occlusion data.¹⁹ These curves were obtained from data taken after the initial decline seen in the LV pressure. All data in which there was a change in the heart rate of over 5% was discarded to minimize the effects of cardiovascular reflexes; indices of myocardial energetics, including PV area (correlating with oxygen consumption); external mechanical work (area circumscribed by the PV loop); and the potential energy (dissipated as heat during contraction) were obtained from representative end-systolic and end-diastolic relationships as described by Suga.²⁶ Myocardial mechanical efficiency was defined as the ratio of the external work to the total PV area.

Fig 1. End-systolic elastance pressure-volume (PV) loops. Inflow occlusion PV loops obtained from one dog. The slope of the end-systolic PV relationship decreases at peak HF compared with baseline. The decreased slope persists at 3 months of recovery.

Statistical tests were performed by using standard computer software (SigmaStat; Jandel Scientific, San Rafael, Calif; and STATISTICA; StatSoft Inc, Tulsa, Okla). All data are expressed as means $\pm$ SEM. End-systolic elastance and PRSW were assessed by using analysis of covariance with changing covariates (volume axis intercept [Vo] and EDV axis intercept [Mo]) and repeated measures followed by the Newman-Keuls multiple comparison method. All other differences between time points were assessed by using analysis of variance with repeated measures followed by the multiple comparison method of Newman and Keuls.

Results

PV loops obtained from one dog are shown in Fig 1. These loops are representative of an inflow occlusion

study that was used to calculate end-systolic elastance. The slope of the end-systolic PV relationship decreased with 10 weeks of pacing and remained depressed at 3 months of recovery.

Creation of HF. By the end of pacing (HF), LV function had deteriorated significantly from baseline (Figs 2, 3, and 4). Signs indicative of cardiac failure, including ascites, anorexia, inspiratory crackles, and a third heart sound, were present in all dogs by the end of pacing. Systolic parameters of PRSW, end-systolic elastance, maximum dP/dt, and echocardiographic ejection fraction were all depressed (PRSW, $P = .000003$; end-systolic elastance, $P = .000619$; maximum dP/dt, $P = .0000008$; ejection fraction, $P = 1.45 \times 10^{-14}$; Fig 3). Similarly, diastolic dysfunction was evident by a sig-

nificant rise in relaxation rates and minimum dP/dt (τ , $P = .0013$; minimum dP/dt, $P = .00005$; Fig 4). LV end-diastolic pressure had increased by 155% ($P < .05$ vs baseline, Fig 4). Chamber EDV had increased significantly from 69.5 ± 4.1 mL to 125.3 ± 5.5 mL ($P < .05$, Fig 2). LV mass increased significantly and remained elevated throughout the recovery period ($P = .0000007$, Fig 5). Cardiac output measured by thermodilution decreased from 3603 ± 562 mL at baseline to 1908 ± 167 mL at peak HF ($P < .05$). Conversely, cardiac output returned to baseline levels at 2 months of recovery.

Echocardiographic time course of recovery.

Cessation of pacing led to an increase in LV systolic performance with small changes in LV chamber size (Fig 2). At 2 weeks of recovery, EDVs decreased to 92% of peak failure volumes ($P = 7 \times 10^{-15}$), whereas ejection fraction increased to $40.1\% \pm 2.2\%$ ($P < .05$ vs HF and baseline). However, as Fig 2 shows, reverse remodeling and improvements in ejection fraction were halted by 2 weeks of recovery. EDV and ejection fraction at each subsequent biweekly interval continued to be significantly different from baseline ($P < .05$).

PV analysis of recovery. PV analysis conducted at 8 weeks of recovery showed that the load-independent index of contractility (PRSW) had also improved from peak HF ($P < .05$, Fig 3) but still remained depressed compared with baseline values ($P < .05$). Maximum dP/dt and end-systolic elastance at 8 weeks were similar to those at peak failure ($P =$ not significant) and were significantly different from baseline values ($P < .05$). Similarly, diastolic dysfunction was indicated by a persistently elevated relaxation rate and minimum dP/dt ($P < .05$ vs HF, and $P < .05$ vs baseline; Fig 4). LV end-diastolic pressure had, however, returned to baseline levels.

PV analysis at 12 weeks of recovery revealed no significant change in systolic indices of function (end-systolic elastance, PRSW, and maximum dP/dt; all $P =$ not significant vs 8 weeks of recovery). In addition, all systolic indices were different from baseline values ($P < .05$). Diastolic dysfunction was also persistent ($P < .05$ vs baseline). Finally, in a subset of dogs ($n = 4$) studied at 6 months after cessation of pacing, systolic and diastolic indices were similar to those seen at 12 weeks of recovery. The nadir values of all indices at peak failure for these 4 dogs were within the range seen for the group.

Effects of recovery on myocardial energetics. At peak HF, there was a 37% decrease in stroke work compared with baseline (external work, $P = .05$; Table I). In addition, the potential energy that was generated and presumably dissipated as heat increased significantly

Fig 2. Echocardiographic time course of recovery after cessation of rapid ventricular pacing. Biweekly echocardiograms assessed recovery from pacing-induced failure in 7 dogs. By peak failure (HF), there is a significant decrease in ejection fraction (EF) and an increase in end-diastolic volume (EDV). By 2 weeks, EF partially improves ($P < .05$ vs HF and baseline [B]), but there is no further improvement thereafter ($P =$ not significant for 2 weeks vs 4 weeks, 4 weeks vs 6 weeks, 6 weeks vs 8 weeks, and 8 weeks vs 12 weeks). A similar pattern is seen for EDV, where partial recovery is apparent by 2 weeks, but EDV is stable thereafter. 2D, Two-dimensional; ANOVA, analysis of variance.

by 86% (potential energy, $P = .01$). These opposite changes in the determinants of total PV area (a correlate of oxygen consumption) caused it to increase by 24%, but this was not significant. However, myocardial mechanical efficiency, defined as the external work (stroke work) done from the total energy within the system (total PV area), declined significantly ($P = .00002$).

After cessation of pacing, at both 8 and 12 weeks of recovery, stroke work marginally improved ($P =$ not significant vs HF for 8 weeks and $P < .05$ vs HF for 12 weeks; Table I), but potential energy remained stable. As a result, total PV area and myocardial efficiency both marginally increased in parallel ($P =$ not significant vs HF for 8 or 12 weeks of recovery).

Discussion

Chronic tachycardia-induced HF is a reliable and reproducible model of biventricular dilated cardiomy-

Fig 3. Recovery of indices of contractility after cessation of pacing. In 9 dogs undergoing PV analysis, contractility indices of end-systolic elastance (*Ees*) and maximum dP/dt do not significantly improve after termination of pacing. Preload recruitable stroke work (*PRSW*), however, does, but at 8 and 12 weeks of recovery it is still significantly different from baseline values. There is no significant difference between 8 and 12 weeks of recovery in any of these indices of contractility. In a subset of these dogs (n = 4), PV analysis carried out at 22 weeks of recovery (dotted lines) showed no further improvement. Indices of LV systolic function at peak failure in this subset were within the range seen for the group as a whole. B, Baseline; HF, heart failure; ANCOVA, analysis of covariance; ANOVA, analysis of variance.

Fig 4. Diastolic indices after prolonged tachycardia. In 9 dogs undergoing PV analysis, diastolic indices of minimum dP/dt and τ partially improve after termination of pacing but are still different from baseline (B). In a subset of dogs (n = 4) studied at 22 weeks of recovery (dotted lines), no further improvement was seen. LV end-diastolic pressure (LVEDP), however, returns to baseline values at 8 weeks of recovery and remains normal in the subset of dogs studied at 22 weeks. Diastolic indices at peak failure in this subset were within the range seen for the whole group. ANOVA, Analysis of variance.

Fig 5. LV hypertrophy. The LV mass, measured by means of echocardiography, increased significantly at peak heart failure when compared with baseline values (B; $P = .0000007$). The hypertrophy continued at 8 and 12 weeks of recovery.

Table I. Indices of myocardial energetics

Parameter	Baseline	Peak failure	8-wk recovery	12-wk recovery	P values (ANOVA)
EW (mm Hg · mL)	1266 ± 173	796 ± 120*	970 ± 111	1184 ± 136†	.05
PE (mm Hg · mL)	1146 ± 139	2139 ± 200*	2054 ± 256*	2245 ± 355*	.015
PV area (mm Hg · mL)	2365 ± 241	2935 ± 286	3023 ± 338	3372 ± 413	.2
Efficiency (%)	53.1 ± 5.0	26.8 ± 2.1*	32.2 ± 2.0*	35.9 ± 3.2*	.00002

All data are expressed as mean ± SEM. ANOVA, Analysis of variance; EW, external work; PE, potential energy; PV, pressure-volume.

* $P < .05$ versus baseline, as determined by repeated-measures analysis of variance followed by the Newman-Keuls multiple comparison procedure.

† $P < .05$ versus peak failure, as determined by repeated-measures analysis of variance followed by the Newman-Keuls multiple comparison procedure.

opathy. Within 1 week of pacing, systolic and diastolic dysfunction are evident, and sequelae of circulatory overload are seen shortly thereafter.¹⁻⁵ Cardiac volumes rise progressively throughout the pacing period.^{1,4,5,7,11,13} Loss of compensation in failure is characterized by elevation of circulating neurohormones, including catecholamines, atrial natriuretic peptide, renin, angiotensin II, and aldosterone.³⁻⁶ On a cellular and molecular level, chronic tachycardia results in abnormalities in Ca^{++} handling, leading to systolic and diastolic dysfunction²⁷⁻³¹; disruption of the extracellular matrix, leading to myocyte slippage with concomitant increases in cardiac volumes^{4,32,33}; and cytoskeletal aberrations, leading to systolic dysfunction.⁴

Cessation of 2 to 4 weeks of pacing, however, is characterized by a spontaneous diuresis that reduces filling pressures to normal levels within 72 hours.^{1,3,4,9} Systolic function also rapidly returns to normal within 1 week,⁸ although Spinale and coworkers¹³ have shown

persistent myocyte shortening abnormalities at 4 weeks of recovery. Prior studies have also shown disparate recovery of systolic and diastolic function.^{13,15} In contrast to load-sensitive systolic indices, parameters of relaxation remain altered at up to 4 weeks of recovery. Diastolic volumes also remain elevated, and there is a compensatory hypertrophy after discontinuation of pacing that presumably results in a return of normal wall stresses.^{13,15}

We hypothesized that prolonged rapid ventricular pacing may induce either more severe or more permanent changes in the myocardium when compared with standard shorter pacing protocols. Serial evaluation of the heart in this study extended long beyond the cessation of pacing. The data presented here describe novel findings that after prolonged tachycardia, global systolic and diastolic LV function remains different from baseline for an extended period of time. In contrast to other reports with shorter intervals of rapid ventricular

pacing, we show that maximum positive and negative dP/dt show a small rise. PV analysis showed that the end-systolic elastance and PRSW, which are relatively load-independent indices of contractility, were also abnormal. Longitudinal analysis revealed that there is only partial LV recovery after discontinuation of pacing seen in this study. The partial recovery that is seen is essentially complete within 2 weeks. Also, indices of myocardial energetics revealed a decrease in contraction efficiency at peak failure. This improved during recovery, although not significantly, and was mediated in part by an increase in stroke work, without a concomitant decrease in wasted potential energy (ie, heat dissipated during contraction).

Consistent with past reports, persistent LV diastolic dysfunction during recovery was demonstrated in this study.¹³⁻¹⁵ This persistent dysfunction may be due to permanent changes that occur in the extracellular matrix (altering EDV), as well as in intracellular Ca⁺⁺ handling (affecting intrinsic myocyte relaxation). Although the commonly measured relaxation parameters are partly dependent on loading conditions, prolonged relaxation seen after cessation of pacing is likely due to abnormal intrinsic myocyte relaxation.^{4,13} In contrast, significant dysfunction in systole seen long after cessation of pacing in this study may require prolonged pacing. The additional insult of several extra weeks of pacing may be necessary to induce permanent changes in Ca⁺⁺ homeostasis and sarcolemmal function known to occur during rapid pacing.^{29,30}

Potential concerns include that this study was artificially terminated at 12 weeks of recovery and that additional improvement in function could occur thereafter. However, in a subset of dogs studied by PV analysis 6 months after cessation of rapid ventricular pacing, systolic and diastolic dysfunction was confirmed. Although statistical comparisons were not possible in this subset, the values of indices of function were within the range seen at 12 weeks of recovery and were different from baseline. Thus we believe that the recovery after prolonged pacing is incomplete and that this is a long-term model of LV dysfunction.

Additional studies assessing cardiac responsiveness to β -adrenergic stimulation, as well as alterations in the neurohormonal status during recovery from prolonged pacing, would provide further insight into recovery from prolonged pacing. As has been shown after cessation of shorter pacing protocols, however, it is likely that β -receptor response dysfunction is also present in this model.¹³

In summary, we describe novel data on the long-term recovery after cessation of prolonged rapid pacing,

showing persistence of significant systolic and diastolic dysfunction, as well as increased ventricular volumes. We also demonstrate that partial reverse remodeling with concomitant improvement in function in this model is complete by 2 weeks of recovery. The stability and the persistent dilation, as well as LV systolic and diastolic dysfunction, make it a suitable model for the study of novel surgical and mechanical therapies for end-stage dilated cardiomyopathies.

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