Changes in Left Ventricular Volume, Mass, and Function During the Development and Regression of Supraventricular Tachycardia-Induced Cardiomyopathy

Disparity Between Recovery of Systolic Versus Diastolic Function

Masaaki Tomita, MD; Francis G. Spinale, PhD; Fred A. Crawford, MD; and Michael R. Zile, MD

Chronic supraventricular tachycardia causes a dilated cardiomyopathy in man. Terminating this tachycardia appears to result in symptomatic improvement; however, its effects on left ventricular (LV) volume, mass, and function have not been fully examined. Accordingly, hemodynamic studies using simultaneous echocardiography and catheterization were performed in three groups of pigs: 1) those subjected to rapid left atrial pacing (240 beats/min) for 3 weeks (SVT, n=8), 2) those subjected to supraventricular tachycardia for 3 weeks followed by termination of pacing and a 4-week recovery period (PSVT, n=9), and 3) sham-operated controls (CTR, n=10). Systolic pump function was assessed using fractional shortening (FS), peak ejection rate [peak (-)dD/dt], and maximum rate of pressure development [peak (+)dP/dt]. Diastolic function was assessed using the time constant of isovolumic pressure decay (τ), peak early diastolic filling rate [peak (+)dD/dt], the chamber stiffness constant (Kc), and the myocardial stiffness constant (Km). Supraventricular tachycardia caused LV dilation (end-diastolic dimension [EDD] increased from 3.5±0.4 cm in CTR to 4.9±0.5 cm in SVT, p<0.05) but no change in LV mass (LV weight-to-body weight ratio [LV/BW]) was 2.58±0.3 g/kg in CTR and 2.66±0.4 g/kg in SVT, all indexes of systolic function became abnormal (FS fell from 30±4% in CTR to 13±5% in SVT, p<0.05), and the indexes of relaxation and filling were slowed [τ increased from 36±3 msec in CTR to 51±13 msec in SVT, p<0.05]. There were no significant changes in Kc or Km. After terminating the supraventricular tachycardia, LV volume fell but remained greater than that in CTR (EDD was 4.2±0.4 cm in PSVT, p<0.05 versus CTR) and substantial LV hypertrophy developed (LV/BW was 3.48±0.5 g/kg in PSVT, p<0.05 versus CTR). Systolic function returned to normal (FS was 31±5% in PSVT) but diastolic function remained abnormal. In PSVT, τ remained prolonged (49±12 msec, p<0.05 versus CTR), Kc increased from 3.7±1.0 in CTR to 7.4±1.2 (p<0.05), and Km increased from 4.4±1.5 in CTR to 13.9±9.7 (p<0.05). Thus, the improvement in systolic function that occurs after the termination of supraventricular tachycardia is associated with the development of LV hypertrophy and persistent diastolic dysfunction. (Circulation 1991;83:635–644)

Chronic ventricular and supraventricular tachycardias have been shown to produce a dilated, congestive cardiomyopathy in humans and experimental animals.1–11 Clinical and experimental studies have shown that when the tachycardia is terminated, there is an improvement in clinical...
symptoms, a reduction in left ventricular (LV) chamber size, and an increase in systolic ejection fraction.2-8 However, the mechanisms causing this recovery in systolic function have not been determined. Possible mechanisms include a reduction in LV wall stress and/or an increase in the contractile state. The purpose of the current study was to test the hypothesis that once the hemodynamic burden of tachycardia is removed, the increase in systolic ejection fraction is associated with the normalization of LV wall stress and the return to a normal contractile state.

Recent studies have made it clear that changes in diastolic function play an important pathophysiological role in the development of and recovery from many cardiomyopathic and hypertrophic states.12-16 However, no previous experimental or clinical study of chronic tachycardia has examined diastolic function. Therefore, the second purpose of this study was to define the changes in diastolic function that occur during the development and regression of tachycardia-induced cardiomyopathy.

Methods

Studies were performed using a swine model of supraventricular tachycardia. Changes in LV volume and mass and systolic and diastolic function were assessed using simultaneous echocardiography and catheterization.

Experimental Model

Thirty age- and weight-matched pigs (Yorkshire, 23-25 kg, 4-6 months old) were randomly assigned to one of three study groups. The first group (SVT, n = 10) consisted of pigs subjected to supraventricular tachycardia (left atrial pacing at a rate of 240 beats/min) for 3 weeks (18-24 days). This heart rate was chosen because it is twice the normal basal heart rate for swine (120 beats/min).17 The second group (PSVT, n = 10) consisted of pigs subjected to supraventricular tachycardia (pacing at 240 beats/min) for 3 weeks, followed by termination of the pacing, then a 4-week (28-day) recovery period during which the animals’ hearts were allowed to beat at their own spontaneous heart rate. The third group (CTR, n = 10) consisted of sham-operated control pigs.

To implant the left atrial pacemaker or perform the sham operation, the pigs were anesthetized with 2% isoflurane (1.5 l/min) and nitrous oxide (0.5 l/min), intubated, and ventilated. Through a left thoracotomy and pericardiotomy, a shielded stimulating electrode was sutured onto the left atrium, connected to a programmable pacemaker modified for programming heart rates up to 300 beats/min (Spectrax, Medtronic Inc., Minneapolis, Minn.), and placed in a subcutaneous pocket. The pericardium was left widely opened, the thoracotomy was closed, the pleural space was evacuated of air, and the pigs were allowed to recover. The 10 CTR pigs underwent a thoracotomy and pericardiotomy. In five of the 10, a stimulating electrode was sutured onto the left atrium but was not connected to a pacemaker; this pacing wire was buried subcutaneously for later use (see below). In the other five CTR pigs, neither a pacemaker nor a stimulating electrode was implanted. Seven to 10 days after surgery a baseline echocardiogram was performed on each pig. The SVT and PSVT pigs underwent a second echocardiogram 3 weeks after the initiation of pacing.

During atrial pacing, the SVT and PSVT pigs underwent cardiac auscultation daily and an electrocardiogram (ECG) every 3 days to ensure proper operation of the pacemaker and 1:1 conduction. All animals were fed and cared for in an identical manner. At the end of each protocol, the pigs underwent simultaneous echocardiography and catheterization to assess changes in LV volume, mass, and function. Five of the CTR pigs were studied 3 weeks after the sham operation, and the other five were studied 7 weeks after the sham operation.

Simultaneous Echocardiography and Catheterization

The pigs were anesthetized with 0.5% isoflurane (1.5 l/min), intubated, and ventilated. Ventilation was adjusted to maintain pH at 7.38-7.45, Pco2 at 35-40 torr, and Po2 at >100 torr. Body temperature was maintained at 37°C with a heating pad. Both the right and left carotid arteries and the left jugular vein were isolated. A 7-French micromanometer-tipped catheter (PPG Biomedical Systems, Pleasantville, N.Y.) was externally calibrated to mercury at 37°C and advanced into the left ventricle. The calibration of this micromanometer was confirmed and matched that of a 7-French fluid-filled pigtail catheter connected to a transducer (P23dB Statham, Oxnard, Calif.) placed at the midchest level. After calibration of the micromanometer, the fluid-filled catheter was positioned in the ascending aorta. A 7.5-French thermodilution Swan-Ganz catheter (Baxter Healthcare Corp., Irvine, Calif.) was advanced to the pulmonary capillary wedge position under hemodynamic guidance.

Two dimension-directed, M-mode echocardiographic studies (2.25- and 3.5-MHz transducers, ATL Ultramark VI, Bothell, Wash.) were performed from the right parasternal area. The short- and long-axis views were readily visible in all pigs. These methods have been described in detail18 and are similar to those reported by Morioka and Simon.19 Echocardiographic data were measured using American Society of Echocardiography criteria,20 including the leading edge convention. The end of diastole was defined as the onset of the Q wave of the ECG. The end of systole was defined as the time of peak downward motion of the interventricular septum. The time of mitral valve opening was determined using three methods. First, we examined the mitral valve itself using M-mode echocardiography. Second, we determined the time at which the LV minor-axis dimension began to increase and the time at which the LV posterior wall began to thin. Third, we determined the pulmonary capillary wedge pressure at the peak
of the V wave and reasoned that LV pressure falls to a value equal to the pulmonary capillary wedge pressure at the peak of the V wave, which occurs around the time of mitral valve opening. In so doing, we took into account the delay between pressure transients in the left atrium and pressure transients measured by the pulmonary capillary wedge catheter.

Simultaneous LV, aortic, and pulmonary capillary wedge pressures and the LV echocardiogram were recorded at a paper speed of 100 mm/sec, with inspiration held at end expiration. In the CTR and PSVT pigs, recordings were made at spontaneous heart rates. In the SVT pigs, atrial pacing was stopped 20 minutes prior to the induction of anesthesia to reduce the hemodynamic compromise attendant to induction of anesthesia. Data from the SVT pigs presented in Tables 2 and 3 were obtained after the pacemaker was deactivated, at a spontaneous heart rate.

LV pressure tracings and echocardiograms were processed using a semiautomated technique similar to that used in previous studies. Pressure and M-mode echocardiographic records were placed on a digitizing tablet (Summasketch, Summagraphics, Corp., Fairfield, Conn.) and manually traced with a cursor. The position of the cursor was detected and converted to digital coordinates for processing by a microcomputer system (PC8, NCR, Akron, Ohio). LV pressure, minor-axis dimension, and wall thickness was digitized with a sampling interval of 5 msec. Data were smoothed with a seven-point third-order least-squares orthogonal polynomial fit. The derivatives of LV pressure (P), dimension (D), and thickness (Th) with respect to time were obtained from the smoothed data.

Calculations

LV mass was calculated using the recently validated formula of Feneley et al as CSA×long-axis dimension, where CSA (echocardiographic cross-sectional area) is calculated as $\pi (EDD/2 + Th_{ed})^2 - \pi (EDD/2)^2$, EDD is the end-diastolic minor-axis dimension, and Th_{ed} is the end-diastolic wall thickness. In our laboratory, there is a good correlation between echocardiographically derived LV mass and LV mass measured at autopsy in all three groups of pigs (Figure 1). Linear regression analysis yielded the following relation: echocardiographic LV mass = $0.99 \times$ autopsy LV mass − 3.8 g ($r=0.99$).

Systolic pump function was evaluated by examining fractional shortening (FS), peak ejection rate [peak $(-)dD/dt$, $(+)$dTh/dt], and the maximum rate of LV pressure development [peak $(+)$dP/dt]. FS was calculated as $[(EDD - ESD)/EDD] \times 100\%$, where ESD is the end-systolic dimension. Indexes of peak ejection rate were obtained from dimension and wall thickness transients. Peak rate of decrease in the minor-axis dimension [peak $(-)dD/dt$] and peak thickening rate [peak $(+)$dTh/dt] were measured in centimeters per second and normalized by dividing their maximum values by the instantaneous dimension or thickness;

they were therefore expressed as $(-)dD/dt/D$ and $(+)dTh/dt/Th$ in seconds$^{-1}$. The maximum rate of LV pressure development in millimeters mercury per second was obtained by differentiating LV pressure with respect to time.

Because the three indexes of systolic function are both preload and afterload dependent, the afterload FS relation in each group was also examined. In five of the CTR pigs, an afterload FS relation (Figure 2) was derived by infusing intravenous phenylephrine in doses sufficient to raise the blood pressure from 100 to 200 mm Hg in 20–30-mm Hg increments. Heart rate was kept constant throughout the protocol by pacing the left atrium at a constant rate (100–120 beats/min). Left atrial pacing was accomplished by exteriorizing the previously implanted (see above) left atrial wire and connecting it to an external pacemaker (Medtronic). The multiple coordinates of the FS versus end-systolic wall stress relation obtained from each of these five CTR pigs were fit by linear regression using a least-squares analysis; 99% confidence intervals around this line were calculated. A single coordinate of wall stress and FS was derived from the simultaneous echocardiography-catheterization data in the SVT and PSVT pigs and was plotted with reference to the normal (CTR) curve. Using this analysis, we attempted to distinguish the effect of changes in afterload from the effects of changes in contractile state.

Circumferential, global average wall stress ($\sigma$) was calculated as grams per square centimeter, assuming a spherical geometry, as $[P \times D + 4Th \times (1 + Th/D)] \times 1.36$, where $P$ is the LV pressure, $D$ is the minor-axis dimension, and Th is the wall thickness. Wall stress was measured throughout the cardiac cycle and will be presented as the value at end diastole ($\sigma_{ed}$), peak

![Figure 1. Comparison of left ventricular (LV) mass derived from echocardiographic measurements (echo) and LV mass measured at autopsy in control pigs, pigs paced for 3 weeks, and pigs studied 4 weeks after termination of pacing. Direct linear relation exists between these measurements, with echocardiography underestimating actual LV mass by approximately 4 g.](image-url)
systole ($\sigma_{pea}$), end systole ($\sigma_{es}$), and mitral valve opening ($\sigma_{mv}$).

Diastolic function was evaluated by examining the rate of LV filling, the rate of isovolumic pressure decline, chamber stiffness, and myocardial stiffness. Indexes of the peak early diastolic rate of LV filling were obtained from dimension and wall thickness transients. The peak rate of increase in dimension [peak ($+dD/dt$)] and the peak thinning rate [peak ($-dD/dt$)] were measured in centimeters per second and normalized by dividing their maximum values by the instantaneous dimension or thickness; they were therefore expressed as ($+dD/dt$)/D and ($-dD/dt$)/D in seconds\(^{-1}\).

The left atrial–to–LV transmirtal pressure gradient was not measured directly. Rather, the difference between the pulmonary capillary wedge pressure at the peak of the V wave (PB,\(_{PV}\)) and the LV minimum pressure ($LV_{P_{min}}$) was used as an index of the early diastolic transmirtal pressure gradient.

The time constant of isovolumic pressure decline ($\tau$) was calculated from time-expanded recordings of LV pressure digitized at 5-msec intervals beginning at peak ($-dP/dt$) and ending at mitral valve opening. $\tau$ was calculated using the original method described by Weiss et al,\(^{23}\) with the assumption that $P_B$ (the baseline pressure toward which the monoexponential relation decays) equals zero, as $P=P_c e^{-\frac{t}{\tau}}$, where $e$ is the base of the natural logarithm, $t$ is the time in milliseconds after peak ($-dP/dt$), and $P_c$ is the pressure at peak ($-dP/dt$). $\tau$ is defined as the time required for LV pressure to fall to the value $P_c/e$ and is obtained from the linear regression analysis of the natural logarithm of pressure versus time. It is recognized that $P_B$ may not be 0 in this preparation. However, a number of published studies suggest that directional changes in $\tau$ are not dependent on $P_B$.\(^{24,25}\) Yellin et al\(^{26}\) have shown that the assumption that $P_B=0$ introduces a small, insignificant underestimation in the value of $\tau$.

A regional chamber stiffness constant ($K_c$) and a regional myocardial stiffness constant ($K_m$) were calculated from the LV echocardiography-catheterization data. The calculations of chamber stiffness and muscle stiffness are based on analyses of the curvilinear diastolic pressure–volume–stress–strain relations. Methods used to apply these concepts to the pressure–dimension–thickness data in this study were developed by Mirsky and Pasipoularides.\(^{27}\) Assuming that the ventricle can be modeled as a cylindrical anulus, $K_c$ normalized for LV volume and mass was calculated as $P=Ae^{K_c(\pi D^2)/4CSA}$, where the relation between $dP/d(\pi D^2)/4CSA$ and $P$ is linear. $K_m$ is the normalized modulus of the regional chamber stiffness. $K_m$ was calculated as $3/4 D \times D \times \sigma_{es}/dD$, where the stress difference ($\sigma_{es}$) is calculated as $|P \times (D+2h)|^2 + 2h \times (D+h)$.

### Statistical Analysis

Data are presented as mean±SD in the text and tables and as mean±SEM in the figures. Differences among groups were examined for significance using analysis of variance and the Newman-Keuls multiple-comparison test\(^{28}\); $p<0.05$ was considered to be significant.

All pigs received humane care in compliance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

### Results

#### Control

All pigs underwent baseline echocardiography 7–10 days after pacer implantation or sham operation. The LV dimension, wall thickness, FS, and mass data obtained in the baseline state from all three groups are presented in Table 1. These studies demonstrate that prior to the onset of pacing, pigs assigned to the SVT and PSVT protocols were comparable to the CTR pigs.

In five of the 10 CTR pigs, phenylephrine was infused intravenously to generate multiple coordinates of the FS versus $\sigma_{es}$ relation. The phenylephrine infusion resulted in an increase in LV pressure, which ranged from 80 to 200 mm Hg. In each animal, at least five levels of LV pressure were obtained. During the phenylephrine infusion, FS ranged from 25% to 40%. The five coordinates of the FS versus $\sigma_{es}$ relation for all five pigs were used to derive the inverse linear relation $FS=0.1 \times \sigma_{es} + 38$ g/cm\(^2\) ($r=-0.7, p<0.01$; Figure 2). This relation is comparable to that derived by Borow et al.\(^{29}\)

#### Supraventricular Tachycardia

All 10 pigs in the SVT group developed clinical signs of congestive heart failure (dyspnea, ascites, and peripheral edema) 18–23 days after the onset of pacing. Two pigs died of congestive heart failure prior to completion of the protocol, leaving a sample size of eight in this group.

**LV volume and mass.** Tachycardia caused LV dilation and significant LV wall thinning but no change in LV mass (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SVT</th>
<th>PSVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDD (cm)</td>
<td>3.5±0.4</td>
<td>3.6±0.3</td>
<td>3.6±0.2</td>
</tr>
<tr>
<td>The (cm)</td>
<td>0.75±0.05</td>
<td>0.73±0.04</td>
<td>0.74±0.05</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30±4</td>
<td>32±4</td>
<td>33±5</td>
</tr>
<tr>
<td>Long axis (cm)</td>
<td>5.9±0.2</td>
<td>5.9±0.4</td>
<td>5.8±0.3</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>63±8</td>
<td>61±7</td>
<td>59±6</td>
</tr>
</tbody>
</table>

**SVT, supraventricular tachycardia; PSVT, 4 weeks following termination of SVT; EDD, end-diastolic dimension; Te, end-diastolic wall thickness; FS, fractional shortening; LV, left ventricle.**

| TABLE 1. Baseline Echocardiographic Data for Three Study Groups of Pigs |
|------------------------|---------|-----|------|
| Variable               | Control | SVT | PSVT |
| EDD (cm)               | 3.5±0.4 | 3.6±0.3 | 3.6±0.2 |
| The (cm)               | 0.75±0.05 | 0.73±0.04 | 0.74±0.05 |
| FS (%)                 | 30±4 | 32±4 | 33±5 |
| Long axis (cm)         | 5.9±0.2 | 5.9±0.4 | 5.8±0.3 |
| LV mass (g)            | 63±8 | 61±7 | 59±6 |
**TABLE 2. Effects of Supraventricular Tachycardia on LV Volume and Mass and Systolic Function in Pigs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SVT</th>
<th>PSVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>102±10</td>
<td>141±22*</td>
<td>105±10*†</td>
</tr>
<tr>
<td>LV/BW (g/kg)</td>
<td>2.58±0.3</td>
<td>2.66±0.4</td>
<td>3.48±0.5*†</td>
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<tr>
<td>Catheterization</td>
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<tr>
<td>LV pressure (mm Hg)</td>
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</tr>
<tr>
<td>Peak</td>
<td>88±7</td>
<td>90±18</td>
<td>97±17</td>
</tr>
<tr>
<td>ES</td>
<td>75±11</td>
<td>80±16</td>
<td>83±17</td>
</tr>
<tr>
<td>(+)dP/dt (mm Hg/sec)</td>
<td>1.4±0.2</td>
<td>0.9±0.2*</td>
<td>1.3±0.4†</td>
</tr>
<tr>
<td>Echocardiography</td>
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<tr>
<td>Dimension</td>
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</tr>
<tr>
<td>EDD (cm)</td>
<td>3.5±0.4</td>
<td>4.9±0.5*</td>
<td>4.2±0.4*†</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>2.5±0.3</td>
<td>4.3±0.6*</td>
<td>2.9±0.6*†</td>
</tr>
<tr>
<td>Thsd (cm)</td>
<td>0.75±0.05</td>
<td>0.6±0.1*</td>
<td>1.0±0.08*†</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30±4</td>
<td>13±5*</td>
<td>31±5†</td>
</tr>
<tr>
<td>(−)dD/dt/D (sec−1)</td>
<td>1.9±0.3</td>
<td>0.9±0.3*</td>
<td>1.6±0.4†</td>
</tr>
<tr>
<td>(+)dTh/dt/Th (sec−1)</td>
<td>2.4±0.8</td>
<td>2.0±0.8*</td>
<td>2.4±0.9†</td>
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<tr>
<td>Wall stress (g/cm²)</td>
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<td></td>
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<tr>
<td>Peak</td>
<td>90±15</td>
<td>180±49*</td>
<td>101±36†</td>
</tr>
<tr>
<td>ES</td>
<td>39±8</td>
<td>142±37*</td>
<td>48±20†</td>
</tr>
</tbody>
</table>

SVT, supraventricular tachycardia; PSVT, 4 weeks following termination of SVT; LV, left ventricle; LV/BW, LV weight (autopsy) to body weight ratio; ES, at end of systole; P, pressure; ED, at end of diastole; Thsd, end-diastolic wall thickness; FS, fractional shortening. †p<0.05 vs. control. *p<0.05 vs. SVT.

**LV systolic function.** FS, (−)dD/dt/D, (+)dTh/dt/Th, and (+)dP/dt all fell during pacing (Table 2, Figure 2). Both σp and σes more than doubled (Table 2). Some of the reduction in the indexes of systolic function was probably consequent to an increase in wall stress. However, the single FS versus σes coordinates measured in the SVT pigs fell below the normal range (Figure 2). These data support the conclusion that supraventricular tachycardia also resulted in a fall in the contractile state.

**LV diastolic function.** LV end-diastolic pressure, pulmonary capillary wedge pressure, and σed more than tripled and τ increased, while (−)dD/dt/D and dTh/dt/Th fell (Table 3). The decreases in filling rate indexes occurred in spite of an increase in the PCWP, LVP min gradient and an increase in σino (Table 3). Kc was 3.7±1.0 in the CTR pigs and 5.3±2.8 in the SVT pigs. This difference was not significant. Km was 4.4±1.7 in the CTR pigs and appeared to increase in the SVT pigs (12.5±5.9, p<0.05). However, the ranges of LV diastolic pressures and wall stresses over which these calculations were made differed markedly in the SVT and CTR groups. Therefore, direct comparisons of Kc and Km between CTR and SVT pigs at ambient preload may not be appropriate. To address this potential problem, Kc and Km were calculated in five CTR pigs following a rapid intravenous infusion of dextran sufficient to raise the LV end-diastolic pressure to a minimum of 20 mm Hg. In these five preloaded control pigs, 250–500 ml dextran was infused over 5–15 minutes, resulting in an LV end-diastolic pressure of 20–30 mm Hg and a σed of 30–60 g/cm²; Kc was 6.0±2.8 and Km was 10.4±3.5. There were no significant differences in Kc or Km between the preloaded controls and the SVT pigs (Figure 3). Thus, when examined at comparable diastolic pressures and wall stresses, supraventricular tachycardia did not change either chamber or muscle stiffness.

In the SVT group, atrial pacing was stopped 20 minutes prior to the induction of anesthesia to reduce the attendant hemodynamic compromise. Data from the SVT group presented in Tables 2 and 3 were obtained ≤60 minutes after deactivating the pacemaker. This method was used in previous studies from this and other laboratories. However, to determine if there were acute hemodynamic differences consequent to deactivating the pacemaker, eight pigs from the SVT group underwent echocardiography-catheterization both at a spontaneous heart rate and during atrial pacing at a rate of 240 beats/min. There were no significant differences in LV dimension, wall thickness, or FS between the studies done during a spontaneous heart rate and those done during pacing (Table 4). Therefore, the data presented in Tables 2 and 3 for the SVT group were derived from echocardiography-catheterization during a nonpaced, spontaneous heart rate. This protocol increased the ease and reproducibility of obtaining the echocardiographic data and allowed data from the SVT group to be obtained at a heart rate more comparable to that in the CTR and PSVT groups. It should be noted, however, that even after deactivation of the pacemaker heart rate in the SVT pigs remained faster than that in the CTR and PSVT pigs.

**Recovery From Supraventricular Tachycardia**

All 10 pigs in the PSVT group developed clinical signs of congestive heart failure (dyspnea, ascites,
and peripheral edema) after 3 weeks of tachycardia. These clinical signs resolved within 7–10 days after terminating the pacing. One pig died of congestive heart failure prior to completion of the protocol, leaving a sample size of nine for this group. All data presented below were obtained 4 weeks after termination of the pacing tachycardia.

LV volume and mass. After tachycardia was terminated, EDD fell but remained larger than that in the CTR group and significant LV hypertrophy developed (Table 2). LV wall thickness and LV/BW increased significantly compared with both the SVT and CTR groups.

LV systolic function. Indexes of systolic function returned to normal. FS, (−)dD/dt/D, (+)dTh/dt/Th, and (−)dP/dt all increased and returned to values comparable to those of the CTR pigs; σpeak and σes fell and returned to CTR values (Table 2). The FS versus σes coordinates measured in the PSVT group fell within the normal range (Figure 2). These data suggest that LV contractile function returned to normal 4 weeks after terminating the pacing tachycardia.

LV diastolic function. Unlike indexes of systolic function, indexes of diastolic function remained abnormal. LV end-diastolic pressure and pulmonary capillary wedge pressure fell but remained significantly higher than values in the CTR group; τ remained prolonged compared with the CTR group and was unchanged compared with the SVT group (Table 3). Both (+)dD/dt/D and (−)dTh/dt/Th in-

Figure 3. Changes in chamber (left) and myocardial (right) stiffness constants produced by chronic supraventricular tachycardia (SVT) and following termination of tachycardia (PSVT) in pigs. Compared with preloaded (dextran infused) controls, SVT did not cause significant changes in left ventricular chamber or myocardial stiffness constants. PSVT, however, caused significant increase in both chamber and myocardial stiffness constants. *p<0.05 vs. control.
increased following termination of the pacing but remained less than those in the CTR group (Table 3). These indexes of filling rate were associated with a persistently elevated PCWPv-LVPmin gradient and an increased σes (Table 3). $K_s$ increased to 7.4 ± 1.2 and $K_m$ to 13.9 ± 5.2. Both were significantly greater than CTR values ($p < 0.05$). While LV end-diastolic pressure and σes remained increased in the PSVT pigs, the range of diastolic pressures and wall stresses over which $K_s$ and $K_m$ were calculated was comparable to that in the CTR pigs. Therefore, while the SVT data were compared with preloaded control data, the PSVT data were compared with CTR data (Figure 3). Thus, terminating the supraventricular tachycardia was associated with a significant increase in both chamber and myocardial stiffness.

Echocardiography was performed in each PSVT pig after 3 weeks of atrial pacing to ensure that the extent of LV dilation and dysfunction in these animals was comparable to that in the SVT pigs. Table 5 demonstrates that the changes in EDD, wall thickness, and FS attendant to atrial pacing were comparable in the SVT and PSVT groups after 3 weeks of tachycardia.

### Table 4. Comparison of Data During Pacing and Spontaneous Heart Rate in SVT Pigs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spontaneous heart rate</th>
<th>Pacing (240 beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>141 ± 22</td>
<td>240*</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>4.9 ± 0.5</td>
<td>4.7 ± 0.3</td>
</tr>
<tr>
<td>Thd (cm)</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.03</td>
</tr>
<tr>
<td>FS (%)</td>
<td>13 ± 5</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Peak</td>
<td>103 ± 7</td>
<td>92 ± 9</td>
</tr>
<tr>
<td>End diastole</td>
<td>28 ± 7</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>103 ± 7</td>
<td>92 ± 9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>56 ± 2</td>
<td>56 ± 2</td>
</tr>
</tbody>
</table>

SVT, supraventricular tachycardia; EDD, end-diastolic dimension; Thd, end-diastolic wall thickness; FS, fractional shortening. *$p < 0.05$ vs. spontaneous heart rate.

### Table 5. Changes in Echocardiographic Data After 3 Weeks of Pacing Tachycardia in Pigs Assigned to SVT and PSVT Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>SVT</th>
<th>PSVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDD (cm)</td>
<td>3.5 ± 0.4</td>
<td>4.9 ± 0.5*</td>
<td>4.7 ± 0.2*</td>
</tr>
<tr>
<td>Thd (cm)</td>
<td>0.75 ± 0.05</td>
<td>0.6 ± 0.1*</td>
<td>0.6 ± 0.05*</td>
</tr>
<tr>
<td>FS (%)</td>
<td>30 ± 4</td>
<td>13 ± 5*</td>
<td>11 ± 4*</td>
</tr>
<tr>
<td>Long axis (cm)</td>
<td>5.9 ± 0.2</td>
<td>6.8 ± 0.5*</td>
<td>6.7 ± 0.2*</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>63 ± 8</td>
<td>72 ± 6</td>
<td>68 ± 6</td>
</tr>
</tbody>
</table>

SVT, supraventricular tachycardia; PSVT, 4 weeks following termination of SVT; EDD, end-diastolic dimension; Thd, end-diastolic wall thickness; FS, fractional shortening; LV, left ventricle. *$p < 0.05$ vs. control.

### Discussion

The purpose of our current study was to determine whether, and by what mechanism, terminating chronic supraventricular tachycardia results in the reversal of chronic tachycardia–induced cardiomyopathy. LV volume, mass, wall stress, and systolic and diastolic function were assessed during the development of tachycardia-induced cardiomyopathy and 4 weeks after the termination of chronic supraventricular tachycardia. The major findings of this study were 1) chronic supraventricular tachycardia produces severe systolic and diastolic dysfunction, 2) termination of supraventricular tachycardia results in the recovery of systolic function, 3) recovery of systolic function is associated with the development of LV hypertrophy, normalization of LV wall stress, and a return to the normal contractile state, and 4) diastolic function remains abnormal after the termination of supraventricular tachycardia.

### Systolic Function

We measured changes in systolic pump function by examining both the isovolumic-phase [(+ dp/dt)] and the ejection-phase (ejection fraction, ejection rate) indexes of systolic function. Because these indexes are both preload and afterload dependent, changes in contractile state can be assessed only by examining these indexes in light of the simultaneous changes in loading conditions.

LV chamber preload, measured as LV end-diastolic pressure, volume, or stress, increased during supraventricular tachycardia. It is unclear, however, whether these changes were also associated with a significant change in end-diastolic sarcomere length (fiber preload). Nonetheless, it is likely that if any changes in preload occurred during supraventricular tachycardia, preload would have tended to increase. Thus, the decrease in systolic performance that occurred in the SVT group was probably unrelated to or occurred in spite of these changes in preload.

In contrast, changes in systolic performance during supraventricular tachycardia were clearly associated with the changes in afterload. Pacing caused marked increases in systolic wall stress; these increases were responsible, at least in part, for the marked decrease in LV systolic pump function. Despite the difficulties attendant to assessing changes in contractile state in chronic heart disease, our data suggest that systolic pump function was also depressed because of a decreased contractile state. The relation between FS and $\sigma_e$ in the SVT pigs fell below the normal range.

Our results are concordant with those of previous clinical and experimental studies of chronic tachycardia.1–11 Previous studies have shown that both chronic ventricular and supraventricular tachycardia produced LV dilation,1,4,5,7–9,11 no LV hypertrophy,1,8,9,11 and a fall in systolic pump function.1–11 Our data indicate that 4 weeks after the termination of chronic tachycardia, a decrease in LV volume and an increase in LV mass resulted in a significant
fall in LV systolic wall stress and a substantial improvement in the measured indexes of systolic pump function. Chamber preload fell significantly in the PSVT group. As in the SVT group, however, it is unclear whether there were associated changes in fiber preload. Nonetheless, it is likely that the increase in systolic performance in the PSVT group was unrelated to or occurred in spite of ambient changes in preload. In contrast, concurrent changes in afterload clearly contributed to the improvement in systolic performance in the PSVT pigs. In addition, the relation between FS and \( \sigma_r \) returned to normal.

We interpret these data to support the hypothesis that termination of chronic supraventricular tachycardia allowed the development of LV hypertrophy, the normalization of LV wall stress, and a return to the normal contractile state.

The finding of LV hypertrophy and persistent LV enlargement in the PSVT pigs may be highly dependent on the time after termination of pacing that the animals were examined. It is unclear whether these changes would persist, progress, or regress over time. Therefore, future studies should include both earlier and later studies to determine the time course of changes in LV volume, mass, and function after the termination of chronic pacing tachycardia.

Our data clearly demonstrate that LV hypertrophy did not develop during the 3 weeks of pacing tachycardia but did develop once the tachycardia was terminated. However, our data do not indicate what mechanisms control or influence these events. It is possible that during pacing the “signal” for hypertrophy was present but the myocytes were unable to respond. Our previous studies have demonstrated that chronic supraventricular tachycardia causes reduced mitochondrial density, fibrosis, and ultrastructural evidence of myocyte injury. Studies by Rieger and Liebau indicate that ventricular tachycardia causes an increase in norepinephrine levels, which can in itself cause myocardial injury. Coleman et al. reported that myocardial high-energy phosphate levels were significantly reduced following chronic ventricular tachycardia in dogs. Thus, myocyte injury, catecholamine toxicity, and reduced stores of high-energy phosphates may result in the failure of protein synthesis within myocytes during supraventricular tachycardia. Once the tachycardia is terminated, the inciting causes of cellular injury are removed, norepinephrine levels fall, high-energy phosphate levels rise, and the myocytes may be able to respond to the hypertrophic stimulus. The hypertrophic response may be further stimulated by persistent LV enlargement and as a response to the presence of subendocardial injury.

There are a limited number of previous clinical and experimental studies that have examined the consequences of terminating a chronic tachycardia. In clinical series (predominately in the pediatric age group), antiarrhythmic drugs, cryoablation, and/or cardiac surgery have been used to terminate chronic tachycardia. Terminating the chronic tachycardia resulted in an improvement in clinical symptoms, a decrease in LV volume, and an increase in systolic ejection fraction. However, none of these clinical studies identified the mechanisms responsible for the changes in LV volume and ejection fraction. Data from our current study suggest that once the hemodynamic burden of chronic tachycardia was removed, improvement in systolic function was associated with the development of LV hypertrophy and a consequent decrease in afterload.

**Diastolic Function**

Previous clinical and experimental studies have demonstrated that chronic ventricular and supraventricular tachycardia cause an increase in LV end-diastolic and pulmonary capillary wedge pressures. However, no previous studies have fully characterized the changes in diastolic function nor identified the mechanisms that cause these increases in diastolic pressures during supraventricular tachycardia. Furthermore, no previous studies have examined diastolic function during recovery from pacing tachycardia. In several recent reviews, the causes of increased LV diastolic (or pulmonary capillary wedge) pressures were divided into four general mechanisms: abnormal LV relaxation, increased LV stiffness, LV dilation, and factors extrinsic to the left ventricle (pericardium, right ventricle). We analyzed our data using this conceptual framework. It is clear, however, that there is overlap and interaction between these four mechanisms.

In our study, supraventricular tachycardia caused a marked increase in LV diastolic and pulmonary capillary wedge pressures. Data suggest that these increases were associated with impaired LV relaxation and LV dilation. Since all pigs had their pericardia removed, pericardial restraint probably did not play a significant role in increasing LV diastolic pressures.

Supraventricular tachycardia caused the LV pressure decline and LV early filling rates to be slowed. These abnormalities in LV relaxation were associated with abnormal loading conditions and a decreased myocardial deactivation rate. Previous studies have demonstrated that there is an inverse relation between \( \tau \), or peak early diastolic filling rate, and LV afterload.

In those studies, increased systolic wall stress (or afterload) caused prolongation in the relaxation and filling rates. Thus, it is likely that during pacing tachycardia \( \tau \) and the indexes of filling rate were prolonged, at least in part, secondary to the marked increases in afterload. In addition, LV relaxation and filling may have been impaired because of a decreased rate of myocardial deactivation. \( \tau \) has been postulated to parallel the process of deactivation. In the SVT group, \( \tau \) was markedly prolonged, suggesting a significant slowing in the rate of myocardial deactivation.

In addition, LV diastolic pressures were increased during supraventricular tachycardia secondary to the marked LV chamber dilation. Even in the absence of
overall changes in $K_c$ or $K_m$, the curvilinear nature of the diastolic pressure–volume curve obligates an increase in LV volume to be associated with an increase in LV diastolic pressure (preload-dependent increase in operating, end-diastolic stiffness). Thus, our data suggest that LV diastolic pressures were increased because of abnormalities in the rate and extent of myocardial relaxation, increased afterload, and LV dilation.

Our data indicate that the termination of supraventricular tachycardia resulted in persistent increases in LV diastolic and pulmonary capillary wedge pressures. These persistent increases were associated with slowed myocardial relaxation, LV hypertrophy, and increased LV chamber and myocardial stiffness. As discussed above, these changes in diastolic function may be highly dependent on the time after termination of pacing that the animals were studied.

In the PSVT group, LV systolic wall stress (afterload) returned to control values. Therefore, abnormalities in the relaxation rate were not caused by altered afterload. In contrast, the rate of myocardial deactivation was probably still prolonged, as indicated by persistent increases in $\tau$. It is curious that $\tau$ was prolonged but the LV early diastolic filling rate was near normal in the PSVT group. This apparent dichotomy can be explained when LV loading conditions during early filling are measured and integrated into the analysis. A primary (some would say the primary) determinant of peak early filling rate is the left atrial–to–LV transmitral pressure gradient. When this gradient is increased, peak filling rate can be normalized even in a disease process usually associated with a decreased filling rate. This “pseudonormalized” peak filling rate was consequent to increased LV stiffness and the increased left atrial pressure that results from it. If the transmitral pressure gradient were reduced to normal in the PSVT group, the peak filling rate would likely be less than normal. This same pattern of pseudonormalized filling rates has been seen in other disease processes associated with LV hypertrophy. For example, when patients with aortic stenosis or hypertrophic cardiomyopathy develop symptoms of congestive heart failure, the early diastolic filling rates become normal.

The termination of pacing caused both $K_c$ and $K_m$ to increase. In part, chamber stiffness was increased consequent to LV hypertrophy and increased LV mass. It is probable (although no data are available from this study) that, as in other disease processes in which LV hypertrophy occurs, there were changes in the composition of the extracellular (and perhaps intracellular) matrix that contributed to an increase in muscle stiffness.

**Clinical Significance**

To date, clinical studies examining chronic tachycardia have reported an improvement in clinical symptoms when the tachycardia is terminated. However, it is not clear from these reports whether patients were completely symptom-free both at rest and with exertion. Persistent abnormalities in diastole may not cause dyspnea at rest but may reduce exercise tolerance, cause dyspnea on exertion, and reduce subendocardial blood flow during exercise. The presence of isolated diastolic dysfunction following the termination of chronic tachycardia may necessitate the persistent use of diuretics or nitrate venodilators.

In addition, these changes in diastolic function may render the patient more dependent on the atrial contribution to filling to maintain a normal cardiac output and low filling pressures.

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**References**


KEY WORDS • chronic tachycardia • diastole • heart failure • hypertrophy
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