Complete Reversibility of Cat Right Ventricular Chronic Progressive Pressure Overload

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SUMMARY. Chronic, progressive pressure overload of the cat right ventricle produces persistent, ongoing abnormalities of contractile, energetic, and biochemical function in vitro at a time when in vivo pump function is still normal. The present study tested the reversibility of the in vitro changes in this clinically relevant hypertrophy model. Fourteen sham-operated and 14 reversal cats were studied. After banding the animals as 1-kg kittens, right ventricular pressures were normal. Before band removal (25.2 ± 0.5 weeks later for the control group and 25.5 ± 0.3 weeks later for the hypertension reversal group), systolic right ventricular pressures were 24 ± 1 mm Hg for controls and 71 ± 5 mm Hg for the hypertension reversal group (P < 0.05). At study, 19.5 ± 1.1 weeks after a second sham operation for controls or 18.7 ± 0.7 weeks after band removal for the hypertension reversal group, these pressures were 24 ± 1 mm Hg for controls and 23 ± 1 mm Hg for the hypertension reversal group (P = NS); cardiac output was 0.18 ± 0.01 liters/kg per min for controls and 0.19 ± 0.01 liters/kg per min for the hypertension reversal group (P = NS). The ratio of right ventricle to body weight was normal in both groups, as was the right ventricular papillary muscle myocyte cross-sectional area and the myocardial collagen concentration. A right ventricular papillary muscle from each cat was studied at 29°C in a polarographic myograph. Preloaded shortening velocity was 0.79 ± 0.04 muscle lengths/sec for controls and 0.86 ± 0.03 muscle lengths/sec for the hypertension reversal group (P = NS); extent of shortening was 0.15 ± 0.01 muscle lengths for controls and 0.16 ± 0.01 muscle lengths for the hypertension reversal group (P = NS). At optimum isometric length, active tension was 59.7 ± 3.1 mN/mm² for controls and 57.0 ± 1.9 mN/mm² for the hypertension reversal group (P = NS); resting tension was 15.6 ± 1.2 mN/mm² for controls and 13.6 ± 1.6 mN/mm² for the hypertension reversal group (P = NS). Active and resting oxygen consumption levels did not differ in the two groups. This study demonstrates that—in the compensated stage of chronic, progressive pressure overload of the cat right ventricle—the contractile, energetic, and biochemical abnormalities of the hypertrophied myocardium are fully reversible. (Circ Res 54: 323-331, 1984)
The purpose of the present investigation was to determine whether the cardiac hypertrophy and the associated functional and biochemical abnormalities produced by a chronic progressive pressure overload are reversible.

Methods

Preparation of the Experimental Model

The proximal pulmonary artery of 7- to 9-week-old kittens weighing 0.6–1.1 kg was encircled with a biologically inert band 3.5 mm in internal diameter (Cooper and Satava, 1974). A second group of kittens of the same age and weight from the same litters had a sham operation that included pericardiectomy and mobilization of the main pulmonary artery. Six months later, each group of cats underwent a second operation, which included band removal in the first group and pulmonary artery mobilization in the second. Right ventricular systolic pressure was recorded by direct needle puncture during each operative procedure. These procedures were done through a left thoractomy, during anesthesia with ketamine hydrochloride, 25 mg/kg, im. There was significant perioperative mortality with each procedure, usually due to respiratory infections; however, all survivors were healthy at the time of study.

Evaluation of the Experimental Model

Right Ventricular Mass

The extent of any hypertrophy of the right ventricle as a whole was determined from the ratio of the wet weight of the right ventricular free wall to the weight of the cat. The ratio of the weight of the left ventricle plus interventricular septum to body weight served as a control for any independent changes in body weight.

Any residual right ventricular hypertrophy on the cellular level was sought from the cross-sectional areas of cardiocytes in the right ventricular papillary muscles of control and reversal animals. The concordance of papillary muscles with the remaining right ventricle was assured by comparing these data with right ventricular free wall data in several animals. Formalin-fixed samples of the tissue were dehydrated, cleared, embedded in paraffin, and cut in cross-section. Outlines of the cardiocyte cross-sections in which a central nucleus appeared were traced with a digitizer which calculated planar area (Cooper et al., 1981). Cross-sectional orientation of the cardiocyte was assured by (1) properly oriented mounting for cutting of true cross-sections of these columnar muscles in which the cardiocyte long axis parallels muscle long axis, (2) the required ob- 

servation of circular capillary profiles for this tissue in which capillaries run in parallel with cardiocyte long axis, and (3) the required absence of striations caused by myofibrils cut in longitudinal or oblique section. Whereas this method of tissue preparation resulted in substantial cell shrinkage, so that cardiocyte cross-sectional areas are smaller than we usually report (Cooper et al., 1981; Marino et al., 1983), the comparison between similarly prepared tissues remains valid. In addition, each sample was examined for evidence of myocardial necrosis and fibrosis.

Right Ventricular Function

At the conclusion of each study, a hemodynamic evaluation was made during anesthesia with ketamine hydrochloride, 25 mg/kg, im. Cardiac output was obtained by using dye dilution techniques. After the rapid injection of a 0.6-mg bolus of indocyanine green into the right ventricle, the resultant arterial dye dilution curve and a calibration curve for each experiment were analyzed. The mean of three determinations was used as the value for each cat. Pressures were measured through stiif, fluid-filled catheters attached to strain gauges; the mid-chest position was taken as a zero reference point.

Evaluation of the Myocardium

Contractile and Energetic Function

Immediately after the hemodynamic determinations, rapid cardiectomy was performed. A right ventricular papillary muscle was excised and immediately mounted in a flow respirometer. The chordal end of the muscle was fixed to the lever of a photoelectric differential displacement transducer by a short tie at the junction of the chorda with the muscle. The ventricular end of the muscle was enclosed rigidly in a clip sintered to a metal rod; the other end of this rod was screwed directly onto a semiconductor strain gauge. The measured transient response of this transducer and recording system to induced step changes in tension and displacement predicted a uniform full-scale frequency response ±5% of 61 Hz for tension and 227 Hz for displacement. Both the damped and the undamped natural frequencies were >200 Hz. The measured response of this system to sinusoidal tension and displacement changes spanning the full experimental range was flat ±5% to ±70 Hz for both. The area under the tension tracing (f active tension) was obtained from a digital summing circuit with a frequency response of dc to 500 Hz, +1 dB, -3 dB, and a reset time of 5 msec. The rate of change of tension or displacement was obtained from a single-order high-pass filter with a low-frequency cutoff −3 dB of 50 Hz. We calibrated tension and displacement after each experiment by imposing known loads and motions over the experimental range. The digital summing circuit then was calibrated by square waves from a low frequency function generator, where the y axis was referenced to the above tension calibration. Similarly, the rate of change in signal amplitude was calibrated from triangular ramps. Time-to-peak force was calculated as the time from the initial deflection of the high-pass filter until that deflection became zero at the time of peak active force; relaxation time began at this latter instant and terminated when the output of this filter was once again zero. This apparatus allowed tension generated by the muscle to be measured with a stray compliance of less than 0.7 µm/mN over the range of force studied, and the enclosed clip produced only localized end-segment damage and excluded the damaged tissue below the clip from the metabolic measurements. A detailed description of the transducer systems and the associated equipment is presented elsewhere (Cooper, 1976, 1983).

Each muscle was superfused in the respirometer at 29°C by a solution of the following millimolar composition: CaCl₂, 2.5; KCl, 4.7; MgSO₄, 1.2; KH₂PO₄, 1.1; NaHCO₃, 24.0; Na acetate, 20.0; NaCl, 98.0; and glucose, 10.0, with 10 units of zinc insulin added per liter. This solution was equilibrated with 95% O₂-5% CO₂, with a resultant pH of 7.4, and circulated past the muscle from a 1-liter reservoir. The muscle was preloaded lightly and stimulated at 0.2 Hz until a stable mechanical response was obtained. Field stimuli 5–10% above threshold of alternating polarity with no intervening d.c. offset were employed to minimize electrolytic contamination.
Myocardial oxygen consumption (MVO₂) was measured polarographically according to well-defined criteria (Carlson et al., 1950). The dimensions and other characteristics of the respirometer were the same as those described before (Cooper, 1976). The configuration (Cooper, 1983) and performance (Cooper, 1979, 1981) of this flow respirometer are also illustrated elsewhere.

Force-velocity and force-shortening curves were constructed simultaneously during 0.5-Hz contractions of each muscle as follows: first, a preload of about 5 mN/mm² muscle cross-sectional area was used to define the initial point on these curves. Successive afterload increments of 5 mN/mm² then were added to define further points on these curves, until a maximum isotonic force was reached. The maximum velocity and extent of shortening at each load was measured. Following this, an isometric length-tension curve was constructed by beginning at a relatively short muscle length at which active tension generation was first noted and then proceeding in 0.2-mm increments in muscle length until maximum isometric tension, L₁₀₀, was exceeded slightly. Further details of these techniques have been described before (Cooper et al., 1973).

At each isotonic load and isometric length, 120 contractions during a 4-minute period were studied. The MVO₂ associated with each group of contractions was calculated from the solubility of oxygen at 29°C, a calibration curve of oxygen cathode current vs. different oxygen concentrations, and the deflection in the oxygen cathode current record above the resting level produced by each intervention at a constant flow.

After each experiment, muscle length was measured by a micrometer with a known preload attached to the muscle. This length, along with the passive tension portion of the length-tension relationship, allowed calculation of muscle length at L₁₀₀. Muscle cross-sectional area was obtained from this length and from the dry weight obtained as the constant weight reached at 100°C. A wet-to-dry weight ratio of four, and a specific gravity of one, were assumed. That is, area (mm²) = dry weight × 4 (mm³)/muscle length (mm). Results were normalized in terms of muscle length at L₁₀₀, and cross-sectional area. The values for the two ventricular samples were averaged.

Hydroxyproline Concentration

At the time of rapid cardiectomy, and after the myocardial samples were weighed, two transmural specimens from the free wall of each right ventricle were removed and frozen in liquid nitrogen. In five instances, a papillary muscle, other than that used for contractile studies, was removed and assayed for hydroxyproline concentration, separately. After drying to constant weight, the tissue was disrupted in a Tenbroeck glass-to-glass homogenizer, hydrolyzed, and used to estimate collagen concentration by a spectrophotometric method for determining hydroxyproline (Bergman and Loxley, 1963; Lund et al., 1979). The values for the two ventricular samples were averaged.

Statistical Analysis

Each value is expressed as mean ± se. For linear regression data, a t-test was used to compare slopes and ordinate intercepts (Dixon and Massey, 1969, pp. 202–215); in all other cases, Student's unpaired two-tailed t-test was employed for comparisons between the two groups. A significant difference was said to exist when P was less than 0.05.

Results

Characteristics of the Experimental Model

The four important features of this model are shown in Table 1. First, right ventricular (RV) pressure rose substantially before unbanding to a level somewhat higher than that observed after a similar period of banding in our previous study of this model (Cooper et al., 1981, group I), when hypertrophy and the associated functional and biochemical abnormalities were fairly pronounced. Second, despite the fact that the somewhat higher RV systolic pressure might have predicted even more hypertrophy at this time than we observed in that prior study, no residual RV pressure overload or hypertrophy was apparent in the reversal animals in the present study. Third, no evidence of abnormal RV performance is apparent for the reversal group, nor is there evidence of RV failure in terms of liver-to-body weight ratio, RV end-diastolic pressure, or cardiac output; also, no evidence of pleural effusion, ascites, or hepatic congestion was found at study. Fourth, at the time of terminal study for the present reversal group, the long-term hypertrophy animals from the prior study of this model were showing progressive structural, functional, and biochemical abnormalities (Cooper et al., 1981, group II). Thus, we can compare the present reversal group to the

<table>
<thead>
<tr>
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<th>Sham</th>
<th>Reversal</th>
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<tr>
<td>First operation intervention (wks)</td>
<td></td>
<td></td>
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<tr>
<td>Body wt (kg)</td>
<td>19.5 ± 1.1</td>
<td>18.7 ± 0.7</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>23.5 ± 1.1</td>
<td>23.4 ± 0.9</td>
</tr>
<tr>
<td>Second operation intervention (wks)</td>
<td></td>
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</tr>
<tr>
<td>Body wt (kg)</td>
<td>3.48 ± 0.20</td>
<td>4.01 ± 0.27</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>23.5 ± 1.1</td>
<td>23.4 ± 0.9</td>
</tr>
<tr>
<td>RV-to-body wt ratio (g/kg)</td>
<td>0.52 ± 0.02</td>
<td>0.56 ± 0.02</td>
</tr>
<tr>
<td>LV-to-body wt ratio (g/kg)</td>
<td>1.86 ± 0.06</td>
<td>1.96 ± 0.08</td>
</tr>
<tr>
<td>Terminal study</td>
<td></td>
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<tr>
<td>Body wt (kg)</td>
<td>23.22 ± 0.3</td>
<td>28.51 ± 0.85</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mmHg)</td>
<td>2.7 ± 0.3</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Cardiac output (liters/kg per min)</td>
<td>0.18 ± 0.01</td>
<td>0.19 ± 0.01</td>
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</table>

Results are expressed as mean ± se. There were 14 cats in the control group and 14 cats in the reversal group. The asterisk indicates a significant difference between the two groups.

TABLE 1
Characteristics of the Experimental Animals
subjects of the prior study, both in terms of any abnormalities that may have been reversed, and in terms of any abnormalities that would have persisted or worsened had the pressure overload been maintained.

Characteristics of the Myocardium

Structure and Hydroxyproline Concentration

Cardiocyte enlargement was observed both in the free wall and in the papillary muscles of the hypertrophied right ventricle in the previous study of this model (Cooper et al., 1981). This 45% increase in cardiocyte cross-sectional area with hypertrophy was not found in the present study. Table 2 shows that the mean of this value for the papillary muscles in the reversal group did not differ from control, and in no reversal animal was the cardiocyte cross-sectional area greater than the mean control value. In addition, cell sizes in the right ventricular free wall did not differ from those of papillary muscles from the same ventricles.

The hydroxyproline concentration of hypertrophied myocardium was found in the previous study (Cooper et al., 1981) to increase by 46% by the time that reversal was done in the present study, and by 80% if the pressure overload were maintained until the time of terminal study, rather than being reversed. The data in Table 2 show that the right ventricular free wall hydroxyproline concentration returned to normal in the reversal group. Further, a value of 3.54 ± 0.50 μg/mg dry weight was found for the five right ventricular papillary muscles from the reversal group. This did not differ statistically from either the sham or the reversal right ventricular values.

Myocardial Contractile and Energetic Function

The dimensions of the right ventricular papillary muscles selected from cats for the study of contractile and energetic behavior are shown in Table 2; they were similar in the sham and reversal groups. The upper limit of cat papillary muscle cross-sectional area for metabolic support by diffusion at 29°C has been found to be about 1.10 mm² (Cooper, 1979). No muscle larger than this was used in the present study.

The mechanical data for the isotonic contractions, shown in Figure 1, show that the decrease in the velocity and extent of shortening at all loads we observed during hypertrophy (Fig. 3 in Cooper et al., 1981) returned to normal in the present reversal group. Similarly, external work, the product of shortening and load, also returned to normal in the reversal group.

The mechanical data for the isometric contractions are shown in Figure 2 and in Table 3. In contrast to the progressive decrements in active force and the progressive increments in resting force found during hypertrophy (Fig. 4 in Cooper et al., 1981), both of these measurements returned to normal in the present reversal group. The multiple contractile defects shown before at L_max (Table 3 in Cooper et al., 1981), that muscle length at which developed tension is greatest, returned to normal in the present reversal group as documented in the present Table 3.

The metabolic data for the isotonic contractions are shown in Figure 3. The progressive reduction of isotonic MVO₂ along with the parallel decline of contractile performance that we observed before (Fig. 5 in Cooper et al., 1981) returned fully to normal in the present reversal group.

The metabolic data for the isometric contractions are shown in Figure 4. The upper panel displays the linear regression data of MVO₂ vs. active force for the contractions of the group of control muscles. These MVO₂ data were collected at the same time as the mechanical data of Figure 2. The lower panel of Figure 4 displays the linear regression data of MVO₂ vs. active force for the contractions of the group of reversal muscles, again collected while the length-tension relationship of Figure 2 was being defined. In contrast to the reduced isotonic MVO₂ found during hypertrophy (Fig. 6 in Cooper et al., 1981), the two sets of data for the reversal animals and their controls in the present study do not differ statistically. As was the case during hypertrophy, resting oxygen consumption was not abnormal for the experimental group. These values in the present study were 3.41 ± 0.17 μl/mg dry weight per hour for the control muscles and 3.47 ± 0.10 for the reversal muscles.

Discussion

Three major conclusions may be drawn from this study. First, both the cardiac hypertrophy and the associated functional and biochemical abnormalities produced by a chronic progressive pressure overload are fully reversible when the pressure overload is removed from a nonfailing ventricle. Second, this
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**FIGURE 1.** Left panel: average force-velocity values ± se for the control and unloaded muscles. Right panel: extent of shortening vs. force for the same muscles.

**TABLE 3**

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<thead>
<tr>
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<th>Sham</th>
<th>Reversal</th>
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<tr>
<td>Active force (mN/mm²)</td>
<td>59.73 ± 3.14</td>
<td>57.02 ± 1.86</td>
</tr>
<tr>
<td>Resting force (mN/mm²)</td>
<td>15.56 ± 1.20</td>
<td>13.62 ± 1.62</td>
</tr>
<tr>
<td>Resting/total force</td>
<td>0.21 ± 0.03</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>τ Active force (mN/mm²</td>
<td>25.30 ± 2.36</td>
<td>24.52 ± 1.68</td>
</tr>
<tr>
<td>per sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+dF/dt (mN/mm² per sec)</td>
<td>305.72 ± 13.93</td>
<td>307.57 ± 13.32</td>
</tr>
<tr>
<td>Time-to-peak force (msec)</td>
<td>342 ± 9</td>
<td>330 ± 9</td>
</tr>
<tr>
<td>-dF/dt (mN/mm² per sec)</td>
<td>202.61 ± 6.59</td>
<td>203.72 ± 6.37</td>
</tr>
<tr>
<td>Relaxation time (msec)</td>
<td>578 ± 20</td>
<td>550 ± 20</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se. There were 14 cats in the control group and 14 cats in the reversal group. τ active force is the product of active force and time integrated throughout the duration of a single twitch contraction. There was no significant difference between the two groups with respect to any of these measurements.

**FIGURE 2.** Average length-tension values ± se for the control and reversal muscles. The convex pair of lines, beginning on the left with the upper pair of points nearest the ordinate, represents active tension. The concave pair of lines, beginning on the left with the lower pair of points nearest the ordinate, represents resting tension.

**FIGURE 3.** Average isotonic oxygen consumption values ± se for the contractions defining the force-velocity and force-shortening curves. Note that, for the same abscissa force values, Figure 1 shows the velocity and extent of shortening, whereas, this figure shows the associated MVO₂.

reversibility does not represent functional cardiac recovery from an acute injury, since we know—from our prior study of this model (Cooper et al., 1981)—that no apparent injury is produced and that progression, rather than recovery from, the cardiac abnormalities occurs when the pressure overload is left in place. Third, while it might be expected that the progressive increases in collagen concentration and passive stiffness that we observed with this model would remain as fixed features of the tissue, both of these factors returned to normal when the pressure overload was relieved.

**Hypertrophy Reversibility**

The most compelling rationale for this study was the need for basic information about the extent to which pathological hypertrophy in man, with its associated cardiac abnormalities, can be returned toward normal following surgical or pharmacological interventions.

Recent clinical observations of hypertrophy induced by volume (Clark et al., 1980) or pressure...
(Henry et al., 1980) overloads show that only a partial rather than full anatomical regression of ventricular enlargement follows replacement of an abnormal cardiac valve. The functional abnormalities associated with each hemodynamic overload also show only a partial reversal (Kennedy et al., 1977; Pantely et al., 1978). This partial, rather than full, return of structure and function to normal is due either to the residual gradients left by most prosthetic valves, variable and prolonged hypertrophy duration, or irreversible defects intrinsic to hypertrophied myocardium. However, when initially compensated hypertrophy progresses to frank congestive heart failure, the potential for anatomical or functional reversal is even more limited (Dodge et al., 1974).

An experimental basis for these clinical observations has become available over the past decade. Following our initial demonstration (Cooper et al., 1974) that both the structural and functional abnormalities produced by an abrupt, fixed pressure overload are reversed when the pressure overload is removed, similar observations were made for an abrupt, fixed volume overload (Papadimitriou et al., 1974). When each hemodynamic abnormality was allowed to progress to heart failure, both pressure (Coulson et al., 1977) and volume (Newman et al., 1982) overloads were found to produce irreversible abnormalities. Indeed, we have recently found (Wiesenbaugh et al., 1983a) that a severe acute afterload increase produces largely irreversible hypertrophy, even before the progression to heart failure has occurred.

Model Dependence

Whereas there seems to be a general concordance of the clinical and experimental observations sum-
marized above, abrupt fixed increments of either the pressure or the volume loads on human myocardium are distinctly unusual pathological events. Thus, the experimental models have failed to reproduce a basic feature of most clinical pathophysiology: the chronic, progressive nature of the hemodynamic overload. In addition, variations in experimental techniques and species are of very significant rather than only superficial importance (Cooper, 1983).

As an example of possible technical differences, we have not found (Marino et al., 1983), with the moderate pulmonary artery banding used in our studies, the areas of focal necrosis reported by others (Bishop and Melsen, 1976) with more severe banding during an ultrastructural examination of acutely pressure overloaded cat right ventricular myocardium. In addition, mild pressure or volume overloads have not been found to produce fixed ultrastructural cardiac lesions (Sung et al., 1982).

As an example of species differences, full reversibility of electrophysiological (Capasso et al., 1982a) and biochemical (Capasso et al., 1982b) abnormalities produced by a progressive pressure overload has been reported in rodents, but we have shown that the contractile and energetic abnormalities found during rodent hypertrophy differ strikingly from those observed in the cat (Cooper and Tomanek, 1983). This last finding is probably based on a myosin ATPase isoenzyme shift during rodent cardiac hypertrophy which we do not find in larger animals (Wisenbaugh et al., 1983b), including the cat, and which does not occur in man (Mercadier et al., 1983).

Both because of these technical and species differences and because the hemodynamics of our model of chronic progressive pressure overload of the cat right ventricle (Cooper et al., 1981) have a substantial resemblance to human pathophysiology (Cooper, 1983), we chose this latter model for the present study of hypertrophy reversal. However, while this right ventricular model has the additional advantage over left ventricular models of not changing the coronary perfusion hemodynamics along with ventricular loading, it must be recognized that most clinical disease affects the left rather than the right ventricle, and that the pressure overload was applied here, at least initially, in juvenile animals.

**Fibrosis and Compliance**

Stiff myocardial tissue results either from impaired relaxation of the cardiocyte component, as in ischemia (Mann et al., 1979), or from fibrosis of the interstitial component, as in either volume or pressure overload-induced hypertrophy (Hess et al., 1981). These clinical observations are important, in that relief of a hemodynamic overload resulting in improved systolic performance may be of little benefit if decreased myocardial compliance persists. Valve replacement in man for volume or pressure overloads may result in improved, but not normal, myocardial compliance (Schwarz et al., 1978). In deed, there is reason to think that anatomical interstitial fibrosis, as opposed to functionally impaired relaxation, may be irreversible (Perloff, 1982).

Turning again to experimental models, it has been shown that both volume (Hickson et al., 1979) and pressure (Cutilella et al., 1975) overload hypertrophy, when induced rapidly, result in a cardiac collagen increase which persists after the hemodynamic overload is removed. With the clinically more relevant gradual pressure overload, a fairly minor degree of hypertrophy does not alter myocardial compliance (Serizawa et al., 1982), but substantial hypertrophy is associated with myocardial fibrosis (Thiedemann et al., 1983), which we have found to be progressive with time (Cooper et al., 1981).

To elucidate the clinical problem stated above, it is important to know whether the abnormal myocardial stiffness and fibrosis that occur with a pathophysiologically appropriate model of chronic, progressive pressure overload are reversible.

In one such model, pharmacological reversal of hypertrophy in the spontaneously hypertensive rat is actually associated with an increase in the proportion of collagen in the myocardium (Sen et al., 1976). If this finding applies to clinical cardiac hypertrophy, the implications are serious indeed. However, the cardiac hypertrophy seen in the spontaneously hypertensive rat probably has only limited relevance to that seen in clinical or other models of experimental pressure overload-induced hypertrophy. Cardiac hypertrophy precedes the development of hypertension in this strain, and prevention of the hypertension with a vasodilator does not alter the extent of hypertrophy (Sen et al., 1974). Further, chemical peripheral sympathectomy prevents hypertension in this strain, but not the cardiac hypertrophy or dysfunction (Cutilella et al., 1977). Thus, while this animal strain may have a genetic predisposition to a catecholamine-induced hypertrophic cardiomyopathy, it is not an appropriate model for myocardial hypertrophy in response to a pressure overload.

In distinct contrast to the finding of progressive fibrosis during hypertrophy regression in the spontaneously hypertensive rat, in the present study there was a full regression of the increased tissue collagen concentration in parallel with the anatomical regression of hypertrophy. This is in further contrast to our previous data (group II in Cooper et al., 1981), showing that, had the pressure overload not been removed, the increase in myocardial stiffness and collagen concentration of the right ventricular free wall and papillary muscles would have been progressive. To the extent that it may be applicable to humans, the clinical implication of this finding is that—in pressure overload, prior to the development of massive hypertrophy or frank congestive heart failure—both the systolic and diastolic abnormalities can be reversed if the pressure overload is fully relieved. Nonetheless, since the reversal was complete in this study, no direct insight
is provided into why, in the clinical situation, there is so much variability in the myocardial response to therapeutic interventions following pathological pressure overloads.

Conclusion

The major finding of this study is that both hypertrophy and the associated abnormalities produced by a chronic, progressive pressure overload are fully reversible. In contrast to previous studies of acute pressure overload, both by ourselves (Cooper et al., 1974), and by others, the present findings cannot be ascribed to spontaneous recovery from a severe initial hemodynamic load.

Although it seems reasonably clear that the mechanism of hypertrophy reversal involves, primarily, decreased protein synthesis, rather than enhanced degradation (Cutilletta, 1980), the relative importance of the potential factors which trigger changes in heart size is controversial. There is some evidence (Ostman-Smith, 1981), as noted above for the spontaneously hypertensive rat, that sympathetic nerves may play the primary role in some models. In our hands (Cooper and Tomanek, 1982; Thompson et al., 1983), changes in the mass of both the cardiocyte component and the connective tissue component of the heart occur, primarily, in response to load alone.

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