Effects of Intermittent Pressure Loading on the Development of Ventricular Hypertrophy in the Cat

MELVIN L. MARCUS, DWAIN L. ECKBERG, JAMES L. BRAXMEIER, AND FRANCOIS M. ABBoud

SUMMARY Although the effects of persistent pressure loading on the development of ventricular hypertrophy have been studied extensively, the effects of intermittent pressure loading have not been examined. To study the effects of intermittent pressure loading we subjected the right ventricle of cats to intermittent pulmonary artery constriction over a 2-week period. Two intermittent pressure loading schedules were employed. The first consisted of a right ventricular systolic pressure of 60 mm Hg for 3.5 days and normal right ventricular pressure for 3.5 days; and the second consisted of a right ventricular systolic pressure of 60 mm Hg for 2.3 days and normal right ventricular pressure for 4.7 days. The intermittent pressure-loaded cats were compared with normal unoperated controls, sham-operated controls, and cats with a persistent right ventricular pressure load for either 1-week or 1- to 2-month duration. The data indicate that intermittent pressure loading caused significant right ventricular hypertrophy. Since significant residual ventricular hypertrophy was present in both intermittent pressure loading groups, regression of ventricular hypertrophy involves a slower process than the progression of hypertrophy.

THE LEFT ventricle of patients with systemic hypertension is subjected to an intermittent pressure load for several reasons. The inherent intensity of the disease process is variable;1 the antihypertensive effects of several commonly used drugs in the treatment of hypertension are partially dependent on posture;2 and the compliance of patients to antihypertensive drug regimens frequently is inconsistent.3 Although the effects of persistent pressure loads on the development of ventricular hypertrophy have been examined extensively4-5 the effects of an intermittent pressure load on the development of ventricular hypertrophy have not received much attention.

If the net rate at which hypertrophy progresses is equal to the net rate at which it regresses, then intermittent pressure loading using a schedule in which the periods of pressure loading and unloading are of equal duration would not result in residual ventricular hypertrophy. Alternatively, if progression of ventricular hypertrophy occurs at a faster rate than regression, net intermittent pressure loading would result in significant ventricular hypertrophy.

To examine this question, we studied chronically instrumented docile cats in which we could increase the right ventricular pressure intermittently by producing pulmonary artery constriction with an inflatable balloon. Using this model, we were able to estimate the net rate at which hypertrophy progresses and regresses by using different intermittent pressure loading schedules. The results indicate that intermittent pressure loading is a potent stimulus to the development of ventricular hypertrophy and that the net rate at which ventricular hypertrophy progresses is faster than the net rate at which it regresses.

Methods

GENERAL PROTOCOL

Forty cats of both sexes were included in the study. Eight cats served as unoperated controls and eight cats...
MEASUREMENT OF RIGHT VENTRICULAR PRESSURE

A sealed cylindrical Lucite chamber (46 cm long; 26.5 cm in diameter) was built and the cats subjected to intermittent or short-term fixed pressure loading were accustomed to it. The pressure signal from the solid state transducer could be recorded when the cats were in the chamber. Chamber pressure was monitored with a mercury column and could be increased by pumping air into it.

OPERATIVE PROCEDURES

The 32 cats that had sterile surgical procedures were anesthetized with sodium pentobarbital (25 mg/kg, ip), intubated, and ventilated with room air via a Harvard respirator. The right chest was opened and in the 12 cats subjected to intermittent pressure loading and in the six cats subjected to fixed obstruction for 1 week, a 4-mm solid state transducer (Konigsberg, model P-13) was placed in the right ventricle via a stab wound in the right ventricular free wall and secured with a 5-0 nylon suture.

In eight sham-operated cats an electrically inactive, similarly shaped device was placed in the right ventricle via a stab wound in the right ventricular free wall. The main pulmonary artery was mobilized in all cats that were operated on. In cats subjected to intermittent pressure loading and in cats subjected to fixed obstruction for 1 week an inflatable cuff [6 mm, inside diameter (i.d.)] filled with mercury was placed around the main pulmonary artery. In the six cats with 1-2 months of fixed obstruction, a ring (3.1 mm, i.d.) was placed around the main pulmonary artery. The proximal ends of the transducers and the inflatable cuff were brought onto the chest wall. In sham-operated cats, a fixed ring (6-mm i.d.) was placed around the main pulmonary artery. The chest was closed and all cats were allowed 1-3 weeks to recover. Antibiotics and supplemental fluids were given during the first 1-3 postoperative days.

INTERMITTENT PRESSURE LOADING

Thus, by increasing the pressure in the chamber by a known amount (usually 20 mm Hg) the transducer could be calibrated in vivo, assuming that the lowest right ventricular diastolic pressure was 0.0 mm Hg (Fig. 1A). In addition, the calibration was checked at the conclusion of each study by recording right ventricular pressure with a fluid-filled catheter and the solid state transducer simultaneously. The pressure difference between end-diastolic pressure and peak systolic pressure recorded with the two systems never differed by more than 2-4 mm Hg.

Right ventricular pressure was measured daily during the high phase of the pressure cycle, and cuff inflation was adjusted to maintain right ventricular systolic pressure at about 60 mm Hg above baseline. Peak right ventricular pressures obtained in a single cat during an entire cycling sequence are shown in Figure 2. Note that this cat (and all
of the other cats subjected to intermittent pressure loading) was studied after the low pressure phase of the intermittent pressure loading cycle.

Most cats subjected to intermittent pressure loading tolerated well increases in right ventricular systolic pressure of 25–60 mm Hg above baseline over a 1- to 3-minute period. However, in 33% of the cats, on the 1st day that the pressure was increased syncope occurred when right ventricular pressure exceeded 40–50 mm Hg above baseline. When this occurred, the cuff was deflated quickly and all cats recovered immediately.* At 15–30 minutes later the pulmonary artery cuff was reinflated to 5 mm Hg less than the right ventricular pressure that precipitated syncope. This lower pressure was tolerated well. On the following day, in almost all cats, right ventricular pressure could be increased to 60 mm Hg above baseline pressure without recurrence of syncope. The occurrence of syncope and a lesser pressure load on day 1 of the cycle did not systematically alter the amount of right ventricular hypertrophy that occurred in response to the pressure load. When right ventricular pressure was in the high phase, it seldom varied more than 5 mm Hg from day to day. When right ventricular pressure was normal (during cuff deflation) pressure was measured on the day that it was returned to normal and on the day that it was increased. If right ventricular systolic pressure with the cuff deflated exceeded 30 mm Hg, the cat was excluded from the study. Pressures were recorded at a paper speed of 50 mm/sec so that artifacts due to transducer compression within the right ventricular cavity could be detected.

In normal cats, sham-operated cats, and cats with 1–2 months of fixed obstruction, right ventricular pressure was measured at the conclusion of this study during cardiac catheterization (Fig. 2).

CARDIAC CATHETERIZATION

On the final day of each study all cats were anesthetized with sodium pentobarbital (25 mg/kg, i.p.), intubated, and ventilated with a respirator using room air and supplemental oxygen. Arterial blood gases were monitored and maintained within the physiological range by adjusting the respirator and oxygen flow. Silastic catheters (0.076 mm, i.d.) were placed in the femoral artery and vein and a no. 4 Swan-Ganz catheter was placed in the right ventricle via an internal jugular or femoral vein. Right ventricular pressure was monitored with a strain gauge pressure transducer positioned at the midchest level. A high gain tracing (0–20 mm Hg full scale) from the right ventricular catheter was used to measure right ventricular end-diastolic pressure. Cardiac output was measured in triplicate using the dye-dilution technique and the measurements were averaged. The data in Table 1 and Figure 3 indicate that both intermittent pressure loading schedules resulted in significant increases in right ventricular mass. Left ventricular hypertrophy did not occur. Thus, in this model, hypertrophy developed during the 1st week after the onset of the pressure load. Cats included in this study did not have evidence of heart failure; right ventricular end-diastolic pressure in all cats was less than 7 mm Hg and cardiac output was greater than 76 ml/min per kg.* At autopsy, no pleural or peritoneal effusions were found.

INTERMITTENT PRESSURE LOADING

Data in Table 1 and Figure 3 indicate that both intermittent pressure loading schedules resulted in significant increases in right ventricular mass. Left ventricular hypertrophy did not occur. No evidence of heart failure was found in either group of cats.

Discussion

There are two principal new observations in this study. First, intermittent pressure loading is a potent stimulus to the development of ventricular hypertrophy; second, the rate at which ventricular hypertrophy progresses is faster than the rate at which it regresses.

The experimental design used excluded several factors that could have affected our results. First, the effects of the metabolic abnormalities that occur during the first few days following surgery on the rate at which ventricular hypertrophy develops or regresses were eliminated by performing the study in chronically instrumented cats. Second, the magnitude of the stimulus to the process of the development or regression of ventricular hypertrophy was carefully controlled by frequently adjusting the inflation of the pulmonary artery and monitoring the right ventricular pressure with a chronically implanted transducer that could be calibrated in vivo. Third, the possible
TABLE 1  Effects of Intermittent Pressure Loading and Persistent Pressure Loading

<table>
<thead>
<tr>
<th></th>
<th>Unoperated controls</th>
<th>Sham-operated controls</th>
<th>1-2 mo fixed obstruction</th>
<th>1 wk fixed obstruction</th>
<th>Intermitted pressure loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 6)</td>
<td>(n = 6)</td>
<td>Schedule I (n = 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schedule II (n = 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>2.59 ± 0.17</td>
<td>3.01 ± 0.24</td>
<td>3.32 ± 0.26</td>
<td>2.69 ± 0.16</td>
<td>2.53 ± 0.20</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Low</td>
<td>23 ± 2</td>
<td>26 ± 1</td>
<td>69 ± 6</td>
<td>55 ± 3</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>High</td>
<td>2.4 ± 0.6</td>
<td>2.7 ± 0.3</td>
<td>3.2 ± 0.9</td>
<td>2.0 ± 0.3</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>Cardiac output (ml/kg/min)</td>
<td>174 ± 10</td>
<td>181 ± 27</td>
<td>150 ± 14*</td>
<td>164 ± 19</td>
<td>170 ± 18*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>204 ± 7</td>
<td>202 ± 8</td>
<td>150 ± 18</td>
<td>187 ± 20</td>
<td>153 ± 20</td>
</tr>
<tr>
<td>RV mass (g/kg)</td>
<td>0.63 ± 0.03 ± 0.05*</td>
<td>0.63 ± 0.06 ± 0.06*</td>
<td>1.03 ± 0.07 ± 0.09**</td>
<td>1.08 ± 0.04 ± 0.02**</td>
<td>0.92 ± 0.04 ± 0.03*</td>
</tr>
<tr>
<td>LV mass (g/kg)</td>
<td>1.59 ± 0.09 ± 0.06</td>
<td>1.29 ± 0.06 ± 0.06</td>
<td>1.52 ± 0.07 ± 0.10</td>
<td>1.42 ± 0.10 ± 0.20</td>
<td>1.46 ± 0.09 ± 0.20</td>
</tr>
<tr>
<td>RV/LV ratio</td>
<td>0.39 ± 0.03 ± 0.04</td>
<td>0.48 ± 0.06 ± 0.08</td>
<td>0.68 ± 0.07 ± 0.19</td>
<td>0.79 ± 0.04 ± 0.20</td>
<td>0.57 ± 0.04 ± 0.01</td>
</tr>
</tbody>
</table>

RSVP = right ventricular systolic pressure; RVEDP = right ventricular end-diastolic pressure; RV and LV mass = right and left ventricular mass, respectively; n = number of cats; P = probability. NS = not significant. The heart rate reported is the heart rate when the cardiac output was measured.

Multiple comparisons were made by using the method of Scheffé. Results are expressed as mean ± SE.

a Difference between schedule I and schedule II is significant (P < 0.05).
b Difference between sham-operated controls and unoperated controls is significant (P < 0.05).
c Difference between sham-operated controls vs. unoperated controls is not significant.
d Difference between 1-week fixed obstruction vs. 1- to 2-month fixed obstruction is not significant.
e Difference between sham-operated controls and unoperated controls as significant (P < 0.01).
f Difference between 1-week fixed obstruction vs. 1- to 2-month fixed obstruction is significant.
g Difference between schedule II vs. schedule I is not significant.
h Difference between schedule I and unoperated controls is significant (P < 0.05).
i Difference between schedule I and unoperated controls is significant (P < 0.05).
j Difference between sham-operated controls and unoperated controls is not significant.
k Difference between sham-operated controls and unoperated controls is significant (P < 0.01).
l Difference between 1-week fixed obstruction vs. 1- to 2-month fixed obstruction is significant.
m Difference between schedule II vs. schedule I is not significant.

Effects of cardiac failure on the development and regression of ventricular hypertrophy were eliminated by including in the study only those cats that did not have hemodynamic or postmortem evidence of heart failure.

Three studies have been made previously in which the effects of intermittent pressure loading on the development of ventricular hypertrophy were examined. Folkow and Rubinstein produced intermittent systemic hypertensive and tachycardia acutely by stimulating the hypothalamic defense area in rats. They applied a similar stimulus to the rats for 10 sec/min. 12 hours/day, over a 4-month period; this probably caused intermittent pressure loading. Even though the rats developed an increase of about 15 mm Hg in systemic pressure, significant cardiac hypertrophy did not develop. Cowley et al. produced intermittent hypertension in dogs by denervating the baroreceptors. Although transient episodes of hypertension occurred frequently during a single day, the hypertension lasted for only a few seconds to several minutes. Even though the dogs had barodenervation for many months, none of them developed significant ventricular hypertrophy.

These studies, and the results of the present investigation, suggest that very transient (seconds to minutes) elevations of ventricular pressure do not cause ventricular hypertrophy, but more prolonged (hours to days) intermittent increases of ventricular pressure can cause significant ventricular hypertrophy.

Studies in animals and man have shown that...
pressure-induced ventricular hypertrophy regresses if the pressure load is relieved. In most studies, however, the relative rate at which hypertrophy occurs and regresses cannot be ascertained. Determining the relative rate at which hypertrophy occurs or regresses is difficult because neither process is a linear function of time. The development of hypertrophy is most rapid during the first few days after the pressure load is applied, as demonstrated in this and previous studies, and the regression of hypertrophy is most rapid during the first few days after the pressure load is removed. In the present study, the progression and regression of ventricular hypertrophy were studied by applying intermittent pressure loads for relatively short periods of time. Thus, both the development and regression of hypertrophy were compared during the rapid phase of the process. Our data indicate that the net rate at which hypertrophy occurs is more than 2 times as fast as the net rate at which it regresses, since both intermittent pressure loading schedules resulted in ventricular hypertrophy.

Extrapolation of data obtained from experimental studies of right ventricular hypertrophy in animals to clinical situations should be approached cautiously. Nonetheless, there are two clinical implications of our studies. First, the data suggest that the intermittent pressure loading that occurs in some patients with treated systemic hypertension may stimulate the development of ventricular hypertrophy or prevent its orderly regression. Second, the relatively slow rate of the regression of ventricular hypertrophy observed in this study may, in part, explain the relatively slow regression of ventricular hypertrophy observed clinically.

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References

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