LABORATORY INVESTIGATION
CATECHOLAMINES

β-Adrenergic receptor and cyclic AMP alterations in the canine ventricular septum during long-term norepinephrine infusion: implications for hypertrophic cardiomyopathy

WILLIAM J. RAUM, M.D., PH.D., MICHAEL M. LAKS, M.D., DANIEL GARNER, AND RONALD S. SWERDLOFF, M.D.

ABSTRACT  Norepinephrine infusion in dogs has been shown to cause ventricular septal hypertrophy that mimics the syndrome of hypertrophic cardiomyopathy in humans. To characterize the mechanisms involved in septal hypertrophy, the adrenergic system of the right and left ventricles and the septum were analyzed before and after norepinephrine infusion. In the normal unperturbed state, the septum was found to be more sensitive to β-adrenergic stimulation than either the right or left ventricles. That is, more cyclic AMP could be generated with a smaller dose of β-agonist (isoproterenol) in septal tissue homogenate than in homogenates of the right or left ventricles. With infusions of norepinephrine (1.4 μg/min) to subhypertensive levels over 3 months, β-receptor number increased twofold to threefold in the ventricles and septum. Adenylate cyclase activity also increased in the ventricles, but not in the septum. The sensitivity of adenylate cyclase to β-agonist stimulation increased in the septum but remained unchanged in the right and left ventricles. We conclude that the alterations in the myocardial adrenergic system occur in response to the norepinephrine infusion and are not a consequence of hypertrophy. We formulated a hypothesis suggesting that depleted tissue stores of cyclic AMP and or adenosine triphosphate may be one of the mechanisms involved in the development of hypertrophic cardiomyopathy.


HYPERTROPHIC CARDIOMYOPATHY (HCM) is a disease entity characterized by left ventricular hypertrophy that involves principally the superior interventricular septum and occurs in the absence of hypertension, aortic stenosis, coarctation, or any other definable cause. In addition, biochemical changes in the myocardium, echocardiogram, and histologic appearance of the septum have been reported by our laboratories and others, no distinct biochemical changes in the septum have been described.

We have developed an experimental animal model to study the various pathologic changes associated with HCM. The model, dogs infused over a long term (3 to 6 months) with a subhypertensive dose of norepinephrine, developed histologic and physiologic characteristics similar to HCM and has been described extensively. Although use of this model suggests that excessive concentrations of circulating norepinephrine or enhanced sensitivity to norepinephrine may play a role in the development of HCM, the effect of norepinephrine on the septal adrenergic system has not been described. This study examines the effects of norepinephrine on ventricular and septal β-adrenergic receptors, cyclic AMP, and adenylate cyclase activity.

Materials and methods

Materials. We obtained (−) isoproterenol, (+) propranolol, theophylline, phosphocreatine, creatine kinase, adenosine triphosphate (sodium salt), (±) synephrine HCl, and (−) norepinephrine HCl from the Sigma Chemical Co. (St. Louis). Infusaid infusion pumps (Model 100) were purchased from the Metal Bellows Co. (Sharon, MA). Hydroxybenzylpindolol was a gift from Sandoz Pharmaceuticals (East Hanover, NJ). We purchased (125I) iodohydroxybenzylpindolol and cyclic AMP kits from New England Nuclear Corp. (Boston).

Infusion methods and norepinephrine assays. The pump used for norepinephrine is completely self-contained and implantable. The reservoir (capacity — 47 ml) is filled by injection through the skin and a resealable septum approximately every 2 weeks. The power is provided by vapor pressure from a fluoro-
carbon liquid (separate from the reservoir) in equilibrium with its vapor phase. Filling the reservoir condenses the driving vapor, and body heat causes vaporization, which forces the infusate out of the reservoir and into the blood stream. The flow rate (1.0 to 6.0 ml/day) is preadjusted at the factory and is maintained by a flow-regulating resistance element.

The pump was implanted subcutaneously in the flank region of seven male mongrel dogs (20 to 25 kg) and connected to a silicone rubber cannula that was inserted in the deep circumflex iliac vein with the tip ending in the inferior vena cava. Two additional catheters of polyvinyl chloride were implanted to monitor blood pressure, myocardial function, and to obtain blood samples. These catheters were inserted in the right jugular and common carotid vessels through a right cervical incision. By fluoroscopic guidance, the catheter in the carotid artery was positioned into the midthoracic aorta, and the other catheter was positioned in the right atrium. Both were tunneled subcutaneously, exteriorized in the dorsal cervical region, and housed in a specially designed dog jacket. Heparinized saline solution (40 U/ml) was flushed through the catheters biweekly to maintain patency. A second group of four control dogs was implanted with intra-arterial catheters as above, but the pumps were not implanted.

Hemodynamic measurements were obtained in the conscious dogs after a 1 week postoperative recovery period. Blood pressure was determined with fluid-filled transducers, \(^{10}\) cardiac output by the green-dye technique, \(^{11}\) and ejection fraction by arteriography. \(^{12}\) The dogs were free-roaming and received water ad libitum and Purina Dog Chow except during surgical procedures or while hemodynamic measurements were performed.

Dogs demonstrating normal baseline hemodynamic function were started on the norepinephrine infusion at a rate of 0.45 \(\mu g/\)min. This was increased weekly to a total dose of 1.4 \(\pm\) 0.2 \(\mu g/\)min for 3 months. Arterial plasma samples were obtained for determinations of norepinephrine levels at 8 A.M. and 4 P.M. once a week to monitor the infusion rate in experimental dogs and for comparison with any stress-related changes in plasma norepinephrine in the control dogs.

After the dogs received norepinephrine over 3 months, hemodynamic measurements were again obtained, and the dogs were killed. Each chest was opened rapidly, the heart was removed, and the ventricles were weighed. Sections (approximately 2 g wet weight) of the free walls of the right and left ventricles approximately midway between the base and apex and of the ventricular septum one-third of the way from the base to the apex were obtained with a stainless steel punch. Sections were obtained for both histologic and biochemical examination. The time from the death of the dogs until tissue samples were placed in iced buffer or fixative was approximately 5 min.

Plasma norepinephrine was measured by radioimmunoassay (RIA) \(^{13}\) after acid hydrolysis was performed to yield a measure of both free and sulfate-conjugated norepinephrine. \(^{14}\) Myocardial norepinephrine was measured by RIA as previously described. \(^{15}\) Protein was estimated with the Biorad kit (Biorad Laboratories, Richmond, CA).

**\(\beta\)-Adrenergic receptor assays.** The procedures are minor modifications of those described by others. \(^{16}\) Approximately 2 g of myocardium was placed in 40 ml of ice-cold buffer (0.25M sucrose, 20 mM Tris base, 1 mM MgSO\(_4\), and 140 mM NaCl, pH 7.5) and homogenized for 15 sec in a Polytron homogenizer (Brinkman Instruments, Inc., Westbury, NY) at a setting of 5. The homogenate was filtered through a single layer of cheesecloth, then centrifuged at 300 g for 10 min at 4°C. The pellet was discarded and the supernatant was centrifuged at 30,000 \(g\) for 15 min. The supernatant was discarded, and the pellet was washed with 40 ml of homogenization buffer without sucrose (incubation buffer) and centrifuged at 30,000 \(g\) for 15 min. The final pellet was resuspended with incubation buffer to give a final protein concentration of approximately 2.5 mg/ml. The recovery of membrane protein was approximately 20 mg/g of initial tissue wet weight.

Aliquots of membrane protein (200 \(\mu g\) protein) in triplicate were incubated with various concentrations of hydroxybenzylpindolol (noniodinated) (0.5 to 50 nM) with approximately 90,000 cpm of \(^{125}\)I iodohydroxybenzylpindolol (specific activity 2.2 Ci/\(\mu\)mol) in incubation buffer in a total volume of 300 \(\mu l\) for 60 min at 37°C in the presence or absence of 0.3 \(\mu M\) (+) propranolol. After incubation, the samples were diluted with 5 ml of buffer (10 mM Tris base, 140 mM NaCl, pH 7.5) and filtered through Whatman GF/C glass fiber filters (American Scientific Products, Irvine, CA). The filters were washed with an additional 15 ml of buffer at room temperature and were then placed in glass culture tubes; the radioactivity retained on the filters was quantitated in a Micromedic 4/600 gamma counter.

**Assays of cyclic AMP and adenylyl cyclase activity in the heart.** The procedures are modifications of those described by others. \(^{16}\) Approximately 3 g of myocardial tissue was homogenized in 10 volumes of ice-cold buffer (50 mM Tris base, 10 mM MgSO\(_4\), pH 7.5) in a Polytron homogenizer (Brinkman Instruments, Inc., Westbury, NY) for 15 sec at a setting of 5. Aliquots (50 \(\mu l\) containing approximately 500 \(\mu g\) protein) were incubated at 30°C for 10 min in the reaction mixture containing 50 mM Tris base (pH 7.5), 10 mM MgSO\(_4\), 8 mM theophylline, 20 mM phosphocreatine, 50 \(\mu g\) creatine phosphokinase, 0.2 mM adenosine triphosphate (ATP), and 1 mM ascorbic acid, in the presence or absence of (—) isoproterenol (10\(^{-9}\) to 10\(^{-3}\)M) in a total volume of 150 \(\mu l\). We stopped the reaction by immersing the tubes in a boiling water bath for 2 min. The tubes were then centrifuged at 10,000 \(g\) for 20 min, and aliquots of the supernatant were taken directly for RIA measurement of the cyclic AMP formed.

**Statistical methods.** The sensitivity of adenylyl cyclase to isoproterenol stimulation was obtained as the concentration of isoproterenol, producing half-maximal adenylyl cyclase activity as estimated by Probit analysis. \(^{17}\) Student’s \(t\) test and analysis of variance (ANOVA) were used for statistical analysis of the data.

**Histologic studies.** When the dogs were killed, additional sections of tissue, adjacent to those obtained for biochemical studies, were placed in 10% buffered Formalin (pH 7.4). Routine histologic techniques were used to obtain hemotoxylin-eosin–stained, paraffin sections that were examined by light microscopy.

**Results**

**Plasma and myocardial norepinephrine.** Norepinephrine infusion resulted in a significant increase (approximately threefold) in total (free and conjugated) plasma norepinephrine (figure 1). Free plasma norepinephrine also increased approximately threefold (control, 352 \(\pm\) 125 pg/ml; dogs receiving infusions, 1324 \(\pm\) 253 pg/ml). Plasma concentrations, and therefore infusion rates, did not vary significantly from morning to afternoon or weekly, either from dog to dog or within an individual dog. Also, no significant differences occurred in control dogs over these periods.

Myocardial norepinephrine content decreased significantly (twofold to threefold) during the infusion in the right and left ventricle and the septum. The concentration of myocardial norepinephrine in control dogs...
and in dogs receiving infusions was not significantly different across the three regions (figure 1).

**Hemodynamic studies.** In dogs weighing 25 kg, short-term norepinephrine infusions at 1.4 μg/min will cause a significant increase in blood pressure, heart rate, cardiac output, and ejection fraction. However, we started the norepinephrine infusion at a lower dose (0.45 μg/min) and gradually increased it at weekly intervals to the total dose of 1.4 ± 0.2 μg/min. As intended, this resulted in no significant increase in blood pressure during the initial phases of the infusion or at 3 months (table 1). Cardiac output also did not increase significantly, but the ejection fraction, which did not change initially, increased 15.8% by 3 months and is statistically significant (table 1).

**Tissue studies.** Myocardial ventricular weight (corrected for body weight) did not significantly increase during the infusion (table 1). Likewise, histologic examination of the right and left ventricles and the septum demonstrated no significant changes as a result of the norepinephrine infusion.

**β-Receptor studies.** A representative Scatchard plot of the data obtained for binding of (125I) iodohydroxybenzylpindolol to membrane preparations of the septum is given in figure 2. Data for the right and left ventricles and the septum are summarized in figure 4. With norepinephrine infusion, β-receptor density increased in all three portions of the myocardium; however, the increase in the right ventricle was not statistically significant. The greatest increase (222%) occurred in the septum, which interestingly had the lowest β-receptor number in control animals. The infusion, then, had the net effect of abolishing the difference in β-receptor density between the ventricles and septum of the control hearts.

**Adenylate cyclase activity.** Isoproterenol-stimulated adenylate cyclase activity for the septum is illustrated in figure 3. Although isoproterenol at two of the higher doses (10⁻⁵ and 10⁻⁴ M) generated more cyclic AMP in the dogs receiving norepinephrine than in controls,

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Systolic/diastolic (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Ejection fraction (%)</th>
<th>Heart weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>135 ± 6/83 ± 5</td>
<td>4.36 ± 0.34</td>
<td>50.1 ± 3.2</td>
<td>131 ± 9</td>
</tr>
<tr>
<td><strong>Infused</strong></td>
<td>143 ± 6/87 ± 5</td>
<td>4.63 ± 0.23</td>
<td>58.0 ± 4.3</td>
<td>139 ± 7</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>NS</td>
<td>NS</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Plasma and myocardial tissue norepinephrine (NE) concentration in control dogs and dogs receiving norepinephrine. Controls are represented by the open bars and dogs receiving norepinephrine by the shaded bars. *p < .05 to < .001.

**FIGURE 2.** Scatchard plot of (125I) iodohydroxybenzylpindolol (IHYP) binding to membrane preparation of the canine ventricular septum. The ratio of bound/free (B/F) counts is plotted on the y axis in relation to the quantity of IHYP bound, which is plotted on the x axis. The solid line represents the mean and the shaded area ± SE of seven plots, one from each dog infused with norepinephrine, and four plots from control dogs. Aliquots of membrane protein (200 μg) were incubated in triplicate with at least nine different concentrations of hydroxybenzylpindolol (0.5 to 50 nM) and 90,000 cpn of IHYP with and without 0.3 μM (±) propranolol (nonspecific binding).
FIGURE 3. Adenylate cyclase activity as determined by stimulation with isoproterenol in tissue homogenate of the ventricular septum from four control dogs (open circles) and seven dogs receiving norepinephrine (closed circles). Values are mean ± SD. ANOVA (two-way) and area under the curve by t test, no significant difference (p > .05).

statistical testing of the values integrated over the entire dose-response curve by analysis of variance and by t test of the area under the curves demonstrated no significance. Neither the difference in the amount of cyclic AMP generated at the half-maximal dose of isoproterenol (1.25 × 10⁻⁸M for control; 4.45 × 10⁻⁸M for dogs receiving norepinephrine), nor the maximal response of cyclic AMP to isoproterenol (10⁻⁶M for control; 10⁻⁵M for dogs receiving norepinephrine) were statistically significant based on the Studentized range, Q test.¹⁸

Adenyl cyclase activity for the right and left ventricles and septum is summarized on the right half of figure 4 as the mean activity generated over all eight doses of isoproterenol and is qualitatively equivalent to the area under the curves. β-Receptor density for all three portions of the myocardium is summarized in the left half of figure 4.

In controls, the septum had the highest level of adenylate cyclase activity for a given dose of isoproterenol (statistically significant from the right ventricle but not the left), despite the fact that the septum had the lowest number of β-receptors. This suggests that the septal β-receptor–adenyl cyclase system might be more sensitive to β-agonist stimulation than the right and left ventricles. A measure of this sensitivity is the concentration of isoproterenol required to produce half-maximal stimulation of adenyl cyclase (EC₅₀). Figure 5 illustrates that in the noninfused control state, septal adenylate cyclase is stimulated half maximally by significantly less isoproterenol (12.0 ± 2.0 nM) than either the right or left ventricle (45.0 ± 6.9 and 48.4 ± 4.8 nM, respectively). With norepinephrine infusion, both ventricles demonstrated significant increases in adenylate cyclase activity, which tends to parallel the norepinephrine-induced increase in β-receptor number (figure 4). However, the septum, which had the greatest increase in β-receptor number, had no significant increase in adenylate cyclase activity. Changes in sensitivity could again account for this lack of increase in adenylate cyclase activity. Figure 5 illustrates that significantly more isoproterenol is required to stimulate septal adenyl cyclase half maximally in the dogs receiving norepinephrine (44.5 ± 10.4 nM) than in controls (12.0 ± 2.0 nM).

Tissue concentrations of cyclic AMP (table 2) in controls were significantly higher in the left ventricle and septum than in the right ventricle. With norepinephrine infusion, cyclic AMP concentration decreased in the septum and increased in the right and left ventricles, although none of these changes were significant.

Tse et al.'¹⁹ also reported that the increase in adenylyl cyclase activity in the hyperthyroid rat heart was not accompanied by a change in cyclic AMP content. The explanation offered for this phenomenon was that a lower intracellular concentration of ATP prevented a significant increase in cyclic AMP formation. Although ATP tissue levels were not measured in this study, we suspect the cause is similar.

Discussion

This study demonstrates that the adrenergic system of the ventricular septum is initially different and responds differently to long-term elevation of plasma catecholamine levels compared with that of the right and left ventricles. Studies in other animal models have shown that other inducers of myocardial hypertrophy, including thyroxine,¹⁹ mild coarctation of the aorta,²⁰,²¹ and low doses of isoproterenol,¹⁶ cause an increase in myocardial β-receptors. In this study, we demonstrated that the increase in β-receptors occurs before significant hypertrophy develops. Therefore, the receptor changes are specifically related to the norepinephrine infusion and are not secondary to the hypertrophy process.

It has been a frequent observation that most agonists cause a down regulation in their respective target receptors, but our data appear to contradict this observation. However, it may be that the infused circulating norepinephrine is not exerting its major effect on the postsynaptic myocardial β-receptors, but rather on the noradrenergic neurons innervating the myocardium.
Here, circulating norepinephrine may bind to presynaptic α-receptors inhibiting neuronal norepinephrine release and synthesis. Such an effect could lead to a decrease in myocardial norepinephrine content. The inhibition of neuronal norepinephrine release and decreased β-receptor stimulation could result in a compensatory rise in β-receptor number and adenylate cyclase activity in the attempt to maintain normal tissue concentrations of cyclic AMP.

Although this sequence of events has not been validated experimentally, all of the consequences of an inhibition of neuronal norepinephrine synthesis and release, i.e., decreased myocardial norepinephrine content, increased β-receptor density, increased adenylate cyclase activity (except in the septum), and maintenance of normal cyclic AMP tissue concentration, have been observed in this study. A test of the hypothesis could conceivably be accomplished by confusing an α-receptor blocker (i.e., phentolamine) with norepinephrine, and demonstrating no change in myocardial norepinephrine content or β-receptor density.

Because all other experimental models use small animals, specific assessments of different anatomic localizations cannot be done. Since the dog is a much larger animal, we were able to examine the ventricular septum separate from the right and left ventricles. In normal control dogs, the septal β-receptor–adenyl cyclase system has the highest adenylate cyclase activity (figure 4), cyclic AMP content (table 2), and sensitivity to β-agonist stimulation (figure 5). Norepinephrine infusion results in an increase in β-receptors in the ventricles, which is accompanied by a rise in adenylate cyclase activity (figure 4). The septum develops a marked rise in β-receptor number but no increase in adenylate cyclase activity. The lack of an increase in activity is most likely due to the demonstrated decrease

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Effect of norepinephrine (NE) infusion on β-receptor density (left) and adenylate cyclase (A.C.) activity (right) is compared among the right and left ventricles and the ventricular septum. Values are given as mean ± SE. β-Receptor density was obtained from the x-axis intercept of figure 2 (septum) and from similar analyses of the right and left ventricles. Adenylate cyclase activity is the calculated mean activity generated by all eight concentrations of isoproterenol reported in figure 3 for the septum and from similar data obtained for the right and left ventricles. The numbers in parenthesis refer to the mean percent increase. *p < .05 to < .005 comparing control (open bars) and dogs receiving NE (shaded bars).

![Figure 5](http://circ.ahajournals.org/)

**FIGURE 5.** The sensitivity of adenylate cyclase to β-agonist stimulation expressed as the concentration of isoproterenol that produces half-maximal adenylate cyclase activity (EC50) in tissue homogenates of the right and left ventricles and the ventricular septum from four control dogs (open bars) and seven dogs receiving norepinephrine (shaded bars). Values are given as mean ± SE. *Significantly different from control (p < .01).

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclic AMP content in three regions of the myocardium in control dogs and dogs receiving norepinephrine</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Infused</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

Statistical comparisons: *Significantly different from control (right and septum; p < .05); **Significantly different from control (right and left; p < .05).
in sensitivity of septal adenylate cyclase to β-agonist stimulation (figure 5). It may be that septal cyclase activity in the basal state is at its theoretical maximum and is unable to generate additional substrate for cyclic AMP (i.e., ATP) when the system is perturbed. Although the decrease in septal cyclic AMP tissue content was not significant after 3 months of norepinephrine infusion, a longer period may cause a greater depletion. Similarly, no detectable hypertrophy occurred at 3 months, but does occur after 6 to 8 months as reported in previous studies.1–7 If the septum cannot maintain tissue cyclic AMP levels under long-term norepinephrine perturbation, it might suggest that myocardial hypertrophy in general, and septal hypertrophy (HCM) specifically, is initiated by decreased concentration of myocardial cyclic AMP. Data reported on two other models, isoproterenol- and thyroxine-induced hypertrophy in the rat,16,19 indicate both are associated with decreased tissue cyclic AMP and ATP, or the ability to synthesize cyclic AMP, and tend to support the hypothesis that cyclic AMP depletion initiates myocardial hypertrophy.

A controversy has existed concerning the role of the adrenergic system in the development of myocardial hypertrophy. Most studies have attempted to demonstrate that the adrenergic system does not play a role. Blocking β-receptors or performing surgical or clinical sympathectomies with 6-hydroxydopamine23 or nerve growth factor antiserum24 has in all cases failed to prevent the development of hypertrophy induced by afterload production (aortic banding) or genetic predisposition (spontaneously hypertensive rat). Even in our own studies, propranolol has not been effective in preventing norepinephrine-induced hypertrophy (unpublished observations). If the adrenergic system is not involved, an explanation of the effect of adrenergic agonists such as isoproterenol and norepinephrine in causing myocardial hypertrophy can be difficult. One possible explanation is that adrenergic stimulation is not the primary inducer of hypertrophy, but the net effect on cyclic AMP (or possibly ATP) tissue levels is. This hypothesis would then predict that β-receptor blockers and destruction of sympathetic nerves would not prevent hypertrophy and could even enhance it by causing a further decrease in cyclic AMP tissue concentrations. Although not discussed by Malik and Geha,25 their data did show that practolol-treated control rats developed significant left ventricular hypertrophy (10 ± 2%) compared with nontreated controls in a study designed to demonstrate that practolol does not prevent hypertrophy induced by aortic banding. Cyclic AMP levels were not measured in this study, but practolol, a β-antagonist, most likely would have caused a decrease in myocardial cyclic AMP. An appropriate test of the hypothesis would be to demonstrate that maintaining cyclic AMP tissue production prevents hypertrophy. This has been indirectly accomplished. Rats pretreated by hypoxia (to increase ATP stores and provide ample substrate for cyclic AMP synthesis) did not develop myocardial hypertrophy in response to aortic banding.26 Although this study supports our hypothesis, additional rigorous testing is required.

Although not demonstrated in this relatively short-term study, dogs infused with norepinephrine for 6 months develop moderate ventricular and marked septal hypertrophy, which is indistinguishable from the syndrome of HCM in humans.4 Thus, a defect similar to HCM can be reproduced in dogs by simply increasing circulating norepinephrine. However, we are not implying that HCM in humans occurs only with increased circulating norepinephrine, only that the end result in dogs is similar. We have hypothesized that myocardial hypertrophy occurs with the depletion of cyclic AMP regardless of the cause, and we have provided data suggesting that the canine ventricular septum may be susceptible to cyclic AMP depletion. To confirm our hypothesis on the mechanism of myocardial hypertrophy and our experimental data, a study of patients with HCM might demonstrate increased adrenergic activity and decreased stores of ATP and cyclic AMP proportional to the degree of septal hypertrophy in the patients.

The etiology for the development of HCM could be the result of increased septal sympathetic activity, decreased ability to maintain critical substrates (i.e., ATP and cyclic AMP), or increased sensitivity to catecholamines. It may be that the enhanced septal sensitivity to catecholamines demonstrated in normal control dogs is similar to that in patients who are prone to develop HCM and is not characteristic of other animal models or normal humans.

We thank Vincent Atienza and Deanna Hockett for their expert technical assistance.

References


19. Tse J, Wreenn RW, Kuo JF: Thyroxine-induced changes in characteristics and activities of β-adrenergic receptors and adenosine 3',5'-monophosphate systems in the heart may be related to reputed catecholamine supersensitivity in hyperthyroidism. Endocrinology 107: 6, 1980
Beta-adrenergic receptor and cyclic AMP alterations in the canine ventricular septum during long-term norepinephrine infusion: implications for hypertrophic cardiomyopathy.

W J Raum, M M Laks, D Garner and R S Swerdloff

doi: 10.1161/01.CIR.68.3.693

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/68/3/693

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/